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Ultrasound Estimation of Right Atrial Pressure Predicts Readmission in Patients with Heart Failure

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ABSTRACT

Background: Acute decompensated heart failure (ADHF) is a leading cause of hospital readmissions, resulting in high healthcare costs and poor outcomes. Non-invasive risk stratification tools are needed to reduce 30-day readmission rates. This study evaluated whether a point-of-care ultrasound (POCUS)-measured distensibility index (DI) of the right internal jugular vein (RIJV) predicts 30-day readmission risk in ADHF patients.

Methods: A prospective, observational cohort study was conducted in 288 ADHF patients at a tertiary academic center and an affiliated urban community hospital. DI was calculated as the percentage change in RIJV cross-sectional area during the Valsalva maneuver. Patients with DI≥66% were classified as having normal right atrial pressure (RAP), and those with DI<66% as having elevated RAP. The outcome was 30-day readmission due to ADHF, determined from patient charts and verified through follow-up phone calls. Multivariable logistic regression assessed the association between DI and 30-day readmission.

Results: Thirty-day readmission occurred in 52 (18%) patients. Patients discharged with DI<66% had a higher readmission risk (odds ratio (OR): 5.29, 95% confidence interval (CI): 2.77-10.60, p<0.001). After adjustment for age, sex, chronic kidney disease, and HFpEF, DI<66% remained independently associated with readmission (adjusted OR: 15.24; 95% CI, 3.79-61.29; p<0.001). DI<66% at discharge had a NPV of 92%. Stratified analyses demonstrated a consistent direction of association across hospital settings.

Conclusions: POCUS-derived DI is a reliable and non-invasive method for RAP assessment and predicting 30-day readmissions in ADHF patients. This rapid, non-invasive assessment may enhance discharge risk stratification and support physiologic evaluation of residual congestion.

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Keywords: Acute Decompensated Heart Failure, Point-of-Care Ultrasound, Right Atrial Pressure, Jugular Vein Distensibility, 30-Day Readmission, Residual Congestion

Abbreviations

ADHF: Acute Decompensated Heart Failure
BNP: Brain Natriuretic Peptide
CI: Confidence Interval
CSA: Cross-Sectional Area
CVP: Central Venous Pressure
DI: Distensibility Index
HF: Heart Failure
NPV: Negative Predictive Value
OR: Odds Ratio
POCUS: Point-of-Care Ultrasound
RAP: Right Atrial Pressure
RIJV: Right Internal Jugular Vein

Introduction

Heart failure (HF) remains a major public health problem, with a lifetime risk approaching 24%, such that nearly one in four individuals will develop HF during their lifetime [1]. Acute decompensated heart failure (ADHF) is a leading cause of hospitalization and contributes substantially to healthcare expenditures worldwide. In the United States, annual HF-related costs exceed $30 billion, with hospitalizations accounting for the largest proportion of expenditures [2,3]. Nearly one in four patients hospitalized with HF are readmitted within 30 days, and recurrent hospitalizations represent a major driver of both morbidity and cost [4]. Despite efforts to reduce early rehospitalization, 30-day readmission rates remain high, underscoring the need for improved discharge risk assessment strategies.

Persistent congestion and elevated cardiac filling pressures are central features of ADHF and are associated with adverse outcomes. Accurate assessment of right atrial pressure (RAP) is therefore critical in evaluating volume status and determining discharge readiness. However, bedside estimation of jugular venous pressure by physical examination is frequently inaccurate and lacks reproducibility [5,6]. There is a need for practical, noninvasive, and reproducible bedside tools that can objectively assess right-sided filling pressures prior to discharge.

A point-of-care ultrasound (POCUS) method has been previously validated to measure the distensibility index (DI) of the right internal jugular vein (RIJV), defined as the percent change in cross-sectional area during the Valsalva maneuver [7]. This technique is based on the nonlinear relationship between venous compliance and pressure: reduced distensibility reflects elevated RAP. In prior hemodynamic validation studies, a DI <66% was associated with elevated RAP and demonstrated high negative predictive value (NPV) for excluding elevated right-sided pressures [7,8]. The method demonstrated excellent intra- and interobserver reproducibility. (Intraclass correlation coefficient for CSA change: 0.8752 and 0.8779; κ for classification of elevated RAP: 1.0 and 0.9, respectively).

Whether a discharge RIJV DI is associated with early readmission in patients hospitalized for ADHF remains incompletely defined. Accordingly, we evaluated the association between POCUS-derived DI measured at discharge and 30-day readmission in a prospective cohort of patients hospitalized with ADHF across the tertiary academic and community hospital settings.

Materials and Methods

Study Population

Consecutive patients admitted between June 2022 and June 2024 to a tertiary academic center and an affiliated urban community hospital for management of ADHF were eligible for enrollment. Inclusion criteria were an admission diagnosis of ADHF, a DI of less than 66% at admission, and age ≥18 years. Exclusion criteria included anatomical incompatibilities such as RIJV thrombus, repaired congenital heart disease, severe tricuspid regurgitation, and hypertrophic cardiomyopathy, as well as patients with a left ventricular assist device, metastatic cancer, end stage renal disease, MELD-Na score >12, dementia, or discharge to hospice. Imaging was not performed in patients receiving vasoactive inotropes (e.g., milrinone or dobutamine) due to their effects on venous compliance. Eligible patients were enrolled through an institutional review board-approved consent process. Demographic and clinical characteristics, including age, gender, body mass index (BMI), length of stay, comorbidities, laboratory values, ejection fraction, and B-type natriuretic peptide (BNP) levels, were recorded along with details on home and inpatient medications. HF etiology was classified as ischemic or nonischemic cardiomyopathy based on review of the medical record. Written informed consent was obtained from all patients prior to participation in the study. The study protocol complied with the Declaration of Helsinki and approved the Institutional Review Board.

Point-of-Care Ultrasonography Imaging

Two-dimensional ultrasound images of the RIJV were obtained daily using the Butterfly iQ+ probe, with images stored on the Butterfly Network platform (Butterfly Network, Inc., Guilford, CT, USA). Imaging was performed at the bedside with patients in a supine position, with the head of the bed elevated to 45°. The probe was placed between the vertex of the triangle formed by the sternal and clavicular heads of the sternocleidomastoid muscle, allowing visualization and differentiation of the RIJV from the internal carotid artery based on compressibility of the vein and arterial pulsation. POCUS images were acquired by a team including cardiologists with expertise in HF and ultrasound imaging as well as resident and medical students who had undergone structured training in the protocol. The majority of images were obtained by non-experts after limited training, under expert supervision. All ultrasound examinations were performed using standardized protocols, as previously described, to ensure consistency and reproducibility across providers [7]. For each patient, two images of the RIJV were captured daily: one at end-expiration (rest) and one at maximal expansion during the Valsalva maneuver. Images were stored online, converted to tagged image file format, and analyzed using open-source ImageJ software (National Institutes of Health). The RIJV lumen was manually outlined to calculate the DI as the CSA change from baseline end-expiration to maximal expansion during Valsalva (Figure 1).

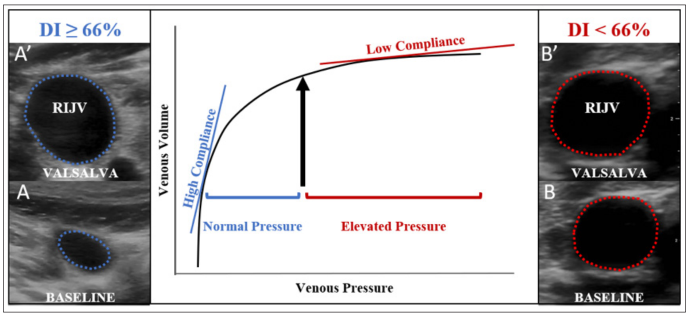


Figure 1: POCUS Images at End-Expiration (A, B, C) and after Valsalva (A’, B’, C’) showing High Compliance (A, A’), Mildly Decreased Compliance (B, B’), and Low Compliance (C, C’)

Outcomes

Patients were followed throughout their hospital stay with RIJV ultrasound imaging planned daily. For the present analysis, only ultrasound images obtained on the day of discharge were available and were used to categorize patients based on RAP estimation: those discharged with a DI ≥66% were classified as having normal RAP, and those with a DI <66% were classified as having elevated RAP, according to previously validated thresholds [7]. Readmissions due to ADHF were identified from patient charts 30 days post-discharge and verified through follow-up phone calls.

Statistical Analysis

Baseline patient demographics, comorbidities, and clinical characteristics were reported and compared between two outcome groups: patients who had readmission for ADHF within 30 days and patients who did not have readmission within 30 days. The normality of the data was assessed using the Kolmogorov-Smirnov test, with a p-value <0.05 indicating a non-normal distribution. For comparisons between two independent groups, Student's t-test was applied to normally distributed continuous variables, while the Mann-Whitney U test was used for nonnormally distributed variables. For categorical variables, percentages were reported and compared using the Chi-square test. Sensitivity, specificity, PPV and NPV were calculated from the contingency table, with a previously validated cut-off of 66% entered to assess the utility of DI in association with 30-day readmission [7]. Associations between individual clinical variables and 30-day ADHF readmission were initially evaluated using univariable logistic regression. Because BNP levels were nonnormally distributed, BNP was log-transformed before its inclusion in the univariable analysis. Given the number of outcome events, the number of covariates included in each multivariable model was limited to reduce the risk of overfitting. Covariates were selected based on clinical relevance. The association between discharge DI and 30-day readmission was then evaluated using two multivariable logistic regression models. Model I included discharge DI category, age, sex, chronic kidney disease, and HFpEF. Model II included discharge DI category, age, sex, chronic kidney disease, and ischemic cardiomyopathy. Odds ratios with 95% confidence intervals were reported. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. Model discrimination was assessed using the c-statistic (area under the receiver operating characteristic curve). Effect modification by hospital was evaluated by including a DI x hospital interaction term in the multivariable logistic regression model. A two-sided p-value of <0.05 was considered as statistically significant for all the tests. All the statistical analyses were performed using SPSS version 29.

Results

A total of 344 patients admitted to a tertiary academic center and an affiliated urban community hospital with a primary diagnosis of ADHF were screened and enrolled. Of these, 56 patients were excluded from readmission analysis due to in-hospital mortality, discharge to hospice, or lack of discharge RIJV images, leaving 288 patients for analysis (Figure 2). Of the 288 remaining patients, 170 patients were admitted to the tertiary academic center and 118 patients were admitted to the affiliated urban community hospital. Baseline characteristics are presented in Table 1. Baseline characteristics of patients admitted to the tertiary academic center versus the community hospital are shown in the Supplemental Table 1. Patients at the community hospital were more likely to have hypertension, chronic obstructive pulmonary disease, and HFpEF, while other characteristics were comparable between the two groups. Patients with 30-day hospital readmission had a higher number of comorbidities. At discharge, 41% of patients exhibited an abnormal DI (<66%). During follow-up, 52 patients (18.1%) were readmitted due to ADHF. Readmission rate was four times higher in the DI <66% group compared to the DI ≥66% group (32% vs. 8%, p<0.001). (Table 2, Figure 3) At discharge, DI had an overall NPV of 92% for avoiding 30-day readmission, with a sensitivity of 73% and a specificity of 66%. (Figure 4) In the overall cohort, compared to those with a normal DI, patients discharged with an abnormal DI had a 5.3 times higher risk of readmission (odds ratio (OR): 5.29, 95% CI, 2.77-10.60, p<0.001) (Table 3, Central illustration). DI <66% remained independently associated with 30-day readmission in Model I, which adjusted for age, sex, chronic kidney disease, and HFpEF (adjusted OR, 15.24; 95% CI, 3.79-61.29; p<0.001), and in Model II, which adjusted for age, sex, chronic kidney disease, and ischemic cardiomyopathy (adjusted OR, 17.37; 95% CI, 4.05-74.50; p<0.001) (Table 3). The Hosmer-Lemeshow test showed no evidence of poor model fit for either Model I (p=0.140) or Model II (p=0.495). Both models demonstrated good discrimination, with c-statistics of 0.822 (95% CI, 0.740-0.904, p<0.001) and 0.852 (95% CI, 0.769-0.930, p<0.001), respectively. There was no statistically significant evidence that this association differed by hospital setting (DI x hospital interaction p=0.058). Given the limited power to detect interaction effects, we additionally report hospital-stratified results as exploratory analyses.

Table 1: Baseline Characteristics by the Status of 30-Day Readmission in the Overall

	Overall population (n=288)	30-day readmission (-) (n=236)	30-day readmission (+) (n=52)	P value
Age (years)	71±13	71±13	71±14	0.216
Male gender (%)	60	59	67	0.262
BMI (kg/m2)	33.8±11.4	33.8±11.9	34.0±9.5	0.145
CAD (%)	57	54	71	0.021
Type 2 DM (%)	44	37	67	<0.001
HTN (%)	73	69	90	0.002
CKD (%)	37	28	77	<0.001
COPD (%)	35	28	67	<0.001
HFpEF (%)	39	31	75	<0.001
Ischemic cmp (%)	56	53	71	0.018
BNP (pg/ml)	639 (270-1760)	638 (252-1535)	1106 (330-4023)	0.081
Length of stay (days)	4.7 (3.1-6.8)	4.8 (3.1-6.8)	3.2 (2.6-6.9)	0.499
DI <66% (%)	41	34	73	<0.001

Population

Mean± SD or Median (IQR 25-75) were reported for continuous variables and percentages were reported for categorical variables. Comparisons were performed between patients with and without 30-day readmission. BMI: body mass index, BNP: brain natriuretic peptide, CAD: coronary artery disease, CKD: chronic kidney disease, cmp: cardiomyopathy, COPD: chronic obstructive pulmonary disease, DI: distensibility index, DM: diabetes mellitus, HTN: hypertension, HFpEF: heart failure with preserved ejection fraction.

Table 2: Thirty-Day Readmission According to DI Category

	30-day readmission (-) (n=236)	30-day readmission (+) (n=52)
DI<66% (n, %)	80 (68)	38 (32)
DI≥66% (n, %)	156 (92)	14 (8)

Abbreviations as in Table 1.

Table 3: Association of Clinical Factors and DI with 30-day Readmission: Univariate and Multivariable Logistic Regression Analysis for the Overall Cohort

	Univariable		Multivariable Model I		Multivariable Model II	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.99 (0.97 - 1.03)	0.863	1.01 (0.96-1.06)	0.742	1.02 (0.97-1.07)	0.490
Male	1.44 (0.77 - 2.76)	0.263	1.58 (0.48-5.19)	0.454	2.35 (0.62-8.95)	0.210
CKD	8.54 (4.22-17.28)	<0.001	0.95 (0.29-3.13)	0.927	1.12 (0.32-3.95)	0.857
HFpEF	6.66 (3.35-13.22)	<0.001	1.23 (0.39-3.95)	0.725	Not included	
Ischemic cmp	2.17 (1.13-4.17)	0.020	Not included		3.59 (0.93-13.88)	0.064
logBNP	1.87 (0.65 -5.40)	0.249	-		-	
DI <66%	5.29 (2.77 -10.6)	<0.001	15.24 (3.79-61.29)	<0.001	17.37 (4.05-74.50)	<0.001

CI; confidence interval, CKD: chronic kidney disease, cmp: cardiomyopathy, logBNP; log transformed brain natriuretic peptide levels, OR; odds ratio, other abbreviations as in Table 1.

Table 4: Association of Clinical Factors and DI with 30-Day Readmission: Univariate and Multivariable Logistic Regression Analysis for the Patients from Community Hospital

	Univariate		Multivariable Model I	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.99 (0.95 - 1.03)	0.618	1.00 (0.96-1.05)	0.991
Male	0.7 (0.29 - 1.67)	0.427	1.46 (0.42-5.08)	0.548
CKD	2.39 (0.99-5.76)	0.051	1.10 (0.32-3.87)	0.882
HFpEF	1.11 (0.46-2.66)	0.811	-	
Ischemic cmp	1.60 (0.67-3.82)	0.286	-	
logBNP	1.32 (0.84 - 2.15)	0.242	-	
DI <66%	11.7 (4.38 - 35.4)	**<0.001**	13.68 (3.30-56.62)	**<0.001**

Abbreviations as in Table 2.

Supplemental Table 1: Baseline Characteristics of Patients Admitted to the Tertiary Center Versus the Community Hospital

	Tertiary hospital (n=170)	Community hospital (n=118)	P value
Age (years)	71±12	64±16	0.052
Male gender (%)	69	48	<0.001
BMI (kg/m2)	34±11	39±9	0.306
CAD (%)	54	62	0.178
Type 2 DM (%)	46	43	0.598
HTN (%)	60	92	<0.001
CKD (%)	33	43	0.091
COPD (%)	26	48	<0.001
HFpEF (%)	27	57	<0.001
Ischemic cmp (%)	54	61	0.230
BNP at admission (pg/ml)	601 (255-1573)	1624 (897-2148)	0.111
Length of stay (days)	4.6 (2.8-6.8)	5.3 (4.9-6.2)	0.217
DI<66% (%)	64	55	0.122

Mean± SD or Median (IQR 25-75) were reported for continuous variables and percentages were reported for categorical variables.

BMI; body mass index, BNP; brain natriuretic peptide, CAD, coronary artery disease, CKD; chronic kidney disease, COPD, chronic obstructive pulmonary disease, DI; distensibility index, DM; diabetes mellitus, HTN; hypertension, HFpEF; heart failure with preserved ejection fraction.

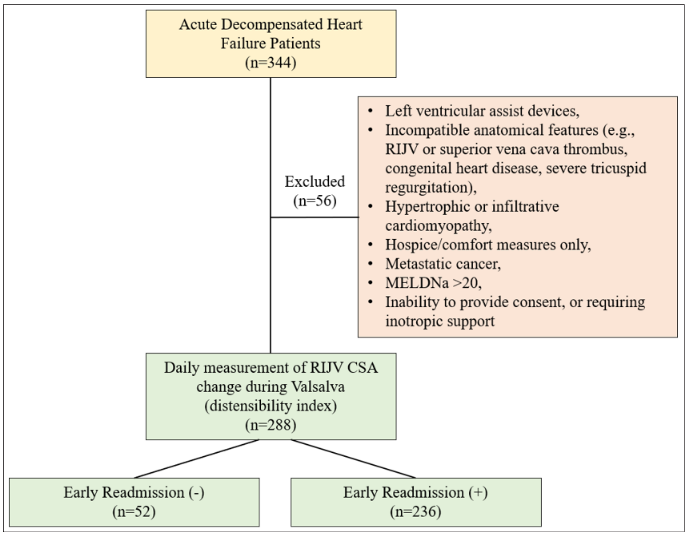


Figure 2: Study Flow Chart

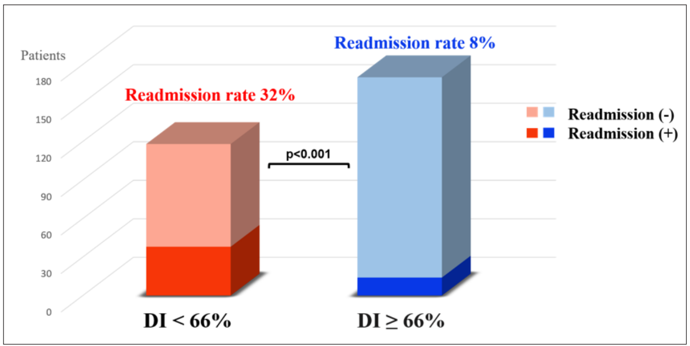


Figure 3: 30-Day Readmission Rates by Distensibility Index (DI) Category

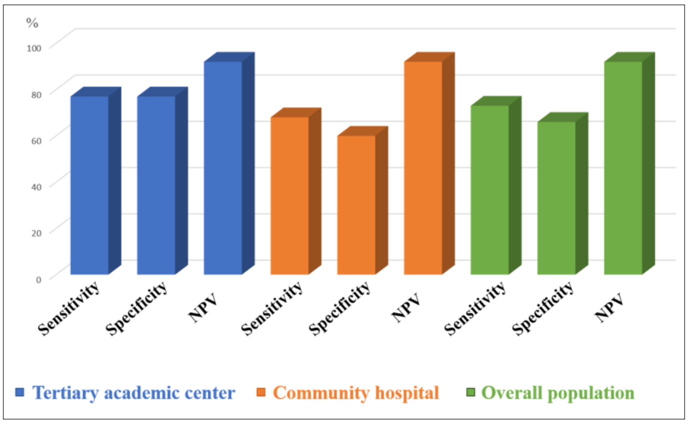
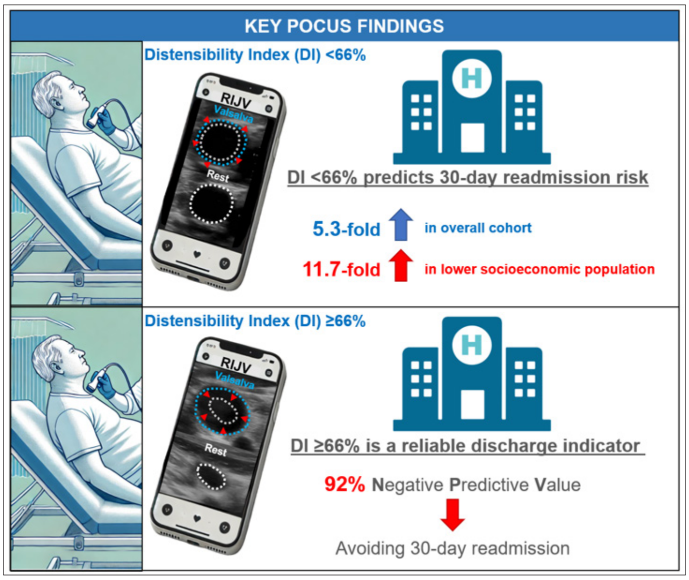


Figure 4: Sensitivity, Specificity, Negative Predictive (NPV) Value among Study Subgroups and All Population

Central Illustration: POCUS assessment of the RIJV DI in patients with ADHF. A DI < 66% is a key POCUS finding, which may indicate elevated right atrial pressure and persistent congestion. The red arrowheads indicate the change in cross-sectional area between rest and the Valsalva maneuver. This finding is associated with an increased risk of 30-day hospital readmission. ADHF: acute decompensated heart failure, DI: distensibility index, POCUS: Point-of- care ultrasound, RIJV: right internal jugular vein.



Exploratory Comparison Across Hospital Settings

Hospital-stratified results are presented as exploratory analyses to evaluate whether the association between DI and 30-day readmission was observed across different hospital settings. Notably, among the subset of patients enrolled in a community hospital setting (n=118), those discharged with an abnormal DI were 11.7 times more likely to experience 30-day readmission than those with a normal DI (OR:11.7, 95 % CI, 4.38-35.4, $p<0.001$). This association remained significant after adjustment for age, sex, and CKD (adjusted OR, 13.68; 95% CI, 3.30-56.62; $p<0.001$). (Table 4, Central illustration) At discharge from the community hospital, DI had an overall NPV of 92% for avoiding 30-day readmission, with a sensitivity of 68% and a specificity of 60 %. (Figure 4) Additionally, the subset of patients enrolled at a tertiary academic hospital (n=170), were 3.1 times more likely to be readmitted within 30 days when discharged with an abnormal DI compared to those with a normal DI (OR: 3.1, 95 % CI, 1.29-8.03 p=0.014).

Discussion

In this study, discharge assessment of residual congestion using POCUS-derived RIJV DI was independently associated with 30-day readmission in patients hospitalized for ADHF. Patients discharged with DI <66% experienced significantly higher rehospitalization rates, and this association persisted after adjustment for established clinical risk factors. These findings support the concept that objective bedside assessment of right-sided filling pressures may capture clinically meaningful residual congestion not fully reflected by routine clinical evaluation [9].

Residual hemodynamic congestion at discharge remains a major driver of early readmission in HF. While physical examination and natriuretic peptides are widely used, both have recognized limitations in sensitivity and reproducibility [10,11]. For instance, previous studies have demonstrated that POCUS techniques, including IJV measurements, offer practical bedside tools for assessing volume status in HF patients [9,12]. In line with prior studies, a study by Hossein-Nejad et al. found that the IJV/common carotid artery ratio had a strong correlation with CVP, suggesting that ultrasound-based volume assessment can reliably guide fluid management [7,8,12]. In addition, Malagón et al. reported that residual congestion assessed by POCUS at discharge (including systemic venous congestion measures) was associated with adverse outcomes, reinforcing the prognostic relevance of subclinical congestion at the time of discharge [13]. Building on these prior studies, the present investigation prospectively evaluated RIJV DI measured specifically at hospital discharge across both tertiary academic and community hospital settings. Our findings provide additional evidence supporting the potential role of RIJV DI as an adjunctive physiologic measure of discharge readiness. Compared with more technically demanding approaches (e.g., portal venous Doppler-based metrics), ultrasound-based assessment of jugular venous dynamics offers a physiologically grounded and operator-accessible alternative [8]. In this context, RIJV DI provides a rapid and reproducible estimate of RAP that may serve as a surrogate marker of systemic venous congestion [7]. Unlike more technically demanding Doppler-based venous indices, DI can be obtained within minutes and does not require advanced imaging infrastructure, increasing its potential scalability [8].

Silber et al. reported differences in short-term outcomes by hospital teaching status, which may reflect variation in care processes and available resources [14]. In contrast, community hospitals often face challenges such as limited specialized care and staffing, which may increase readmission risk. Socioeconomic factors also play a role in these disparities. Spatz et al. reported that hospitals serving socioeconomically disadvantaged populations have higher readmission rates, driven by challenges in healthcare access, medication adherence, and follow-up care [15]. Similarly, when stratified by hospital type, the association between abnormal DI and readmission was observed in both the tertiary academic center and the affiliated community hospital in our study. Although the magnitude of association differed numerically, formal interaction testing did not demonstrate statistically significant heterogeneity. These findings should therefore be interpreted as exploratory but suggest that the prognostic signal of discharge DI is not confined to a single institutional context. The consistently high NPV across settings further supports its potential role as adjunctive evidence of discharge readiness when integrated with clinical judgment.

The broader clinical implications are notable. An abnormal discharge DI may identify patients with unresolved congestion who could benefit from intensified decongestion strategies, optimization of diuretic therapy, or closer early follow-up. Conversely, a normal DI may provide supportive reassurance in conjunction with other clinical parameters. Importantly, this approach emphasizes physiologic assessment rather than reliance solely on symptom-based evaluation.

From a systems perspective, readmissions remain a substantial economic burden. Incorporating a rapid, non-invasive congestion assessment into discharge workflows may represent a cost-conscious strategy to improve risk stratification. According to the most recent statistics from the U.S. Department of Health and Human Services (HCUP Statistical Brief #307, 2024), a calculation based on the reported 2020 cost data yielded an estimated average readmission cost of approximately $16,300, representing a 12.4% increase relative to the average cost of an index hospitalization [16]. However, whether achieving a target DI threshold translates into net cost savings, particularly if it requires prolonged hospitalization, requires formal cost-effectiveness evaluation. Larger, multicenter prospective studies are needed to confirm generalizability, define the incremental predictive value of DI within contemporary risk models, and determine whether DI-guided discharge strategies can meaningfully reduce early rehospitalization.

Limitations

Our study has several limitations. First, relatively small sample size limits generalizability, indicating the need for multi-center studies with diverse populations. The relatively wide CI in the adjusted model reflects the limited number of outcome events and warrants cautious interpretation of the magnitude of effect. Additionally, in our study the POCUS technique estimated right-sided pressures, which may not fully reflect left-sided pressures. The assessment was limited to the RIJV, so right-left variability could not be evaluated. Nevertheless, prior studies indicate that right atrial or central venous pressure typically correlates with overall volume status in ADHF, supporting the clinical utility of this approach [7,17]. In the present study, DI was analyzed using a prespecified dichotomous cut-off of 66%. Although this approach facilitated clinical interpretability, we did not assess the prognostic value of DI as a continuous variable. Future studies with larger cohorts should evaluate DI both categorically and continuously. Moreover, RIJV DI was recorded only at discharge, and variability during hospitalization or its impact on readmission was not evaluated.

A key limitation is the lack of data on whether providers were aware of POCUS results prior to making daily medication adjustments. This could influence the relationship between POCUS findings and clinical decision-making. Further research should examine the impact of real-time POCUS data on therapeutic choices and discharge planning.

Furthermore, the absence of a control group precludes definitive conclusions regarding the efficacy of POCUS-DI in reducing readmission rates. Additionally, discharge guideline directed medical therapy data were not consistently available across the entire cohort, and variations in post-discharge management, including follow-up care and medication adherence, were not systematically captured; therefore, their potential influence on readmission outcomes could not be fully evaluated. Lastly, unmeasured social determinants, including socioeconomic status and healthcare access, particularly in community hospitals, may have contributed to observed differences in readmission rates.

Conclusion

POCUS-derived DI of the RIJV may provide a reliable, non-invasive approach for estimating RAP and predicting 30-day readmission in ADHF patients. A DI <66% at discharge was associated with significantly higher readmission rates, particularly in community hospital settings. Integrating POCUS-DI into discharge planning may improve risk stratification and support targeted interventions to reduce readmissions, especially in resource-limited healthcare settings.

Data Availability

The data supporting this article are available from the corresponding author upon reasonable request and with approval from the University of Pittsburgh.

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Ethical Statement

The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board (STUDY20070162). All authors have reviewed and approved the final version of the manuscript. This work has not been published previously and is not under consideration for publication elsewhere, in whole or in part, in any language, except in abstract form. The authors declare no conflicts of interest or relationships with industry relevant to the content of this manuscript. John Pacella is the corresponding author.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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