Risk Prediction of Hyponatremia in Patients Hospitalised from Heart Failure

Saepudin
Student Number: 274820

Supervisors:
Professor Patrick A. Ball
Dr Hana Morrissey
Professor Akhmad Fauzy

May 2016
Table of Contents

List of Tables ................................................................................................................. vi
List of Figures ................................................................................................................. viii
List of Appendices ........................................................................................................ x
Abbreviations ............................................................................................................... xi
Thesis declaration ....................................................................................................... xiv
Acknowledgements ..................................................................................................... xv
Abstract .................................................................................................................... xvii
Chapter I – Executive summary ................................................................................ 1
Chapter II – Literature review ................................................................................... 7
  2.1. Heart failure ....................................................................................................... 7
      2.1.1. Global trend of heart failure epidemiology .............................................. 8
      2.1.2. Abnormal activation of neurohormones in heart failure ................. 11
      2.1.3. Main therapeutic options for treatment of chronic heart failure .......... 16
  2.2. Acute heart failure ............................................................................................ 22
      2.2.1. Significant Burden of acute heart failure ............................................. 23
      2.2.2. Shifting paradigms on pathophysiology of acute heart failure ........ 27
      2.2.3. Loop diuretics as the main therapeutic measure to manage acute heart failure ................................................................. 31
  2.3. Hyponatremia ................................................................................................... 35
      2.3.1. Clinical and economic burden of hyponatremia in patients with heart failure ................................................................. 36
2.3.2. Classification of hyponatremia ...............................................39

2.3.3. The role of arginine vasopressin in pathophysiological process of heart failure and hyponatremia ........................................42

2.3.4. Problems assessing hyponatremia...........................................47

2.3.5. Antagonists of arginine-vasopressin receptors (vaptan) as new treatment option .................................................................49

2.3.6. Awareness of hyponatremia by healthcare professionals ....53

2.4. Summary.......................................................................................55

Chapter III – Study conceptual framework ..............................................56

3.1. Study question ..............................................................................57

3.2. Clinical prediction model .............................................................58

3.2.1. The role of prediction models in clinical practice.....................59

3.2.2. Developing a prediction model ...............................................60

3.2.3. Prediction models within heart failure issues ......................62

3.2.4. Prediction models for hyponatremia ....................................65

3.3. Research aims ..............................................................................66

3.4. Research objectives .....................................................................66

3.5. Hypotheses ..................................................................................67

3.6. Summary.......................................................................................68

Chapter IV – Methods ........................................................................69

4.1. Research setting............................................................................69

4.2. Research design ............................................................................70
4.3. Ethics clearance and approval .......................................................... 70
4.4. Power and required sample size ....................................................... 71
4.5. Sample and subject selection ............................................................ 72
4.6. Definition of hyponatremia .............................................................. 73
4.7. Data collection and storage .............................................................. 73
4.8. Data analysis ..................................................................................... 74
  4.8.1. Assessing the prevalence of hyponatremia and its relationship with hospital stay and in-hospital mortality .......... 75
  4.8.2. Investigation of current/practiced management for treatment of hyponatremia ............................................................. 75
  4.8.3. Derivation of prediction model ............................................ 76
  4.8.4. Identification of variables associated with hyponatremia during hospitalisation ............................................................. 82
  4.8.5. Assessing the performance of the obtained prediction model .............................................................................................. 82
  4.8.6. Assessment of predictors’ contribution to the model .......... 82
  4.8.7. Assessment of overall performance ........................................ 83
  4.8.8. Assessment of discrimination ability .................................................. 84
  4.8.9. Assessment of calibration ability ................................................... 85
  4.8.10. Validation of prediction model ............................................. 86
  4.8.11. Presentation format of the prediction model ...................... 87
4.9. Limitations and risks ........................................................................ 88
Chapter V – Results ............................................................................................... 91

5.1. Subject selection ............................................................................... 91

5.2. Prevalence of hyponatremia and its association with clinical outcomes .................................................................................................. 92

5.3. Patient characteristics ....................................................................... 97

5.4. Management of hyponatremia ........................................................ 103

5.5. Derivation of the prediction model ................................................. 105

5.6. Factors contributing to the development of hyponatremia during hospitalisation ........................................................................................ 118

5.7. Performance of the prediction model .............................................. 119

5.7.1. Overall performance .......................................................... 119

5.7.2. Discrimination ability ........................................................ 122

5.7.3. Calibration ability .............................................................. 128

5.8. Validation of the preliminary final model ...................................... 130

5.9. Presentation of the final prediction model ...................................... 132

5.10. Summary ....................................................................................... 135

Chapter VI – Findings and discussion ................................................................. 137

6.1. Research overview .......................................................................... 137

6.2. Sample size and research design .................................................... 139
List of Tables

Table 1 - Neurohormones involved in the pathophysiology of heart failure .......... 14
Table 2 - The roles of several classes of drugs for treatment of chronic heart failure proved by clinical evidence ................................................................. 22
Table 3 - Common precipitating factors of acute heart failure ......................... 23
Table 4 - The locations of each arginine-vasopressin receptor and associated physiologic actions when arginine-vasopressin is bound to the receptor .......... 44
Table 5 - Predictors derived from vital signs and symptoms at admission .......... 78
Table 6 - Predictors derived from concomitant diagnosis .................................. 78
Table 7 - Predictors derived from medical history ............................................ 79
Table 8 - Predictors derived from medication administered during hospitalisation . 79
Table 9 - Predictors derived from blood chemistry at admission ..................... 80
Table 10 - General classification of discrimination ability of regression model according to area under receiver operating characteristic curve .......... 85
Table 11 – Research timeline ......................................................................... 90
Table 12 - Comparison between sodium and potassium disturbances observed in patients hospitalised for heart failure .................................................. 93
Table 13 - Gender and age as matched variables between case and control groups.. 94
Table 14 - Distribution of the lowest serum sodium level during hospitalisation among patients who developed hyponatremia during hospitalisation .............. 94
Table 15 - Association between hyponatremia during hospitalisation and clinical outcomes ................................................................................................. 96
Table 16 - Symptoms and vital signs at admission ............................................ 97
Table 17 - Medical history ............................................................................... 98
Table 18 - Medical problems concomitantly diagnosed at during admission ...... 99
Table 19 - Profile of blood chemistry at admission ............................................ 100
Table 20 - Medications administered during admission ..................................... 103
Table 21 - Distribution of treatment options administered to hyponatremic patients based on serum sodium level ......................................................... 105
Table 22 - Predictors with p-value <0.05 resulting from univariate logistic regression and predictors previously reported as risk factors for hyponatremia .......... 107
Table 23 - Result of multivariate logistic regression analysis including significant predictors from univariate analysis ....................................................... 108
Table 24 - Significant predictors included in smaller model resulted from the second multivariate logistic regression analysis ................................................................. 109
Table 25 - Changes of regression coefficients of predictors included in smaller model compared to the previous large model .......................................................... 110
Table 26 - Predictors not included in initial multivariate model and their associated p-value when added into the smaller model ...................................................... 110
Table 27 - Summary of univariate logistic regression analysis for interaction terms that were considered to be included in the model ............................................... 114
Table 28 - Summary of significance value of considered interaction terms added into the smaller model .................................................................................................. 114
Table 29 - Output summary of multivariate logistic regression analysis by adding two significant interactions into the smaller model ................................................. 115
Table 30 - Output summary of further multivariate logistic regression analysis by only adding one significant interaction into the smaller model ............................. 115
Table 31 - Value of variable inflation factor and tolerance of all predictors included in the model resulting from multicollinearity test .................................................... 117
Table 32 - Preliminary final model containing six predictors ......................................... 117
Table 33 - Value of Nagelkerke R² and Brier score indicating overall performance of the preliminary final model .............................................................. 120
Table 34 - Contribution of predictors included in the preliminary final model into its overall predictive performance ................................................................. 121
Table 35 - Contribution of predictors included in the preliminary final model to its discrimination ability indicated by increased area under the curve of receiver operating characteristic curve values ............................................................ 128
Table 36 – The p-values of the Hosmer-Lemeshow test with several different group numbers obtained using the hoslem.test of Resource Selection packages in R ...... 130
Table 37 - Shrunken regression coefficient resulted from original regression coefficient multiplied by shrinkage factor .......................................................... 133
Table 38 - Final regression coefficients of predictors in the final model .................. 134
Table 39 - Common formulas for estimating infusion rate of saline solution ........... 152
List of Figures

Figure 1 - American College of Cardiology/American Heart Association heart failure staging classification as general guidance for therapeutic management in patients with heart failure ................................................................. 19
Figure 2 - New York Heart Association functional classes of patients with symptomatic heart failure based on severity of the symptoms ......................... 20
Figure 3 - Cause of death during first year after hospital discharge among patients previously hospitalised from acute heart failure ........................................ 25
Figure 4 - Comparison of hospital readmission rate during the first 30 days among patients previously hospitalised from acute heart failure, pneumonia and acute myocardial infarction ................................................................. 26
Figure 5 – Patients with acute heart failure receiving loop diuretics during hospitalisation ................................................................. 32
Figure 6 – the role of arginine-vasopressin in the pathophysiological process of heart failure and hyponatremia through non-osmotic regulation stimulated by inadequate cardiac output [66, 188, 210] ................................................................. 45
Figure 7 - Conceptual framework of the research emphasising the importance of providing a prediction model to identify heart failure patients at high risk of developing hyponatremia ......................................................... 57
Figure 8 - Summary of the seven steps in selecting predictors to fit the prediction model by following purposeful predictor selection ................................ 81
Figure 9 - Selection of patients included in the research and patient allocation to case and control group ................................................................. 92
Figure 10 - Comparison of mean of serum sodium level at admission between patients developing and not developing hyponatremia during hospitalisation ........ 94
Figure 11 - Depletion serum sodium level in patients who developed hospital-acquired hyponatremia ................................................................. 95
Figure 12 – Depletion of serum sodium level in patients encountering persistent hyponatremia ........................................................................ 95
Figure 13 - Distribution of treatment options administered to hyponatremic patients ........................................................................ 104
Figure 14 - Linearity of the logit of serum sodium level as the only one continuous predictor in the smaller model ........................................ 113
Figure 15 – Receiver operating characteristic curve of the preliminary performance model including six predictors resulting in an area under the curve of 0.90 .......................... 122

Figure 16 – Receiver operating characteristic curve of the model including five predictors (excluding administration of antibiotics) resulting in an area under the curve of 0.89 ............................................................................................................. 123

Figure 17 – Receiver operating characteristic curve of the model including four predictors (excluding administration of antibiotics and positive inotropes) resulting in an area under the curve of 0.88 ............................................................................................................. 124

Figure 18 – Receiver operating characteristic curve of the model including three predictors (serum sodium level at admission and history of fatigue and ascites) resulting in an area under the curve of 0.86 ...................................................................................................... 125

Figure 19 – Receiver operating characteristic curve of the model including two predictors (serum sodium level at admission and history of fatigue) resulting in an area under the curve of 0.85 .......................................................................................................... 126

Figure 20 – Receiver operating characteristic curve of model including only serum sodium level at admission as predictor resulting in an area under the curve of 0.83 .......................................................................................................................... 126

Figure 21 - Calibration plot of the preliminary final model obtained using the val.prob function of rms packages in R .................................................................................................................. 129

Figure 22 - Output resulted from bootstrapping validation approach of the preliminary final model using the “validate” function of rms packages in R........... 131

Figure 23 - Overall shrinkage factors generated by “shrink” function of “shrink” packages in R ............................................................................................................... 133
List of Appendices

Appendix 1 – Paper resulting from this research published in BMC Cardiovascular:


Appendix 3 – Paper resulting from this research submitted to the Journal of General Internal Medicine: Risk prediction of hyponatremia in patients hospitalized from heart failure
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology Foundation</td>
</tr>
<tr>
<td>ACEI</td>
<td>angiotensin converting enzymes</td>
</tr>
<tr>
<td>ADH</td>
<td>antidiuretic hormone</td>
</tr>
<tr>
<td>ADHF</td>
<td>acute decompensated heart failure</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>AHF</td>
<td>acute heart failure</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine amino-transferase</td>
</tr>
<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td>ANP</td>
<td>atrial natriuretic peptide</td>
</tr>
<tr>
<td>ANS</td>
<td>autonomic nervous systems</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate amino-transferase</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>AVP</td>
<td>arginine-vasopressin</td>
</tr>
<tr>
<td>BNP</td>
<td>beta-type natriuretic peptide</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>c-statistic</td>
<td>concordance statistic</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
</tbody>
</table>
CI  : confidence interval
CNP  : C-type natriuretic peptide
COPD : chronic obstructive pulmonary diseases
CRT  : cardiac resynchronization therapy
CVCU : cardiovascular care unit
CVD  : cardiovascular diseases
EF   : ejection fraction
ESC  : European Society of Cardiology
EVP  : events per-variable
FRS  : Framingham Risk Score
GoF  : goodness-of-fit
HAH  : hospital-acquired hyponatremia
HF   : heart failure
HFrEF: heart failure with reduced ejection fraction
HFrEF: heart failure with preserved ejection fraction
HFSA : Heart Failure Society of America
HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome
HL   : Hosmer-Lemeshow
HRQOL: health-related quality of life
ICD  : international classification of diseases
ICU  : intensive care unit
LMWH: low molecular weight heparin
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>NCC</td>
<td>nested case-control</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>NP</td>
<td>natriuretic peptides</td>
</tr>
<tr>
<td>NR²</td>
<td>Nagelkerke $R^2$</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PFM</td>
<td>preliminary final model</td>
</tr>
<tr>
<td>PH</td>
<td>persistent hyponatremia</td>
</tr>
<tr>
<td>PM</td>
<td>prediction model</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised-controlled trial</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SHFM</td>
<td>Seattle Heart Failure Model</td>
</tr>
<tr>
<td>SIADH</td>
<td>syndrome of inappropriate antidiuretic hormone secretion</td>
</tr>
<tr>
<td>SNS</td>
<td>sympathetic nervous system</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
</tr>
<tr>
<td>SSRIs</td>
<td>selective serotonin receptor inhibitors</td>
</tr>
<tr>
<td>USA FDA</td>
<td>United States of America Food and Drug Administration</td>
</tr>
<tr>
<td>VIF</td>
<td>variance inflation factor</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
</tbody>
</table>
Thesis declaration

I hereby declare that the work herein, submitted to Charles Darwin University for the degree of Doctor of Philosophy, is the result of my own investigation and all references to the ideas and work of other researchers have been specifically acknowledged. I hereby certify that the work embodied in this thesis has not already been accepted in substance for any degree and is not being currently submitted in candidature for any other degree.

Candidate: Saepudin
Acknowledgements

Alhamdulillah, all praise is due to Allah Ta’ala Almighty, the Giver of bountiful blessings and gifts. It has been a challenging journey to pursue my PhD degree while being away from family and home. Nevertheless, I am very grateful for my research experiences and the opportunity to meet many wonderful people who supported my work during my study. Hence, it is my great pleasure to express my gratitude to the people who have given their support and help so that I can arrive at this step.

The first person I would like to express my sincere gratitude to is my principal supervisor, Professor Patrick Ball, for his great support, patience and encouragement throughout my study. It was a long journey from Yogyakarta – Wagga Wagga – Darwin but I was so fortunate to always receive his kind help and support. I would also like to express my sincere appreciation to my co-supervisor, Dr Hana Morrissey, for her wonderful support since my arrival in Darwin and continuously during my distressing writing process. My sincere appreciation is also to Professor Akhmad Fauzy as my co-supervisor, who assisted me in performing and interpreting statistical analysis. My sincere thanks is also to Professor Lexin Wang as my supervisor when I was doing part of my study at Charles Sturt University in Wagga Wagga.

I would like also to express my thanks to the following institutions:

- Directorate General of Higher Education, Ministry of Research and Technology, Republic of Indonesia, for the PhD scholarship supporting my study
- Rector of Universitas Islam Indonesia, who gave me permission to leave my job while doing my PhD study
- Management and committee of Fatmawati Hospital in Jakarta, Indonesia, for allowing me to collect the data.

I would not be able to achieve this important milestone in my life without support from my family: my mother and father whose prayers and thoughts always calm me; my beloved wife, Zakiyah, for her patience and endurance in looking after our children alone while I was doing my study far away from home; my beloved sons: Hudzaifah, Niazy and Oruzgan, and my beautiful smart daughter Nisrina, for putting up with the long distance separating us during my study overseas. My sincere love and thanks to you all.

My sincere thanks also to all my friends and fellows: Ibu Tessa Bremner and Ian Macdonald for their kindness when I was in Wagga Wagga, Dr Ataur Rahman and Dr Waseem Afzal for their help and support, my colleagues in the Department of Pharmacy - Universitas Islam Indonesia for their support and encouragement, Dr Rohmatul Fajriyah for helping me to understand “R”, Brother Mohammad Kurniawan and his family for sharing their house in Darwin, and to all Indonesian fellows doing PhD and master degrees in CDU.

Finally, thanks to Professional editor, Rosemary Purcell, who provided copyediting and proofreading services according to the guidelines laid out in the university-endorsed national Guidelines for editing research theses.

Saepudin
Abstract

**Background:** Hyponatremia is the most common electrolyte disturbance in heart failure patients. It significantly affects morbidity and mortality, also increasing expenditure in heart failure patients. It is rarely recognised or treated sufficiently due to inadequate diagnostic measurements and doubts concerning the effectiveness of treatment. An important step to proper management is to recognise patients at high risk.

**Aims:** To develop a reliable prediction model for the risk of hyponatremia in patients hospitalised with heart failure.

**Design and methods:** Information was retrieved manually from medical records of patients, and hyponatremia was defined as sodium level <135 mmol/L. A nested case-control design was applied and logistic regression analysis was performed to derive the prediction model. Purposeful selection was used to select predictors and statistical analysis was performed using SPSS™ IBM(R) and the R software.

**Results:** From 464 patients included, 102 patients (22%) were hyponatremic during hospitalisation. Hyponatremia was significantly associated with longer stay (OR = 2.1, 95% confidence interval [1.3–3.3]) and higher mortality rate (3.4, [1.8–6.4]). Other than fluid restriction and diuretics, sodium chloride based therapies were used in the research site, but >50% of patients with severe hyponatremia did not receive active treatment. Six variables were significantly associated with increased risk: serum sodium at admission (0.77, [0.72–0.83]), fatigue (3.71, [1.99–6.9]), ascites (3.73, [1.55–8.99]), inotropes (2.95, [1.38–6.34]), heparin (2.98, [1.33–6.66]) and antibiotics (2.87, [1.56–5.29]). These were included in the prediction model with good predictive ability both overall (Brier-score = 0.107, NR² = 0.531). The
prediction model was then presented in a regression formula format as $Hyponatremia = 128.1 - Sodium + 5.2 \ Fatigue + 5.2 \ Ascites + 4.3 \ Positive \ inotropes + 4.3 \ Heparin + 4.2 \ Antibiotics$.

**Conclusion:** A risk-prediction model to stratify the risk for developing hyponatremia during hospitalisation was derived by including predictors selected from patient- and medication-related factors identified. The prediction model exhibits good predictive performance indicating that it can be practically used.

**Keywords:** heart failure, hyponatremia, prediction model, predictive performance, sodium
Chapter I – Executive summary

Heart failure (HF) is a clinically complicated syndrome resulting from any disorder, anatomical or physiological, reducing the ventricular ability to produce an adequate ejection fraction (EF). The obvious symptoms of HF include shortness of breath leading to a limitation in physical activity and accumulation of fluid in the lungs and/or peripheral tissues leading to congestion and oedema. Due to its complicated characteristics, a careful physical examination and documentation of the patient’s history should be performed before making the diagnosis.

As an advanced stage of cardiovascular disorder, HF is the most common cause of death from cardiovascular diseases around the world. Although the trend of HF morbidity and mortality varies between countries, epidemiological data show that the mortality rates of HF globally are higher than mortality rates from cancer and infectious diseases. In spite of the variability in morbidity and mortality between countries, it is clear that elderly people are the most vulnerable group suffering from HF complications.

One of the most important problems that potentially presents in managing patients with HF is hyponatremia, which shares many pathophysiologic and prognostic features with HF. Patients with HF have a high probability of suffering from hyponatremia either as a result of disease progression or the adverse effect of medications. As well as being a common and important complication, hyponatremia is also a strong independent predictor of quality of life and mortality in patients with HF.

Besides choosing the treatment option, the most important step in managing hyponatremia is to recognise the condition. Identification of patients with
hyponatremia should happen immediately, and once the patient is identified as hyponatremic the condition must be assessed. Assessment requires a series of measurements including exploration of the patient’s history, identification of clinical symptoms, and determination of laboratory investigations. Despite the significance of hyponatremia, several studies have shown that healthcare professional awareness towards the condition and an appropriate assessment to determine the hyponatremic status of the patients, especially for mild chronic conditions, is lacking.

As an important complication potentially encountered by HF patients, hyponatremia requires more attention in terms of identification of risk, investigation and treatment. Whether in a chronic condition or acute hospitalisation, hyponatremia is always associated with worse clinical outcomes. In addition, it is also associated with higher healthcare costs. Therefore, attempts to reduce the negative impact of hyponatremia in HF patients are urgently needed.

In medical research and practice, prediction models (PM) have been gaining attention and are increasingly published. In a practical setting, PMs developed either for diagnostic or prognostic purposes can assist healthcare providers in estimating the risk of a particular event or outcome, and provide a further guide when deciding appropriate strategies to reduce the risk. Well-developed and validated PMs guide healthcare providers in choosing efficient and cost-effective strategies.

Based on the review of the literature, the researcher identified a need to provide tools for early identification of HF patients with a high risk of developing hyponatremia during hospitalisation as the first and most important step in managing hyponatremia so that further negative impact can be prevented. The specific aim of this research was to develop a PM that can be used to predict the risk of developing hyponatremia during hospitalisation among patients hospitalised with HF. The PM was derived by
including predictors from patient characteristics and developed by logistic regression analysis. Several steps were needed before deciding that the model has good performance and practical utility, including an external validation step involving a different patient population. A model with good predictive performance and robust internal validation could be useful initially in the local setting where the sample was taken as long as it is well-developed and involves an adequate sample size representative of the population.

This thesis is divided into 10 chapters to present the research in a logical framework. Chapter II presents the literature review that establishes the importance of this research. Commencing from the recent global epidemiology of HF, this chapter also reviews hyponatremia as an important problem in HF patients, both pathophysiologically and clinically, and its role in predicting short and long-term clinical outcome of patients with HF. To strengthen the importance of this research, problems related to hyponatremia in terms of making the diagnosis and appropriate treatment found frequently in practical setting were also reviewed.

Chapter III describes conceptual framework that leads to confirming the aim and aided in developing the study question. Based on all evidence found in the literature review it was decided that the main goal of this research was to obtain a risk-PM that can be used to develop an algorithm or a model that can be used to predict the risk of hyponatremia in patients hospitalised who also have HF. Some other objectives have also arisen to get more comprehensive results. In order to achieve the intended goal and objectives, some basic and practical concepts of developing a PM along with methods commonly used to assess and validate PMs are elaborated in this chapter. The important roles of PMs for either diagnostic or prognostic purposes are also presented, as well as PMs for HF that have already been developed and applied.
Chapter IV elucidates methods applied in this research including the study design, subject selection criteria, ethics approval, data collection process and the steps in deriving the PM. Purposeful selection method was chosen to select predictors to be included in the PM. Methods used to assess the predictive ability of the PM both of overall and specific ability in terms of discrimination and calibration ability is also elaborated. The internal validation process of the PM performed by a bootstrapping approach for measuring the optimism of the PM is also described, followed by the method of presentation of the PM.

Results of this research are presented in Chapter V. Important findings resulting from this research included the prevalence of hyponatremia during hospitalisation and its association with hospital length of stay and in-hospital mortality, the current practice for management of hyponatremia in HF patients in the research site, and the obtained PM. The prevalence of hyponatremia found in this research is within the range of prevalence reported by other research, and its association with hospital length of stay and in-hospital mortality confirms the findings of other research. Although data on the treatment of hyponatremia found in this research were quite limited, its presentation is important to increase awareness of the identification and treatment of hyponatremia. The PM obtained from this research was intended to be used to predict the risk of developing hyponatremia during hospitalisation among patients hospitalised from HF. Six predictors have been found to have a significant contribution to outcomes: serum sodium level, presence of fatigue and ascites, administration of positive inotropes, heparin and antibiotics. These predictors were then included in the PM resulting in a PM with good predictive ability both of overall and specific ability. Overall performance of the PM assessed by Brier-score and Nagelkerke $R^2$ (NR²) indicate that the PM is an informative model.
Discrimination ability of the model was assessed by area under the curve (AUC) of receiver operating characteristic (ROC) curve, and it was found that the PM exhibits outstanding discrimination ability. Calibration ability was assessed by calibration plot and Hosmer-Lemeshow (HL) tests and both indicate that the PM has good calibration ability. Subsequently, reproducibility of the PM assessed by internal validation using a bootstrapping approach is presented in this chapter, in which optimism was observed but did not substantially reduce performance of the PM. The final section of this chapter presents the PM in the format of a regression formula in which the regression coefficients have been shrunken to get more accurate prediction.

Chapter VI discusses the important findings presented in Chapter V. All findings are discussed in connection with related findings resulting from other research so that the place of this research as well as its importance and contribution within a broader context can be established. Other than the primary finding on the obtained risk-PM for hyponatremia during hospitalisation in patients hospitalised with HF, other findings supporting the importance of the primary finding are also discussed. The prevalence of hyponatremia and its association with hospital length of stay and in-hospital mortality is discussed and compared to other published research. Likewise, current treatment of hyponatremia in the research site is also discussed.

Chapter VII lists some limitations that could not be overcome in this research, mainly associated with the nature of retrospective data collection. However, those limitations did not substantially reduce the quality of the research results.

Chapter VIII presents the conclusions of this research, along with relevant recommendations. The chapter answers the main question of this research, and includes support for the importance of the primary conclusion. The primary
Conclusion generated from this research is that a PM with good predictive performance can be obtained by including predictors taken from information related to the patient’s condition and medication administered during admission. Other findings of this research confirm findings resulting from other research that conclude that hyponatremia is an important clinical problem associated with worse clinical outcomes.

The significance of the findings resulting from this research for the current body of knowledge is presented in Chapter IX. By identifying important risk factors and further obtaining a PM containing those risk factors this research can significantly contribute towards targeting patients needing more adequate monitoring in association with increased risk of hyponatremia. Subsequently, appropriate treatment can be administered into hyponatremic patients so that its adverse effects can be attenuated. In a broader context this research can also contribute towards raising awareness of hyponatremia, as studies report that it is still a neglected problem.

The last chapter of this thesis is Chapter X, which lists potential follow-up and future research related to this current research. Specifically, temporal validation and further external validation of the PM obtained from this research should be conducted in the near future to make sure that the PM can be practically used. More broadly in relation to hyponatremia in HF patients, development of the PM to target patients in the community or outpatient setting is also important.

Appendices 1 and 2 are papers resulting from this research published in the journals *BMC Cardiovascular* and *International Journal of Clinical Pharmacy*, and Appendix 3 is a paper on risk prediction of hyponatremia in patients hospitalised from HF currently in submission to the *Journal of General Internal Medicine*. 

6
Chapter II – Literature review

This chapter presents a review of the literature relevant to the topic of this research in which two main issues are discussed: HF and hyponatremia. The main purpose of this review is to identify gaps that need to be addressed. HF in general, and specific issues related to acute HF are reviewed based on findings in terms of the resultant burden and the progress of its pathophysiological and therapeutic concept. Issues related to hyponatremia as an important problem frequently encountered by patients with HF discussed in this review include its epidemiology, pathophysiology, therapeutic options and problems practically found in terms of recognition and diagnosis.

2.1. Heart failure

Among cardiovascular diseases (CVDs), HF is considered to be the end stage [1]. It is a chronic disease, developing progressively and presenting a high impact on a significant proportion of the population, especially the elderly [2-4]. Population ageing is a major factor contributing to the high prevalence of HF, particularly as the substantial increase in the proportion of the middle-aged population having obesity and diabetes mellitus will also potentially increase the prevalence of HF [1, 5-7]. It is estimated that in the next decade HF patients will become older with more complex comorbidities [4]. While some studies report an improvement in the survival of HF patients, the prognosis overall is still poor given that less than 50% of patients survive more than five years after first hospitalisation [6, 8]. More effective strategies, including pharmacological and non-pharmacological managements, are required to improve survival and quality of life of HF patients [9].

HF is a syndrome that is complicated to manage, resulting from any disorder, either
anatomical or physiological, that reduces the ventricular ability to produce an adequate EF [6, 10]. The obvious symptoms are fatigue and shortness of breath leading to a limitation in physical activity, and the accumulation of fluid leading to congestion and oedema in peripheral tissues and lungs [10]. Due to its complicated characteristics, a careful physical examination and documentation of the patient’s history is required before making the diagnosis [6, 11, 12].

Even though the impairment of any part of the heart can lead to HF, in the majority of cases it originates from the impairment of the ventricles [13]. Left ventricular dysfunction resulting in reduced EF is the most common feature of HF. However, the prevalence of HF with preserved EF is increasing more commonly in women and older patients [14]. To a lesser extent, patients with HF resulting from diastolic dysfunction are mostly asymptomatic for several years and slowly become symptomatic along with the disease progression and aging [14].

2.1.1. Global trend of heart failure epidemiology

Despite the implementation of evidence-based therapeutic guidelines, HF remains the most common cause of death of all cardiovascular diseases globally [15-18], mostly affecting the elderly population and causing complications and poor quality of life [2, 19, 20]. HF burden is becoming a public health problem around the world; it has approached an epidemic proportion in most developed and developing countries [21]. Overall, the chance of developing HF after 40 years of age in most developed countries is 20%. The incidence and prevalence of HF increases substantially with advanced age. It is estimated that the risk for having HF will increase twofold for each 10 years of life and that one in 10 people aged over 75 years has a probability of suffering from HF [1].
HF is more common in men than in women up until age 65, reflecting the greater incidence of coronary artery disease (CAD) in men [22]. While CAD is the most common aetiology of HF in men, hypertension and valvular disorder are more common in women. However, CAD is a greater risk factor for developing HF in women compared to hypertension [23]. Given that women with HF have longer survival than men, studies report that the prevalence of HF is not significantly different between men and women despite the higher incidence of HF in men [23].

More successful management of some acute conditions such as myocardial infarction as well as some chronic conditions such as hypertension and diabetes mellitus tend to shift the epidemiological picture of HF to become more prevalent among elderly [4]. The incidence of HF among those individuals aged 75 years or older is 10 times higher than that of younger groups, and the prevalence is almost five times higher [1, 24, 25]. Both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) make up almost the same proportion of the total HF burden [26]. As the majority of patients with HF are elderly, their HF problems are usually more complicated by the medicine use (the natural pharmacokinetic and pharmacodynamic changes caused by ageing), and also by the presence of multiple comorbidities that potentially worsen morbidity and mortality [24, 27].

In most cases HF is associated with a complex array of numerous risk factors [17]. While hypertension is the most common risk factor for HF around the globe, myocardial infarction is the most common cause among populations in developed nations [17, 28]. Dysfunction of heart valves, cardiopulmonary obstruction and rheumatic heart disease are some of risk factors found in smaller numbers of HF patients [17, 25]. Given that the characteristics of the disease patterns and the related
health problems in each country are different, the most definite risk factor of HF in each country around the world is also different [17, 25].

Some recent studies have found that mortality rates among HF patients have declined and survival has improved [29-31]. However, hospitalisation resulting from HF problems still becomes an important burden around the world [9, 32]. Several reasons probably have contributed to the improvement of HF patient survival and mortality, but improved adherence to evidence-based guidelines seems to be the most important [33, 34]. The increasing use of several cardiac devices such as pacemakers and valves is also contributing, but the impact is smaller given this therapy is applied to a small group of patients only [35].

As a public health problem, HF also becomes an economic burden for countries around the world [36]. Hospitalisation takes a significant portion of total cost of HF management followed by medical doctor visits [37, 38]. Almost 50% of the total cost for managing HF patients is hospitalisation, which is caused by the high risk of ongoing re-hospitalisation [39]. The cost for hospitalisation escalates if the patient is suffering from a complication such as atrial fibrillation (AF) or hyponatremia [40]. Despite the difference in total allocated cost for health expenditure in every country around the world, total cost spent for managing HF globally was estimated at more than US$100 billion in 2012 alone [36].

Despite the improvements in pharmacological therapy, the health-related quality of life (HRQOL) of HF patients is low [41]. The existence of multiple comorbidities will further reduce the HRQOL of HF patients, particularly for conditions that affect cognitive and or physical functions such as dementia, depression and hyponatremia [42-44]. Other than cardiac resynchronisation therapy (CRT), delivering educational programs and disease self-management can help to improve the HRQOL of HF
patients [44–46]. To improve HRQOL among HF patients is very important as it has been known to be significantly associated with increased morbidity and mortality especially among elderly patients [47].

2.1.2. Abnormal activation of neurohormones in heart failure

The main function of the heart is to pump an adequate blood volume into the systemic circulation, called cardiac output, in order to maintain tissue perfusion. The main regulator maintaining the ability of the heart to pump the blood is the autonomic nervous systems (ANS), which regulates the diastolic and systolic functions of each component of the heart [48, 49]. In simple terms, cardiac output is the result of heart rate and the stroke volume, both adjusted to always deliver adequate cardiac output. Under normal physiologic regulation, heart rate and the MAP will compensate each other under control of the ANS so that cardiac output can be maintained accordingly [49].

HF is a heart disorder that develops progressively initiated by an event that impairs the systolic and/or diastolic function of the heart [10, 50]. The impairment leading to HF may be an acute process, such as myocardial infarction, or a chronic long-term process like hypertension [50, 51]. Whatever the initial event is, once the heart’s capacity to eject an adequate volume of blood into the systemic circulation is reduced it will put the heart into dependence on compensatory processes to maintain an adequate cardiac output [52]. Activation of the sympathetic nervous system (SNS) is the major compensatory process to maintain cardiac output, which further will induce other mechanisms including vasoconstriction and remodelling of the heart ventricle [49, 53]. Within normal physiological circumstances, these compensatory processes will be activated acutely to increase cardiac output due to acute decrease of blood pressure or inadequate renal blood flow [49]. To some extent, these processes
enable the heart to pump an adequate blood volume into systemic circulation.

However, inadequate cardiac output occurring persistently induces long-term activation of these compensatory processes, which leads to some counter-productive changes that predispose to the progression of HF [52].

The basic concepts of HF pathophysiology have been changing over decades. The oldest concept is called the cardio-renal model, stating that the main problem in HF is the retention of sodium and water, thus diuretic therapy was applied as the main treatment. The cardio-circulatory model was then introduced, stating that the main problem is inadequate cardiac output, thus cardiac glycosides and other positive inotropic drugs were used as the main treatment. Unfortunately, these two concepts failed to explain the progressive characteristic of HF. The most recent neurohormonal concept was then introduced, as angiotensin converting enzyme inhibitors (ACEIs) showed a positive long-term effect among HF patients [54]. This concept emphasises that although the first event initiating the inadequacy of cardiac output originates from the heart, it will then induce a systemic process regulated by neurohormones [54].

Several neurohormones have been identified as having a contribution to the progression of HF, including angiotensin II, norepinephrine, aldosterone, arginine-vasopressin (AVP), natriuretic peptides (NP), and also some important pro-inflammatory cytokines [55, 56]. Each neurohormone has an important role in the progression of HF, and potentially becomes a therapeutic target in attempts to slow progression [56]. While current drug therapy targets such important neuro-hormones, investigations to understand more deeply the role of each neurohormone and how to alleviate the negative effects are still needed [48, 56].
Angiotensin II is the most well-known substance as having an important role in the progression of HF as it has the ability to affect several sites within the cardiovascular regulation system [57]. Within the ANS system, it can trigger adrenergic nerve terminals to release norepinephrine that will cause activation of the SNS. It is also a very potent vasoconstrictor, both as a direct vasoconstrictor and by inducing the release of other vasoconstrictor agents such as arginine vasopressin (AVP) and endothelin-1 [10, 48]. Its ability to cause sodium retention, through its action inducing aldosterone release, also has an obvious role in the progression of HF. Finally, it has the ability to stimulate hypertrophy within the ventricular muscle that further causes a ventricular remodelling so that the cardiac ventricles lose the ability to pump the blood adequately [50].

Norepinephrine (NE) is another neurohormone that plays an important role in the progression of HF through its direct ability to stimulate the SNS [48, 58]. Its detrimental effects include vasoconstriction, increased heart rate and increased contractility, which in long-term activation can lead to ventricular remodelling and predisposing the progression of HF [58]. The plasma concentration of NE has a significant correlation with the severity of HF in which patients who have a higher NE plasma concentration tend to have a worse prognosis [58].
Table 1 - Neurohormones involved in the pathophysiology of heart failure [55, 58]

<table>
<thead>
<tr>
<th>Neurohormone</th>
<th>Contribution to progression of heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II</td>
<td>To increase systemic vascular resistance resulting in reduction of cardiac output, to stimulate cardiac hypertrophy and ventricular remodelling and induce secretion of other neurohormones contributing to the progressiveness of HF: aldosterone, NE and AVP</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>To increase sodium retention leading to volume overload and induction of cardiac fibrosis resulting in decreased ventricular diastolic function</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Increased heart rate and contractility and vasoconstriction leading to reduced cardiac output To stimulate cardiac hypertrophy and remodelling</td>
</tr>
<tr>
<td>Arginine vasopressin</td>
<td>To increase renal free water reabsorption leading to volume overload and hyponatremia, increase arterial vasoconstriction and induce ventricular hypertrophy leading to reduction of cardiac output</td>
</tr>
<tr>
<td>Natriuretic peptides</td>
<td>To balance the negative effects of other neurohormones by inducing diuresis, natriuresis, vasodilation, decreased aldosterone release, decreased hypertrophy, and inhibition of the SNS and the RAAS</td>
</tr>
</tbody>
</table>

Note: HF = heart failure; NE = norepinephrine; AVP = arginine vasopressin; SNS = sympathetic nervous system; RAAS = renin-angiotensin-aldosterone system

The role of aldosterone in the progression of HF is observed particularly through its effect on sodium retention [55]. However, it also has a direct effect on cardiac muscle by increasing collagen deposition leading to cardiac fibrosis [51, 59]. Its direct effects on the heart is believed to have a more significant role in the progression of HF, as it can directly impair the heart’s ability to pump blood normally, reducing cardiac output [51]. Although aldosterone is produced mainly in the adrenal cortex, some tissues also have the ability to produce aldosterone, including the heart and vascular smooth muscle, which together increase the progression of HF [60].
Another neurohormone involved in the pathophysiology of HF is NP [61]. Three types of neurohormone from this family have been identified: atrial natriuretic peptide (ANP), beta-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) [61]. While CNP is stored mostly in the brain and has only a peripheral role in the pathophysiology of HF, ANP and BNP are found mostly in the heart and are actively involved [61]. In patients with HF, ANP and BNP induce diuresis, natriuresis and vasodilatation, decrease hypertrophy and aldosterone release, and inhibit the SNS and renin-angiotensin-aldosterone system (RAAS) actions [61, 62]. However, BNP is the only member of the NPs that has been used as a biomarker both for diagnostic and therapeutic purposes [63, 64].

AVP, formerly known as antidiuretic hormone (ADH), is a pituitary peptide that also has an important role in the progression of HF [65]. Maintaining body fluid homeostasis is the main physiologic role of this neurohormone in which its secretion is regulated mainly by the changes of plasma osmolality [65, 66]. Vasoconstriction and increased cardiac contractility can also occur when this neurohormone is bound to its receptor located in vascular smooth muscle and cardiac muscle [67].

In patients with HF, higher serum levels of AVP have been found to be associated with the severity of HF [56]. Increased AVP serum levels, stimulated by low cardiac output, results in increased renal free water reabsorption, which further leads to volume overload and hyponatremia [56, 67]. To some extent, acute increased AVP serum levels also increase arterial vasoconstriction resulting in further reduction of cardiac output. In addition, continuous increased AVP serum levels contribute to ventricular hypertrophy resulting in cardiac remodelling leading to more severe HF [56, 65].
2.1.3. Main therapeutic options for treatment of chronic heart failure

In general, the major goals of therapeutic management in patients with HF is to relieve the symptoms, as well as to maintain vital organ function by maintaining adequate cardiac output and tissue perfusion so that the patient’s morbidity and mortality can be reduced [11, 12]. Meanwhile, underlying conditions causing HF also need to be identified and corrected properly to prevent further a worsening HF condition [11, 12]. For the longer term, the patient’s quality of life and survival should be also targeted [11, 12].

Several guidelines on the management of patients with HF have been produced by elaborating evidence resulting from clinical trials, observational studies and expert opinion. Two of the most prominent guidelines are those developed by the American College of Cardiology/American Heart Association (ACC/AHA) [12] and the European Society of Cardiology (ESC) [11]. Although both guidelines have general overlap, there are some differences in regard to specific issues and recommendations.

For more than two decades ACE inhibitors have been the backbone for the treatment of patients with HF [68]. The beneficial effects of ACE inhibitors have been proven by clinical trials, and as a result these drugs were listed as main therapeutic options in guidelines on HF management replacing the previous main therapeutic options, diuretics and digoxin [69, 70]. A systematic overview conducted by Flather et al. (2000) is the most cited evidence showing the beneficial effects of ACE inhibitors in reducing morbidity and mortality in patients with HF [70]. While previous main therapeutic options reduced only morbidity, ACE inhibitors have been proven to have prominent effects in reducing morbidity as well as mortality [69].

The ACE inhibitors main pharmacological action is to reduce the production of angiotensin II by inactivating the enzyme converting angiotensin I to angiotensin II
leading to decreased circulating angiotensin II [71]. Subsequently, circulating aldosterone is also decreased because aldosterone secretion is activated by the binding of angiotensin II onto its receptor [72]. Reduced angiotensin II levels directly result in decreased cardiac workload by reducing afterload through vasodilation of arterial beds and concomitantly by decreasing preload due to attenuation of water reabsorption resulting from decreased circulating aldosterone [71]. These short-term actions underlie the ability of ACE inhibitors do relieve the symptoms of HF [73]. Moreover, long-term reduced angiotensin action on myocytes attenuates the progress of ventricular hypertrophy resulting in slower progression of HF, diminished cardiac remodelling and cardiac hypertrophy leading to better survival of patients with HF [74-76].

These effects have been proven in a number of clinical trials [70]. In long-term therapy, ACE inhibitors have proven effectiveness to improve cardiac function measured by several common parameters, such as cardiac index and MAP. In addition to symptom reduction, ACE inhibitors do decrease the mortality rate of HF patients as well as decrease hospital readmission rates and improve quality of life [69, 70]. The benefits are independent of the aetiology and severity of HF [69]. In addition to patients already diagnosed as having HF, ACE inhibitors also have proven effectiveness to slow the progression of developing HF among patients with high risk, such as among patients with diabetes mellitus [77].

Following their inclusion as main therapeutic options for treatment of HF, studies reported that ACE inhibitors have been used widely [18, 78]. However, several studies also reported that these agents are used sub-optimally, leading to a failure in achieving therapeutic goals [78-80]. The major reason for this is adverse reactions, especially in patients with concomitant kidney failure [81]. Many clinicians still
believe that ACE inhibitors can potentially deteriorate worsening kidney function so that either they avoid prescribing the drugs or reduce the dose. In fact, several studies have shown more beneficial effects of ACE inhibitors in patients with decreased renal function [81, 82].

Other than ACE inhibitors, beta-blockers have also been included in the main therapeutic options in the guidelines for treatment of patients with HF [11, 12]. Although it was previously thought that the negative inotropic actions of beta-blockers could potentially worsen HF, studies show that beta-blockers have beneficial effects in suspending the progress of ventricular remodelling [83, 84]. Clinical trials on beta-blockers in patients with HF have concluded beta-blockers prescribed correctly in terms of doses and the patient’s condition, lead to decreased mortality and hospital readmission [83]. However, compared to ACE inhibitors beta-blockers are more likely to be prescribed sub-optimally due to the concern about adverse reactions [78-80].

In the case of patients who cannot tolerate the adverse effects of ACE inhibitors and beta blockers, other classes of drugs have also been recommended for use as alternatives, including the angiotensin receptor blockers (ARBs) and some classes of vasodilators [11, 12]. ARBs have been reported to have similar positive effects to ACE inhibitors, so they can be prescribed as a first alternative for patients having intolerance to ACE inhibitors [85, 86]. Due to more severe adverse effects, the combination of any ACE inhibitor with ARB should be avoided unless the patient is closely monitored [86]. Hydralazine and nitrates are the most common vasodilators prescribed in patients having contraindication to ACE inhibitors and ARBs, but their potent hypotensive effect means these drugs have a narrower therapeutic window [87].
While the first guideline on management of HF was released by ACC/AHA in 1995, in the guideline released in 2001 ACC/AHA established a new milestone in the management of HF by classifying HF patients into four stages based on the existence of structural damage on the heart and the presence of symptoms as depicted in Figure 1 [88]. This staging system not only classifies the patient based on the progression of HF, but also emphasises risk factor modification and preventive treatment strategies so that therapeutic managements are recommended according to the stage [88].

Currently, this staging system is still used in the ACC/AHA guidelines for the management of HF, and is even used in the guidelines used by other institutions [11, 12]. For patients falling within Stage A and Stage B the main goal of therapeutic management is to modify existing risk factors and to treat structural heart disease respectively, in which beta-blockers are recommended as pharmacologic options for patients in Stage B [12, 89]. Meanwhile, the goal of therapeutic management for patients at Stages C and D is mainly to reduce mortality and risk of hospitalisation [12, 89].

*Figure 1 - American College of Cardiology/American Heart Association heart failure staging classification as general guidance for therapeutic management in patients with heart failure*
In addition to the ACC/AHA staging classification of HF, a classification based on the severity of the symptoms also widely used both in clinical trials and real practice is the New York Heart Association (NYHA) functional class of HF, as shown in Figure 2 [12, 88]. This classification system was first developed almost a century ago, and is intended primarily to classify symptomatic HF based on subjective assessment in regard to the presence of typical symptoms of HF that are mostly encountered by patients at Stages C and D within the ACC/AHA staging classification [90]. In spite of the questions on reproducibility and validity, the NYHA functional class has been known as an independent predictor of mortality and is widely used in practice as well as clinical trials and studies related to HF [90-92].

For patients in all stages, ACE inhibitors are recommended as the primary therapeutic options [11, 12]. While the effectiveness of beta-blockers for the treatment of patients in Stages B and C has been proved, the use of beta-blockers in
patients within Stage D is still questionable [11, 12]. Overall, the effectiveness of
ACE inhibitors and beta blockers in achieving several desired therapeutic outcomes
in patients with chronic HF have been supported by more and stronger clinical
evidence compared to other drug classes as listed in Table 2 [11, 12]. Other than
medications and invasive intervention, education and supports to improve
knowledge, medication adherence and ability to carry out self-monitoring are
required to achieve targeted therapeutic goals.
Table 2 - The roles of several classes of drugs for treatment of chronic heart failure proved by clinical evidence [11, 12]

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Achieved clinical outcomes proved by clinical evidence</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Reduction of morbidity and symptoms in mild-severe HF</td>
<td>A*</td>
</tr>
<tr>
<td></td>
<td>Reduction of mortality in mild to moderate HF</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Reduction of mortality in severe HF</td>
<td>A</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Reduction of morbidity and symptoms in mild-severe HF</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Reduction of mortality in mild to moderate HF</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Reduction of mortality in severe HF</td>
<td>A</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>Reduction of morbidity and symptoms in mild-severe HF</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Reduction of mortality in severe HF</td>
<td>A</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Reduction of mortality and symptoms in patients not tolerating an ACE inhibitor</td>
<td>A</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Symptomatic improvement of congestion, improvement of exercise capacity</td>
<td>A</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Reduction of morbidity and symptoms in mild to severe HF</td>
<td>A</td>
</tr>
</tbody>
</table>

Note: *Level A: Evidence resulting from well-conducted, large and reliable randomised controlled trials (one or more) or their overview with clear results

ACE = angiotensin converting enzyme; HF = heart failure

2.2. Acute heart failure

Acute heart failure (AHF) is a complex syndrome characterised by abrupt onset of severe symptoms and signs of HF that requires urgent medical attention and usually leads to hospitalisation [93-95]. Generally, AHF can either result from deteriorating conditions in patients with ongoing treatment of chronic HF – known as acute decompensated heart failure (ADHF) – or severe acute cardiac dysfunction of patients without prior history of HF – named as *de novo* HF [94, 95]. In patients without previous history of HF, AHF can be a result of a specific pathologic process leading to abrupt cardiac dysfunction. Meanwhile, abrupt presentation of severe
symptoms and signs in almost all cases of AHF in patients with chronic HF are preceded by one or more precipitating factors [11, 96]. Table 3 lists several factors commonly triggering AHF.

Table 3 - Common precipitating factors of acute heart failure [11, 96]

<table>
<thead>
<tr>
<th>Factors commonly leading to rapid worsening symptoms and signs</th>
<th>Factors commonly leading to less rapid of worsening symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td>Superimposed infection</td>
</tr>
<tr>
<td>Rapid arrhythmia or severe bradycardia</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Exacerbation of COPD/asthma</td>
</tr>
<tr>
<td>Surgery and perioperative problems</td>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td>Peripartum cardiomyopathy</td>
<td>Non-adherence to treatment or diet</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>Endocrine abnormalities (diabetes mellitus, hypo or hyperthyroidism)</td>
</tr>
</tbody>
</table>

Note: COPD = chronic obstructive pulmonary diseases

Around two thirds of patients with AHF are patients with worsening conditions of chronic HF. Most patients have one or more precipitating factors and are admitted to hospital with presentation of peripheral or acute pulmonary oedema, and in a smaller proportion, cardiogenic shock with hypotension and poor vital organ perfusion are observed, mostly in patients with acute de novo HF. Immediate and careful recognition of the patient’s clinical presentation, as well as differentiation between ADHF and acute de novo HF, is very important in deciding appropriate therapeutic management.

2.2.1. Significant Burden of acute heart failure

Despite improved outcomes for patients with chronic HF resulting from implementation of evidence-based practice, AHF is still the most common reason for hospitalisation around the world, with poor in-hospital and post-discharge clinical outcomes, especially among elderly people [97, 98]. Reported length of hospital stay
globally ranges from four to 20 days with in-hospital mortality rate varying from four to 30% [99]. In addition to the high in-hospital mortality rate, almost one third of patients hospitalised from AHF die during the first year after hospital discharge [99]. Among survivors after hospitalisation, rehospitalisation rates are also reported as very high, with around one fifth of survivors readmitted to the hospital during the first month and more than one third readmitted during a three-month period following hospital discharge [100-102].

In their study, O’Connor et al. (2010) found that overall one-year mortality and hospital re-admission rates among patients hospitalised from AHF were 25.5% and 57.6%, respectively [103]. Among patients who died during the first year after hospital discharge, the study also found that AHF was the cause of death in nearly half of the patients, as shown in Figure 3. Likewise, AHF was also the most common cause of hospital readmission during the first year after hospital discharge [103]. Therefore, compared to other cardiovascular problems, AHF was the most common cause of death and hospital re-admission after one year of hospital discharge among patients hospitalised from AHF [103, 104]. Even in patients hospitalised from acute myocardial infarction (AMI), AHF was the most common cause of hospital readmission [105].
Ranasinghe et al. (2014) examined rehospitalisation rates during the first 30 days of the patient journey after hospital discharge among patients hospitalised from AHF, pneumonia and AMI [105]. As shown in Figure 4, the highest rate was found in patients hospitalised from AHF. In addition, while the majority of studies reported that AHF was the most common cause of hospitalisation among elderly individuals [94, 95, 106], this study reported different results. Hospital readmission from AHF was found to be higher among patients aged <65 years compared to older patient groups and after adjusting for some variables, the study concluded that younger patients hospitalised from AHF have an equal risk of hospital readmission during the first 30 days after hospital discharge [105].
The high rate of hospitalisation among patients with AHF results in significant financial burden, even placing it as the most important contributor to the large financial burden related to HF [3, 99, 107]. In 2010, almost US$40 billion has been spent for the treatment of patients with HF in the United States and the largest proportion of it was for hospitalised patients [3, 107]. Given that the prevalence of HF tends to increase mainly due to the aging population and improved survival from myocardial infarction, annual costs for managing hospitalised patients with AHF will increase close to twofold by 2030 [107]. The same burden of expenditure due to high demand of hospital care among patients with AHF also happened in Europe and even worldwide [36, 108].

Despite the advancement in therapeutic management, prognosis of patients with AHF still remains poor [109]. Even with aggressive and earlier treatment, mortality rates, both in-hospital and shortly after hospital discharge, in patients with AHF is
still very high [97-99, 110], and likewise the rehospitalisation rate is also high [109, 111]. The remaining poor prognosis of patients with HF represents the necessity of improvement in therapeutic strategies [112-115].

2.2.2. Shifting paradigms on pathophysiology of acute heart failure

While evidence supporting better understanding about disease progression and therapeutic management of chronic HF are abundantly available, many aspects related to AHF are still poorly understood, including its pathophysiological processes [93, 94, 116]. Several pathophysiological processes are believed to be involved in a broad spectrum of signs and symptoms in patients presenting with AHF. However, limited evidence means researches on the detailed mechanisms of those processes are required [95, 117].

In general, AHF pathophysiological processes involve similar haemodynamic and neurohormone changes to chronic HF [94]. However, common signs and symptoms presented by patients with AHF originate mainly from pulmonary congestion [116, 118]. Hence, pulmonary congestion has been a central point of the pathophysiology of AHF [113, 119]. For several decades, the pathophysiological concept of AHF has been focused on the decrease in left ventricular contractility and excessive fluid accumulation as the main causes of pulmonary congestion [116]. Accordingly, loop diuretics were the first therapeutic option for treatment of patients with AHF [95, 114, 116].

According to the conventional point of view, the pathophysiological process of AHF is evoked by a significant decrease in cardiac output stimulating neurohormonal activity to increase water and sodium reabsorption [117]. Fluid accumulation then occurs and a vicious cycle generating more severe decreased cardiac output and the development of pulmonary oedema is switched on [120]. As studies have gained new
evidence, several new approaches have been proposed to explain the detailed pathophysiological process of AHF [116, 118]. In contrast to the conventional insight, a new concept of ‘fluid redistribution’ with several causality mechanisms was introduced, postulating a different AHF pathophysiological mechanism [121, 122]. Another contradictive concept placing pulmonary oedema as the initial step of pathophysiological process has been also introduced [123].

The concept of fluid redistribution was first introduced by Cotter et al. (2002) after elaborating newer evidence about AHF [124, 125]. This concept states that rather than resulting from fluid accumulation, pulmonary oedema encountered by the majority of patients presenting with AHF is a consequence of fluid redistribution [125]. According to this new concept, pulmonary congestion can arise without the significant addition of fluid from the extravascular compartment. This concept is supported by evidence showing that most of AHF patients have pulmonary oedema without a significant increase in body weight [122].

In addition to this concept, Cotter et al. (2008) also state that the fluid redistribution is triggered mainly by the increase in vascular resistance [125]. ‘Arterial stiffness’ is thought to be the main cause of elevated vascular resistance as it is commonly found in patients with HF and older individuals [125, 126]. Other mechanisms are suggested as involved in increasing vascular resistance, including increased release of neurohormonal and inflammatory mediators that not only affect arterial beds but also the veins [125]. While increased arterial stiffness leading to elevation of arterial resistance results in an increase of afterload, decreased venous capacitance can lead to an increase of venous return, and in turn results in increased preload [122]. A significant increase of both afterload and preload concomitantly in the abnormal ventricle can further increase end diastolic volume, and to some extent increase the
possibility of the blood being pushed back to the lung, leading to the pulmonary oedema [122, 127].

Responding to the fluid redistribution concept postulated by Cotter et al., Metra et al. (2008) still believe that fluid accumulation remains the central key of AHF, especially among patients with a history of chronic HF [120]. This is supported by several different findings showing that clinical deterioration leading to AHF in patients with a history of chronic HF develops slowly and is marked by weight gain and peripheral oedema [128, 129]. In addition, decongestion is still a strong predictor for better prognosis among patients with AHF [119].

Fallick et al. (2011) propose a similar idea to the one proposed by Cotter et al. (2008). They propose that, instead of fluid accumulation, pulmonary congestion encountered by patients with AHF results from fluid movement [130]. However, the main cause of fluid movement postulated by Fallick et al. (2011) is different from that proposed by Cotter et al. (2008) [125, 130]. While Cotter et al. (2008) propose that fluid redistribution results from an increase of vascular resistance caused mainly by arterial stiffness, Fallick et al. (2011) suggest that the fluid movement is mediated by the activity of the SNS [130].

Given that more than two thirds of blood in the vascular system is retained in the venous system, mainly within the splanchnic veins, and that the system has many more adrenergic receptors, a more significant effect from activation of the SNS will happen in the venous system [130]. This will lead to a reduction of venous capacitance and subsequently the movement of blood from the splanchnic veins into the active circulating blood system. Significant movement of the blood from splanchnic veins will result in increased venous return that in turn will increase the cardiac preload [123, 130]. With lower contractile ability in the left ventricle,
significant increase of the preload will subsequently reduce cardiac output as well as hold the blood back in the lung leading to pulmonary oedema [130, 131].

Although inhibiting activity of the SNS has become a part of the main therapy for patients with HF, those medications are unable to completely block SNS activity, particularly within splanchnic venous beds [130, 132]. Current agents used to inhibit SNS activity in patients with HF work to block β-adrenergic receptors, whereas within splanchnic venous beds α-adrenergic receptors are predominant [122]. In addition, the agents work as competitive inhibitors in which the effect is masked during excessive SNS stimulation. Therefore, the activation of the SNS leading to reduced venous capacitance can still happen even in patients receiving therapy that blocks SNS activity [122, 130].

An additional hypothesis has been proposed by Burchell et al. (2013) to the approach postulated by Fallick et al. (2011). In agreement with that approach, Burchell et al. propose that the fluid movement from splanchnic veins specifically induced by intermittent hyperactivity of the SNS, caused by the changes to the reflex system working within the ANS [133]. Peripheral chemoreceptors become more sensitive in patients with HF, resulting in hyperactivity of the SNS. Hypoxia is one trigger that can drive this intermittent hyperactivity, and once it happens subsequent reduction of venous capacitance will occur leading to fluid movement from splanchnic venous beds into the active circulatory system [133].

Interpreting several different findings, Colombo et al. (2015) state a different hypothesis on AHF [134]. Instead of placing pulmonary and peripheral congestion as the result of the pathophysiological process of AHF, they propose that such congestion is a trigger for decompensation in patients with AHF [121, 134]. Studies both in animals and humans reflect that vascular congestion can activate several
pathways, including endothelial, neurohormonal and inflammatory reactions, leading to more severe congestion resulting in cardiac decompensation [123, 135]. Venous congestion causes endothelial stretch that stimulates the action of vasoconstrictor substances including endothelin-1 and angiotensin-II [121, 123]. Venous congestion can also trigger the release of inflammatory mediators that drive the increase of vascular resistance and in turn lead to vasoconstriction [123, 136]. Moreover, venous congestion can activate sympathetic baroreflex, resulting in an increased release of neurohormonal leading to vasoconstriction [131, 137, 138]. Overall, these mechanisms result in deterioration of cardiac preload-afterload marked mainly by pulmonary oedema [121, 134].

Although all these new postulated concepts are still in progress towards their final conclusion, they will drive a shifting paradigm of AHF pathophysiology and further therapeutic management. More evidence is needed for acceptance of the new postulated approaches. Whilst pulmonary congestion is still the main therapeutic target in patients presenting with AHF, several therapeutic strategies based on new postulated pathophysiological concepts to minimise adverse events in patients with HF are concurrently being studied.

### 2.2.3. Loop diuretics as the main therapeutic measure to manage acute heart failure

Whilst more details and advanced approaches on the pathophysiology of AHF are still being investigated, current treatment guidelines of AHF place loop diuretics as the main option for treatment [11, 12, 139]. Indeed, the recommendations are driven by the findings that most AHF patients are hospitalised from severe symptoms and clinical signs provoked by pulmonary congestion [119, 140]. As rapidly relieving severe symptoms is the main target of therapeutic measures in the management of
patients with AHF, alleviating the congestion is the most important measure and this can be achieved by administering loop diuretics that can produce rapid diuresis. Hence, administration of intravenous loop diuretics is recommended during the first step in managing patients with AHF [113, 118].

In their review on global health and economic burden of hospitalisations for HF reviewing data resulting from global HF registries, Ambrosy et al. (2014) found that an average of 84.5% of patients from all registries received loop diuretics during hospitalisation, as shown in Figure 5 [99]. The loop diuretics administration rate was even higher in a randomised controlled trial (RCT), that is 90%, as found by Ezekowitz et al. (2012) in their study comparing patient characteristics, in-hospital and discharge management, and the clinical outcomes of RCT and registry patients [141]. In addition to loop diuretics, vasodilators and positive inotropes were used at lower rates. In the current guidelines vasodilators and positive inotropes are also listed in the main recommendation for treatment of AHF for reducing filling pressures and increasing cardiac output respectively.

Figure 5 – Patients with acute heart failure receiving loop diuretics during hospitalisation [113]
Several studies have proved the importance of decongestion in managing patients with AHF. Incomplete decongestion during hospitalisation has been found to be associated with increased mortality and hospital readmission [97]. However, evidence supporting the effectiveness and safety of loop diuretics as the main measure to relieve congestion is still limited [142, 143]. Despite loop diuretics for decongestion purposes in patients with AHF having been used for more than 50 years, recommendations about the administration of loop diuretics in such patients are supported by limited evidence [143, 144]. The 2013 ACC/AHA treatment guidelines for patients with HF, recommending intravenous loop diuretics administration is only supported by Level B evidence, that is evidence derived from a single RCT or studies with a non-RCT design [12]. Likewise, recommendations on the administration of loop diuretics in treatment guidelines released by the ESC and the Heart Failure Society of America (HFSA) were also not supported by strong clinical evidence [11, 145].

Apart from its common use to eliminate congestion, issues concerning the adverse effects of loop diuretics have also been raised as it often dissuades the optimal use of loop diuretics and further drives unsuccessful decongestion. Diuretic resistance is one problem limiting the use of loop diuretics, in which loop diuretics cannot produce adequate decongestion despite dose increment [146-148]. This can be triggered by different aetiologies through several mechanisms involving neurohormonal compensation resulting from SNS and RAAS stimulation [146]. Physiological changes in patients with HF influencing pharmacokinetics of loop diuretics, suboptimal doses and concomitant medications have been known to stimulate diuretic resistance [143, 146]. Other than resistance, severe electrolyte
disturbances and renal impairment are other adverse effects potentially resulting from loop diuretics use [149, 150].

Given its importance in alleviating congestion in patients with AHF, several strategies have been studied to increase the diuresis effect, as well as to overcome loop diuretic resistance and other adverse effects. Different intravenous administration strategies, bolus and continuous infusion have been studied in relation to clinical outcomes and adverse effects [151]. Although no significant difference in respect to clinical outcomes was found, administration of loop diuretics by continuous infusion can reduce the risk of developing diuretics resistance and other adverse effects [151-153]. The addition of another diuretic from different classes into the loop diuretic regimen has also been studied, finding that the addition of thiazide-type diuretics or aldosterone antagonist result in a greater diuresis effect to further reduce the risk for the development of diuretic resistance [154, 155]. Nevertheless, the dose and type of administration of loop diuretics are not the only factors determining clinical outcomes. Initial kidney function, hemodynamic status and severity of congestion have also been identified as having a contribution on the decongestion effect of loop diuretics [156, 157].

Deteriorating kidney function is another issue limiting the use of loop diuretics in higher doses, which leads to incomplete decongestion [147, 156, 157]. However, the Diuretic Optimization Strategies Evaluation trial (2011) investigated the risk for renal impairment from different loop diuretics dose regimens, reporting that compared to the lower dose regimen, loop diuretics administered in a higher dose can result in better clinical outcomes without increasing the risk for renal impairment [158, 159]. In addition, studies have also found that loop diuretics administered by continuous infusion shows no significant impact on kidney function [158].
Along with the progression of the concept on the pathophysiological processes of AHF, several new therapeutic approaches have also been studied to improve clinical outcomes of patients with AHF [112, 160-162]. While the best measures for administering loop diuretics as the main option in current therapeutic guidelines are still under investigation, several therapeutic approaches for decongestion are also being investigated [163-165]. AVP receptor antagonists that promote water excretion without disturbing electrolyte balance have been studied both singly and in combination with diuretics, and show good prospects for eliminating congestion [166-168]. Nonetheless, robust evidence is still needed to support their use. Other drugs showing potential benefit for decongestion purpose in the treatment of patients with AHF include gut sequesterants, serelaxin – a recombinant from human relaxin-2, and istaroxime – a compound with lusitropic effect [169-173].

2.3. Hyponatremia

Among electrolyte abnormalities, hyponatremia is the most often observed particularly in hospital settings. However, it appears that it is rarely recognised and treated sufficiently [174, 175]. This may be because the symptoms are very similar to dementia or delirium, or may be due to the low awareness of healthcare professionals, lack of diagnostic measurements, and doubt about the effectiveness of available treatment options [174, 176]. Although the type and degree of hyponatremia varies among patients, it is clear that hyponatremia significantly contributes to patient morbidity and mortality, as well as increasing medical expenditure [177-179].

When hyponatremia is defined as serum sodium concentration < 135 mEq/L the incidence is between 15 and 30% among hospitalised patients [180-183]. Moreover, the incidence of hyponatremia in a general geriatric ward can be higher than in an
intensive care unit (ICU) indicating that hyponatremia is not only a common problem in patients with severe and critical condition [182, 184]. Although the incidence of hyponatremia in ambulatory and community settings is lower, its negative impact on patient morbidity has been established [175, 185-187].

Basically, hyponatremia is an electrolyte disorder that occurs when the total body water relatively exceeds the total sodium in the body [188, 189]. The occurrence of hyponatremia is always related to disruption of the hormone regulating water and electrolyte balance in the body – AVP – which was formerly known as ADH [66]. AVP is a hormone produced by several neurones in the hypothalamus and stored within the posterior pituitary [188]. This hormone regulates the balance of body fluid through its role in adjusting water reabsorption within distal tubules and collecting ducts in the kidneys [65, 188]. Secretion of this hormone from the posterior pituitary is stimulated either by osmoreceptor or baroreceptor reflex [66].

2.3.1. Clinical and economic burden of hyponatremia in patients with heart failure

Many studies on hyponatremia in patients with HF have been published, finding that hyponatremia is an important problem increasing the risk for hospitalisation and death [190, 191]. Not only sharing pathophysiologic features, hyponatremia also shares prognostic features with HF [180, 182, 192, 193]. Patients with HF have a high probability of suffering from hyponatremia, either as a result of disease progression or the adverse effect of medications [192, 194]. As well as being a common and important complication, hyponatremia is also a strong independent predictor of the quality of life and mortality in patients with HF [183, 195, 196].

The association between hyponatremia either at admission or during hospitalisation and clinical outcomes of patients hospitalised with HF has been investigated by
several studies. Sato et al. (2013) studied the association between hyponatremia at admission and in-hospital mortality by including 4837 patients hospitalised with HF [197]. The study found that hyponatremia at admission has a strong association with longer hospital stay and higher in-hospital mortality rate. Compared to patients with normal serum sodium level, in-hospital mortality among patients with hyponatremia is almost three times higher [197]. Whilst Sato et al. (2013) investigated the importance of hyponatremia at admission, Konishi et al. (2012) studied the importance of hyponatremia encountered by patients hospitalised with HF during their hospitalisation as a predictor of their long-term clinical outcome [179]. The study included 662 patients hospitalised with HF, in which 11.5% developed hospital-acquired hyponatremia (HAH). It found that development of hyponatremia during hospitalisation is associated with poor long-term clinical outcomes in terms of cardiac events within one year of hospital discharge [179]. Shchekochikhin et al. (2013) compared the impact of hyponatremia at admission and during hospitalisation with the length of hospital stay and in-hospital mortality [198]. This study confirmed the results of other studies, concluding that hyponatremia both at admission and acquired during hospitalisation serves as an importance predictor of clinical outcomes [198]. The findings of this study emphasise the importance of hyponatremia encountered by HF patients during hospitalisation; it has the same important role as hyponatremia at admission in terms of increasing the risk of prolongation of hospital stay and in-hospital mortality [198].

Among studies assessing the impact of hyponatremia on long-term clinical outcomes are studies conducted by Madan et al. (2011) and Bettari et al. (2012). Madan et al. (2011) investigated the impact of serum sodium level at admission on long-term survival of patients hospitalised with HF [195]. The study included 322 patients
using retrospective data with median follow-up of 610 days, and found that serum sodium level has a strong association with mortality in which patients with decreased serum sodium level were associated with higher mortality [195]. In addition, the study also concluded that hyponatremia in patients hospitalised with HF is not only an important predictor for untoward outcomes, but is also an important problem needing more attention in terms of treatment strategy [195]. Bettari et al. (2012) conducted quite a similar study with a longer average follow-up – 4.5 years [191]. The study found that hyponatremia is an important marker independently related to the increased risk of death both of all-cause and cardiovascular death, as well as risk of hospital readmission [191].

Studies on the importance of hyponatremia in HF patients with specific condition have been also reported. Arao et al. (2013) report on the role of hyponatremia as a predictor of deteriorating HF among HF patients receiving CRT [199]. The study concludes that hyponatremia is independently associated with deteriorating conditions of HF after implantation of CRT [199]. Given that most studies on hyponatremia in HF patients included patients with HFrEF, Bavishi et al. (2014) conducted a study to compare the prevalence of hyponatremia between patients with HFrEF and HFpEF as well as to assess the impact of hyponatremia on clinical outcomes in those two groups of patients [200]. Still, in groups of HFpEF patients, hyponatremia plays an important role as a predictor of mortality [200]. However, while in groups of patients with HFrEF hyponatremia can be used to predict hospital readmission, it cannot in groups of patients with HFpEF [200].

In addition to the impact on clinical outcomes, the economic burden of hyponatremia has also been studied. In unselected patients the economic burden of hyponatremia has been reported by Boscoe at al. (2006), who conclude that hyponatremia gives a
salient economic burden due mostly to the need for hospitalisation [201]. The findings of this study are confirmed by a similar study conducted by Shea et al. (2008), who conclude that hyponatremia contributes significantly to medical cost [202]. Specifically in patients with HF, the economic burden of hyponatremia has been reported by Shorr et al. (2011) from their study including 24,585 HF patients with hyponatremia at hospital admission [203]. Compared to patients with normal serum sodium level, the cost of treatment during hospitalisation for patients with severe hyponatremia is around 20% higher [203]. Even for patients with mild hyponatremia the cost was significantly higher compared to patients with normal serum sodium level. Another investigation performed by Amin et al. (2013) concludes that other than prolong hospital stay hyponatremia in patients hospitalised with HF also results in significant incremental healthcare costs [40]. In this study, the cost of treatment during hospitalisation for HF patients with hyponatremia at admission was around 25% more expensive compared to patients with normal serum sodium level [40]. More appropriate management strategies for the treatment of hyponatremia in this group of patients are urgently needed to diminish the cost burden [40].

2.3.2. Classification of hyponatremia

Hyponatremia is almost always associated with plasma hypo-osmolality because sodium and its associated anions are the main solutes in the plasma [181]. Therefore, the term hyponatremia is almost always referred to as hypotonic hyponatremia, which can result either from excessive water retention or a significant loss of sodium [204]. However, more detail assessments are needed to classify hyponatremic status appropriately so that adequate treatment can be administered [205].
The basic classification of hyponatremia is based on the level of sodium in plasma, which classifies hyponatremia as mild (sodium serum level 130–134 mmol/L), moderate (125–129 mmol/L) and severe (<125 mmol/L) [206]. Other than classification based on serum sodium level, hyponatremia is commonly classified based on volume status so that hyponatremic status can be hypovolemic, euvoletic or hypervolemic [181, 205]. In addition, hyponatremia is also classified based on rapidity and duration of hyponatremic development so that hyponatremia can be differentiated between acute and chronic; based on symptom presentation hyponatremia can be classified as symptomatic or asymptomatic [205]. Regardless of type, hyponatremia should be managed; acute severe symptomatic hyponatremia indicates a condition in which aggressive treatment is needed compared to chronic mild asymptomatic hyponatremia [181, 205].

Dilutional hyponatremia resulting from excessive water retention is commonly found in patients with HF, cirrhosis or kidney failure [181]. Meanwhile, depletional hyponatremia caused by excessive solutes loss through the kidney commonly occurs as a diuretic adverse effect or in patients with mineralocorticoid deficiency [181]. Likewise, excessive loss of plasma solute caused by diarrhoea, vomiting, and excessive sweating can also lead to depletional hyponatremia [181, 204].

It is not easy to find a timely specific etiology of hyponatremia once hyponatremic status is observed. However, the basic approach of assessing the patient’s body fluid status and urine sodium level is helpful in guiding further relevant assessment as well as in choosing appropriate therapy [181]. By carefully assessing the patient’s body fluid status, blood chemistry and urine sodium level, and osmolality, hyponatremic status can be defined as being associated with hypervolemia, hypovolemia or euvoletic [180, 181].
Hypervolemic hyponatremia is always presented with noticeable fluid overload [181]. Peripheral oedema and ascites are obvious signs of fluid overload commonly found in patients with hypervolemic hyponatremia, such as in patients with HF, kidney failure and cirrhosis [181, 204]. The RAAS is commonly activated in those patients’ conditions, so renal sodium conservation occurs leading to a lower urine sodium level [181]. Elevation of plasma BNP and creatinine levels is also an important clue indicating volume overload and kidney failure, respectively [181].

Hypovolemic hyponatremia is always caused by significant loss of body fluid [181]. As a direct measurement of body fluid is not easily performed, physical examination and blood chemistry assessment is the best approach to identify hypovolemic status [181]. In addition to physical findings, increased creatinine and blood urea nitrogen (BUN) level in the plasma as well as uric acid level are important signs reflecting extracellular volume loss [207].

Hyponatremia with normal plasma volume, named euvolemic hyponatremia, is mostly found in patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH) [204]. Thyroid disorder and glucocorticoid deficiency are also potential causes of euvolemic hyponatremia [181, 204]. Normal plasma levels of creatinine, BUN and uric acid almost always accompany euvolemic hyponatremia [207]. In addition, higher urine sodium level is the most important finding commonly found in patients with euvolemic hyponatremia [181, 204].

Whilst hypotonic hyponatremia is the most common type of hyponatremia resulting in medical problems, non-hypotonic hyponatremia can occur as hypertonic hyponatremia and pseudohyponatremia [181, 204]. Hypertonic hyponatremia occurs when plasma contains other effective solute besides sodium; hyperglycaemia is the most common cause of this condition [181, 205]. Pseudo-hyponatremia potentially
occurs when lipid or protein level in the plasma are excessively increased, resulting in attenuation of sodium in the plasma because more spaces in the plasma are occupied by the lipid or protein [181, 207]. These hypertonic hyponatremia and pseudo-hyponatremia should be ruled out by carefully assessing the relevant condition so that the diagnosis of hypotonic hyponatremia can be established [181, 205].

2.3.3. The role of arginine vasopressin in pathophysiological process of heart failure and hyponatremia

In HF patients, hyponatremia may occur with a complex process of pathophysiology related to some disturbances contributing to HF, including hormonal and neurologic disorders [181, 208]. Chronic activation of the RAAS concurrently with stimulation of the SNS as a response to inadequate tissue perfusion stimulates a counter-productive effect including cardiac remodelling and water-sodium retention [196, 208]. However, among neurohormones contributing to the progressiveness of HF, AVP is the most important neurohormone involved in the development of hyponatremia [193].

In the pathophysiological process of HF, AVP is released as a response to low cardiac output, basically to increase intravascular volume. However, the effect is even further counter-productive for cardiac workload as the preload will increase [194, 209].

AVP plays an important role in maintaining the balance of body water by controlling water reabsorption within distal tubules and collecting ducts in the kidneys [65]. The release of this neurohormone from the posterior pituitary is stimulated by either the activation of osmoreceptors or baroreceptors [65, 66]. The action of AVP stimulated by the activation of osmoreceptors is called osmotic regulation, in which the process
is activated by the changes of plasma osmolality [65, 66]. The action stimulated by
the activation of baroreceptors is called non-osmotic regulation, in which the process
has no relationship with plasma osmolality, but with the stretch of smooth muscles
within some regions in cardiovascular system [65, 66]. The tone of such smooth
muscle stretch in a particular region is determined by blood volume reaching the
region itself; more volume produces stronger stretch [65].

Physiologically the increased release of AVP from the posterior pituitary through
osmotic regulation occurs when plasma osmolality is increased, such as in condition
of dehydration or excessive water excretion through non-renal pathways [67]. Such
conditions trigger the release of AVP in order to increase water reabsorption in the
kidney so that plasma osmolality can be returned to normal [67]. Meanwhile,
increased release of AVP through non-osmotic regulation is triggered by
extracellular volume depletion, such as in conditions when an inadequate volume of
blood is pumped by the left ventricle into the aorta [67]. Such conditions also trigger
the release of AVP from the posterior pituitary in order to increase water
reabsorption in the kidney to return extracellular volume to normal so that adequate
tissue perfusion can be maintained [65-67]. Three types of AVP receptors have been
known to mediate the actions of AVP either through osmotic or non-osmotic
regulation, including $V_{1A}$, $V_{1B}$ and $V_2$ [65, 66, 193]. The location of each receptor
along with associated physiologic actions when AVP is bound to such receptor are
summarized in Table 4.
Table 4 - The locations of each arginine-vasopressin receptor and associated physiologic actions when arginine-vasopressin is bound to the receptor [65, 66, 193]

<table>
<thead>
<tr>
<th>Subtype of vasopressin receptor</th>
<th>Primary location</th>
<th>Main physiologic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{1A}$</td>
<td>Vascular smooth muscles, myocytes, hepatocytes, platelets, adrenal cortex</td>
<td>Vascular constriction, myocardial hypertrophy, platelet aggregation, glycogenolysis, elevation of cardiac afterload</td>
</tr>
<tr>
<td>$V_{1B}$</td>
<td>Anterior pituitary glands</td>
<td>Stimulation of adrenocorticotropic hormone and B-endorphin</td>
</tr>
<tr>
<td>$V_{2}$</td>
<td>Renal collecting ducts</td>
<td>Water reabsorption through mobilisation of aquaporin-2 vesicles towards plasma membrane of collecting ducts, elevation of cardiac preload</td>
</tr>
</tbody>
</table>

Under normal physiologic conditions, osmotic regulation has a predominant role in controlling AVP actions [65, 67]. However, in HF in which abnormal function of the ventricles occurs, non-osmotic regulation becomes more active [65, 66]. Persistent inadequate cardiac output causing intravascular volume depletion results in activation of AVP release leading to excessive water reabsorption from the kidney, which in turn increases intravascular volume [66]. Subsequently, cardiac venous return is increased leading to increased cardiac preload [65]. Given that left ventricle function in HF has been already reduced, higher preload will further increase cardiac workload, consequently resulting in more reduction of cardiac output [210]. This vicious cycle then stimulates the RAAS and the SNS to become more active, which subsequently releases more AVP from the posterior pituitary and more severe water retention as well as hyponatremia occurring [65, 211].

Basically, activation of the baroreceptor is part of the neurohormonal compensation process, with the main purpose to maintain adequate arterial pressure and tissue perfusion [65]. Neurohormonal compensation involving the RAAS and the SNS will further stimulate AVP release through non-osmotic regulation leading to renal hemodynamic changes and increased water reabsorption [66, 188]. In compensated
HF, increased baroreceptor activity producing a vasoconstriction effect is balanced by increased activity of vasodilators, such as natriuretic peptides, so that excessive increased cardiac workload can be diminished [212]. However, non-osmotic regulation predominantly occurs in patients with HF causing excessive AVP release and subsequently leading to increased intravascular volume and cardiac preload [213]. Other than increasing cardiac workload, hyponatremia is a detrimental effect of excessive AVP release [210]. Figure 6 simply depicts the role of AVP within the pathophysiological process of HF and hyponatremia.

Figure 6 – the role of arginine-vasopressin in the pathophysiological process of heart failure and hyponatremia through non-osmotic regulation stimulated by inadequate cardiac output [66, 188, 210]

HF itself constitutes a high risk of hyponatremia; however, the risk increases with the severity of HF [180, 191]. When the severity of ventricular dysfunction increases, the counter-productive regulation of neurohormonal response will also increase, leading to excessive water reabsorption, after which hyponatremia will potentially occur [208]. The lower the cardiac output, the more AVP hormone will be released, and prolonged elevation of this hormone in the systemic circulation will result in an
increase of water retention leading to a dilutional process, which in turn will result in hyponatremia [192, 196].

In addition to pathophysiological development, hyponatremia in HF patients may be exacerbated by an adverse reaction of medications, either directly or indirectly related to HF treatment [214, 215]. Diuretics, for example, which are used as a main medication for HF patients with congestive conditions, achieve their effect by the excretion of sodium; with the desired water excretion as a side effect [211, 216]. They therefore have high potential to induce hyponatremia through a variety of mechanisms. Increase of water reabsorption will potentially occur as a result of diuretic actions in Na-Cl co-transport, particularly when AVP is also acting in ductus collectivus [217]. Diuretic-induced hyponatremia can also occur when potassium is excreted excessively via urine, causing sodium shifting to intracellular fluid, resulting in a lower intravascular sodium concentration. In addition, increased water intake as a result of thirst induced by diuretics can also contribute to hyponatremia [181, 196].

Some medications that are not directly related to HF treatment can also contribute to hyponatremia by causing inappropriate ADH release. Among those medications, antidepressant drugs are the most popular ones as the drugs are also commonly used in HF patients, particularly in elderly patients [194, 218]. Paracetamol and some non-steroid anti-inflammatory drugs are also commonly used for symptomatically relieving pain, and have been known to increase the risk of hyponatremia [194]. Hyponatremia is well known as playing an important role as a prognostic parameter among HF patients. However, further studies to ensure that correction of hyponatremia will result in better outcomes on treatment of HF patients are still
needed. Moreover, studies to find out the best approach to manage hyponatremia in patients with HF are also very important to improve its management [180, 191].

In some particular conditions hyponatremia may only be encountered by a small proportion of patients, with older age being the strong independent risk factor [219, 220]. Tseng et al. (2012) found anaemia, hypouricemia and placement of any tubes as contributing risk factors to hyponatremia among elderly people [221]. Stelfox et al. (2010) also reported that age, diabetes, APACHE II score, mechanical ventilation, length of stay in ICU, serum glucose level and serum potassium levels are associated with ICU-acquired hyponatremia [220].

In cases of medication-induced hyponatremia, several classes of drugs are top of the list, including diuretics, selective serotonin receptor inhibitors (SSRIs) and antagonist of the RAAS [220, 222-224]. Several studies also report contributing risk factors for developing of hyponatremia among patients taking antidepressants and diuretics. Movig et al. (2002) studied antidepressant-induced hyponatremia and found that older age and concomitant diuretics used increased the risk of hyponatremia [225]. Jacob and Spinler (2006) studied SSRIs-induced hyponatremia and found that older age, female gender, concomitant use of diuretics, lower body weight and lower baseline sodium level are risk factors for development of hyponatremia in patients taking SSRIs [226]. For diuretic-induced hyponatremia, Chow et al. (2003) reported that older ages, lower body weight and lower serum potassium level contribute to the development of hyponatremia among patients taking thiazides diuretics [227].

### 2.3.4. Problems assessing hyponatremia

In order to properly manage hyponatremia, careful attention to some important key facets of the patient’s condition is needed [196, 228]. Some measurements, including
physical examination and laboratory investigation, must be done to decide whether the patient is in severe acute hyponatremia and needs to be treated immediately, or in mild chronic hyponatremia, during which aggressive treatment must be avoided [178, 228, 229].

With careful assessment, hyponatremia patients can be classified accordingly as having acute or chronic, symptomatic or asymptomatic, or dilutional or depletional hyponatremia [192, 208].

Whilst symptoms of severe acute hyponatremia can be recognised more easily through apparent severe neurologic symptoms, more attention should be paid deliberately to recognise symptoms in patients with chronic hyponatremia, as these patients mostly are asymptomatic [178, 230]. In addition to confusion and dizziness, patients with other persistent neuro-cognitive and motor deficit should be suspected as hyponatremic [231, 232]. History of gait instability falls and fracture has been found to be associated with hyponatremia as well as osteoporosis [175, 233, 234].

Despite hyponatremia being a common problem in hospital settings, and making an accurate diagnosis is very important to decide the treatment of choice, there is no gold standard for assessing and classifying patients [174, 229].

Generally, there is no crucial problem in identifying patients as in an acute or chronic and symptomatic or asymptomatic condition. However, it is still a crucial problem to determine a patient’s volume status [181]. Identification of a patient’s volume status is very important to direct the clinicians into the treatment of choice [196, 228].

There are some available measurements that can determine a patient’s volume status. Identification of urinary sodium concentration and fractional excretion of sodium is one of the useful measurements to differentiate hyponatremia patients as being in
hypovolemic or euvolemic conditions [235]. As an alternative, assessment using bedside bioelectrical impedance can also provide fast and accurate data on a patient’s volume status [236, 237]. However, there is no evidence stating which measurement is better than another, so the decision to choose the measurement method depends on each hospital setting and agreement [237, 238].

2.3.5. Antagonists of arginine-vasopressin receptors (vaptan) as new treatment option

Conventionally, hyponatremia can be managed with several treatment options. One of the most used as a standard treatment of hyponatremia is limitation of fluid intake, which is known to be the safest option [239]. However, this option is not efficacious for patients with acute and symptomatic hyponatremia, as the goal of serum sodium concentration cannot be rapidly achieved, especially knowing that the thirst induced by the treatment may potentially lower patient adherence [239, 240].

Another option for treating hyponatremic patients, especially in the hospital setting, is the administration of sodium chloride solution [181, 241]. Isotonic solution of sodium chloride is very good for patients with hypovolemic hyponatremia, whereas hypertonic hyponatremia has an efficacious effect for hyponatremic patients in hypervolemic or euvolemic conditions [239, 241, 242]. The most important aspect in administering the solution is the rate of administration, particularly for patients with acute hyponatremia. Overly rapid administration of hypertonic solution of sodium chloride can induce neuron obstruction leading to severe neurologic disorder [239, 240].

Several drugs have also been known to have a useful effect in the treatment of hyponatremia. Loop diuretics can be used as an option for the treatment of hyponatremia in hypervolemic patients, either singly or in combination with sodium
chloride solution or tablet [181, 215]. The dose of diuretic must be adjusted accordingly based on serum sodium concentration, so the serum sodium concentration must be monitored adequately. Demeclocycline is another drug that has been used for treating hyponatremic patients, particularly for patients with fluid restriction resistance, but the use of this drug is limited as it can induce severe renal dysfunction [181, 242]. Urea has also been widely used in the treatment of hyponatremia orally, as an alternative to sodium chloride tablets, showing good effectiveness and safety profile [243, 244]. The biggest disadvantage of urea is an uncomfortable taste leading patients to reject the treatment [181, 194].

The newest drugs approved for use in the treatment of hyponatremia are derivatives of AVP receptor antagonist, more famous as the vaptan group [176, 239, 245]. The drugs act by directly inhibiting the receptors of AVP so then causing an aquaretis effect, an increase in water excretion with an insignificant effect on solute excretion [181]. Given that three types of AVP receptors have been identified, several compounds from this class of drugs that have been investigated show different ability in antagonising AVP receptors that is either selectively or non-selectively antagonising V1A, V1B and V2 receptors [181, 246].

While the first candidate of AVP receptor antagonist was developed more than five decades ago, the first vaptan compound with good bioavailability was developed by Yamamura et al. in the early 1990s, leading to the invention of newer and better vaptan [247]. The newer vaptans were derived from non-peptide compound and have a good effectiveness for the treatment of hyponatremic patients either in hypervolemic or euvolemic status with a tolerable adverse effect in short-term use [180, 192]. The effectiveness of vaptan as AVP receptor antagonist for the treatment of hyponatremia is believed to be determined by aquaretis effect produced by the
drugs. In addition, limitation of fluid intake is not needed in patients receiving vaptan therapy, making the patients more comfortable with the treatment [178, 245, 248]. Conivaptan and tolvaptan are the members of the vaptan group that have been approved by the United States of America Food and Drug Administration (USA FDA).

Results from clinical trials show that the vaptans have a good effectiveness and safety profile in the treatment of hyponatremic patients [181, 249]. Conivaptan is a non-selective antagonist of AVP receptors antagonising $V_{1A}$ and $V_2$ and the first vaptan approved by the FDA [181, 250]. Hemodynamic and aquaretic effects of conivaptan had been investigated in NYHA Classes III and IV of HF patients with left ventricle systolic dysfunction receiving standard therapy for HF [168, 250]. It was found that conivaptan administered as single dose effectively increases serum sodium level as well as increases urine volume and decreases urine osmolality [251]. In addition, conivaptan shows insignificant effect on heart rate, cardiac index, and vascular resistance, both systemic and pulmonary, and common adverse effects of the drug are also well tolerated [252] However, due to its ability to interact with other drugs, conivaptan is only approved for intravenous administration [250, 253].

Following the approval of conivaptan, another vaptan approved by the USA FDA was tolvaptan [254]. Several clinical trials including ACTIV (Acute and Chronic Therapeutic Impact of a Vasopressin antagonist (tolvaptan) in congestive HF [255], EVEREST (Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan) [256] and SALTWATER (Safety and Sodium Assessment of Long Term Tolvaptan with Hyponatremia [257] showed the effectiveness of tolvaptan. The drug can rapidly increase serum sodium level with common tolerable adverse effects including thirsty, dry mouth and polyuria [258]. While conivaptan is only approved
for intravenous administration, tolvaptan is an orally active vaptan with minimal potency for drug interactions [254, 259].

Lixivaptan is another vaptan drug that was clinically investigated and showed positive results [260]. As shown by other previously approved vaptans, lixivaptan also effectively increases serum sodium level with tolerable detrimental effects [260, 261]. However, in 2012 the USA FDA rejected the use of lixivaptan. Several questions related to the effect size of clinical trials still need to be answered before approval is granted [262].

In addition to the potential for bias in regard to the results of the clinical trials of vaptan drugs, some experts also question the end-point outcomes measured in the clinical trials [263-265]. Elevation of serum sodium level is the most used end-point in the majority of clinical trials on vaptans and trials focused on long-term end-point, including quality of life are limited [265]. Hence, long-term safety is also an issue concerning some experts. Although one of the vaptans has been studied for its long-term safety profile, it showed an insignificant benefit compared with conventional treatment [265, 266]. Moreover, the drugs are highly expensive, making the cost of treatment a concern, especially for its use in developing countries [266]. Practically, whilst vaptans have been recommended for the treatment of hyponatremia in the guidelines released in the USA, it has not yet been in Europe [176, 266, 267].

While studies of vaptans for the treatment of hyponatremia are still developing, several studies on the use of conventional treatment options for hyponatremia have also shown that conventional treatment options are still feasible, and should be the treatment of choice in some situations [266]. The use of urea tablets shows good effectiveness for treatment of chronic cases with an insignificant difference in effectiveness and safety profile compared with vaptans [244].
2.3.6. Awareness of hyponatremia by healthcare professionals

Studies have obviously concluded that hyponatremia is an important medical problem significantly associated with worse short and long-term clinical outcomes [179, 195]. Moreover, studies also found that inappropriate management of hyponatremia is associated with more severe conditions leading to the increased necessity of more complex treatment and death [191, 198, 206]. However, some other studies found that hyponatremia is still under-recognised as well as under-managed [268-270]. This lack of awareness of hyponatremia may be due to the wrong perspective; that hyponatremia is a self-limiting problem and the symptoms are unspecific, magnified by some available conventional treatment options being ineffective [174, 176].

Insufficient attention to hyponatremia has been reported Huda et al. (2006) report that almost half of patients with hyponatremia were not diagnosed properly [271]. Among identified patients, only around 25% received appropriate assessment to find out more detail about their condition. Surprisingly, this study also found that that one third of patients receive notable inappropriate treatment [271]. A similar report was also published by Siddique et al. (2009), who found that almost half of patients with hyponatremia had no record of their hyponatremic status in their medical records [272]. The proportion of patients receiving adequate assessment was similar to the rate reported by Huda et al.

Another study reported by Marco et al. (2013) also found that hyponatremia as a medical problem suffers from a lack attention [270]. Despite hyponatremia being the most common electrolyte disturbance significantly related to poor clinical outcomes, it was only reported officially in 1.5% of cases in their study. This lack of attention leads to inappropriate treatment and increased detrimental effects [270]. A similar
problem was reported by Tzoulis et al. (2014) in their multicentre retrospective study in which less than 20% of hyponatremic patients received adequate assessment [268]. In addition, only lightly over one third of patients received appropriate treatment for their hyponatremic problem [268].

Hoorn et al. (2006) report that almost a quarter of patients with severe hyponatremia did not receive adequate treatment, and this was associated with an increased mortality rate [273]. The study also found that hyponatremia developing during hospitalisation tended to be associated with significant delayed treatment. In addition, the study underlines the important of immediate identification of hyponatremia [273].

Such aforementioned findings showing hyponatremia as an underrated problem despite its significant role as a predictor of clinical outcomes and indicate the urgent need for better understanding. One of the most important aspects in managing hyponatremic patients, besides choosing the treatment option, is to recognise the condition. Identification of hyponatremia must be done immediately, and once the patient is identified as hyponatremic then details of the patient’s condition must be determined through a series of measurements including exploration of the patient’s history, identification of clinical symptoms, and determination of laboratory parameters [194, 242].

Improving awareness of hyponatremia with regard to both the diagnosis and treatment is a critical demand in order to diminish its detrimental impact. Lack of awareness and knowledge on the issues will potentially become an obstacle and barrier to making appropriate management decisions [176]. On a practical level, providing useful algorithms as well as PMs will facilitate better recognition and management of hyponatremia [222]. Those efforts to improve awareness can be done
simultaneously with efforts to find out the best options for diagnosing and treating patients with hyponatremia [174].

2.4. Summary

As an advanced stage of cardiovascular disorder, HF is still the most common cause of death from cardiovascular diseases around the world. Hyponatremia is one of the important problems that potentially presents in managing patients with HF, sharing many pathophysiologic and prognostic features with HF. However, it is still rarely recognised and treated sufficiently due to a lack of diagnostic measurement and doubts about the effectiveness of available treatment options. The early important step needed to properly manage hyponatremic patients is to recognise patients at high risk of encountering the problem.
Chapter III – Study conceptual framework

Inappropriate management of hyponatremia may affect morbidity and mortality of HF patients. As hyponatremia is one of the most reported clinical presentations of the complex problem of HF, an appropriate clinical strategy for its management is urgently needed [209]. This approach can improve clinical outcomes, quality of life, and further decrease morbidity and mortality from hyponatremia [229].

The question underlying this research emerged from previous published research concluding that hyponatremia is an important problem in patients hospitalised with HF, associated with worse clinical outcomes, both short- or long-term [179, 195]. Those studies also acknowledged that hyponatremia is still underrated both in diagnosis and treatment [268-270]. As an important problem in patients with HF, several issues related to hyponatremia need to be adequately addressed including:

- Increasing awareness of hyponatremia as a problem to enable adequate diagnosis through and/or by providing a simple tool that could help healthcare providers identify patients with high risk.
- Improving treatment or developing prevention methods to optimise both conventional and newer vaptan therapies.
- Improving patient knowledge and awareness of the problem so they are able to reduce risk factors related to both their daily activities and medications.

This research is focused on the issue of diagnosis by attempting to provide a simple, practical tool that can assist healthcare providers in identifying HF patients at high risk of developing hyponatremia during hospitalisation. Diagnosis is the earliest and the most important step to be rectified in order to reduce the negative impact of hyponatremia. This study developed a PM derived statistically by including patient
and treatment related factors as predictors of the model. The negative impacts of hyponatremia are conceptualised briefly in Figure 7.

3.1. Study question

The question of this research is: Can patient characteristics and pharmacological treatment-related factors be used to develop a PM with good performance to identify HF patients at high risk of developing hyponatremia during hospitalisation?

*Figure 7 - Conceptual framework of the research emphasising the importance of providing a prediction model to identify heart failure patients at high risk of developing hyponatremia*
3.2. Clinical prediction model

Development of a PM is an interesting topic in the health research area [274-277]. PMs are used to address or answer certain scientific or practical dilemmas, or to determine risks associated with disease prognosis, or to discover new determinants that can be added to an established model and result in better model performance [275, 277]. In a practical setting, well-developed and validated PMs can help clinicians to understand the variables determining patient risk of developing medical problems or to provide an accurate estimation in predicting therapeutic outcomes [276, 278].

During the last three decades, the number of publications on clinical PMs have been increasing significantly, with some used globally [274]. Along with the discovery of new concept pathophysiological concepts, therapeutic options, disease markers or interventions could be incorporated to improve PMs [274]. In this evidence-based and patient-oriented era, clinical PMs are very useful in the decision-making process as they present the level of risk of getting particular outcomes. However, the process to obtain a reliable and generalisable PM, is complex [274].

Estimating risks or the possibility of occurrence of certain events is the main objective of PMs [275]. Additionally, PMs are developed for hypotheses testing [274]. Technically, both purposes of making estimations and testing hypotheses are performed by using suitable statistical analysis resulting in a statistical equation or formula [274].

While the outcome of interest as an independent variable of the model can be easily chosen, more attention is needed in selecting variables that will be incorporated as predictors in the model [274, 275]. Some predictors can be selected based on theoretical relationships with the outcome. However, it is harder to choose predictors
having no direct relationship with the outcome [274, 275]. In this case, statistical analysis has an important role to help selecting such important predictors [276].

Other than helping in selecting important predictors, statistical analysis is also needed to evaluate the model in order to test its applicability to the variables in a similar population [274, 276].

3.2.1. The role of prediction models in clinical practice

Generally, PMs are useful for both health practice and research. In a clinical setting, PMs can be used to classify patients at risk of having a particular disease or complication [277]. This can further help healthcare providers in deciding appropriate strategies to either delay disease progression or improve the patient’s quality of life by reducing the impact of the disease or complication [275]. In other clinical situations, PMs can identify patients that will benefit from particular advanced intervention; this further helps healthcare providers in communicating the decision to the patient [277]. In a broader setting within a community, PMs can guide in choosing suitable interventions for a group of people predicted to have a high risk of developing particular problems [275]. Nonetheless, to become a practically useful tool there are several steps to ensure that a PM is valid and reliable [274, 278].

Within health research areas, PMs can be developed to optimise research designs [274, 279]. In clinical trials, PMs can help in selecting patients for inclusion in clinical trials by analysing the basic characteristic of the patients in relation to the outcomes of interest and intended intervention [274, 279]. In observational studies, PMs can help identify confounding variables that potentially contribute to the outcome of interest so that such confounding variables can be optimally controlled [274].
Predicting prognosis and clinical outcomes are part of clinical practice in order to optimise treatment strategies [280]. Providing multivariate PMs is important to facilitate easier way to make such predictions [280]. PMs that can help clinicians to identify patients at risk of developing particular medical problems are valuable as they minimise the negative impacts of such problems [279, 280]. Rather than omitting the roles of other objective measurements, PMs can be jointly used in patient care processes to improve therapeutic outcomes and quality of life [279, 281, 282].

3.2.2. Developing a prediction model

The main goal of developing a PM is to estimate the probability of an outcome of interest occurring based on the value of several predictors [274, 283]. Therefore, a specific outcome of interest and a set of predictors should be defined before deciding to develop a PM. Developing a PM commonly involves a multivariable analysis following three major steps: derivation, assessment and validation [274].

In the derivation step a model is fitted using suitable statistical methods in which three statistical methods are commonly used: regression, classification and neural network [274]. Regression is the most common as it can be broadly used for both the outcome and predictors with either categorical or numerical scales. After establishing a specific outcome of interest in which is then set as dependent variable of the model, selecting predictors that will be included as independent variables of the model is the most crucial aspect in the derivation step. Predictors can be selected from demographic variables, medical and medication history, particular signs and symptoms or laboratory profiles. Generally, any variable can be considered as a predictor of the model: either it has a direct causal relationship or not, and several methods can be used to select candidate predictors of the model. The purposeful
selection method proposed by Hosmer et al. (2013) is the most commonly used approach in the predictor selection process for developing a PM using the logistic regression method [276]. A final fitted model will result from this step after a decision is made to include particular predictors in the model.

Despite circumspection in including significant and important predictors in the model, an assessment step must be carried out to make sure that the obtained model has a good predictive performance [274, 275]. Therefore, assessment is an important step that needs to be performed after obtaining a model [283, 284]. Discrimination and calibration ability are of most concern in assessing the performance of PMs [283]. While discrimination ability indicates the ability of a model to differentiate subjects encountering the outcome from those not encountering the outcome, calibration ability indicates the agreement between the probability for having the outcome ability predicted by the model and the observed outcome [283, 284]. For PMs derived by the logistic regression method the area under the ROC curve, which is equal to the concordance (c)-statistic, is the most commonly used measure to assess discrimination ability [274, 275, 277]. For calibration ability, calibration plot is the most commonly used measure [275]. In addition to discrimination and calibration ability, overall performance of the PM is also commonly assessed using the $R^2$ measure, which indicates the difference between predicted and actual outcome [274]. There are several analogue measures of $R^2$ for PMs derived by different statistical methods. $NR^2$ is the most common measure to assess overall performance of generalised linear models, including logistic regression models, as an analogue of $R^2$ in linear regression [274, 276].

Whilst the assessment step aims to evaluate predictive performance of the model in the same sample used to derive the model itself, the validation step also needs to be
performed to evaluate the model’s predictive performance in new different samples [281, 285]. Validation can be performed using different samples but still from the same source of population – called internal validation, or using different samples from different populations – called external validation [281, 285]. For a PM to be practically used in the general population, external validation is a must, especially for the model derived using a relatively small sample size [286]. Therefore, a PM with good predictive performance validated internally can only be used for practical purposes within the same population as the model was derived [285]. Three methods commonly used to internally validate a PM are split sample method, cross-validation and the bootstrapping method [274, 285]. Compared to other methods, the bootstrapping method results in more accurate estimates of model performance [287].

3.2.3. Prediction models within heart failure issues

In general cardiovascular issues, Framingham Risk Score (FRS) published by the Framingham Heart Study might be the most prominent PM developed to predict an individual’s chances of developing cardiovascular disease [288, 289]. Whilst the first effort to investigate the risk for cardiovascular diseases had been started by the Framingham Heart Study in the late 1940s, the first paper describing the scoring system with multivariate risk factors was only published in 1961 [289]. During the following years, the scoring system was then continuously enhanced to produce a better one for estimating the risk for developing coronary heart disease (CHD) [289, 290]. This scoring system has been applied in clinical practice and gives a significant impact in lowering CVD mortality worldwide [289]. The scoring system can not only be applied for individuals in developed nations but also individuals in developing countries [290, 291].
Whilst the FRS was developed in the USA, a similar PM was also derived from European populations [289, 292]. The SCORE project is one of them, which developed a scoring system with a focus on the risk of fatal cardiovascular events [292]. The endpoint of the model is cardiovascular mortality from CHD, HF, sudden death and peripheral vascular disease [292]. The project gathered longitudinal data from 12 countries in Europe for more than 10 years and six variables were finally included in the model, including age, gender, total cholesterol, high density lipoprotein, systolic blood pressure (SBP) and smoking [289, 292].

Specifically within HF as a syndrome, PMs have been developed for several purposes, particularly on predicting risks for particular invasive interventions, hospitalisation and mortality [288, 293-296]. The usefulness of a PM incorporating several risk factors has been shown significantly in estimating clinical outcomes of patients with HF [280]. The need for PMs within HF issues will increase as the prevalence of HF is increasing and the therapeutic management is also evolving [3, 280].

More than two decades ago PMs to predict HF patients needing of cardiac transplantation were developed [297, 298]. The PM to estimate the risk of death among HF patients was first developed by Kearney et al. (2002) with all causes of death as the outcome of interest, and variables incorporated in the models were variables obtained from non-invasive assessments [299, 300]. Variables included in the final model include serum creatinine, serum sodium level, left ventricular hypertrophy and five variables derived from electrocardiogram measurements [299]. The model has good performance and provides useful guidance for both clinicians and patients in deciding appropriate treatment strategies [299].
Among PMs with survival as the outcome of interest, the Seattle HF Model (SHFM) might be the most prominent [301]. This model was first developed by Levy et al (2006) with the main purpose of predicting survival of HF patients by using variables derived from information commonly collected in practice [301]. The model has a good performance in predicting one-, two- and three-year survival among patients with HF [301]. Other than being very useful in improving adherence and predicting a patient’s prognosis, the model is also helpful in deciding if particular patients will benefit from any medication or cardiac device [301]. Following its publication, several modifications have been published, either modifying the outcome of interest or incorporating new variables [294, 302, 303].

Given that the SHFM was obtained by elaborating data resulting from clinical trials, May et al. (2007) conducted external validation to assess its applicability in the general HF population [304]. Using data gathered from hospitals, they found that the SHFM still has good performance when applied to a different population [304]. In addition, while the longest survival assessed in the original model is three years, the study also found that the model is still applicable to estimate longer survival – five years [304]. External validation of the SHFM was also conducted also by Stefanescu et al. (2014) in a group of patients with congenital heart disease [305]. The study found that it has a good ability to predict cardiovascular outcomes among patients with congenital heart disease so that the model can benefit healthcare providers as well as the patients in deciding the treatment strategy [305].

Validation of the SHFM in patients with advanced HF and different races has been conducted by Kalogeropoulos et al. (2009), finding that it is not applicable in these two groups of patients [306]. The study found that the model overestimates survival of patients with advanced HF and in the meantime underestimates patients from
black-skinned populations [306]. Giamouis et al. (2009) also conducted a study to assess the validity of the SHFM in patients with advanced HF as well as to modify the model by adding a variable derived from kidney function [307]. The study found that among variables commonly used to measure kidney function, BUN has a robust association with the outcome when incorporated into the original model and results in better prediction [307]. Nonetheless, BUN has no significant impact on the discrimination ability of the model [307].

3.2.4. Prediction models for hyponatremia

As an important complication potentially encountered by HF patients, hyponatremia requires more attention during hospital admission and discharge investigation, and in the primary care setting. It also needs to be considered as a parameter that requires correction through treatment or removal of the underlying cause. Studies demonstrate that hyponatremia significantly contributes to clinical outcomes in HF patients, and that the awareness towards addressing it as a problem is still lacking [183, 191, 195, 199, 308]. Development of hyponatremia during hospitalisation is independently related to in-hospital mortality and long-term survival after hospital discharge [179, 308-310]. Furthermore, hyponatremia in chronic conditions and acute hospitalisation is associated with higher expenditure [201, 202, 311]. Therefore, attempts to reduce its negative impact in HF patients are urgently needed. The development of PMs can help in recognising HF patients at high risk of developing hyponatremia to enable adequate measures to be delivered to high-risk patients to avoid further worse conditions [269]. Appropriate management of hyponatremia, including early identification of such high-risk patients, will significantly decrease morbidity and mortality of HF patients [192].
A PM to stratify the risk of developing hyponatremia has been developed by Rastogi et al. (2012) among patients using thiazide diuretics [312]. Several factors leading to the development of some drug-induced hyponatremia have been also identified. However, there has been no study on a PM for stratifying the risk of hyponatremia among HF patients. Already identified variables can be used as predictors for the development of a PM to identify HF patients at high risk of developing hyponatremia. The predictors can be jointly combined with several specific variables of HF patients, for example, EF and medication commonly used, such as diuretics. It is not easy to develop a good and practically useful PM [279, 282, 284, 285]. Several steps are needed before deciding that the model has good performance and is practically useful, including an external validation process involving a different patient population [286]. However, a PM with good predictive performance from an internal validation process can be practically used as long as it is developed well and involves a large sample size [285, 286].

3.3. Research aims

This research aims to obtain PM with good performance that will identify HF patients at high risk of developing hyponatremia during hospitalisation by including patient and treatment-related factors as predictors.

3.4. Research objectives

The aim of this study is achieved through the following objectives:

1. To retrospectively identify the prevalence of hyponatremia during hospitalisation among patients hospitalised with HF at the study site and its association with hospital length of stay and in-hospital mortality.
2. To investigate current management of hyponatremia in patients hospitalised with HF at the study site.
3. To identify significant contributing risk factors of developing hyponatremia among patients with HF during their hospitalisation and further to include those identified risk factors for deriving a risk-PM for hyponatremia during hospitalisation in patients hospitalised with HF.

4. To assess the predictive ability of the obtained risk-PM based on measures commonly used to evaluate the predictive ability of PMs.

5. To evaluate reproducibility of the fitted model through internal validation so that its practical utility within the population where the sample for deriving the PM was taken can be justified.

3.5. Hypotheses

The main outcome studied in this research was hyponatremia during hospitalisation, which then is set as a binary outcome: presence or absence. Several predictors from patient and treatment-related factors were included in the model either with binary, categorical or numeric scales. Consequently, the most suitable statistical method for developing the model was deemed to be logistic regression. Based on the research question, the null hypothesis and alternative hypothesis are:

Null hypothesis (H₀): There are no factors related to neither patients nor treatment that can function as predictor for hyponatremia during hospitalisation in hospitalised HF patients. This means that none of the predictors derived from patient and treatment-related factors can predict the probability of the occurrence of hyponatremia during hospitalisation.

Alternative hypothesis (Hₐ): There are factor(s) related to patients or treatment that can function as predictor for hyponatremia during hospitalisation in hospitalised HF patients.
The hypotheses were then tested by performing logistic regression analysis with an \( \alpha \)-level of 5\% for the final PM.

3.6. Summary

It is clear that hyponatremia is a significant problem contributing to morbidity and mortality, as well as health expenditure, among patients with HF. As part of the research within hyponatremia topics, this research is of importance both for scientific and practical reasons. In the scientific domain this research will drive further research on identification of contributing risk factors for the development of hyponatremia among patients with HF during their hospitalisation. Practically, this research will help improve awareness of hyponatremia in HF patients by providing information about contributing risk factors, as studies have revealed that awareness on this problem is still lacking. Furthermore, this research will provide a PM for identifying HF patients at high risk of suffering from hyponatremia, a useful tool that can be used as an early step in deciding appropriate management for such high-risk patients. These outcomes will help reduce morbidity and mortality related to hyponatremia among patients with HF.
Chapter IV – Methods

This chapter describes the methodology used in this research, including the study design, subject selection criteria, ethics approval, data collection process and the steps in deriving the PM. Methods used to assess performance as well as to internally validate the PM are also elucidated in this chapter.

4.1. Research setting

Data for this research were collected from Fatmawati Hospital, a tertiary teaching hospital located in Jakarta, Indonesia, controlled directly by the Ministry of Health, Republic of Indonesia. Located in urban area of South Jakarta the hospital is one of 32 general hospitals in South Jakarta that serves a population of around two million people. Of the hospitals serving the population of South Jakarta, Fatmawati Hospital is the largest, with a total of 747 beds of which 25 are in the cardiovascular care unit (CVCU) ward. Several issues considered in choosing the hospital to gain data for this research included:

1. availability of complete patient records
2. probability of gaining a sufficient sample size
3. probability of the research proposal being administratively approved.

Fatmawati Hospital was chosen because it fulfilled the above criteria. It is a teaching hospital, thus patient records would be more complete compared to a non-teaching hospital in Indonesia. With more than 700 hospital beds, it was estimated that the required sufficient sample size could be sourced. In addition, there is an established memorandum of understanding for education and research purposes between the hospital and the investigator’s home university that could accommodate this research.
4.2. Research design

A case-control design was used for identifying contributing risk factors for developing hyponatremia during hospitalisation and deriving a PM in this research in which cases comprising patients who developed hyponatremia during their hospital stay and patients with normal sodium levels both at admission and during hospital stay served as controls. Each patient in the case group was matched by age and gender to three patients as controls. Although a higher case:control ratio will decrease variability estimates, the ratio of 1:1, 1:2, 1:3 and 1:4 between case and control have shown similar estimates of accuracy compared to the full study population [313, 314]. Therefore, the 1:3 ratio used in this study was considered an appropriate design.

Although prospective data collection provides complete data and minimises missing information, data for this research were collected retrospectively due to limited time and funding. Regardless of its disadvantage, retrospective data collection is more favourable in terms of simplicity and feasibility, as well as low research costs.

As the outcome of interest in this research, hyponatremia then was set up as a dependent variable in developing the PM. Independent variables included in the model were candidate predictors derived from patient characteristics, including demographic, medical history before hospitalisation, vital signs and symptoms at admission, blood chemistry profiles at admission and medication administered during hospitalisation.

4.3. Ethics clearance and approval

Ethics approval for this research has been granted by Charles Sturt University Human Research Ethics Committee (HREC) with protocol number 2013/203 and also by Fatmawati Hospital Ethics Committee with approval number
Reciprocal ethics approval has also been granted by Charles Darwin University HREC (Appendix – 1).

4.4. Power and required sample size

Development of a PM is part of a multivariable analysis involving several predictors. The involvement of multi predictors makes the estimated sample size required for the studies difficult. Some general rules considered in estimating the required sample size in order to obtain a good model with sufficient statistical power are as follows:

1. Several hundred outcome events are needed to develop a good PM. Therefore, given that the average prevalence of hyponatremia among patients hospitalised with HF reported by previous published research was 20% [180, 182, 192, 193], and 100 outcome events of hyponatremia were targeted in this research, a sample of 500 patients hospitalised with HF are needed to develop the PM.

2. To obtain a good and stable PM, the number of events per-variable (EPVs) should be considered. The minimum number of EPVs in order to get a stable model is five, meaning that at least 100 positive outcomes of interest are needed to include 20 candidate predictors in the model. On the other hand, the more predictors included in the model, the higher the optimism of the model. Therefore, general principles of model parsimony should also be considered in order to obtain a good and more practical model. The basic principle of model parsimony is to include as simplest predictors as possible so that the model becomes much easier to use. Following this principle of model parsimony, four to six predictors were targeted to be included in the model. Prevalence of hyponatremia during hospitalisation was estimated as 20% based on the prevalence of hyponatremia in patients hospitalised with...
HF reported by previous studies, thus the minimum required sample size to derive a PM by including 20 candidate predictors with an EVP of five is 400.

3. The minimum required sample size in multivariate regression analysis depends on intended effect size – how well predictors included in the model predict the outcome – and statistical power intended to detect that effect size. The minimum sample size required to build a model with medium effect size, 80% of statistical power and six predictors included in the model is 98. For a small effect size, the minimum required sample size is 667.

By considering all the general rules mentioned above, the minimum required sample size to build a PM in this research was between 98 and 500.

4.5. Sample and subject selection

Patients included as subjects of this research were patients admitted to hospital with HF. To be included in this research, a patient should:

1. be diagnosed as having HF coded with I.50.0 according to the internal classification of diseases (ICD)-10
2. have been hospitalised for at least three days
3. have a reasonably complete record on demographic profiles, clinical problems, medical history, vital signs and symptoms at admission, blood chemistry at admission, medication records during hospitalisation and serum sodium level during hospitalisation.

Patients who fulfilled all the above-mentioned inclusion criteria were excluded if they had adrenal insufficiency, hypothyroidism, SIADH, or having diseases/disorders known as causes of SIADH (any malignancies, central nervous
system disorders, pulmonary and human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS]).

4.6. Definition of hyponatremia

In this research, a patient was categorised as encountering hyponatremia if their serum sodium level was lower than 135 mEq/L [191, 197]. Serum sodium level can be converted to mmol/L by multiplying the serum sodium level in mEq/L by 1.0. A patient was categorised as developing hyponatremia during hospitalisation if at least one episode of hyponatremia occurred on the day following admission, regardless of serum sodium level on admission. Based on this definition, hyponatremia during hospitalisation in this research comprised two categories of hyponatremia:

1. **Persistent hyponatremia (PH):** patient has been already hyponatremic at admission and serum sodium level either did not increase or even decreased during hospitalisation.

2. **HAH:** patient with normal serum sodium level at admission became hyponatremic during hospitalisation.

To minimise the chance of standard deviation of the laboratory measurement confounding the definition, the decrease of serum sodium level for patients with normal sodium level at admission should be at least at a 3 mEq/L (3 mmol/L) level. Serum sodium levels were also corrected for patients with a blood glucose level >200mg/dL (equal to 11 mmol/L) using a correction factor of 2.4 per 100mg/dL (equal to 5.5 mmol/L) increase of blood glucose level.

4.7. Data collection and storage

Patients hospitalised with HF were identified electronically by using the ICD-10 code of I.50.0. Identification was begun for patients hospitalised in 2013 and then
backward to 2012 and 2011 to get the required minimum sample size. Patients’ medical records were then retrieved by authorised staff at the division of medical record of the hospital. The investigator then extracted patient data manually from those medical records in accordance with regulations on extracting data from medical records established by the Ministry of Health, Republic of Indonesia. Extracted information included demographic data, vital signs and symptoms at admission, medical history, concomitant diagnosis of present hospitalisation, medication administered during hospitalisation, treatment of hyponatremia during hospitalisation, laboratory profiles and outcome of hospital discharge. All data were collected using data collection forms and stored in a locked filing cabinet. Microsoft excel® was used to input the data and all data were saved into password protected files.

4.8. Data analysis

Data were analysed in order to answer the main question as well as to achieve the objectives of this research. Accordingly, the first step of data analysis was performed in order to assess the prevalence of hyponatremia during hospitalisation and its association with hospital length of stay and in-hospital mortality. The second step was to investigate the current practiced management for the treatment of hyponatremia at the research site. The third step of data analysis was to derive the PM, in which other than obtaining a fitted model, risk factors for developing hyponatremia during hospitalisation could also be identified. The next steps were to assess the performance and validate the fitted model. The final step was to present the obtained model. Each step of the data analysis process is detailed below.
4.8.1. Assessing the prevalence of hyponatremia and its relationship with hospital stay and in-hospital mortality

Prevalence of hyponatremia in this research was calculated simply as the proportion of patients developing hyponatremia during hospitalisation. Statistical analysis to assess the association between hyponatremia during hospitalisation and in-hospital mortality was performed using the univariate logistic regression method with in-hospital mortality serving as a dependent variable. In-hospital mortality in this research was defined as death from any cause during hospitalisation. $p$-value and odds ratio (OR) with its 95% confidence interval (CI) were used to assess the association.

4.8.2. Investigation of current/practiced management for treatment of hyponatremia

The main objective of this step was to ascertain the therapeutic options administered to patients developing hyponatremia during hospitalisation. Specific information on the administered therapeutic option was only retrieved from medical records by identifying conventional therapeutic options commonly administered, including fluid restriction, normal saline and hypertonic saline. Although some new drugs have been approved for the treatment of hyponatremia, they are still not commonly used in practice, especially in developing countries. Therefore, some conventional options are still chosen as the treatment of choice.

According to administered therapeutic options, patients were then classified and statistical analysis was performed to assess the association between therapeutic options and in-hospital mortality.
4.8.3. Derivation of prediction model

The outcome of interest in this research was hyponatremia during hospitalisation and was set up as binomial categorical dependent variable for developing the PM. Hence, binomial multivariate logistic regression was used to develop the model in which the dependent variable was valued as zero (0) for the absence of hyponatremia and one (1) for the presence of hyponatremia. Candidate predictors as independent variables with their measurement scale are listed in Tables 5–9 and purposeful predictor selection proposed by Hosmer et al. (2013) was followed to find the most significant predictors. Purposeful predictor selection is a method for selecting potential predictors consisting of seven steps as follows:

Step 1

In this first step all available patient characteristic were set up as candidate predictors, and each candidate predictor was then analysed by using univariable logistic regression either for categorical or continuous predictors. Any predictor whose univariable test has a p-value less than 0.25 was further involved in multivariable analysis in the next step.

Step 2

All candidate predictors screened from the first step were then included to fit the multivariable model in this step. The p-value of its Wald statistics was used to assess the importance of each predictor in which the non-significance predictor, with p-value >0.05, then eliminated. The new smaller model including only significant predictors was compared to the bigger model including all predictors screened from the first step using a partial likelihood test.
Step 3

The values of the estimated coefficients in the smaller model resulting from the second step were compared to their respective values in the larger model. In this step, any predictor whose coefficient changed more than 20% was checked to find if one or more important predictors should be added back into the model.

Step 4

After concluding the model resulting from the cycling analysis through Steps 2 and 3, in this fourth step each variable not selected in Step 1 was added to the concluded model. The significance of each predictor then was checked by its Wald statistics $p$-value. The purpose of this step is to find any predictor that has a non-significant contribution to the outcome, but with its contribution marked significant by the presence of other predictors.

Step 5

In this fifth step, all predictors included in the model resulting from the fourth step were examined more closely. For a continuous predictor, examination focused on the linearity of the logit, whether the logit has a linear function of the predictor or not.

Step 6

This sixth step was performed to find any interaction among predictors in the model. However, only interactions that make sense from a clinical perspective were assessed in this step. Any potential interaction was analysed by univariate logistic regression and then significant interactions were added to the model resulting from the fifth step to assess their significance in the multivariable model. Any interaction with a significant contribution known from univariate analysis was then added to the model,
including significant interaction, and assessed following assessment described in Step 2. This step generated the final PM.

**Step 7**

In this final step, performance of the final model was assessed both for its overall and specific performance, which was then described later on the assessment of model performance. Figure 8 shows the summary of the seven steps in selecting predictors to fit the PM by following purposeful predictor selection. All steps of the predictor selection as described above were performed using Statistical Package for Social Science (SPSS) IBM® software version 22.0.

**Table 5 - Predictors derived from vital signs and symptoms at admission**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Measurement scale</th>
<th>Unit/value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>Continuous</td>
<td>mmHg</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>Continuous</td>
<td>mmHg</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Continuous</td>
<td>Times/minute</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Continuous</td>
<td>Times/minute</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnoea</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Orthopnoea</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Cough</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Nausea</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Pitting edema</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Ascites</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
</tbody>
</table>

**Table 6 - Predictors derived from concomitant diagnosis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Measurement scale</th>
<th>Unit/value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Unspecified infection</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
</tbody>
</table>
Table 7 - predictors derived from medical history

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Measurement scale</th>
<th>Unit/value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>COPD</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Stroke</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
<tr>
<td>Previous hospitalisation from heart disease</td>
<td>Binomial categorical</td>
<td>0=absence, 1=presence</td>
</tr>
</tbody>
</table>

Note: COPD = chronic obstructive pulmonary diseases

Table 8 - predictors derived from medication administered during hospitalisation

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Measurement scale</th>
<th>Unit/value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Potassium supplement</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Positive inotropes</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Organic nitrates</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Heparin</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Laxative agent</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>H2-receptor antagonists</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Albuterol+Ipratopium</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Insulin</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Binomial categorical</td>
<td>0=No, 1=Yes</td>
</tr>
</tbody>
</table>
Note: ACE = angiotensin converting enzymes

Table 9 - predictors derived from blood chemistry at admission

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Measurement scale</th>
<th>Unit/value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>Continuous</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>Continuous</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Random blood glucose</td>
<td>Continuous</td>
<td>g/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Continuous</td>
<td>g/dL</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Continuous</td>
<td>g/dL</td>
</tr>
<tr>
<td>High density lipoprotein</td>
<td>Continuous</td>
<td>g/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>Continuous</td>
<td>g/dL</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Continuous</td>
<td>g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Continuous</td>
<td>%</td>
</tr>
<tr>
<td>White blood cells</td>
<td>Continuous</td>
<td>Cells/L</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>Continuous</td>
<td>Cells/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>Continuous</td>
<td>Units/L</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>Continuous</td>
<td>Units/L</td>
</tr>
</tbody>
</table>

As previously mentioned, Figure 8 summarizes the seven steps used to select the predictors.
Figure 8 - Summary of the seven steps in selecting predictors to fit the prediction model by following purposeful predictor selection.
4.8.4. Identification of variables associated with hyponatremia during hospitalisation

While developing the PM, variables associated with hyponatremia during hospitalisation could be identified. These variables were identified during Step 4 of the purposeful predictor selection described above. Other than the \( p \)-value of Wald statistic, OR and its 95% CI were assessed in identifying those variables.

4.8.5. Assessing the performance of the obtained prediction model

Performance of the model was assessed for contribution of predictors included in the final model, overall model performance, discrimination and calibration ability.

4.8.6. Assessment of predictors’ contribution to the model

This assessment was performed to know the individual contribution of predictors included in the final PM. The measures used to assess the contribution are \( z \)-statistic, also known as Wald statistic, and OR. Wald statistic is a common measure used to assess the contribution of predictors into a model developed by logistic regression, and it explains whether the estimated regression coefficient of a particular predictor is significantly different from zero or not. This measure was automatically reported in the SPSS output when performing logistic regression analysis in which a predictor contributing significantly into the model had a \( z \)-statistic less than 0.05, that is, the estimated regression coefficient of that predictor is significantly different from zero.

To ensure that the estimated regression coefficients of predictors also fall within population value, 95% CI of each estimated regression coefficient was also assessed. This assessment was performed by the bootstrap option provided by SPSS and could be shown in the SPSS output as Bootstrap for variables in the equation. Other than informing standard error of the estimated regression coefficients, this output also informed the CI of those estimated regression coefficients. From the CI range, the
estimated regression coefficient of each predictor included in the model could be assessed to see if it fell within its population value or not. The OR for each predictor included in the model was also calculated by SPSS by asking SPSS to perform this calculation when performing logistic regression analysis. In logistic regression, OR of any predictor is the exponential value of its estimated regression coefficient so that it is shown in SPSS output as exp(B), and it explains the change of OR resulting from a unit change of any predictor. The value of an OR higher than 1 means that as the value of predictor increases the probability of the outcome to occur will also increase. Conversely, the value of an OR less than 1 means that increasing the value of the predictor will decrease the probability of the outcome to occur. In addition to OR, 95% CI of this OR was also calculated in order to make sure that there is not any OR equal to 1 within the population. An OR equal to 1 indicates that any change of predictor value has no impact towards the outcome.

4.8.7. Assessment of overall performance

In linear regression, $R^2$ is the most common measure used to assess model performance, and it indicates the overall difference between actual values and values predicted by the regression model. There are some analogues to $R^2$ in logistic regression and in this research $NR^2$ was used to assess overall performance of the fitted model. $NR^2$ is the most common measure to assess overall performance of generalised linear models, including logistic regression models, as an analogue of $R^2$ in linear regression. In this research, $NR^2$ was generated by SPSS as it is by default reported within SPSS output when performing logistic regression analysis. $NR^2$ value ranges between 0% and 100% in which 0% indicates that the predictors included in the model explain none of the variability of the outcome while the value
of 100% indicates that predictors included in the model explain all the variability of the outcome. Thus, \( \text{NR}^2 \) of any perfect logistic regression model is 100%.

**4.8.8. Assessment of discrimination ability**

Discrimination ability of the model was assessed using area under the ROC curve in which the area for a useless model is equal to 0.5 and score for the perfect one is 1. The ROC curve is a measure that equals to the c-statistic commonly used to assess discriminative ability of generalised linear models. The curve is a plot of the model’s sensitivity against 1-specificity of the model. The model’s sensitivity refers to the true positive rate, that is, the rate of positive actual outcome that is also positively predicted by the model. Conversely, model specificity refers to the true negative rate that is the rate of negative actual outcome that also negatively predicted by the model, hence 1-specificity refers to a false positive rate, that is, the rate of negative actual outcome that predicted by the model as positive. A model with high discrimination ability will have high sensitivity and specificity simultaneously resulting in a larger area under the ROC curve. In this research R software [315] was used to generate the ROC curve using the pROC package [316]. To generate the ROC curve, the model previously fitted by SPSS was also fitted by R using glm package. After fitting the final model, the ROC curve was generated by following commands:

```r
Model’s_Hyponatremia <- glm(Hyponatremia~final predictors, family=“binomial”, link=“logit”)
```

```r
Predicted_probability <- predict(Model’s_name, type=c(“response”))
```

The pROC package was then activated by loading the package and the ROC curve could be further generated as follow:
library(pROC)

ROCcurve <- roc(Hyponatremia~predicted_probability)

plot(ROCcurve)

Other than generating a ROC curve, this function also informed the AUC that could further be used to assess the discrimination ability of the model. According to the AUC, discrimination ability of the model could be determined following common classification, as shown in Table 10.

<table>
<thead>
<tr>
<th>Area under the curve</th>
<th>Discrimination ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 0.5</td>
<td>No discrimination</td>
</tr>
<tr>
<td>0.5 &lt; AUC &lt; 0.7</td>
<td>Poor discrimination</td>
</tr>
<tr>
<td>0.7 &lt; AUC &lt; 0.8</td>
<td>Acceptable discrimination</td>
</tr>
<tr>
<td>0.8 &lt; AUC &lt; 0.9</td>
<td>Excellent discrimination</td>
</tr>
<tr>
<td>≥ 0.9</td>
<td>Outstanding discrimination</td>
</tr>
</tbody>
</table>

Note: AUC = area under the curve

4.8.9. Assessment of calibration ability

The calibration ability of a regression model indicates the degree of agreement between actual outcome and predicted outcome. In this research, the calibration ability of the PM was assessed using calibration plot and HL calibration test. The calibration plot was obtained by plotting predicted probabilities on the x-axis versus actual outcome on the y-axis, in which the model with perfect calibration ability will show a 45° line. The calibration slope of the calibration plot will always equal one (1) when it is assessed using the samples used for developing the model because the model is best fitted on that sample. Hence, the calibration slope resulting from the validation step, which is described later, was then used to assess its real value.
The $p$-value HL test indicates the agreement between predicted probabilities and actual outcomes, in which a $p$-value $\geq 0.05$ indicates that there is no significant different between predicted probabilities and actual outcomes.

All calibration ability measures were assessed by R software using the rms package [317] for generating a calibration plot, and the resource selection package for performing the HL test [318].

4.8.10. Validation of prediction model

The main purpose of this validation step was to calculate the average estimate of the amount of model optimism. Commonly, a PM can predict the outcome within the sample used to develop the model quite well, but its prediction ability decreases in a new sample. In the other words, performance of such a PM is quite good when assessed using its apparent sample, but the performance then decreases when assessed using another new sample. This problem is called the optimism of PM. To overcome this issue, validity of the model needs to be assessed either through internal or external validation.

Due to limited time and resources, only internal validation was conducted in this research. The main purpose of internal validation is to ensure that the obtained PM has good reproducibility – the PM retains its good performance in predicting hyponatremia in another sample derived from the same population source. For a PM with good performance, internal validation can also generate more accurate estimates of the model’s performance.

A bootstrap resampling approach was chosen for conducting the internal validation in this research as it has been known an efficient method and can give better results compared to other methods commonly used for internal validation. Five hundred
bootstrap resampling produced a stable average indices, and bootstrapping for the purpose of internal validation in this research was performed by R software using the “validate” function within the rms package [317].

4.8.11. Presentation format of the prediction model

Regression formula was chosen to present the PM obtained from this research. Although the simplest form of presenting a PM, it can be further developed for another format. As the PM in this research was fitted by logistic regression, the common formula for logistic regression was used to present the PM. The common formula for logistic regression is:

\[ Y = B_0 + B_1 P_1 + B_2 P_2 + B_3 P_3 + \ldots + B_i P_i \]

In which

- \( Y \) = outcome of interest
- \( B_0 \) = constant of the model
- \( B_1, B_2, B_3, B_i \) = regression coefficient estimates of particular predictor
- \( P_1, P_2, P_3, P_i \) = value of each predictor included in the model

After obtaining value of the outcome, predicted probability of the outcome can be further calculated by using formula: \( p = \frac{1}{1 + e^{y}} \) in which \( p \) is the probability of the outcome to occur.

To obtain a more accurate the prediction, uniform shrinkage was applied to shrink the regression coefficient estimates. Shrinkage of regression coefficients is a common method applied to minimise the optimism of the PM when it is applied to different samples. In this research uniform shrinkage was chosen to shrink the regression coefficients, in which the obtained shrinkage factor was then used to get
shrunken regression coefficients by multiplying the original regression coefficient estimates by the shrinkage factor resulting from bootstrapping analysis. The uniform shrinkage factor was obtained by a bootstrapping method performed by the “shrink” package in R software [319].

4.9. Limitations and risks

Data for this research were collected retrospectively, so some important information could not be completely retrieved. Unavailability of information related to HF and the management of hyponatremia limited the analysis and scope of this research. Although imputation analysis can resolve problems of missing data for the purpose of building a model it will of course potentially increase the bias.

In the research site electronic data were only available for information on the patients’ medical record codes and their diagnosis group, age and gender. Details of information related to hospitalisation had to be retrieved manually, and even though good practice on medical record storage had been implemented, missing medical records still became a big problem – reducing sample size.

A clinical trial on the management of hyponatremia was targeted at the first stage of building the research concept, but practically it could not be conducted. Other than to find the best approach in managing hyponatremia, data resulting from the trial can also be used to derive models related to hyponatremia. In addition to the research budget, intensive collaboration between academic/research institution and healthcare facilities as research sites was not yet built to support this activity.

4.10. Summary

Obtaining a PM that can be used to identify HF patients at high risk of developing hyponatremia was the specific aim of this research. To achieve that aim, the data of
patients hospitalised with HF were collected retrospectively from medical records. The prevalence of hyponatremia during hospitalisation was measured and its association with hospital length of stay and in-hospital mortality were assessed by univariate logistic regression analysis. The current therapeutic options administered in patients who developed hyponatremia during hospitalisation was also investigated, descriptively reported and its association with in-hospital mortality analysed. The PM was derived following a purposeful selection method for selecting significant predictors, and predictive performance of the obtained model was assessed. Whilst \( \text{NR}^2 \) was used as the main measure to assess overall predictive performance of the model, discrimination and calibration ability of the model were assessed by area under ROC curve and calibration plot as main measures, respectively. Internal validation of the model was conducted by bootstrapping approach to full optimization of the model. To optimize the model estimation when it is used in different samples, shrinkage factors were calculated and then used to shrink regression coefficients of all predictors included in the final model. The final model was presented in a format regression formula.

For the purpose of this thesis, optimization refers to “model over-fitting”.

### 4.11. Research timeline

Table 11 shows the research timeline.
Table 11 – Research timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Month</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>11</td>
<td>Conducting literature review</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Formulating research questions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Formulating relevant research methodology</td>
</tr>
<tr>
<td>2013</td>
<td>1</td>
<td>Developing research proposal</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Applying for ethical approval</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Writing paper publication on results of literature review</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Arranging data collection form</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Applying for data collection into hospitals in Australia and Indonesia</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Application into hospital in Australia was declined due to financial support</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Presenting research proposal at Fatmawati Hospital for approval consideration</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Data collection</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Cleaning-up the data</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Data analysis</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Assessing relationship between hyponatremia and in-hospital mortality</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Derivation of prediction model</td>
</tr>
<tr>
<td>2014</td>
<td>1</td>
<td>Validation of prediction model</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Presentation of prediction model</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Thesis writing</td>
</tr>
<tr>
<td>2015</td>
<td>4</td>
<td>Thesis editing</td>
</tr>
<tr>
<td>2016</td>
<td>5</td>
<td>Thesis submission</td>
</tr>
</tbody>
</table>
Chapter V – Results

This chapter presents the results of the research in order to answer the research questions. Subject selection is followed by the prevalence of hyponatremia during hospitalisation and its association with hospital length of stay, and in-hospital mortality. The third and fourth sections present the characteristics of the patients included in the research and the findings on management of hyponatremia. Although information about the management of hyponatremia found in this research was quite limited, its presentation is important to increase awareness about its identification and treatment. The fifth and sixth sections present the main findings related to the process of deriving the PM and assessing its performance. After presenting the findings supporting reproducibility of the obtained PM through the bootstrapping validation process, the final section of this chapter presents the PM in its simple form.

5.1. Subject selection

During the period between 2011 and 2013, 663 hospitalised patients in Fatmawati Hospital were coded with I50.0 according to the ICD-10 for their main diagnosis of hospitalisation – congestive HF. Of the 663 patients, 464 met all inclusion criteria for this research and were therefore included, while 199 were excluded due to incomplete laboratory records, pregnancy, routine hemodialysis or other reasons. Figure 9 depicts the process of patient selection and further allocation of patients into case and control groups based on the occurrence of hyponatremia during hospitalisation.
5.2. Prevalence of hyponatremia and its association with clinical outcomes

In the 464 hospitalised patients with HF included in this study, hyponatremia was found in 19% on admission and 22% during hospitalisation. Compared to other electrolyte disturbances, this study found that hyponatremia, both on admission and during hospitalisation, was the most prevalent. Table 12 shows that the prevalence of
hyponatremia in patients hospitalised with HF was around double that for hypokalemia.

Table 12 - Comparison between sodium and potassium disturbances observed in patients hospitalised for heart failure

<table>
<thead>
<tr>
<th>Type of electrolyte abnormality</th>
<th>Prevalence based on time of occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On admission (%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>19</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>10</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>7</td>
</tr>
</tbody>
</table>

Out of 102 patients with hyponatremia during their hospital stay, as defined in this research, 45 patients (44%) had HAH and 57 patients (56%) were patients with PH. These 102 hyponatremic patients then served as the case group and, 306 patients were selected from the non-hyponatremic patients to serve as the control group resulting in 1:3 ratio of case-control. Controls were matched by gender and age, and Table 13 presents the comparison of gender and age between the case and control groups, showing that the distribution of gender between the case and control groups is equal, and the mean age in the control group is slightly older but not significantly different from the case group ($p = 0.607$).

Figure 10 shows the distribution of serum sodium levels at admission of both case and control groups. The mean of serum sodium level at admission of the case group was $133 \pm 6.2$ mmol/L, significantly lower ($p < 0.001$) than that of the control group, which was $140 \pm 4.4$ mmol/L. Specifically among the case group, the mean of serum sodium level at admission of patients with PH was also significantly lower than patients with HAH ($p < 0.001$), $129 \pm 4.7$ and $138 \pm 2.9$ respectively.
Table 13 - Gender and age as matched variables between case and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 102)</th>
<th>Control (n = 306)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>51%</td>
<td>51%</td>
<td>1.000</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53(18)</td>
<td>54(19)</td>
<td>0.607</td>
</tr>
</tbody>
</table>

Figure 10 - Comparison of mean of serum sodium level at admission between patients developing and not developing hyponatremia during hospitalisation

Overall in hyponatremic patients the lowest serum sodium level during hospitalisation was $128.1 \pm 4.8$ mmol/L, and the lowest serum sodium level in patients with PH was significantly lower ($p < 0.001$) than patients with HAH, $126.1 \pm 4.9$ mmol/L and $130.7 \pm 3.2$ mmol/L respectively. Most hyponatremic patients had the lowest serum sodium level, between 125 and 129 mmol/L, as shown in Table 14.

Table 14 - Distribution of the lowest serum sodium level during hospitalisation among patients who developed hyponatremia during hospitalisation

<table>
<thead>
<tr>
<th>Serum sodium level (mmol/L)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;125</td>
<td>20.6</td>
</tr>
<tr>
<td>125–129</td>
<td>45.1</td>
</tr>
<tr>
<td>130–134</td>
<td>34.3</td>
</tr>
</tbody>
</table>
Figures 11 and 12 show the depletion of serum sodium levels among patients with HAH and PH respectively. Among patients with HAH, the mean of serum sodium depletion was $7.8 \pm 3.8$ and significantly sharper ($p < 0.001$) than patients with PH, which was $3.1 \pm 2.4$ mmol/L.

**Figure 11** - Depletion serum sodium level in patients who developed hospital-acquired hyponatremia

**Figure 12** – Depletion of serum sodium level in patients encountering persistent hyponatremia
Two clinical outcomes were assessed in relation to hyponatremia during hospitalisation: hospital length of stay and in-hospital mortality. Patients who developed hyponatremia during hospitalisation showed a significantly longer length of hospital stay ($p = 0.002$) compared to patients without hyponatremia, with the median and interquartile range at 11(7) and 8(7) days respectively. In-hospital mortality rate was also observed to be significantly higher ($p < 0.001$) in hyponatremic patients compared to patients without hyponatremia, at 22.6% and 7.8% respectively.

The association between hyponatremia and clinical outcomes was assessed with logistic regression analysis. To put hyponatremia as an independent variable in logistic regression analysis, the hospital length of stay was converted into a dichotomous categorical scale with 11 days as the cut off (0 = hospital length of stay < 11 days, 1 = hospital length of stay $\geq$ 11 days). As shown in Table 15, hyponatremia during hospitalisation was significantly associated with both hospital length of stay and in-hospital mortality. The unadjusted OR for the longer hospital stay was 2.1 (95%CI [1.3–3.3]) meaning that the risk of a longer hospital stay among patients with hyponatremia during hospitalisation was two times higher compared to non-hyponatremic patients. These patients also had a higher risk of in-hospital mortality with three times higher than non-hyponatremic patients (unadjusted OR = 3.4, 95% CI [1.8–6.4]).

Table 15 - Association between hyponatremia during hospitalisation and clinical outcomes

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>$p$-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital length of stay</td>
<td>0.001</td>
<td>2.1</td>
<td>1.3–3.3</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>&lt;0.001</td>
<td>3.4</td>
<td>1.8–6.4</td>
</tr>
</tbody>
</table>
5.3. Patient characteristics

Tables 16–20 show the characteristics of the patients both in the control and case groups with regard to symptoms and vital signs at admission, medical history and medical problems concomitantly diagnosed at admission, clinical laboratory at admission and medications administered from admission until time of inclusion.

*Table 16 - Symptoms and vital signs at admission*

<table>
<thead>
<tr>
<th>No.</th>
<th>Symptom/vital sign</th>
<th>Non-hyponatremia</th>
<th>Hyponatremia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>History of dyspnea on effort</td>
<td>100%</td>
<td>100%</td>
<td>1.000</td>
</tr>
<tr>
<td>2</td>
<td>History of chronic fatigue</td>
<td>26.6%</td>
<td>51%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>History of orthopnea</td>
<td>69.9%</td>
<td>71.6%</td>
<td>0.754</td>
</tr>
<tr>
<td>4</td>
<td>History of PND</td>
<td>52%</td>
<td>58.8%</td>
<td>0.229</td>
</tr>
<tr>
<td>5</td>
<td>Chest pain</td>
<td>26.8%</td>
<td>20.6%</td>
<td>0.211</td>
</tr>
<tr>
<td>6</td>
<td>Peripheral pitting edema</td>
<td>61.4%</td>
<td>72.5%</td>
<td>0.043</td>
</tr>
<tr>
<td>7</td>
<td>Ascites</td>
<td>9.2%</td>
<td>21.6%</td>
<td>0.001</td>
</tr>
<tr>
<td>8</td>
<td>Cough</td>
<td>18.6%</td>
<td>18.6%</td>
<td>1.000</td>
</tr>
<tr>
<td>9</td>
<td>Nausea</td>
<td>14.7%</td>
<td>17.6%</td>
<td>0.477</td>
</tr>
<tr>
<td>10</td>
<td>Vomiting</td>
<td>7.5%</td>
<td>7.8%</td>
<td>0.914</td>
</tr>
<tr>
<td>11</td>
<td>Systolic blood pressure (mmHg)</td>
<td>122(34)</td>
<td>120(22)</td>
<td>0.122</td>
</tr>
<tr>
<td>12</td>
<td>Diastolic blood pressure (mmHg)</td>
<td>80(27)</td>
<td>80(19)</td>
<td>0.054</td>
</tr>
<tr>
<td>13</td>
<td>Heart rate (times/minute)</td>
<td>92(18)</td>
<td>97.5(25.5)</td>
<td>0.269</td>
</tr>
<tr>
<td>14</td>
<td>Respiratory rate (times/minute)</td>
<td>26(8)</td>
<td>28(10)</td>
<td>0.394</td>
</tr>
</tbody>
</table>

Note: PND = Paroxysmal nocturnal dyspnea

As listed in Table 16, all patients both in the case and control groups had a history of dyspnoea on effort prior to hospital admission. Whilst the history of orthopnoea and paroxysmal nocturnal dyspnoea in hyponatremic patients was not different from non-hyponatremic patients, the history of chronic fatigue was found significantly more frequently in hyponatremic patients ($p < 0.001$). More patients with hyponatremia had peripheral pitting edema at admission compared to non-hyponatremic patients ($p = 0.043$). Likewise, the proportion of patients presenting ascites at admission was
significantly higher among hyponatremic patients compared to non-hyponatremic patients ($p = 0.001$). Hyponatremic patients had slightly lower blood pressure at admission, both systolic and diastolic, but were not significantly different from non-hyponatremic patients.

In terms of medical history as listed in Table 17, only the history of hospitalisation from heart disease was found significantly higher among patients with hyponatremia compared to patients with non-hyponatremia, 52% and 40.5% respectively ($p = 0.044$). The proportion of patients with hypertension, diabetes mellitus, chronic obstructive pulmonary diseases (COPD) and asthma was slightly higher in hyponatremic patients but was not significantly different. While more non-hyponatremic patients had a history of stroke, more hyponatremic patients had history of pulmonary tuberculosis. However, the proportions were not significantly different.

### Table 17 - Medical history

<table>
<thead>
<tr>
<th>No.</th>
<th>Medical history</th>
<th>Non-hyponatremia (%)</th>
<th>Hyponatremia (%)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypertension</td>
<td>52.3</td>
<td>59.8</td>
<td>0.187</td>
</tr>
<tr>
<td>2</td>
<td>Diabetes mellitus</td>
<td>23.9</td>
<td>24.5</td>
<td>0.894</td>
</tr>
<tr>
<td>3</td>
<td>COPD</td>
<td>4.6</td>
<td>7.8</td>
<td>0.206</td>
</tr>
<tr>
<td>4</td>
<td>Asthma</td>
<td>2.4</td>
<td>3.6</td>
<td>0.545</td>
</tr>
<tr>
<td>5</td>
<td>History of stroke</td>
<td>4.6</td>
<td>2</td>
<td>0.239</td>
</tr>
<tr>
<td>6</td>
<td>History of pulmonary tuberculosis</td>
<td>4.6</td>
<td>7.8</td>
<td>0.206</td>
</tr>
<tr>
<td>7</td>
<td>Hospitalisation from heart diseases</td>
<td>40.5</td>
<td>52</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Note: COPD = chronic obstructive pulmonary diseases

Table 18 lists the same medical problems concomitantly diagnosed at admission in both hyponatremic and non-hyponatremic patients. Whilst AF was found at the same rate in both groups, renal failure was diagnosed significantly more frequently among
hyponatremic patients ($p < 0.001$). Ventricular arrhythmia was diagnosed in almost
the same rate in both groups, and unspecified infections were diagnosed more
frequently among hyponatremic patients, but the rates were not significantly
different ($p = 0.498$).

**Table 18 - Medical problems concomitantly diagnosed at during admission**

<table>
<thead>
<tr>
<th>No.</th>
<th>Medical history</th>
<th>Non-hyponatremia (%)</th>
<th>Hyponatremia (%)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atrial fibrillation</td>
<td>12.7</td>
<td>12.7</td>
<td>1.000</td>
</tr>
<tr>
<td>2</td>
<td>Ventricular arrhythmia</td>
<td>5.6</td>
<td>5.9</td>
<td>0.901</td>
</tr>
<tr>
<td>3</td>
<td>Renal failure</td>
<td>17</td>
<td>33.3</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>4</td>
<td>Unspecified infections</td>
<td>18</td>
<td>26.5</td>
<td>0.064</td>
</tr>
</tbody>
</table>

Table 19 shows the clinical laboratory profiles of both hyponatremic and non-
hyponatremic patients obtained during admission. As presented previously, serum
sodium levels among hyponatremic patients were significantly lower compared to
non-hyponatremic patients ($p < 0.001$). As associated anion of sodium, the chloride
level was also found significantly lower among hyponatremic patients ($p < 0.001$).
Other than creatinine and albumin, the rest of the blood chemistries at admission
were not significantly different between hyponatremic and non-hyponatremic
patients. Among hyponatremic patients, serum creatinine was significantly higher
compared to non-hyponatremic patients. Although ureum level was found slightly
higher among hyponatremic patients, it was not significantly different ($p = 0.057$).
These findings might correlate with the higher prevalence of renal failure diagnosed
at admission among hyponatremic patients, as presented previously. The means of
serum albumin in both groups were lower than normal range (3.5–5.5 g/dL) and the
mean among hyponatremic patients was significantly lower than non-hyponatremic
patients.
Table 19 - Profile of blood chemistry at admission

<table>
<thead>
<tr>
<th>No.</th>
<th>Blood chemistry</th>
<th>Non-hyponatremia</th>
<th>Hyponatremia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sodium (mmol/L)</td>
<td>140 ± 4.5</td>
<td>133 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Potassium (mmol/L)</td>
<td>4.5 ± 0.9</td>
<td>4.3 ± 0.9</td>
<td>0.759</td>
</tr>
<tr>
<td>3</td>
<td>Chloride (mmol/L)</td>
<td>103 ± 7.7</td>
<td>96 ± 8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>Glucose (mg/dL)</td>
<td>142 ± 71</td>
<td>137 ± 75</td>
<td>0.545</td>
</tr>
<tr>
<td>5</td>
<td>Uric acid (mg/dL)</td>
<td>9.3 ± 4.7</td>
<td>9.1 ± 3.1</td>
<td>0.661</td>
</tr>
<tr>
<td>6</td>
<td>Urea (mg/dL)</td>
<td>65 ± 30</td>
<td>73 ± 51</td>
<td>0.057</td>
</tr>
<tr>
<td>7</td>
<td>Creatinine (mg/dL)</td>
<td>1.4 ± 1.1</td>
<td>1.7 ± 1.4</td>
<td>0.020</td>
</tr>
<tr>
<td>8</td>
<td>Total cholesterol (mg/dL)</td>
<td>157 ± 41</td>
<td>154 ± 26</td>
<td>0.479</td>
</tr>
<tr>
<td>9</td>
<td>High density lipoprotein (mg/dL)</td>
<td>35 ± 15.2</td>
<td>33 ± 7.1</td>
<td>0.222</td>
</tr>
<tr>
<td>10</td>
<td>Total protein (g/dL)</td>
<td>6.5 ± 0.8</td>
<td>6.4 ± 1.1</td>
<td>0.095</td>
</tr>
<tr>
<td>11</td>
<td>Albumin (g/dL)</td>
<td>3.4 ± 0.5</td>
<td>3.1 ± 0.4</td>
<td>0.002</td>
</tr>
<tr>
<td>12</td>
<td>Globulin (g/dL)</td>
<td>3.2 ± 0.6</td>
<td>3.2 ± 0.6</td>
<td>0.198</td>
</tr>
<tr>
<td>13</td>
<td>Hemoglobin (g/dL)</td>
<td>12.9 ± 2.5</td>
<td>12.8 ± 2.3</td>
<td>0.742</td>
</tr>
<tr>
<td>14</td>
<td>Hematocrit (%)</td>
<td>40 ± 8.1</td>
<td>40 ± 6.9</td>
<td>0.784</td>
</tr>
<tr>
<td>15</td>
<td>White blood cell (x10^6/L)</td>
<td>9180 ± 3696</td>
<td>10.170 ± 5351</td>
<td>0.612</td>
</tr>
<tr>
<td>16</td>
<td>Thrombocyte (x10^9/L)</td>
<td>261 ± 102</td>
<td>256 ± 115</td>
<td>0.392</td>
</tr>
<tr>
<td>17</td>
<td>AST (IU/L)</td>
<td>34(28)</td>
<td>41(57)</td>
<td>0.137</td>
</tr>
<tr>
<td>18</td>
<td>ALT (IU/L)</td>
<td>26(33)</td>
<td>34(71)</td>
<td>0.253</td>
</tr>
</tbody>
</table>

Note: AST = aspartate amino-transferase; ALT = alanine amino-transferase

Medication administered to hyponatremic patients during admission until inclusion time, and the same medications administered to non-hyponatremic patients during admission are listed in Table 20. Furosemide was administered to both hyponatremic and non-hyponatremic patients at the same rate. More patients in the hyponatremic group received sparing diuretic, 29.4% and 25.8% respectively, but it was not significantly different (p = 0.477). ACE inhibitors were administered at a significantly lower rate into hyponatremic patients compared to non-hyponatremic patients, 64.7% versus 77.8% respectively (p = 0.009). A potassium supplement, commonly prescribed to avoid the occurrence of potassium serum depletion.
associated with the administration of loop diuretics, was administered to both hyponatremic and non-hyponatremic patients in a non-significantly different rate.

More patients in the hyponatremic group received amiodarone, 22.5% versus 15.7%, but its prescription rates were not significantly different between the groups. While digoxin was prescribed in almost the same rate to both hyponatremic and non-hyponatremic patients, more patients in the hyponatremic group received positive inotropes compared to non-hyponatremic patients, 30.4% versus 8.5% respectively ($p < 0.001$). Organic nitrates, calcium channel blockers (CCBs), beta blockers and ubiquinone were prescribed in lower rates to hyponatremic patients, but the prescription rates were not significantly different from non-hyponatremic patients. Aspirin, clopidogrel, simvastatin and warfarin were also prescribed to both hyponatremic and non-hyponatremic patients in non-significantly different rates. More patients in the hyponatremic group received heparin compared to non-hyponatremic patients, 18.6% versus 9.5% respectively ($p = 0.013$).

Other than medications administered to treat the main problems associated with HF, some medications listed in Table 20 were administered to manage medical problems indirectly associated with HF. Laxative agents, proton pump inhibitors and histamine-2 receptor antagonists are medications commonly prescribed to manage gastrointestinal problems, and these medications were administered to both hyponatremic and non-hyponatremic patients in non-significantly different rates. A combination of albuterol/ipratropium is commonly prescribed to manage respiratory problems, and both hyponatremic and non-hyponatremic patients in this research received this combination in non-significantly different rates.

Patients in both groups also received medications to control blood glucose level, oral antidiabetics and insulin. The proportion of patients receiving oral antidiabetics in
both hyponatremic and non-hyponatremic groups was almost the same, 5.9% and 6.2% respectively, and although the proportion of patients receiving insulin in the hyponatremic group was higher, it was not significantly different from non-hyponatremic patients \( (p = 0.124) \). Antibiotics were prescribed to hyponatremic patients in a significantly higher rate compared to non-hyponatremic patients, 71.6% versus 34% respectively \( (0.001) \).
### Table 20 - Medications administered during admission

<table>
<thead>
<tr>
<th>No.</th>
<th>Medication</th>
<th>Non-hyponatremia (%)</th>
<th>Hyponatremia (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Furosemide</td>
<td>95.1</td>
<td>95.1</td>
<td>1.000</td>
</tr>
<tr>
<td>2</td>
<td>ACE inhibitors</td>
<td>77.8</td>
<td>64.7</td>
<td>0.009</td>
</tr>
<tr>
<td>3</td>
<td>Sparing diuretics</td>
<td>25.8</td>
<td>29.4</td>
<td>0.477</td>
</tr>
<tr>
<td>4</td>
<td>Potassium supplements</td>
<td>56.2</td>
<td>53.9</td>
<td>0.687</td>
</tr>
<tr>
<td>5</td>
<td>Amiodarone</td>
<td>15.7</td>
<td>22.5</td>
<td>0.113</td>
</tr>
<tr>
<td>6</td>
<td>Positive inotropes</td>
<td>8.5</td>
<td>30.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7</td>
<td>Organic nitrates</td>
<td>60.5</td>
<td>54.9</td>
<td>0.323</td>
</tr>
<tr>
<td>8</td>
<td>Digoxin</td>
<td>26.1</td>
<td>26.5</td>
<td>0.948</td>
</tr>
<tr>
<td>9</td>
<td>Aspirin</td>
<td>50.5</td>
<td>43.1</td>
<td>0.208</td>
</tr>
<tr>
<td>10</td>
<td>Clopidogrel</td>
<td>28.4</td>
<td>33.3</td>
<td>0.348</td>
</tr>
<tr>
<td>11</td>
<td>Simvastatin</td>
<td>47.4</td>
<td>41.2</td>
<td>0.276</td>
</tr>
<tr>
<td>12</td>
<td>Warfarin</td>
<td>25.8</td>
<td>21.6</td>
<td>0.389</td>
</tr>
<tr>
<td>13</td>
<td>Heparin</td>
<td>9.5</td>
<td>18.6</td>
<td>0.013</td>
</tr>
<tr>
<td>14</td>
<td>Ubiquinone</td>
<td>16.4</td>
<td>10.8</td>
<td>0.169</td>
</tr>
<tr>
<td>15</td>
<td>Calcium channel blockers</td>
<td>14.4</td>
<td>8.8</td>
<td>0.148</td>
</tr>
<tr>
<td>16</td>
<td>Beta blockers</td>
<td>14.4</td>
<td>9.8</td>
<td>0.238</td>
</tr>
<tr>
<td>17</td>
<td>Laxative agents</td>
<td>39.9</td>
<td>38.2</td>
<td>0.770</td>
</tr>
<tr>
<td>18</td>
<td>Proton pump inhibitors</td>
<td>15</td>
<td>22.5</td>
<td>0.079</td>
</tr>
<tr>
<td>19</td>
<td>H$_2$ receptor antagonists</td>
<td>21.9</td>
<td>30.4</td>
<td>0.082</td>
</tr>
<tr>
<td>20</td>
<td>Allopurinol</td>
<td>19.3</td>
<td>20.6</td>
<td>0.773</td>
</tr>
<tr>
<td>21</td>
<td>Benzodiazepines</td>
<td>21.2</td>
<td>22.5</td>
<td>0.781</td>
</tr>
<tr>
<td>22</td>
<td>Albuterol + ipratoprium</td>
<td>9.8</td>
<td>15.7</td>
<td>0.104</td>
</tr>
<tr>
<td>23</td>
<td>Insulin</td>
<td>8.5</td>
<td>13.7</td>
<td>0.124</td>
</tr>
<tr>
<td>24</td>
<td>Oral antidiabetic</td>
<td>6.2</td>
<td>5.9</td>
<td>0.905</td>
</tr>
<tr>
<td>25</td>
<td>Antibiotics</td>
<td>34</td>
<td>71.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: ACE = angiotensin converting enzyme

### 5.4. Management of hyponatremia

Investigation of the management of hyponatremia in this research was intended to provide a general snapshot on treatments delivered to resolve hyponatremia. Given that data were collected retrospectively, information obtained on this issue is limited. Distribution of the treatment type administered to hyponatremic patients is presented...
in Figure 13, showing that more than half of hyponatremic patients did not receive specific treatment, meaning that no treatment options commonly administered to resolve hyponatremia were delivered to this group of hyponatremic patients. Among patients receiving treatment, only sodium chloride-based treatments were administered: sodium chloride solution 0.9% (normal saline), sodium chloride solution 3% (hypertonic saline) and sodium chloride capsule. Normal saline is commonly administered to patients with mild hyponatremia – serum sodium level 130–134 mmol/L – and it was administered to 20.6% of hyponatremic patients in this study, higher than hypertonic saline and sodium chloride capsule, which was administered to 12.7% and 7.8% hyponatremic patients respectively.

![Figure 13 - Distribution of treatment options administered to hyponatremic patients](image)

The main group of patients with the lowest serum level during hospitalisation receiving no treatment (71.4%) were those classified as having mild hyponatremia, as shown in Table 21. Although hypertonic saline is commonly recommended as a treatment option for patients with moderate–severe hyponatremia, 8.6% of patients with mild hyponatremia received this treatment option. Meanwhile, only 33% and 6.5% of patients with severe and moderate hyponatremia respectively received
hypertonic saline treatment. Most patients with moderate hyponatremia received normal saline solution (28.3%) and, other than hypertonic saline, which was administered to one third of patients, 19.1% of patients with severe hyponatremia received a sodium chloride capsule.

Table 21 - Distribution of treatment options administered to hyponatremic patients based on serum sodium level

<table>
<thead>
<tr>
<th>Lowest sodium level (mmol/L)</th>
<th>Number of patients</th>
<th>Percentage of patients receiving treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NaCl 0.9%</td>
</tr>
<tr>
<td>&lt;125</td>
<td>21</td>
<td>9.5</td>
</tr>
<tr>
<td>125–129</td>
<td>46</td>
<td>28.3</td>
</tr>
<tr>
<td>130–134</td>
<td>35</td>
<td>17.1</td>
</tr>
</tbody>
</table>

In order to achieve a therapeutic effect as well as to minimise the risk of adverse effect, infusion rate is an important aspect of treatment that needs to be considered when administering sodium chloride solution for resolving hyponatremia, especially for hypertonic saline. However, it was difficult to find specific information on the infusion rate and only general information was found on the administration of sodium chloride. While normal saline solutions were administered with an infusion rate of 500ml/24hours and 500ml/12hours, all hypertonic saline was administered with an infusion rate of 500ml/24hours. Most oral sodium chlorides, administered as sodium chloride capsules, were administered with a dosage of 3x500mg/day.

5.5. Derivation of the prediction model

To derive a PM with good performance, the selection of the predictors to be included is paramount. In this research the selection of predictors was performed mainly by following the purposeful selection method as proposed by Hosmer et al. (2013), which involves seven steps to conclude the final model.
According to the purposeful selection method, the first step is to screen potential predictors by performing univariate analysis. Following this step, all variables listed in Tables 16–20 were analysed except for variables with $p$-value = 1, indicating that the value of such predictors in hyponatremic and non-hyponatremic patients were exactly the same. Univariate analysis was performed by logistic regression both for continuous and categorical variables using IBM® SPSS software version 22.

Although Hosmer et al. (2013) recommends selecting predictors resulting in $p$-values of <0.2 or <0.25 from univariate analysis for inclusion in the next step of multivariate analysis, a $p$-value of <0.05 was used in this research. Table 23 lists 17 predictors with $p$-value <0.05 resulting from univariate logistic regression analysis, and one predictor – administration of insulin – with $p$-value >0.05, but it was included in the initial multivariate analysis because it was reported by a previous study to be a risk in developing hyponatremia [320]. Hence, in the second step, a total of 18 predictors as listed in Table 22 were included in the multivariate logistic regression analysis.
Table 22 - Predictors with p-value <0.05 resulting from univariate logistic regression and predictors previously reported as risk factors for hyponatremia

<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>History of fatigue</td>
<td>1.389</td>
<td>0.243</td>
<td>32.586</td>
<td>&lt;0.001</td>
<td>4.01</td>
<td>2.49</td>
</tr>
<tr>
<td>2</td>
<td>Peripheral pitting edema</td>
<td>0.506</td>
<td>0.251</td>
<td>4.064</td>
<td>0.044</td>
<td>1.66</td>
<td>1.01</td>
</tr>
<tr>
<td>3</td>
<td>Ascites</td>
<td>1.004</td>
<td>0.312</td>
<td>10.372</td>
<td>0.001</td>
<td>2.73</td>
<td>1.48</td>
</tr>
<tr>
<td>4</td>
<td>Hypertension</td>
<td>-0.639</td>
<td>0.242</td>
<td>6.953</td>
<td>0.008</td>
<td>0.53</td>
<td>0.33</td>
</tr>
<tr>
<td>5</td>
<td>Hospitalisation from heart disease</td>
<td>0.462</td>
<td>0.230</td>
<td>4.043</td>
<td>0.044</td>
<td>1.59</td>
<td>1.01</td>
</tr>
<tr>
<td>6</td>
<td>Diastolic blood pressure</td>
<td>-0.024</td>
<td>0.008</td>
<td>9.594</td>
<td>0.002</td>
<td>0.98</td>
<td>0.96</td>
</tr>
<tr>
<td>7</td>
<td>Renal failure</td>
<td>0.893</td>
<td>0.259</td>
<td>11.850</td>
<td>0.001</td>
<td>2.44</td>
<td>1.47</td>
</tr>
<tr>
<td>8</td>
<td>ACE inhibitors</td>
<td>-0.647</td>
<td>0.249</td>
<td>0.853</td>
<td>0.009</td>
<td>0.52</td>
<td>0.32</td>
</tr>
<tr>
<td>9</td>
<td>Positive inotropes</td>
<td>1.548</td>
<td>0.297</td>
<td>4.702</td>
<td>&lt;0.001</td>
<td>4.71</td>
<td>2.63</td>
</tr>
<tr>
<td>10</td>
<td>Heparin</td>
<td>0.782</td>
<td>0.321</td>
<td>5.955</td>
<td>0.015</td>
<td>2.19</td>
<td>1.17</td>
</tr>
<tr>
<td>11</td>
<td>Insulin</td>
<td>0.538</td>
<td>0.353</td>
<td>2.322</td>
<td>0.128</td>
<td>1.71</td>
<td>0.86</td>
</tr>
<tr>
<td>12</td>
<td>Antibiotics</td>
<td>1.587</td>
<td>0.250</td>
<td>40.140</td>
<td>&lt;0.001</td>
<td>4.89</td>
<td>2.99</td>
</tr>
<tr>
<td>13</td>
<td>Sodium</td>
<td>-0.254</td>
<td>0.029</td>
<td>75.253</td>
<td>&lt;0.001</td>
<td>0.78</td>
<td>0.73</td>
</tr>
<tr>
<td>14</td>
<td>Ureum</td>
<td>0.015</td>
<td>0.003</td>
<td>24.646</td>
<td>&lt;0.001</td>
<td>1.02</td>
<td>1.01</td>
</tr>
<tr>
<td>15</td>
<td>Creatinine</td>
<td>0.199</td>
<td>0.090</td>
<td>4.885</td>
<td>0.027</td>
<td>1.22</td>
<td>1.02</td>
</tr>
<tr>
<td>16</td>
<td>Albumin</td>
<td>-0.770</td>
<td>0.248</td>
<td>9.646</td>
<td>0.002</td>
<td>0.46</td>
<td>0.29</td>
</tr>
<tr>
<td>17</td>
<td>AST</td>
<td>0.802</td>
<td>0.253</td>
<td>10.044</td>
<td>0.002</td>
<td>2.23</td>
<td>1.36</td>
</tr>
<tr>
<td>18</td>
<td>ALT</td>
<td>0.730</td>
<td>0.233</td>
<td>9.789</td>
<td>0.002</td>
<td>2.07</td>
<td>1.31</td>
</tr>
</tbody>
</table>

Note: SE = standard error; CI = confidence interval; ACE = angiotensin converting enzymes interval; AST = aspartate amino-transferase; ALT = alanine amino-transferase

Table 23 shows a summary of output resulting from multivariate logistic regression in which six predictors out of 18 included in the analysis have p-value <0.05: history of fatigue (p < 0.001), presence of ascites at admission (p = 0.002), administration of positive inotropes (p = 0.011), heparin (p = 0.024) and antibiotics (p = 0.001), and sodium level at admission (p < 0.001).
Table 23 - Result of multivariate logistic regression analysis including significant predictors from univariate analysis

<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>History of fatigue</td>
<td>1.394</td>
<td>0.338</td>
<td>16.999</td>
<td>&lt;0.001</td>
<td>4.03</td>
<td>2.08 - 7.82</td>
</tr>
<tr>
<td>2</td>
<td>Peripheral pitting edema</td>
<td>0.381</td>
<td>0.382</td>
<td>0.995</td>
<td>0.319</td>
<td>1.46</td>
<td>0.69 - 3.09</td>
</tr>
<tr>
<td>3</td>
<td>Ascites</td>
<td>1.523</td>
<td>0.491</td>
<td>9.635</td>
<td>0.002</td>
<td>4.59</td>
<td>1.75 - 12.00</td>
</tr>
<tr>
<td>4</td>
<td>Hypertension</td>
<td>0.658</td>
<td>0.354</td>
<td>3.468</td>
<td>0.063</td>
<td>1.93</td>
<td>0.97 - 3.86</td>
</tr>
<tr>
<td>5</td>
<td>Previous hospitalisation from heart diseases</td>
<td>0.122</td>
<td>0.332</td>
<td>0.134</td>
<td>0.715</td>
<td>1.13</td>
<td>0.59 - 2.17</td>
</tr>
<tr>
<td>6</td>
<td>Diastolic blood pressure</td>
<td>–0.019</td>
<td>0.11</td>
<td>2.664</td>
<td>0.103</td>
<td>0.98</td>
<td>0.96 - 1.00</td>
</tr>
<tr>
<td>7</td>
<td>Renal failure</td>
<td>0.616</td>
<td>0.480</td>
<td>1.646</td>
<td>0.200</td>
<td>1.85</td>
<td>0.72 - 4.74</td>
</tr>
<tr>
<td>8</td>
<td>ACE inhibitors</td>
<td>–0.400</td>
<td>0.378</td>
<td>1.120</td>
<td>0.290</td>
<td>0.67</td>
<td>0.32 - 1.40</td>
</tr>
<tr>
<td>9</td>
<td>Positive inotropes</td>
<td>1.131</td>
<td>0.443</td>
<td>6.517</td>
<td>0.011</td>
<td>3.09</td>
<td>1.30 - 7.38</td>
</tr>
<tr>
<td>10</td>
<td>Heparin</td>
<td>1.026</td>
<td>0.454</td>
<td>5.112</td>
<td>0.024</td>
<td>2.79</td>
<td>1.15 - 6.79</td>
</tr>
<tr>
<td>11</td>
<td>Insulin</td>
<td>0.021</td>
<td>0.472</td>
<td>0.002</td>
<td>0.965</td>
<td>1.02</td>
<td>0.41 - 2.58</td>
</tr>
<tr>
<td>12</td>
<td>Antibiotics</td>
<td>1.062</td>
<td>0.329</td>
<td>10.398</td>
<td>0.001</td>
<td>2.89</td>
<td>1.52 - 5.52</td>
</tr>
<tr>
<td>13</td>
<td>Sodium</td>
<td>–0.250</td>
<td>0.038</td>
<td>43.818</td>
<td>&lt;0.001</td>
<td>0.78</td>
<td>0.72 - 0.84</td>
</tr>
<tr>
<td>14</td>
<td>Ureum</td>
<td>–0.007</td>
<td>0.006</td>
<td>1.679</td>
<td>0.195</td>
<td>0.99</td>
<td>0.98 - 1.00</td>
</tr>
<tr>
<td>15</td>
<td>Creatinine</td>
<td>0.272</td>
<td>0.142</td>
<td>3.677</td>
<td>0.055</td>
<td>1.31</td>
<td>0.99 - 1.73</td>
</tr>
<tr>
<td>16</td>
<td>Albumin</td>
<td>0.112</td>
<td>0.361</td>
<td>0.097</td>
<td>0.756</td>
<td>1.12</td>
<td>0.55 - 2.27</td>
</tr>
<tr>
<td>17</td>
<td>AST</td>
<td>–1.111</td>
<td>0.816</td>
<td>1.854</td>
<td>0.173</td>
<td>0.33</td>
<td>0.07 - 1.63</td>
</tr>
<tr>
<td>18</td>
<td>ALT</td>
<td>1.308</td>
<td>0.764</td>
<td>2.929</td>
<td>0.087</td>
<td>3.70</td>
<td>0.83 - 16.53</td>
</tr>
</tbody>
</table>

Note: SE = standard error; OR = odds ratio; CI = confidence interval; ACE = angiotensin converting enzymes interval; AST = aspartate amino-transferase; ALT = alanine amino-transferase

Subsequently, these six predictors were included in the next multivariate logistic regression analysis including only these six predictors; the output summary of the analysis is presented in Table 24. Although a previous study reported that administration of insulin is one risk factor for developing hyponatremia, it was not significantly associated with hyponatremia based on the result of multivariate analysis performed in this research, so it was not included in the next step.
Table 24 - Significant predictors included in smaller model resulted from the second multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue</td>
<td>1.312</td>
<td>0.316</td>
<td>17.189</td>
<td>&lt;0.001</td>
<td>3.71</td>
<td>1.99</td>
</tr>
<tr>
<td>2</td>
<td>Ascites</td>
<td>1.316</td>
<td>0.449</td>
<td>8.578</td>
<td>0.003</td>
<td>3.73</td>
<td>1.55</td>
</tr>
<tr>
<td>3</td>
<td>Positive inotropes</td>
<td>1.082</td>
<td>0.390</td>
<td>7.718</td>
<td>0.005</td>
<td>2.95</td>
<td>1.38</td>
</tr>
<tr>
<td>4</td>
<td>Heparin</td>
<td>1.092</td>
<td>0.410</td>
<td>7.085</td>
<td>0.008</td>
<td>2.98</td>
<td>1.33</td>
</tr>
<tr>
<td>5</td>
<td>Antibiotics</td>
<td>1.054</td>
<td>0.312</td>
<td>11.447</td>
<td>0.001</td>
<td>2.87</td>
<td>1.56</td>
</tr>
<tr>
<td>6</td>
<td>Sodium</td>
<td>–0.256</td>
<td>0.035</td>
<td>54.437</td>
<td>&lt;0.001</td>
<td>0.77</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Note: SE = standard error; OR = odds ratio; CI = confidence interval

After identifying significant predictors in the smaller model resulting from multivariate analysis, the third step was performed to identify any important predictor that was excluded from this smaller model. This step was performed by comparing the regression coefficient of each predictor included in the smaller model with the regression coefficient resulting from the large model in the previous analysis. Any predictor with a regression coefficient that has changed >20% should be further analysed because it indicates that important predictors have been excluded from the smaller model. As presented in Table 25, regression coefficients of all predictors included in the smaller model have changed, but none of the coefficients has changed >20%, indicating that none of the important predictors has been omitted from the smaller model.
The fourth step of the purposeful selection method is to add each predictor not included in the initial large model into the smaller model, including the six predictors. One predictor was added at a time and its contribution significance to the model was assessed by the resulting $p$-value. Table 26 lists all predictors that were not included in the initial large model and associated $p$-value of each predictor when added to smaller model. As listed in Table 25, there is no predictor having $p$-value <0.05, indicating that all listed predictors do not significantly contribute to the model.
<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Vomiting</td>
<td>–0.343</td>
<td>0.551</td>
<td>0.388</td>
<td>0.533</td>
<td>0.71</td>
<td>0.24 2.08</td>
</tr>
<tr>
<td>9</td>
<td>Cough</td>
<td>0.246</td>
<td>0.389</td>
<td>0.402</td>
<td>0.526</td>
<td>1.28</td>
<td>0.59 2.74</td>
</tr>
<tr>
<td>10</td>
<td>Diabetes mellitus</td>
<td>–0.034</td>
<td>0.349</td>
<td>0.009</td>
<td>0.923</td>
<td>0.97</td>
<td>0.49 1.92</td>
</tr>
<tr>
<td>11</td>
<td>Stroke</td>
<td>0.354</td>
<td>0.834</td>
<td>0.180</td>
<td>0.672</td>
<td>1.42</td>
<td>0.28 7.31</td>
</tr>
<tr>
<td>12</td>
<td>Asthma</td>
<td>–0.101</td>
<td>1.175</td>
<td>0.007</td>
<td>0.932</td>
<td>0.91</td>
<td>0.09 0.04</td>
</tr>
<tr>
<td>13</td>
<td>COPD</td>
<td>0.324</td>
<td>0.672</td>
<td>0.232</td>
<td>0.630</td>
<td>1.38</td>
<td>0.37 5.16</td>
</tr>
<tr>
<td>14</td>
<td>Tuberculosis</td>
<td>–0.196</td>
<td>0.619</td>
<td>0.100</td>
<td>0.752</td>
<td>0.82</td>
<td>0.24 2.77</td>
</tr>
<tr>
<td>15</td>
<td>Atrial fibrillation</td>
<td>0.341</td>
<td>0.467</td>
<td>0.532</td>
<td>0.466</td>
<td>1.41</td>
<td>0.56 3.51</td>
</tr>
<tr>
<td>16</td>
<td>Ventricular arrhythmia</td>
<td>0.222</td>
<td>0.605</td>
<td>0.134</td>
<td>0.714</td>
<td>1.25</td>
<td>0.38 4.09</td>
</tr>
<tr>
<td>17</td>
<td>Unspecific infection</td>
<td>–0.355</td>
<td>0.660</td>
<td>0.258</td>
<td>0.612</td>
<td>0.72</td>
<td>0.19 2.61</td>
</tr>
<tr>
<td>18</td>
<td>Sparing diuretics</td>
<td>0.161</td>
<td>0.353</td>
<td>0.208</td>
<td>0.649</td>
<td>1.18</td>
<td>0.59 2.35</td>
</tr>
<tr>
<td>19</td>
<td>Potassium supplements</td>
<td>0.155</td>
<td>0.313</td>
<td>0.245</td>
<td>0.621</td>
<td>1.17</td>
<td>0.63 2.15</td>
</tr>
<tr>
<td>20</td>
<td>Organic nitrates</td>
<td>0.352</td>
<td>0.331</td>
<td>1.129</td>
<td>0.228</td>
<td>1.42</td>
<td>0.74 2.72</td>
</tr>
<tr>
<td>21</td>
<td>Amiodarone</td>
<td>0.452</td>
<td>0.383</td>
<td>1.393</td>
<td>0.238</td>
<td>1.57</td>
<td>0.74 3.33</td>
</tr>
<tr>
<td>22</td>
<td>Ubiquinone</td>
<td>–0.059</td>
<td>0.449</td>
<td>0.017</td>
<td>0.896</td>
<td>0.94</td>
<td>0.39 2.27</td>
</tr>
<tr>
<td>23</td>
<td>CCB</td>
<td>–0.067</td>
<td>0.527</td>
<td>0.016</td>
<td>0.898</td>
<td>0.94</td>
<td>0.33 2.63</td>
</tr>
<tr>
<td>24</td>
<td>Digoxin</td>
<td>0.101</td>
<td>0.355</td>
<td>0.082</td>
<td>0.775</td>
<td>1.11</td>
<td>0.55 2.22</td>
</tr>
<tr>
<td>25</td>
<td>Aspirin</td>
<td>–0.330</td>
<td>0.337</td>
<td>0.959</td>
<td>0.327</td>
<td>0.72</td>
<td>0.37 1.39</td>
</tr>
<tr>
<td>26</td>
<td>Clopidogrel</td>
<td>0.229</td>
<td>0.368</td>
<td>0.388</td>
<td>0.534</td>
<td>1.26</td>
<td>0.61 2.59</td>
</tr>
<tr>
<td>27</td>
<td>Simvastatin</td>
<td>–0.007</td>
<td>0.321</td>
<td>0.000</td>
<td>0.983</td>
<td>0.99</td>
<td>0.53 1.86</td>
</tr>
<tr>
<td>28</td>
<td>Warfarin</td>
<td>–0.094</td>
<td>0.367</td>
<td>0.065</td>
<td>0.798</td>
<td>0.91</td>
<td>0.44 1.87</td>
</tr>
<tr>
<td>29</td>
<td>Beta blockers</td>
<td>–0.736</td>
<td>0.526</td>
<td>1.962</td>
<td>0.161</td>
<td>0.48</td>
<td>0.17 1.34</td>
</tr>
<tr>
<td>30</td>
<td>Laxative agents</td>
<td>–0.316</td>
<td>0.320</td>
<td>0.973</td>
<td>0.324</td>
<td>0.73</td>
<td>0.39 1.37</td>
</tr>
<tr>
<td>31</td>
<td>PPI</td>
<td>–0.016</td>
<td>0.392</td>
<td>0.002</td>
<td>0.968</td>
<td>0.99</td>
<td>0.46 2.12</td>
</tr>
<tr>
<td>32</td>
<td>H2RA</td>
<td>0.062</td>
<td>0.342</td>
<td>0.033</td>
<td>0.856</td>
<td>1.06</td>
<td>0.55 2.08</td>
</tr>
<tr>
<td>33</td>
<td>Albuterol + ipratropium</td>
<td>–0.070</td>
<td>0.461</td>
<td>0.023</td>
<td>0.880</td>
<td>0.93</td>
<td>0.38 2.30</td>
</tr>
<tr>
<td>34</td>
<td>Allopurinol</td>
<td>0.192</td>
<td>0.374</td>
<td>0.263</td>
<td>0.608</td>
<td>1.21</td>
<td>0.58 2.52</td>
</tr>
<tr>
<td>35</td>
<td>Benzodiazepines</td>
<td>0.172</td>
<td>0.363</td>
<td>0.223</td>
<td>0.637</td>
<td>1.19</td>
<td>0.58 2.42</td>
</tr>
<tr>
<td>36</td>
<td>Oral antidiabetics</td>
<td>–0.168</td>
<td>0.621</td>
<td>0.073</td>
<td>0.787</td>
<td>0.85</td>
<td>0.25 2.85</td>
</tr>
<tr>
<td>No.</td>
<td>Independent variable</td>
<td>Regression coefficient</td>
<td>SE</td>
<td>Wald statistic</td>
<td>p-value</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----</td>
<td>---------------</td>
<td>---------</td>
<td>----</td>
<td>--------</td>
</tr>
<tr>
<td>37</td>
<td>Potassium</td>
<td>–0.008</td>
<td>0.029</td>
<td>0.077</td>
<td>0.782</td>
<td>0.99</td>
<td>0.94 1.05</td>
</tr>
<tr>
<td>38</td>
<td>Blood glucose</td>
<td>–0.003</td>
<td>0.002</td>
<td>2.44</td>
<td>0.118</td>
<td>0.99</td>
<td>0.99 1.00</td>
</tr>
<tr>
<td>39</td>
<td>Total protein</td>
<td>0.037</td>
<td>0.167</td>
<td>0.049</td>
<td>0.825</td>
<td>1.04</td>
<td>0.75 1.44</td>
</tr>
<tr>
<td>40</td>
<td>Globulin</td>
<td>0.274</td>
<td>0.259</td>
<td>1.115</td>
<td>0.291</td>
<td>1.32</td>
<td>0.79 2.19</td>
</tr>
<tr>
<td>41</td>
<td>Total cholesterol</td>
<td>–0.002</td>
<td>0.004</td>
<td>0.452</td>
<td>0.502</td>
<td>0.99</td>
<td>0.99 1.01</td>
</tr>
<tr>
<td>42</td>
<td>HDL</td>
<td>0.005</td>
<td>0.013</td>
<td>0.151</td>
<td>0.698</td>
<td>1.01</td>
<td>0.98 1.03</td>
</tr>
<tr>
<td>43</td>
<td>Uric acid</td>
<td>–0.048</td>
<td>0.061</td>
<td>0.607</td>
<td>0.436</td>
<td>0.95</td>
<td>0.85 1.08</td>
</tr>
<tr>
<td>44</td>
<td>Hemoglobin</td>
<td>–0.048</td>
<td>0.061</td>
<td>0.601</td>
<td>0.436</td>
<td>0.95</td>
<td>0.85 1.08</td>
</tr>
<tr>
<td>45</td>
<td>Hematocrit</td>
<td>–0.010</td>
<td>0.019</td>
<td>0.265</td>
<td>0.607</td>
<td>0.99</td>
<td>0.95 1.03</td>
</tr>
<tr>
<td>46</td>
<td>White blood cell</td>
<td>–0.797</td>
<td>0.514</td>
<td>2.402</td>
<td>0.121</td>
<td>0.45</td>
<td>0.17 1.24</td>
</tr>
<tr>
<td>47</td>
<td>Thrombocytes</td>
<td>–0.027</td>
<td>0.387</td>
<td>0.005</td>
<td>0.944</td>
<td>0.97</td>
<td>0.46 2.08</td>
</tr>
</tbody>
</table>

Note: SE = standard error; OR = odds ratio; CI = confidence interval; PND = paroxysmal nocturnal dyspnea; COPD = chronic obstructive pulmonary diseases; CCB = calcium channel blocker; PPI = proton pump inhibitor; H2RA = Histamine-2 receptor antagonists; HDL = high density lipoprotein

After ensuring that none of the important predictors have been omitted from the model, the fifth step of the purposeful selection method is to assess linearity of the logit of the continuous predictor included in the smaller model. This step is important to ensure that continuous predictors included in the model have the correct scale.

There is only one continuous predictor in the smaller model – serum sodium level at admission – and a design variables method was used to assess the linearity. Figure 14 illustrates linearity of the logit of serum sodium level as the only continuous predictor in the smaller model. As shown by the figure, although it is not perfectly linear, the logit of serum sodium level at admission is almost linear. It means that the serum sodium level as a continuous predictor in the model was presented in the correct scale.
Assessing significant interactions between one predictor and another included in the smaller model is the sixth step of the purposeful selection method. Although all interactions can be considered, only three interactions were considered in this model based on clinical reasons, such as the interaction between serum sodium level and history of fatigue, serum sodium level and ascites, and history of fatigue and ascites. Clinically, serum sodium level potentially has a relationship with fatigue and ascites in which a person with lower serum sodium level tends to have the symptom of fatigue. Likewise, a person having ascites tends to have lower serum sodium level.

Fatigue can also potentially have an interaction with ascites in which a person with ascites tends to have a lower serum sodium level clinically manifested by a fatigue symptom. Beginning with univariate logistic regression analysis to identify contribution of each considered interaction term into the outcome of interest, significant interactions were then added into the smaller model to be further analysed in the multivariate level.
Tables 27 and 28 show the output summary resulting from univariate and multivariate logistic regression analysis respectively including interaction terms. Table 27 shows that all considered interactions have a significant contribution to the occurrence of hyponatremia during hospitalisation, thus all interactions were added to the smaller model. Table 28 shows the output summary resulting from multivariate logistic regression analysis by including predictors in the smaller model and three considered interactions. Table 28 shows that there were only two interactions significantly contributing to the model, which were then further analysed multivariately by adding them to the smaller model.

*Table 27 - Summary of univariate logistic regression analysis for interaction terms that were considered to be included in the model*

<table>
<thead>
<tr>
<th>No.</th>
<th>Interaction</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue – Ascites</td>
<td>1.419</td>
<td>0.518</td>
<td>7.513</td>
<td>0.006</td>
<td>4.13</td>
<td>1.49 11.41</td>
</tr>
<tr>
<td>2</td>
<td>Sodium – Ascites</td>
<td>0.007</td>
<td>0.002</td>
<td>9.543</td>
<td>0.002</td>
<td>1.01</td>
<td>1.00 1.01</td>
</tr>
<tr>
<td>3</td>
<td>Sodium – Fatigue</td>
<td>0.009</td>
<td>0.002</td>
<td>28.713</td>
<td>&lt;0.001</td>
<td>1.01</td>
<td>1.01 1.01</td>
</tr>
</tbody>
</table>

Note: SE = standard error; OR = odds ratio; CI = confidence interval

*Table 28 - Summary of significance value of considered interaction terms added into the smaller model*

<table>
<thead>
<tr>
<th>No.</th>
<th>Interaction</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue – Ascites</td>
<td>−1.086</td>
<td>0.874</td>
<td>4.269</td>
<td>0.039</td>
<td>0.16</td>
<td>0.03 0.91</td>
</tr>
<tr>
<td>2</td>
<td>Sodium – Ascites</td>
<td>0.208</td>
<td>0.069</td>
<td>8.982</td>
<td>0.003</td>
<td>1.23</td>
<td>1.08 1.41</td>
</tr>
<tr>
<td>3</td>
<td>Sodium – Fatigue</td>
<td>0.033</td>
<td>0.066</td>
<td>0.245</td>
<td>0.620</td>
<td>1.03</td>
<td>0.91 1.18</td>
</tr>
</tbody>
</table>

Note: SE = standard error; OR = odds ratio; CI = confidence interval

Table 29 shows the output summary of the multivariate logistic regression analysis after the addition of two significant interactions into the smaller model. The table shows that only one interaction contributed significantly to the model: interaction between serum sodium level and ascites. Hence, further multivariate logistic
regression analysis was performed by only adding this one significant interaction into the smaller model. The output summary of this analysis is presented in Table 30.

Table 29 - Output summary of multivariate logistic regression analysis by adding two significant interactions into the smaller model

<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue</td>
<td>1.612</td>
<td>0.361</td>
<td>19.922</td>
<td>&lt;0.001</td>
<td>5.01</td>
<td>2.47 10.17</td>
</tr>
<tr>
<td>2</td>
<td>Ascites</td>
<td>–25.818</td>
<td>9.809</td>
<td>6.928</td>
<td>0.008</td>
<td>0.00</td>
<td>0.00 0.01</td>
</tr>
<tr>
<td>3</td>
<td>Positive inotropes</td>
<td>1.180</td>
<td>0.388</td>
<td>9.234</td>
<td>0.002</td>
<td>3.26</td>
<td>1.52 6.97</td>
</tr>
<tr>
<td>4</td>
<td>Heparin</td>
<td>1.131</td>
<td>0.423</td>
<td>7.157</td>
<td>0.007</td>
<td>3.09</td>
<td>1.35 7.09</td>
</tr>
<tr>
<td>5</td>
<td>Antibiotics</td>
<td>1.109</td>
<td>0.316</td>
<td>12.295</td>
<td>&lt;0.001</td>
<td>3.03</td>
<td>1.63 5.63</td>
</tr>
<tr>
<td>6</td>
<td>Sodium</td>
<td>–0.292</td>
<td>0.040</td>
<td>53.913</td>
<td>&lt;0.001</td>
<td>0.23</td>
<td>0.69 0.81</td>
</tr>
<tr>
<td>7</td>
<td>Fatigue – Ascites</td>
<td>–1.461</td>
<td>0.821</td>
<td>3.167</td>
<td>0.075</td>
<td>0.23</td>
<td>0.05 1.16</td>
</tr>
<tr>
<td>8</td>
<td>Sodium – Ascites</td>
<td>0.201</td>
<td>0.071</td>
<td>9.914</td>
<td>0.005</td>
<td>1.22</td>
<td>1.06 1.41</td>
</tr>
</tbody>
</table>

Note: SE = standard error; OR = odds ratio; CI = confidence interval

Table 30 - Output summary of further multivariate logistic regression analysis by only adding one significant interaction into the smaller model

<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue</td>
<td>1.364</td>
<td>0.323</td>
<td>17.835</td>
<td>&lt;0.001</td>
<td>3.91</td>
<td>2.08 7.37</td>
</tr>
<tr>
<td>2</td>
<td>Ascites</td>
<td>–29.717</td>
<td>9.605</td>
<td>9.572</td>
<td>0.002</td>
<td>0.00</td>
<td>0.00 0.00</td>
</tr>
<tr>
<td>3</td>
<td>Positive inotropes</td>
<td>1.133</td>
<td>0.390</td>
<td>8.429</td>
<td>0.004</td>
<td>3.11</td>
<td>1.45 6.67</td>
</tr>
<tr>
<td>4</td>
<td>Heparin</td>
<td>1.122</td>
<td>0.423</td>
<td>7.043</td>
<td>0.008</td>
<td>3.07</td>
<td>1.34 7.04</td>
</tr>
<tr>
<td>5</td>
<td>Antibiotics</td>
<td>1.099</td>
<td>0.316</td>
<td>12.061</td>
<td>0.001</td>
<td>3.00</td>
<td>1.61 5.58</td>
</tr>
<tr>
<td>6</td>
<td>Sodium</td>
<td>–0.302</td>
<td>0.041</td>
<td>55.057</td>
<td>&lt;0.001</td>
<td>0.74</td>
<td>0.68 0.80</td>
</tr>
<tr>
<td>7</td>
<td>Sodium – Ascites</td>
<td>0.226</td>
<td>0.070</td>
<td>10.344</td>
<td>0.001</td>
<td>1.25</td>
<td>1.09 1.44</td>
</tr>
</tbody>
</table>

As shown in Table 30, interaction between the serum sodium level and ascites remains to contribute significantly into the model \((p = 0.001, OR = 1.25, 95\% CI [1.09–1.44])\). However, the addition of this interaction into the model changed the regression coefficient of the ascites predictor markedly. In addition, the OR of ascites also changed to zero. As the basic principle of adding interaction terms is that none of the predictors already included in the model should be considered for removal, it
was decided that the interaction between serum sodium level and ascites was not to be included in the model.

In addition to the assessment of significant interaction, a multicollinearity test had also been performed to ensure that none of predictors included in the model highly correlated with one with another. The two most widely used measures, variance inflation factor (VIF) and tolerance, were used to assess multicollinearity of the model. Table 31 lists the VIF and tolerance value of predictors included in the model.

Despite the difference of the accepted value of VIF and tolerance in order to decide whether strong collinearity exists among predictors in a model, the generally accepted rule is that a VIF higher than 2.5 indicates strong multicollinearity. Likewise, the value of tolerance close to 0 indicates serious collinearity among predictors. As listed in Table 31, VIF values of all predictors are only slightly higher than 1 indicating that collinearity does not exist. The Tolerance values of all predictors are also close to 1, indicating only a little collinearity [276]. Hence, none of predictors needed to be omitted.
Table 31 - Value of variable inflation factor and tolerance of all predictors included in the model resulting from multicollinearity test

<table>
<thead>
<tr>
<th>Predictor</th>
<th>VIF</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>1.03</td>
<td>0.97</td>
</tr>
<tr>
<td>Ascites</td>
<td>1.04</td>
<td>0.96</td>
</tr>
<tr>
<td>Positive inotropes</td>
<td>1.09</td>
<td>0.92</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.02</td>
<td>0.98</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1.12</td>
<td>0.89</td>
</tr>
<tr>
<td>Sodium</td>
<td>1.14</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Note: VIF = variable inflation factor

After performing the six steps of selecting the predictors to be included in the model, it was decided that the six predictors as listed in Table 32 should be included in the model. The model resulting from the end of the sixth step is called the preliminary final model (PFM) [276]. Before deciding on the final model, the last step is assessing the predictive performance of the PFM. The output resulting from this step is presented in the section on performance of the PM.

Table 32 - Preliminary final model containing six predictors

<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue</td>
<td>1.312</td>
<td>0.316</td>
<td>17.189</td>
<td>&lt;0.001</td>
<td>3.71</td>
<td>1.99</td>
</tr>
<tr>
<td>2</td>
<td>Ascites</td>
<td>1.316</td>
<td>0.449</td>
<td>8.578</td>
<td>0.003</td>
<td>3.73</td>
<td>1.55</td>
</tr>
<tr>
<td>3</td>
<td>Positive inotropes</td>
<td>1.082</td>
<td>0.390</td>
<td>7.718</td>
<td>0.005</td>
<td>2.95</td>
<td>1.38</td>
</tr>
<tr>
<td>4</td>
<td>Heparin</td>
<td>1.092</td>
<td>0.410</td>
<td>7.085</td>
<td>0.008</td>
<td>2.98</td>
<td>1.33</td>
</tr>
<tr>
<td>5</td>
<td>Antibiotics</td>
<td>1.054</td>
<td>0.312</td>
<td>11.447</td>
<td>0.001</td>
<td>2.87</td>
<td>1.56</td>
</tr>
<tr>
<td>6</td>
<td>Sodium</td>
<td>−0.256</td>
<td>0.035</td>
<td>54.437</td>
<td>&lt;0.001</td>
<td>0.77</td>
<td>0.72</td>
</tr>
<tr>
<td>7</td>
<td>Constant</td>
<td>32.427</td>
<td>4.710</td>
<td>47.408</td>
<td>&lt;0.001</td>
<td>47.408</td>
<td>47.408</td>
</tr>
</tbody>
</table>

Note: SE = standard error; OR = odds ratio; CI = confidence interval
5.6. Factors contributing to the development of hyponatremia during hospitalisation

The main purpose of deriving the PM is to estimate the probability of getting a particular outcome of interest. However, as multivariate analysis is commonly involved in the process of deriving the PM, it can also help identify significant factors that concomitantly contribute to the outcome of interest. As listed in Table 32, there are six factors contributing to the development of hyponatremia during hospitalisation in this study population. Three are related to patient clinical condition: history of fatigue, presence of ascites and serum sodium level at admission; while the other three are related to medication received: positive inotropes, heparin and antibiotics.

Whilst five factors show a positive association with the occurrence of hyponatremia during hospitalisation – history of fatigue, presence of ascites at admission, administration of positive inotropes, heparin and antibiotics – serum sodium level at admission shows a negative association. The regression coefficient of serum sodium level at admission is negative (–0.256) and accordingly its OR is less than 0 (OR = 0.77, 95% CI [0.72–0.83]) indicating that the higher the serum sodium level at admission the lower the probability of developing hyponatremia during hospitalisation. The OR of 0.77 means that every unit of increased serum sodium level at admission decreases the risk of developing hyponatremia during hospitalisation by 77%, if other factors are kept at a fixed value. Conversely, every decreased unit of serum sodium level at admission potentially increases the risk of developing hyponatremia during hospitalisation by 30% (1/0.77 = 1.3), if other factors are kept at a fixed value.
A history of fatigue and the presence of ascites at admission have positive regression coefficients (1.312 and 1.316, respectively) indicating that both factors positively increase the risk of developing hyponatremia during hospitalisation, with ORs of both factors close to 4, (OR = 3.71, 95% CI [1.99–6.9] and OR = 3.73, 95% CI [1.55–8.99], respectively). This means that patients having a history of fatigue are at almost four times higher risk of developing hyponatremia during hospitalisation, if other factors are kept at a fixed value, compared to patients without a history of fatigue. Likewise, for patients presented with ascites at admission.

The OR of all medication-related factors are close to 3, meaning that patients receiving such medication have almost three times higher the risk of developing hyponatremia during hospitalisation.

5.7. Performance of the prediction model

The performance of the PM can be assessed according to its overall performance, discrimination ability and calibration ability.

5.7.1. Overall performance

Assessment of predictive performance of a model derived for the purpose of estimating the probability of getting a particular outcome of interest is a crucial step. The first assessment conducted in this research in order to assess predictive performance of the model was for overall performance. Performance was assessed using two common used measures: NR² and Brier-score. The values of both measures are presented in Table 33.
As presented in Table 33, the values of NR² and the Brier-score of the PFM are 0.531 and 0.107, respectively. There are no exact acceptable ranges for both measures; however, a model with better predictive performance will have NR² value close to 1 and Brier-score close to 0. A NR² value of 0.531 means that 53.1% variance of the outcome is explained by the model; in other words, the predictors included in the model explain 53.1% variance of the outcome. Simply, the Brier-score is the sum of the mean squared difference between the probability predicted by the model and the actual outcome in which the predicted probability ranges continuously between 0 and 1, and the actual outcome is either 0 or 1. Hence, a smaller Brier score is a better predictive performance of the model. According to the Brier score’s value of 0.107 the PFM showed a good overall performance.

In addition to the NR² and Brier score of the PFM, Table 34 presents the contribution of predictors included in the PFM to its overall predictive performance. Other than NR² value of –2 likelihood and overall percentage of correct prediction are presented in the table. Likelihood is a measure indicating unexplained information of the outcome predicted by the model, with the larger value of likelihood, the more unexplained information. Meanwhile, the overall percentage of correct prediction presents the ability of the model to correctly predict the outcome. As presented in Table 34, given that every addition of one predictor resulted in smaller –2 likelihood value, the addition of the predictor into the model improves its predictive ability.
Likewise, every addition of one predictor included in the PFM resulted in a higher percentage of correct predictions of the outcome. Thus, all predictors included in the PFM contribute to improving the predictive performance of the model.

Table 34 - Contribution of predictors included in the preliminary final model into its overall predictive performance

<table>
<thead>
<tr>
<th>Included predictor(s)</th>
<th>Value of measures</th>
<th>Overall percentage of correct prediction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2 Log likelihood</td>
<td>Nagelkerke $R^2$</td>
</tr>
<tr>
<td>Baseline model</td>
<td>458.9</td>
<td>-</td>
</tr>
<tr>
<td>Sodium</td>
<td>341.7</td>
<td>0.370</td>
</tr>
<tr>
<td>Sodium, Fatigue</td>
<td>319.4</td>
<td>0.429</td>
</tr>
<tr>
<td>Sodium, Fatigue, Antibiotics</td>
<td>303.8</td>
<td>0.468</td>
</tr>
<tr>
<td>Sodium, Fatigue, Antibiotics, Positive inotropes</td>
<td>291.8</td>
<td>0.497</td>
</tr>
<tr>
<td>Sodium, Fatigue, Antibiotics</td>
<td>284.5</td>
<td>0.515</td>
</tr>
<tr>
<td>Sodium, Fatigue, Positive inotropes, Ascites</td>
<td>277.5</td>
<td>0.531</td>
</tr>
</tbody>
</table>
5.7.2. Discrimination ability

Discrimination ability of the model was assessed using the ROC curve. The curve is a plot of the model’s specificity against its sensitivity and, in this research, the curves were plotted using rms packages in R in which, along with plotting the curves, the AUC could be also identified. Figure 15 shows the ROC curve of the PFM including six predictors with an AUC of 0.90. Subsequently, Figures 16–20 show ROC curves of the model with reduced predictors containing 5, 4, 3, 2 and 1 predictor respectively, and the AUC of each curve is listed in Table 35.

Figure 15 – Receiver operating characteristic curve of the preliminary performance model including six predictors resulting in an area under the curve of 0.90

Figure 16 depicts the ROC curve of the model containing only five predictors, that is, six predictors minus antibiotics, with an AUC of 0.89. Although the resulting AUC for this curve indicates excellent discrimination ability of the model, it is lower than the AUC of the model containing all six predictors.
Figure 16 – Receiver operating characteristic curve of the model including five predictors (excluding administration of antibiotics) resulting in an area under the curve of 0.89.

Figure 17 depicts the ROC curve of the PFM containing only four predictors, that is the six predictors minus antibiotics and positive inotropes, resulting in an AUC of 0.88, indicating that the model has excellent discrimination ability but the AUC is lower than the AUC for the model containing all six predictors.
Figure 17 – Receiver operating characteristic curve of the model including four predictors (excluding administration of antibiotics and positive inotropes) resulting in an area under the curve of 0.88.

Figure 18 depicts the ROC curve of the model containing only three predictors: serum sodium level at admission, history of fatigue and presence of ascites. The resulting AUC of 0.86 indicates that the model has excellent discrimination ability, but the AUC is lower than that of the model containing all six predictors.
Figure 18 – Receiver operating characteristic curve of the model including three predictors (serum sodium level at admission and history of fatigue and ascites) resulting in an area under the curve of 0.86.

Figures 19 and 20 consecutively depict the ROC curve of the model containing only two and one predictors, resulting in AUCs of 0.85 and 0.85 respectively. The resulting AUCs of those ROC curves also indicate that each model has excellent discrimination ability, but the AUCs are lower than the AUC of model containing all six predictors.
Figure 19 – Receiver operating characteristic curve of the model including two predictors (serum sodium level at admission and history of fatigue) resulting in an area under the curve of 0.85

Figure 20 – Receiver operating characteristic curve of model including only serum sodium level at admission as predictor resulting in an area under the curve of 0.83
Generally accepted classification classifies a model with an AUC of ROC curve of \( \geq 0.90 \) as a model with outstanding discrimination ability [276] and, hence, the PFM exhibits very good discrimination ability, meaning that subjects with low and high probability of developing hyponatremia during hospitalisation can be well distinguished by the model. Although the model containing only one predictor also exhibits excellent discrimination ability (AUC = 0.83), as illustrated in Figure 20, the addition of another predictor improves the model’s discrimination ability manifested by increased AUC values. This indicates that each predictor included in the PFM contributes to improved discrimination ability.
Table 35 - Contribution of predictors included in the preliminary final model to its discrimination ability indicated by increased area under the curve of receiver operating characteristic curve values

<table>
<thead>
<tr>
<th>Included predictor(s)</th>
<th>AUC of ROC curve</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>0.83</td>
<td>0.77–0.87</td>
</tr>
<tr>
<td>Sodium, Fatigue</td>
<td>0.85</td>
<td>0.81–0.89</td>
</tr>
<tr>
<td>Sodium, Fatigue, Ascites</td>
<td>0.86</td>
<td>0.83–0.91</td>
</tr>
<tr>
<td>Sodium, Fatigue, Ascites, Heparin</td>
<td>0.88</td>
<td>0.84–0.91</td>
</tr>
<tr>
<td>Sodium, Fatigue, Ascites, Heparin, Positive inotropes</td>
<td>0.89</td>
<td>0.85–0.92</td>
</tr>
<tr>
<td>Sodium, Fatigue, Ascites, Heparin, Positive inotropes, Antibiotics</td>
<td>0.90</td>
<td>0.86–0.93</td>
</tr>
</tbody>
</table>

Note: AUC = area under the curve; ROC = receiver operating characteristic; CI = confidence interval

5.7.3. Calibration ability

Another specific predictive performance commonly assessed in the process of developing a PM is its calibration ability, indicating agreement between predicted and actual probability of getting the outcome. In this research the calibration ability of the PFM was assessed by calibration plot and p-value of the HL test. The calibration plot and the p-value of the H-L test were obtained using the `val.prob` function of rms packages and the `hoslem.test` function of Resource Selection
packages in R respectively. Figure 21 shows the calibration plot of the PFM, and the $p$-value of the H-L test is listed in Table 36.

As shown in Figure 21, the calibration ability of the PFM is not completely ideal, as the model shows good agreement between predicted and actual probability only for low and high probability, with higher prediction seen for probability at medium levels. This indicates that the regression coefficients of the predictors included in the model need to be adjusted to produce a better prediction. Adjustment of regression coefficients is presented in the section on presentation of the final model.

In addition to calibration plot the $p$-value of the H-L test can help explain the calibration ability of the model. The resulting $p$-value of 0.899 from the default H-L test, which divides the probabilities into 10 groups, indicates no significant
difference between predicted and actual probabilities among the groups. To make sure that this no significant difference is also observed in other different group numbers, the H-L test was also performed for group numbers ranging from five to 15, and the resulting \( p \)-value is presented in Table 36.

Table 36 – The \( p \)-values of the Hosmer-Lemeshow test with several different group numbers obtained using the \texttt{hoslem.test} of Resource Selection packages in R

<table>
<thead>
<tr>
<th>Number of groups</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.948</td>
</tr>
<tr>
<td>6</td>
<td>0.106</td>
</tr>
<tr>
<td>7</td>
<td>0.392</td>
</tr>
<tr>
<td>8</td>
<td>0.737</td>
</tr>
<tr>
<td>9</td>
<td>0.283</td>
</tr>
<tr>
<td>10</td>
<td>0.899</td>
</tr>
<tr>
<td>11</td>
<td>0.845</td>
</tr>
<tr>
<td>12</td>
<td>0.204</td>
</tr>
<tr>
<td>13</td>
<td>0.657</td>
</tr>
<tr>
<td>14</td>
<td>0.620</td>
</tr>
<tr>
<td>15</td>
<td>0.812</td>
</tr>
</tbody>
</table>

As listed in Table 36, all \( p \)-values of the H-L test with different group numbers are >0.05, indicating no significant differences between predicted and actual probability among the groups, showing that the PFM has good calibration ability.

5.8. Validation of the preliminary final model

Validation of the PFM is performed to assess its predictive performance in different samples. Ideally, external validation should be performed to assess the predictive performance of the model in different samples taken from different populations, but only internal validation was performed in this research. A bootstrapping approach was chosen to internally validate the model, performed using the “validate” function of rms packages in R. Five hundred bootstrap repetitions were performed to obtain
stable estimates, and the output of this bootstrapping process, is presented in Figure 22.

The first column (index.orig) of the output in Figure 22 lists the value of the measures resulting from the original sample, that is, the model was fitted and assessed in the original sample. The second and third column (training and test) list the mean value of the measures when the model was fitted in the bootstrap samples and assessed in both the bootstrap samples and the original sample respectively. The optimism value of each measure listed in the fourth column was obtained by subtracting the value in the third column (test) from the second column (training) to get the corrected value of each measure (index.corrected) by subtracting the optimism value from the value in the first column. The last column of the output (n) indicates the number of bootstrap sampling repetitions.

![Hypo.Model.Valid](image)

Figure 22 - Output resulted from bootstrapping validation approach of the preliminary final model using the “validate” function of rms packages in R

As shown in Figure 22, the corrected values of all measures indicate that performances of the model are lower than those obtained from the original sample. This means that the model is over-fitting when assessed in the same sample used to derive the model. The $D_{xy}$ measure, which indicates Somer’s D measure, can then be used to calculate the c-statistic (equal to the AUC of the ROC curve) by using the
formula: \( C = \frac{1 + D_{xy}}{2} \). Given that the \( D_{xy} \) corrected value is 0.775, the AUC of the ROC curve resulting from bootstrap validation is 0.89 – lower than the AUC obtained from the original sample.

Whilst the \( D_{xy} \) measure can be used to assess discrimination ability of the model in the validation samples, after converting to the c-statistic, the intercept and slope measures can be used to assess the calibration ability of the model. The corrected intercept and slope values are –0.04 and 0.93 respectively, and are lower compared to ones obtained from the original sample. However, these values are still within acceptable ranges.

All measures obtained from the bootstrap validation process indicate that the PFM still has good discrimination and calibration ability when fitted in different samples taken from the same population, meaning that the model can be generalised into the population where the original sample was taken. By the end of this step, if no changes of predictors are required, the PFM becomes the final model.

### 5.9. Presentation of the final prediction model

After deciding the final PM, the next step is presenting the model in a simple format. Whilst the PM can be presented in several presentation formats, regression formula was chosen to present the PM obtained from this research. Before presenting the final model in regression formula, the regression coefficient of the predictors was shrunk in order to obtain a more accurate prediction. As presented earlier in the section on assessment of calibration ability and validation of the model, the model exhibits optimism in predicting the outcome, which needs to be minimised. The main purpose of shrinking regression coefficients is to minimise this optimism.
Figure 23 presents an overall shrinkage factor of 0.949 resulting from analysis using the “shrink” function package in R. This shrinkage factor was then used to obtain a shrunken-regression coefficient of each predictor in the final model as listed in Table 37.

```
> Shrinkage.Factors <- shrink(FINAL.MODEL, type="global", method="dfbeta")
> print(Shrinkage.Factors)
Shrinkage Factors (type=global, method=dfbeta):
[1] 0.9493288

Shrunken Regression Coefficients:
  (Intercept) Sod.Level Hist. Fatigue Asc.Adn Positives Hepar Antibio
  30.7459701 -0.2433963 1.2450410 1.2493669 1.0276009 1.0369045 1.0007411
```

Figure 23 - Overall shrinkage factors generated by “shrink” function of “shrink” packages in R

Table 37 - Shrunken regression coefficient resulted from original regression coefficient multiplied by shrinkage factor

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Regression coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.312</td>
</tr>
<tr>
<td>Ascites</td>
<td>1.316</td>
</tr>
<tr>
<td>Positive inotropes</td>
<td>1.082</td>
</tr>
<tr>
<td>Hepar</td>
<td>1.092</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1.054</td>
</tr>
<tr>
<td>Sodium</td>
<td>-0.256</td>
</tr>
<tr>
<td>Constant</td>
<td>32.427</td>
</tr>
</tbody>
</table>

To reach a simpler regression formula, all regression coefficients, including regression coefficients of the constant, were divided by the smallest regression coefficient – the regression coefficient of serum sodium level at admission – resulting in final regression coefficients as listed in Table 38.
### Table 38 - Final regression coefficients of predictors in the final model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Final regression coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>5.2</td>
</tr>
<tr>
<td>Ascites</td>
<td>5.2</td>
</tr>
<tr>
<td>Positive inotropes</td>
<td>4.3</td>
</tr>
<tr>
<td>Heparin</td>
<td>4.3</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>4.2</td>
</tr>
<tr>
<td>Sodium</td>
<td>-1</td>
</tr>
<tr>
<td>Constant</td>
<td>128.1</td>
</tr>
</tbody>
</table>

After obtaining the final regression coefficients, the PM can be presented as follows:

\[ \text{Hyponatremia} = 128.1 - \text{Sodium} + 5.2 \text{ Fatigue} + 5.2 \text{ Ascites} + 4.3 \text{ Positive inotropes} + 4.3 \text{ Heparin} + 4.2 \text{ Antibiotics} \]

in which each predictor is included: serum sodium level at admission, history of fatigue, presence of ascites at admission, administration of positive inotropes, heparin and antibiotics. Serum sodium level at admission is presented in a continuous scale expressed in mmol/L or mEq/L, and the rest of the predictors are presented in categorical value, in which 0 and 1 indicate the absence and presence of the predictors respectively. Once the value of “Hyponatremia” has been obtained, it can be then converted into the probability of developing hyponatremia during hospitalisation using the formula:

\[ p = \frac{1}{1 + e^{-y}} \]

in which \( p \) denotes probability of developing hyponatremia during hospitalisation and \( y \) denotes the value of “Hyponatremia” resulting from the equation.

The following are two examples to elaborate on the application of the model and calculating the probability:
1. A patient hospitalised with HF presented at admission with serum sodium level of 140 mmol/L, admitting history of fatigue, ascites is observed and receiving positive inotropes, heparin and antibiotics during admission. The probability of developing hyponatremia during hospitalisation of this patient can be calculated as follows:

\[ \text{Hyponatremia} = 128.1 - 140 + 5.2(1) + 5.2(1) + 4.3(1) + 4.3(1) + 4.2(1) \]

\[ \text{Hyponatremia} = 11.3 \]

\[ \text{Probability} = \frac{1}{1 + \exp(-11.3)} = 0.808 \]

Probability of developing hyponatremia during hospitalisation is 81%.

2. A patient hospitalised with HF presented at admission with serum sodium level of 140 mmol/L, admitting history of fatigue, ascites is observed, receiving positive inotropes, heparin, or antibiotics during admission. Probability of developing hyponatremia during hospitalisation of this patient can be calculated as follows:

\[ \text{Hyponatremia} = 128.1 - 140 + 5.2(1) + 5.2(1) + 4.3(0) + 4.3(0) + 4.2(0) \]

\[ \text{Hyponatremia} = -1.5 \]

\[ \text{Probability} = \frac{1}{1 + \exp(1.5)} = 0.223 \]

Probability of developing hyponatremia during hospitalisation is 22%.

5.10. Summary

Hyponatremia during hospitalisation was observed in 102 out of 464 patients hospitalised with HF in this research population, resulting in a prevalence of 22%. In a nested case-control (NCC) design, the association between hyponatremia during hospitalisation and clinical outcomes was assessed, and it was found that
hyponatremia during hospitalisation was significantly associated with a longer hospital stay and higher in-hospital mortality rate. Whilst hyponatremia during hospitalisation was found to contribute to negative clinical outcomes, this research reveals that more than half of hyponatreemic patients in this research population received non-specific treatment. Six patient–medication-related factors were found to contribute to the development of hyponatremia during hospitalisation: serum sodium level at admission, history of fatigue, presence of ascites at admission, administration of positive inotropes, heparin and antibiotics. These six factors were then included as predictors of the PM proposed for identifying the risk of developing hyponatremia during hospitalisation among patients hospitalised with HF. Assessment of predictive performance of the PM including those six predictors were performed, finding that the PM exhibits good predictive performance of both overall performance and specific performance assessed discrimination and calibration ability. Internal validation of the PM was performed using a bootstrapping approach, and the output showed that the PM exhibits good performance in validation samples. The shrinkage factor was then calculated and used to shrink regression coefficients of the predictors in order minimise optimism of the PM when it is used in different samples. The PM was then presented in a regression formula as: \[ \text{Hyponatremia} = 128.9 - \text{Sodium} + 5.2 \times \text{Fatigue} + 5.3 \times \text{Ascites} + 4.3 \times \text{Positive inotropes} + 4.3 \times \text{Heparin} + 4.2 \times \text{Antibiotics}. \]
Chapter VI – Findings and discussion

This chapter discusses the important findings of the research related to hyponatremia and compares them with other research either in general conditions or specifically in patients with HF. By presenting the important research findings the issue of hyponatremia can be further elaborated and established.

6.1. Research overview

The main pioneering characteristic of this research, to our knowledge, is that it is the first research to develop a risk-PM for hyponatremia during hospitalisation in patients hospitalised with HF. Research on hyponatremia in relation to HF is increasing but the topics are mostly on the impact of hyponatremia to clinical outcomes in general. Research on predicting the risk factors of hyponatremia in HF patients using a PM are scarce, and to the best of the researcher’s knowledge could not be found in the published papers. Although the main aim of this research was to obtain a risk-PM for hyponatremia during hospitalisation in patients hospitalised with HF, an additional five objectives were achieved, gaining a more comprehensive understanding of the main research aim.

The first objective of this research was to identify the prevalence of hyponatremia during hospitalisation among patients hospitalised with HF at the study site. The presence of hyponatremia was then reviewed to establish if it had any association with the length of hospital stay and in-hospital mortality. It was found that the prevalence of hyponatremia in patients hospitalised with HF at the research site was 22%, and it was significantly associated with longer hospital stay (11 versus eight days, \( p = 0.002 \)) and higher in-hospital mortality (22.6% versus 7.8%; OR: 3.4, 95% CI [1.8–6.4]).
The second objective was to investigate the current management of hyponatremia in patients hospitalised with HF at the study site. Other than fluid restriction combined with the administration of furosemide, sodium chloride-based therapies were administered to hyponatremic patients in the research site. Sodium chlorides were administered as normal saline solution, hypertonic saline solution and sodium chloride capsules. Although sodium chloride correction is known as a critical factor for cerebral oedema and hypervolemia, the rate of this correction should be considered in order to achieve optimum therapeutic targets of administering saline solution, especially in patients with severe hyponatremia. However, there was no information found in relation to serum sodium correction rates. This finding indicates that several aspects in managing hyponatremia in patients with HF in the research site need improvement.

The third objective was to identify significant contributing risk factors for developing hyponatremia among patients with HF during their hospitalisation, and further to include those identified risk factors to derive the development of a risk prediction model. Six factors were found to have an association with increased risk of hyponatremia, and were addressed in this thesis: lower serum sodium level, history of fatigue, presence of ascites at admission, and administration of positive inotropes, heparin and antibiotics. These significant factors were then included as predictors in the PM.

The fourth objective was to assess the predictive ability of the obtained risk-PM based on measures commonly used to evaluate the predictive ability of PMs. The developed PM based on the six predictors showed good performance both in overall performance, assessed statistically by NR² (0.531) and the Brier score (0.107), and specific performance assessed by its discrimination and calibration ability. The AUC
of the ROC curve of 0.9 indicates that the PM has a good ability to discriminate subjects at high and low risk of developing hyponatremia during hospitalisation.

Based on the HL test, the PM showed good calibration ability in which predicted outcomes were not significantly different from the actual probabilities in the study population at high risk of hyponatremia. However, the calibration plot shows that the PM result was higher than actually occurred in the subjects with medium risk probability.

The last objective was to evaluate the reproducibility of the fitted PM utilising an internal validation method. The purpose was to ensure the PM will perform at the same level in a population similar to that used to develop it. Internal validation was performed using a bootstrap approach, and it was found that although the PM shows optimism when applied in the bootstrap samples, corrected measures of discrimination and calibration abilities are still within acceptable values. To minimise that optimism when the PM is applied to different samples, the regression coefficient of all predictors were then shrunk using overall shrinkage factors and the PM is presented as regression formula containing six predictors with those shrunk regression coefficients.

6.2. Sample size and research design

Sample size and research design are two important issues for consideration in deriving PMs [274]. Usable PMs can only be generated from research with appropriate design and an adequate sample size. Other than statistical power, the number EPVs was considered in determining the minimum sample size. There is no algorithm to calculate the statistical power for multivariable research, so some assumptions were made in determining the sample size with optimum statistical power, using previous similar research as a guide. The number of EPVs is explained
later in this chapter in conjunction with the predictor selection in the process of deriving the PM.

Considering factors related to multivariate study and the derivation of the PM 500 patients was considered as a reasonable sample size to obtain optimum power. To gain that sample size within a limited timeframe, retrospective data collection was chosen for this research. Despite the superiority of prospective data collection retrospective was more feasible due to time constraints for data collection within the research timeline and limited resources. With the target of including 500 patients, patients hospitalised with HF during three consecutive years from 2011 to 2013 were retrieved. Unfortunately, complete electronic data in the research site were only available for the purpose of patient identification, so complete data during patient hospitalisation had to be collected manually from medical records. Although 663 patients were identified as hospitalised with HF during the period between 2011 and 2013 and coded with I50.0 for their main problem of hospitalisation, 199 out of those identified patients had to be excluded, mostly because the medical records were unavailable (40%). This is not an uncommon problem for retrospective data collection using patient’s medical records. Another 19% were excluded due to unavailability of laboratory data in their medical records. Although imputation can be applied for treating missing data, advanced imputation techniques need to be performed to minimise bias of the results [321]. Therefore, it was decided that only patients with complete data would be included in this research.

To achieve the main aim of this research, that is deriving the PM, an NCC design was applied. NCC design has been used widely for developing PMs, especially for diagnostic purposes, within several disease conditions [322-324]. The utility of NCC design within diagnostic studies of cardiology is well recognised [314].
Following NCC design, each patient in the case group was matched by age and gender to three patients in the control group. Although a higher case to control ratio will decrease variability estimates, as found in other studies, the ratio 1:1, 1:2, 1:3 and 1:4 between case and control have shown similar estimates of accuracy compared to the full study population [313, 314]. Therefore, the 1:3 ratio used in this research was considered appropriate.

6.3. Prevalence of hyponatremia and its association with clinical outcomes

This research clearly confirmed the findings of previous studies reporting that hyponatremia is the most prevalent electrolyte disturbance in patients hospitalised for HF both on admission and during hospitalisation [183, 197, 325]. Although potassium disorders have also been reported as one of electrolyte disorders commonly encountered by patients with HF, its prevalence is lower compared to hyponatremia, as also found in this research. Both on admission and during hospitalisation the prevalence of hypokalemia was approximately half that for hyponatremia. Hypernatremia and hyperkalemia were also found to be lower when compared to hyponatremia.

Hyponatremia on admission was found in 88 patients (19%) of 464 patients included in this research, but only 65% of those patients continued to be hyponatremic during days following hospitalisation. On the other hand, another 45 patients with a non-hyponatremic condition on admission developed hyponatremia during hospitalisation, resulting in HAH equating to 9.7% of the total sample. Using the same serum sodium level for defining hyponatremia, the prevalence of hyponatremia on admission found in this research is similar to the prevalence reported by Shchekochikhin et al. (2013); 19.4% of 5347 patients hospitalised with HF had hyponatremia [198]. However, the prevalence of HAH in their study was just over
two and a half times higher compared to the prevalence found in this research, 24.4% and 9.7% respectively. Konishi et al. (2012) reported a prevalence of 11.5% HAH out of the 662 HF patients in their study [179], and a lower prevalence of hyponatremia on admission among patients hospitalised with HF was reported by Sato et al. (2013), 11.6% out of 4387 patients [197].

In regard to PH, the prevalence found in this research was similar to the prevalence reported by Gheorghiade et al. (2007) [326]. Using the same serum sodium level for defining hyponatremia in the 433 patients with severe HF included in their study, hyponatremia on admission was found in 23.8% of patients admitted to hospital with HF, with 70% observed as having PH [326]. The patient records investigated in this study revealed that HAH occurred in 12% of patients who were not hyponatremic on hospital admission but had hyponatremia during their hospital stay during the study period.

In terms of the lowest serum sodium level the majority of patients encountering hyponatremia during hospitalisation in this study had moderate hyponatremia according to the most used classification of hyponatremia based on serum sodium level (125–129 mmol/L). However, there was a significant difference of serum sodium level at admission between patients with PH and HAH – patients with HAH had a significantly higher serum sodium level at admission. Patients with HAH showed a sharper decrease of serum sodium level between admission and their lowest level in the days following hospitalisation. The median time for developing hyponatremia among patients with HAH in this research is quite similar to the median reported by Shchekochikhin et al. (2013); five and four days respectively [198]. The sharp decrease of serum sodium level between admission and during the
days following hospitalisation among patients with HAH may contribute to the requirement for more complex treatments as reported by Hoorn et al. (2006) [273].

Studies on the prevalence of hyponatremia and its association with clinical outcomes have mostly analysed hyponatremia on admission and HAH separately. Using the data from the OPTIME-CHF trial, Klein et al. (2005) analysed the association between serum sodium level at admission and the number of hospitalisation days and all-cause death within 60 days [327]. Sato et al. (2013) also investigated the impact of hyponatremia at admission on in-hospital mortality [197]. Konishi et al. (2012) focused on hyponatremia acquired during hospitalisation and its association with clinical outcomes [179]. Although both hyponatremia at admission and developing during hospitalisation were analysed in the study conducted by Shchekochikhin et al. (2013) each type of hyponatremia was analysed separately [198]. In their study Gheorghiade et al. (2007) also identified both hyponatremia on admission and developing during hospitalisation, but only hyponatremia on admission that persistently remained uncorrected was further analysed [328].

The difference between the findings of this study compared to previously reported studies on hyponatremia in patients hospitalised with HF is that this research combined hyponatremia on admission that persistently remained uncorrected during the days following hospitalisation and HAH together in one definition as hyponatremia during hospitalisation. The main reason driving the decision to combine these two types of hyponatremia in one definition is that regardless of when hyponatremia becomes prevalent, both types represent a clinical state of hyponatremia in a patient admitted to hospital with HF that is known to be associated with that patient’s clinical short- and long-term health outcomes. As reported by Klein et al. (2005), Konishi et al. (2012), Sato et al. (2013) and Shchekochikhin et al.
hyponatremia at admission is significantly associated with worse clinical outcomes, including longer hospitalisation, higher in-hospital mortality and within 60 days following hospital discharge, as well as hospital readmission [179, 197, 198, 327]. With a focus only on HAH in their study, Konishi et al. (2012) found that HAH is a significant predictor of longer clinical outcomes of patients hospitalised with HF, including survival and being free of cardiovascular episodes during the year after hospital discharge, even when HAH was adjusted by other important predictors such as left ventricular ejection fraction (LVEF) and BNP [179].

In addition to the findings supporting the importance of both hyponatremia on admission and developed during hospitalisation, not all patients having hyponatremia on admission continue to be hyponatremic during the days following hospitalisation, as reported by Gheorghiade et al. (2007) and found in this research, in which 35% of patients with hyponatremia at admission were self-corrected during the days following hospitalisation [328]. Gheorghiade et al. in (2007) report that persistently uncorrected hyponatremia was associated with more complex clinical outcomes, including a higher mortality rate during the six months following hospital discharge, a higher rate of hospital readmission, and a composite of both outcomes. On the other hand, hyponatremia at admission was only associated with a higher mortality rate after six months of hospital discharge [328].

In the context of real practice, whilst hyponatremia during admission can be easily recognised from laboratory records as part of normal routine measurements taken at admission, HAH as well as PH are less readily recognised, especially when laboratory measurements are not taken on a daily basis. Other than increasing the risk of mortality, a delayed recognition of HAH can potentially increase the
requirements for complex and costly treatments, as found by Hoorn et al. (2006) [273].

In this research, the overall in-hospital mortality rate is 11%; higher than the average in-hospital mortality rates of 6.7% reported by Siswanto et al. (2010) in their report on behalf of the Acute Decompensated Heart Failure National Registry (ADHERE) research team in Indonesia [329]. This is also higher compared to in-hospital mortality rates of HF patients in developing countries reported by Callender et al. (2014) and in the Asia Pacific reported by Atherton et al. (2012), at 8% and 4.8% respectively [19, 21]. The higher in-hospital mortality rate found in this study might be due to more severe conditions of the patients included in this study. In their report, Siswanto, et al. (2010) found that patients hospitalised for HF in Indonesia tend to have severe symptoms and lower LVEF [329]. It is a challenge for primary care providers and general practitioners in Indonesia to improve the management of HF so that patients with HF will not be delayed in receiving appropriate treatment [330].

The unadjusted OR obtained from univariate logistic regression indicates that patients with hyponatremia during hospitalisation tend to have around two times higher risk of longer hospitalisation compared to non-hyponatremic patients during hospitalisation. Likewise, patients with hyponatremia during hospitalisation tend to have around a three times higher risk of in-hospital mortality. Ideally, some variables indicating severity of HF should be included in the analysis to obtain adjusted OR. Unfortunately, two variables commonly used to indicate the severity of HF found in this research, LVEF diagnostic results and the NYHA functional class, were not available in all patients records. In patients with and without hyponatremia during hospitalisation information about LVEF was available for less than 50%, and the
problem was similar to information on the NYHA functional class. Nevertheless, findings from this research on the association between hyponatremia and hospital length of stay and in-hospital mortality confirmed the findings of previously reported studies on the association between hyponatremia and clinical outcomes where the LVEF and NYHA were available or collected. In addition, given that hyponatremia analysed in this research consisted of PH and HAH, this finding not only confirms the previously reported findings, but also indicates the importance of both PH and HAH. This further indicates that factors associated with an increased risk of developing hyponatremia during hospitalisation in patients hospitalised for HF are important to be studied.

6.4. Characteristics of patients

Information on patient characteristics during admission is important for patients hospitalised due to complications from or with HF. Some of the patient characteristics are important in guiding the necessary treatment, and others can be used to provide information about the prognosis of the disease. As this research focused on hyponatremia during hospitalisation, patient characteristics were compared between the active “patients with hyponatremia” and the control “patients without hyponatremia” groups during hospitalisation.

Based on information on vital signs and symptoms at admission, it was found that patients in this study sample who were admitted to hospital with hyponatremia tended to have a more severe condition than those who did not or who developed hyponatraemia during hospitalisation. Compared to patients without hyponatremia during hospitalisation, peripheral edema and ascites were found to be more prevalent in patients who encountered hyponatremia during hospitalisation. Patients with more severe HF would potentially have these symptoms as a result of poor cardiac
function, that is, more severe ventricular dysfunction. LVEF is well known as an indicator of cardiac pump function, in which lower LVEF indicates poorer cardiac pump function [299]. In this study, the average LVEF is not significantly different between patients with normonatremia and patients with hyponatremia during hospitalisation, but the average was calculated from only 47.6% and 43.4% of patients with and without hyponatremia during hospitalisation respectively. In their research, Sato et al. (2013) reported a difference in LVEF between HF patients admitted with and without hyponatremia, but it was not significant [197].

Although the average SBP at admission was found to be slightly lower in patients with hyponatremia during hospitalisation, it was not significantly different from the non-hyponatremic group. The averages of SBP of the two groups in this research are within the range of the average SBP among patients hospitalised with acute HF reported by several clinical trials, which was significantly lower compared to the SBP among patients hospitalised with AHF reported by other studies gaining data from clinical registries [331, 332]. Lower SBP has been reported to be associated with poorer condition of patients with HF, and it has been found to be significantly associated with poor prognosis; patients hospitalised with HF having lower SBP tend to have a higher risk of mortality.

In regard to medical history, this study found that a higher proportion of patients developing hyponatremia during hospitalisation had a history of hospitalisation for cardiac diseases, but the disease was not mentioned specifically in medical records. Previously published studies also reported that more hyponatremic patients had previous hospitalisation for HF compared to non-hyponatremic patients [197, 200] and this might be related to the poorer condition of HF in hyponatremic patients. Hypertension and diabetes are the prominent risk factors for HF and whilst Sato et al.
(2013) found a significantly higher prevalence of hypertension among HF patients admitted with a hyponatremic condition, the prevalence was not significantly different between the two groups in this research [197]. The prevalence of diabetes mellitus was also not different between the two groups. Although pseudo-hyponatremia tends to be encountered by patients with severe hyperglycaemia [181], the proportion of patients with hyperglycaemia whose serum sodium levels are required to be adjusted (blood glucose level > 200 mg/dL or > 11 mmol/L) were not significantly different between the groups with and without hyponatremia, 8.8% and 8.5% respectively.

AF is a common complication in patients with HF [333] and the proportion of patients presenting with AF at admission was not significantly different between the groups with and without hyponatremia during hospitalisation in this research. Renal failure was the only one concomitant diagnosis found in this study with a significantly different proportion between hyponatremic and non-hyponatremic patients, and this was determined in accordance with the average of serum creatinine of the hyponatremic group, which was significantly higher compared to the non-hyponatremic group. The average of BUN in hyponatremic patients was also found to be higher than in non-hyponatremic patients, but it was not significantly different. In acute conditions, the serum creatinine of HF patients may be increased owing to hypoperfusion and congestion [94] and worsening renal function in HF patients with congestion has been found as a predictor for poorer prognosis [334]. Serum albumin was found to be significantly lower among patients with hyponatremia, and this might correlate with more prevalence of ascites among patients in this group. However, liver function, detected by aspartate amino-transferase (AST) and alanine amino-transferase (ALT), was not significantly different between the two groups.
although it was slightly higher among patients within the hyponatremic group. In HF patients, liver function abnormalities indicate the presence of cardio-hepatic syndrome and, specifically, higher levels of AST and or ALT indicate ischemia within hepatocytes that should be considered both in managing the patient and predicting the long-term outcome [335].

Medication history needs to be gained from all patients admitted to hospitals. Studies report that around 4% of patients admitted to hospital are due to adverse drug reactions [336, 337] and several classes of medication are known to have the ability to induce or exacerbate HF [338]. Specifically in relation to hyponatremia, several classes of medication have been identified as potentially causing hyponatremia as an adverse reaction, such as antidepressants and even medication used to manage the symptoms of HF, such as diuretics [181, 225]. Unfortunately, detailed information on medication history was only available for less than 10% of the patients included in this research. Accordingly, patient characteristics related to their medication history prior to admission cannot be considered as reliable or applicable to the whole population. However, it is indicative and future research in this area should find more confirmative results.

Almost all patients in the two groups, with and without hyponatremia, received furosemide during hospitalisation – 95.1% in both groups – and this indicates that almost all patients were admitted with a hypervolemic problem. This might correlate with dyspnea; all patients in both group had symptoms of dyspnea on effort before admission – 100% in both groups – although prominent peripheral edema and ascites were significantly found to be more prevalent among patients with hyponatremia during hospitalisation. Around one quarter of patients in each group received sparing diuretics, mostly in combination with furosemide. Sparing diuretics such as
spironolactone are administered along with furosemide to minimise furosemide-induced electrolytes disorder, especially hypokalemia.

Patients in this research with hyponatremia during hospitalisation received less ACE inhibitors or ARBs compared to patients with normonatremia. However, the rate of 75% overall use of ACE inhibitors or ARBs found in this study is higher than the rate reported by Callender et al. (2014) in their systematic review on HF in low-middle income countries and Siswanto et al. (2010) in their study on HF in Indonesia, 57% and 68%, respectively [21, 329]. In contrast, patients with hyponatremia received more positive inotropes, heparin, insulin and antibiotics. This information on medication might also indicate a more severe condition in patients with hyponatremia. The most used ACE inhibitors or ARBs are administered orally, and patients with a severe condition would have difficulty taking oral medication. In contrast, positive inotropes and heparin are administered parenterally and mostly used in patients with severe conditions.

6.5. Management of hyponatremia

The main purpose of investigating treatment delivering to hyponatremic patients in this research is to capture a raw picture on how, to some extent, hyponatremia as an important clinical problem is managed during hospitalisation, and if it receives appropriate attention as an integral part of overall patient stabilisation. Corona et al.’s meta-analysis (2015), which included 19 studies in which seven were specifically concerned with hyponatremia in patients with HF, concluded that correcting sodium level during hospitalisation decreases the risk of mortality in hyponatremic patients [339]. This finding emphasises that hyponatremia is an important clinical problem that needs to be addressed, and further adequate strategies to correct serum sodium level are required. Unfortunately, inappropriate management of hyponatremia has
been revealed by several studies, indicating that more effort is still required to increase awareness [340, 341]; however, no further studies other than this study have developed a prediction method to address the issue.

Among 102 patients encountering hyponatremia during hospitalisation in this research, more than half did not receive any active treatment – only fluid restriction was prescribed. However, these patients also received furosemide as part of the medication prescribed for the treatment of their main clinical problems, HF and its related complications. In patients with a hypervolemia condition, furosemide is recommended to correct volume, which occurs as a result of enhancing the excretion of additional retained sodium. However, if not administered with adequate attention as it can also potentially later lead to hyponatremia. Fluid restriction is known as the safest option for correcting hyponatremia in mild–asymptomatic patients, but intolerance of thirst as side effect is an important limitation of this option [342], and administration of furosemide can attenuate this side effect. Nevertheless, studies report that when prescribed adequately, fluid restriction improves serum sodium level effectively [193, 343].

The remaining hyponatremic patients received sodium chloride both as capsules and intravenous solution. However, sodium chloride capsules were administered mostly in combination with sodium chloride solution to patients with severe hyponatremia. Isotonic solution of sodium chloride is very good for patients with hypovolemic hyponatremia, whereas the hypertonic solution has an efficacious effect for hyponatremic patients with hypervolemic or euvolemic conditions [241, 267]. The most important aspect of administering the sodium chloride solution is the rate of correction, particularly for patients with acute hyponatremia. Overly rapid
administration of hypertonic solution of sodium chloride can induce neuron obstruction leading to severe neurologic disorder [181, 267].

In terms of the rate of serum sodium level correction, the same infusion rates of 500 ml/24 hours were administered into all patients receiving hypertonic saline solution in this research, and further monitoring on changes of serum sodium level were not found. Administering hypertonic saline solution in an appropriate infusion rate is important in avoiding serious adverse events. Table 39 lists two common formulas used to estimate the rate of serum sodium correction in order to achieve optimum correction while minimising adverse effects. However, it is important to bear in mind that the formulas in Table 39 do not replace the need for adequate monitoring and clinical assessment. Instead of using these formulas alone, careful monitoring of electrolytes and assessment of clinical signs and symptoms are needed to adjust the infusion rate and further avoid harmful adverse effects.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Pros and Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrogue-Madias Formula (Androgue and Madias, 2000)</td>
<td>Easy to calculate, underestimate the change in serum sodium</td>
</tr>
<tr>
<td>Barsoum-Levine Equation (Liamis et al., 2006)</td>
<td>More precise in estimation, more complex formula which considers urinary losses</td>
</tr>
</tbody>
</table>

Interestingly, hypertonic saline solution was only administered to one third of patients with severe hyponatremia, while more than one third did not receive any active treatment other than fluid restriction and furosemide. However, the severity of hyponatremia in this research was only based on serum sodium level. Other than serum sodium level, it is important to identify the duration of the hyponatremic condition so it can be classified accordingly as acute or chronic. Moreover, clinical symptoms of hyponatremia also need to be identified to detect hyponatremia in those
patients with moderate to severe symptoms while still showing lower than normal laboratory results. The required treatment will be different between patients with severe acute symptomatic and severe asymptomatic chronic hyponatremia. Therefore, reasons behind the findings still need further investigation.

Uncorrected hyponatremia among hospitalised patients are still a common problem, not only among patients with mild hyponatremia but also among patients with severe hyponatremia. In their study investigating delivered treatment to relieve hyponatremia among patients in ICU Dasta et al. (2015) found that despite the findings concluding that corrected sodium level among hyponatremic patients decreases the risk of death, almost half of the hyponatremic patients in their study were uncorrected [341]. Likewise, Geoghegan et al. (2015) conclude that the proportion of patients with severe hyponatremia receiving appropriate correction for their serum sodium level was still insufficient [340]. Around half of the patients with severe hyponatremia included in the study still had their serum sodium level non-optimally corrected.

To date, specific guidelines on the therapeutic management of hyponatremia in HF patients is not available. Limited evidence is one of the most probable reasons behind this. Therefore, empirical treatment is most commonly used for managing hyponatremia in HF patients. In the last published guideline on the management of HF, the ACCF/AHA recommended the use of vasopressin receptor antagonists for the treatment of hypervolemic hyponatremia in patients with active cognitive symptoms [12]. While the vaptans might be available in some developed countries, it is not easy to provide these drugs in developing countries due to the cost of the medication. Therefore, the first strategy to minimise hyponatremia-related problems in patients hospitalised for HF should be to optimise guideline-driven therapy and to
assess hyponatremia more appropriately [269, 345-347]. Furthermore, conventional options for managing hyponatremia, such as the use of saline solution, either isotonic or hypertonic, are still important considerations [189, 241].

Interdisciplinary approaches are needed to achieve optimum therapeutic outcomes in managing hyponatremic patients, especially patients with severe hyponatremia. Other than physicians and nurses, pharmacists can also contribute to the management of hyponatremia, including among patients with HF, along with routine pharmaceutical care implementation [348, 349]. Whatever treatment option is being prescribed, monitoring of the patient’s response should be a part of a pharmacist’s responsibility. Although vaptans as new promising agents for the treatment of hyponatremia have been approved, several more affordable conventional treatment options still need to be optimised to achieve optimum correction among hyponatremic patients [349].

6.6. Derivation of the prediction model and factors significantly associated with hyponatremia

One of the most important steps of deriving a clinical PM is to select candidate predictors that will be included in the final model. Several approaches have been proposed on selecting such predictors in order to obtain a robust PM with excellent prediction performance. The clinical approach is the best, in which predictors are selected based on clinical relevancy to the outcome of interest. Following this approach, all predictors clinically relevant to the outcome of interest can be included in the model. However, overfitting and further optimism will be a serious problem if too many predictors are included. Stepwise selection is an alternative for selecting predictors by using a statistical significance approach in determining the relationship between predictor and outcome of interest assessed within the sample using to derive
the model. Although practically simple to be performed stepwise selection has some disadvantages including resulting in coefficients with biased estimates.

Candidate predictors included in the final PM in this research were selected by following the purposeful selection method proposed by Hosmer et al. (2013), which shows better ability in selecting important predictors compared to the stepwise selection method [276, 350]. Using this method, any clinically relevant predictor can be included in the final model only if the predictor significantly contributes to the model based on a statistical significance test. Several steps involved in the process of selecting significant predictors in this method provide a chance not only to screen important predictors, but also any confounding predictors influencing the significant contribution of other predictors.

In addition to the issue of choosing the appropriate method for selecting candidate predictors, the number of EVPs is an important consideration to obtain a good PM for a model with a binary outcome [274, 351]. The number of EVPs is the number of positive outcomes in the sample used to derive the model divided by candidate predictors included in the model. This number has been known to be associated with the degree of optimism of the obtained model, in which the larger the number of EVPs the smaller the model optimism is. Despite the difference of findings on the optimum number of EVPs resulting in the lowest optimism, five EVPs have been found to be the minimum number needed to obtain a good PM. Based on this approach, although the purposeful selection method recommends all independent variables with $p$-value $<0.25$ resulting from univariate analysis can be included into the large model, only independent variables with $p$-value $<0.05$ were included in the large model in this research. There were 32 predictors with $p$-value $<0.25$ resulting from univariate analysis, and if all these predictors were included in the large model
it would result in the number of EVPs being less than five. Therefore, instead of $<0.25$, $p$-value $<0.05$ was used to screen independent variables from univariate analysis, and this resulted in 17 independent variables as candidate predictors included in the large model. Administration of insulin had $p$-value $>0.05$ but was included in the large model because previous studies reported that it was associated with HAH, and in addition its $p$-value was $<0.25$. Overall, there were 18 independent variables included as candidate predictors in the large model, resulting in 5.7 EVPs.

From the multivariate analysis, six out of 18 candidate predictors had $p$-value $<0.05$ and subsequently two steps were performed to make sure that there were no important candidate predictors excluded. However, no more candidate predictors were found that significantly contributed to the outcome. Serum sodium level at admission as the only one continuous predictor was then assessed to make sure that it has been presented in the correct scale. By following the design variables method, the resulting graph showed that the logit of serum sodium level at admission is almost linear indicating that the predictor was presented in a proper scale.

Another step that needs to be performed after finding significant candidate predictors is assessing significant interaction between the predictors. Three interaction terms were considered based on clinical consideration, and although all these interactions showed significant association with the outcome in univariate analysis, only interaction between serum sodium level and the presence of ascites at admission significantly contributed to the outcome when it was added to the candidate predictors in the multivariate analysis. However, it was decided not to include the interaction between serum sodium level and presence of ascites at admission because addition of this interaction to the model markedly changed the regression coefficient and OR of ascites predictor.
Other than assessing interaction, a multicollinearity test was also performed to make sure that there were no predictors among candidate predictors where its value was significantly dependent on, or determined by, the value of other predictors. VIF and tolerance were used to assess multicollinearity among candidate predictors, and based on these two parameters it was found that there was no multicollinearity among candidate predictors. Therefore, all six candidate predictors remained in the model.

After following all steps of the predictor selection process required by the purposeful selection method, it was decided that six predictors would be included in the PM. Serum sodium level at admission is the only one continuous predictor, and five other predictors are categorical binomial predictors: presence of fatigue and ascites at admission, administration of positive inotropes, heparin and antibiotics.

Other than the patient’s condition before and at admission, this study found that medication administered during hospitalisation could worsen hyponatremia. While higher serum sodium levels at admission lowers the risk of hyponatremia during hospitalisation, a history of fatigue before admission and the presence of ascites at admission conversely increases the risk. Patients who received positive inotropes, heparin and antibiotics in this study appeared to have around a three-fold higher risk of developing hyponatremia during hospitalisation, with OR 2.95 (95% CI [1.38–6.34]), 2.98 [1.33–6.66] and 2.87 [1.56–5.29]) respectively.

Factors associated with an increased risk of hyponatremia have been reported by several studies, but mostly for general patients or related to drug-induced hyponatremia such as antidepressants- and thiazide diuretic-induced hyponatremia. Although patients with HF have been identified as one of the vulnerable groups for encountering hyponatremia, studies investigating factors associated with increased
risk for hyponatremia in this patient group in a multivariate level have not yet been found. In the study conducted by Sato et al. (2013) several variables were found to be associated with hyponatremia in patients hospitalised with HF in univariate level, but the findings were not further discussed [197]. Until recently most studies on hyponatremia in HF patients focused on association between hyponatremia and clinical outcomes.

In general conditions, older age has been known as an important risk factor for hyponatremia [352]. In relation to drug-induced hyponatremia, lower body weight, hypokalemia, hyperlipidemia and type-2 diabetes were found as risk factors. Specifically associated with increased risk of HAH in general patients, several factors have been reported by Hoorn et al. (2006) and Beukhof et al. (2007) [273, 320]. Hoorn et al. analysed treatment-related factors, founding several factors that administration of thiazide diuretics, medication stimulating ADH, administration of hypotonic intravenous fluid and surgery had a significant association. In their multivariate analysis, Beukhof et al. found that the administration of insulin, opioids and antibiotics have a significant association with HAH [320].

Lower serum sodium level at admission was found as one risk factor associated with an increased risk of hyponatremia during hospitalisation in this research. Bissram et al. (2007) reported a similar finding from their study investigating risk factors associated with increased risk for severe symptomatic hyponatremia in general patients [353]. Previously uncorrected hyponatremia is one among several factors found in the study. This indicates that patients with hyponatremia or nearly in hyponatremic status at admission should receive adequate monitoring with regard to the higher risk for developing hyponatremia, or more severe hyponatremia, during hospitalisation.
History of fatigue was found in this research to potentially increase the risk of hyponatremia during hospitalisation almost four-fold. In addition to dyspnoea on effort, fatigue is a common symptom encountered by patients with HF [12]. Even among patients with stable HF, fatigue was reported by around half [354]. Perez-Moreno et al. (2014) also found that among HF patients with NYHA Class II to IV, only 5% did not have fatigue on exertion and another 9% had fatigue only with heavy exercise. Meanwhile, 86% reported fatigue on mild to moderate activities [355]. Other than as a common symptom, fatigue has also been found to be associated with poor prognosis and worse clinical outcomes in patients with HF [354-356]. Even though fatigue is a subjective symptom, it has been concluded by many studies that more severe fatigue indicates clinical problems that may be due to worsening HF, its complications or other chronic conditions or medications. Although Guglin et al. (2012) found that overall symptoms had no correlation with objective parameters of HF the study found that fatigue had association with lower serum sodium levels [357].

Other than history of fatigue, this research found the presence of ascites at admission as another patient-related factor associated with an increased risk of hyponatremia during hospitalisation in patients hospitalised with HF. Ascites is a symptom commonly observed in HF patients with marked volume overload occurring, especially when pressure on the right side of the heart is increased [12]. Activity of the RAAS as well as the SNS, is increased in severe HF leading to greater release of AVP, the neurohormone responsible for the development of hyponatremia [188, 193]. In addition to the increased release of AVP, the tendency of water retention in HF patients increases, presenting as oedema and ascites, which is usually seen as a result of increased solute-free water reabsorption caused by the increase of renal
vasoconstriction. Dilutional hyponatremia is a common consequence of severe water retention.

Ascites was found in 9.2% and 21.6% of patients without and with hyponatremia during hospitalisation in this research respectively. Among patients with chronic HF, ascites was found in 3% of the patients, and it was associated with poor prognosis [358]. Comparing patients with different worst symptoms in regard to hemodynamic profile and response to therapy, Kato et al. (2012) found ascites in 17% of overall patients and 50% among patients grouped within abdominal discomfort as the worst symptom [359]. Compared to other worst-symptom groups, the patients in the abdominal discomfort group, in which 50% presented with ascites, had lower sodium levels. This indicates that other than representing a more severe condition of HF, ascites is a risk factor of hyponatremia in HF patients [359].

Heparin was found among medication-related factors associated with increased risk for hyponatremia during hospitalisation in this research. Heparin found in this research was administered as low molecular weight heparin (LMWH), either fondaparinux or enoxaparin. Heparin is an intravenous anticoagulant commonly prescribed to patients with HF to prevent venous thromboembolism (VTE). HF is an important risk factor for VTE, and it has been reported that around 20% of HF patients with a high risk for VTE not receiving appropriate prophylaxis developed VTE.

Heparins, both unfractionated and LMWH, have an effect on the aldosterone metabolism resulting in electrolyte changes, especially hyperkalemia [360] and to a lower incidence of hyponatremia resulting from natriuresis as an effect of hypoaldosteronism [361, 362]. Heparin decreases aldosterone levels by reducing the number as well as the affinity of adrenal angiotensin II receptors, which further
attenuates the aldosterone release from the adrenal cortex. Although the decreased aldosterone level is reversible with short-term use of heparin, prolonged use may result in the reduction of aldosterone levels leading, or at least pre-disposing to severe hyperkalemia and hyponatremia [362].

In addition to heparin, this research found the administration of positive inotropes is another medication-related factor associated with increased risk for hyponatremia. Positive inotropes found to be administered to HF patients in this research were dobutamine and dopamine, either singly or in combination. Positive inotropes are recommended for HF patients with a low cardiac index showing profound signs of inadequate organ perfusion [12]. Although its use has been reported to be associated with increased mortality due to severe arrhythmia, appropriate administration of positive inotropes is reported to increase morbidity of patients with end-stage HF [363, 364].

Reports on hyponatremia in association with positive inotropes have not yet been found. As positive inotropes are administered mostly to HF patients with severe conditions mainly indicated by profound low EF, it is likely that administration of positive inotropes indicate a severe condition and low EF of the patients. Information on EF as one of the important objective parameters indicating severity of HF patients was not available for all patients in this research, thus administration of positive inotropes could be the surrogate factors of HF severity among these patients. It is known that patients with more severe HF have a higher risk of developing hyponatremia due to greater non-osmotic regulation of vasopressin release stimulated by low EF.

Antibiotics also show a significant association with increased risk of hyponatremia in this research. Several studies on antibiotic-induced hyponatremia have been reported,
mostly on the use of co-trimoxazole [365, 366], and to a lesser extent ciprofloxacin [367] has been also reported to cause hyponatremia. However, among hyponatremic patients receiving antibiotics in this research, ceftriaxone and its combination with azithromycin were the most administered antibiotics, and studies reporting hyponatremia associated with either antibiotic have not yet been found.

Administration of antibiotics has been also reported by Beukhof et al. (2007) as one risk factor associated with HAH [320]. Although it was found that administration of antibiotics is a significant factor associated with increased risk for HAH, the study also found that all prescribed antibiotics have not yet reported having an association with hyponatremia. Therefore, it has been suggested that administration of antibiotics is more likely a surrogate risk factor for infection considering that many studies report an association between infection and hyponatremia [368].

The association between several viral infections as well as central nervous system infections and hyponatremia has been reported by many studies [369-372]. However, pneumonia was more likely to be risk factor for hyponatremia in this research. It was found in this research that around three quarters of patients with unspecified infections at admission in the hyponatremic group were assigned as pneumonic during the days following hospital admission. The association between pneumonia and hyponatremia has been reported by several studies, and it was hypothesised that inflammatory reactions commonly taking part in the pathophysiological process of infectious diseases plays an important role in the development of hyponatremia among pneumonic patients [373, 374]. Interleukin-6, as an important cytokine in inflammatory reactions, has been found to have the ability to induce vasopressin release through non-osmotic regulation leading to the development of hyponatremia [368].
Findings related to the factors associated with an increased risk of hyponatremia found in this research will provide important information needed to improve the management of hyponatremia. As inadequate treatment of hyponatremia is still reported by many studies, it is important for clinicians as well as pharmacists and nurses to recognise the factors associated with an increased risk of hyponatremia so that appropriate treatment and monitoring can be administered appropriately [208]. Risk factors found in this research are slightly different to risk factors reported by other studies. In addition to specific patient conditions included in the research, the clinical setting of the research might also contribute to this difference. Despite the difference between some of the findings, there is a similarity with previously reported risk factors of hyponatremia in terms of the finding that some medications used to treat this group of patients with HF can potentially increase the risk for hyponatremia.

While all diuretics, especially thiazide diuretics, are known to have potential for affecting the electrolytes balance in hospitalised HF patients [273], this study could not support this finding. The research sample did not include any patients receiving thiazide diuretics; only furosemide and potassium sparing diuretics were recorded for all patients hospitalised during this research data collection period. Although furosemide and potassium sparing diuretics can also induce hyponatremia, to a lesser extent, the associated hyponatremia with them is dose-related.

### 6.7. Performance of the prediction model

The main purpose of assessing performance of a PM is to evaluate the goodness-of-fit (GoF) of the model, which mainly indicates the discrepancy between actual outcomes and predicted outcomes [274]. A good PM will show only a small discrepancy between actual–observed outcomes and the outcome predicted by the
model. Generally, the discrepancy is measured both overall and specifically in terms of discrimination and calibration ability of the model using common relevant statistical measures. Despite the importance and ease of assessing the GoF of PMs, studies reveal that appropriate evaluation of GoF are still seldom reported in papers studying clinical PMs [375, 376].

For a PM with a binary outcome, the Brier-score is the most used statistical measure for assessing the overall GoF. The score ranges between 0 and 0.25, in which scores of 0 and 0.25 indicate a perfect and an un-useful PM respectively. However, the maximum Brier score relies on the proportion of positive outcomes within the sample used to derive the PM. The maximum score of 0.25 is for a model with a 50% proportion of positive outcomes. For this research, given that the proportion of the sample having positive outcomes is 25%, the maximum value of the Brier score is 0.188, resulting from the formula: 0.25*(1 – 0.25)^2 + (1 – 0.25)*0.25^2 [274]. The Brier score of the obtained PM in this research was 0.107, indicating that the PM does not perfectly predict the outcomes, but it is still within the range of an informative model.

In addition to the Brier score, the $\text{NR}^2$ is commonly used to evaluate the GoF of generalised linear models was also used to assess overall performance of the PM resulted from this research. As $\text{NR}^2$ indicates the proportion of variance of the outcomes explained by the model, the $\text{NR}^2$ of 0.531 as found for the obtained PM in this research indicates that the model explains around 53% variance of the studied outcome. In more detailed analysis evaluating the contribution of each predictor included in the model, it was also found that each predictor contributes to the improved performance of the model as indicated by the increased value of the $\text{NR}^2$, along with the addition of the predictor. Contribution of the predictors to the PM was
also indicated by the increased percentage of correct prediction, in which the highest percentage of correct prediction was achieved when all six predictors were included in the PM. Quite similar to the Brier score, the obtained NR² of the PM indicates that it does not perfectly explain all variances determining the outcome, but still can explain around 50% of the variance.

Discrimination and calibration ability are two characteristics commonly assessed to specifically evaluate the GoF of the PM. A good PM should exhibit both good discrimination and calibration ability, and these two characteristics should be assessed together because assessing one of them is meaningless without the other [377]. However, which characteristic is more important is determined by the main purpose of deriving the PM; whether the PM is derived for scientific or practical purposes. Whilst discrimination ability is more important to be considered for PMs derived for research purposes, calibration ability is more important for PMs derived for practical purposes [277].

Discrimination expressing the ability of the model to discriminate subjects with and without the outcome is commonly assessed using the e-statistic, which for a binary outcome equals the AUC of ROC curve. In terms of this discrimination ability, the PM obtained from this research shows excellent discrimination ability indicated by an AUC of ROC curve of 0.9 (95% CI [0.86–0.93]). This means that the PM developed in this research has a very good ability to discriminate subjects at high risk and low risk of developing hyponatremia. Furthermore, each predictor included in the PM contributes to the increased discrimination ability, in which the addition of each predictor to the PM resulted in an increased AUC of ROC curve.

In the context of a PM, calibration ability refers to the agreement between actual outcomes and the probability of getting the outcome predicted by the model. In this
research, calibration ability of the PM was assessed primarily by calibration plot and also with the HL test, and both tests indicate that the PM has good calibration ability. Although the calibration plot showed that the probabilities predicted by the model were systematically higher than actual outcome, the \( p \)-values of the HL test indicate that there were no significant differences between the actual outcome and the predicted probabilities.

The intercept and calibration slope of the calibration plot, 0.266 and 1.047 respectively, indicate that the predicted probabilities were systematically higher compared to the actual outcomes. According to the calibration plot the PM showed only very good calibration ability for subjects with a low or high probability of getting the outcome, and the predictions were too high for subjects with a medium probability of getting the outcome. However, the \( p \)-value of the HL test indicates that there was no significant difference between predicted probability and the actual outcomes, indicating that the model has good calibration ability. Given that the default of the HL test divides the subjects into 10 groups, based on the value of the predicted probability the HL test in this research was also performed by changing the group number from five until 15. It was found that even when the group number was changed, the \( p \)-value of each group number indicated that there was no significant difference between predicted probability and actual outcomes, indicating that the PM has good calibration ability.

Despite the importance of assessing the discrimination and calibration ability of the PM, studies reveal that it is commonly reported inappropriately, especially for calibration [376, 378]. Among studies reporting calibration ability, the HL test is more commonly reported compared to the calibration plot. The major disadvantage of the HL test in terms of calibrating a PM is that the power of the test tends to be
poor for PMs derived from within a small dataset. In addition, the test assesses only the differences between actual outcome and predicted probabilities, denoted by \( p \)-value of chi-square test, without indicating the deviations of calibration. Meanwhile, calibration plot with more attractive illustrations can elucidate more information on the calibration profiles of the PM in terms of how far predicted probabilities are away from actual outcomes. In fact, these two calibration measures can be assessed together to result in more detail on calibration profiles of the PM [379].

6.8. Validation of the prediction model

The main purpose of validating a PM is to assess its optimism [380]. It is well known that overfitting is an important problem in deriving the PM, in which the model almost always shows good criteria of GoF when being assessed within the sample used to derive the model, but its performance is not good enough when assessed in different samples either taken from same or different populations [379]. This phenomenon is referred as optimism of the PM. Hence, assessing optimism of the PM is a very important step in obtaining a valid PM. Whilst external validation is needed before generalising the PM, and using it in different populations, internal validation is an important bridge to assess the performance of the PM within different samples taken from the same population so that at least can be decided whether the PM will be practically useful in that population or not.

Despite the importance of assessing the optimism of the PM by at least performing an internal validation, several reviews of clinical prediction studies found that it is still rarely reported. In their systemic review on the use of molecular markers in cancer prognostic models, Vickers et al. (2008) found that more than 90% of the reviewed studies did not assess optimism of the model [375]. Likewise, a systemic review on reporting and methods in clinical prediction research conducted by
Bouwmeester et al. (2012) found that only 17 out of 71 papers on clinical predictions included in the review reported internal validation [376]. In fact, internal validity can be used as estimation of external validity, especially when sample size and number of EVPs used to derive the model are large enough [287].

In this research a bootstrapping approach was used to internally validate the PM. This method has been reported as an efficient method for validating PMs, especially for models derived using a small sample size and lower number of EVPs compared to other methods, such as split-sample and cross-validation methods [287, 381, 382]. A bootstrapping method validates a PM in the same sample size as used to derive it by drawing a new sample from the original sample as a replacement. In terms of validating the PM, the number of bootstrap repetitions is important. Although 100–200 repetitions are considered adequate to gain steady estimates 500 bootstrap repetitions were performed in this research, as it has been reported as resulting in more stable estimates [274].

It was found from the bootstrap analysis that optimism of overall performance indicated by $R^2$ was 0.028 resulting in a 5% reduction of $R^2$. The corrected $R^2$ indicates that overall the PM is still within the range of informative models. The optimism of discrimination ability of the PM was 0.018, indicated by reduced AUC of ROC curve to 0.89 from its original 0.9. The reduced AUC of 0.89 indicates that optimism of the PM in terms of discrimination ability is small enough that the model still exhibits very good discrimination ability when it is implemented in different samples. In regard to calibration ability, the optimism of the calibration slope was also small and it resulted in a corrected calibration slope of 0.9343, indicating that the PM still has good calibration ability when implemented in different samples.
Minimising optimism of the PM is important in order to obtain a more accurate prediction for practical use. To shrink the regression coefficient of the PM to zero is an approach known to achieve this goal. This approach requires that regression coefficients should be shrunk using shrinkage factors resulting in shrunken regression coefficients. A uniform shrinkage factor of 0.9493 was obtained for the PM in this research, resulting from bootstrap analysis performed using the “Shrink” package in R software. The shrinkage factor was then used to get shrunken regression coefficients of the PM.

Internal validation indicates that the PM is suitable for use in the same population where the sample for deriving the PM was taken. In the other words, internal validation assesses only “reproducibility” of the PM so that it can be assessed whether the model is useful for implementation in that limited population or not [274]. In regard to this research, the results of the internal validation step show that the obtained PM can be used for risk prediction of hyponatremia during hospitalisation among patients hospitalised for HF at Fatmawati Hospital in Jakarta, Indonesia. However, additional assessment, such as decision-curve analysis still needs to be performed to assess clinical usefulness of the PM [375].

External validation is an important step that needs to be conducted in order to assess generalisability of the PM. Although the PM resulting from this research has been internally validated and shows good performance in validation samples, further external validation still needs to be performed before implementing it in wider clinical practice. More severe reduction of the model would potentially be identified during external validation, especially for PMs derived using a small sample size and a lower number of EVPs [277, 286]. However, external validation is beyond of this research.
6.9. Presentation of the prediction model

After a final PM has been decided, it can be then presented in several forms, such as regression formula, nomogram or score chart [274]. The FRS is an example of a prominent clinical PM in cardiovascular diseases using a score chart for its presentation. The scoring format was also used by Rastogi et al. (2012) in presenting their PM developed specifically for determining the risk for hospitalisation associated with thiazide-induced hyponatremia [312]. Risk predictions in various forms have been used, showing significant benefit in improving outcomes of several diseases including HF.

The PM obtained from this research was presented in regression formula, as this presentation format is the simplest form compared to other formats. It can also be presented as a risk score, but the problem is that the minimum and maximum value of serum sodium levels as one of the predictors included in the PM are not easily defined. However, regression formula also can be further presented in various computerised programs such as a simple formula in Microsoft® Excel™, which then can be implemented in several computer devices.

By using this PM, with the absence of all predictors other than serum sodium level at admission and 0.5 used as the cut off to classify patients into low and high risk, a serum sodium level lower than 129 mmol/L will put a patient in the category of high risk for hyponatremia during hospitalisation. Inversely, with the presence of other predictors – history of fatigue and presence of ascites at admission, administration of positive inotropes, heparin and antibiotics – a patient will have a high risk of developing hyponatremia during hospitalisation, even if the serum sodium level at admission is 150 mmol/L, and the risk will become higher with a lower serum sodium level at admission. This kind of prediction will be very helpful for
physicians, nurses and pharmacists in setting up appropriate strategies to minimise the adverse outcomes of hyponatremia.

6.10. Limitations

Like many retrospective studies, many of the limitations this study faced were due to the non-standardised manual or electronic data entry, patient admission and hospitalisation records. This study was conducted in a single tertiary referral hospital, and because the numbers of tertiary hospitals in Indonesia are limited in comparison to secondary hospitals, it might not be a true representation of the whole HF population hospitalised in Indonesia. Hence, further studies involving more centres and secondary hospitals need to be conducted to get a better picture of hyponatremia in patients hospitalised for HF in Indonesia. However, in terms of predictors included in the PM, those predictors would most probably be gained in all hospitals as they are related to basic information commonly gained during admission and hospitalisation.

This research intended to include predictors that can easily be gained as part of a routine examination or treatment of HF patients. Of course there are some basic or more advanced predictors that objectively indicate the severity of HF, and that are also strongly associated with hyponatremia, such as LVEF, pro-BNP and its derivate, or cytokines, that can be included in the PM. However, an echocardiogram to measure the LVEF and overall heart function is still not routine for all patients with HF in the research site, and possibly not in other developing countries either. Measurement of advanced markers such as pro-BNP and some relevant cytokines are even more unavailable in general hospitals in Indonesia. Therefore, the PM obtained from this research might only be reproducible when applied as a country-specific
PM, or at least applied to developing countries, as the predictors included in the model are only basic variables related to HF.

Patients in this study included only HF patients hospitalised with code I50.0 as their main diagnosis, which is only for patients with congestive HF and right ventricular failure (secondary to left HF). Therefore, other types of HF were not included in this study. Furthermore, hyponatremia in this study was only assessed by serum sodium level. Hence, patient hyponatremic status could not be differentiated as being euvolemic, hypervolemic or pseudo-hyponatremia. In terms of the severity of hyponatremia, serum sodium level was the only parameter used to assess severity, which could not distinguish between acute and chronic hyponatremia. However, serum sodium level is still the most important variable to assess the severity of hyponatremia, and more detailed information related to symptoms and duration of hyponatremia is further needed as the basis for administering appropriate treatment.

As frequently occurs with retrospective studies, some important information, such as information about medication history before hospitalisation, could not be gathered in this study. In terms of medication-related factors, dosing records of some medications were missing, so the effect of dose variation could not be analysed, especially for diuretics. All this information can be gained adequately with prospective data collection, but it is not impossible to add any new predictors related to this information to the obtained PM if it significantly contributes to the model. Therefore, this could be one issue for future research on the risk prediction for hyponatremia in patients hospitalised with HF.

6.11. Summary

This research found the prevalence of hyponatremia in patients hospitalised for HF within the range of the prevalence previously reported by other studies, and it was
also found that hyponatremia during hospitalisation, comprising PH and HAH, is significantly associated with an increased rate of in-hospital mortality and longer hospital stay. Conventional treatments consisting mostly of sodium chloride regimen were administered to hyponatremic patients in this research, but more adequate treatment is still needed, especially in selecting patients who will benefit from hypertonic saline solution and optimising the correction rate among patients with severe hyponatremia. The PM, consisting significant predictors that have been selected using a purposeful selection method, shows good performance both overall and specifically in terms of discrimination and calibration ability. This good performance was also exhibited in validation samples, indicating stable performance of the PM. The PM was presented in regression formula, which can be further transformed into a simpler calculation through applying a formula, which can be implemented in various computerised devices. The availability of a PM that can be used to identify HF patients at high risk for hyponatremia during hospitalisation will help healthcare teams arrange appropriate management strategies. With advances in therapeutics and the findings of more reliable markers of particular diseases, the role of the PM will continuously evolve.
Chapter VII – Conclusion and recommendations

The primary aim of this research was to obtain a PM that can be used to predict the risk for developing hyponatremia during hospitalisation in patients hospitalised with HF. The intended PM is a model which included predictors easily and commonly identified within affordable resources and facilities.

This research found that several factors, both patient- and treatment-related, are commonly identified during HF admission to hospitals that can be used as predictors to derive a standardised PM. Patient-related factors that can be identified during admission, and found in this research to have a significant association with hyponatremia during hospitalisation, are serum sodium level, history of fatigue, and presence of ascites. Additionally, the administration of positive inotropes, heparin and antibiotics were found to be medication-related factors showing significant association.

The PM derived by including these six predictors exhibited good performance both of overall and specific performance in terms of discrimination and calibration ability. Although optimism was identified when the PM was internally validated, it did not reduce the predictive performance of the PM significantly, indicating that the PM can be implemented in different samples taken from the same population used to derive the PM. Hence, the intended PM with good performance was obtained, and it has potential for application in identifying HF patients at high risk of hyponatremia during hospitalisation.

The PM was presented in regression formula, which needs at least two steps of calculations to obtain predicted probability. It therefore needs further elaboration into a more convenient form to make it user-friendly. As the sample used to derive the
PM was taken from patients hospitalised during the period between 2011 and 2013, further temporal validation using sample taken subsequently can be conducted to assess its reproducibility within the population where the PM can primarily be implemented. Furthermore, validating the PM in some samples taken from a different population will be valuable for assessing its generalisability.

In addition to the finding fulfilling the primary aim, this research also confirms findings of other research concluding that hyponatremia is an important problem in patients with HF that is significantly associated with worse clinical outcomes. Combining PH and HAH in one definition as hyponatremia during hospitalisation, this research found that negative impact of hyponatremia in this definition is also similar to other types of hyponatremia assessed in other research, such as admission hyponatremia, PH and HAH. Therefore, hyponatremia of any type should be considered an important clinical problem.

At the research site, hyponatremia has been addressed and some different treatments have been administered. Nevertheless, more than half of the patients encountering hyponatremia during hospitalisation in this research did not receive any active treatment, and most were patients with severe hyponatremia according to their serum sodium level. This may indicate that hyponatremia is still not considered an important clinical problem, or in some cases it was unrecognised, especially in patients encountering HAH as previously reported from other research. Therefore, studies specifically aimed towards making sure that hyponatremia has been considered as an important clinical problem, and further treatments have been administered adequately, are important. This issue is more important for consideration for patients with severe hyponatremia, as this group of patients is vulnerable to the adverse effects of hyponatremia.
7.1. Significance to current body of knowledge

Studies report that hyponatremia is still an underrated problem, despite its significant role as a predictor of clinical outcomes. This indicates the urgent need for better understanding and practical approaches to minimise hyponatremia’s detrimental effects. One of the most important aspects in managing hyponatremic patients, besides choosing the treatment option, is to recognise the condition. However, until recently research on hyponatremia in patients with HF mostly investigated the importance of hyponatremia in association with clinical outcomes.

This research identified important risk factors and further developed a PM containing those risk factors, and the resultant findings can significantly contribute towards targeting patients needing more adequate monitoring in association with increased risk of hyponatremia. Subsequently, appropriate treatment can be administered to hyponatremic patients so that the adverse effects of hyponatremia can be attenuated. In a broader context this research also contributes towards raising awareness of hyponatremia; a neglected problem.

PMs presented in various forms have shown significant roles in improving prognosis as well as quality of life of patients with several disease conditions, either acute or chronic. In the context of chronic diseases the demand on PMs will tend to increase as global epidemiological data shows that their prevalence is increasing and becoming a global burden. A PM with good predictive performance will be helpful in both identifying patients with an increased risk of developing any chronic disease, or those having a poor prognosis. A PM can also help in making decisions about whether a patient will benefit from any particular treatment or not based on the probability of getting the benefit predicted. Likewise, the probability of adverse effects of any medication or treatment can be also predicted using PMs.
Unfortunately, until recently, most PMs come from developed countries, which are not easily used in developing countries because predictors included are commonly too advanced and not affordable in developing countries. Hence, the development of country-specific PMs or those containing more affordable predictors that can be applied in developing countries is very important.

7.2. Follow-up and future research

Locally in Indonesia, this research is just a beginning – both in the context of hyponatremia and PMs. Specifically related to this research, conduct of temporal validation and further external validation of the PM obtained from this research are very important in the near future to make sure that the PM can be practically used. In the broader issue of hyponatremia in HF patients, the development of the PM to target patients in the community or outpatient setting is also important. Although the prevalence of hyponatremia among HF patients in the community is reported as lower than the prevalence in hospitalised patients, it cannot be ignored because its detrimental effects have been reported by many studies.

It is well known that sodium restriction is part of an important lifestyle modification in patients with cardiovascular diseases. However, it is possible that the correct amount of daily sodium in the diet is still not yet understood by most patients. On the other hand, medications commonly prescribed to manage cardiovascular problems have the ability to impair sodium-water regulation. Therefore, it is important to investigate sodium in the diet of patients with cardiovascular problems, the prevalence of hyponatremia in this population, and the relationship between sodium in the diet and medications used by patients with hyponatremia, such as those with hypertension and HF.
Despite the incompleteness of the data, this research also found that hyponatremic patients were inadequately treated. Hence, research aiming to improve the treatment of hyponatremic patients is also important. Appropriate differentiation between patients with chronic and acute hyponatremia, and intensification of factors associated with increased risk of each type of hyponatremia are important parts of such research. Subsequently, finding appropriate treatment for each type of hyponatremia can be investigated. In patients with severe hyponatremia, investigation of appropriate sodium correction rates in order to prevent untoward effects of either uncorrected or overcorrected hyponatremia is also important.
References


69. Emdin CA, Callender T, Cao J, McMurray JJ, Rahimi K: Meta-Analysis of Large-Scale Randomized Trials to Determine the Effectiveness of Inhibition of the Renin-


131. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM, Jr., Abraham WT, Smart FW, Stevenson LW et al: *Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights*


191


240. Peri A, Combe C: Considerations regarding the management of hyponatraemia secondary to SIADH. Best Practice & Research Clinical Endocrinology & Metabolism 2012, 26:516-526.


326. Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O’Connor CM, She L, Yancy CW, Young J, Fonarow GC et al: *Relationship between


20th November 2014

Prof Patrick Ball and Mr Saepudin
School of Psychological and Clinical Sciences
Via email: Patrick.Ball@cdu.edu.au

Dear Patrick and Saepudin,

RE: H14088 – Development of prediction model to identify heart failure patients with high risk of developing hyponatremia during hospitalisation.

[Project 2013/2015: Approved by Charles Sturt University HREC. EC00115]

Institutional approval for previously approved HREC proposals

Thank you for submitting the above proposal for institutional approval. The proposal has been considered under the auspices of the Charles Darwin University and has been authorised to proceed.

Annual Report Due: 26/11/2015

An annual progress report and the details of any approved variations, renewals, incidences or final reports approved by the reviewing institute must be provided to the Ethics Office. This reciprocal approval is contingent on submission of a satisfactory annual progress report. Annual reports and Approval from the reviewing HREC can be submitted to ethics@cdu.edu.au

Should you wish to discuss the above research project further, please contact the Research Ethics Coordinator of the Ethics Office via email: ethics@cdu.edu.au or telephone: (08) 8946 6923.

Best wishes for the success of your project.

Yours sincerely,

Dr Bev Turnbull
Chair, Human Research Ethics Committee
Charles Darwin University, NHMRC Registration No. EC00154

OFFICE OF RESEARCH AND INNOVATION ETHICS
T: +61 8 8946 8933 | F: +61 8 8946 7006 | E: ethics@cdu.edu.au
Casuarina Campus
21 November 2013

Mr Saepudin Saepudin
School of Biomedical Sciences
CSU Locked Bag 588
WAGGA WAGGA NSW 2678

Dear Mr Saepudin,

Thank you for the additional information forwarded in response to a request from the Human Research Ethics Committee (HREC).

The CSU HREC reviews projects in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Research Involving Humans.

I am pleased to advise that your project entitled “Development of prediction model to identify heart failure patients with high risk of developing hyponatremia during hospitalisation” meets the requirements of the National Statement; and ethical approval for this research is granted for a twelve-month period from 21 November 2013.

The protocol number issued with respect to this project is 2013/203. Please be sure to quote this number when responding to any request made by the Committee.

Please note the following conditions of approval:

- a Waiver of Consent approved
- you must notify the Committee immediately in writing should your research differ in any way from that proposed. Forms are available at: [http://www.csu.edu.au/_data/assets/word_doc/0010/176833/ehrc_anmrep.doc](http://www.csu.edu.au/_data/assets/word_doc/0010/176833/ehrc_anmrep.doc) (please copy and paste the address into your browser)
- you must notify the Committee immediately if any serious and or unexpected adverse events or outcomes occur associated with your research, that might affect the participants and therefore ethical acceptability of the project. An Adverse Incident form is available from the website: as above;
- amendments to the research design must be reviewed and approved by the Human Research Ethics Committee before commencement. Forms are available at the website above;

Approval after further information.doc

Last updated: February 2013
Next review: February 2014

www.csu.edu.au

CHIUC Provider Numbers for Charles Sturt University - CE0103 (NSW), 014975 (VIC) and 000963 (ACT). ABN: 80 127 399 561

203
• If an extension of the approval period is required, a request must be submitted to the Human Research Ethics Committee. Forms are available at the website above;

• you are required to complete a Progress Report form, which can be downloaded as above, by 17 October 2014 if your research has not been completed by that date;

• you are required to submit a final report, the form is available from the website above.

YOU ARE REMINDED THAT AN APPROVAL LETTER FROM THE CSU HREC CONSTITUTES ETHICAL APPROVAL ONLY.

If your research involves the use of radiation, biological materials, chemicals or animals a separate approval is required from the appropriate University Committee.

The Committee wishes you well in your research and please do not hesitate to contact the Executive Officer on telephone (02) 6338 4628 or email ethics@csu.edu.au if you have any enquiries.

Yours sincerely

[Signature]

Julie Hicks
Executive Officer
Human Research Ethics Committee
Direct Telephone: (02) 6338 4628
Email: ethics@csu.edu.au
Ct: Professor Lesie Wang, Professor Patrick Bell

---

This HREC is constituted and operates in accordance with the National Health and Medical Research Council’s (NHMRC) National Statement on Ethical Conduct in Human Research (2007).

---

Approval_after_further_information.doc
Last updated: February 2013
Next review: February 2014
Surat Persetujuan Etik (Ethical Approval)
Nomor: Lj5 /TU.DM/ VIII / 2014

Dengan ini Tim Kaji Etik Rumah Sakit Umum Pusat Fatmawati dalam upaya melindungi hak asasi manusia dan kesejahteraan subyek penelitian kesehatan/ penelitian medik, setelah melakukan pembahasan, penilaian serta mengkaji secara teliti terhadap proposal penelitian, yang berjudul:

"Pengembangan Model Prediksi Untuk Mengidentifikasi Pasien Gagal Jantung Yang Memiliki Risiko Tinggi Mengalami Hiponatremia"

Peneliti Utama : Saepudin, M.Si., Apt
NIK. 006130102

Nama Institusi : Fakultas Matematika Dan Ilmu Pengetahuan Alam
Universitas Islam Indonesia Yogyakarta

Memutuskan bahwa penelitian disetujui pelaksanaannya. Persetujuan ini berlaku sejak tanggal ditetapkan sampai batas waktu penelitian yang tertera dalam proposal. Sehubungan dengan penelitian ini, peneliti berkewajiban untuk:
1. Menjaga kerahasiaan subyek penelitian.
2. Memberi status penelitian apabila:
   a. Setelah sampai batas waktu berlaku persetujuan etik, penelitian masih belum selesai, dalam hal ini persetujuan etik harus diperpanjang,
   b. Penelitian berhenti ditengah jalan/ peneliti mengundurkan diri.
3. Melaporkan kejadian serius yang tidak diinginkan (serious adverse events)
4. Peneliti tidak boleh melakukan tindakan apapun pada subyek sebelum penelitian lolos kaj etik dan informed consent
5. Melaporkan hasil penelitian jika pelaksanaan penelitian telah selesai kepada tim kaji etik penelitian kesehatan RSUP Fatmawati.

Demikian surat persetujuan etik penelitian ini dikeluarkan agar dapat dipergunakan dengan penuh tanggungjawab.

Jakarta, 18 Agustus 2014

Ketua Tim Kaji Etik Penelitian Kesehatan
RSUP Fatmawati

Dr. Zainal Adhim, Sp.TM-HKL, PhD
NIP. 197009192005011006
Hyponatremia during hospitalization and in-hospital mortality in patients hospitalized from heart failure

S. Saepudin1, Patrick A. Bail3 and Hana Morrissey1

Abstract

Background: To date, the majority of studies on hyponatremia focused on hyponatremia at admission, and came from developed countries. This study aimed to identify the prevalence of hyponatremia during hospitalization in patients hospitalized for HF and its association with in-hospital mortality.

Methods: This was an observational study using retrospective data from patients’ records between 2010–2013. It focused on those patients carrying an ICD-10 code of 150.0 (Congestive Heart Failure) as their primary diagnosis. Hyponatremia during hospitalization was defined as serum sodium level lower than 135 mEq/L, obtained from a blood chemistry measurement on the next days after admission. Patients’ characteristics were examined and the association between hyponatremia during hospitalization and in-hospital mortality was analyzed.

Results: Among 464 patients hospitalized for HF, hyponatremia during hospitalization was observed in 22% of patients with 44% of this group had normal serum sodium level on admission. Hyponatremia during hospitalization was associated with lower blood pressure on admission, both systolic and diastolic, peripheral oedema, ascites and fatigue. Patients having history of hospitalization for cardiac diseases and renal failure were higher in patients developing hyponatremia during hospitalization. In this group, amiodarone, heparin, insulin and antibiotics were administered more frequently. Factors potentially increase the risk of hyponatremia during hospitalization include history of fatigue (OR = 3.23, 95% CI 1.79–5.83), presence of ascites (OR = 1.4, 1.64–9.31), and administration of heparin (OR = 3.85, 1.78–8.31) and antibiotics (OR = 1.71, 0.75–5.54). Length of hospital stay was significantly longer in patients with hyponatremia during hospitalization and in-hospital mortality was also higher compared to non-hyponatremic patients, 7.7% and 29.1% respectively.

Conclusion: This study found that the prevalence of hyponatremia during hospitalization in patients hospitalized for HF was almost the same as hyponatremia on admission and administration of heparin and antibiotics can potentially worsen hyponatremia during hospitalization. In this study population, hyponatremia during hospitalization was found to be associated with in-hospital mortality.

Background

Hyponatremia is an under-rated problem in managing patients with heart failure (HF). It shares many pathophysiologic and prognostic features with HF [1, 2]. Patients with HF have a high probability of suffering from hyponatremia, either as a result of disease progression or the effects of medications [3, 4]. Diuretics cause fluid loss by excreting sodium, and medications that inhibit the production or action of aldosterone, (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, spironolactone) prevent sodium re-uptake from the kidney. Additionally, hyponatremia is a strong independent predictor of quality of life and mortality in patients with HF [5–11]. In both hospitalized patients, and those in the community, the role of sodium depletion as a predictor of short-term and long-term prognosis, has been documented [12, 13].

In HF patients, hyponatremia may occur through a complex process of pathophysiology related to the changes contributing to HF, including hormonal and neurological...
disorders [3, 4]. Chronic activation of the renin-angiotensin-aldosterone system (RAAS) concurrently with stimulation of the sympathetic nervous system as a response to inadequate tissue perfusion, stimulates a counter-productive effect including cardiac remodeling and water and sodium retention [2, 3]. Arginine vasopressin (AVP) is also released as a response to low cardiac output, to increase intravascular volume. However, the effect is further counter-productive for cardiac workload as preload is increased [1, 15, 16].

The risk of hyponatremia among patients with HF is associated with the severity of the HF [11]. When ventricular dysfunction is severe, the counter-productive neurohormonal response will also increase, leading to excessive water reabsorption, after which hyponatremia can occur [15]. The lower the cardiac output, the greater the AVP release. Prolonged elevation of this hormone in the systemic circulation, results in an increase of water retention leading to a dilution process that may result in hyponatremia [3, 4].

Most published studies on hyponatremia in patients with HF have been conducted in developed countries with advanced resources. Additionally, most studies focused on the prevalence of hyponatremia on admission and its association with in-hospital mortality or long-term prognosis. Studies on hyponatremia from developing countries with limited resources, and also studies focusing on hyponatremia during hospitalization are still lacking. This study aimed to assess the prevalence of hyponatremia during hospitalization in patients hospitalized from HF and its relationship with in-hospital mortality.

Methods
This was an observational retrospective study conducted at Fatmawati Hospital, a tertiary teaching hospital, located in Jakarta Indonesia. A cross-sectional study was designed to assess the prevalence of hyponatremia during hospitalization and its relationship with in-hospital mortality. Patients hospitalized for HF between January 2010 and December 2013 aged 18 years or older, coded with ICD-10 according to International classification of diseases, 10th edition (ICD-10) system and having a reasonably complete record during hospitalization were included in this study. Patients diagnosed as having any malignancy, hepatic cirrhosis, pregnant women and patients on dialysis, and those with missing records were excluded from this study. Patient information collected included demographic profiles, vital signs and symptoms at admission, past medical history, medication during hospitalization and blood chemistry profiles. All were retrieved manually from medical records.

In this study, a patient was categorized as hyponatremic if serum sodium level was lower than 135 mEq/L. A patient was categorized as developing hyponatremia during hospitalization, if at least one episode of hyponatremia occurred on the next day after admission regardless of serum sodium level on admission. Serum sodium levels were corrected for patients with blood glucose level >200 mg/dL using correction factor of 2.4 per 100 mg/dL increase of blood glucose level [17]. In-hospital mortality in this study was defined as death from any cause during hospitalization.

Continuously variable data with normal distribution are presented as mean ± SD, and Student's t-test was used to compare the means of the groups. If the data was not normally distributed, median with interquartile ranges is quoted and Mann–Whitney U tests were used to compare groups, respectively. Nominal data were presented as proportion (percentage) and Chi-square tests were used to compare the groups. Logistic regression analysis was performed to identify variables associated with hyponatremia during hospitalization by including all variables available at admission and during hospitalization as independent variables. Logistic regression analysis was also performed to assess the relationship between hyponatremia, both at admission and during hospitalization, and in-hospital mortality. Two tailed p values < 0.05 and odd ratios were considered to indicate a statistically significant relationship. All statistical analyses were performed using Statistical Package for Social Sciences software for Windows version 23.0 (SPSS Inc., Chicago, USA).

This study was conducted in accordance with the regulations on extracting patients’ information from medical records established by Ministry of Health Republic of Indonesia and has been approved by Fatmawati Hospital Ethics Committee and The Charles Darwin University Ethics Committee.

Results
During 2011–2013, 543 hospitalized patients were coded with ICD-10 for their main diagnosis of hospitalization. Seventy-nine patients were excluded, due to incomplete laboratory records, pregnancy or routine hemodialysis. Compared to other electrolyte disturbances, this study found that hyponatremia, both on admission and during hospitalization, was the most prevalent. Table 1 shows that the prevalence of hyponatremia in patients hospitalized for HF is around double that for hypokalemia. In 464 hospitalized patients with HF included in this study, hyponatremia was found in 19 % on admission and 22 % during hospitalization. Distribution of serum sodium levels is shown in Fig. 1. The mean lowest measured serum sodium level in patients with hyponatremia during hospitalization was not significantly different from the mean lowest serum sodium level of patients with hyponatremia on admission, 129.8 ± 6.2 mEq/L and
Table 1 Comparison between sodium and potassium disturbances observed in patients hospitalized for HF

<table>
<thead>
<tr>
<th>Type of electrolyte disturbance</th>
<th>Prevalence based on time of occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On admission</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>10%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>19%</td>
</tr>
</tbody>
</table>

130 ± 4.2 mmHg/L, respectively, but hyponatremia during hospitalization comprised more severe serum sodium depletion (p < 0.001).

As this study focused on hyponatremia during hospitalization, comparison of patients’ characteristics was listed between patients with and without hyponatremia during hospitalization as shown in Table 2. Compared to those with normonatremia, patients with hyponatremia during hospitalization were of similar age and gender. However, patients with hyponatremia had lower blood pressure, both systolic and diastolic, more peripheral oedema, ascites and fatigue; but chest pain was found to be less frequent. In terms of past medical history, the proportion of patients having a history of hypertension was lower in patients with hyponatremia but the proportion of patients having a history of hospitalization for cardiac diseases was higher. Among comorbid diagnoses, renal failure was found more prevalence in hyponatremic patients. Other than the serum sodium and chloride levels, patients with hyponatremia during hospitalization had significantly different levels of blood urea nitrogen, lipid profile, albumin, and hepatic enzymes levels (Alanine transaminase- ALT and Aspartate transaminase- AST) from patients without hyponatremia. Hyponatremic patients had lower total cholesterol and high density lipoprotein (HDL) levels. Serum albumin of patients with hyponatremia during hospitalization was lower than patients without, and this might be associated with the higher proportion of patients having ascites in the hyponatremic group. Elevated hepatic enzymes level, both AST and ALT, were more prevalent in patients with hyponatremia during hospitalization.

Table 3 listed medication administered to patients hospitalized for HF during hospitalization. While the proportion of patients receiving diuretics, both furosemide and potassium sparing diuretics, was not different, the proportion of patients receiving angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) was lower in patients with hyponatremia during hospitalization. The number of patients receiving amiodarone, heparin, insulin and antibiotics was higher in those developing hyponatremia during hospitalization compared to others without hyponatremia.

Table 4 lists variables associated with hyponatremia during hospitalization found during multivariable logistic regression analysis. Other than serum sodium level at admission, other factors associated with hyponatremia during hospitalization found in this research are history of fatigue, history of hypertension, presence of ascites at admission, and administration of heparin and antibiotics during hospitalization.

Patients developing hyponatremia during hospitalization showed a significantly longer length of hospital stay compared to patients without hyponatremia, with median and interquartile range at 11 (8–15) and 8 (5–12) days, respectively. In-hospital mortality rate was also observed higher (p < 0.001) in hyponatremic patients compared to patients without hyponatremia, at 29.1 % and 7.7 %, respectively.

In term of in-hospital mortality, as showed in Table 5, while hyponatremia on admission has no association with in-hospital mortality, hyponatremia during hospitalization has an association with odds ratio 3.473 (95 % CI 1.899–6.351).

Discussion

The present study clearly demonstrates that hyponatremia is the most prevalent electrolyte disturbance in patients...
Table 2 Comparisons of patients’ characteristics between patients with normoxemia and patients with hypoxemia during hospitalization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-hypoxemia during hospitalisation (n = 362)</th>
<th>Hypoxemia during hospitalisation (n = 362)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.2 ± 15.3</td>
<td>53.1 ± 12.9</td>
<td>0.192</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>55.6%</td>
<td>50.9%</td>
<td>0.041</td>
</tr>
<tr>
<td>Ejection fraction (Fr) *</td>
<td>39.3 ± 18.4</td>
<td>31.0 ± 20.1</td>
<td>0.046</td>
</tr>
<tr>
<td>Inhertia as cause of HF</td>
<td>583.3%</td>
<td>51.9%</td>
<td>0.254</td>
</tr>
<tr>
<td>Vital signs and symptoms on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>125.4 ± 27.4</td>
<td>117.8 ± 24.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP</td>
<td>85.1 ± 18.2</td>
<td>76.9 ± 16.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart rate</td>
<td>94.8 ± 17.6</td>
<td>97.4 ± 18.9</td>
<td>0.212</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>26.7 ± 5.9</td>
<td>27.6 ± 6.1</td>
<td>0.181</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>896.9%</td>
<td>715.0%</td>
<td>0.705</td>
</tr>
<tr>
<td>PND</td>
<td>52.5%</td>
<td>58.3%</td>
<td>0.257</td>
</tr>
<tr>
<td>Cough</td>
<td>186.8%</td>
<td>186.0%</td>
<td>0.971</td>
</tr>
<tr>
<td>Chest pain</td>
<td>26.7%</td>
<td>7.8%</td>
<td>0.003</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>41.1%</td>
<td>72.5%</td>
<td>0.033</td>
</tr>
<tr>
<td>Asthenes</td>
<td>88.4%</td>
<td>21.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>215.5%</td>
<td>50.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>45.1%</td>
<td>31.4%</td>
<td>0.014</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22.7%</td>
<td>26.5%</td>
<td>0.064</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>4.1%</td>
<td>7.8%</td>
<td>0.128</td>
</tr>
<tr>
<td>Asthma</td>
<td>4.0%</td>
<td>1.9%</td>
<td>0.351</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>4.7%</td>
<td>7.8%</td>
<td>0.214</td>
</tr>
<tr>
<td>Arthrosis</td>
<td>22.4%</td>
<td>29.0%</td>
<td>0.500</td>
</tr>
<tr>
<td>Previous hospitalization for cardiac disease</td>
<td>489.9%</td>
<td>51.9%</td>
<td>0.046</td>
</tr>
<tr>
<td>Concomitant diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>15.5%</td>
<td>12.7%</td>
<td>0.035</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15.7%</td>
<td>30.6%</td>
<td>0.128</td>
</tr>
<tr>
<td>Renal failure</td>
<td>17.7%</td>
<td>33.3%</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac anhythmias</td>
<td>4.9%</td>
<td>5.9%</td>
<td>0.714</td>
</tr>
<tr>
<td>Infectious diseases (other than pneumonai)</td>
<td>4.1%</td>
<td>5.9%</td>
<td>0.456</td>
</tr>
<tr>
<td>Blood chemistry at admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>139.0 ± 4.5</td>
<td>133.1 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.4 ± 0.8</td>
<td>4.3 ± 0.9</td>
<td>0.24</td>
</tr>
<tr>
<td>Glucose (mEq/L)</td>
<td>102.9 ± 7.4</td>
<td>96.2 ± 8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>142.1 ± 71.2</td>
<td>137.1 ± 76.7</td>
<td>0.555</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>507.7 ± 33.7</td>
<td>73.1 ± 50.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.4 ± 1.1</td>
<td>1.7 ± 1.4</td>
<td>0.075</td>
</tr>
<tr>
<td>Urace acid (mg/dL)</td>
<td>54.5 ± 5.7</td>
<td>90.0 ± 40</td>
<td>0.33</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>168.0 ± 48.3</td>
<td>137.4 ± 48.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>35.5 ± 17.9</td>
<td>31.4 ± 12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protein total (g/dL)</td>
<td>62.5 ± 9.0</td>
<td>63.5 ± 12</td>
<td>0.007</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.6 ± 0.6</td>
<td>3.2 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>127.7 ± 25</td>
<td>128.6 ± 23</td>
<td>0.319</td>
</tr>
</tbody>
</table>

*Fr * = Fraction; DBP = Diastolic Blood Pressure; PND = Perinatal Nephropathy;
Table 2: Comparisons of patients' characteristics between patients with normonatremia and patients with hyponatremia during hospitalization (Continued)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Non-hyponatremia (n=100)</th>
<th>Hyponatremia (n=100)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte (k×10^-4)</td>
<td>461±1.25</td>
<td>461±1.25</td>
<td>0.996</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39.5±7.0</td>
<td>40.2±6.9</td>
<td>0.544</td>
</tr>
<tr>
<td>Liacase (k×10^-4)</td>
<td>8.4 (6.3-11.3)</td>
<td>8.5 (7.0-12.8)</td>
<td>0.187</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>24 (22-55)</td>
<td>40 (28-83)</td>
<td>0.012</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>29 (18-51)</td>
<td>35 (19-88)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Table 3: Medication administered during hospitalization

<table>
<thead>
<tr>
<th>Medication</th>
<th>Non-hyponatremia during hospitalization (n=100)</th>
<th>Hyponatremia during hospitalization (n=100)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>95.5%</td>
<td>95.5%</td>
<td>0.931</td>
</tr>
<tr>
<td>ACEs or ARBs</td>
<td>77.3%</td>
<td>66.7%</td>
<td>0.01</td>
</tr>
<tr>
<td>Sparing diuretics</td>
<td>24.3%</td>
<td>29.4%</td>
<td>0.296</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>15.5%</td>
<td>22.5%</td>
<td>0.093</td>
</tr>
<tr>
<td>Potassium supplement</td>
<td>55.5%</td>
<td>53.9%</td>
<td>0.774</td>
</tr>
<tr>
<td>Positive isotopes</td>
<td>9.1%</td>
<td>31.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Organic nitrates</td>
<td>62.7%</td>
<td>54.9%</td>
<td>0.186</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>26.5%</td>
<td>26.5%</td>
<td>0.785</td>
</tr>
<tr>
<td>Acarbose</td>
<td>48.1%</td>
<td>43.1%</td>
<td>0.376</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>28.7%</td>
<td>33.3%</td>
<td>0.369</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>46.4%</td>
<td>41.2%</td>
<td>0.348</td>
</tr>
<tr>
<td>Heparin</td>
<td>9.1%</td>
<td>18.6%</td>
<td>0.007</td>
</tr>
<tr>
<td>Warfarin</td>
<td>26.5%</td>
<td>21.6%</td>
<td>0.311</td>
</tr>
<tr>
<td>CCBs</td>
<td>44.4%</td>
<td>8.8%</td>
<td>0.144</td>
</tr>
<tr>
<td>Lurascon</td>
<td>14.7%</td>
<td>10.8%</td>
<td>0.314</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>13.5%</td>
<td>9.8%</td>
<td>0.318</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>40.9%</td>
<td>38.2%</td>
<td>0.630</td>
</tr>
<tr>
<td>PPH</td>
<td>14.9%</td>
<td>22.5%</td>
<td>0.069</td>
</tr>
<tr>
<td>H2RA</td>
<td>22.1%</td>
<td>30.4%</td>
<td>0.083</td>
</tr>
<tr>
<td>Alfapaprot</td>
<td>18.6%</td>
<td>20.6%</td>
<td>0.683</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>21.8%</td>
<td>22.5%</td>
<td>0.976</td>
</tr>
<tr>
<td>Insulin</td>
<td>7.5%</td>
<td>13.7%</td>
<td>0.126</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>66.8%</td>
<td>59.6%</td>
<td>0.786</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>33.4%</td>
<td>71.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta blockers on discharge</td>
<td>16.8%</td>
<td>12.9%</td>
<td>0.225</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>8 (5-12)</td>
<td>11 (8-15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>7.7%</td>
<td>29.1%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

hospitalized for HF [7, 8, 10]. Based on information on vital signs and symptoms at admission, this study also shows that patients with hyponatremia presented with more severe disease and their prognosis, in terms of in-hospital mortality, was also worse. Compared to patients without hyponatremia during hospitalization, peripheral edema and ascites at admission were found to be more prevalent in patients who developed hyponatremia during hospitalization. Patients with more severe HF would potentially have these symptoms as a result of poor cardiac function, i.e. more severe ventricular dysfunction. Left ventricular ejection fraction (LVEF) has been well known as an indicator of cardiac pump function, in which lower LVEF indicates poorer cardiac pump function [12]. In this study, the average of LVEF is not significantly different between patients with normonatremia and patients with hyponatremia during hospitalization, but the average was calculated from only 47.6 % and 43.4 % of patients with and without hyponatremia during hospitalization, respectively. In their research, Soto et al. reported signs of a difference LVEF between these groups but this was not significant [8].

This study found that a higher proportion of patients developing hyponatremia during hospitalization had a history of hospitalization for cardiac diseases but the disease was not mentioned specifically in medical records. Previous published studies also reported that more hyponatremic patients have previous hospitalization for HF compared to nonhyponatremic patients [8, 13] and this might be related to the poorer condition of HF in hyponatremic patients. Renal failure was the only one

Table 4: Factors associated with hyponatremia during hospitalization

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of fatigue</td>
<td>&lt;0.001</td>
<td>3.23</td>
<td>1.79-5.83</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0.022</td>
<td>0.49</td>
<td>0.27-0.91</td>
</tr>
<tr>
<td>Serum sodium at admission</td>
<td>&lt;0.001</td>
<td>0.77</td>
<td>0.73-0.81</td>
</tr>
<tr>
<td>Presence of ascites</td>
<td>0.001</td>
<td>4.14</td>
<td>1.85-9.31</td>
</tr>
<tr>
<td>Administration of heparin</td>
<td>0.001</td>
<td>3.85</td>
<td>1.78-8.31</td>
</tr>
<tr>
<td>Administration of antibiotics</td>
<td>&lt;0.001</td>
<td>3.08</td>
<td>1.71-5.53</td>
</tr>
</tbody>
</table>
Table 5 Association between hyponatremia and in-hospital mortality

<table>
<thead>
<tr>
<th>Type of hyponatremia based on time of occurrence</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia on admission</td>
<td>0.004</td>
<td>1.874</td>
<td>0.989-3.551</td>
</tr>
<tr>
<td>Hyponatremia during hospitalization</td>
<td>&lt;0.001</td>
<td>3.475</td>
<td>1.899-6.351</td>
</tr>
</tbody>
</table>

Concomitant diagnosis found in this study with a significant correlation between hyponatremic and non-hyponatremic patients but serum creatinine of both groups was found not significantly different. However, the average of blood urea nitrogen in hyponatremic patients was found higher than non-hyponatremic patients. In acute conditions, serum creatinine of HF patients may be increased owing to hyperperfusion and congestion [16] and worsening renal function in HF patients with congestion has been found as a predictor for poorer prognosis [19]. Liver function abnormalities, detected by AST and ALT, was also found higher in patients with hyponatremia during hospitalization in this study. In HF patients, liver function abnormalities indicate the presence of cardiogenic syndrome and, specifically, higher level of AST and or ALT indicates ischemia within hepatocytes that should be considered both in managing the patients and predicting of long-term outcome [20].

In terms of medication administered during hospitalization, patients with hyponatremia during hospitalization received less ACEIs or ARBs compared to patients with normonatremia. In contrast, patients with hyponatremia received more amiodarone, heparin, insulin and antibiotics. This information on medication might also indicate more severe condition of patients with hyponatremia. The most used ACEIs or ARBs are administered orally and patients with severe condition would have difficulty to take oral medication. In contrast, amiodarone and heparin are administered parenterally and mostly used in patients with severe conditions. However, the rate of overall use of ACEIs or ARBs found in this study at 75 % is higher compared to the rate reported by Callender et al. [21] in their systematic review on HF in low-middle income countries and Siswanto et al. [22] in their study on HF in Indonesia, 57 % and 68 %, respectively.

Other than patient's condition before and at admission, this study found that medication administered during hospitalization could also worsen hyponatremia. While higher serum sodium level at admission and history of hypertension lowers the risk of hyponatremia during hospitalization, history of fatigue before admission and the presence of ascites at admission conversely increase the risk. Patients received heparin and antibiotics in this study appeared to have around a three fold higher risk of developing hyponatremia during hospitalization with odds ratios 3.85 (95 % CI 1.78-8.31) and 3.08 (1.71-5.53), respectively. While heparin has been known can induce hyponatremia [23], administration of antibiotics might induce hyponatremia by involving a complex association with pathophysiological process of infection.

The overall in-hospital mortality rate found in this study is 11 % and this is higher than the average of in-hospital mortality rates reported by Siswanto, et al. in their report on behalf of The Acute Decompensated Heart Failure National Registry (ADHERE) research team in Indonesia at 6.7 % [22]. This is also higher compared to in-hospital mortality rates of HF patients in developing countries reported by Callender, et al. [21] and in Asia Pacific reported by Allerton, et al. [24], 8 % and 4.8 %, respectively. The higher in-hospital mortality rate found in this study might be due to more severe conditions of the patients included in this study. In their report, Siswanto, et al. found that patients hospitalized for HF in Indonesia tend to have severe symptoms and lower LVEF [22]. It is a challenge for primary care providers and general practitioners in Indonesia to improve management of HF so that patients with HF will be not delayed to receive appropriate treatment [25].

While previous studies have revealed the association between hyponatremia on admission and in-hospital mortality in patients hospitalized for HF [8, 26, 27], the results of this study are slightly different. Instead of hyponatremia on admission, hyponatremia during hospitalization was found to have an association with in-hospital mortality as shown in Table 4. In this study, only 56 % of patients developing hyponatremia during hospitalization were hyponatremic on admission and this means that 45 out of 464 patients (9.7 %) included in this study developed hospital-acquired hyponatremia. In a study with unselected patients, hospital-acquired hyponatremia was found in around one third of hospitalised patients and the condition was associated with increase of length of hospital stay and in-hospital mortality [28]. Therefore, factors associated with increased risk of developing hyponatremia during hospitalization in patients hospitalized for HF are important to be studied.

Other than serum sodium levels several other factors should be considered to assess the hyponatremic status of a patient hospitalized for HF. Although HF patients have a high probability of developing hypervolemic hyponatremia, the possibility of the occurrence of pseudo-hyponatremia and other types of hyponatremia need also to be considered in order to administer appropriate management. Pseudo-hyponatremia, for instance, should be considered in HF patients with hyperglycemia or hypercholesterolemia [29].

As the use of arginine vasopressin receptor antagonists, also known as the vaptans, in patients with HF have been approved, American College Cardiology Foundation/American Heart Association put these drugs
on their recommendation for managing HF patients developing hypervolemic hyponatremia [36]. However, role of the vaptans in reducing all-cause mortality and cardiovascular mortality in patients with HF, including their acceptability for long-term use, are still questionable [31–33]. While the vaptans are now might be available in some developed countries, it is not easy to provide these drugs in developing countries due to the cost of the medication. Therefore, the first strategy to minimize hyponatremia-related problem in patients hospitalized for HF should be to optimize guideline-driven therapy and to assess hyponatremia more appropriately [34–37]. Furthermore, conventional options for managing hyponatremia such as the use of saline solution, either isotonic or hypertonic, are still important to be considered [29,38,39].

Limitations
This study was conducted in a single tertiary referral hospital, as the number of tertiary hospitals in Indonesia are more limited compared to secondary hospitals, this study might not be a true representation of the whole population hospitalized for HF in Indonesia. Hence, further studies involving more centers and secondary hospitals need to be conducted to get better picture on hyponatremia in patients hospitalized for HF in Indonesia. Patients included in this study were only HF patients hospitalized with code IS0.0 as their main diagnosis in which the code is only for patients with congestive HF and patients with right ventricular failure (secondary to left HF). Therefore, other types of HF were not included in this study. Furthermore, hyponatremia in this study was only assessed by serum sodium level. Hence, patients’ hyponatremic status could not be differentiable whether it was euvoletic, hypervolemic or might be pseudo-hyponatremia.

As frequently occurs with retrospective studies, some important information, such as information on medication history before hospitalization, could not also be gathered in this study.

Conclusion
This study confirmed the findings of previous studies on hyponatremia in patients hospitalized for HF in which hyponatremia was reported as the most prevalent electrolyte disturbances. In addition, this study found that 56% of patients having hyponatremia on admission continue to be hypotonic during hospitalization. Factors influencing the development of hyponatremia during hospitalization found in this study include history of fatigue, the presence of ascites, and administration of heparin and antibiotics. In this study population, in-hospital mortality was found to be more associated with hyponatremia during hospitalization than hyponatremia on admission.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
Conception and study design (PA), SS. Data collection (SS). Data analysis and interpretation (PA, PAH). Manuscript writing (PA, PAH, HM). All authors read and approved the final manuscript.

Acknowledgements
The authors would like to thank Directorate General of Higher Education (DGHE), Ministry of Education Republic of Indonesia for PhD scholarship supporting this study.

Received 10 January 2015 Accepted 4 August 2015
Published online: 14 August 2015

References


Appendix 4

Patient and medication-related factors associated with hospital-acquired hyponatremia in patients hospitalized from heart failure

S. Saepudin, Patrick A. Ball & Hana Morrissey

International Journal of Clinical Pharmacy
International Journal of Clinical Pharmacy and Pharmaceutical Care
ISSN 2210-7703
Int J Clin Pharm
DOI 10.1007/s11096-016-0296-3
Your article is protected by copyright and all rights are held exclusively by Springer International Publishing. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer’s website. The link must be accompanied by the following text: “The final publication is available at link.springer.com”.

Springer
Patient and medication-related factors associated with hospital-acquired hyponatremia in patients hospitalized from heart failure

S. Saopudin 1,2 • Patrick A. Ball 1 • Hana Morrisoy 1

Received: 7 September 2015/Accepted: 29 March 2016 © Springer International Publishing 2016

Abstract Background Hyponatremia has been known as an important predictor of clinical outcomes in patients with heart failure (HF). While information on hyponatremia in patients with HF has been available abundantly, information on factors associated with increased risk of developing hospital-acquired hyponatremia (HAH) is still limited. Objective To identify patients and medication-related factors associated with HAH in patients hospitalized from HF. Setting Fatmawati Hospital in Jakarta, Indonesia. Methods This is a nested case-control study with patients developing HAH served as case group and each patient in case group was matched by age and gender to three patients in control group. Patients included in this study are patients hospitalized from HF, and coded with I50 according to ICD-10, during 2011–2013 at Fatmawati Hospital in Jakarta, Indonesia. Information retrieved from patients’ medical records included demographic profiles, vital signs and symptoms at admission, past medical history, medication during hospitalization and clinical chemistry laboratory records. Multivariable logistic regression analysis was performed to find out patient and treatment-related factors associated with the development of HAH. Main outcome measures Patients and medication related factors having significant association with HAH. Results Four hundreds sixty-four patients were included in this study and 45 of them (9.7 %) met criteria of developing HAH so then, accordingly, 135 patients were selected as controls. 36 patient- and 22 treatment-related factors were analyzed in univariate logistic regression resulted in 20 factors having p value <0.2 and were included in multivariable logistic regression analysis. Final factors showing significant association with HAH are presence of ascites at admission (odds ratio = 4.7, 95 % confidence interval 1.9–11.5) and administration of amiodarone (3.2, 1.3–7.4) and heparin (3.1, 1.2–7.3) during hospital stay. Conclusion Presence of ascites at admission was found as patient-related factors associated with HAH in this study. In addition, administration of amiodarone and heparin during hospital stay were found as medication-related factors associated with HAH in patients hospitalized from HF.

Keywords Heart failure · Hyponatremia · Indonesia · Serum sodium level

Impacts on practice

- Patients hospitalized from heart failure (HF) presenting with ascites at admission and receiving heparin and amiodarone during hospitalization appear to have an increased risk of developing hospital-acquired hyponatremia (HAH).
- The serum sodium level should be monitored closely in hospitalised heart failure patients who have ascites.

Introduction

Hyponatremia is the most prevalent electrolyte disorder found among patients hospitalized with HF [1–3]. It may be observed at admission or develop during hospitalization,
and is commonly associated with worse clinical outcomes both in short and long-term [1, 4-6]. Despite its significant negative impacts, hyponatremia still appears inadequately understood leading to sub-optimal management [7, 8].

While hyponatremia at admission can be easily recognized from laboratory records as part of the normal routine measurements taken at admission, HAH is less readily recognized especially when laboratory measurements are not taken on a daily basis. A delayed recognition of HAH can potentially increase the requirement for complex and costly treatment as well as increased risk of mortality [7].

Identification of patients with a high risk of developing HAH is important in order to target patients who should be monitored more closely. This will further help in guiding appropriate therapy to reduce negative consequences of HAH.

Aims of the study

This study aimed to identify the prevalence of HAH and to identify patient and medication-related factors associated with the occurrence of hospital acquired hyponatremia in patients hospitalized from HF.

Ethics approval

This study was conducted in accordance with regulation on extracting patients’ information from medical records established by Ministry of Health Republic of Indonesia and has been approved by Fatmawati Hospital Ethics Committee and The Charles Darwin University Ethics Committee.

Methods

Definition of hyponatremia

In this study, serum sodium level between 135 and 150 mEq/L was considered a normal serum sodium level and hyponatremia was defined as a serum sodium level lower than 135 mEq/L [1, 9]. A patient was classified as developing HAH if admitted to the hospital with normal serum sodium level and had at least one episode of hyponatremia during their hospital stay. This was taken to be a serum sodium decrease of at least 3 mEq/L (>2x the standard deviation of the measurement).

Study design

To identify factors associated with HAH, a nested case-control design was developed in which cases comprised patients developing hyponatremia during a hospital stay with normal sodium level at admission and patients with normal serum sodium level both at admission and during hospital stay served as controls. Each patient in the case group was matched by age and gender to three patients in controls. Although a higher case-control ratio will decrease variability estimates, the ratio of 1:1, 1:2, 1:3 and 1:4 between case and control have shown similar estimates of accuracy compared to the full study population [10, 11]. Therefore, the 1:3 ratio used in this study was considered an appropriate design.

Data collection

The study was conducted using retrospective data of patients hospitalized with a main diagnosis of HF at Fatmawati Hospital, in Jakarta, Indonesia. Data of patients hospitalized during 2011–2013 were retrieved and patients were included in the study if they were coded with ICD-10 code according to International classification of diseases, 10th edition (ICD-10) system for their main diagnosis. Only patients aged 18 years or older and having reasonably complete information during hospital stay were included in this study. Patients were excluded if diagnosed as having any neoplasm, hepatic cirrhosis, receiving dialysis treatment during hospital stay and females who were pregnant. Information retrieved from patients’ medical records included demographic profiles, vital signs and symptoms at admission, past medical history, medication during hospitalization and clinical chemistry laboratory records.

Statistical analysis

Continuous variables distributed normally were presented as mean ± SD, and Student’s t tests were used to compare the means of the groups. Otherwise, median with interquartile ranges is quoted and Mann–Whitney U tests were used to compare groups, respectively. Categorical variables were presented as proportion (percentage) and Chi square tests were used to compare the groups. To identify factors associated with HAH, logistic regression analysis was performed. Variables with \( p \) value <0.2 resulted from univariate logistic regression, either for continuous or categorical variable, were included as covarites in multivariate logistic regression analysis.

Two tailed \( p \) values <0.05 were considered significant and, in addition, odds ratio for each potential associated factor along with its 95% confidence interval were measured to describe its contribution for developing HAH. All statistical analyses were performed using Statistical Package for Social Sciences software for Windows version 22.0 (SPSS Inc., Chicago, USA).
Results

Out of 464 patients included in this study, 45 patients (9.7%) met criteria of HAH used in this study and served as cases. Three patients with normal serum sodium levels both at admission and during hospital stay were selected and matched to each patient in the control group resulting in 135 patients being selected. Table 1 shows comparison of serum sodium level at admission between case and control group, along with matched variables and it shows that serum sodium level at admission of patients in case group was not significantly different from patients in control group.

Figure 1 shows the decrease of serum sodium level of patients in case group. Among patients in this group, maximum decrease of sodium level was 18 mEq/L with average of 7.8 ± 3.9 mEq/L, and average of lowest serum sodium level during hospital stay was 130.7 ± 3.4 mEq/L.

If serum sodium level <125 mEq/L is used to define severe hyponatremia, 6.7% patients in case group encountered severe hyponatremia in this study.

There was no difference between patients in case and control groups in regard to ejection fraction, as shown in Table 2. Among vital signs and symptoms as listed in Table 2, only the presence of ascites and history of fatigue were significantly different between the case and control group in which both symptoms were found more among patients in case group. In terms of medical history retrieved in this study, there was no difference between the case and control groups. While atrial fibrillation, pneumonia and renal failure were not significantly different, ventricular arrhythmia was found as a concomitant diagnosis more often in the case group compared to the control group, 11.1% and 2.2%, respectively. In regard to blood chemistry at admission, other than serum potassium and chloride levels, patients in case group had significantly higher levels of blood urea nitrogen, 72.4 ± 47.8 and 55.4 ± 40.9, respectively.

Table 3 listed medication administered during hospital stay to both patients in case and control groups. Whilst the proportion of patients receiving furosemide, ACEI or ARB and potassium-sparing diuretics were not significantly different, the proportion of patients receiving amiodarone in the case group was significantly higher compared to control group, 28.9% and 11.9%, respectively. Compared to patients in the control group, more patients in the case group also received positive isotopes (11.9 and 31.1%), respectively, heparin (13.3 and 28.9%, respectively) and antibiotics (43.7 and 68.9%, respectively).

In this study, two general clinical outcomes were measured i.e. length of hospital stay and in-hospital mortality as presented in Table 4. Compared to patients in the control group, patients with HAH had significantly longer hospital stay and higher in-hospital mortality.

From univariate logistic regression analysis, 20 variables were found to have p value <0.2 and included as covariates in multivariate logistic regression. Table 5 listed final variables resulted from multivariable logistic regression having significant association with HAH and its associated odds ratio. The presence of ascites at admission along with administration of amiodarone and heparin during hospital stay were associated with the occurrence HAH as found in this study.

Discussion

Previous studies reported the prevalence of HAH in general hospitalized patients ranges from 3 to 38%, depending on the setting being studied and the variation of the hyponatremia definition and parameters being used [7, 12, 13]. Among Hospital departments being studied is the department of internal medicine which found to have the highest prevalence of HAH [7]. Regardless of the difference in the prevalence, all studies indicate that HAH has a significant association with poorer clinical patient outcomes [7, 13].

Table 1 Serum sodium level at admission and matched variables between cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 45)</th>
<th>Control (n = 135)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium level at admission (mEq/L)</td>
<td>138.5 ± 2.9</td>
<td>137.6 ± 6.5</td>
<td>0.386</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>44.4%</td>
<td>45.2%</td>
<td>0.901</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.1 ± 13.6</td>
<td>50.8 ± 13.9</td>
<td>0.893</td>
</tr>
</tbody>
</table>
In this study HAH was defined as decreased serum sodium level of at least 3 mEq/L, between serum sodium levels measured at hospital admission and the following measurements during the patient hospital stay. HAH was found in 9.7% of patients hospitalized at the sample sites due to HF, which is lower than that previously reported by Shchekochikhin et al. [14] (24.4%). The definition of hyponatremia used in this study may have contributed to this difference. However, there was no difference in regard with association between HAH and longer hospital stay and higher in-hospital mortality as reported by Shchekochikhin et al. [14] in their study.
Table 3: Medication administered during hospital stay to both patients in case and control group.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cases (n = 45) (%)</th>
<th>Control (n = 135) (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>95.6</td>
<td>96.3</td>
<td>0.824</td>
</tr>
<tr>
<td>ACEs or ARBs</td>
<td>68.9</td>
<td>74.8</td>
<td>0.436</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>28.9</td>
<td>28.9</td>
<td>1.000</td>
</tr>
<tr>
<td>Amodiazone</td>
<td>28.9</td>
<td>11.9</td>
<td>0.007*</td>
</tr>
<tr>
<td>Potassium supplement</td>
<td>62.2</td>
<td>50.4</td>
<td>0.168*</td>
</tr>
<tr>
<td>Positive isotopes</td>
<td>31.1</td>
<td>11.9</td>
<td>0.020*</td>
</tr>
<tr>
<td>Organic anions</td>
<td>62.2</td>
<td>54.8</td>
<td>0.395</td>
</tr>
<tr>
<td>Epsinoloids</td>
<td>31.1</td>
<td>28.1</td>
<td>0.785</td>
</tr>
<tr>
<td>Aspirin</td>
<td>53.3</td>
<td>41.5</td>
<td>0.667</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>51.1</td>
<td>41.2</td>
<td>0.260</td>
</tr>
<tr>
<td>Heparin</td>
<td>28.9</td>
<td>13.3</td>
<td>0.017*</td>
</tr>
<tr>
<td>Warfarin</td>
<td>22.2</td>
<td>26.7</td>
<td>0.544</td>
</tr>
<tr>
<td>CCBs</td>
<td>11.1</td>
<td>12.6</td>
<td>0.793</td>
</tr>
<tr>
<td>Ubiquinone</td>
<td>15.6</td>
<td>14.1</td>
<td>0.807</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>11.1</td>
<td>17.0</td>
<td>0.342</td>
</tr>
<tr>
<td>Laxative agents</td>
<td>40.0</td>
<td>38.5</td>
<td>0.860</td>
</tr>
<tr>
<td>PPIs</td>
<td>22.2</td>
<td>14.1</td>
<td>0.198*</td>
</tr>
<tr>
<td>H2RAs</td>
<td>28.9</td>
<td>21.5</td>
<td>0.309</td>
</tr>
<tr>
<td>Allopentol</td>
<td>24.4</td>
<td>17.0</td>
<td>0.272</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>22.2</td>
<td>21.5</td>
<td>0.917</td>
</tr>
<tr>
<td>Insulin</td>
<td>13.3</td>
<td>8.9</td>
<td>0.389</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>68.9</td>
<td>43.7</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

*p* included as covariates in multivariate logistic regression.

Table 4: Length of hospital stay and in-hospital mortality of both case and control groups.

<table>
<thead>
<tr>
<th>General clinical outcome</th>
<th>Cases</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay (days)</td>
<td>11(7)</td>
<td>8(3)</td>
<td>0.002</td>
</tr>
<tr>
<td>In-hospital death (%)</td>
<td>74.4</td>
<td>11.1</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Table 5: Factors associated with HAH resulted from multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>0.001</td>
<td>4.7</td>
<td>1.9–11.5</td>
</tr>
<tr>
<td>Amodiazone</td>
<td>0.012</td>
<td>3.2</td>
<td>1.3–7.4</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.034</td>
<td>3.1</td>
<td>1.2–7.3</td>
</tr>
</tbody>
</table>

Studies on factors associated with HAH in general hospitalized patients have been conducted by Hoon et al. [7] and Beukhof et al. [12]. Hoon et al. analyzed treatment-related factors and found that administration of thiazide diuretics, medication stimulating antidiuretic hormone, administration of hypotonic intravenous fluid and surgery had significant association. In their multivariate analysis, Beukhof et al. found that administration of insulin, opioids and antibiotics have significant association with HAH. The results of these two studies differed mainly due to the difference of clinical settings and the research study designs.

While factors associated with HAH in general hospitalized patients have been reported, reports in patients hospitalized from HF are still not yet available. This study may be the first study investigating factors associated with HAH in patients hospitalized from HF.

Compared to the factors found to be associated with HAH in general hospitalized patients, factors found in this study are slightly different. In terms of patient-related factors, this study found that the presence of ascites at admission was significantly associated with HAH in patients hospitalized for HF. In addition, administration of heparin and amiodaione during hospitalization were found to be medication-related factor which were significantly associated with HAH. Despite the difference of some of the findings, there is a similarity in term of the finding that some medications used to treat this group of patients with HF can potentially increase the risk for HAH.

This study found that patients who presented with ascites at admission have almost of five folds increase in
their risk of developing HAH (OR = 4.7). Ascites is a symptom commonly observed in HF patients with marked volume overload occurring especially when the pressure in right side of the heart is increased [15]. Activity of renin angiotensin aldosterone system (RAAS) as well as sympathetic nervous system (SNS) is increased in severe HF leading to greater release of arginine vasopressin (AVP), the neurohormone responsible for the development of hyponatraemia [16,17]. In addition to the increased release of AVP, tendency of water retention in HF patients increases, presents as oedema and ascites, which usually are seen as a result of increased solute-free water reabsorption caused by the increase of renal vasoconstriction. Dilutional hyponatraemia is a common consequence of severe water retention.

Amiodarone is commonly used to treat ventricular arrhythmia. Due to its broad antiarrhythmic spectrum, amiodarone is considered as the medication of choice for treatment of various types of cardiac arrhythmia [18]. Although atrial fibrillation is the most common type of cardiac arrhythmia found in patients with HF, ventricular arrhythmia found especially in patients with left ventricular dilatation and decreased ejection fraction and account for large number of patients in this study sample [19]. In this study, ventricular arrhythmia was the concurrent diagnosis found to be around five times more prevalent in patients developing HAH (p = 0.012). Several case reports on the incidence of hyponatraemia after administration of amiodarone have been reported [20–22]. Amiodarone potentially causes hyponatraemia by inducing the occurrence of syndrome of inappropriate secretion of antidiuretic hormone [20–22]. Whilst the definitive mechanism of amiodarone induced SIADH is not yet understood, hyponatraemia after acute administration of amiodarone was reported to occur within 5 days of administration [21]. The presence of other factors may possibly augment the effect of amiodarone in development of hyponatraemia.

This study also found that the administration of heparins during hospitalization had a significant association with HAH. Heparins, both unfractionated and low molecular weight heparin, have an effect on the aldosterone metabolism resulting in electrolyte changes, especially hyperkalemia [23]. In a lower extent incidence of hyponatraemia resulting from natriuresis as an effect of hypaldosteronism [24,25]. Heparin decreases aldosterone levels by reducing the number as well as the affinity of adrenal angiotensin II receptors which attenuates the aldosterone release from the adrenal cortex. Although the decreased aldosterone level is reversible in short-term use of heparin, prolonged use may result in reduction of aldosterone levels leading, or at least pre-disposing of severe hyperkalemia and hyponatraemia [25].

While all diuretics, especially thiazide diuretics, are known to have the potential of affecting electrolytes balance in hospitalized HF patients [7]; this study could not support this finding. The study sample did not include any patients receiving thiazide diuretics; only furosemide and potassium sparing diuretics were recorded for all patients hospitalised during the study data collection period. Although furosemide and potassium sparing diuretics can also induce hyponatraemia, to a lesser extent, the associated hyponatraemia with them is dose-related.

In their study, Beukhof et al. [12] found that administration of insulin, opioids and antibiotics have significant association with HAH. While opioids were not used by any of the patients enrolled in this study, insulin and antibiotics were recorded for some patients. This study could not support Beukhof et al. finding regarding antibiotics association with HAH. From univariate logistic regression analysis antibiotics use was significantly associated with HAH, but it was not when analyzed simultaneously with other factors by multivariate logistic regression.

This study found that patients hospitalized from HF should receive adequate monitoring of serum sodium levels in order to prevent negative impact of hyponatraemia despite of their normal serum sodium level at admission. Presenting symptoms and signs at admission should be the trigger to considering the development of patients’ specific plan in order to minimize severe consequences of worsening hyponatraemia.

Several therapeutic options are already available for the treatment of hyponatraemia in patients with HF [26,27]. In addition to hypertensive saline and some other conventional treatments, AVP receptor antagonists have been also recommended for the treatment of hyponatraemia in certain condition [15,28]. Nevertheless, in order to achieve intended therapeutic outcomes and to minimize adverse effects, the detailed characteristics of hyponatraemia being encountered by the patient are very important to be examined before deciding which treatment option needs to be administered [26,27].

There are some limitations of this study. Firstly, the severity of patients’ hyponatraemic status was not differentiated because hyponatraemia in this study was only assessed by serum sodium levels depression by 3 mEq/l, or more between serum sodium levels measured at hospital admission and the following measurements during the patient hospital stay. In terms of medication-related factors, dosing records of some medications were missing so that the effect of doses variation could not be analyzed, especially for diuretics. Furthermore, this study did not include patients’ medication history prior to hospitalization in the list of independent variables because the data were not completely available.
Conclusion

The risks for developing HAH could be identified by using information available at admission and also during hospital stay. In addition to the presence of ascites at admission, this study found that administration of amiodarone and heparin during hospitalization potentially increase the risk for developing HAH in patients hospitalized from HF. Further studies are needed to support findings resulted from this study.

Acknowledgments

The authors would like to thank: Directorate of Higher Degree Education, Ministry of Education Republic of Indonesia, for Ph.D. scholarship supporting this study.

Funding

None.

Conflicts of interest

Nothing needs to be declared.

References

Patient and medication-related factors associated with hospital-acquired hyponatremia in patients hospitalized from heart failure

S. Saepudin, Patrick A. Ball & Hana Morrissey
Appendix 5

Risk Prediction of Hyponatremia in Patients Hospitalized from Heart Failure

S. Saepudin1,2*, Patrick A. Ball1, Hana Morrissey1, Ahmad Fauzy3

1School of Psychological and Clinical Sciences, Charles Darwin University, NT – Australia
2Department of Pharmacy, Universitas Islam Indonesia, Yogyakarta – Indonesia
3Department of Statistics, Universitas Islam Indonesia, Yogyakarta – Indonesia

*Corresponding author: S. Saepudin (saepudin@edu.edu.au)

Abstract

Background: Despite its significant contribution to morbidity and mortality, studies reported that hyponatremia is still inadequately recognised and treated. The aim of this research was to obtain prediction model for predicting the risk of hyponatremia in patients hospitalized from heart failure as an important step for better recognition and treatment of hyponatremia.

Methods and findings: Patients included in this research were patients hospitalized from heart failure at Fatmawati Hospital in Jakarta, Indonesia, during 2011-2013. Nested case control was designed and logistic regression analysis was performed for derivation of prediction model by including variables obtained during admission as the model’s predictors. Brier-score and Nagelkerke R² (NR²) were measured to assess overall predictive ability and area under the curve (AUC) of the Receiver Operating Characteristics (ROC) and calibration plot along with Hosmer-Lemeshow test were measured to assess discrimination and calibration ability, respectively. Internal validation was performed using bootstrapping approach. Out of 464 patients included in the research 102 (22%) were hyponatremic during hospitalization and
served as cases. Accordingly, 306 non-hyponatremic patients were selected as controls matched by age and gender. Six variables at admission were found to be significantly associated with hyponatremia: serum sodium level, fatigue, ascites, positive inotropes, heparin and antibiotics. Prediction model containing those six variables exhibits good predictive ability both overall (brier-score=0.107, \( \text{NR}^2=0.531 \)) and specifically in term of discrimination (AUC of ROC curve=0.90) and calibration ability (\( p \)-value of HL test=0.899). Optimism observed from internal validation did not reduce its predictive performance.

Conclusion: Risk prediction model for predicting the risk of hyponatremia in patients hospitalized from heart failure can be derived by including predictors taken from information obtained during admission.

Key Words: Heart failure, hyponatremia, risk prediction

Introduction

Hyponatremia is the most prevalent electrolyte disturbance in patients hospitalised for heart failure (HF) both on admission and during hospitalisation [1-3] and it was found is an important medical problem significantly associated with worse short and long-term clinical outcomes [4, 5]. However, some other studies found that hyponatremia is still under-recognised as well as under-managed [6-8]. Inappropriate management of hyponatremia is associated with more severe conditions leading to the increased necessity of more complex treatment and death [9-12]. Whilst hyponatremia during admission can be easily recognised from laboratory records as part of normal routine measurements taken at admission, hyponatremia during hospitalization is less readily recognised, especially when laboratory measurements are not taken on a daily basis.
Attempts to reduce untoward impact of hyponatremia in HF patients are urgently needed. The development of risk prediction models (PM) can help in recognising heart failure patients at high risk of developing hyponatremia to enable adequate measures to be delivered to high-risk patients to avoid further worse conditions [7]. This research was aimed to obtain a PM for predicting the risk of hyponatremia in patients hospitalized from heart failure so that appropriate treatments can be administered into high-risk patients in order to prevent negative impacts of hyponatremia.

Methods

Research setting and subject selection

Patients included in this research were patients admitted to Fatmawati Hospital in Jakarta, Indonesia, during 2011-2013 coded with ICD-10 according to the internal classification of diseases (ICD)-10 for their main diagnosis, were hospitalised for at least three days and had a reasonably complete record on demographic profiles, clinical problems, medical history, vital signs and symptoms at admission, blood chemistry at admission, medication records during admission and hospitalisation and serum sodium level during hospitalisation. Patients were excluded if they had adrenal insufficiency, hypothyroidism, syndrome of inappropriate of antidiuretic hormone secretion (SIADH), or having diseases/disorders known as causes of SIADH (any malignancies, central nervous system disorders, pulmonary and human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS]).

Definition of hyponatremia

In this research, a patient was categorised as encountering hyponatremia if their serum sodium level was lower than 135 mEq/L [2, 10]. A patient was categorised as developing hyponatremia during hospitalisation if at least one episode of
hyponatremia occurred on the day following admission, regardless of serum sodium level on admission. Serum sodium levels were corrected for patients with a blood glucose level >200mg/dL (equal to 11 mmol/L) using a correction factor of 2.4 per 100mg/dL (equal to 5.5 mmol/L) increase of blood glucose level.

Research Design

A nested case-control design was used for deriving risk prediction model in this research in which cases comprising patients who developed hyponatremia during their hospital stay and patients with normal sodium levels during hospital stay served as controls. Each patient in the case group was matched by age and gender to three patients as controls and this ratio was considered as an appropriate design [13, 14].

Data Collection

Data were collected retrospectively from medical records in accordance with regulations on extracting data from medical records established by the Ministry of Health, Republic of Indonesia. Extracted information included demographic data, vital signs and symptoms at admission, medical history, concomitant diagnosis of present hospitalisation, medication administered during admission and hospitalisation and laboratory profiles.

Statistical Analysis

Derivation of the risk prediction model

Binomial multivariate logistic regression was used to develop the model and the purposeful predictor selection method proposed by Hosmer et al. (2013) [15] was followed to find out the most significant predictors which were selected from variables obtained during admission including vital signs and symptoms, medical history, concomitant diagnosis, administered medication and laboratory profiles.
Assessment of the performance of the risk prediction model

Performance of the model was assessed for both overall performance and specifically in terms of discrimination and calibration ability. Nagelkerke R² (NR²) and Brier score were used to assess overall performance. Meanwhile, discrimination ability of the model was assessed using area under the receiver operating characteristic (ROC) curve in which the area for a useless model is equal to 0.5 and score for the perfect one is 1. Calibration ability of the model was assessed using calibration plot and Hosmer-Lemeshow (HL) calibration test. The p-value of HL test indicates the agreement between predicted probabilities and actual outcomes, in which a p-value ≥0.05 indicates that there is no significant difference between predicted probabilities and actual outcomes.

Validation of the prediction model

A bootstrap resampling approach was chosen for conducting internal validation in this research as it is an efficient method and can give better results compared to other methods commonly used for internal validation. Internal validation through five hundred bootstraps resampling to produce a stable average estimate was performed.

Presentation of the prediction model

Regression formula was chosen to present the risk prediction model and uniform shrinkage factor resulting from bootstrapping analysis was applied to shrink the regression coefficients in order to obtain a more accurate the prediction.

All statistical analysis was performed using R software [16].

Ethics Approval
Ethics approvals for this research have been granted by Charles Darwin University Human Research Ethics Committee and also by Patmawati Hospital Ethics Committee.

Results

The risk prediction model

During the period between 2011 and 2013, 663 hospitalised patients in Patmawati Hospital were coded with ICD-10 according to the ICD-10 for their main diagnosis of hospitalisation – congestive HF. Of the 663 patients, 464 met all inclusion criteria for this research and were therefore included, while 199 were excluded due to incomplete laboratory records, pregnancy and routine hemodialysis. In the 464 hospitalised patients with HF included in this study, hypotension during hospitalization was found in 102 patients (22%) and these patients were then served as cases. Accordingly, 306 patients without hypotension during hospitalization were matched by age and gender as controls.

Table 1 shows a summary output resulting from multivariate logistic regression in which six predictors out of 18 included in the analysis have \( p \)-value < 0.05: history of fatigue, presence of ascites at admission, administration of positive inotropes, heparin and antibiotics, and serum sodium level. These six predictors were then included in the multivariate analysis including only these six predictors and the output summary of the analysis is presented in Table 2.

After identifying significant predictors resulting from multivariate analysis, the third and fourth steps were performed to identify any important predictor that was excluded from the model. Nevertheless, there was no more predictors significantly contribute to the model. The next step of the purposeful selection method is to assess
linearity of the logit of the continuous predictor included in the model. There was only one continuous predictor in the model – serum sodium level at admission – and a design variables method was used to assess the linearity. Although it was not perfectly linear, the logit of serum sodium level at admission is almost linear meaning that the serum sodium level was presented in the correct scale.
### Table 1 – Result of multivariate logistic regression analysis including significant predictors from univariate analysis

<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th><em>p</em>-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>History of fatigue</td>
<td>1.394</td>
<td>&lt;0.001</td>
<td>4.03</td>
<td>2.08 – 7.82</td>
</tr>
<tr>
<td>2</td>
<td>Peripheral edema</td>
<td>0.381</td>
<td>0.319</td>
<td>1.46</td>
<td>0.69 – 3.09</td>
</tr>
<tr>
<td>3</td>
<td>Ascites</td>
<td>1.523</td>
<td>0.002</td>
<td>4.59</td>
<td>1.75 – 12.00</td>
</tr>
<tr>
<td>4</td>
<td>Hypertension</td>
<td>0.658</td>
<td>0.063</td>
<td>1.93</td>
<td>0.97 – 3.86</td>
</tr>
<tr>
<td>5</td>
<td>Previous hospitalization from heart diseases</td>
<td>0.122</td>
<td>0.715</td>
<td>1.13</td>
<td>0.59 – 2.17</td>
</tr>
<tr>
<td>6</td>
<td>DBP</td>
<td>-0.019</td>
<td>0.103</td>
<td>0.98</td>
<td>0.96 – 1.00</td>
</tr>
<tr>
<td>7</td>
<td>Renal failure</td>
<td>0.616</td>
<td>0.200</td>
<td>1.85</td>
<td>0.72 – 4.74</td>
</tr>
<tr>
<td>8</td>
<td>ACE inhibitors</td>
<td>-0.400</td>
<td>0.290</td>
<td>0.67</td>
<td>0.32 – 1.406</td>
</tr>
<tr>
<td>9</td>
<td>Positive isotropes</td>
<td>1.131</td>
<td>0.011</td>
<td>3.09</td>
<td>1.30 – 7.38</td>
</tr>
<tr>
<td>10</td>
<td>Heparin</td>
<td>1.026</td>
<td>0.024</td>
<td>2.79</td>
<td>1.15 – 6.79</td>
</tr>
<tr>
<td>11</td>
<td>Insulin</td>
<td>0.021</td>
<td>0.965</td>
<td>1.02</td>
<td>0.41 – 2.58</td>
</tr>
<tr>
<td>12</td>
<td>Antibiotics</td>
<td>1.062</td>
<td>0.001</td>
<td>2.99</td>
<td>1.52 – 5.52</td>
</tr>
<tr>
<td>13</td>
<td>Sodium</td>
<td>-0.250</td>
<td>&lt;0.001</td>
<td>0.78</td>
<td>0.72 – 0.84</td>
</tr>
<tr>
<td>14</td>
<td>Uremia</td>
<td>-0.007</td>
<td>0.195</td>
<td>0.99</td>
<td>0.98 – 1.00</td>
</tr>
<tr>
<td>15</td>
<td>Creatinine</td>
<td>0.272</td>
<td>0.055</td>
<td>1.31</td>
<td>0.99 – 1.73</td>
</tr>
<tr>
<td>16</td>
<td>Albumin</td>
<td>0.112</td>
<td>0.736</td>
<td>1.12</td>
<td>0.55 – 2.27</td>
</tr>
<tr>
<td>17</td>
<td>AST</td>
<td>-1.111</td>
<td>0.173</td>
<td>0.33</td>
<td>0.07 – 1.63</td>
</tr>
<tr>
<td>18</td>
<td>ALT</td>
<td>1.308</td>
<td>0.087</td>
<td>3.70</td>
<td>0.83 – 16.53</td>
</tr>
</tbody>
</table>

Note: OR = odds ratio; CI = confidence interval; ACE = angiotensin converting enzymes interval; DBP = diastolic blood pressure; AST = aspartate amino-transferase; ALT = alanine amino-transferase

### Table 1 – Predictors included in the final risk prediction model of hyponatremia in patients hospitalized from heart failure

<table>
<thead>
<tr>
<th>No.</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th><em>p</em>-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue</td>
<td>1.312</td>
<td>&lt;0.001</td>
<td>3.71</td>
<td>1.99 – 6.90</td>
</tr>
<tr>
<td>2</td>
<td>Ascites</td>
<td>1.316</td>
<td>0.003</td>
<td>3.73</td>
<td>1.55 – 8.99</td>
</tr>
<tr>
<td>3</td>
<td>Positive isotropes</td>
<td>1.082</td>
<td>0.005</td>
<td>2.95</td>
<td>1.38 – 6.34</td>
</tr>
<tr>
<td>4</td>
<td>Heparin</td>
<td>1.092</td>
<td>0.008</td>
<td>2.98</td>
<td>1.33 – 6.66</td>
</tr>
<tr>
<td>5</td>
<td>Antibiotics</td>
<td>1.054</td>
<td>0.001</td>
<td>2.87</td>
<td>1.56 – 5.29</td>
</tr>
<tr>
<td>6</td>
<td>Sodium</td>
<td>-0.256</td>
<td>&lt;0.001</td>
<td>0.77</td>
<td>0.72 – 0.83</td>
</tr>
<tr>
<td>7</td>
<td>Constant</td>
<td>32.427</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: OR = odds ratio; CI = confidence interval
Assessing significant interactions is the sixth step of the purposeful selection method. Three interactions were considered in this model based on clinical reasons, such as the interaction between serum sodium level and history of fatigue, serum sodium level and ascites, and history of fatigue and ascites. All considered interactions showed a significant contribution to the occurrence of hyponatremia during hospitalisation in univariate level but there were only two interactions significantly contributing to the model in multivariate level. However, the addition of this interaction into the model changed the regression coefficient and OR of the ascites predictor markedly. As the basic principle of adding interaction terms is that none of the predictors already included in the model should be considered for removal, it was decided that the interaction between serum sodium level and ascites was not to be included in the model.

**Performance of the risk prediction model**

The values of \(NR^2\) and the Brier-score as overall performance indices of the PM were 0.531 and 0.107, respectively. The obtained \(NR^2\) indicates that 53.1% variance of the outcome is explained by the model; in other words, the predictors included in the model explain 53.1% variance of the outcome. According to the Brier score's value of 0.107 the PM showed a good overall performance.

Figure 1 shows the ROC curve with an AUC of 0.90 (95% CI [0.66 – 0.93]) indicating excellent discrimination ability of the prediction model. Meanwhile, calibration plot depicted in Figure 2 indicates that calibration ability of the PM is not completely ideal, as the model shows good agreement between predicted and actual probability only for low and high probability, with higher prediction seen for probability at medium levels.
The resulting \( p \)-value of 0.899 from the default H-L test, which divides the probabilities into 10 groups, indicates no significant difference between predicted and actual probabilities among the groups. The H-L test was also performed for group numbers ranging from five to 15, and the resulting \( p \)-value is presented in Table 3 and the Table shows that even when the group number was changed, the \( p \)-value of each group number indicated that there was no significant difference between predicted probability and actual outcomes.

![Receiver operating characteristic curve](image)

**Figure 1** – Receiver operating characteristic curve of the prediction model including six predictors resulting in an area under the curve of 0.90 (95% CI [0.86 – 0.93])
Figure 2 - Calibration plot of the risk prediction model

Table 3 – The $p$-values of the Hosmer-Lemeshow test with several different group numbers

<table>
<thead>
<tr>
<th>Number of groups</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.948</td>
</tr>
<tr>
<td>6</td>
<td>0.106</td>
</tr>
<tr>
<td>7</td>
<td>0.392</td>
</tr>
<tr>
<td>8</td>
<td>0.737</td>
</tr>
<tr>
<td>9</td>
<td>0.283</td>
</tr>
<tr>
<td>10</td>
<td>0.899</td>
</tr>
<tr>
<td>11</td>
<td>0.845</td>
</tr>
<tr>
<td>12</td>
<td>0.204</td>
</tr>
<tr>
<td>13</td>
<td>0.657</td>
</tr>
<tr>
<td>14</td>
<td>0.620</td>
</tr>
<tr>
<td>15</td>
<td>0.812</td>
</tr>
</tbody>
</table>
Validation of the risk prediction model

The second column (original) of the output in Table 4 lists the value of the indices resulting from the original sample, that is, the model was fitted and assessed in the original sample. The third and fourth column (training and test) list the mean value of the indices when the model was fitted in the bootstrap samples and assessed in both the bootstrap samples and the original sample, respectively. The optimism value of each index listed in the fifth column was obtained by subtracting the value in the third column (test) from the second column (training) to get the corrected value of each index (corrected) by subtracting the optimism value from the value in the first column.

As shown in Table 4, the corrected values of all indices indicate that performances of the model are lower than those obtained from the original sample indicating that the model is over-fitting. The Dxy index, which indicates Somer’s D measure, was then used to calculate the c-statistic (equal to the AUC of the ROC curve) by using the formula: \( C = (1 + Dxy)/2 \). Given that the Dxy corrected value is 0.775, the AUC of the ROC curve resulting from bootstrap validation is 0.89 – lower than the AUC obtained from the original sample.

The corrected intercept and slope values are –0.04 and 0.93 respectively, and are lower compared to ones obtained from the original sample. However, these values are still within acceptable ranges. All indices obtained from the bootstrap validation process indicate that the risk prediction model still has good discrimination and calibration ability when fitted in different samples taken from the same population.
Table 4 - Output resulting from bootstrapping validation analysis of the prediction model

<table>
<thead>
<tr>
<th>Index</th>
<th>Original</th>
<th>Training</th>
<th>Test</th>
<th>Optimism</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dxy</td>
<td>0.7931</td>
<td>0.8006</td>
<td>0.7825</td>
<td>0.0181</td>
<td>0.7750</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.5255</td>
<td>0.5407</td>
<td>0.5126</td>
<td>0.0280</td>
<td>0.4975</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.0000</td>
<td>0.0000</td>
<td>-0.0442</td>
<td>0.0442</td>
<td>-0.0442</td>
</tr>
<tr>
<td>Slope</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.9343</td>
<td>0.0657</td>
<td>0.9343</td>
</tr>
<tr>
<td>Emax</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0226</td>
<td>0.0226</td>
<td>0.0226</td>
</tr>
</tbody>
</table>

Uniform shrinkage factor of 0.949 was obtained from analysis using the “shrink” function package in R and this shrinkage factor was then used to obtain a shrunken-regression coefficient of each predictor in the final model as listed in Table 5.

Table 5 - Shrunken regression coefficient resulted from original regression coefficients multiplied by shrinkage factor

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>Shrunken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.312</td>
<td>1.25</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.316</td>
<td>1.25</td>
</tr>
<tr>
<td>Positive inotropic</td>
<td>1.082</td>
<td>1.03</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.092</td>
<td>1.04</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1.051</td>
<td>1.00</td>
</tr>
<tr>
<td>Sodium</td>
<td>-0.256</td>
<td>-0.24</td>
</tr>
<tr>
<td>Constant</td>
<td>32.427</td>
<td>30.75</td>
</tr>
</tbody>
</table>