Fibrinogen Levels at Admission and Outcomes of Patients with Acute Heart Failure

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ABSTRACT **Background:** Despite a significant advance in prevention and treatment of heart failure (HF), patients still struggle with decreased quality of life, high mortality, and recurrent hospitalizations. Several inflammatory cytokines have been widely investigated in the pathogenesis of HF.

Objectives: To investigate the prognostic value of fibrinogen on clinical outcomes of patients admitted with acute HF.

Methods: This retrospective study was based on data of patients hospitalized with acute HF. Demographics, laboratory, and clinical outcomes including length of stay and readmissions were obtained. We compared outcomes of patients with normal (< 430 mg/dl) and high (> 430 mg/dl) fibrinogen levels.

Results: We included 149 patients (mean age 67.6 ± 12.3 years, 73.8% male). In our cohort, 24 (16.1%) had normal fibrinogen (< 430 mg/dl) and 125 (83.9%) had high fibrinogen levels (> 430 mg/dl). Among patients with readmissions for HF, fibrinogen levels were higher (622 ± 136 vs. 470 ± 68, $P < 0.001$) and were associated with longer hospital stay. Fibrinogen remains an independent risk factor after adjusting to age, diabetes status, and left ventricular ejection fraction.

Conclusions: High fibrinogen levels may predict readmissions in patients with HF.

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KEY WORDS: fibrinogen, heart failure, inflammation, quality of life, readmission

Heart failure (HF) is an emerging pandemic with increasing prevalence due to the increasing ageing population [1]. Despite advances in therapeutic options, HF is still associated with decreased quality of life, recurrent hospitalizations, and high mortality [2-4]. Despite the advance in pharmacological therapy, functional deterioration and readmissions remain very common in HF across all the spectrum of ejection fraction [5].

In acute HF, there are several scores for risk stratification based on hemodynamic as well as laboratory parameters [6]. Of the available laboratory parameters, N-terminal B type natriuretic peptide (NT-proBNP) is the most common in routine use for diagnosis and risk stratification [2]. Inflammation plays a central role in the pathogenesis of all forms of HF [7]. Some of the biomarkers that have been investigated are tumor necrosis alpha, several interleukins, galectin 3, C-reactive protein, myeloperoxidase, and inducible nitric oxide synthase [8].

Fibrinogen, a biomarker of inflammation, is synthesized and assembled by hepatocytes and fibroblasts and plays a role in coagulation cascade [9,10]. Following tissue injury, fibrinogen is cleaved by thrombin to control the damage. It functions in damage repair along with other matrix proteins [11]. During acute inflammation, there are several alterations in hemostatic pathways shifting the balance toward prothrombotic states indicated by changes in the levels of several biomarkers, including fibrinogen [11].

Plasma fibrinogen levels are relatively high in patients with cardiovascular disease and may mediate the harmful effect of other traditional risk factors [12]. In acute HF, neurohormonal activation and inflammation may impair endothelial function and homeostasis beyond the acute event and may be associated with readmissions [13,14]. In this study, we investigated the impact of fibrinogen levels on outcomes of patients admitted with acute HF.

PATIENTS AND METHODS

STUDY DESIGN

The retrospective study was conducted based on data of hospitalized patients at Galilee Medical Center in Israel. Demographic, echocardiographic, and laboratory data were extracted from patient files within a span of 4 years (January 2020 to December 2023).

PATIENTS

We included patients with ICD-10 discharge diagnosis of Heart Failure in the cardiology department. Patients with missing fibrinogen values (13) and those with infectious trigger (20) were excluded from the final analysis. Data included co-morbidities, left ventricular ejection fraction (LVEF), length of stay (LOS), laboratory values, and re-admissions for HF. Troponin levels were measured using high sensitivity assay and presented as ng/L. Fibrinogen levels were measured at presentation and provided as mg/dl (normal < 430 mg/dl). NT-proBNP levels are presented in pg/ml (normal < 125 pg/ml). LVEF was calculated using the standard Simpson's method during transthoracic echocardiography.

OUTCOMES

Clinical outcomes included readmissions for HF and total LOS. Readmission for HF was defined as any hospitalization or unplanned emergency room visit for congestion symptoms necessitating intravenous diuretic therapy. Congestion symptoms included dyspnea, pleural effusion, or leg edema. The diagnosis of acute HF was confirmed with accompanied X-ray or elevated NT-proBNP.

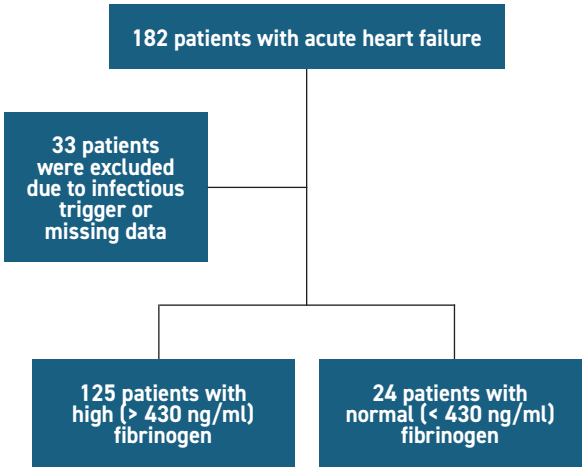
STATISTICAL METHODS

Categorical variables are presented as percentages whereas continuous variables were shown as mean ± standard deviation or median with interquartile range (IQR). Mann-Whitney and Spearman tests were applied to evaluate the correlation between fibrinogen levels and LOS. Kaplan-Meier curve was applied for readmissions for acute HF during 1-year follow-up. Multivariate logistic regression was used to estimate adjusted odds of outcomes after controlling for age, sex, LVEF, and diabetes. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 27 (SPSS, IBM Corp, Armonk, NY, USA). The study was approved by the local ethical committee of Galilee Medical Center.

RESULTS

During the study period, 182 patients with acute HF were defined. Of them, 20 were excluded due to clear evidence of infectious trigger, and 13were excluded for missing fibrinogen values. The study flow chart is depicted in Figure 1.

Figure 1. Study flowchart



In total, 149 patients (mean age of 67.6 ± 12.3, 73.8% male) were included in the final analysis. The mean LVEF was 34 ± 13%, and 57 % of the patients had ischemic cardiomyopathy. When stratified by LVEF, 55 patients (37%) had HF with reduced ejection fraction (LVEF < 40%), 22 (14.7%) with mildly reduced ejection fraction (LVEF 40–50%), and 72 patients (48.3%) with heart failure with preserved ejection fraction (HFpEF). There was no difference in fibrinogen levels between the groups (P = 0.23). The baseline characteristics are summarized in Table 1. Laboratory and hemodynamic data are listed in Table 2.

In our cohort, 125 patients (83.9%) had high (> 430 mg/dl) and 24 (16.1%) had normal (< 430 mg/dl) fibrinogen levels. Patients with abnormally high fibrinogen had longer LOS (4, IQR 3–5) compared to patients with normal fibrinogen levels (3, 2–4.75), P = 0.045. When assessing fibrinogen levels as a continuous parameter, it was also associated with increased LOS (r=0.386, P < 0.001). Sixty-two patients (41.6%) had readmissions due to HF within one year, 92% of them had high fibrinogen levels, and 8% had normal levels (P = 0.04). Fibrinogen levels were higher in patients with readmissions for HF, (622 mg/dl ± 136 vs. 470 mg/dl ± 68, P < 0.001), even after controlling for age, sex, diabetes status, and LVEF (odds ratio= 3.2, 95% confidence interval 1.1–9.0; P = 0.034) [Figure 2].

Table 1. Baseline characteristics of the study population

Characteristic	N=149
Age in years	68 ± 12.3
Male, n (%)	110 (73.8)
IHD, n (%)	85 (57)
T2DM, n (%)	92 (62)
Hypertension, n (%)	126 (85)
Hyperlipidemia, n (%)	127 (85)
Tobacco use, n (%)	105 (70)
LVEF %	34 ± 13%
CKD, n (%)	52 (34.9)
CVA/TIA, n (%)	14 (9.4)
ICD/CRT, n (%)	40 (26.8)
Medications	
ACE inh/ARB, n (%)	101 (67.8)
ARNI, n (%)	15 (10)
SGLT2 inh, n (%)	115 (77.2)
Beta blockers, n (%)	122 (81.8)
MRA, n (%)	52 (34.9)
Statins, n (%)	130 (87.2)
Aspirin, n (%)	135 (90.6)

ACE inh = angiotensin converting enzyme inhibitor, ARNI = angiotensin receptor-neprilysin inhibitor, ARB = angiotensin receptor blocker, CKD = chronic kidney disease, CRT = cardiac resynchronization therapy, CVA = cerebrovascular accident, ICD = implantable cardiac defibrillator, IHD = ischemic heart disease, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, SGLT2 inh = sodium glucose co transporter 2 inhibitor, T2DM = type 2 diabetes mellitus, TIA = transient ischemic attack

Table 2. Laboratory and hemodynamic data of the study population

Characteristic	N=149
SBP, mmHg	130 ± 27
HR, bpm	70 ± 12
Creatinine, mg/dl	1.5 ± 0.7
BUN, mg/dl	24 ± 6
NT-pro BNP, pg/ml (median, IQR)	4954 (2144–11000)
Fibrinogen, mg/dl (median, IQR)	508 (454–597)
CRP, mg/l (median, IQR)	11 (4–44)
LOS, days (median, IQR)	4 (3–5)

BUN = blood urea nitrogen, CRP = C-reactive protein, HR = heart rate, IQR = interquartile range, LOS = length of stay, NT-pro BNP = N-terminal B-type natriuretic peptide, SBP = systolic blood pressure

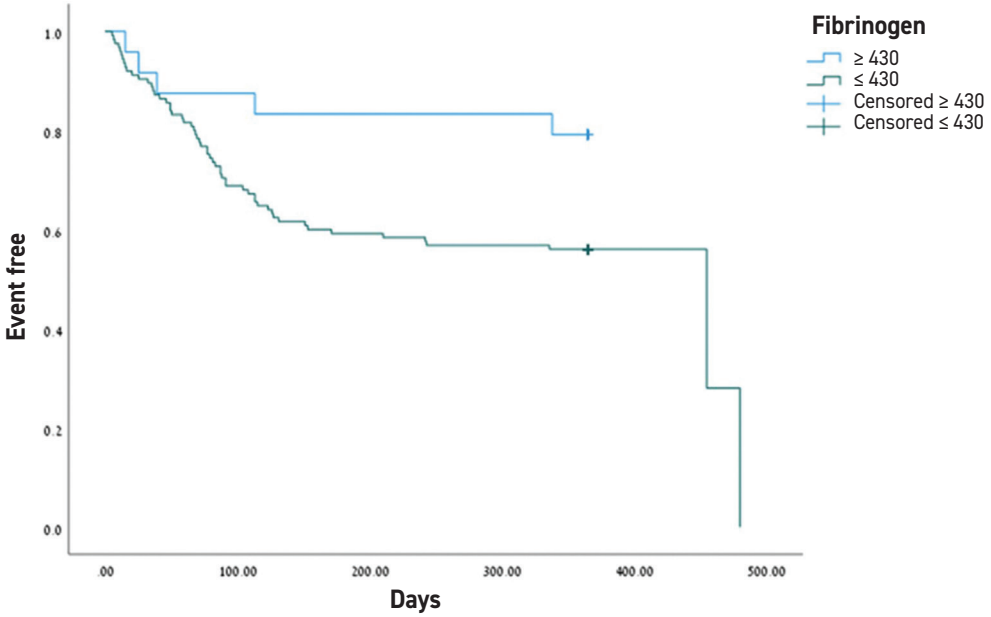
DISCUSSION

In the current study, we evaluated the prognostic value of fibrinogen levels after HF admission and found that high levels were associated with increased risk for readmissions. Fibrinogen is a high molecular weight plasma adhesion protein that reflects the amount of inflammation and may identify individuals at high risk for cardiovascular events [15]. Inflammation is associated with myocardial damage and plays a role in the pathogenesis of acute and chronic HF, particularly in patients with HFpEF [2-4]. Co-morbidities such as obesity, hypertension, type 2 diabetes mellitus, chronic lung disease, and chronic kidney disease are common in HFpEF and play a central role in the pathogenesis and progression of this inflammatory disease [2]. In the study by Meng et al. [16], critically ill patients (identified by several clinical scores) with HF and fibrinogen levels > 284 mg/dl had increased 90-day mortality. The fibrinogen-to-albumin ratio was also shown to be associated with increased all-cause mortality and LOS among hospitalized patients with HF in the intensive care units and in diabetic patients with HF [17,18]. Chin et al. [19] found no correlation between fibrinogen levels and all-cause mortality in patients with chronic HF. In a recent metanalysis, an inverted U-shaped association was observed between baseline fibrinogen levels and readmission within 6 months without increase in mortality risk [20]. However, this metanalysis included both patients with acute HF and those with deteriorating chronic HF.

The difference in results in the studies can be explained by different study populations (e.g., acute decompensated, critically ill patients, or chronic HF) and different measurements (baseline vs. maximal) of fibrinogen levels. In our study, we included hemodynamically stable patients without infectious trigger to eliminate the effect of infection on fibrinogen levels. This selection isolated the effect of fibrinogen on the course of HF. Readmission for HF is one of the major adverse events in the journey of HF patients as these episodes are associated with poor outcomes and has become more prevalent with disease progression [3].

The comparison between fibrinogen and NT-proBNP levels in predicting outcomes of HF is not applicable according to our findings and does not reflect the prognostic value of each biomarker due to measurements pitfalls. We measured fibrinogen levels at admission while NT-proBNP levels were usually drawn later (after routine workup of the patient) or at discharge when the patient was decongested. Fibrinogen levels may be used in addition to other well-established laboratory markers such as

Figure 2. Kaplan Meier curve for readmissions stratified by fibrinogen levels
Patients with high fibrinogen levels (> 430 mg/dl) experienced more admission rates due to heart failure decompensation



NT-proBNP and the routine clinical parameters. In addition, fibrinogen is not specific and may be elevated in patients with infectious trigger. Currently, there are several ongoing trials of novel therapies targeting inflammation in HF. In the future, large studies measuring fibrinogen levels at admission should be incorporated with other biomarkers for risk stratification in patients with HF.

STUDY LIMITATIONS

Our study has several limitations. First, the retrospective study was conducted at a single center with small number of patients, which may limit the interpretation for the large population. Our findings need to be further validated by larger prospective studies and longer follow-up time. Second, we did not include data on mortality, which is an important endpoint in such studies. However, a clear relationship exists between readmissions and HF mortality from several previous studies. Third, due to the retrospective design and the small number of patients, we did not include several other parameters and confounders that may have also affected the results.

CONCLUSIONS

Admission fibrinogen levels among patients with acute HF may predict LOS and readmission rate. Further prospective and large studies are warranted to reinforce the results.

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Capsule

Neutrophils at the heart of the matter

Despite decades of research advances and improved clinical outcomes, cardiovascular disease is still the most common cause of death worldwide. A major cause of mortality after myocardial infarction is arrhythmia resulting from injury to the cardiac muscle. During an ischemic event such as myocardial infarction, neutrophils are recruited to the heart. **Kumowski** and co-authors uncovered a direct link between these neutrophils and subsequent arrhythmias. Using mouse models supported by human data, the authors determined that resistin-like molecule gamma (RELMγ) is highly expressed in neutrophils after myocardial infarction. In the heart, RELMγ damages the cell membrane of cardiomyocytes, promoting cell death directly and also causing ion leaks that disrupt the heart's electrical activity and result in arrhythmias.

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Capsule

Spatiotemporal interaction of immune and renal cells controls glomerular crescent formation in autoimmune kidney disease

Rapidly progressive glomerulonephritis (RPGN) is the most aggressive group of autoimmune kidney diseases and is characterized by glomerular crescent formation with proliferation of parietal epithelial cells (PECs). **Sultana** and co-authors provided a high-resolution spatial kidney cell atlas of 57 samples from patients with RPGN (ANCA-associated GN, lupus nephritis and anti-glomerular basement membrane-GN) to characterize the cell signaling pathways in glomerular crescent development. Early platelet-derived growth factor (PDGF) signaling from epithelial and mesangial cells caused PEC activation and proliferation in glomerular crescents, whereas later transforming growth factor (TGF)-β signaling from macrophages, T cells and epithelial and mesangial cells triggered expression of extracellular matrix components in PECs associated with glomerulosclerosis and disease progression. These findings were similar across the different GNs and were functionally validated in experimental GN by PDGF and TGFβ blockade. These results highlight a spatiotemporally conserved progression program into glomerular crescents and sclerosis and indicate new treatment options for autoimmune kidney disease.

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