IJC Heart & Vasculature 54 (2024) 101502

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Prognostic roles of neutrophil–lymphocyte, monocyte-lymphocyte and platelet-lymphocyte ratios for long-term all-cause mortality in heart failure

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ARTICLE INFO

Keywords:
Heart failure
All-cause mortality
Neutrophil–lymphocyte ratio
NLR
Monocyte-lymphocyte ratio
MLR
Platelet-lymphocyte ratio
PLR

ABSTRACT

Background: Heart failure (HF) and inflammation have a bidirectional relation leading to activation and adaptation of multiple cellular lines, including leucocyte subtypes and platelets. We aimed to assess and compare the predictive value of the neutrophil–lymphocyte (NLR), monocyte-lymphocyte (MLR) and platelet-lymphocyte (PLR) ratios for all-cause long-term mortality in HF.

Methods: This is an observational retrospective cohort study that included patients from the HI-HF cohort that survived the initial hospitalization. Vital status and survival time were assessed in June 2020.

Results: We analyzed 1018 HF patients with a mean age of 72.32 ± 10.29 years and 53.54 % women. All-cause long-term mortality was 38.21 % after a median follow-up time of 68 [38 – 82] months. NLR (AUC 0.667, 95 %CI 0.637 – 0.697), MLR (AUC 0.670, 95 %CI 0.640 – 0.700) and PLR (AUC 0.606, 95 %CI 0.574 – 0.636) were predictors of all-cause mortality. In multivariable Cox proportional hazards analysis, NLR≥3.56 was the only hematological index independent predictor of fatality (HR 1.36, 95 %CI 1.05 – 1.76).

Conclusions: Of the three hematological indices, NLR was the only independent predictor of all-cause long-term mortality of HF patients. We suggest NLR≥3.56 as an auxiliary prognostic biomarker for the evaluation of HF patients.

1. Introduction

The modern perspective on the pathophysiology of heart failure (HF) includes the bidirectional relationship between this condition and inflammation [1]. The activation of the immune system, although potentially protective in the short term, is involved not only in the development of HF but also in its progression, both in reduced and preserved ejection fraction (EF) phenotypes[2–4]. This interdependence is reflected in the close connection between the various subtypes of inflammatory cells and inflammatory biomarkers and the prognosis of HF [5–9]. Neutrophilia secondary to delayed apoptosis participates in myocardial remodeling and alteration of systolic function [9–11]. Congestion, hypoxia and cardiac remodeling determine the activation and recruitment of monocytes, but also lymphopenia by accelerating the apoptosis of lymphocytes [11,12]. The neurohormonal activation which characterizes heart failure and inflammatory mediators are responsible for platelet activation, which contributes to ventricular dysfunction, but also increases the inflammatory process [13].

The consistency of the involvement of inflammation in the physiopathological process of heart failure and the simplicity of detecting various changes in the leukocyte formula represented attractive arguments for the search for hematological indices that better characterize the prognosis of heart failure. The increase of neutrophil-to-lymphocytes ratio (NLR) was associated with increased mortality in acute heart failure [14–17]. Several studies indicate the platelet-to-lymphocytes ratio (PLR) to be associated with in-hospital and short-term mortality in acute decompensated HF [18–22], though these findings were not confirmed by others [23,24]. A high monocytes-to-lymphocytes ratio

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https://doi.org/10.1016/j.ijcha.2024.101502
Received 8 April 2024; Received in revised form 25 July 2024; Accepted 7 August 2024

(MLR) was strongly associated with NT-proBNP and left ventricular ejection fraction (LVEF) and predicted HF hospitalizations in a cohort of patients with HF and stable coronary disease [25]. In another analysis MLR was associated with increased mortality at 6 months in patients after an episode of acute HF [26].

In a clinical setting characterized by a myriad of biomarkers, with increasing interest for novelty restricted by limited availability and cost-efficiency [27], these hematological indices initially studied in patients with malignancy [28] or infections [29], have a promising perspective for HF patients.

Since scarce data is available regarding which is best suited for the long-term survival prognosis of HF patients, the aim of our study was to confirm the predictive value of NLR, MLR and PLR, as well as to compare their utility in relation to all-cause mortality in HF patients.

2. Materials and methods

2.1. Type of study

This in an observational, retrospective cohort study that includes the follow-up data of the Hematological Indices in Heart Failure (HI-HF) cohort. The study protocol was designed in concordance to the Declaration of Helsinki's ethical principles and was approved by the Colentina Clinical Hospital's Ethical Research Committee on September 10th 2018.

2.2. Study population

All patients with HF consecutively admitted to the Cardiology Department of the Colentina Clinical Hospital in Bucharest, Romania, from January 1st 2011, to December 31st 2014 were considered for inclusion in the HI-HF cohort. The detailed protocol was previously published [30]. In addition to the selection criteria for the HI-HF cohort, for the purpose of this study, we included only the patients that survived the index hospitalization. We further excluded all patients whose survival status was not available.

2.3. Definitions

HF diagnosis for considering patients' inclusion was adapted according to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure [31]. Subgroups of patients were defined by the values of the left ventricular (LV) ejection fraction (EF), into reduced EF (rEF) for LVEF<40 %, mildly reduced EF (mrEF) for LVEF between 40 – 49 %, and preserved EF (pEF) if LVEF≥50 % [31].

Atrial fibrillation (AF) diagnosis included paroxysmal, persistent, permanent, valvular and non-valvular AF, as well as atrial flutter.

Anemia was diagnosed according to the World Health Organization definition, respectively for a hemoglobin level < 12 g/dL for women and < 13 g/dL for men [32].

All-cause mortality was evaluated using the National Health Insurance House database. Time of death was retrieved from the records of the National Population Registry. Survival status was assessed in June 2020. June 30th 2020 was the reference date for calculating survival time, which was calculated in months.

2.4. Parameters

Demographical data, clinical, biological and echocardiographic parameters were recorded for each patient. Details regarding the analysis of blood samples and echocardiographic imaging of the HI-HF cohort were presented previously.

The three hematological indices were obtained from the complete blood count at admission for the index hospitalization. NLR was calculated by dividing the neutrophil count by the lymphocyte count. MLR was calculated by dividing the monocyte count by the lymphocyte count. PLR was obtained by dividing the platelet count by the lymphocyte count.

2.5. Statistical analysis

The primary endpoint was all-cause long-term mortality.

Numerical variables with normal distribution were expressed as mean ± standard deviation. Numerical variables with non-Gaussian distribution were expressed as median [interquartile range]. Categorical variables were expressed as absolute numbers and percentages.

The lower limit of the third tertile was considered the cut-off level for the elevated values of the hematological indices and used for statistical analysis of outcome prediction, as previously utilized in other studies [21,33].

ROC analysis was used for correlating continuous variables with the predefined outcome. DeLong test was applied for comparison of areas under the curve of the ROC analyses. Yates' corrected chi-square test was employed for correlating dichotomous variables.

Chi-square test for trend was employed for comparing the incidence of the outcome in the tertile groups. Kaplan-Meier survival curves were generated for univariable survival analysis. Cox proportional hazards regression analysis, forward conditional method was used to determine the independent predictors of all-cause mortality. Backward conditional and Enter methods were used to confirm the independent variables.

Survival analysis comprised of three steps. The first step was to determine the variables that were significantly associated with mortality in the univariable analysis. The second step was to include these parameters in a multivariable Cox proportional hazards regression in order to determine the independent predictors of all-cause mortality. The third step was to include in the regression the independent variables from the first step and the hematological indices, to assess the value of the latter parameters.

Logarithmic transformation in the base of 10 was used for the NT-proBNP values in the multivariable analysis. Hematological indices were included as continuous as well as dichotomous variables in the Cox regressions, using the cut-off values previously defined. Clinical congestion, cardiovascular diseases and risk factors and non-cardiovascular comorbidities were analyzed as dichotomous variables, while all other parameters were analyzed as continuous variables.

Statistical significance was considered for a p value < 0.05.

Data was analyzed using IBM SPSS Statistics version 23 (IBM Corp. in Armonk, NY) and MedCalc Statistical software version 19.0.7 (MedCalc Softwave bvba, Ostend, Belgium).

3. Results

3.1. General characteristics

Our cohort included 1018 HF patients discharged alive after admission for decompensated HF (Fig. 1) with a mean age of 72.32 ± 10.29 years and 53.54 % women. All-cause long-term mortality was 38.21 % after a median follow-up time of 68 [38 – 82] months. The median survival time of deceased patients was 27 [9 – 46] months (Table 1).

Half of the patients had dyspnea at rest or at mild effort at admission. HFpEF was more prevalent than HFrEF and HFmrEF, which had similar incidence. Ischemic heart disease affected approximately 45 % of patients. Atrial fibrillation was present in half of the studied population. Approximatively 20 % of patients had severe valvular disease and 43 % associated criteria for pulmonary hypertension. The most common risk factors were arterial hypertension and dyslipidemia (Table 1).

Incidence of all-cause mortality increased proportionally to increasing tertiles of NLR (from 24.48 % to 55.88 %, p < 0.001), MLR (from 23.89 % to 58.11 %, p < 0.001) and PLR (from 28.82 % to 50.74 %, p < 0.001) (Table 2). Kaplan Meier analysis showed decreased

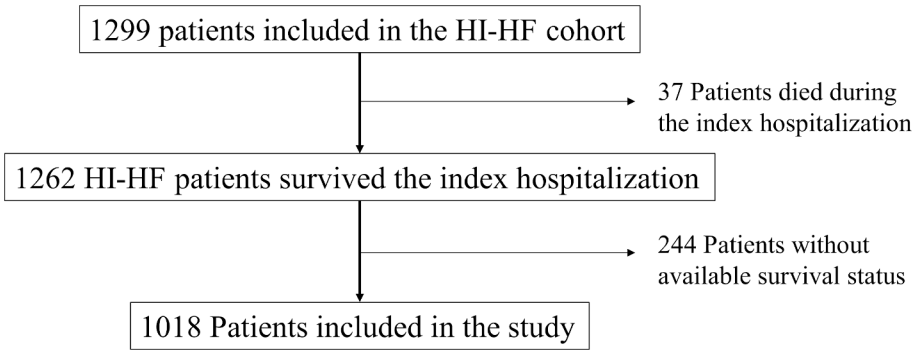

Fig. 1. PRISMA consort flow diagram of the study cohort.

survival with increasing tertiles of NLR (from a median of 70 to 60 months, $p < 0.001$), MLR (from a median of 70 to 56 months, $p < 0.001$) and PLR (from a median of 69 to 65 months, $p < 0.001$) (Fig. 2).

3.2. All-cause long-term mortality

NLR, MLR and PLR were all predictors of all-cause long-term mortality in ROC analysis. NLR and MLR had superior predictive values compared to PLR (Table 3).

Kaplan Meier analysis showed decreased survival with increasing tertiles of NLR, MLR and PLR (Fig. 2).

In univariable analysis, the strongest predictors of all-cause long-term mortality included dyspnea at rest, NYHA class, the presence of clinical congestion, age, chronic kidney disease (CKD), anemia, severe valvular disease, pericardial effusion, LVEF, NT-proBNP (Table 4).

The clinical, biological and echocardiographic parameters significantly associated with all-cause mortality identified in the initial analysis (Table 4) were included in the multivariable Cox regression (Table 5). The independent variables positively correlated with the endpoint were age, NYHA class, the presence of clinical congestion, chronic obstructive pulmonary disease, anemia, severe aortic stenosis, pericardial effusion, NT-proBNP, and those inversely correlated included LVEF, serum sodium and the presence of dyslipidemia (Table 5).

Adding all three of the hematological indices as dichotomic variables, only NLR≥3.56 was an additional independent predictor of mortality, outperforming MLR≥0.47 and PLR≥148.12. Adding all three hematological indices as continuous variables, only NLR was an independent predictor of mortality, outperforming MLR and PLR (Table 5).

4. Discussion

In this study we evaluated and compared the predictive value of three hematological indices, NLR, MLR and PLR, for all-cause long-term mortality of heart failure patients included in the HI-HF cohort, discharged alive from the initial hospitalization. Our main findings were that 1) NLR, MLR, and PLR were correlated with all-cause long-term mortality in HF, with higher values associating higher fatality rates and shorter life expectancy, 2) NLR and MLR had superior predictive power compared to PLR, and 3) NLR was the only hematological index with independent predictive value in multivariable survival analysis, alongside clinical, biological and echocardiographic parameters such as age, NYHA class, clinical congestion, NT-proBNP, LVEF, COPD, anemia, severe aortic stenosis, pericardial effusion, serum sodium.

To the best of our knowledge, this is among the first papers to assess the three hematological indices together in relation to HF survival after a follow-up period of over 5 years. Similar results were recently reported by Wu et al. from a cohort of 1207 HF patients from the NHANES database, followed-up for 66 months, the main difference being the analysis of only NLR and PLR [34]. Similar to our findings, in univariable analysis both NLR and PLR were associated with all-cause mortality, however in multivariable analysis, after adjusting for age, gender, race, body mass index, diabetes mellitus, COPD, CKD, history of MI and use of diuretics, only NLR remained an independent predictor of the endpoint [34]. HR for NLR evaluated as a continuous variable was 1.05 (95 %CI 1.02 – 1.08) similar to 1.04 (1.02 – 1.07) found in our study. HR for the forth quartile of NLR was 1.59 (95 %CI 1.18 – 2.15) comparable to 1.36 (95 %CI 1.05 – 1.76) for the third tertile found in our study.

Arfsten et al. also evaluated the predictive power of NLR, MLR and PLR for all-cause mortality prediction after a shorter median follow-up of 21 (10–28) months, in outpatients with HFrEF [35]. In their studied cohort of 443 stable chronic HFrEF patients, in univariable analysis, all three hematological indices were correlated with the outcome, similar to our results. However, in multivariable Cox analysis, MLR and PLR remained independent predictors of fatality, after adjustment for NYHA class, age, sex, body mass index, and laboratory parameters, while NLR did not [35]. The differences in methodology of the two cohorts could explain the contradictory results of the multivariable analysis. The HI-HF cohort included patients surviving a hospitalization, arguably with more advanced or severe heart failure. The follow-up period of our study was three times longer than that of the aforementioned one. Initial analysis of the HI-HF cohort for in-hospital mortality, also endorsed MLR and NLR as independent predictors for short-term survival, with MLR having the strongest association with the outcome, alongside NT-proBNP levels, dyspnea at rest, COPD, age and systolic blood pressure [30]. Compared to the in-hospital mortality, long-term survival in the HI-HF population was independently influenced by additional factors such as LVEF, severe AS, pericardial effusion, anemia and hyponatremia, with NLR maintaining an autonomous predictive power for fatality [30]. Our sample included not only HFrEF, but also HFmrEF and HFpEF, and our multivariable analysis included LVEF as a continuous variable in order to adjust for this parameter and avoid confounders. Moreover, our Cox analysis included all variables with independent predictive value, including but not limited to those utilized by Arfsten et al, respectively additional potential confounding factors such as anemia, valvular disease, chronic kidney disease, cardiac and non-cardiac comorbidities. Another important aspect that could contribute to the absolute values of the hematological indices as well as to the survival expectancy is the exclusion from the HI-HF cohort of patients with comorbidities potentially influencing the leukocyte and platelet count, such as solid or hematological malignancy, autoimmune disease, infections, acute coronary syndromes.

NLR, MLR, and PLR were all previously evaluated in relation to HF short and long-term outcomes, NLR [17] and PLR [22] being the most independently studied in this setting. Although many papers assessed the utility of NLR for HF survival, the majority had a follow-up duration of up to 3 years. In patients with an episode of acute decompensated HF, Uthamalingan et al. showed the association of the upper NLR tertile with a 2.1 fold increase in mortality, compared to the first tertile, during a

Table 1
General characteristics.

	N=1018 patients
Demographics	
Age (years)	72.32 ± 10.29
Women	545 (53.54 %)
Survival outcome	
All-cause long-term mortality	389 (38.21 %)
Survival time of deceased patients (months)	27 [9 – 46]
Heart failure characteristics	
HFpEF	446 (43.81 %)
HFmrEF	301 (29.56 %)
HFrEF	271 (26.62 %)
NYHA II	518 (50.88 %)
NYHA III	398 (39.10 %)
NYHA IV	102 (10.02 %)
Length of hospital stay (days)	5 [4 –7]
Comorbidities and cardiovascular risk factors	
Ischemic heart disease	450 (44.20 %)
Prior myocardial infarction	196 (19.25 %)
Stable angina	197 (19.35 %)
Atrial fibrillation	531 (52.16 %)
Arterial hypertension	815 (80.06 %)
Diabetes mellitus	302 (29.67 %)
Dyslipidemia	809 (79.47 %)
Obesity	425 (41.75 %)
History of stroke/ TIA	133 (13.06 %)
Chronic kidney disease	619 (60.80 %)
COPD	68 (6.68 %)
Echocardiographic characteristics	
LVEF (%)	43.01 ± 12.19
Severe aortic stenosis	27 (2.65 %)
Severe aortic regurgitation	22 (2.16 %)
Severe mitral regurgitation	141 (13.85 %)
Pulmonary hypertension	435 (42.73)
Pericardial effusion	67 (6.58 %)
Biological characteristics	
NT-proBNP (ng/L)	1164 [488.2 – 2954]
eGFR (mL/min)	68.38 ± 22.38
Creatinine (mg/mL)	0.95 [0.80 – 1.20]
Uric acid (mg/dL)	6.10 [5.10 – 7.60]
Serum sodium (mmol/L)	139.89 ± 7.44
Serum potassium (mmol/L)	4.38 ± 0.51
Total cholesterol (mg/dL)	172.46 ± 49.98
AST (UI/L)	20.5 [16.70 – 26.95]
ALT (UI/L)	18.7 [13.9 ± 27.1]
Complete blood count	
White blood count (/uL)	7000 [4850 – 8910]
Neutrophils (/uL)	4881 [3820 – 6564]
Lymphocytes (/uL)	1728 [1320 – 2210]
Monocytes (/uL)	650 [500 – 831]
Platelets (/uL)	219,000 [179000 –26600]
Hemoglobin (g/dL)	13.12 ± 1.95
Hematocrit (%)	39.93 ± 5.51
Hematological indices	
NLR	2.82 [2.04 – 4.21]
MLR	0.37 [0.27 – 0.53]
PLR	126.25 [95.45 – 171.20]

LOS – length of stay, HFpEF – Heart Failure with Preserved Ejection Fraction, HFmrEF – Heart Failure with Mid-Range Ejection Fraction, HFrEF – Heart Failure with Reduced Ejection Fraction, NYHA – New York Heart Association, TIA – Transient Ischemic Attack, COPD – Chronic Obstructive Pulmonary Disease, LVEF – Left Ventricular Ejection Fraction, eGFR – Estimated Glomerular Filtration Rate, AST – Aspartate Transaminase, ALT – Alanine Transaminase, NLR – Neutrophil-Lymphocyte Ratio; PLR – Platelet Lymphocyte Ratio; MLR – Monocyte-Lymphocyte Ratio.

Table 2
Survival analysis across hematological indices' tertiles.

	Neutrophil-Lymphocyte Ratio			
	1st tertile 0.32 – 2.29	2nd tertile 2.30 – 3.54	3rd tertile 3.56 – 22.75	p value for trend
All-cause mortality, N (%)	83 (24.48 %)	116 (34.21 %)	190 (55.88 %)	< 0.001
Survival time (months), median [IQR]	70 [62 – 86]	68 [48 – 83]	60 [17 – 71]	< 0.001
	Monocyte-Lymphocyte Ratio			
	1st tertile 0.04 – 0.30	2nd tertile 0.31 – 0.46	3rd tertile 0.47 – 2.35	p value for trend
All-cause mortality, N (%)	81 (23.89 %)	111 (32.64 %)	197 (58.11 %)	<0.001
Survival time (months), median [IQR]	70 [63 – 88]	68 [45 – 82]	56 [16 – 71]	< 0.001
	Platelet-Lymphocyte Ratio			
	1st tertile 52.35 – 104.50	2nd tertile 104.61 – 148.05	3rd tertile 148.12 – 391.06	p value for trend
All-cause mortality, N (%)	98 (28.82 %)	119 (35.10 %)	172 (50.74 %)	< 0.001
Survival time (months), median [IQR]	69 [54—86]	68 [48 – 83]	65 [21—76]	< 0.001

CI – confidence interval; N – number of patients.

mean period of 26 months [14]. In a similar study of patients with an episode of acute HF requiring hospitalization, followed-up for a mean of 28.6 ± 20.7 months, Huang et al. proved the independent predictive value of NLR in multivariable analysis alongside NT-proBNP (HR 1.137, p = 0.03) or alongside age, sex, mean blood pressure, LVEF, serum sodium, hemoglobin, kidney function and HF treatment (HR 1.162, p < 0.01) [36]. NLR also proved to be an independent predictor of all-cause mortality in a cohort of HF patients with LVEF<35 % during a 660 days follow-up [37].

PLR was also previously assessed for HF prognosis, the longest follow-up period being 5 years. In a cohort of 1923 patients hospitalized for HF, in multivariable regression alongside age, sex, LVEF, NT-proBNP, serum sodium, hemoglobin, GFR, and heart failure treatment, PLR was an independent predictor of survival at 1, 3 and 5 years [36]. In a different sample of patients admitted for acute pulmonary edema followed-up for a mean of 20.8 ± 16.1 months after hospital discharge, PLR was an independent predictor of mortality, in a multivariable analysis including age, blood pressure, hemoglobin, ischemic heart disease, LVEF and ACE inhibitor treatment [38]. PLR was also an independent predictor of all-cause mortality after a mean follow-up of 4.4 ± 1.3 years of 367 patients with advanced HF and diabetes mellitus, alongside atrial fibrillation and red blood cell distribution width [39]. Although all these studies proved the independent value of PLR, none have evaluated this biomarker in the same multivariable analysis as NLR and MLR, as opposed to our research.

For medium and long-term HF prognosis, we found scarce data evaluating MLR. In a sample of 390 patients hospitalized for decompensated HF, followed-up for 6 months, in multivariable analysis a lymphocyte-monocyte ratio < 2 associated a 2.28 fold increase of cardiovascular mortality risk and a 2.39 fold increase of all-cause mortality risk, after adjustment for age, NYHA class, ischemic heart disease, arterial hypertension, NT-proBNP levels, hemoglobin levels, eGFR, and heart failure treatment [26]. Given the shorter duration of follow-up, and corroborated with results for in-hospital mortality of the HI-HF cohort [30], we could argue that the monocyte-lymphocyte ratio could play an independent role in short-term outcome prediction.

Undoubtedly, acute and chronic inflammation influence the evolution and prognosis of HF, involving multisystem and organ interdependency [1,11,40]. Part of this pathophysiological loop is also the response and adaptive transformation of different blood cell populations, including neutrophils, monocytes, lymphocytes and platelets, leading to objective alterations of their proportions [13,41,42]. Mirroring molecular and cytokine modifications, NLR, MLR and PLR, reflect the severity of the underlying mechanisms, and therefore gain prognosis value. In addition to the preexisting data in favor of their use in clinical practice, our study proves the independent and superior predictive value of NLR compared to MLR and PLR for all-cause long-term mortality, during a follow-up period longer than previously investigated and

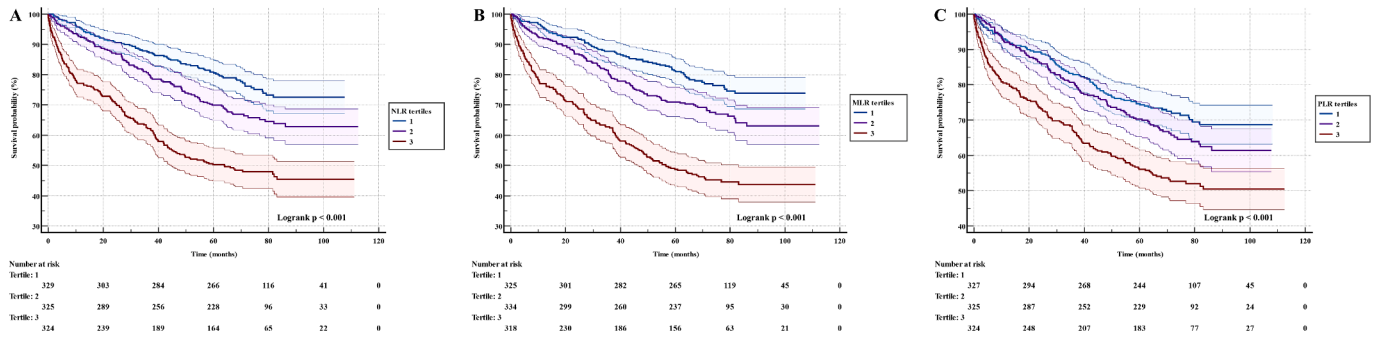

Fig. 2. Kaplan-Meyer Survival Plots. 2A NLR tertiles survival analysis. 2B MLR tertiles survival analysis. 2C PLR tertiles survival analysis.

Table 3
Comparison of ROC analysis for all-cause long-term mortality.

Hematological index	AUC (95 %CI)	p value for AUC comparison NLR	MLR	PLR
NLR	0.667 (95 %CI 0.637 – 0.697)	–	0.828	<0.001
MLR	0.670 (95 %CI 0.640 – 0.700)	0.828	–	<0.001
PLR	0.606 (95 %CI 0.574 – 0.636)	<0.001	<0.001	–

NLR – Neutrophil-Lymphocyte Ratio; PLR – Platelet Lymphocyte Ratio; MLR – Monocyte-Lymphocyte Ratio.

alongside a larger panel of potential confounding parameters.

The main limitation of our study is the retrospective inclusion. The methodology was designed to allow a long-term follow-up period for all-cause mortality, therefore we aimed to retrospectively enrol patients in order to achieve a follow-up period of over 5 years. In addition, the retrospective inclusion empowered us to recruit a larger number of patients, which, in turn, represents a strength of this research.

Another potential drawback is the inclusion from a single center; however we argue that belonging to a university hospital, patients are referred to our department from surrounding cities, therefore increasing the diversity of inclusion.

Our endpoint was all-cause mortality. While lack of assessment of cardiovascular mortality could be a limitation of our study, we argue that all-cause mortality is a strong primary endpoint used in majority of HF trials, more robust and less prone to uncertainty and bias [43,44]. Moreover, all-cause mortality was the endpoint in previous research regarding the hematological indices in HF, as compared to our results in the Discussion section.

5. Conclusions

NLR, MLR, and PLR are easily obtainable and financially feasible biomarkers that could be used as auxiliary predictors of all-cause long-term mortality in HF.

NLR evaluated as either a continuous or dichotomic variable had an independent predictive capability for death of any cause in HF patients, alongside clinical, biological, and echocardiographic parameters already validated in previous research. We suggest NLR≥3.56 as an independent predictor of all-cause long-term mortality in HF patients surviving hospital admission.

CRediT authorship contribution statement

Caterina Delcea: Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Formal analysis, Conceptualization. **Catalin Adrian Buzea:** Writing – review & editing, Writing – original draft, Conceptualization. **Dobromir Dobrev:** Writing – review & editing, Supervision. **Gheorghe Andrei Dan:** Writing – review & editing, Supervision.

Table 4
Predictors of all-cause long-term mortality – univariable analysis.

Clinical characteristics			
	RR	95 %CI	p value
Dyspnea at rest	1.64	1.27 – 2.11	< 0.001
Clinical congestion	1.45	1.29 – 1.62	< 0.001
	AUC	95 % CI	p value
NYHA class	0.678	0.644 – 0.712	< 0.001
Age	0.655	0.619 – 0.690	< 0.001
Cardiovascular diseases and comorbidities			
	RR	95 %CI	p value
Stable angina	1.13	1.02 – 1.26	0.035
Chronic Kidney Disease	1.41	1.25 – 1.58	< 0.001
COPD	1.31	1.02 – 1.68	0.018
Pulmonary Hypertension	1.26	1.14 – 1.39	< 0.001
Dyslipidemia	1.21	1.10 – 1.33	< 0.001
Stroke/TIA	1.26	1.06 – 1.51	0.003
Atrial Fibrillation	1.18	1.07 – 1.29	<0.001
Anemia	1.55	1.36 – 1.76	< 0.001
Echocardiographic parameters			
	RR	95 %CI	p value
Severe aortic stenosis	2.86	1.41 – 5.81	< 0.001
Severe mitral regurgitation	1.63	1.33 – 2.01	< 0.001
Severe tricuspid regurgitation	1.63	1.31 – 2.02	< 0.001
Pericardial effusion	1.85	1.32 – 2.58	<0.001
	AUC	95 %CI	p value
LVEF	0.649	0.611 – 0.687	< 0.001
Laboratory parameters			
	AUC	95 %CI	p value
NT-proBNP	0.692	0.658 – 0.726	< 0.001
eGFR*	0.626	0.590 – 0.662	< 0.001
Serum sodium*	0.565	0.526 – 0.604	0.001
Creatinine	0.595	0.559 – 0.632	< 0.001
AST	0.568	0.530 – 0.606	< 0.001
Total cholesterol*	0.573	0.536 – 0.610	< 0.001
Hemoglobin*	0.638	0.601 – 0.674	< 0.001
Hematological indices			
	RR	95 % CI	p value
NLR ≥ 3.56	1.48	1.31 – 1.68	< 0.001
MLR≥0.47	1.57	1.38 – 1.79	< 0.001
PLR≥148.12	1.29	1.15 – 1.45	< 0.001

SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, NYHA – New York Heart Association, COPD – Chronic Obstructive Pulmonary Disease, MI – Myocardial Infarction, LVEF – Left Ventricular Ejection Fraction, PASP – Pulmonary Artery Systolic Pressure, NT-proBNP – NT-proB-type Natriuretic Peptide, eGFR – Estimated Glomerular Filtration Rate, AST – Aspartate Transaminase, NLR – Neutrophil-Lymphocyte Ratio; PLR – Platelet Lymphocyte Ratio; MLR – Monocyte-Lymphocyte Ratio.

Funding

This research was supported by "Net4SCIENCE: Reţea de cercetare doctorală şi postdoctorală aplicativă în domeniile de specializare

Table 5
Predictors of all-cause long-term mortality – multivariable analysis.

	Cox regression 1	Cox regression 2*	Cox regression 3**
	HR (95 %CI)	HR (95 %CI)	HR (95 %CI)
Age	1.03 (1.02 – 1.04) p < 0.001	1.03 (1.02 – 1.04) p < 0.001	1.03 (1.02 – 1.04) p < 0.001
NYHA class	1.38 (1.14 – 1.67) p = 0.001	1.36 (1.12 – 1.65) p < 0.001	1.35 (1.11 – 1.64) p = 0.002
Clinical congestion	1.54 (1.17 – 2.03) p = 0.002	1.49 (1.13 – 1.98) p = 0.004	1.52 (1.15 – 2.01) p = 0.003
COPD	1.73 (1.14 – 2.63) p = 0.001	1.57 (1.03 – 2.39) p = 0.035	1.64 (1.08 – 2.49) p = 0.020
Dyslipidemia	0.73 (0.54 – 0.97) p = 0.032	0.74 (0.55 – 1.00) p = 0.050	0.73 (0.54 – 0.98) p = 0.038
Anemia	1.53 (1.20 – 1.97) p < 0.001	1.45 (1.13 – 1.86) p = 0.004	1.46 (1.14 – 1.88) p = 0.003
Severe AS	2.20 (1.30 – 3.72) p = 0.003	2.31 (1.36 – 3.92) p = 0.002	2.28 (1.34 – 3.87) p = 0.002
Pericardial effusion	1.49 (1.05 – 2.14) p = 0.026	1.49 (1.05 – 2.14) p = 0.028	1.49 (1.04 – 2.14) p = 0.028
LVEF	0.98 (0.97 – 1.00) p = 0.046	0.99 (0.98 – 1.001) p = 0.087	0.99 (0.98 – 1.00) p = 0.049
Log_{10}NT-proBNP	1.67 (1.25 – 2.23) p = 0.001	1.52 (1.13 – 2.05) p = 0.005	1.51 (1.12 – 2.02) p = 0.006
Serum sodium	0.98 (0.97 – 0.99) p = 0.001	0.98 (0.97 – 0.99) p = 0.001	0.98 (0.97 – 0.99) p = 0.002
NLR	N/I	1.36 (1.05 – 1.76) p = 0.019	1.04 (1.02 – 1.07) p = 0.001
MLR	N/I	1.006 (0.75 – 1.35) p = 0.970	0.99 (0.91 – 1.07) p = 0.790
PLR	N/I	1.05 (0.79 – 1.41) p = 0.721	1.00 (0.99 – 1.00) p = 0.325

*Analysis including the hematological indices as dichotomous variables using the third tertile cut-off; **Analysis including the hematological indices as continuous variables.
AS, aortic stenosis; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; Log_{10}NT-proBNP, logarithmic transformation in the base of 10 of NT-proBNP; MLR, monocyte-lymphocyte ratio; N/I, not included; NLR, neutrophil–lymphocyte ratio; NYHA, New York Heart Association; PLR, platelet-lymphocyte ratio.

inteligentă Sănătate și Bioeconomie", under the project code POCU/993/6/1/154722.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank Daha IC, MD, PhD, Andrus A, MD, Breha A, MD, Hogea I, MD, Niculescu L, MD, Lupan M, MD, Lefter A, MD, Pavalean M, MD, Moise A, MD, and Angheluta S, MD, for their help in data collection and database completion.

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