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Predictive value of admission and pre-discharge sodium, osmolality, and kidney function for 90-day rehospitalization in patients with heart failure reduced ejection fraction

Valor predictivo del sodio, la osmolaridad y la función renal al ingreso y al alta para la rehospitalización a 90 días en pacientes con insuficiencia cardíaca con fracción de eyección reducida

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SUMMARY

Background: *Heart failure (HF) affects 64.3 million people worldwide, with over half of them having preserved ejection fraction (HFpEF). In Indonesia, the prevalence is 900.90 per 100,000, the second-highest in Asia. Rehospitalization rates are notably high, with 40% of patients readmitted within 90 days contributing to higher healthcare costs. Sodium and creatinine levels serve as crucial prognostic markers for HF, with low levels correlating with poor outcomes. This study aimed to evaluate sodium and creatinine levels as independent predictors of rehospitalization in patients with HF.* **Methods**: *This retrospective cohort study analyzed patients with congestive heart failure (CHF) diagnosed at the Wahidin Sudirohusodo Hospital Cardiac Center (March 2023–July 2023). Data on demographics, medical history, and laboratory results were collected from the Heart Failure Registry and medical records. A 90-day follow-up was conducted to assess the rehospitalization rates and clinical outcomes.* **Results**: *Among 108 patients with heart failure and reduced ejection fraction (mean age 56.59 ± 12.29 years, 71.3% male), those with low sodium levels (<135.5 mmol/L) had a 6.78-fold higher risk of rehospitalization (p<0.001), while those with high osmolality (≥296.6 mOsm/kg) had a 45-fold higher risk (p<0.001). Elevated creatinine levels (≥1.3 mg/dL) and low eGFR (<49.5 mL/min/1.73 m²) were also significant predictors, with OR values of 4.857 (95% CI: 1.925 - 12.259) and 17.68 (95% CI: 3.724 - 83.941), respectively. Osmolality at admission demonstrated the highest predictive power, with an AUC of 90.7%. The comorbidity of chronic kidney disease (CKD) was significantly associated with an increased risk of rehospitalization (p=0.002).* **Conclusion**: *Sodium, creatinine, derived osmolality, and eGFR values were strong predictors of rehospitalization in patients with Heart Failure Reduced Ejection Fraction. The inclusion of both admission and pre-discharge parameters enhanced the predictive power of these factors.*

Keywords: *Heart failure, Rehospitalization, Sodium, Creatinine, Osmolality, eGFR*

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RESUMEN

Antecedentes*: La insuficiencia cardíaca (IC) afecta a 64,3 millones de personas en todo el mundo, de las cuales más de la mitad tienen fracción de eyección preservada (ICFEP). En Indonesia, la prevalencia es de 900,90 por cada 100.000 habitantes, la segunda más alta de Asia. Las tasas de rehospitalización son notablemente altas, con un 40% de los pacientes rehospitalizados en los 90 días, lo que contribuye a un aumento de los costos de atención médica. Los niveles de sodio y creatinina son marcadores pronósticos cruciales en la IC, y los valores bajos se correlacionan con peores resultados. Este estudio tiene como objetivo evaluar el sodio y la creatinina como predictores independientes de rehospitalización en pacientes con IC.* **Métodos***: Se realizó un estudio de cohorte retrospectivo que analizó a pacientes con insuficiencia cardíaca congestiva (ICC) diagnosticados en el Centro Cardiológico del Hospital Wahidin Sudirohusodo (marzo de 2023 - julio de 2023). Se recopilaron datos sobre la demografía, antecedentes médicos y resultados de laboratorio a partir del Registro de Insuficiencia Cardíaca y de los registros médicos. Un seguimiento de 90 días evaluó las tasas de rehospitalización y los resultados clínicos.* **Resultados***: Entre los 108 pacientes con insuficiencia cardíaca y fracción de eyección reducida (edad media 56,59 ± 12,29 años, 71,3% hombres), aquellos con niveles bajos de sodio (<135,5 mmol/L) tenían un riesgo 6,78 veces mayor de rehospitalización (p < 0,001), mientras que los pacientes con alta osmolalidad (≥296,6 mOsm/kg) tenían un riesgo 45 veces mayor (p < 0,001). Los niveles elevados de creatinina (≥1,3 mg/dL) y la baja tasa de filtrado glomerular estimada (eGFR) (<49,5 mL/min/1,73 m²) también fueron predictores significativos, con valores de OR de 4,857 (IC 95%: 1,925 - 12,259) y 17,68 (IC 95%: 3,724 - 83,941), respectivamente. La osmolalidad al ingreso mostró el mayor poder predictivo, con un AUC de 90,7%. La comorbilidad de la enfermedad renal crónica (ERC) se asoció de manera significativa con un aumento del riesgo de rehospitalización (p = 0,002).* **Conclusión***: El sodio, la creatinina y los valores derivados de la osmolalidad y del eGFR fueron predictores sólidos de rehospitalización en pacientes con insuficiencia cardíaca con fracción de eyección reducida. Incluir tanto los parámetros de ingreso como los de alta mejoró el poder predictivo de estos factores.*

Palabras clave: *Insuficiencia cardíaca, Rehospitalización, Sodio, Creatinina, Osmolalidad, eGFR*

INTRODUCTION

Heart failure (HF) is one of the most common heart diseases worldwide, with a very high prevalence rate. It is estimated that 64.3 million people suffer from heart failure, more than half of whom have heart failure with preserved ejection fraction (HFpEF). The prevalence of heart failure in Indonesia is 900.90 per 100,000 people, making Indonesia the country with the second-highest prevalence in Asia, after China. Furthermore, the incidence rate of heart failure in Asia is high, with China reporting an incidence of 275 per 100,000 people per year (1,2).

The high prevalence and incidence rates of heart failure add to the healthcare burden and treatment costs, especially due to the high rates of rehospitalization. In a study by O'Connor et al., 2159 of 4133 patients with systolic heart failure and EF <40% were rehospitalized at least once. The most common cause of rehospitalization was heart failure, accounting for 31.1% of the entire population (3). Additionally, rehospitalization increases the cost burden, with the average cost for one rehospitalized patient reaching $14,631 in the United States (4). Another study compared costs among patients with HF who were rehospitalized within the first 30 days. The cost for rehospitalized patients was $15,618 ± 25,264, compared with $11,845 ± 22,710 for nonrehospitalized patients (5).

Sodium and creatinine levels are important prognostic indicators in patients with heart failure. Studies have shown that patients with hyponatremia, as defined by sodium levels <135 mg/dL, have worse outcomes than those with higher sodium levels (6). Interestingly, hyponatremia is associated with hypoosmolality, which is defined as <285 mOsm/kg. Yet, a study by Arévalo-Loridoa et al. in 2016 found that hyperosmolality, defined as> 296.6 mOsm/kg, is associated with a high rehospitalization rate. This finding is intriguing, as it raises the question of what causes this discrepancy, since osmolality is based not only on blood sodium levels but also on BUN and blood glucose levels (7).

A similar finding was observed for creatinine clearance: patients with poor kidney function, as defined by a clearance <60 mL/min, had a poorer prognosis than those with higher clearance. The interrelationship between the kidney and heart functions indicates a reciprocal relationship between these two organs (8).

Various scoring systems, such as LACE and HOSPITAL, have been used to assess the risk of rehospitalization in patients with HF, incorporating parameters such as sodium and creatinine levels (9,10). However, these systems are not specific to patients with heart failure. The Readmission after heart failure (RAHF) score also considers sodium and creatinine levels but does not specifically isolate the impact of sodium (11).

This study aimed to evaluate whether sodium levels, osmolality, and kidney function are independent predictors of rehospitalization in patients with heart failure. The primary data are sodium and creatinine levels, which can be obtained by measurement in a laboratory blood test. However, as discussed above, high osmolality is associated with higher rehospitalization rates, whereas low sodium levels are not. Thus, we also measure osmolality by measuring blood glucose and BUN levels. As for kidney function, eGFR is superior to creatinine alone. We convert creatinine levels to eGFR and compare them to see whether eGFR is also superior in predicting rehospitalization, or whether creatinine alone is sufficient.

METHODS

Study design and settings

This is an observational study with a retrospective cohort design, involving data collection from patients with congestive heart failure admitted to the Integrated Heart Center at Dr. Wahidin Sudirohusodo Hospital. Clinical and laboratory data were collected within the first 24 hours of patient admission and pre-discharge. Observations were conducted periodically for 90 days post-discharge to assess rehospitalization rates.

Populations and samples

The population in this study comprises all patients admitted with a diagnosis of CHF and registered in the Heart Failure Registry (HF Registry) from March to July 2023.

Inclusion criteria include patients aged 18 years or older with a diagnosis of congestive heart failure and an ejection fraction of less than 50%. Exclusion criteria include patients who have undergone interventions to correct structural heart disorders, those with pericardial diseases, those with atrioventricular (AV) dyssynchrony, and individuals unwilling to participate in the study procedures or examinations.

Variables

According to medical records, age is determined based on the data recorded in the HF Registry. The age considered in this study is 18 years or older. Smoking history is based on the data from the HF Registry as recorded in the medical records. Gender is determined according to the HF Registry data, which distinguishes between male and female. Body Mass Index (BMI) is calculated using the weight and height recorded in the HF Registry. Admission dates and times are determined based on HF Registry data. Rehospitalization is tracked by monitoring the patient's condition 90 days after discharge, through contact with the patient or their family to inquire about their condition and whether the patient has been readmitted to a hospital or healthcare facility for congestive heart failure. If the patient is readmitted to the Wahidin Sudirohusodo Hospital's Heart Center during the 90-day monitoring period with a diagnosis of congestive heart failure, the readmission is automatically classified as such.

Chronic heart failure is defined by clinical symptoms such as shortness of breath on exertion (dyspnea on exertion), shortness of breath when lying down (orthopnea), fluid retention, rales, jugular venous distension, and pulmonary edema. Patients with reduced ejection fraction and no clinical evidence of heart failure are not classified as having chronic heart failure. Heart failure with low ejection fraction can be categorized into two types: Heart Failure with Reduced Ejection Fraction (HFrEF) with an ejection fraction of ≤ 40%, and Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF) with an ejection fraction of 41-49% (12). Ejection fraction values are determined based on data recorded in the HF Registry.

Several comorbidities can influence the conditions. Heart failure has several etiologies, of which we selected the most common. Namely, ischemic heart disease, hypertension, valvular heart disease, arrhythmias, and cardiomyopathy. We selected these comorbidities to assess whether certain etiologies are associated with worse heart failure outcomes compared with others. Hypertension is the most commonly sought-after comorbidity, since it is often associated with kidney failure.

Myocardial infarction or coronary artery disease (ischemic heart disease) can be diagnosed in patients with a history of at least one myocardial infarction episode before hospital admission, or those who have previously undergone myocardial reperfusion procedures such as PCI, CABG, or angioplasty. Diagnosis can also be made if the patient shows one of the following criteria: pathological Q wave findings on electrocardiography, with or without symptoms, with no evidence of other non-ischemic etiology; radiological or imaging findings showing loss of myocardial viability, such as thinning or decreased contractility, with no evidence of other non-ischemic etiology; or myocardial infarction findings based on histopathological examination One of high risk factors for ischemic heart disease is smoking, thus we also include it in comorbidities.

A hypertensive diagnosis can be made based on several findings. First, patients with a history of diagnosed hypertension and those receiving pharmacological therapy, diet, or physical activity. Second, patients with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg without diabetes or chronic kidney disease, or systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg in patients with diabetes or chronic kidney disease, were recorded in at least two repeated measurements. Third, patients who are receiving antihypertensive therapy (13).

Valvular heart disease encompasses patients previously diagnosed with valve abnormalities, such as mitral regurgitation, mitral stenosis, tricuspid regurgitation, tricuspid stenosis, aortic regurgitation, aortic stenosis, pulmonary regurgitation, or pulmonary stenosis, as well as those with a history of valve replacement surgery involving prosthetic or bioprosthetic valves. Cardiomyopathy encompasses patients diagnosed with any type of cardiomyopathy, including dilated cardiomyopathy, hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC/ARVD), and restrictive cardiomyopathy.

Atrial fibrillation is strongly associated with heart failure, and findings of heart failure caused by atrial fibrillation are common. Thus, we also include it as a cause of heart failure. It is diagnosed by an ECG showing irregularities and a fibrillatory P wave on admission.

Diabetes mellitus can cause hyperglycemia, thereby affecting the patient's osmolality. Therefore, we also selected this condition for comorbidities. It can be diagnosed in patients with a history of diabetes or those receiving diabetes therapy, based on the following criteria: HbA1c ≥ 6.5%, fasting blood glucose ≥ 126 mg/dL, 2-hour postprandial glucose ≥ 200 mg/dL on an oral glucose tolerance test, or patients with classic diabetes symptoms (polyuria, polydipsia, polyphagia) or diabetes crisis accompanied by random blood glucose ≥ 200 mg/dL. This diagnosis does not include gestational diabetes (14).

Chronic kidney disease (CKD) is diagnosed when a patient has an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for ≥ 3 months, as determined by the CKD-EPI formula.

Sodium (Na^+) levels are based on the first sodium measurement during the patient's treatment, as recorded in the HF Registry and medical records. These values are measured using a laboratory test on a blood sample. Hyponatremia is defined by a blood sodium level < 135 mg/dL.

Creatinine levels are based on laboratory measurements taken during the patient's hospital stay, as recorded in the HF Registry and medical records. eGFR is calculated using the CKD-EPI formula. Urea levels are based on the initial urea measurement taken during the hospital stay. We convert urea levels to BUN levels using the formula (urea/2,1).

Blood osmolality is calculated using the formula: (2xNa) + (BUN/2.8) + (Random Glucose/18). Additionally, treatment status is determined by using data from the HF Registry and medical records.

Some patients are on chronic heart failure, thus are taking medication on admission. This should maintain volume status, especially in patients on diuretics. Also, some antihypertension drugs, such as ACEi and ARB, may worsen kidney function if used in people with worse kidney failure levels. Thus, diuretics and other heart failure drugs are taken into consideration for this study to see whether people on medication previously have better outcomes than those who are not.

Data Analysis

The analysis method used consists of several interconnected stages. The first step is to describe the characteristics of the respondents, including demographic and clinical data, such as age, gender, and comorbid conditions relevant to heart failure and rehospitalization risk.

Next, a comparison of electrolyte and kidney function parameters is conducted between patients who experienced rehospitalization and those who did not, using either the independent t-test or the Mann-Whitney U test, depending on the data distribution. This test aims to determine whether there are significant differences in parameters such as sodium, osmolality, creatinine, and eGFR between the two patient groups. The results provide initial insights into how each parameter affects the likelihood of rehospitalization.

The next step is to determine the cutoff values for electrolyte and kidney function parameters using ROC curve analysis and the Youden Index to identify the optimal cutoff. The ROC curve is used to evaluate the ability of each parameter to distinguish between patients at risk of rehospitalization and those not at risk. At the same time, the Youden Index helps select the cutoff point that best balances sensitivity and specificity. The AUC (Area Under the Curve) is calculated to assess the overall accuracy of the predictive model.

Following this, a Chi-square test is used to analyze the relationship between the cutoff values of electrolyte and kidney function parameters and rehospitalization status. This test assesses whether there is a significant association between the identified parameters and 90-day rehospitalization. A p-value less than 0.05 indicates that the variables are significantly associated with rehospitalization.

Finally, a CART (Classification and Regression Tree) analysis is performed to build a predictive model based on the parameters analyzed earlier. The CART model is used to identify the most effective combination of parameters for predicting rehospitalization. This model is then evaluated using accuracy, sensitivity, specificity, and AUC to assess its performance in predicting rehospitalization. The results from this model provide valuable insights for identifying high-risk patients who are likely to be rehospitalized, thereby assisting in making more accurate clinical decisions.

Ethics

Patients are informed of the consent to this study during blood sampling, and the consent is signed on an information form about the diagnostic procedure. The research proposal has been approved by the Biomedical Research Ethics Committee for Human Subjects at the Faculty of Medicine, Hasanuddin University, and Dr. Wahidin Sudirohusodo Hospital, Makassar, with the letter number 1036/UN 4.6.4.5.31/ PP36/2024.

Characteristics Respondent

A total of 254 patients were included in the HF Registry from March to July 2023. Among these, 93 patient records had incomplete admission and pre-discharge laboratory results, and 53 patients could not be followed up after 90 days due to inability to contact them or their families. Therefore, the final sample size for the study was 108 patients (Table 1).

RESULTS

Basic Clinical Profile of the Study Subjects

The following Table 2 presents the comorbidities and medications taken by the study subjects, specifically patients with heart failure and reduced ejection fraction. It highlights the prevalence of various comorbid conditions, such as coronary artery disease (CAD), hypertension, smoking, and diabetes mellitus, among others. Additionally, the table provides an overview of the medications used by these patients, focusing on common heart failure treatments such as ACE inhibitors, calcium channel blockers (CCBs), diuretics, and others. The data provide valuable insights into the clinical characteristics of the study population, helping us understand the relationships among comorbidities, medication use, and patient outcomes.

Based on Table 2, the baseline clinical profile of heart failure patients with reduced ejection fraction shows a high prevalence of comorbidities, including CAD (58.33%), hypertension (50.93%), and smoking (53.7%). Other notable comorbidities include diabetes mellitus (34.26%), dyslipidemia (26.85%), valvular heart disease (18.52%), and CKD (17.59%). Medication is predominantly characterized by high utilization of CCBs (87.96%), ACE inhibitors or ARBs (64.81%), and diuretics (68.52%). However, the use of beta blockers is relatively low (23.15%), and newer medications, such as ARNI and Ivabradine, are rarely used (2.78% each). Data for some variables were unavailable for 8.33% of patients.

Comparison of Electrolyte Parameters and Kidney Function in Patients at Admission and Pre-discharge

Based on the previous results, it is evident that patients with lower sodium levels, higher osmolality, higher creatinine levels, and lower eGFR have a significantly higher risk of rehospitalization. This analysis is crucial for

Table 1. Distribution of Respondent Characteristics

Variable	Total (n= 108)	Rehospitalized (n=38)	Not Rehospitalized (n=70)
Age (Years)	56.94 ± 12.29	53 ± 12.97	58.74 ± 11.61
Sex			
Male	77	24	53
Female	31	14	17
BMI	23.92 ± 3.73	23.27 ± 4.32	24.28 ± 3.34
Ejection Fraction	33.63 ± 8.02	34.02 ± 7.47	33.42 ± 8.35
Sodium admission	135.92 ± 5.87	135.42 ± 5.74	136.20 ± 5.96
Sodium pre-discharge	135.88 ± 4.34	135.57 ± 5.47	136.05 ± 3.63
Osmolality admission	289.70 ± 13.05	291.38 ± 11.92	288.78 ± 13.62
Osmolality pre-discharge	288.88 ± 10.99	290.72 ± 13.49	287.88 ± 9.32
Creatinine admission	1.58 ± 1.81	2.05 ± 2.84	1.32 ± 0.75
Creatinine pre-discharge	1.39 ± 1.13	1.58 ± 1.63	1.30 ± 0.73
eGFR admission	69.62 ± 31.89	67.10 ± 36.13	70.98 ± 29.52
eGFR pre-discharge	70.30 ± 30.86	69.78 ± 31.33	70.58 ± 30.82

Table 2. Comorbid Factors and Previous Medications in Respondents

Comorbid Diseases			Medications		
Variable	**Category**	n (%)	**Variable**	**Category**	n (%)
Atrial Fibrillation	NA	9 (8.33)	ACE-i/ARB	NA	9 (8.33)
	No	86 (79.63)		No	29 (26.85)
	Yes	13 (12.04)		Yes	70 (64.81)
CAD	NA	9 (8.33)	ARNI	NA	9 (8.33)
	No	36 (33.33)		No	96 (88.89)
	Yes	63 (58.33)		Yes	3 (2.78)
Valvular Heart Disease	NA	9 (8.33)	CCB	NA	9 (8.33)
	No	79 (73.15)		No	4 (3.7)
	Yes	20 (18.52)		Yes	95 (87.96)
Cardiomyopathy	NA	9 (8.33)	Beta Blocker	NA	9 (8.33)
	No	97 (89.81)		No	74 (68.52)
	Yes	2 (1.85)		Yes	25 (23.15)
Smoker	NA	9 (8.33)	Diuretic	NA	9 (8.33)
	No	41 (37.96)		No	25 (23.15)
	Yes	58 (53.7)		Yes	74 (68.52)
Hypertension	NA	9 (8.33)	Tolvaptan	NA	9 (8.33)
	No	44 (40.74)	(Vasopressin V_2 receptor antagonists)	No	99 (91.67)
	Yes	55 (50.93)		Yes	0 (0)
Diabetes Mellitus	NA	9 (8.33)	Ivabradine	NA	9 (8.33)
	No	62 (57.41)		No	96 (88.89)
	Yes	37 (34.26)		Yes	3 (2.78)
Dyslipidemia	NA	9 (8.33)	Digoxin	NA	9 (8.33)
	No	70 (64.81)		No	82 (75.93)
	Yes	29 (26.85)		Yes	17 (15.74)
Chronic Kidney Disease	NA	9 (8.33)	SGLT-2 Inhibitor	NA	9 (8.33)
	No	80 (74.07)		No	99 (91.67)
	Yes	19 (17.59)		Yes	0 (0)

NA: Not available

understanding how these electrolyte and kidney function parameters can serve as predictors of 90-day rehospitalization. The data provide valuable clinical insights that can aid in identifying high-risk patients, thereby enabling earlier and more targeted interventions. Below is a comparison of the incidence of rehospitalization by sodium levels, osmolality, creatinine, and eGFR at admission and pre-discharge among patients with heart failure.

Figure 1 shows that the sodium levels at admission in the rehospitalized group (135.4 ± 5.7 mmol/L) were significantly lower than those in the non-rehospitalized group (139.1 ± 5.7 mmol/L) ($p = 0.00024$, $p<0.001$). Osmolality also differed significantly between the two groups, with the rehospitalized group having a higher value (292.91 ± 10.9 mOsm/kg). Creatinine levels were higher in the rehospitalized group (2.06 ± 2.84 mg/dL) compared to the non-rehospitalized group (1.04 ± 0.27 mg/dL) ($p = 0.035$, $p < 0.05$). Finally, eGFR was lower in the rehospitalized group (67.11 ± 36.13 mL/min/1.73 m²) compared to the non-rehospitalized group (79.2 ± 21.6 mL/min/1.73 m²) ($p=0.0316$, $p<0.05$).

These parameters suggest that patients with lower sodium levels, higher osmolality, higher creatinine levels, and lower eGFR are at a greater risk of rehospitalization. To strengthen these findings, ROC curve analysis can be used to determine the optimal cut-off values for each parameter, providing clinical guidance in identifying high-risk patients and enabling earlier interventions.

Figure 2 shows that sodium levels at pre-discharge were 139.49 ± 7.28 mmol/L in the non-rehospitalized group and 135.58 ± 5.47 mmol/L in the rehospitalized group, with a significant difference ($p = 0.034$, $p < 0.05$). Osmolality also showed a significant difference, with the rehospitalized group having a higher average of 290.73 ± 13.5 mOsm/kg compared to the non-rehospitalized group (282.32 ± 11.47 mOsm/kg, $p = 0.003$, $p < 0.01$). Creatinine levels were higher in the rehospitalized group (1.58 ± 1.64 mg/dL) than in the non-rehospitalized group (1.03 ± 0.34 mg/dL), with a significant difference ($p = 0.042$, $p < 0.05$). Meanwhile, eGFR was lower in the rehospitalized group (69.79 ± 31.34 mL/min/1.73 m²) than in the non-rehospitalized group

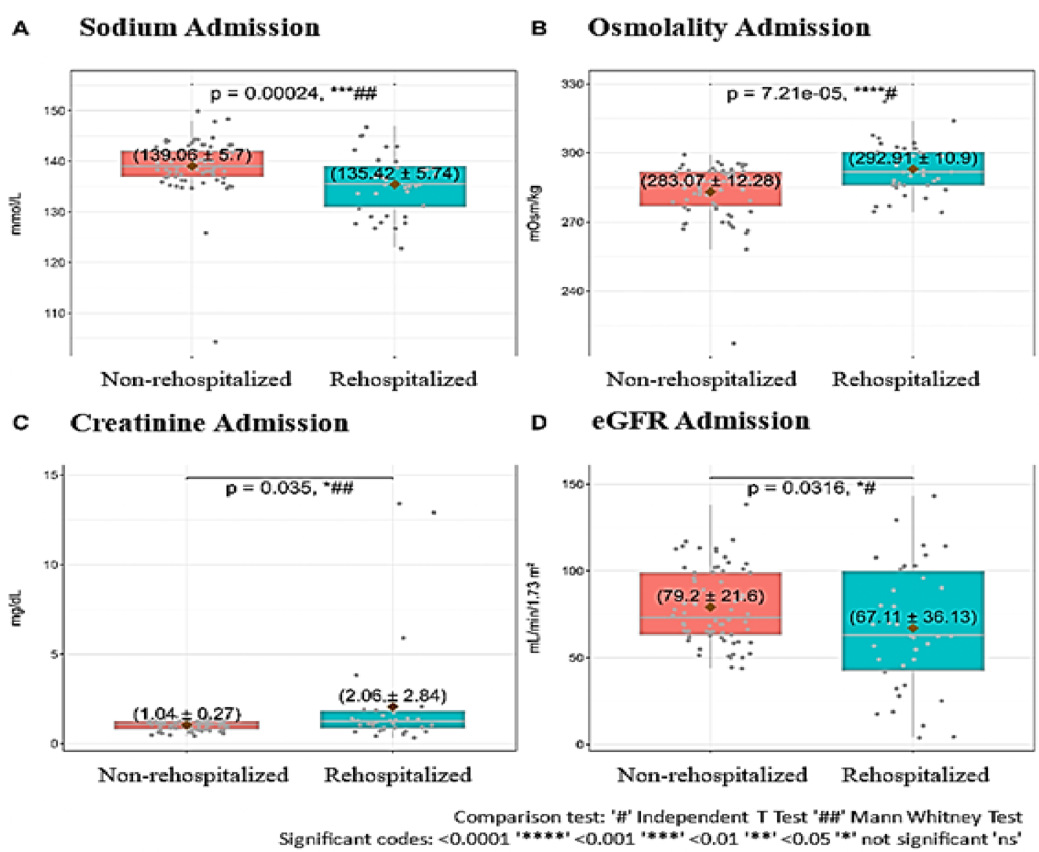

Figure 1. Comparison of Electrolytes and Kidney Function in Heart Failure Patients According to Rehospitalization Status at Admission

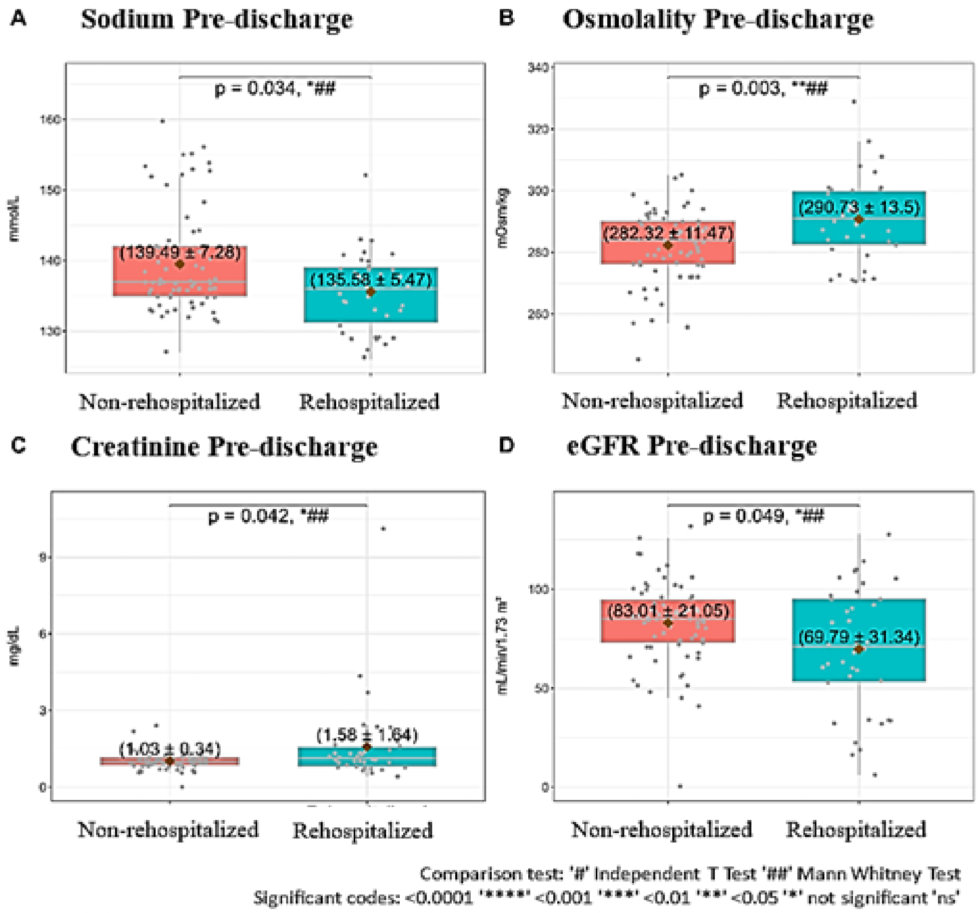

Figure 2. Comparison of Electrolytes and Renal Function in Heart Failure Patients Regarding Rehospitalization Status at Pre-discharge

(83.01 ± 21.05 mL/min/1.73 m²), approaching significance ($p = 0.049$; $p < 0.05$).

Overall, sodium, osmolality, creatinine, and eGFR were significant predictors of 90-day rehospitalization. To strengthen these findings, ROC curve analysis can be used to determine the optimal cut-off values for each significant parameter. Using the ROC curve, we can determine cut-off values that provide the optimal balance between sensitivity and specificity, which can be applied in clinical practice to predict rehospitalization risk and enable more targeted interventions.

Cut-Off Electrolyte and Renal Function Parameters in Patients at Admission

This section analyzes the use of the ROC curve to evaluate electrolyte and renal function parameters for predicting the risk of rehospitalization in heart failure patients with reduced ejection fraction. The analysis determines optimal cutoff values, sensitivity, and specificity for detecting 90-day rehospitalization. These cutoff values serve as clinical references to balance the detection of at-risk patients with the prevention of misidentification of non-rehospitalized patients. The AUC provides an overall accuracy assessment for each parameter at admission and pre-discharge.

Based on the ROC curve results in Figure 3, sodium with a cut-off of 135.5 mmol/L shows a sensitivity of 87.14% and specificity of 50%, indicating its ability to detect rehospitalization risk but with a relatively high false identification rate (AUC 71.41%). Osmolality at a cut-off of 296.6 mOsm/kg demonstrates very high sensitivity (98.57%) but low specificity (39.47%), making it excellent at detecting rehospitalization but less

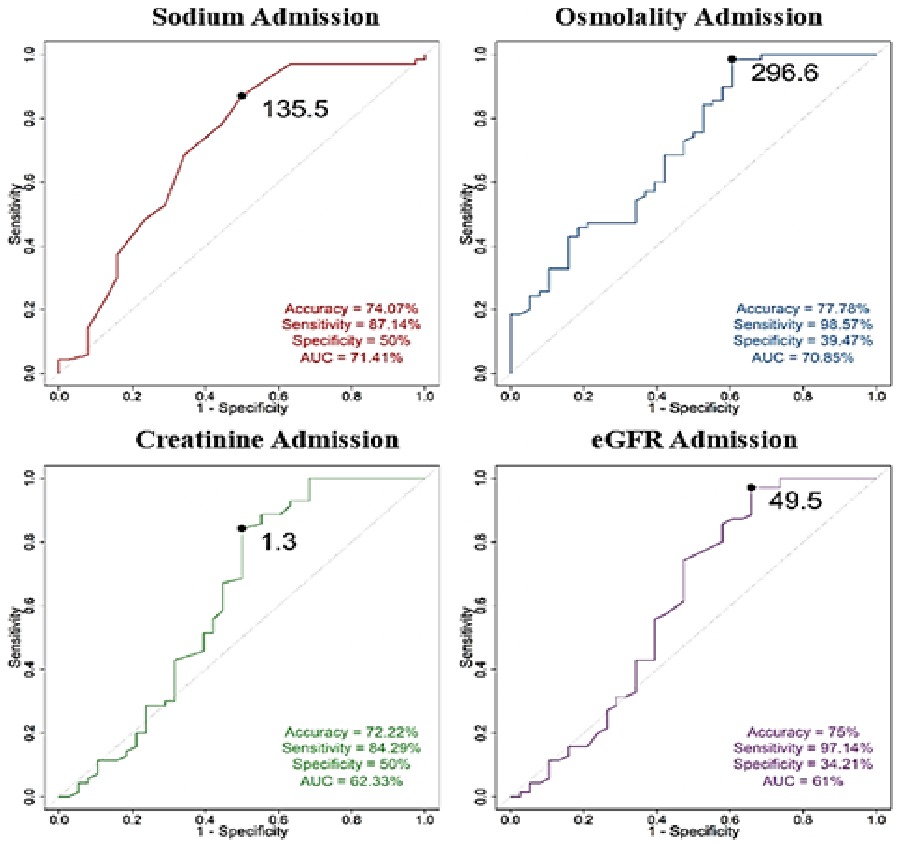

Figure 3. Cut-Off Electrolyte and Renal Function Parameters in Heart Failure Patients Regarding Rehospitalization Status at Admission

effective for identifying patients not rehospitalized (AUC 70.85%). Creatinine at a cut-off of 1.3 mg/dL shows good sensitivity (84.29%) and specificity (50%) for detecting rehospitalization risk (AUC 62.33%). Lastly, eGFR at a cut-off of 49.5 mL/min/1.73 m² shows high sensitivity (97.14%) but low specificity (34.21%), indicating it is effective at detecting rehospitalization but has low accuracy in distinguishing non-rehospitalized patients (AUC 61%).

In summary, osmolality exhibits the highest sensitivity, while sodium, creatinine, and eGFR also show good predictive potential, albeit with lower specificity. Selecting the appropriate cut-off or combining these parameters can enhance the accuracy of predicting rehospitalization in heart failure patients.

Based on the ROC curve analysis in Figure 4, the cut-off values for each parameter are as follows. Sodium with a cut-off of 131.5 mmol/L has high sensitivity (97.14%) but low specificity (26.32%), indicating that it is effective in detecting patients at risk of rehospitalization; however, many patients without rehospitalization are misclassified (AUC 62.35%). Osmolality with a cut-off of 293.1 mOsm/kg shows sensitivity of 87.14% and specificity of 47.37%, with an AUC of 67.39%, indicating a fairly good prediction, though there is room for improvement. A creatinine cut-off of 1.2 mg/dL shows sensitivity of 80% and specificity of 47.37%, with an AUC of 61.9%, indicating moderate predictive potential. eGFR with a cut-off of 73.5 mL/min/1.73 m² has a sensitivity of 74.29% and a specificity of 57.89%, with an AUC of 61.5%, showing moderate predictive ability.

Overall, sodium shows the highest sensitivity but with lower specificity. Osmolality, creatinine, and eGFR also show good potential, although accuracy can still be improved. Using a

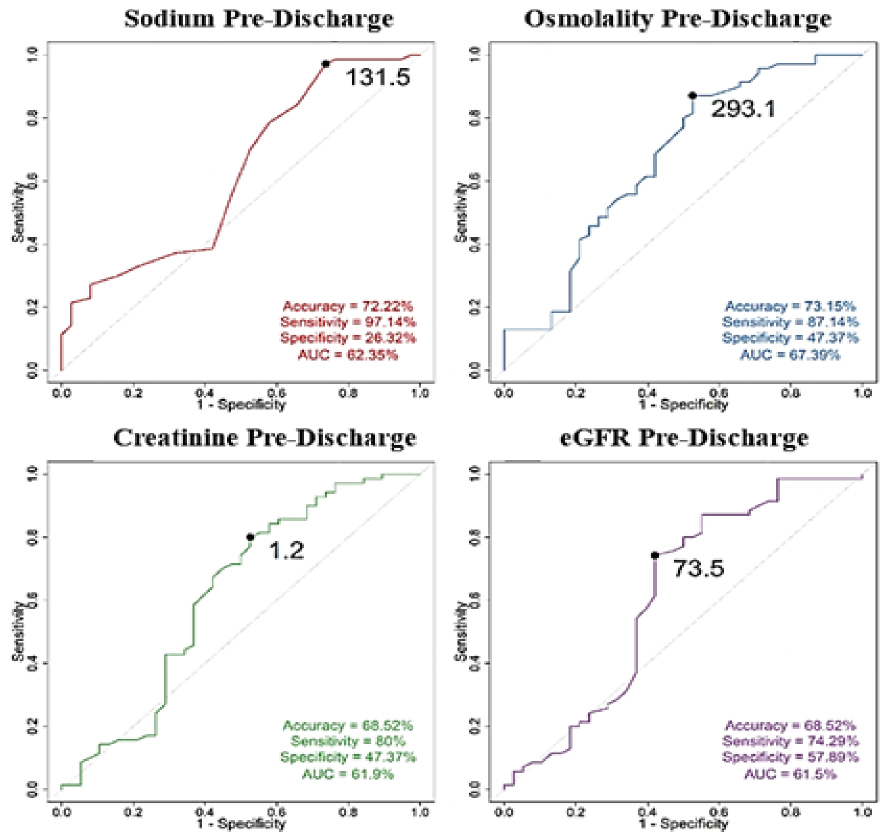

Figure 4. Cut-Off Electrolyte and Renal Function Parameters in Heart Failure Patients Regarding Rehospitalization Status at Pre-discharge

combination of parameters or adjusting the cut-off values can enhance the accuracy in predicting rehospitalization in heart failure patients.

The Relationship Between Electrolyte and Kidney Function Parameter Cut-Offs and 90-Day Rehospitalization Status

This section examines the relationship between sodium, osmolality, creatinine, and eGFR at admission and pre-discharge with 90-day rehospitalization status in patients with heart failure. The Chi-square test was used to assess significant differences between rehospitalized and non-rehospitalized patients. The results indicate a significant relationship between these parameters and the risk of rehospitalization, highlighting the importance of regular monitoring to identify high-risk patients.

Based on Figure 5 the cut-off analysis, sodium <135.5 mmol/L (OR: 6.778, 95% CI: 2.633 - 17.448), osmolality ≥296.6 mOsm/kg (OR: 45, 95% CI not provided), creatinine ≥1.3 mg/dL (OR: 4.857, 95% CI: 1.925 - 12.259), and eGFR <49.5 mL/min/1.73 m² (OR: 17.68, 95% CI: 3.724 - 83.941) are all significantly associated with an increased likelihood of rehospitalization within 90 days. The Chi-square tests showed highly significant differences ($p < 0.001$) for all parameters, indicating that these cut-off values can be used as strong predictors for identifying patients at high risk of rehospitalization.

Based on Figure 6, sodium levels <131.5 mmol/L ($p = 0.000212$, OR = 12.143, 95% CI: 2.499-58.993) are strongly associated with a higher risk of rehospitalization. Osmolality ≥293.1 mOsm/kg ($p = 7.6e-05$, OR = 6.1, 95% CI: 2.368 - 15.713) also significantly predicts

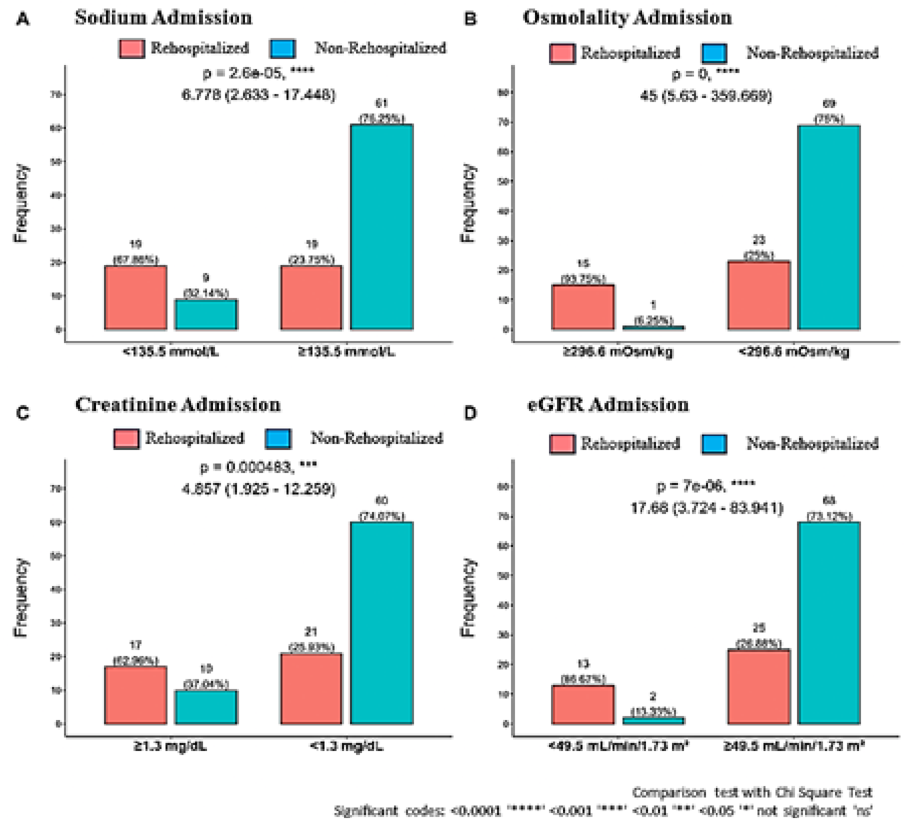

Figure 5. Relationship of Cut-Off Electrolyte and Renal Function Parameters in Patients at Admission

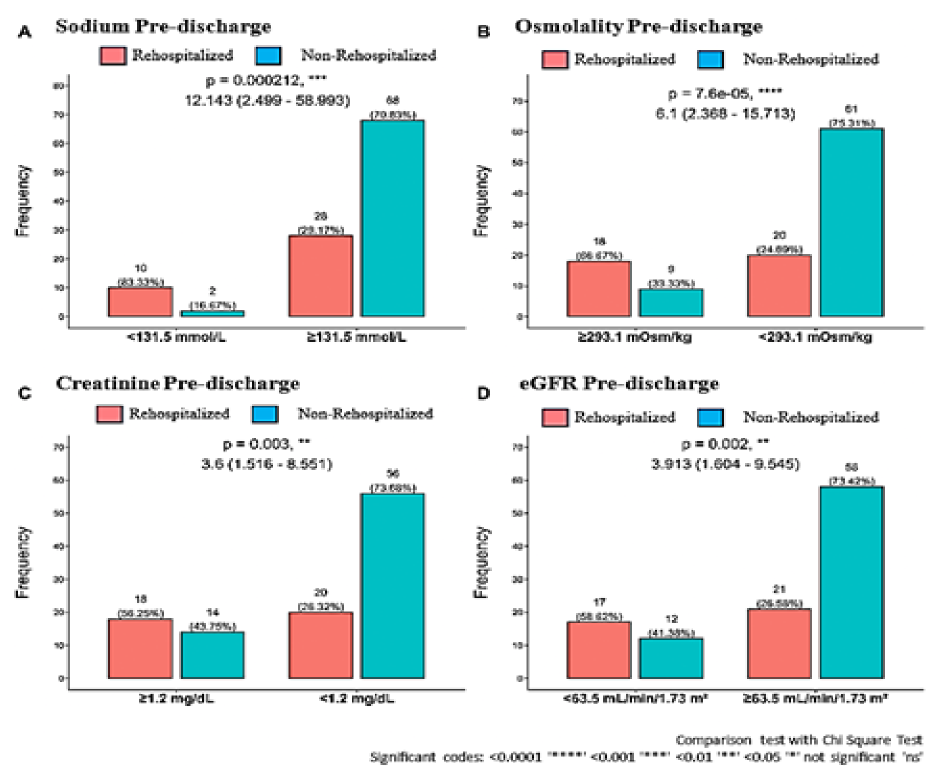

Figure 6. Relationship of Cut-Off Electrolyte and Renal Function Parameters in Patients at Pre-discharge

rehospitalization. For creatinine ≥1.2 mg/dL ($p = 0.003$, OR = 3.6, 95% CI: 1.516 - 8.551) and eGFR <63.5 mL/min/1.73 m² ($p = 0.002$, OR = 3.913, 95% CI: 1.604 - 9.545), both parameters indicate a significantly higher likelihood of rehospitalization. These findings underscore the importance of monitoring these parameters to predict the risk of rehospitalization in patients with heart failure.

The Relationship Between Confounding Variables (Comorbidities and Medications) and 90-Day Rehospitalization Status

Several comorbidities, which we thought could influence the variables in this study, were collected from patient data and analyzed to determine whether they affect the outcomes. Atrial fibrillation, CAD, valvular heart disease, cardiomyopathy, and hypertension are the common etiologies for heart failure. Diabetes mellitus causes a chronic hyperglycemia status, which can affect the osmolality level. We also collect data on previous medications that are used for heart failure to see whether patients with previous HF medication have better outcomes than those who are not.

Based on Table 3, a Chi-square test showed a significant association between CKD and the risk of rehospitalization ($p = 0.022$). Patients with CKD had a higher rate of rehospitalization (28.95%) compared to those without CKD (11.43%). This indicates that CKD increases the risk of rehospitalization in heart failure patients. On the other hand, comorbidities such as atrial fibrillation, CAD, valvular heart disease, cardiomyopathy, hypertension, diabetes mellitus, and dyslipidemia did not show significant differences in rehospitalization status ($p > 0.05$), suggesting that these conditions are not directly linked to an increased risk of rehospitalization in heart failure patients. Therefore, monitoring CKD in patients with heart failure is crucial for identifying those at higher risk of 90-day rehospitalization.

Based on Table 4, the results of the Chi-square test showed no significant association between the use of medications such as ACE-i/ARB, ARNI, CCB, beta blockers, diuretics, tolvaptan, ivabradine, digoxin, and SGLT-2 Inhibitors and rehospitalization ($p > 0.05$ for all medications). Although some medications were consumed more frequently by patients who experienced rehospitalization, there was insufficient evidence to establish a direct link to an increased risk of rehospitalization.

CART Analysis

Several variables were identified as related to 90-day rehospitalization status, including sodium, osmolality, creatinine, and eGFR levels at admission and pre-discharge. The CART method was used to identify the most significant variables for predicting rehospitalization. CART is effective at identifying non-linear relationships and complex interactions, providing a clear decision tree that helps doctors understand risk factors and clinical thresholds.

Based on Figure 7, the CART analysis shows that, of the 8 predictor variables tested, 7 were significant: admission sodium, pre-discharge sodium, admission osmolality, pre-discharge osmolality, pre-discharge creatinine, admission eGFR, and pre-discharge eGFR. This model has an accuracy of 87.04%, sensitivity of 73.68%, specificity of 94.29%, and an AUC of 90.7%, indicating its effectiveness in predicting the risk of rehospitalization in patients with heart failure. Admission osmolality is the primary parameter used in this model, with patients having an admission osmolality ≥296.6 mOsm/kg having a 100% likelihood of rehospitalization. Additionally, admission sodium, pre-discharge eGFR, and pre-discharge sodium and osmolality also play important roles in predicting rehospitalization risk.

Overall, the CART analysis results indicate that admission osmolality is the primary predictor of rehospitalization risk in heart failure patients,

Table 3. Comorbidities and Rehospitalization Rate

Variable n (%)		Rehospitalized (n=38)	Not Rehospitalized (n=70)	p-value
		(%)		
Atrial Fibrillation	NA	3 (7.89)	6 (8.57)	0.387
	No	29 (76.32)	57 (81.43)	
	Yes	6 (15.79)	7 (10)	
CAD	NA	3 (7.89)	6 (8.57)	0.321
	No	15 (39.47)	21 (30)	
	Yes	20 (52.63)	43 (61.43)	
Valvular Heart Disease	NA	3 (7.89)	6 (8.57)	0.312
	No	26 (68.42)	53 (75.71)	
	Yes	9 (23.68)	11 (15.71)	
Cardiomyopathy	NA	3 (7.89)	6 (8.57)	0.291
	No	35 (92.11)	62 (88.57)	
	Yes	0 (0)	2 (2.86)	
Hypertension	NA	3 (7.89)	6 (8.57)	0.145
	No	19 (50)	25 (35.71)	
	Yes	16 (42.11)	39 (55.71)	
Diabetes Mellitus	NA	3 (7.89)	6 (8.57)	0.972
	No	22 (57.89)	40 (57.14)	
	Yes	13 (34.21)	24 (34.29)	
Chronic Kidney Disease	NA	3 (7.89)	6 (8.57)	0.022
	No	24 (63.16)	56 (80)	
	Yes	11 (28.95)	8 (11.43)	

NA: Not available

while sodium, eGFR, and creatinine levels, measured both before and after discharge, also contribute to predicting this risk. This model can help doctors identify patients at high risk for rehospitalization, allowing for earlier intervention and better management to prevent rehospitalization in heart failure patients.

DISCUSSION

This study found that low sodium levels and osmolality are significant predictors of rehospitalization. Hyponatremia has been associated with poor prognosis in heart failure patients. A study using the HARVEST sample

Table 4. Heart Failure Medications Consumed and Rehospitalization Rates

Variable n (%)		Rehospitalized (n=38)	Not Rehospitalized (n=70)	p-value
		(%)		
ACE-i/ARB	NA	3 (7.89)	6 (8.57)	0.204
	No	13 (34.21)	16 (22.86)	
	Yes	22 (57.89)	48 (68.57)	
ARNI	NA	3 (7.89)	6 (8.57)	0.941
	No	34 (89.47)	62 (88.57)	
	Yes	1 (2.63)	2 (2.86)	
CCB	NA	3 (7.89)	6 (8.57)	0.658
	No	1 (2.63)	3 (4.29)	
	Yes	34 (89.47)	61 (87.14)	
Beta Blocker	NA	3 (7.89)	6 (8.57)	0.938
	No	26 (68.42)	48 (68.57)	
	Yes	9 (23.68)	16 (22.86)	
Diuretic	NA	3 (7.89)	6 (8.57)	0.574
	No	10 (26.32)	15 (21.43)	
	Yes	25 (65.79)	49 (70)	
Tolvaptan	NA	3 (7.89)	6 (8.57)	1.000
	No	35 (92.11)	64 (91.43)	
	Yes	0 (0)	0 (0)	
Ivabradine	NA	3 (7.89)	6 (8.57)	0.249
	No	33 (86.84)	63 (90)	
	Yes	2 (5.26)	1 (1.43)	
Digoxin	NA	3 (7.89)	6 (8.57)	0.267
	No	27 (71.05)	55 (78.57)	
	Yes	8 (21.05)	9 (12.86)	
SGLT-2 Inhibitor	NA	3 (7.89)	6 (8.57)	1.000
	No	35 (92.11)	64 (91.43)	
	Yes	0 (0)	0 (0)	

NA: Not available

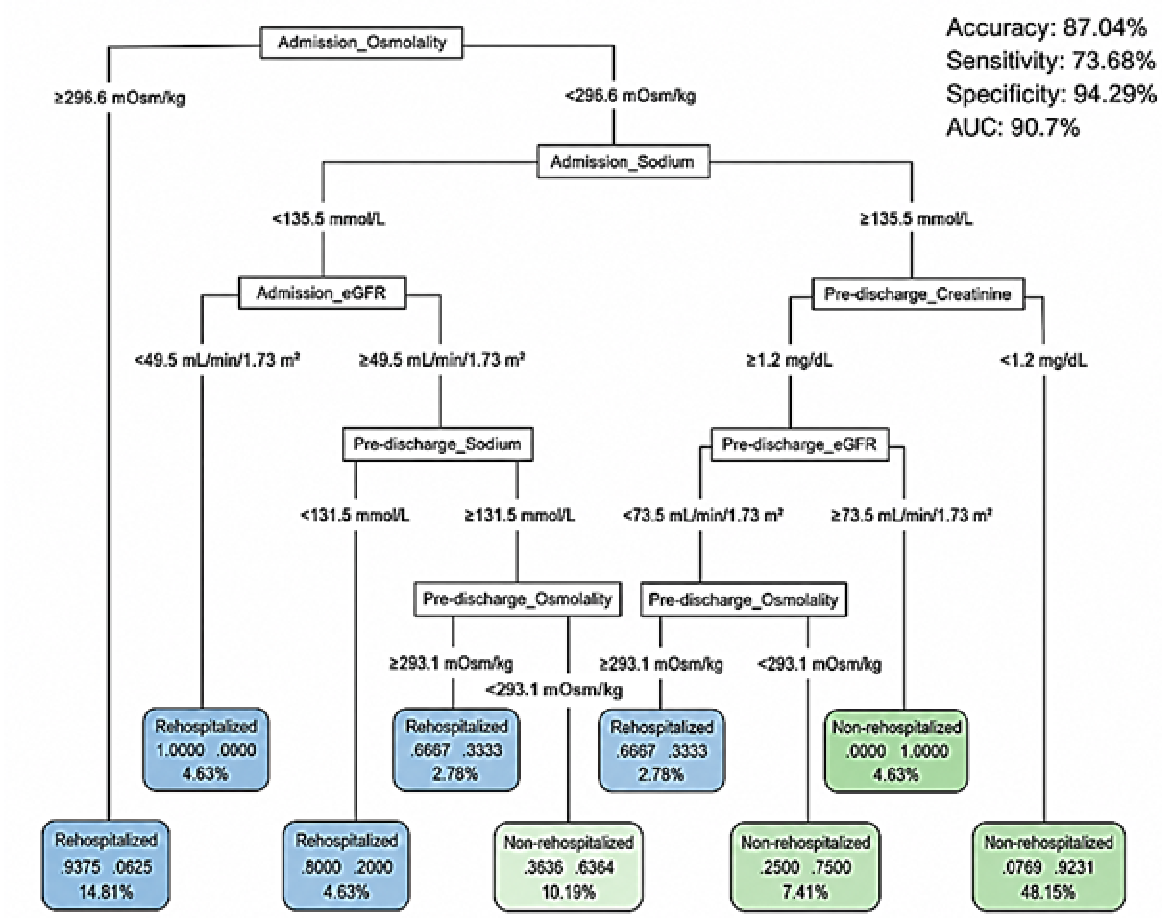

Figure 7. CART Model for Predicting 90-Day Rehospitalization in Heart Failure Patients

found that patients with sodium levels < 135 mg/dL had a high cardiovascular mortality rate. Patients with severe hyponatremia (< 125 mg/dL) had an even worse prognosis (15). The same findings were observed in pre-discharge values, although these studies focused on mortality rather than rehospitalization. A study by Thongprayoon et al. found high mortality rates in patients with hyponatremia (≤137 mEq/L) and hypernatremia (≥143 mEq/L) (16).

One of the factors identified as a risk for rehospitalization is osmolality, with surprising results. It was found that high osmolality (> 296.6 mOsm/kg) was associated with a higher rehospitalization rate. This finding was also observed in a 2016 study conducted in Spain. A study of 2,568 patients from the Spanish National Registry of Heart Failure (RICA) found that mortality rates were higher in patients with osmolality levels above 306, with groups Q3 (306.39–313.23 mOsm/kg) and Q4 (313.23–362.50 mOsm/kg) showing mortality rates of 22 % and 28 %, respectively. High serum osmolality in this group was associated with comorbid DM and CKD. Given that glucose levels and BUN also affect osmolality, elevated glycemic levels and azotemia due to impaired kidney filtration increase serum osmolality, both of which worsen outcomes in heart failure patients (17).

The patient's kidney function is also correlated with rehospitalization rates. Patients with low eGFR both at admission and pre-discharge show high rates of rehospitalization. Impaired kidney function at admission can be attributed to cardiorenal syndrome or CKD as a comorbidity. In patients with kidney impairment due to acute heart failure, improvement in heart failure conditions can enhance circulation, including kidney perfusion, and improve kidney filtration function (18). Khan et al., using the SOLVD (Studies of Left Ventricular Dysfunction) sample found that mortality rates increased in patients with eGFR below 60 mL/min (19). Komukai found that heart failure patients with eGFR $<$45 mL/min per 1.73 m^2 at admission had a high rehospitalization rate. Patients in this group, especially the elderly, have a high risk of anemia and Worsening Renal Function (WRF) (20).

Interestingly, the AUC and specificity values in our patients would increase if the predictor used both admission and pre-discharge data, rather than just one. This is seen in Figure 7. The CART model that includes both admission and pre-discharge parameters has a specificity of 94.29% and an AUC of 90.7%. This shows the importance of considering laboratory results from both parameters at admission and discharge. This illustrates that the success of heart failure therapy, which improves overvolume conditions, hyponatremia, and kidney function, will affect rehospitalization outcomes. In patients with poor kidney function and hyponatremia at admission, therapy to manage heart failure congestion will improve both parameters before discharge. These values will be higher if the patient did not experience deterioration in these parameters at admission. Conversely, if therapy is suboptimal, deterioration in both parameters may occur at discharge, thereby increasing the risk of rehospitalization. This is especially true if both parameters were poor at admission. Gheorghiae et al. further found that hyponatremia and kidney dysfunction, as indicated by eGFR, are good prognostic factors for rehospitalization (21).

The sample's gender characteristics show a higher prevalence in men compared to women, which is in line with heart failure prevalence studies, where the rate of heart failure in women is lower. However, proportionally, women tend to have more HFpEF (Heart Failure with preserved Ejection Fraction) than HFrEF (Heart Failure with reduced Ejection Fraction). The Swede-HF registry data show that 55% of women have HFpEF compared to 29% with HFrEF (22). Since this study used an HFrEF population, it is expected that fewer women were included than men. This study found no difference in rehospitalization rates associated with the use of heart failure medications. This is consistent with a study using the EVEREST data, which found no difference in rehospitalization rates among HF and non-CV patients when considering heart failure medication (3).

Hyponatremia is a common occurrence in heart failure. Multiple pathophysiological mechanisms cause this condition. It usually occurs in patients with advanced chronic heart failure accompanied by severe ventricular dysfunction. This happens due to the synergistic interaction between increased AVP (arginine vasopressin) secretion, increased sympathetic nervous system activity, and RAAS (renin-angiotensin-aldosterone system) activity (23). AVP plays a critical role in causing hyponatremia in heart failure patients. AVP is released into the bloodstream in response to osmotic (hypertonicity) or non-osmotic (decreased cardiac output, intravascular volume, or blood pressure) stimuli. In heart failure patients, non-osmotic AVP plays a central role in the development of hyponatremia due to decreased cardiac output (24). AVP binds to V2R in the renal duct, increasing the expression of the aquaporin-2 water channel. As a result, water permeability and retention increase. When bound to V1aR, which is found in the walls of arteries, arterioles, and veins, AVP causes vasoconstriction, increasing vascular resistance and afterload. High AVP levels stimulate V1aR, causing coronary vasoconstriction that reduces coronary blood flow and cardiac contractility (23).

The findings in this study support existing assessments of predictors of heart failure rehospitalization. The LACE score is one of the most popular scoring systems used as a predictor of rehospitalization, including for patients with heart failure. The parameters used in the LACE acronym are L (length of stay), A (admission acuity), C (Charlson Comorbidity Index), and E (emergency department use in the past 6 months) (9). The Charlson Comorbidity Index includes

CKD points, defined as patients undergoing dialysis, post-kidney transplantation, or with creatinine levels above 3 mg/dL. This suggests that creatinine levels, which reflect kidney function, can be a predictor for rehospitalization (25). Another predictive system is the HOSPITAL score, which includes parameters like Hb <12 g/dL, discharge from oncology, sodium levels <135 mg/dL, special procedures like hemodialysis and catheterization, admission type (elective or emergency), number of readmissions in the past year, and length of stay (≥5 days). Sodium levels are also considered in this score, highlighting the importance of fluid status and kidney function in regulating electrolytes for predicting rehospitalization (26).

Cardiorenal syndrome, which has long been recognized and studied, illustrates how one organ's condition affects the other. Studies have shown that patients with acute or chronic heart failure will experience kidney dysfunction, and vice versa (27). Therefore, acute heart failure patients tend to show acute kidney failure upon admission. This is reflected in data showing that cardiorenal syndrome type 1, which is an acute heart failure worsening kidney function, and chronic kidney failure, especially at high stages, will lead to congestive heart failure due to volume overload and reduced heart function triggered or exacerbated by kidney dysfunction, such as anemia, soft tissue calcification, and uremic toxicity (18).

Current heart failure treatment must also consider and, if possible, address kidney failure, whether as a comorbidity or a consequence of cardiorenal syndrome. Although each subtype of cardiorenal syndrome has a different etiology, the critical interaction between these two systems and how the function of one organ and its system depends on the other is noteworthy. Impaired kidney function can hinder therapeutic progress. It cannot be ruled out that a patient's kidney function can worsen or even trigger heart failure. Treating only one organ without addressing the other's dysfunction may lead to a vicious circle in which the malfunction of one organ affects the function of the other (28). Focusing on treating the underlying risk factors that cause both heart and kidney dysfunction, such as hypertension, diabetes, and atherosclerosis, is essential for preventing chronic organ dysfunction and optimizing cardiac output in cases of acute organ dysfunction.

This study did not find a correlation between value changes in kidney function and sodium levels and rehospitalization. This was beyond our expectations. This is due to a condition called Worsening Renal Function (WRF). Research from the SOLVD (Studies of Left Ventricular Dysfunction) study showed that mortality rates increased with worsening kidney function, as measured by serum creatinine levels. Every 10 mL/min decrease in eGFR from the baseline increased the risk of death (20). Patients with a 10 mL/min decline in eGFR per year had a high mortality rate. Seventeen percent of the patients studied had an eGFR decline of more than 10 mL/min (29). This was further confirmed by a study by Vindhyal et al., who found that a 2.46 mL/min/1.73 m² decrease in eGFR was associated with a high 30-day rehospitalization rate (30). The HARVEST study found that patients with a 3 mg/dL decrease in sodium levels had an increased risk of mortality (15). We hypothesize that changes in these parameters may not have an impact if they do not alter the parameter's status. For example, suppose the eGFR parameter at admission is normal, even if it decreases by 10 during hospitalization. In that case, this decline will not yet categorize the patient as being in kidney failure, and the risk of rehospitalization would remain low. This finding is consistent with the observation that admission and pre-discharge factors are interrelated and mutually reinforce each other.

This study has some limitations. First, the sample size is still small because pre-discharge samples were not collected from some patients in the registry. Second, this study did not focus on other potentially influencing parameters, such as congestion signs and other electrolytes, such as potassium. High osmolality may result from extravasation of fluid from the intravascular space into surrounding tissue. This can be detected by measuring intravascular congestion using ultrasound parameters, such as IVC diameter. Potassium can help sodium regulate water and electrolytes in the kidney, thus indicating the current kidney condition. But we lack the data to conduct a proper analysis.

CONCLUSIONS

Hyponatremia, reduced eGFR, and elevated serum osmolality were independently associated with an increased risk of 90-day rehospitalization in patients with congestive heart failure, whereas creatinine alone showed limited prognostic value. Incorporating both admission and pre-discharge measurements substantially improved predictive performance compared with single time-point assessment. These findings support serial evaluation of sodium, eGFR, and osmolality for risk stratification and identification of patients who may benefit from intensified post-discharge management to reduce early rehospitalization.

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