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Development of prediction model for identifying heart failure patients with high risk of developing hyponatremia

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ABSTRACT

Background: Despite its significant contribution to morbidity and mortality, studies reported that hyponatremia is still inadequately recognised and treated.

Objective: To obtain a prediction model for predicting the risk of hyponatremia in patients hospitalized from heart failure.

Methods: Patients included in this research were patients hospitalized from heart failure at Fatmawati Hospital in Jakarta, Indonesia during the 2011 – 2014 period. Logistic regression analysis was performed for the derivation of prediction model by including variables obtained during admission as the predictors. Brier-score and Nagelkerke R^2 (NR^2) 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 a bootstrapping approach.

Results: Out of 464 patients included in the research 102 (22%) were hyponatremic during hospitalization. Accordingly, 306 non-hyponatremic patients were selected as controls matched by age and gender. Variables significantly associated with hyponatremia were 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, NR2=0.531) and specifically 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 for predicting the risk of hyponatremia in patients hospitalized from heart failure can be derived by including predictors taken from information obtained during admission.

Latar Belakang: *Hiponatremia merupakan gangguan elektrolit yang paling sering dialami oleh pasien gagal jantung yang sedang menjalani perawatan di rumah sakit dan memberikan kontribusi yang signifikan terhadap morbiditas dan mortalitas pasien.*

Tujuan Penelitian: *Mengembangkan model prediksi untuk mengidentifikasi pasien gagal jantung yang memiliki risiko tinggi mengalami hiponatremia selama perawatan di rumah sakit.*

Metode: *Penelitian dilakukan menggunakan data pasien gagal jantung yang dirawat di Rumah Sakit Fatmawati Jakarta selama tahun 2011 – 2014. Model prediksi dikembangkan menggunakan metode*

regresi logistik dengan prediktor berupa variabel terkait kondisi pasien saat masuk rumah sakit. Kemampuan prediktif model secara general dinilai berdasarkan nilai Brier-score dan Nagelkerke R2 (NR2) sedangkan kemampuan diskriminasi dan kalibrasi secara berurutan dinilai berdasarkan luas area di bawah kurva(area under the curve, AUC) dari Receiver Operating Characteristics (ROC) dan plot kalibrasi bersama hasil uji Hosmer-Lemeshow. Validasi internal dilakukan dengan pendekatan bootstrap.

Hasil: *Dari total 464 data pasien yang digunakan dalam penelitian ini, 102 orang (22%) diantaranya mengalami hiponatremia selama rawat inap. Variabel yang signifikan berpengaruh terhadap kejadian hiponatremia adalah kadar natrium, fatigue, asites, pemberian inotropik positif, heparin, serta antibiotik. Model prediksi dengan prediktor keenam variabel tersebut menunjukkan kemampuan prediktif yang baik secara general (Brier-score=0,107, NR2=0,531) maupun spesifik terkait kemampuan diskriminasi (AUC of ROC curve=0,90) dan kalibrasi (nilai-p uji HL=0,899). Hasil validasi internal menunjukkan nilai optimisme yang dihasilkan tidak menurunkan kemampuan prediktif model yang diperoleh.*

Kesimpulan: *Model prediksi untuk mengidentifikasi pasien gagal jantung yang memiliki risiko tinggi mengalami hiponatremia dapat dikembangkan dengan mudah menggunakan prediktor berupa data terkait kondisi pasien pada saat masuk rumah sakit.*

INTRODUCTION

Hyponatremia is the most prevalent electrolyte disturbance in patients hospitalised for heart failure (HF) both on admission and during hospitalisation and it was found as an important medical problem significantly associated with worse short and long-term clinical outcomes.[1-5] 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 daily.

Attempts to reduce the 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 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 I50.0 according to the international 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 hyponatremic if 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 in the days 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 developed for deriving risk prediction model in which cases comprising patients developing hyponatremia during hospital stay and patients with normal sodium levels during the hospital stay served as controls.[13,14]

Data Collection

Data were collected retrospectively from medical records by 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, laboratory profiles, and medication administered during admission and hospitalisation.

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 selected from variables obtained during admission.

Assessment of the performance of the risk prediction model

Performance of the model was assessed for both overall and specifically in term of discrimination and calibration ability. Nagelkerke R^2 (NR^2) and Brier score were used to assess overall performance. Meanwhile, discrimination ability was assessed using the 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 was assessed using calibration plot and Hosmer-Lemeshow (HL) calibration test.

Validation of the prediction model

A bootstrap resampling approach was chosen for internal validation of the risk prediction in which 500 bootstrap resampling was performed to produce stable average estimates.

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

Ethics Approval

Ethics approval for this research has been granted by Fatmawati Hospital Ethics Committee.

RESULTS

The risk prediction model

Among 464 hospitalised patients with HF included in this study, hyponatremia during hospitalization was found in 102 patients (22%) and these patients were then served as cases. Accordingly, 306 patients without hyponatremia 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. These six predictors were then included in the multivariate analysis with the output summary of the analysis is presented in Table 2. After identifying significant predictors resulting from multivariate analysis, the next analysis was performed to identify any important predictor that was excluded from the model. Nevertheless, there were no more predictors significantly contribute to the model.

Performance of the risk prediction model (RPM)

The values of NR^2 and the Brier-score as overall performance indices of the RPM were 0.531 and 0.107, respectively. The obtained NR^2 indicates that 53.1% variance of the outcome is explained by the model. According to the Brier score's value of 0.107, the RPM showed a good overall performance.

Table 1 . Result of multivariate logistic regression analysis including significant predictors from univariate analysis

No.	Independent variable	Regression coefficient	p-value	OR	95%	CI
1	History of fatigue	1.394	<0.001	4.03	2.08	7.82
2	Peripheral edema	0.381	0.319	1.46	0.69	3.09
3	Ascites	1.523	0.002	4.59	1.75	12.00
4	Hypertension	0.658	0.063	1.93	0.97	3.86
5	Previous hospitalisation from heart diseases	0.122	0.715	1.13	0.59	2.17
6	DBP	–0.019	0.103	0.98	0.96	1.00
7	Renal failure	0.616	0.200	1.85	0.72	4.74
8	ACE inhibitors	–0.400	0.290	0.67	0.32	1.406
9	Positive inotropes	1.131	0.011	3.09	1.30	7.38
10	Heparin	1.026	0.024	2.79	1.15	6.79
11	Insulin	0.021	0.965	1.02	0.41	2.58
12	Antibiotics	1.062	0.001	2.89	1.52	5.52
13	Sodium	–0.250	<0.001	0.78	0.72	0.84
14	Ureum	–0.007	0.195	0.99	0.98	1.00
15	Creatinine	0.272	0.055	1.31	0.99	1.73
16	Albumin	0.112	0.756	1.12	0.55	2.27
17	AST	–1.111	0.173	0.33	0.07	1.63
18	ALT	1.308	0.087	3.70	0.83	16.53

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 2. Predictors included in the final risk prediction model of hyponatremia in patients hospitalized from heart failure

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

Note: OR = odds ratio; CI = confidence interval

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.

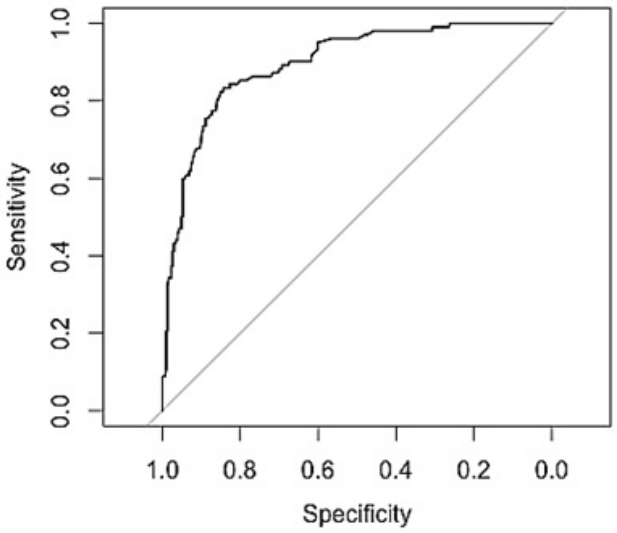

Figure 1. Receiver operating characteristic curve of the prediction model including six predictors resulting in an area under the curve of 0.90 (95% CI [0.86 – 0.93])

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.

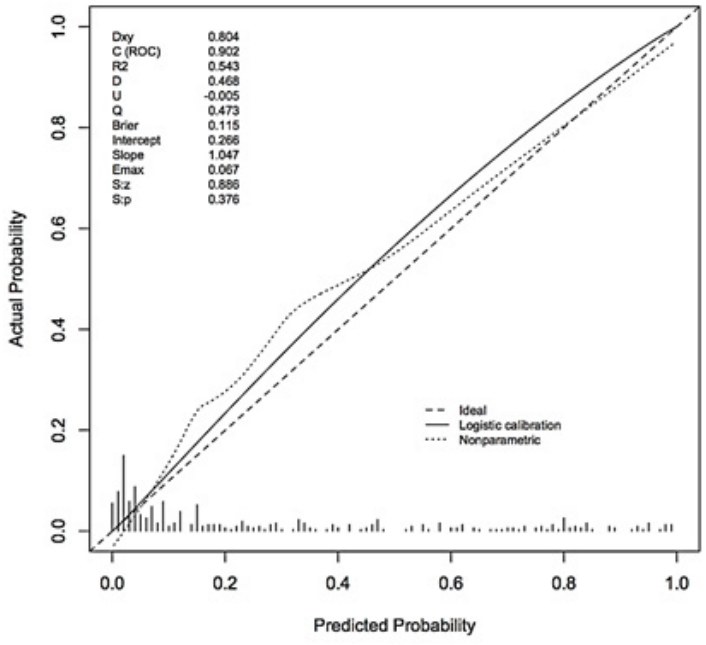

Figure 2. Calibration plot of the risk prediction model

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

Number of groups	*p*-value
5	0.948
6	0.106
7	0.392
8	0.737
9	0.283
10	0.899
11	0.845
12	0.204
13	0.657
14	0.620
15	0.812

Validation of the risk prediction model

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.

Table 4. Output resulting from bootstrapping validation analysis of the prediction model

Index	Original	Training	Test	Optimism	Corrected
Dxy	0.7931	0.8006	0.7825	0.0181	0.7750
R2	0.5255	0.5407	0.5126	0.0280	0.4975
Intercept	0.0000	0.0000	-0.0442	0.0442	-0.0442
Slope	1.0000	1.0000	0.9343	0.0657	0.9343
Emax	0.0000	0.0000	0.0226	0.0226	0.0226

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.

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

Independent variable	Regression coefficient	
	Original	Shrunken
Fatigue	1.312	1.25
Ascites	1.316	1.25
Positive inotropes	1.082	1.03
Heparin	1.092	1.04
Antibiotics	1.054	1.00
Sodium	–0.256	–0.24
Constant	32.427	30.75

DISCUSSION

Candidate predictors included in the final RPM in this research were selected by following the purposeful selection method as it shows better ability in selecting important predictors compared to the stepwise selection method.[15,17] In addition to the issue of choosing the appropriate method for selecting candidate predictors, the number of Event per-variable (EPV) is an important consideration to obtain a good PM for a model with a binary outcome in which this number has been known to be associated with the degree of optimism of the obtained model.[18,19] Despite the difference of findings on the optimum number of EPVs resulting in the lowest optimism, five EVPs are 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 the 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 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 hospital-acquired hyponatremia.[20] Overall, there were 18 independent variables included as candidate predictors in the large model, resulting in 5.7 EVPs.

Six predictors were found to have a significant association with hyponatremia in this research and were then included as predictors in the RPM: serum sodium level, history of fatigue, presence of ascites at admission, administration of positive inotropes, heparin and antibiotics.

Fatigue is a common symptom encountered by patients with HF and even among patients with stable HF, fatigue was reported by around half.[21,22] 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.[22-24] The presence of ascites was found as another factor associated with hyponatremia. 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.[21]

Heparin found in this research was administered as low molecular weight heparin (LMWH) and it is an intravenous anticoagulant commonly prescribed to patients with HF to prevent venous thromboembolism (VTE). Heparins, both unfractionated and LMWH, have an effect on the aldosterone metabolism resulting in electrolyte changes, especially hyperkalemia and to a lower incidence of hyponatremia resulting from natriuresis as an effect of hypoaldosteronism.[25-27] 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.[27]

In addition to heparin, positive inotropes are another medication-related factor associated with hyponatremia. 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 ejection fraction administration of positive inotropes likely indicate a severe condition and low EF of the 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 hyponatremia in this research. Several studies on antibiotic-induced hyponatremia have been reported, mostly on the use of co-trimoxazole.[28,29] However, ceftriaxone and its combination with azithromycin were the most administered antibiotics into patients in this research. As found by another study 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.[20,30]

The main purpose of assessing the performance of a PM is to evaluate the discrepancy between actual outcomes and predicted outcomes.[19] A good PM will show only a small discrepancy between actual outcomes and the outcome predicted by the model. Generally, the discrepancy is measured both overall and specifically in terms of discrimination and calibration ability using common relevant statistical indices.

For a PM with a binary outcome, the Brier-score is the most used statistical measure for assessing the overall performance. 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 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: $0.25x(1 – 0.25)^2 + (1 – 0.25)x0.252$.[19] 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 NR^2 is commonly used and it indicates the proportion of variance of the outcomes explained by the model. The NR^2 of 0.531 for the obtained PM in this research indicates that the model explains around 53% variance of the studied outcome. Quite similar to the Brier score, the obtained NR2 indicates that the model 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 performance. 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.[31]

Discrimination expressing the ability of the model to discriminate subjects with and without the outcome is commonly assessed using the c-statistic, which for a binary outcome equals the AUC of the ROC curve. The model obtained from this research shows excellent discrimination ability indicated by an AUC of the ROC curve of 0.9 (95% CI= 0.86–0.93). This means that the PM has a very good ability to discriminate subjects at high risk and low risk of developing hyponatremia.

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, it was assessed primarily by calibration plot and also with the HL test. Although the calibration plot showed that the probabilities predicted by the model were systematically higher than the actual outcome, the p-values of the HL test indicate that there were no significant differences between the actual outcome and the predicted probabilities. It indicates that the PM has a good calibration ability.

The main purpose of validating a PM is to assess its optimism.[32] It is well known that overfitting is an important problem in deriving the PM, in which the model almost always shows good performance when being assessed within the sample used to derive the model, but its performance is not good enough when assessed in different samples.[33] This phenomenon is referred to as optimism of the PM. While 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.

The bootstrapping approach was used to internally validate the PM because this method has been reported as an efficient method for validating PMs compared to other methods such as split-sample and cross-validation methods.[34-36] Five hundred bootstrap repetitions were performed in this research, as it has been reported as resulting in more stable estimates, and it was found that optimism of overall performance indicated by R^2 was 0.028 resulting in a 5% reduction of R^2.[19] The corrected R^2 indicates that in overall the PM still exhibit an acceptable performance. 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, and the optimism of the calibration slope was also small resulted in a corrected calibration slope of 0.9343, indicating that the PM still has good calibration ability when implemented in different samples.

The internal validation indicates that the PM is suitable for use in the same population where the sample for deriving the PM was taken.[19] However, additional assessment, such as decision-curve analysis still needs to be performed to assess the clinical usefulness of the PM.[37]

Minimising optimism of the PM is important 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.[19]

CONCLUSION

In conclusion, the risk prediction model to stratify the risk for developing hyponatremia during hospitalization can be derived by including predictor selected from the patient- and medication-related factors identified during admission. The prediction model containing predictors of serum sodium level at admission, history of fatigue, and presence of ascites, administration of positive inotropes, heparin and antibiotics exhibits good predictive performance indicating that it can be practically used.

CONFLICT OF INTEREST

None declare.

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REFERENCES

1. Goldsmith SR. Hyponatremia and outcomes in patients with heart failure. Heart. 2012;98(24):1761-2.
2. Sato N, Gheorghiade M, Kajimoto K, Munakata R, Minami Y, Mizuno M, et al. Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND Registry). American Journal of Cardiology. 2013; 111(7):1019-25.
3. Choi DJ, Han S, Jeon ES, Cho MC, Kim JJ, Yoo BS, et al. Characteristics, outcomes and predictors of long-term mortality for patients hospitalized for acute heart failure: A report from The Korean Heart Failure Registry. Korean circulation journal. 2011;41(7):363-71.
4. Madan VD, Novak E, Rich MW. Impact of change in serum sodium concentration on mortality in patients hospitalized with heart failure and hyponatremia. Circulation: Heart Failure. 2011;4(5):637-3.

5. Konishi M, Haraguchi G, Ohigashi H, Sasaoka T, Yoshikawa S, Inagaki H, et al. Progression of hyponatremia is associated with increased cardiac mortality in patients hospitalized for acute decompensated heart failure. Journal of Cardiac Failure. 2012;18(8):620-5.
6. Tzoulis P, Evans R, Falinska A, Barnard M, Tan T, Woolman E, et al. Multicentre study of investigation and management of inpatient hyponatraemia in the UK. Postgraduate Medical Journal. 2014;90(1070):694-8.
7. Whyte M, Down C, Miell J, Crook M. Lack of laboratory assessment of severe hyponatraemia is associated with detrimental clinical outcomes in hospitalised patients. International Journal of Clinical Practice. 2009;63(10):1451-5.
8. Marco J, Barba R, Matia P, Plaza S, Mendez M, Canora J, et al. Low prevalence of hyponatremia codification in departments of internal medicine and its prognostic implications. Current Medical Research and Opinion. 2013;29(12):1757-62.
9. Shchekochikhin DY, Schrier RW, Lindenfeld J, Price LL, Jaber BL, Madias NE. Outcome differences in community- versus hospital-acquired hyponatremia in patients with a diagnosis of heart failure. Circulation: Heart Failure. 2013;6(3):379-86.
10. Bettari L, Fiuzat M, Shaw LK, Wojdyla DM, Metra M, Felker GM, et al. Hyponatremia and long-term outcomes in chronic heart failure--an observational study from the Duke Databank for Cardiovascular Diseases. Journal of Cardiac Failure. 2012;18(1):74-81.
11. Corona G, Giuliani C, Parenti G, Norello D, Verbalis JG, Forti G, et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. PLoS ONE. 2013;8(12):e80451.
12. Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. Nephrology Dialysis Transplantation. 2006;21(1):70-6.
13. Essebag V, Genest J, Suissa S, Pilote L. The nested case-control in cardiology. American Heart Journal. 2003;146:581-90.
14. Biesheuvel CJ, Vergouwe Y, Oudega R, Hoes A, Grobbee DE, Moons KG. Advantages of the nested case-control design in diagnostic research. BMC Medical Research Methodology. 2008;8(48):1-7.
15. Hosmer DW, Stanley L, Sturdivant RX. Applied logistic regression. New Jersey USA: Wiley; 2013.
16. R Development Core Team. R: A languange and environment for statistical computing. In. 3.1.3 edn: R Foundation for Statistical Computing, Vienna, Austria; 2015.
17. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code for Biology and Medicine. 2008;3(17):1-8.
18. Wynants L, Bouwmeester W, Moons KG, Moerbeek M, Timmerman D, Van Huffel S, et al. A simulation study of sample size demonstrated the importance of the number of events per variable to develop prediction models in clustered data. Journal of Clinical Epidemiology. 2015;68(12):1406-14.
19. Steyerberg EW. Clinical prediction models: A practical approach to development, validation, and updating. Springer; 2010.
20. Beukhof CM, Hoorn EJ, Lindemans J, Zietse R. Novel risk factors for hospital-acquired hyponatremia: A matched case-control study. Clinical Endocrinology (Oxford). 2007;66:367-72.
21. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Journal of the American College of Cardiology. 2013; 62(16):e147-239.
22. Conley S, Feder S, Redeker NS. The relationship between pain, fatigue, depression and functional performance in stable heart failure. Heart & Lung. 2015;44(2):107-12.
23. Perez-Moreno AC, Jhund PS, Macdonald MR, Petrie MC, Cleland JG, Bohm M, et al. Fatigue as a predictor of outcome in patients with heart failure: Analysis of CORO-

NA (Controlled Rosuvastatin Multinational Trial in Heart Failure). JACC: Heart Failure. 2014;2(2):187-97.
24. Fink AM, Gonzalez RC, Lisowski T, Pini M, Fantuzzi G, Levy WC, et al. Fatigue, inflammation, and projected mortality in heart failure. Journal of Cardiac Failure. 2012;18(9):711-6.
25. Oster JR, Singer I, Fishman LM. Heparin-induced aldosterone suppression and hyperkalemia. The American Journal of Medicine. 1995;98(6):575-86.
26. Bengalorkar GM, Sarala N, Venkatrathnamma PN, Kumar TN. Effect of heparin and low-molecular weight heparin on serum potassium and sodium levels. Journal of Pharmacology & Pharmacotherapeutics. 2011;2(4):266-9.
27. Norman NE, Sneed AM, Brown C, Ellis CA, Minard G, Brown RO. Heparin-induced hyponatremia. Annals of Pharmacotherapy. 2004;38(3):404-7.
28. Huntsberry AM, Linnebur SA, Vejar M. Hyponatremia after initiation and rechallenge with trimethoprim-sulfamethoxazole in an older adult. Clinical Interventions in Aging. 2015;10:1091-6.
29. Mori H, Kuroda Y, Imamura S, Toyoda A, Yoshida I, Kawakami M, et al. Hyponatremia and/or hyperkalemia in patients treated with the standard dose of trimethoprim-sulfamethoxazole. Internal Medicine. 2003;42(8):665-9.
30. Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: The emerging role of interleukin-6 in osmoregulation. Nephron Physiology. 2011;118(2):45-51.
31. Matheny ME, Ohno-Machado L, Resnic FS. Discrimination and calibration of mortality risk prediction models in interventional cardiology. Journal of Biomedical Informatics. 2005;38(5):367-75.
32. Steyerberg EW, Eijkemans MJC, Harrell FE, Habbema JDF. Prognostic modeling with logistic regression analysis: In search of a sensible strategy in small data sets. Medical Decision Making. 2001;21(1):45-56.
33. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: Seven steps for development and an ABCD for validation. European Heart Journal. 2014;35(29):1925-31.
34. Steyerberg EW, Harrell FE, Borsboom GJ. Internal validation of predictive models: Efficiency of some procedures for logistic regression analysis. Journal of Clinical Epidemiology. 2001;54:774-81.
35. Smith GC, Seaman SR, Wood AM, Royston P, White IR. Correcting for optimistic prediction in small data sets. American Journal of Epidemiology l. 2014;180(3):318-24.
36. Austin PC, Steyerberg EW. Events per variable (EPV) and the relative performance of different strategies for estimating the out-of-sample validity of logistic regression models. Statistical Methods in Medical Research. 2014; 26(2):796-808.
37. Vickers AJ, Jang K, Sargent D, Lilja H, Kattan MW. Systematic review of statistical methods used in molecular marker studies in cancer. Cancer. 2008;112(8):1862-8.