Original Article

Clinical profile and Outcome of patients of Heart Failure with and without Chronic Kidney Disease

Manoj Subedi*, Roshan Chhetri, Surendra Uranw, Sanjib Kumar Sharma

Department of Internal Medicine, B P Koirala Institute of Health Sciences, Dharan, Nepal

Keywords: *Heart Failure, Chronic Kidney Disease, Clinical profile, Outcome*

Abstract

Background: Heart failure is a leading cause of mortality globally. Chronic Kidney Disease is one of the major co-morbidity that is associated with higher morbidity and mortality in Heart failure. Clinical profile and data on outcome of Heart failure patients with Chronic Kidney Disease are limited.

Methods: In this prospective observational study; we enrolled 200 patients of Heart failure from November 2018 to October 2019 and later they were stratified into two groups as Heart failure with and without Chronic Kidney Disease. Their clinical profile, risk factors, laboratory parameters and echocardiography were compared. Patients were followed up after a period of 3 months and their outcome was analyzed.

Results: The mean age of patient was 64.7±14.9 years in Heart failure with Chronic Kidney Disease and 60±16.4 years among those without Chronic Kidney Disease (p value=0.08). Heart failure patients with Chronic Kidney Disease were more likely to present with orthopnea/Paroxysmal nocturnal dyspnea and bilateral lower limb swelling (p value <0.05).. Heart failure patients with Chronic Kidney Disease had higher blood pressure, more likely to have anemia and albuminuria at presentation (p value=<0.05). The mortality of HF patients with Chronic Kidney Disease and probable Chronic Kidney Disease at 3 months was 34% and 15% in remaining group (p value=0.002).

Conclusions: Heart failure patients with Chronic Kidney Disease are older, have more comorbidity, more orthopneic and edematous at presentation and are less likely to receive optimal medical therapy. 3 month mortality was significantly higher in those with renal dysfunction.

Introduction

Heart failure (HF) is a global epidemic in health care and a leading cause of mortality and morbidity worldwide. Approximately 5 million individuals have HF and over 550,000 are newly diagnosed as having HF every year in the United States[1]. The overall prevalence of heart failure in adult population in developed country is 2% and its prevalence increases with age[2,3]. According to European society of cardiology heart failure pilot survey for the study of co-morbidities, the majority of patients (74%) had a least one co-morbidity, the most prevalent being CKD (41%), then anemia (29%), and diabetes (29%). Co-morbidities were independently associated with higher age (P < 0.001), higher NYHA functional class (P < 0.001), ischemic etiology (P < 0.001), higher heart rate (P = 0.011), history of hypertension (P < 0.001), and Atrial Fibrillation (P < 0.001). Only diabetes, CKD, and anemia were independently associated with a higher risk of mortality and/or hospitalization[4]. Similarly, study done by S. Dhungana et al in 2017 from BPKIHS identifies CAD, hypertension, Diabetes Mellitus and CKD as major comorbidities[5].

While CKD is a risk multiplier for the development of CVD, the largest hazard occurs for HF and also increases the lifetime risk of development of heart failure[6]. Baseline GFR is independent of impaired LVEF and is a stronger predictor of mortality than either LVEF or New York Heart Association class[7]. Patients in the clinical intersection between CKD and HF are at a high risk for poor outcomes. Inter-relationships of CKD and HF include common characteristics, such as common risk factors, bidirectional effects of one disease process on the progression of the other, adverse effects on one disease process when investigating the other, and treatment biases potentially influenced by both diseases[6]. Though these kind of patients are well studied in western population, data are lacking in our population regarding impact of CKD on heart failure. So we aim to study this group of patients and how presence of CKD alters clinical presentation and their outcome.

***Corresponding Author:**

Dr Manoj Subedi

Department of Internal Medicine

B P Koirala Institute of Health Sciences, Dharan, Nepal

E-mail: drmanojsubedi@gmail.com

Methods

In this prospective observational study; we enrolled 200 patients of Heart failure from November 2018 to October 2019 and later they were stratified into two groups as Heart failure with and without Chronic Kidney Disease as a nested case-control study design. Convenience sampling technique was used to enroll the study subjects in the study. Ethical approval was received from Institutional Review Committee and patient were enrolled from Indoor and outdoor patients of Internal medicine department of BPKIHS. For establishing a definite diagnosis of Heart Failure, Framingham criteria was used, for which 2 major criteria or 1 major and 2 minor criteria should be present[8]. CKD was defined as per KDOQI criteria as abnormalities of kidney structure or function , present for ≥3 months, with implications for health[9]. Glomerular Filtration rate(GFR) was computed using simplified Modification of Diet in Renal Disease (MDRD)equation[10].

At the screening visit, all the baseline characteristics and relevant data was collected. Follow up was performed on day 7 or day of discharge, and at 3 months via telephone to know the clinical status of the patient. Data collection was done using predesigned questionnaire in the medicine wards & OPD, CCU of BPHIKS. Demographic profile of study subjects (age, sex, region, mailing address, socioeconomic status, Occupation, Level of education etc.) was noted. History regarding the presenting complaints, past history of diabetes, Hypertension, ischemic heart disease, Chronic liver disease, COPD was taken in detail. Current medications of patients including doses were documented. . General physical examination and pertinent systemic examination was done grossly to find out relevant abnormalities. Laboratory investigations such as CBC, RFT, Iron profile and Urine RME and 2D-Transthoracic Echocardiography was done as needed. Creatinine value after 90th day were collected during follow up period and outcome was assessed via telephone/ cellular network.

Data was entered in SPSS 11.5. Survey Questionnaire was added with a unique code. Descriptive Statistics such as frequency, percentage, mean, Standard Deviation, Median as required was calculated for Quantitative variables. Categorical data regarding the baseline characteristics were described using bar graphs and pie charts. Chi-Square test was used to examine the association between nominal variables under study. Student t test was used for comparison of mean variables in same group. Statistical Analysis was performed with SPSS 11.5 and data were expressed as Mean and Standard Deviation for normally distributed data and as median and in Inter-Quartile Range for skewed data. A p-value <0.05 was considered as statistically significant for all analysis.

Results

A total of 200 patients were enrolled in the study who presented with heart failure. The mean age of patients was 61.77±15.95 years, median age was 63 years. Among this cohort of 200 patients, 50% of the study populations were female. Regarding geographical distribution, 65.5 % of study population were from Terai region and 33% were from hilly and mountain region of Nepal. About 85% of study population were dependent on their family members and 62.5% had history of current or past smoking. The most common comorbidity was systemic hypertension (44.5%), followed by chronic kidney disease (CKD) (38%), diabetes mellitus (35%), ischemic heart disease (IHD) (19.5%).

Table 1 outlines and compares the baseline characteristics of study population. Among the study population, the mean age of patients with CKD (64.7±14.9yrs) was higher than that of patients without CKD. (60±16.41yrs) (p value 0.08). Systemic hypertension and Type 2 Diabetes mellitus was more common in study population with CKD (64% and 52.6%respectively) than without CKD (32% and 24% respectively).Heart failure(HF) patients with CKD were more symptomatic and higher percentage of patients presented with orthopnea /paroxysmal nocturnal dyspnea(PND)and limb swelling. HF patients with CKD were less likely to receive ACE inhibitors/ Angiotensin receptor blockers in comparison to those without CKD (35.5% vs. 54%).However there was no statistically significant difference in use of beta blockers in between two groups. Patients in HF with CKD group had higher systolic blood pressure(SBP) and low hemoglobin in comparison to those without CKD(p value for both being<0.001).Albuminuria was common in HF with CKD group(73.7% vs. 35%). The mean eGFR as calculated by MDRD equation was 28.82±16.6 ml/min/1.73m2 in HF patients with CKD and 86.8±43.3 ml/min/1.73m2 in those without CKD. In comparison to those without CKD, HF patients with CKD had higher percentage of patients in HFmEF and HFpEF respectively(28.9% and 14.5% vs. 20.2 and 13.7%).

Table 1: Patient baseline characteristics (N=200)

Variables	HF with CKD(n=76)	HF without CKD (n=124)	OR with 95% CI	p value
Age, years	64.7±14.9	60±16.41		0.08
HTN	49 (64%)	40 (32%)	3.81(2.08-6.95)	
DM	40 (52.6%)	30 (24%)	3.48(1.89-6.40)	
IHD	19 (25%)	20 (16%)	1.73(0.85-3.51)	
Orthopnea/PND	41(54%)	47(37.9%)	1.91(1.07-3.42)	0.027
Limb swelling	44(57%)	46(37%)	2.33(1.30-4.17)	0.004
Use of βblocker	48(63%)	70(56.5%)	1.29(0.72-2.33)	0.38
ACEI/ARBs	27(35.5%)	67(54%)	0.46(0.26-0.84)	0.01
Pulse(b/min)	94.5±19.4	93.1±21.7		0.64
SBP(mm of Hg)	134±33.3	116.3±23.9		<0.001
DBP(mm of Hg)	78.9±17.6	72.8±15.3		0.012
Hemoglobin(g/dl)	10±2.3	12±2.3		<0.001
Na, meq/L	137±6.8	137.6±5.6		0.45

K, meq/L	4.6±0.7	4.3±0.8		0.02
RBS(mg/dl)	136.5±58	142.3±79		0.45
Creatinine(mg/dl)	3.42±3	1.1±0.8		<0.001
eGFR(ml/min/1.73m2)	28.82±16.6	86.8±43.3		<0.001
Albuminuria	73.7%	35%	5.20(2.77-9.79)	<0.01
HFrEF	56.6%	66%		
HFmEF	28.9%	20.2%		
HFpEF	14.5%	13.7%		

(Data are given as mean±SD or as percentages; HTN Hypertension,DM diabetes mellitus, IHD ischemic heart disease, PND paroxysmal nocturnal dyspnea, ACEI/ARBs angiotensin converting enzyme/angiotensin receptor blockers, SBP systolic blood pressure, DBP diastolic blood pressure, Na sodium, K potassium, RBS random blood sugar, eGFR estimated glomerular filtration rate, HFrEF heart failure with reduced ejection fraction, HFmEF heart failure with mid-range ejection fraction , HFpEF heart failure with preserved ejection fraction)

The 3 month mortality of HF patients with CKD was found to be 20% and 26.9% in those without CKD which was not found to be statistically significant (OR for outcome at 90 days (Alive/death): 1.47, CI 0.73-2.951, p value 0.306). Probable CKD was defined as those with who had eGFR <60ml/min/1.73m2 with anemia and Type 2 Diabetes Mellitus or Systemic Hypertension. So, when comparing outcome among those with CKD and probable CKD into one group and remaining into another, the 3 month mortality among former was 34%, and 15% in those without CKD and probable CKD (p value 0.002). On comparing outcome according to eGFR, those with eGFR <60ml/min/1.73m2 had higher mortality at 3 months follow up (30.4%), in comparison to those with eGFR ≥ 60ml/min/1.73m2 (15.9%) with p value 0.027 and the data was found to be statistically significant.(Table 2,3 and 4)

Table 2: Table comparing outcome at 3 months of HF patients with and without CKD (N=200)

Chronic Kidney Disease	Outcome at 90 days		OR with 95% CI	p value
	Alive	Mortality		
Yes	60(80)	15(20)	1.47(0.73-2.95)	0.306
No	87(73.1)	32(26.9)		

Table 3: Comparing outcome of CKD including probable CKD (N=200)

CKD and Probable CKD	Outcome at 3 months		OR with 95% CI	p value
	Alive	Mortality		
Yes	62(66)	32(34)	0.32(0.17-0.68)	0.002
No	85(85)	15(15)		

Table 4: Comparing outcome as per eGFR (N=200)

eGFR	Outcome at 3 months		OR with 95% CI	p value
	Alive	Mortality		
<60ml/min/1.73m^2	78(69.6)	34(30.4)	0.43 (0.21-0.88)	0.027
≥60ml/min/1.73m^2	69(84.1)	13(15.9)		

Discusion

Our study has highlighted that patients of HF with CKD were more symptomatic and have higher mortality as compared to those without CKD. We know that renal impairment in heart failure has become increasingly recognized as an independent risk factor for morbidity and mortality[11]. Heart failure and CKD represent concurrent chronic disease epidemics and the presence of one condition appears to accelerate the presentation and progression of the other; having both conditions increases the risk of hospitalization, rehospitalization, need for intensive care or kidney replacement therapy, and death[12].

The mean (±SD) age of study population was 61.7(±15.9) years which was similar to studies done by Yu et al and Chong et al where the mean age of the patients were 62.0 and 63.6 years respectively[13,14]. In our study population, the mean age of patients with CKD was (64.7±14.9) years which was higher than those without CKD (60±16.41years) and male patients were in equal number to female which was similar on comparison with results from ANCHOR and CHARM study (71.8 and 65.3 years) respectively[15]. This may be due to increasing prevalence of renal dysfunction with advancing age resulting higher mean age. However, the data was not statistically significant in our study 50% of our study population was male which was slightly lower than the studies done by Yu et al and Tseng CH et al which was 57.6% and 54.5% respectively[13,16]. This difference may be due to increased incidence and prevalence of rheumatic heart disease in female population, which is more common in Nepal[17]. Among 200 Heart Failure patients, 62.5% had history of current or past smoking and as per study done by Daisukel Kamimura et al cigarette smoking is an important risk factor for LV hypertrophy, systolic dysfunction and incident HF hospitalization even after adjusting for effects on coronary heart disease[18]. In our study population, the most common comorbidity was systemic hypertension (44.5%), followed by Chronic Kidney Disease (38%) and Type 2 Diabetes Mellitus (35%) respectively. Hypertension was also the most common comorbidity as found in European heart failure pilot survey (58%) followed by CKD(41%), Diabetes(29%) and Anemia (29%) respectively and their presence was associated with higher risk of mortality and/or HF hospitalization[4]. Similarly study from japan by Shiba and Shimokawa et al found that almost 40% of HF patients had CKD and the close relationship between HF and CKD worsens the prognosis[6].

Among study population, 63.1 % of patients with CKD were on beta blocker which was higher in comparison to those without CKD (56.9%) whereas only 35.5% of patients with CKD were on ACEI/ARBs which was far less on comparison to those without CKD (54%) and this data was found to be statistically significant (p value 0.01). This was far less on comparison to European population as per the European Heart failure pilot survey, among whom 87% of them were on beta blocker therapy and 89% were on RAAS blockade[4]. Our data

showed that less number of patients are on optimal medical therapy which may be due to poor compliance or financial factors . This may also be due to paucity of physicians to start ACEI/ARBs in CKD patients and also due to inherent risk of worsening renal function and hyperkalemia.

Dyspnea was the most common symptom in HF patients with CKD (96%) in comparison to whose without CKD (88%). Among the study population without CKD, 37.9% of patients presented with orthopnea. Similar findings were also noted by O' Conner where 41.4% of patients had orthopnea at presentation[19,20]. However, among those who had HF with CKD, orthopnea was present in 53.9% patients. This may be due volume overload feature added by underlying CKD along with salt retention and decreased urine output. Bilateral lower limb swelling was present in 37 % of study population without CKD, where as 57.8% of patients with CKD had limb swelling on presentation. This may be due to synergistic effect of underlying CKD, which caused increased volume overload status. Anemia was prevalent in 90.7% of patients with CKD which was almost twice in comparisons to patients without CKD(52.4%).Study from Z blazque Bermejo et also found that anemia was twice more prevalent in those with CKD(40% vs 20.8% respectively)[21]. HF patients with CKD had higher SBP (133.9±33.24 mm of Hg) and DBP (78.8±17.6mm of Hg) in comparison to those without CKD (116.3±23.8 and 72.8±15.3 mm of Hg). However study from Matsushita et al in 2009 failed to show any significant difference in SBP between two categories of patients. Since, CKD patients had increased salt and water retention, along with RAAS activation and less use of RAAS blockade, they may had higher blood pressure[22]. Among our study populations, those with CKD had higher number of patients in category HFmEF (28.9%) and HFpEF (14.5%) in comparisons those without CKD (20.2% and 13.7% respectively).Lofman et al also found that those with CKD had more number of patents of HFmEF and HFpEF(21% and 25-28% respectively) on comparing to those with normal renal function (20% and 15% respectively)[23].

When the patients were followed up for 3 months, mortality of HF patients with CKD was 20% and among those without CKD was 26.9%. This finding's doesn't corroborate with the findings from other studies done by Harjola et al and Bytyci et al where mortality due to HF alone was 8.1% and in those patients with CKD was 13%[24,25]. The higher mortality could be due to poor compliance, unaffordability of medications and inability to reach maximum doses of drugs in our settings. But lesser mortality in CKD group was not matching with western scenario. This may be due to exclusion of those cases of CKD with first presentation, where because of lack of previous creatinine diagnosis of CKD could not be established. So we tried to identify those cases by labeling them as probable CKD. Probable CKD was defined as those with eGFR < 60 ml/min/1.73m^2 with history of either Type 2 Diabetes mellitus or systemic hypertension with anemia.

The mortality of HF patients with CKD and probable CKD was 34%, and 15 % in rest of the study populations. Thus, our study also showed increased mortality associated with renal dysfunction. Proposed biological mechanism that renal impairment causes worsening of HF could be up regulation of renin-angiotensin-aldosterone system enhanced basal sympathetic discharges, increased pro-inflammatory factors, exacerbation of underlying anemia, worsening left ventricular hypertrophy and myocyte contractility leading to impaired volume handling, pump failure and death[11]. Also on analyzing mortality at 3 month follow up according to eGFR, those who had eGFR <60 ml/min/1.73m^2 had mortality almost double than those who had eGFR ≥60 ml/min/1.73m^2 (30.4% and 15.9% respectively). Study done by Lofman et al in 2016 also published the data that worsening renal function is associated with increased mortality at 1 month, 6 months and 1 year. They also found the graded relationship between decrease in eGFR and outcome i.e. mortality[23].

Thus we came to now that systemic hypertension, CKD and Type 2 Diabetes mellitus are the common comorbidity associated with heart failure. Also hypertension and diabetes are the most important risk factor for development of CKD. So their presence has implications in both. We also found that HF with CKD patients are more symptomatic at presentation and have more volume overload. They had higher blood pressure at presentation and were more anemic. In comparisons to those without renal dysfunction, these group of patients are less likely to receive optimal therapy. One of the strongest risk factor for poor outcome is decrease in eGFR. Patients with eGFR <60ml/min/1.73m^2 had two times higher mortality in comparison to those with higher eGFR. Similarly patients with CKD had higher percentage of patients of HFmEF and HFpEF.

Our study also have some limitations. A small group of patients who presented with renal dysfunction at presentation who may have CKD were excluded from CKD group due to uncertainty regarding chances of being either acute kidney disease or CKD. This may be the reason for small group of patients in HF with CKD. Also, we could not follow the patients for longer duration. Our study is a single tertiary center study where we receive more sicker patients so larger study with multicenter involvement is needed to generalize the results to our population. We could not confirm whether the drugs were properly optimized on follow up or not, which me have influenced on mortality.

Conclusion

This was a hospital based, prospective observational study on 200 patients of Heart failure with and without CKD which aimed to compare the demographic picture, clinical and biochemical parameters and outcome at 3 months. Patients of HF with CKD were more symptomatic and had higher mortality at 3 months as compared to those without CKD. Thus the present study highlights the need to conduct larger study of similar kind to identify various risk factors and common comorbidities in our set up and also appeals for future studies to control renal dysfunction which may prevent progression of HF.

References

1. Dokainish H, Teo K, Zhu J, Roy A, Alhabib KF, Elsayed A, et al. Heart Failure in Africa, Asia, the Middle East and South America: The INTER-CHF study. Int J Cardiol [Internet]. 2016;204:133–41. Available from: http://dx.doi.org/10.1016/j.ijcard.2015.11.183

2. Roger VL. Epidemiology of heart failure. Circ Res. 2013;113(6):646–59.

3. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: The Framingham Heart Study. Circulation. 2002;106(24):3068–72.

4. Van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, et al. Co-morbidities in patients with heart failure: An analysis of the European heart Failure Pilot Survey. Eur J Heart Fail. 2014;16(1):103–11.

5. Dhungana SP, Chaparia A, Sharma SK. Prevalence of co-morbid conditions in Heart failure: an experience at tertiary care hospital. J Nobel Med Coll. 2018;6(2):35–41.

6. Shiba N, Shimokawa H. Chronic kidney disease and heart failure-Bidirectional close link and common therapeutic goal. J Cardiol [Internet]. 2011;57(1):8–17. Available from: http://dx.doi.org/10.1016/j.jjcc.2010.09.004

7. Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease: Effects on the cardiovascular system. Circulation. 2007;116(1):85–97.

8. McKee PA, Castelli WP, McNamara PM, Kannel WB. The Natural History of Congestive Heart Failure: The Framingham Study. N Engl J Med [Internet]. 1971 Dec 23 [cited 2020 Dec 5];285(26):1441–6. Available from: https://www.nejm.org/doi/full/10.1056/NEJM197112232852601

9. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)z. Kidney Int. 2005;67(6):2089–100.

10. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol. 2005;16(3):763–73.

11. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal Impairment and Outcomes in Heart Failure. Systematic Review and Meta-Analysis. J Am Coll Cardiol. 2006;47(10):1987–96.

12. House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;95(6):1304–17.

13. Yu Y, Gupta A, Wu C, Masoudi FA, Du X, Zhang J, et al. Characteristics, Management, and Outcomes of Patients Hospitalized for Heart Failure in China: The China PEACE Retrospective Heart Failure Study. J Am Heart Assoc. 2019;8(17):e012884.

14. Chong AY, Rajaratnam R, Hussein NR, Lip GYH. Heart failure in a multiethnic population in Kuala Lumpur, Malaysia. Eur J Heart Fail. 2003;5(4):569–74.

15. Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure - The anemia in chronic heart failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation. 2006;113(23):2713–23.

16. Tseng CH. Clinical features of heart failure hospitalization in younger and elderly patients in Taiwan. Eur J Clin Invest. 2011;41(6):597–604.

17. Limbu YR, Maskey A. Current Sta Tus of Rheuma Tic Fever and Rheuma Tic Heart Disease in Nepal. J Nepal Med Assoc. 2003;41(144):514–7.

18. Kamimura D, Cain LR, Mentz RJ, White WB, Blaha MJ, Defilippis AP, et al. Cigarette smoking and incident heart failure: Insights from the jackson heart study. Circulation. 2018;137(24):2572–82.

19. Rudiger A, Harjola VP, Müller A, Mattila E, Säila P, Nieminen M, et al. Acute heart failure: Clinical presentation, one-year mortality and prognostic factors. Eur J Heart Fail. 2005;7(4):662–70.

20. Connor CMO, Stough WG, Gallup DS, Hasselblad VIC, Gheorghiade M. Demographics , Clinical Characteristics , and Outcomes of Patients Hospitalized for Decompensated Heart Failure : Observations From the IMPACT-HF Registry. 2005;11(3):200–5.

21. Z blazquez Bermejo, D Iglesias, E Gracia, J De juan U hospital IS. Authors : Citation : Eur J Hear Fail 19(suppl S1), 445. 2017;445.

22. Matsushita K, Minamishima T, Sakata K, Satoh T, Yoshino H. Prognostic factors for one-year mortality in patients with acute heart failure with and without chronic kidney disease: differential impact of beta-blocker and diuretic treatments. Hypertens Res [Internet]. 2019;42(7):1011–8. Available from: http://dx.doi.org/10.1038/s41440-018-0204-4

23. Löfman I, Szummer K, Hagerman I, Dahlström U, Lund LH, Jernberg T. Prevalence and prognostic impact of kidney disease on heart failure patients. Open Hear. 2016;3(1):e000324.

24. Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, et al. Chronic Kidney Disease Associated Mortality in Diastolic Versus Systolic Heart Failure: A Propensity Matched Study††The Digitalis Investigation Group study was conducted and supported by the National Heart, Lung, and Blood Institute in collaboration with . Am J Cardiol. 2007;99(3):393–8.

25. Grigorian Shamagian L, Varela Román A, Pedreira Pérez M, Gómez Otero I, Virgós Lamela A, González-Juanatey JR. Renal Failure Is an Independent Predictor of Mortality in Hospitalized Heart Failure Patients and Is Associated With a Worse Cardiovascular Risk Profile. Rev Española Cardiol (English Ed. 2006;59(2):99–108.