Heart Failure with Preserved Ejection Fraction and 30-Day Readmission

Manjari Rani Regmi, MD; Mukul Bhattarai MD, MPH, FACP; Priyanka Parajuli, MD;
Odalys Estefania Lara Garcia, MD; Nitin Tandan, MD; Nicolas Ferry, MD, Capt USAF;
Asad Cheema, MD; Youssef Chami, MD; and Robert Robinson, MD, MS, FACP

Objective: Several studies identify heart failure (HF) as a potential risk for hospital readmission; however, studies on predictability of heart failure readmission is limited. The objective of this work was to investigate whether a specific type of heart failure (HFpEF or HFrEF) has a higher association to the rate of 30-day hospital readmission and compare their predictability with the two risk scores: HOSPITAL score and LACE index.

Design: Retrospective study from single academic center.

Methods: Sample size included adult patients from an academic hospital in a two-year period (2015 - 2017). Exclusion criteria included death, transfer to another hospital, and unadvised leave from hospital. Baseline characteristics, diagnosis-related group, and ICD diagnosis codes were obtained. Variables affecting HOSPITAL score and LACE index and types of heart failure present were also extracted. Qualitative variables were compared using Pearson χ^2 or Fisher's exact test (reported as frequency) and quantitative variables using non-parametric Mann-Whitney U test (reported as mean $\pm$ standard deviation). Variables from univariate analysis with P values of 0.05 or less were further analyzed using multivariate logistic regression. Odds ratio was used to measure potential risk.

Results: The sample size of adult patients in the study period was 1,916. All eligible cohort of patients who were readmitted were analyzed. Cumulative score indicators of HOSPITAL Score, LACE index (including the Charlson Comorbidity Index) predicted 30-day readmissions with P values of <0.001 . The P value of HFpEF was found to be significant in the readmitted group ($P < 0.001$) compared to HFrEF ($P = 0.141$). Multivariate logistic regression further demonstrated the association of HFpEF with higher risk of readmission with odds ratio of 1.77 (95% CI: 1.25 – 2.50) and P value of 0.001.

Conclusions: Our data from an academic tertiary care center supports HFpEF as an independent risk factor for readmission. Multidisciplinary management of HFpEF may be an important target for interventions to reduce hospital readmissions.

Keywords: HFpEF; HFrEF; 30-day readmission; Heart Failure; LACE index; HOSPITAL score

Approximately 5 million Americans are currently diagnosed with Congestive Heart Failure (CHF) thereby making CHF a common disease entity. Over 550,000 new cases are diagnosed each year, and it is the most common diagnosis in patients over the age of 65.¹ An estimated \$20-30 billion is the associated annual cost of treatment of heart failure each year.^{2,3}

Heart failure is a clinical syndrome defined as impaired cardiac contractility and ventricular dilatation. There are two types of heart failure: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Heart failure continues to be a primary reason for hospitalization in patients older than 65 years and an issue to health care systems.⁴ In addition to the initial

Corresponding Author: Manjari Rani Regmi, MD; 701 North First Street, Springfield, IL 62781, Tel: (470) 265-1046, Fax: (279) 201-6023, Email: mregmi81@siu.edu; manjariregmi08.mr@gmail.com

Received: August 5, 2019
Revised: February 19, 2020
Accepted: March 13, 2020

doi:10.3121/cmr.2020.1521

admission cases, heart failure remains the leading cause of 30-day hospital readmissions.⁴ National data suggests that heart failure readmission rates have steadily increased over the last decade.⁵ Patients admitted to the hospital for heart failure are prone to readmission risk after their treatment, with some studies finding up to 90% readmission rate within 90 days.⁶ According to the Centers for Medicaid Services, amongst patients initially hospitalized for heart failure, 25% were readmitted within 30 days and 35% among them were readmitted because of heart-failure.⁷

Health care providers as well as policymakers and hospital administrators are actively seeking updated and more effective scoring systems to predict hospital readmissions to help reduce the extremely high rate and costs associated with readmissions of the patient population. Researchers are constantly working towards identifying different variables to develop new scores or further add to the existing scores in an attempt to provide scoring systems that have higher readmission predictability and specificity.⁸ Some of these scores include HOSPITAL score, and LACE index. HOSPITAL score stands for Hemoglobin at discharge, discharge from Oncology service, Sodium level at discharge, Procedure performed, Index of admission Type (elective vs. emergent), number of previous hospital-Admissions, Length of stay, and it was validated by Donzé et al⁹ in a multicenter study. Similarly, LACE index, that stands for Length of stay, Acuity of admission, Comorbidities, Emergency hospital visits, and it was validated by Van Walraven et al¹⁰ to estimate the re-hospitalization risk and showed significant association of higher LACE index score with increased rate of readmissions and mortality.

HOSPITAL scores and LACE indices have been validated and have been known to show correlation with rate of readmissions and mortality.^{9,10} However, a few studies have shown these scores do not reliably predict readmissions or help target the cause of these readmissions.^{11,12} Studies have shown that LACE index is not very effective in accurately predicting 30-day readmissions.^{11,13,14,15} In one retrospective study that included HFpEF patients, both HOSPITAL and LACE index did not show association with increased readmissions.¹⁶ Very few studies have focused determining the association of the type of heart failure in hospital readmissions.¹⁷ This provides a motivation to explore the types of heart failure and identify their association with hospital readmission.

The objective of this work was to investigate whether a specific type of heart failure (HFpEF or HFrEF) has a higher association to the rate of 30-day hospital readmission and compare their predictability with the two risk scores: HOSPITAL score and LACE index.

Materials and Methods

Study Design

All adult medical patients discharged hospitalist service at Memorial Medical Center affiliated with Southern Illinois

University School of Medicine from January 1, 2015 to January 1, 2017 were potentially eligible for this retrospective study. Exclusion criteria included transfer to another acute care hospital, leaving the hospital against medical advice, or death.

Study Setting

The study setting is a 507-bed not-for-profit tertiary care center. The Hospitalist service is the general internal medicine residency teaching service staffed by board certified and eligible hospitalist faculty. Patients for the hospitalist service are primarily admitted via the hospital emergency department or transferred from other regional hospitals with acute medical issues. Elective hospital admissions are extremely rare for this service. Readmissions at other hospitals were not considered for the study since only data from the study hospital was available. This study obtained the approval from the Institutional Review Board. It was determined that this study does not meet the criteria for research involving human subjects according to 45 CFR 46.101 and 45 CFR 46.102.

Data Collection

Data on age, gender, Diagnosis Related Group (DRG), International Classification of Disease (ICD) diagnosis codes, medications on discharge, 30-day readmission status, heart failure and its types, variables needed to calculate HOSPITAL, LACE, and Charlson scores were extracted from the electronic health record. The data was de-identified for analysis for all eligible patients. We looked into both cardiac and non-cardiac readmissions within the aforementioned time frame.

Statistical Analysis

Qualitative variables were compared using Pearson chi² or Fisher's exact test and reported as frequency (%). Quantitative variables were compared using the non-parametric Mann-Whitney U test and reported as mean $\pm$ standard deviation. Variables from univariate analysis with a *P* value of 0.05 or less were further analyzed using multivariate logistic regression in a backwards likelihood ratio method. The HOSPITAL score and LACE index were calculated at the time of discharge. Based on the initial validation study, HOSPITAL scores between 0 and 4 were classified as low risk for readmission (5%), between 5 and 6 as intermediate risk (10%), and 7 or more as high risk (20%). LACE indices ranged from 0 to 19, with an expected probability for readmission of up to 43.7% based on the initial validation study of the LACE score. Statistical analyses were performed using SPSS version 22 (SPSS Inc, Chicago, IL, USA). To test the influence of a variable on readmission, *P* values were calculated for each variable. Two-sided *P* values (<0.05) were considered significant.

Results

Out of 1916 patients, the eligible sample size was 1781. Of them, 456 (25%) were readmitted within 30 days shown in Figure 1. The results shown in Table 1 summarize the statistics of various qualitative and quantitative variables for

Table 1. Baseline characteristics of study population by 30-day readmission (univariate analysis)

Baseline characteristics	Not readmitted within 30 days (n = 1325)	Readmitted within 30 days (n = 456)	P value
Age (mean) (SD)	63 (16.0)	64 (15.5)	0.144
Female (n) (%)	624 (47)	216 (47)	0.919
Length of stay (mean) (SD)	7.7 (7.1)	8.4 (8.8)	0.091
Hospital admissions last year (mean) (SD)	0.71 (0.8)	1.61 (1.7)	<0.001
ED visits in last 6 months (mean) (SD)	0.39 (1.22)	1.21 (3.0)	<0.001
HOSPITAL Score (mean) (SD)	3.86 (1.4)	4.96 (1.8)	<0.001
LACE Index (mean) (SD)	11.31 (2.4)	12.59 (3.72)	<0.001
Charlson Comorbidity Index (mean)(SD)	4.88 (3.27)	6 (3.78)	<0.001
Medical Comorbidities			
Myocardial infarction (n) (%)	344 (26)	150 (33)	0.004
Peripheral artery disease (n) (%)	118 (9)	45 (10)	0.539
Stroke (n) (%)	76 (6)	26 (6)	0.978
Dementia (n) (%)	40 (3)	9 (2)	0.239
Chronic lung disease (n) (%)	357 (27)	144 (32)	0.058
Connective tissue disease (n) (%)	28 (2)	7 (2)	0.443
Peptic ulcer disease (n) (%)	59 (5)	19 (4)	0.797
Cirrhosis (n) (%)	40 (3)	25 (6)	0.016
Cancer (n) (%)	97 (7)	42 (9)	0.194
Metastatic cancer (n) (%)	32 (2)	18 (4)	0.088
Renal disease (n) (%)	243 (18)	142 (31)	<0.001
CKD Stage 1 (n) (%)	0	0	NA
CKD Stage 2 (n) (%)	11 (1)	2 (1)	0.397
CKD Stage 3 (n) (%)	51 (4)	36 (8)	0.001
CKD Stage 4 (n) (%)	20 (2)	15 (3)	0.018
CKD Stage 5 (n) (%)	2 (1)	2 (1)	0.263
End Stage Renal Disease (n) (%)	105 (8)	67 (15)	<0.001
Acute Kidney Injury (n) (%)	265 (20)	111 (24)	0.050
ICD (n) (%)	37 (3)	12 (3)	0.856
Pacemaker (n) (%)	29 (2)	16 (3)	0.121
Heart Failure			
HFrEF (n) (%)	88 (7)	40 (9)	0.141
HFpEF (n) (%)	120 (9)	80 (17)	<0.001
Medications			
Central Alpha Blocker (n) (%)	69 (5)	30 (7)	0.270
Alpha Blocker (n) (%)	41 (3)	9 (2)	0.211
Loop Diuretic (n) (%)	398 (30)	170 (37)	0.004
Thiazide Diuretic (n) (%)	115 (9)	37 (8)	0.709
Potassium sparing diuretic (n) (%)	133 (10)	51 (11)	0.488
Angiotensin Receptor Blocker (n) (%)	113 (9)	46 (10)	0.314
Dihydropyridine CCB (n) (%)	268 (20)	87 (19)	0.597
Non-Dihydropyridine CCB (n) (%)	75 (6)	30 (7)	0.473
Vasodilator (n) (%)	87 (7)	29 (6)	0.878
Beta Blocker (n) (%)	612 (46)	229 (50)	0.137
Angiotensin converting enzyme inhibitor (n) (%)	303 (23)	118 (26)	0.192

1,781 discharged patients. The sample was separated into two groups. The first group comprised of patients who were not readmitted within 30 days and second group consisted of patients who were readmitted within 30 days of discharge. Population demographic and gender indicated no correlation. Of significance was the hospital readmissions in the prior year. The readmission group had an average of 1.61 hospital admissions in the prior year whereas the non-readmission group had an average of only 0.71 (P value <0.001). In addition, the emergency department visits in the last 6-months also differed drastically between these two groups with 0.39 in the non-readmitted and 1.21 in readmitted group (P value <0.001). Cumulative score indicators like HOSPITAL Score (4.96 in readmitted and 3.86 in non-readmitted group), LACE index (12.59 in readmitted and 11.31 in non-readmitted group), and Charlson Comorbidity Index (6.0 in readmitted and 4.88 in non-readmitted group) also indicated significantly higher values in readmitted group with P values of each less than 0.001 in univariate analysis.

From the univariate analysis of medical comorbidities, the proportion of patients with HFpEF was observed to be significantly higher in the readmitted group compared to the non-readmitted group (17% vs. 9%, P value <0.001), whereas the proportion of patients with HFrEF was not significantly different between the two groups (9% vs 7%, P value = 0.141). Renal disease was also observed as one of the significant factors affecting 30-day readmission with results of 18% in non-readmitted group and 31% in readmitted group (P value <0.01). When we further sub-grouped renal disease to acute kidney injury (AKI), chronic kidney disease (CKD

stages I to V), and end stage renal disease (ESRD). We found that CKD stage 3 and 4, and ESRD had significant differences between the readmitted and non-readmitted group. The rates of prevalence of CKD III was 8% in readmitted and 4% non-readmitted group (P value = 0.001). Similarly, the rates of prevalence of CKD IV was 3% in readmitted and 2% non-readmitted group (P value = 0.018). Further, ESRD was prevalent in 15% of readmitted group and 8% of non-readmitted group (P value <0.001). The prevalence of acute kidney injury (AKI) were 24% in readmitted and 20% in non-readmitted with P value of 0.050. Further, we also found that 33% in readmitted group had history of myocardial infarction compared to 26% in the non-readmitted group (P value = 0.004). Similarly, 6% of patients in the readmitted group had cirrhosis compared to 3 % in non-readmitted group (P value = 0.016). Other comorbidities such as myocardial infarction and liver cirrhosis was 7% and 3% higher in readmitted vs. non-readmitted group with P values of 0.004 and 0.016 respectively. We further looked into discharge medications as shown in the Table 1. Among these medications, loop diuretics showed increased association with readmission when compared with non-readmission group (37% vs. 30%, P value = 0.004).

Figure 2 shows the results of multivariate analysis on significant variables from univariate analysis in the form of a forest plot of the odds ratio calculated from the analysis. We excluded parameters that were not significant in multivariate analysis from Figure 2. We found that odds ratio of HOSPITAL score 1.43 (P value <0.001); however, the odds ratio of LACE index was 0.87 with P value of <0.001 . For

Figure 1. Flowsheet of total sample size

HFpEF, odds ratio strengthened our results from univariate analysis with higher odds ratio of 1.77 (95% CI: 1.25-2.50) with *P* value 0.002. Further, renal disease had odds ratio of 1.47 (95% CI: 1.12-2.00) with *P* value of 0.007. Among the subgroup in renal disease, only CKD III was significant in the multivariate analysis with odds ratio of 1.74 (95% CI: 1.05 – 2.86) and *P* value of 0.031.

Discussion

Historically, studies have focused more on strategies to prevent heart failure.¹⁸ While these strategies discuss socioeconomic factors including financial burdens limiting access to resources and healthcare that contribute to readmissions in heart failure, they do not distinguish between the different types of heart failure. The data assessed in this study elucidates an important point that looks into heart failure and the differences in the readmissions risk, which differentiates our study from conventional heart failure studies.

Our study revealed that the proportion of patients with HFpEF was significantly higher in the readmitted group compared to the non-readmitted group (17% vs. 9%, *P* < 0.001). This higher likelihood could be due to a variety of causes. One of the causes being that HFpEF is more commonly seen in patients that have been diagnosed with significant co-morbidities such as severe lung disease, renal failure, diabetes and hypertension.¹⁹⁻²³ Because the etiology of HFpEF may be multifactorial, management often requires a multifaceted approach. These cases cannot be handled solely in the inpatient setting, so it demands equal focus in the

outpatient setting for optimal treatments and minimal hospitalizations. Unlike HFpEF, we did not find an association between HFrEF and 30-day readmissions. The proportion of patients with HFrEF was similar between the two groups (9% vs 7%, *P* = 0.141). A potential reason for this could be the established guidelines per ACA/AHA/HFSA for directed medical therapy on HFrEF targeted at the reduction of morbidity and mortality.²³ The Guideline Directed Medical Therapy (GDMT) for HFrEF includes Angiotensin-Converting Enzyme Inhibitors (ACEI), or Angiotensin-Receptors Blockers (ARB) and Beta Blockers (BB), in all patients as well as Aldosterone Receptors Antagonists (ARA), nitrates and hydralazine in selected patients. The GDMT has shown to improve outcomes and increase survival in patients with HFrEF. With HFpEF, however, there are still ambiguities in evidence-based treatment regimens with no well-established GDMT. We can potentially assume that due to lack of specific evidence-based guidelines for HFpEF treatment, its effective management still remains as one of the challenges for health care providers.

Contradictory to our study, a retrospective study from 2014, conducted in Boston, that compared 30-day readmissions between patients admitted with HFpEF and HFrEF showed that HFrEF have higher 30-days readmissions rate compared to HFpEF.²⁴ But, this was not seen after 30-days period. However, this study was included a different study setting compared to our study. It included only heart failure patients and the sample was from an urban population. While the findings of our study are definitely strong and insightful, it seems worthwhile to conduct large scale studies to identify if

Figure 2. Forest Plot of multivariate analysis showing odds ratio

there is any geographical or demographical factor that could influence the readmission rate.

We found that in our study population HOSPITAL score was effective in predicting readmissions showing higher values in both univariate as well as multivariate analysis. However, the LACE index that showed significantly higher values in readmitted population in univariate analysis failed to do so in multivariate analysis showing odds ratio of less than 1. This is in an agreement with some prior studies that have highlighted that LACE index may not be an effective tool in predicting 30-day readmission.^{11,13-15}

Renal disease was also observed as a notable risk factor that contributed to 30-day readmission risk. Renal disease, by itself, is an independent factor contributing for readmissions.²⁵ Further, in patients with heart failure and co-existing renal failure, the risk becomes more pronounced.¹² The spectrum of diseases that have association of heart diseases with renal diseases is called cardiorenal syndrome. There are different types of cardiorenal syndrome, including acute to chronic disease with complex pathophysiology behind each type. In inpatients, acute heart failure exacerbation is often associated with acute kidney injury due to difficulty in fluid balance.²⁶ This difficulty in controlling fluid balance is also one of the potential reasons for the underlying association of heart failure and renal dysfunction with readmissions. Additionally, it has been noted through previous studies that heart failure, particularly on readmissions to the hospital, has been associated with decreased renal function.¹² Complementary to these studies, our study found renal disease as a significant factor associated with 30-day readmissions. We also found that CKD stage 3 is independently associated with increased 30-day readmissions.

Myocardial infarction and liver cirrhosis are known co-morbidities that have impact on increasing 30-day readmission.^{25,27} A study conducted to establish risk factors of readmissions showed that ischemic heart disease was not one of the top three medical co-morbidities for readmission and similar with liver disease.²⁵ Our study showed initial association of increased risk of admissions in myocardial infarction and liver cirrhosis but failed to do so in multivariate analysis.

Study Limitations

The findings of this study are definitely insightful and add value to the existing knowledge about hospital readmissions. Nevertheless, there are some potential study limitations that need to be understood before generalizing or validating the findings of this study. First, the sample size was not large – the total eligible sample size of this study was 1781. Large sample studies may be needed to confidently assert the findings obtained here. Second, the current study focused on a single center of a mid-western city of the United States. This suggests the need for a wide range of geographical locations

and multi-center study. Third, the eligible readmissions in this study included patients who were readmitted to the same hospital. This criterion could possibly have excluded some patients who were readmitted to another hospital, but we believe that those numbers would be a very tiny fraction since the hospital in the study is the only major hospital around the geographical area. Fourth, when computing HOSPITAL score, one of the components is discharge from oncology service. However, our department did not have a primary oncology service. Instead, we replaced that with patients who were discharged with a diagnosis for cancer. Future studies that could overcome these limitations would add more value and shed better confidence in the findings.

Conclusion

Our data supports HFpEF as an independent risk factor of readmissions in an academic tertiary care center. This association was found to be stronger than already validated HOSPITAL score and LACE index. However, no significant association was identified between HFpEF and 30-day hospital readmissions. This difference could possibly be because of the GDMT available for HFpEF and lack of evidence-based treatment available for HFpEF. Multidisciplinary management of HFpEF in both inpatient and outpatient settings may be an important target for interventions to reduce hospital readmissions.

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Author Affiliations

Manjari Rani Regmi, MD*; Mukul Bhattarai, MD, MPH, FACP*; Priyanka Parajuli, MD*; Odalys Estefania Lara Garcia, MD*; Nitin Tandan, MD*; Nicolas Ferry, MD, Capt USAF†; Asad Cheema, MD*; Youssef Chami, MD*; Robert Robinson, MD, MS, FACP*

*Southern Illinois University School of Medicine, Springfield, Illinois, USA

†San Antonio Memorial Medical Center, San Antonio, Texas, USA