Original Article :

Prevalence, Predictors and Prognostic Impact of Renal Dysfunction among Hospitalized Patients with Systolic Heart Failure

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Received on 16/10/2020 Accepted for Publication on 13/12/2020 dx.doi.org/10.5455/mjhs.2021.02.004

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Abstract

Background and Aims

The interaction between heart and kidneys has increased, and parts of the pathophysiological background for the cardiorenal syndrome have been established. This study aimed to determine the prevalence, predictors, and prognostic impact of Renal Dysfunction (RD) among hospitalized patients with systolic Heart Failure (HF).

Methods

This a cross-sectional study included 1559 patients, who were admitted with a diagnosis of systolic HF during the period from 1-March-2011 till 20-June-2019 at Madinah cardiac center. RD was defined as estimated glomerular filtration rate < 60 mL/min/ 1.73 m2.

Results

Of the total of 1559 patients, 67.2% were males, 51.3% were hypertensive, 56.1% were diabetic and 49.1% were anemic. 60.9% of patients had RD. HF patients with RD were significantly older (p<0.001), had a history of Hypertension (HTN) (p<0.001), Diabetes Mellitus (DM) (p<0.001), anemia (p<0.001), stroke (p<0.003) and smoking (p<0.001). Multivariate analysis showed that older age (OR, 1.1; 95% CI, 1.05-1.07; p<0.001), history of DM (OR, 1.5; 95%

الملخص

الخلفية و الاهداف :

ازدادت العلاقة بين القلب والكلى، وجزء من الخلفية الفسيولوجية بينهما تم معرفتها. تهدف هذه الدراسة لوصف معدلات الإصابة بقصور وظائف الكلى وتحديد الأسباب المؤدية إليه وتأثيره بين المرضى المصابين بفشل القلب.

طريقة البحث

شملت هذه الدراسة المقطعية ١٥٥٩ مريضاً بفشل القلب في الفترة ما بين ١ مارس ٢٠١١ حتى ٢٠ يونيو ٢٠١٩ في مركز أمراض وجراحة القلب بالمدينة المنورة. تم تقسيم المرضى الى مجموعتين على أساس معدل الترشيح الكلوي الخاص بهم. تم تعريف قصور وظائف الكلى إذا كان معدل الترشيح الكلوي اقل من ٦٠ مل/ دقيقة/١,٧٣ م٢.

النتائج

٦٧,٢٪ من العينة كانوا ذكورا، ٥١,٣٪ كانوا مصابين بإرتفاع ضغط الدم، ٥٦,١٪ كانوا مصابين بمرض السكر و٤٩,١٪ كانوا مصابين بفقر الدم. وبينت الدراسة إن من إجمالي ١٥٥٩ مريضا بفشل القلب، ٦٠,٩٪ كانوا مصابين بقصور وظائف الكلى. ولوحظ إن المرضى المصابين بقصور وظائف الكلى كانوا أكبر سنا (p<0.001). بالإضافة إلى وجود تاريخ مرضي لمرض السكري (p<0.001)، الضغط (p<0.001)، فقر الدم (p<0.001)، الجلطة الدماغية (p=0.003) اوالتدخين (p<0.001). تحليل متعدد المتغيرات أظهر إن كبار السن (OR, 1.1; 95% CI, 1.05-1.07;

CI, 1.14-1.86; p=0.003), HTN (OR, 1.4; 95% CI, 1.11-1.81; p=0.005), and anemia (OR, 1.6; 95% CI, 1.30-2.06; p<0.001) were the predictors of RD. Patients with RD had a significantly higher death rate and total length stay (p<0.001). However, the hospitalization rate was not significant (p=0.111).

Conclusion

About 60.9% of systolic HF patients had RD. Older age, history of DM, HTN, and anemia were predictors of RD. Patients with RD had a higher death rate and a total length of stay.

Keywords

Renal Dysfunction, Heart Failure, Glomerular Filtration Rate, Cardiorenal Syndrome

OR, 1.5; 95% CI, 1.14-1.86;) مرض السكري ،p<0.001
OR, 1.4; 95% CI, 1.11-) مرض الضغط المرتفع (p=0.003
1.81; p=0.005) وفقر الدم (OR, 1.6; 95% CI, 1.30-2.06;
p<0.001) كانت أسباب هامة للأصابة بقصور في وظائف الكلى.
أظهرت الدراسة إيضا أن معدل الوفاة وفترة التنويم بالمستشفى كان أعلى لدى المرضى المصابين بقصور وظائف الكلى مقارنة بغير المصابين (p<0.01).

الخلاصة

تقريبا ٦٠,٩٪ من مرضى فشل القلب كان لديهم قصور في وظائف الكلى. كبار السن والمرضى الذين يعانوا من مرض السكري، الضغط المرتفع، او فقر الدم كانت أسباب هامة للأصابة بقصور في وظائف الكلى. معدل الوفاة وفترة التنويم بالمستشفى لدى المرضى المصابين بقصور في وظائف الكلى كان أعلى.

الكلمات المفتاحية

قصور وظائف الكلى، فشل القلب، معدل الترشيح الكلوي، متلازمة القلب والكلى

Introduction

Heart Failure (HF(is defined as an abnormality in cardiac structure or function that leads to the inability of the heart to maintain sufficient blood flow to meet the physiological requirements of the metabolizing tissues or can do so at the expense of high filling pressure [1]. HF has become a high priority health issue due to its high prevalence particularly among the older age group, and the high rates of associated morbidity and mortality [2,3]. Renal Dysfunction (RD) is a disorder of gradual or permanent loss of the renal function, resulting in renal failure [4]. The diagnosis of RD is often made based on estimated Glomerular Filtration Rate)eGFR(which provides a more precise approximation of renal function than elevated serum creatinine alone [5].

Our knowledge about the interaction between kidneys and heart has increased over the years, and many parts of the pathophysiological background of the cardiorenal syndrome have been recognized [6]. The heart and renal function are closely linked together by the sympathetic nervous system and neurohormone [3]. The cardiorenal syndrome is complex, as renal diseases and HF share the same risk factors, which they work together and potentiate each other HF is associated with a reduction in renal blood flow and a further decrease in eGFR [6]. Progressive renal ischemia leads to activation of renin angiotensin aldosterone system (RAAS) and increase in sympathet-

ic activity, which is a normal phenomenon but have toxic effects on the renal tissues if they are prolonged [7]. Angiotensin Converting Enzyme Inhibitors (ACEIs) are pivotal in the management of systolic HF, by blocking the RAAS which preserves renal function and decreases mortality rate[8].

Renal dysfunction in HF patients has a critical role in the pathophysiology and progression of HF over time[9]. HF patients had volume overload which leads to an increase in the central venous pressure in their blood vessels with low systemic pressure, which leads to compromise in the renal perfusion pressure. Also, there is an activation of intrarenal sensors and arterial baroreceptors leading to the activation of the sympathoadrenal system, the RAAS, and intravascular volume. These factors will lead to intrarenal and peripheral vasoconstriction, which causing a further decrease in the renal blood flow and eGFR, leading to RD[15].

Given the growing incidences of RD among HF patients, it is important to know the predictors and prognostic impact of RD among patients with HF. This study aimed to determine the prevalence, predictors, and prognostic impact of RD in hospitalized systolic HF patients in Madinah cardiac center.

Material and Methods

Study design, study period, and study setting

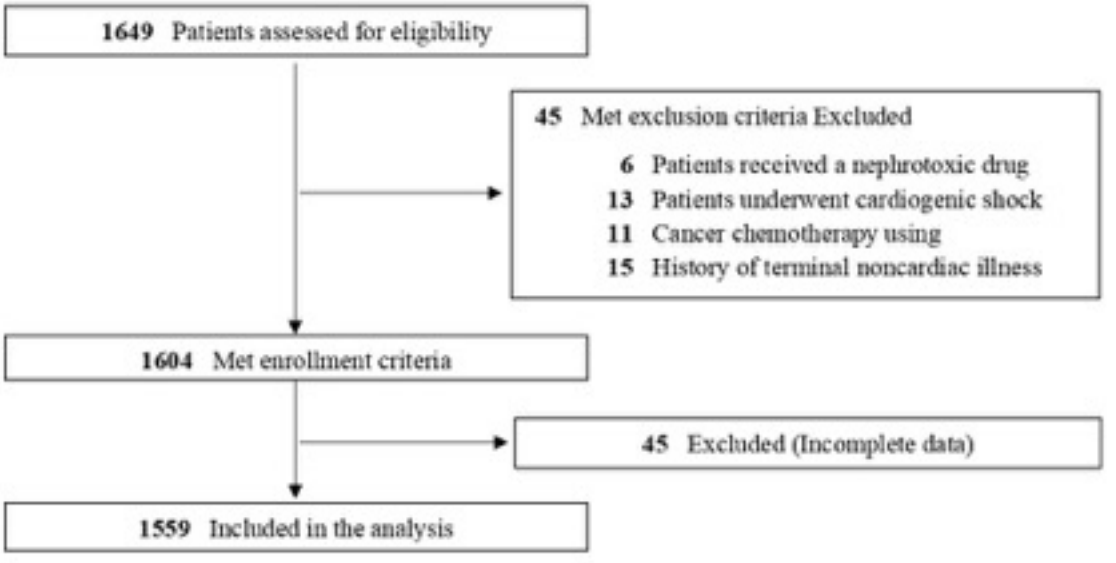
This a cross-sectional study was conducted at Madinah cardiac center involving patients with HF registered in the health management information system database during the period from 1-March-2011 till 20-June-2019.

Study population

The systolic HF registry gathered from an electronic medical records system was retrieved. A total of 1649 patients were identified as having a documented clinical diagnosis of HF and performed a serum creatinine test in the last hospital admission to calculate eGFR.

Patients with systolic HF defined as Left Ventricular Ejection Fraction (LVEF) $\leq$ 45% were included in the study. Patients who had received any nephrotoxic drugs within two days before admission or had cardiogenic shock within one month before admission and those who undergoing cancer chemotherapy were excluded from the study. The presence of terminal non-cardiac illness which could influence the prognosis was set as an exclusion criterion as well. Ninety patients were excluded, 45 of them met the exclusion criteria and the other 45 had incomplete data. The remaining 1559 patients constituted the population of this study [Figure 1].

Figure 1



Blood measurements and eGFR estimation

GFR was estimated depending on the equation made by the chronic kidney disease epidemiology collaboration (GFR = 141 × min (Scr / κ, 1)α × max (Scr / κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black] where:

Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males,[10]. Patients were divided into normal renal function and RD according to eGFR (mL/min/1.73 m2). eGFR ≥60; normal function, and eGFR <60; RD [11]. Anemia was defined as Hemoglobin (Hb) level <13 g/dl and <12 g/dl in male and female respectively, according to world health organization criteria for anemia[12].

Demographic variables, cardiac and non-cardiac history, medications, and laboratory data including renal function tests, complete blood cells count, and lipid profile were retrieved from the electronic medical records.

Ethical Approval

Research ethics committee of Taibah University and the ethical committee board of Madinah cardiac center approved this study protocol (approval number: IRB00010413). All study parts were conforming to the declaration of Helsinki Ethical Principles for medical research involving human subjects as revised in 1975 [13].

Statistical Analysis

Data were analyzed using the Statistical Package for Social Science software version 23. Continuous data were presented as mean ± Standard Deviation (SD) as they were normally distributed when tested by the Shapiro-Wilk test, while the categor-

ical data were presented as frequencies and percentages. Baseline demographic and clinical variables were compared between two groups by using the Pearson chi-squared test for categorical variables. To assess whether the continuous variables differed among the study two groups, we used the independent sample t-test. The predictors of RD were determined by using binary logistic regression. P-value was considered significant if it is ≤ 0.05.

Results

Out of 1559 patients included in the analysis, 1047 (67.2%) were males, 585 (37.5%) had a history of acute coronary syndrome (ACS), 799 (51.3%) were hypertensive, 874 (56.1%) were diabetic, 280 (18.0%) were smokers, 766 (49.1%) were anemic at the time of admission, and 188 (12.2%) were on ACEIs (Table 1).

Table 1. Sociodemographic and clinical characteristics of the study population

Variables	Number (n=1559)	(%)
Gender		
Male	1047	(67.2)
Female	512	(32.8)
Cardiac History		
Atrial Fibrillation	208	(13.3)
Arrhythmias	96	(6.2)
Valvular Heart Disease	344	(22.1)
Acute Coronary Syndrome	585	(37.5)
Rheumatic Heart Disease	34	(2.2)
Family History of Coronary Artery Disease	41	(2.6)
Percutaneous Coronary Interventions	142	(9.1)
Coronary Artery Bypass Grafting	91	(5.8)
Valve Replacement	35	(2.2)
Cardiac Device	96	(6.2)
Cardiac Arrest	47	(3.0)
Noncardiac History		
Current Smoker	280	(18.0)
Anemia	766	(49.1)
Hypertension	799	(51.3)
Diabetes Mellitus	874	(56.1)
Cerebrovascular Diseases	100	(6.4)
Peripheral Vascular Disease	20	(1.3)
Dyslipidemia	117	(7.5)
Preadmission Medications		
Aspirin	69	(4.4)

Variables	Number (n=1559)	(%)
Gender		
Clopidogrel	224	(14.4)
Angiotensin Converting Enzyme Inhibitors	188	(12.1)
Calcium Channel Blockers	31	(2.0)
Beta Blockers	264	(16.9)
Digoxin	143	(9.2)
Anticoagulants	96	(6.2)
Diuretics	107	(6.9)
Statin	179	(11.5)
Ferrous Sulfate	87	(5.6)

About 60.9% of patients had RD. Patients with RD were significantly older. Mean ± SD of age was 70±11 years in patients with RD compared to 57.7±14 years in patients without RD ($p<0.001$). A slightly higher increase in mean Systolic Blood Pressure (SBP) at admission was significant in patients with RD. Mean SBP was 119±23 mmHg in patients with RD compared to 116±15 mmHg in patients without RD ($p=0.006$). However, diastolic blood pressure didn't change between the two groups.

Patients with RD were significantly had a history of ACS ($p=0.002$), rheumatic heart disease ($p<0.043$), Hypertension (HTN) ($p<0.001$), Diabetes Mellitus (DM) ($p<0.001$), anemia ($p<0.001$), stroke ($p<0.003$) and smoking ($p<0.001$). Among all HF patients who used beta blockers, 52.7% of them had RD, compared to 47.3% without RD ($p=0.003$). There was no significant association in valvular heart disease, atrial fibrillation, using ACEIs, prior percutaneous coronary interventions, or coronary artery bypass grafting.

Regarding laboratory data, patients with RD exhibited a significantly lower hematological profile. Mean ± SD of Hb level on admission was 12.2±2.2 g/dl and 13.3±2.2 g/dl in patients with RD and without RD, respectively ($p<0.001$). Mean ± SD of low-density lipoprotein was 2.2±1.0 mmol/L in patients with RD compared to 2.4±1.1 mmol/L in patients without RD ($p<0.001$). Mean ± SD total cholesterol was 4.0±1.3 mmol/L and 3.7±1.3 mmol/L in patients with RD and without RD, respectively ($p=0.005$). Detailed clinical characteristics and laboratory data are shown in (Table 2).

Table 2. Baseline clinical characteristic and laboratory data stratified by renal function (n=1559)

Clinical Variable	Renal Dysfunction (n=949) (60.9%)		Normal Renal Function (n=610) (39.1%)		OR (95% CI)		P value
	Number (%) / Mean ± SD						
Age	70±11		57±14				<0.001
SBP mmHg	119±23		116±15				0.006
DBP mmHg	65±8		66±7				0.965
Gender							
Female	348	(68.0)	164	(32.0)	1.575	(1.261 – 1.967)	<0.001
Male	501	(57.4)	446	(42.6)			
Cardiac History							
Atrial fibrillation	136	(65.4)	72	(34.6)	1.250	(0.921 - 1.697)	0.152
Arrhythmias	54	(56.3)	42	(43.8)	0.816	(0.538 – 1.238)	0.338
Valvular heart disease	195	(56.7)	149	(43.3)	0.800	(0.628 – 1.020)	0.072
ACS	385	(65.8)	200	(34.2)	1.399	(1.131 - 1.732)	0.002
Rheumatic Heart Disease	15	(44.1)	19	(55.9)	0.500	(0.252 – 0.991)	0.043
Family History of CAD	25	(61.0)	16	(39.0)	1.004	(0.532 - 1.897)	0.989
PCI	94	(66.2)	48	(33.8)	1.287	(0.895 – 1.852)	0.173
CABG	63	(69.2)	28	(30.8)	1.478	(0.936 – 2.335)	0.092
Valve Replacement	18	(51.4)	17	(48.6)	0.674	(0.345 – 1.319)	0.247
Cardiac Device	86	(89.6)	10	(10.4)	1.108	(0.562 - 2.181)	0.768
Cardiac Arrest	44	(93.6)	3	(6.4)	0.638	(0.196 - 2.080)	0.452
Medical History							
Current Smoker	137	(48.9)	143	(51.1)	0.551	(0.425- 0.715)	<0.001
Anemia	526	(68.7)	240	(31.3)	1.917	(1.559 – 2.358)	<0.001
Hypertension	570	(71.3)	229	(28.7)	2.502	(2.030 – 3.084)	<0.001
Diabetes Mellitus	607	(69.5)	267	(30.5)	2.280	(1.852 – 2.806)	<0.001
Cerebrovascular Diseases	75	(75.0)	25	(25.0)	2.008	(1.262 – 3.195)	0.003
Peripheral vascular disease	16	(80.0)	4	(20.0)	2.598	(0.864-7.808)	0.078
Medications							
Aspirin	42	(60.9)	27	(39.1)	1.000	(0.610 – 1.640)	1.000
Clopidogrel	146	(65.2)	78	(34.8)	1.240	(0.922 – 1.667)	0.154
ACEIs	105	(55.9)	83	(44.1)	0.790	(0.581 – 1.075)	0.132
Beta Blockers	139	(52.7)	125	(47.3)	0.666	(0.510 – 0.869)	0.003
Digoxin	79	(55.2)	64	(44.8)	0.775	(0.548 – 1.096)	0.148
Anticoagulants	88	(91.7)	8	(8.3)	0.852	(0.405 - 1.794)	0.674
Diuretics	56	(52.3)	51	(47.7)	0.687	(0.464 – 1.019)	0.061
Statin	116	(64.8)	63	(35.2)	1.209	(0.873 - 1.674)	0.809
Ferrous Sulfate	48	(55.2)	39	(44.8)	0.780	(0.505 – 1.205)	0.797
Laboratory Variables							
Complete Blood Count							
Hemoglobin(g/dl)	12.2±2.2		13.3±2.2				<0.001

Clinical Variable	Renal Dysfunction (n=949) (60.9%)	Normal Renal Function (n=610) (39.1%)	OR (95% CI)		P value
	Number (%) / Mean ± SD				
HCT%	37.5±6.3	40.3±6.0			<0.001
RBC $\times 10^{12}/\mu L$	4.3±0.8	4.7±0.8			<0.001
MCV fL	87.1±7.7	86.1±7.5			0.495
WBC $\times 10^{3}/\mu L$	10.5±6.2	8.9±3.8			<0.001
Platelet Count$\times 10^{3}/\mu L$	256.8±97.5	266.9±97.5			0.237
Kidney Function Tests					
eGFR	38±14	80±19			<0.001
Creatinine (µmol/L)	166.0±79.9	87.4±16.8			<0.001
BUN (mmol/L)	13.3±8.7	6.2±2.6			<0.001
Lipid Profile					
LDL (mmol/L)	2.4±1.1	2.2±1.0			<0.001
HDL (mmol/L)	0.9±0.4	0.9±0.5			0.201
Triglycerides (mmol/L)	1.2±0.7	1.3±0.7			0.156
Total cholesterol (mmol/L)	4.0±1.3	3.7±1.3			0.005
Sodium (mEq/L)	136.6±8.2	137.4±5.4			0.080
Troponin (mcg/L)	4.9±11.8	1.8±6.9			<0.001

SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, ACS; Acute Coronary Syndrome, PCI; Percutaneous Coronary Interventions, CAD; Coronary Artery Diseases, CABG; Coronary Artery Bypass Grafting, ACEI; Angiotensin Converting Enzyme Inhibitors, HCT%; Hematocrit, RBC; Red Blood Cells, MCV; Mean Corpuscular Volume, WBC; White Blood Cells, eGFR; estimated Glomerular Filtration Rate, BUN; Blood Urea Nitrogen, LDL; Low Density Lipoprotein, .HDL; High Density Lipoprotein

Multivariate analysis showed that older age (OR, 1.1; 95% CI, 1.05-1.07; p<0.001), history of DM (OR, 1.5; 95% CI, 1.14-1.86; p=0.003), HTN (OR, 1.4; 95% CI, 1.11-1.81; p=0.005), and anemia (OR, 1.6; 95% CI, 1.30-2.06; p<0.001) were the independent predictors of RD (Table 3).

Table 3. Risk factors of renal dysfunction in systolic HF patients

Variables	Sig	Exp(B)	95%C.I.for EXP(B)	
			Lower	Upper
Age	<0.001	1.064	1.054	1.073
Female	0.311	1.139	0.885	1.466
Acute coronary syndrome	0.368	1.116	0.879	1.416
Diabetes mellitus	0.003	1.456	1.141	1.858
Hypertension	0.005	1.420	1.112	1.814
Anemia	<0.001	1.637	1.300	2.060

Patients with RD had a significantly higher death rate compared to patients with normal renal function. About 86.9% of the patients who died had RD (p<0.001). Total length stay was higher among patients with RD. Mean ± SD of the total length of stay was 8±21 days in patients with RD compared to 5±6 days in patients without RD (p<0.001). However, there was no difference regarding the hospitalization rate

between the two groups (Table 4).

Table 4. Outcomes comparison for HF patients with or without renal dysfunction

Outcomes	Renal Dysfunction (n=949) (60.9%)		Normal Renal Function (n=610) (39.1%)		OR (95% CI)	P value
	Number (%) / Mean ± SD					
Death	721	(86.9)	26	(31.1)	4.972 (3.247 – 7.614)	**<0.001**
Hospitalization rate	1.86±1.61		1.73±1.46			0.111
Total length of stays (days)	8±21		5±6			**<0.001**

Discussion

RD in HF patients is becoming more frequent and severe [13]. In the current study, we found that 60.9% of systolic HF patients had RD (defined as eGFR <60ml/ml/min/1.73m2). Previous studies reported a high prevalence of RD in HF patients [14]. A recent retrospective cohort study showed that the overall prevalence of RD was 89%[3]. Similarly, a meta-analysis evaluated the association between RD and HF revealed that 63% of patients had RD[15]. Ronco et al reported that RD has been observed in 45-63% of systolic HF patients[16]. Baydemir et al showed that 81% of HF patients had moderate RD and 19% had severe RD[17]. However, in a study conducted on 1301 patients registered in a systolic HF disease management program, just 26% were found to have CKD [18, 19].

RD is common in HF patients and shares the same risk factors. The current study found that older age, history of DM, HTN, and anemia were predictors of RD. Several predictors of RD have been described in the previous studies. Data from the Framingham HF study found that older age, high Body Mass Index (BMI), DM, and smoking were predictors of RD[20]. Data from the national health and nutrition examination surveys suggest that older ageethnicity [18,22,23], education[18,21], high BMI[23], history of DM[15,19,24], HTN [14,25,26], and cardiovas-.cular disease [3,28] were associated with RD

A study done by Tarantini et al showed that moderate to severe RD was diagnosed in 59% of systolic HF patients at hospital admission and these patients were older and had a high prevalence of HTN, DM, and anemia [29]. Another study showed that the age of more than 75 years remained an important risk factor for RD development in HF patients [28]. Older patients have a higher prevalence of DM, HTN, anemia, MI, and HF hospitalization, thus may explain the high prevalence of RD among this group along with age-related changes and decrease in renal function [29]. However, Fox et al showed that age was not associated with RD, demonstrating that age-related systemic effects are not specifically related to the onset of RD [22].

Among HF patients with RD, the prevalence of DM ranged from 37-55% while the prevalence of HTN ranged from 68-85%. This may be explained by the fact,

that the presence of well-known risk factors of RD like DM and HTN leads to further reduction of eGFR and worsen any pre-existing RD [30]. In univariate analysis, female gender and history of ACS were associated with RD but these links disappeared when the multivariable analysis was conducted. However, McAlister et al showed that HF patients with RD were more likely to be female [30].

Patients with RD had a significantly higher death rate in contrast to patients without RD. About 86.9% of HF patients who died had RD. RD is related to short and long-term mortality among HF patients[18]. Hillege et al found that the death rate in HF patients was associated with a decline in the eGFR than with a decline in the LVEF% [31]. Löfman et al found that the mortality rate increased from 2% in patients without RD to 30% in those with end-stage renal disease (eGFR <15), and the 5 years probability of death was 60% in those with moderate RD and 80% in patients with severe RD [3].

In the current study, the total length of stays was higher among patients with RD. But there was no association between RD and the number of hospital admissions. In the Kor-HF registry, length of hospital stays, and the period of intensive care unit stay were prolonged in systolic HF patients with RD and the hospital death rate was 13.2% [30]. In the candesartan in HF assessment of mortality and morbidity trial, patients with eGFR <60 had increased risk of HF hospitalization and cardiovascular death, and this risk increased with decreasing eGFR [32]. However, Verdiani et al reported that there are no differences in re-hospitalization rates, length of stay, or mortality rate in patients with RD compared with those without RD [20].

Conclusion

About 60.9% of systolic HF patients had RD. Older age, history of DM, HTN, and anemia were the independent predictors of RD. Patients with RD had a significantly higher death rate and total length stays.

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