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Research

Evaluation of the Association Between the CALLY Index, Functional Class, and Mortality in Patients with Heart Failure with Reduced Ejection Fraction

Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliği Hastalarında CALLY İndeksi ile Fonksiyonel Sınıf ve Mortalite Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: Heart failure with reduced ejection fraction (HFrEF) remains a major global health challenge. The New York Heart Association (NYHA) functional classification remains an indispensable instrument for evaluating symptom severity and carries recognized prognostic value in this patient population. Nevertheless, there is a growing need for accessible, objective markers that can help predict outcomes more accurately. The C-reactive protein-albumin-lymphocyte (CALLY) index, derived from C-reactive protein (CRP), albumin, and lymphocyte count, offers a composite measure that reflects systemic inflammation, nutritional status, and immune function. This study aimed to evaluate the association between the CALLY index, NYHA class, and all-cause of mortality in patients with HFrEF.

Methods: Patients diagnosed with HFrEF from January 2023 to April 2025 were retrospectively evaluated. Patients were categorized as survivors or non-survivors. Clinical characteristics, laboratory findings, and NYHA functional class were systematically compared between the two groups. To explore factors independently associated with mortality, both univariate and multivariate logistic regression analyses were conducted. Additionally, the prognostic performance of the CALLY index was assessed using receiver operating characteristic (ROC) curve analysis.

Results: Among 146 patients diagnosed with HFrEF, 29 (19.8%) experienced all-cause of mortality. Compared with survivors, those who died were older, had significantly lower left ventricular ejection fraction (LVEF), and showed higher levels of inflammatory and cardiac biomarkers, including CRP, troponin-T, and pro-brain natriuretic peptide. Advanced heart failure symptoms (NYHA class 3-4) were more common among non-survivors. Notably, the CALLY index—reflecting a combination of inflammation, nutritional status, and immune function—was markedly lower in the mortality group. In both univariate and multivariate logistic regression analyses, LVEF, NYHA class 3-4, and the CALLY index were independently associated with mortality. ROC curve analysis showed that the CALLY index had good predictive value for all-cause of mortality and moderate predictive value for NYHA class 3-4, supporting its potential as a practical tool in clinical risk assessment.

Conclusion: The CALLY index, which integrates markers of inflammation, nutrition, and immune status, was independently associated with all-cause of mortality and correlated with symptom severity in patients with HFrEF.

Keywords: HFrEF, CALLY index, mortality, NYHA

ÖZ

Amaç: Düşük ejeksiyon fraksiyonlu kalp yetersizliği (DEFKY), halen küresel ölçekte önemli bir sağlık sorunu olmaya devam etmektedir. New York Kalp Derneği (NYHA) fonksiyonel sınıflandırması, semptom şiddetinin değerlendirilmesinde vazgeçilmez bir araç olup, bu hasta grubunda prognostik değeri de kabul görmüştür. Bununla birlikte, sonuçları daha doğru tahmin etmeye yardımcı olabilecek erişilebilir ve objektif belirteçlere olan ihtiyaç giderek artmaktadır. C-reaktif protein (CRP), albümin ve lenfosit sayısından türetilen C-reaktif protein-albümin-lenfosit (CALLY) indeksi, sistemik enflamasyon, beslenme durumu ve bağışıklık fonksiyonunu yansıtan bileşik bir ölçüttür. Bu çalışma, DEFKY hastalarında, CALLY indeksi ile NYHA sınıfı ve tüm nedenlere bağlı mortalite arasındaki ilişkiyi değerlendirmeyi amaçlamıştır.

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ÖZ

Gereç ve Yöntem: Ocak 2023 ile Nisan 2025 arasında DEFKY tanısı alan hastalar retrospektif olarak incelendi. Hastalar sağ kalanlar ve mortalite grubuna ayrıldı. Klinik özellikler, laboratuvar bulguları ve NYHA fonksiyonel sınıfları iki grup arasında sistematik olarak karşılaştırıldı. Mortalitenin bağımsız belirleyicilerini saptamak amacıyla tek değişkenli ve çok değişkenli lojistik regresyon analizleri yapıldı. Ayrıca, CALLY indeksinin prognostik performansı receiver operating characteristic (ROC) eğrisi analizi ile değerlendirildi.

Bulgular: Çalışmaya dahil edilen 146 DEFKY hastasının 29'unda (%19,8) tüm nedenlere bağlı ölüm görüldü. Mortalite grubundaki hastalar, sağ kalanlara kıyasla daha yaşlı, daha düşük sol ventrikül ejeksiyon fraksiyonuna (LVEF) sahip ve CRP, troponin-T, pro-brain natriüretik peptid gibi enflamasyon ve kardiyak belirteçler açısından daha yüksek seviyelerdeydi. İleri kalp yetersizliği semptomları (NYHA sınıf 3-4) mortalite grubunda daha sık gözlendi. CALLY indeksi, enflamasyon, beslenme ve bağışıklık durumunu yansıtarak mortalite grubunda anlamlı derecede düşüktü. Hem tek değişkenli hem de çok değişkenli analizlerde LVEF, NYHA sınıf 3-4 ve CALLY indeksi mortalitenin bağımsız belirleyicileri olarak saptandı. ROC analizi CALLY indeksinin mortalite öngörmede iyi, NYHA sınıf 3,4 semptomlarını öngörmede ise orta düzeyde performans gösterdiğini ortaya koydu.

Sonuç: CALLY indeksi, enflamasyon, beslenme ve bağışıklık durumunu gösteren belirteçleri birleştirerek, DEFKY hastalarında tüm nedenlere bağlı mortalite ile bağımsız olarak ilişkili bulunmuş ve semptom şiddeti ile korelasyon göstermiştir.

Anahtar Kelimeler: DEFKY, CALLY indeksi, mortalite, NYHA

INTRODUCTION

Heart failure (HF), a multifaceted clinical condition afflicting 1-3% of the worldwide population, remains a prominent contributor to both mortality and morbidity. It imposes a considerable strain on healthcare systems worldwide, not only in terms of economic expenditure but also in terms of its profound psychosocial impact (1). Patients with HF are stratified into distinct subgroups according to left ventricular function. HF with reduced ejection fraction (HFrEF) is characterized by a left ventricular ejection fraction (LVEF) of ≤40%, accompanied by typical clinical manifestations or symptoms indicative of HF (2). HFrEF remains a substantial public health challenge due to its marked association with increased cardiovascular mortality and frequent HF-related hospitalizations, of which approximately 50% are attributable to this phenotype (3).

Although a decline in HF-related mortality has been observed in recent years, the incidence of cardiovascular death and HF-related hospitalization among patients with HFrEF remains substantially high-ranging from 21.8% to 26.5% in the PARADIGM-HF, despite significant advancements in medical technology and the introduction of novel therapeutic strategies (4-6). Since its introduction in 1928, the New York Heart Association (NYHA) functional classification has undergone several refinements; nevertheless, it remains the most widely used clinical framework for evaluating symptom severity in patients with HF (7). In addition to its utility in characterizing functional limitations, the NYHA classification possesses substantial prognostic significance. Considerable evidence has consistently demonstrated that advanced NYHA functional classification is an independent predictor of increased risk of adverse clinical outcomes, including all-cause of mortality and HF-related hospital admissions (8-11).

The C-reactive protein-albumin-lymphocyte (CALLY) index is a composite biomarker integrating C-reactive protein (CRP), serum albumin, and total lymphocyte count, and provides a comprehensive assessment of systemic inflammation, nutritional status, and immune function. It was first introduced by Iida et al. (12) as a prognostic tool for predicting survival in patients with hepatocellular carcinoma. Since its introduction, the CALLY index has attracted increasing attention in the field of cardiology, with several studies demonstrating its prognostic value across a broad spectrum of cardiovascular conditions. These findings imply that the index may serve as a useful, accessible marker to guide clinical decision-making and predict patient outcomes across diverse cardiac populations (13,14).

The current investigation was undertaken to elucidate the relationship between the CALLY index, NYHA functional classification, and overall mortality in a cohort of patients diagnosed with HFrEF. This investigation was designed to assess the prognostic utility of the CALLY index as a potential biomarker, with the overarching objective of augmenting risk stratification protocols and refining therapeutic decision-making processes within this clinically vulnerable population.

METHODS

Study Population

From January 2023 to April 2025, consecutive patients who presented to our hospital with symptoms of HF and were subsequently diagnosed with HFrEF were retrospectively included in the study. Eligibility criteria included individuals older than 18 years with a definitive diagnosis of HFrEF, based on clinical evaluation and echocardiographic assessment (LVEF ≤40%). Exclusion criteria included refusal to participate, incomplete echocardiographic data, acute

decompensated HF, HF with preserved ejection fraction (HFpEF) or HF with mildly reduced ejection fraction (HFmrEF), end-stage renal disease, active malignancy or active infection, chronic liver disease, chronic inflammatory diseases, and chronic hematological disorders.

Initial demographic variables, in conjunction with a broad range of clinical variables and laboratory parameters, were meticulously extracted from the institutional electronic health record system and the national digital health system. LVEF was quantified by transthoracic echocardiography using the modified Simpson's biplane method. The cohort was dichotomized according to mortality status into survivors and non-survivors. Demographic characteristics, clinical features, laboratory parameters, and NYHA functional classes were systematically compared between the two groups.

Ethical approval for the present investigation was formally conferred by the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2025-15-16, date: 20.08.2025) following a thorough review process. The investigation was conducted in strict accordance with the ethical principles of the Declaration of Helsinki, ensuring the protection of participant rights, welfare, and confidentiality throughout the study. All procedures adhered to established ethical standards governing biomedical research involving human subjects.

Definition

The CALLY index was defined as a composite biomarker integrating serum CRP, albumin concentration, and lymphocyte count, and is designed to provide a comprehensive assessment of both systemic inflammatory burden and nutritional status. The CALLY index was calculated as [serum albumin (g/L)×lymphocyte count (cells/μL)]/[CRP level (mg/L)×10^4] (12). HFrEF was defined as an LVEF ≤40%, accompanied by clinical manifestations and/or symptoms indicative of HF (2).

Statistical Analysis

Continuous data were expressed as means and their respective standard deviations, whereas categorical variables were presented as absolute counts and proportions. Comparative analyses between survivor and non-survivor cohorts were conducted using either the independent Student's t-test or the Mann-Whitney U test, depending on the underlying data distribution. Receiver operating characteristic (ROC) curve analyses were conducted to evaluate the predictive performance of the CALLY index for both mortality and NYHA class 3-4. An initial univariable logistic regression analysis was conducted to explore potential determinants of mortality. Predictor variables with a univariable p-value of <0.05 were subsequently incorporated into a multivariable logistic regression model to assess their independent contributions to the outcome while controlling for confounding influences that could bias the observed relationships. Collinearity was assessed using correlation coefficients; no substantial collinearity (defined as r>0.7) was detected. All inferential statistical procedures and data management processes were executed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), in accordance with established methodological conventions and standards widely recognized in contemporary biomedical research.

RESULTS

A total of 146 individuals were enrolled in the current study, including 117 survivors and 29 who died, resulting in a mortality rate of 19.8%. While the gender distribution was similar between the two groups non-survivors were significantly older than survivors (66.55±9.35 vs. 61.82±11.02 years, p=0.035) and exhibited notably reduced LVEF (30.69±7.03% vs. 34.01±7.65%, p=0.033). Biomarkers indicative of systemic inflammation and myocardial injury—including CRP, troponin-T, and pro-brain natriuretic peptide—were substantially higher in non-survivors than in survivors. Other laboratory parameters did not differ significantly between groups. Additionally, the prevalence of advanced HF symptomatology, as defined by NYHA class 3-4, was markedly higher in the mortality group (31.0% vs. 10.3%, p=0.008). In contrast, the distributions of prevalent comorbid conditions [such as diabetes mellitus (DM), hypertension, and ischemic heart disease] and medication use were comparable between cohorts. Notably, the CALLY index—a composite measure integrating nutritional and inflammatory status—was significantly lower in non-survivors (1.33±2.86 vs. 4.02±9.11, p<0.001), highlighting its potential as a prognostic biomarker (Table 1).

Univariate logistic regression identified several key determinants associated with mortality. Notably, diminished LVEF was significantly associated with death, underscoring the critical role of cardiac function in patient outcomes [odds ratio (OR): 0.946; 95% confidence interval (CI): 0.896-0.998; p=0.044]. The presence of advanced HF symptoms, as indicated by NYHA class 3-4, was strongly predictive of mortality, emphasizing the clinical importance of symptom burden in this population (OR: 3.937; 95% CI: 1.466-10.573; p=0.007). The CALLY index was significantly inversely associated with mortality; higher values were associated

with improved survival (OR: 0.763; 95% CI: 0.626-0.981; p=0.034). Remaining variables failed to demonstrate statistically significant associations with mortality (Table 2).

Multivariate logistic regression analysis elucidated that several variables functioned as independent prognostic determinants of all-cause of mortality within the studied population. Notably, LVEF remained a significant protective factor: higher LVEF was associated with a reduced risk of mortality (OR: 0.958; 95% CI: 0.902-0.997; p=0.048), underscoring the vital role of preserved cardiac function in survival outcomes. In addition, HF symptoms classified as NYHA class 3-4 independently predicted increased mortality risk (OR: 2.845; 95% CI: 1.003-8.068; p=0.049), underscoring the significant influence of clinical symptom burden on patient prognosis. The CALLY index, reflecting the integrated status of nutrition and systemic inflammation, exhibited a significant inverse relationship with mortality (OR: 0.640; 95% CI: 0.438-0.935; p=0.021), highlighting its potential as a valuable prognostic biomarker (Table 3).

As presented in Table 4, patients classified in NYHA functional classes 3-4 (n=21) exhibited significantly lower CALLY index values compared with those in classes 1-2 (n=125) (1.22±1.53 vs. 3.80±8.91, p=0.016). This pronounced disparity highlights a robust correlation between diminished CALLY index values—indicative of compromised nutritional and inflammatory status—and more severe HF symptomatology, thereby underscoring the prognostic utility of the CALLY index in clinical evaluation.

ROC curve analysis was performed to rigorously determine the discriminative ability and prognostic efficacy of the CALLY index for both all-cause of mortality and advanced HF symptoms (defined as NYHA class 3-4). The CALLY

Table 1. Comparison of clinical, demographic, and laboratory parameters between survivors and non-survivors

Variable	Survival group (n=117) [mean±SD/n (%)]	Mortality group (n=29) [mean±SD/n (%)]	p-value
Age (years)	61.82±11.02	66.55±9.35	0.035
DM	42 (35.9)	9 (31)	0.620
HTN	73 (62.4)	15 (51.7)	0.297
IHD	65 (55.6)	17 (58.6)	0.765
ACEI/ARB	82 (70.1)	16 (55.2)	0.184
Beta-blocker	80 (68.4)	22 (75.9)	0.504
MRA	53 (45.3)	17 (58.6)	0.198
Furosemide	52 (44.4)	14 (48.3)	0.711
Antiplatelet	85 (72.6)	18 (62.1)	0.272
OAC	29 (24.8)	8 (27.6)	0.758
LVEF (%)	34.01±7.65	30.69±7.03	0.033
Glucose (mg/dL)	131.54±68.38	131.32±61.91	0.761
Creatinine (mg/dL)	1.19±0.89	1.27±0.90	0.165
Albumin (g/L)	45.12±34.70	40.75±6.63	0.136
CRP (mg/L)	1.32±2.78	1.96±2.41	0.006
Troponin-T (ng/L)	56.99±127.29	115.88±251.80	0.012
Pro-BNP (pg/mL)	2896.54±5366.33	5166.68±6430.90	0.011
LDL-C (mg/dL)	96.19±39.09	93.02±42.91	0.380
Triglyceride (mg/dL)	149.82±82.97	141.75±72.00	0.555
HGB (g/dL)	13.75±4.43	12.80±2.59	0.453
LEU (x10³/μL)	8.78±2.85	9.31±3.67	0.761
LYM (x10³/μL)	2.33±1.76	2.09±1.09	0.317
NYHA 3-4	12 (10.3)	9 (31.0)	0.008
CALLY index	4.02±9.11	1.33±2.86	<0.001

ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, BNP: Brain natriuretic peptide, CALLY: C-reactive protein–albumin–lymphocyte, CRP: C-reactive protein, DM: Diabetes mellitus, HGB: Hemoglobin, HTN: Hypertension, IHD: Ischemic heart disease, LEU: Leukocytes, LDL-C: Low-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, LYM: Lymphocytes, MRA: Mineralocorticoid receptor antagonist, NYHA: New York Heart Association, OAC: Oral anticoagulant, SD: Standard deviation

Table 2. Univariate analysis for factors associated with all-cause of mortality

	OR	95% CI	p-value
Age	1.032	0.993-1.074	0.111
LVEF	0.946	0.896-0.998	0.044
CRP	1.007	0.994-1.020	0.279
Pro-BNP	1.000	0.999-1.001	0.120
Troponin-T	1.002	1.000-1.004	0.111
NYHA 3-4	3.937	1.466-10.573	0.007
CALLY index	0.763	0.626-0.981	0.034

BNP: Brain natriuretic peptide, CALLY: C-reactive protein–albumin–lymphocyte, CI: Confidence interval, CRP: C-reactive protein, LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, OR: Odds ratio

Table 3. Multivariate analysis for determining independent predictors of all-cause of mortality

Variable	OR	95% CI	p-value
LVEF	0.958	0.902-0.997	0.048
CALLY index	0.640	0.438-0.935	0.021
NYHA 3-4	2.845	1.003-8.068	0.049

CALLY: C-reactive protein–albumin–lymphocyte, CI: Confidence interval, LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, OR: Odds ratio

Table 4. CALLY index between two groups of patients based on their NYHA classes

	NYHA class 1-2 (n=125)	NYHA class 3-4 (n=21)	p-value
CALLY index	3.80±8.91	1.22±1.53	0.016

CALLY: C-reactive protein–albumin–lymphocyte, NYHA: New York Heart Association

index exhibited a respectable predictive performance for all-cause of mortality, with an area under the curve (AUC) of 0.728 (95% CI: 0.633-0.823; p<0.001). A threshold value of 0.869 was established, providing a balanced sensitivity of 66.7% and a specificity of 71.4%. CRP demonstrated a moderate predictive ability (AUC=0.702, 95% CI: 0.600-0.803, p=0.001). In contrast, serum albumin (AUC=0.606, 95% CI: 0.483-0.729, p=0.090) and lymphocyte count (AUC=0.596, 95% CI: 0.464-0.727, p=0.127) exhibited lower discriminative capacity. Collectively, these findings suggest that the composite CALLY index provides a more robust and comprehensive prognostic indicator of mortality than any of its individual components. In the context of advanced HF symptoms (NYHA class 3-4), the CALLY index exhibited moderate discriminative ability with an AUC of 0.664 (95% CI: 0.544-0.784, p=0.016). A cut-off value of 0.681 was identified, corresponding to a sensitivity of 68.5% and a specificity of 57.1%. These findings highlight the potential utility of the CALLY index as a meaningful biomarker for risk stratification in patients with HF (Figure 1).

DISCUSSION

In our retrospective investigation aimed at elucidating the association among the CALLY index, NYHA functional classification, and all-cause of mortality in patients diagnosed with HFrEF, the following key findings emerged. Firstly, CALLY index was found to be associated with advanced functional impairment and independently predicted increased all-cause of mortality, demonstrating that lower CALLY values are associated with more severe clinical

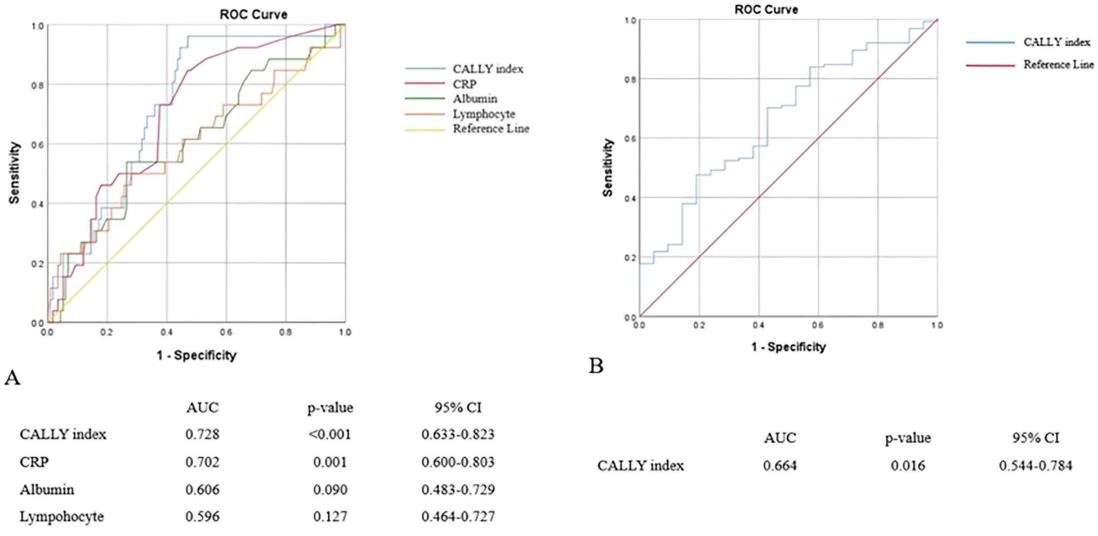

Figure 1. ROC analysis of CALLY index and its individual components for all-cause of mortality and CALLY index for NYHA class 3-4. **A.** ROC analysis of CALLY index and its individual components for all-cause of mortality, **B.** ROC analysis for NYHA class 3-4

AUC: Area under curve, CALLY: C-reactive protein–albumin–lymphocyte, CI: Confidence interval, CRP: C-reactive protein, NYHA: New York Heart Association, ROC: Receiver operating characteristic

symptoms and a heightened risk of mortality in patients with HFrEF. In addition to the CALLY index, LVEF, with a mean value of approximately 30% in the non-survivors, was independently and inversely associated with all-cause of mortality. Ultimately, the investigation identified advanced functional deterioration (NYHA functional class 3-4) as the strongest independent prognostic determinant of all-cause of mortality within the cohort, with an odds ratio of 2.8.

Despite regional variations in the prevalence of HF attributable to differing socioeconomic conditions across countries, it remains a pervasive and significant global public health challenge. Affecting a large number of individuals worldwide, HF contributes substantially to higher mortality and morbidity rates. Furthermore, it imposes a profound economic burden on healthcare systems through heightened utilization of medical resources, frequent hospital admissions, and escalating costs (15). HF is traditionally stratified by LVEF into three principal groups: HFrEF, delineated by LVEF ≤40%; HFmrEF, characterized by LVEF 41-49%; and HFpEF, identified by LVEF ≥50% (2). Among these three classifications, HFrEF is the most frequently observed, representing approximately 60% of cases (16). Moreover, individuals diagnosed with HFrEF have a markedly higher incidence of cardiovascular mortality compared with those with HFmrEF or HFpEF, with documented rates ranging from 8.8% to 16.5%. Indeed, in the PARADIGM-HF trial, all-cause of mortality in the HFrEF subgroup reached as high as 19.8% (4,16). In comparison, the PARAGON-HF trial reported a lower all-cause of mortality rate, ranging from 14.2% to 14.6% (17). In our study, the all-cause of mortality rate was 19.8%, which was consistent with the mortality rates reported in the PARADIGM-HF trial.

Given the substantial impact of HFrEF on both mortality and morbidity, accurate prognostication in this patient population is of critical importance. Consequently, numerous clinical, biochemical, and functional parameters have been investigated to predict adverse cardiovascular outcomes and guide risk stratification. In a pooled analysis of the three distinct CHARM trials that collectively enrolled HF patients across the LVEF spectrum (>40% and ≤40%), age and insulin-dependent DM emerged as two of the most significant independent predictors of mortality (11). The absence of a quantitatively corroborated of age or DM with all-cause of mortality in our cohort may be ascribed to several methodological factors, including the limited sample size and the homogeneous nature of the study population, which consisted exclusively of patients with reduced ejection fraction (LVEF ≤40%). Additional independent clinical predictors of mortality in patients with HFrEF include body mass index, systolic blood pressure, heart rate, advanced symptom burden (NYHA class 3-4), chronic kidney disease, and peripheral arterial disease. Among the aforementioned parameters, advanced functional status, classified as NYHA class 3-4, emerges as the most robust predictor of mortality, conferring approximately a twofold increased risk of mortality (16). In our study, an advanced functional status, defined as NYHA class 3-4, was independently associated with all-cause of mortality (OR: 2.84).

Currently, the mortality benefit conferred by pharmacologic attenuation of the renin-angiotensin-aldosterone axis and antagonism of β-adrenergic receptors in individuals with HFrEF is unequivocally established, rendering these agents foundational to the modern therapeutic paradigm for HFrEF (2,18). Nonetheless, within our study, no statistically significant difference was observed between the survivor and non-survivor cohorts in the administration of these medications. The absence of a discernible difference may be attributable to the limited sample size, which could have reduced the statistical power required to detect subtle but clinically meaningful effects.

Inflammatory pathophysiology has garnered growing recognition as a pivotal determinant in the development and perpetuation of HF. Beyond its role in the underlying pathophysiology, systemic inflammatory activity exerts a profound influence on the clinical course of HF, modulating symptom burden, functional deterioration, and prognostic outcomes. Augmented circulating concentrations of CRP, a robust and extensively validated surrogate marker of systemic inflammatory activity, have been consistently associated with unfavorable cardiovascular outcomes, including heightened mortality risk, increased rates of readmission, and diminished functional capacity. In the Val-HeFT, CRP concentrations were found to be significantly associated with both advanced functional impairment—characterized by NYHA class 3-4—and increased mortality and morbidity among patients with HF (19-22). Beyond CRP, data from the EVEREST trial demonstrated that a relatively low lymphocyte count in patients with HFrEF was independently associated with an increased risk of all-cause of mortality, cardiovascular mortality, and HF-related hospitalization (23). In parallel with relative lymphocyte count, absolute lymphocyte count has demonstrated an inverse association with mortality (24).

Nutritional status also represents a fundamental clinical consideration in patients with HFrEF. Kałużna-Oleksy et al. (25) demonstrated an association between malnutrition and increased mortality in patients with HFrEF. Moreover, in the same study, patients who died had significantly lower serum albumin levels than those who survived. Albumin is

a negative acute-phase reactant, and it is well established that the acute-phase response is linked to deterioration in nutritional status. Hypoalbuminemia in HF can be linked to key underlying mechanisms such as inflammation and immune dysfunction, as well as malnutrition (26).

Considering the immunologic response, systemic inflammation, and nutritional status—each pivotal to the pathophysiology and prognosis of HF—our finding that the CALLY index, calculated from serum albumin concentration, lymphocyte count, and CRP levels, independently predicted all-cause of mortality as well as associated with advanced symptom burden (NYHA class 3-4) in patients with HFrEF appears to be consistent with the existing scientific literature. As albumin and lymphocyte levels decrease and CRP, a surrogate marker of systemic inflammatory response, increases, the CALLY index correspondingly declines. Our results likewise revealed a negative association between the CALLY index and both all-cause of mortality and advanced HF symptoms (NYHA class 3-4).

Furthermore, the complex interrelationships among systemic inflammation, immunologic condition, nutritional status, and myocardial impairment highlight the multifaceted etiology and prognostic landscape of HFrEF. The CALLY index serves as a holistic biomarker, integrating inflammatory, immunological, and nutritional dimensions into a singular measure that mirrors this intricate pathophysiological web. To address its novelty, the CALLY index was evaluated in the HFrEF population, among whom its association with mortality and functional class has not been comprehensively investigated. This study therefore provides novel evidence that the CALLY index may serve as a prognostic marker for clinical risk stratification in patients with HFrEF. The CALLY index complements the MAGGIC HF score by incorporating systemic inflammatory and nutritional parameters, thereby refining risk stratification beyond conventional clinical and demographic predictors. This integrated approach provides clinicians with a more nuanced tool to assess prognosis and guide individualized therapeutic strategies for patients with HFrEF (27).

Study Limitations

This study is subject to several notable limitations that should be acknowledged when interpreting the results. The retrospective and single-center design inherently limits external validity and may reduce the generalizability of the findings to broader or more diverse patient populations. The relatively small sample size likely diminished the statistical power to detect subtle but clinically meaningful associations, particularly with well-established prognostic factors such as age and DM. This limitation increases the potential for type II errors, possibly underestimating the influence of these variables on clinical outcomes. Additionally, the absence of key hemodynamic parameters—such as heart rate and systolic blood pressure—precluded a more comprehensive assessment of cardiovascular status and its relationship with mortality and morbidity. These omitted variables may have concealed important physiological mechanisms or confounding interactions relevant to outcome prediction in patients with HFrEF. Another limitation of our study is that data on sodium-glucose co-transporter-2 inhibitor use were lacking; therefore, the potential impact of these agents on clinical outcomes could not be evaluated. Collectively, these methodological constraints underscore the importance of conducting prospective, multicenter studies with larger, more heterogeneous cohorts and a more exhaustive set of clinical variables to enhance the robustness and applicability of the findings.

CONCLUSION

This study elucidated that the CALLY index serves as an independent predictor of all-cause of mortality and is associated with advanced functional impairment, as denoted by NYHA class 3-4, in individuals with HFrEF. Notably, diminished CALLY index values were significantly correlated with adverse clinical trajectories, underscoring its potential utility as a pragmatic, cost-effective, and readily accessible tool for risk stratification in everyday clinical settings. By consolidating multiple interdependent physiological dimensions into a singular, quantifiable metric, the CALLY index offers a more holistic appraisal of patient vulnerability and long-term prognosis. This integrative approach may be particularly valuable in contexts where conventional risk models fall short of capturing the multifaceted nature of disease burden in HFrEF. Nevertheless, to fully ascertain its prognostic fidelity and operational relevance, further corroboration through prospective, multicenter investigations involving larger and more heterogeneous cohorts is imperative.

ETHICS

Ethics Committee Approval: Ethical approval for the present investigation was formally conferred by the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2025-15-16, date: 20.08.2025) following a thorough review process.

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

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