

Relationship Between the Eosinophil/Monocyte Ratio and Prognosis in Decompensated Heart Failure: A Retrospective Study

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Purpose: The aim of this study was to assess the value of the eosinophil/monocyte ratio (EMR) for predicting the prognosis of decompensated heart failure (HF).

Patients and Methods: This was a retrospective cohort study. We included adults (≥ 18 years old) diagnosed with decompensated HF for whom EMR data were available. The patients were divided into three groups according to EMR tertiles (T1 [EMR ≤ 0.15], T2 [0.15 < EMR ≤ 0.32], and T3 [EMR > 0.32]). The primary endpoint was the composite outcome of cardiovascular death or HF rehospitalization.

Results: Initially, the records of 2264 patients with decompensated HF were screened; 1883 of these patients had EMR data and were therefore included in the study. There were 627 patients in the T1 group, 628 in the T2 group, and 628 in the T3 group. The risk of cardiovascular death or HF rehospitalization was significantly different among the three groups (Log rank test, $P=0.007$). Compared with the T3 group, both the T1 group (hazard ratio [HR]: 1.50, 95% confidence interval [CI]: 1.16–1.94, $P=0.002$) and the T2 group (HR: 1.34, 95% CI: 1.03–1.74, $P=0.030$) had significantly higher rates of cardiovascular death or HF rehospitalization. A Cochran-Armitage test for trend showed a positive correlation between the EMR and the composite outcome of cardiovascular death or HF. There was a significant difference between the three groups in terms of cardiovascular death (Log rank test, $P<0.001$) and HF rehospitalization (Log rank test, $P=0.03$).

Conclusion: The EMR is positively correlated with the risk of cardiovascular death or HF rehospitalization in patients with decompensated HF. Specifically, the lower the EMR, the higher the risk of cardiovascular death or HF rehospitalization.

Keywords: decompensated heart failure, eosinophil/monocyte ratio, prognosis, cardiovascular death, heart failure rehospitalization

Introduction

Decompensated heart failure (HF) is a type of heart disease in which the ejection fraction cannot meet the body's needs due to cardiac dysfunction. The prognosis of patients with HF is poor,¹ as the annual associated mortality rate for these patients is approximately 7.1% (the rate is roughly 10% during the first 3 years, but it drops to approximately 5% in subsequent years).² Indeed, HF is the primary reason for the hospitalization of people over 65 years of age.³

Multiple studies have shown elevated inflammation markers in patients with HF. This suggests that inflammation is involved in the development and progression of HF, and the severity of the inflammation affects a patient's prognosis.^{4,5}

Eosinophils, which are produced in the bone marrow, migrate to specific organs that are involved in antibacterial immunity. Circulating eosinophils contain many cytoplasmic particles that are effective mediators of antibacterial immunity, but they are extremely toxic to heart cells; thus, these particles participate in the cardiac decompensation process.⁶ The eosinophil/monocyte ratio (EMR) is a new type of inflammatory marker,^{7,8} and it can be used to predict the prognosis of cardiovascular (CV) disease with associated underlying inflammation. For example, evidence suggests that the EMR can predict the incidence of major CV events in patients with acute coronary syndrome.⁹ Moreover, the EMR is associated with the prognosis and functional outcomes of patients with ischemic stroke.^{7,8} However, the value of the EMR for predicting the prognosis of decompensated HF is unknown. Therefore, the aim of this study was to evaluate the relationship between the EMR and the prognosis of decompensated HF using a retrospective analysis. We hypothesized that the EMR is related to the prognosis of patients with decompensated HF.

Patients and Methods

Study Population

This was a single-center retrospective cohort study. The participants were patients who were diagnosed with decompensated HF at the Fuwai Hospital Chinese Academy of Medical Sciences (Shenzhen Sun Yat-sen Cardiovascular Hospital) in Shenzhen, China from March 2018 to May 2020 and who also had available baseline EMRs. The exclusion criteria were as follows: 1) non-adult patients (<18 years); 2) patients with autoimmune, allergic, or infectious diseases that affect the EMR. This study was approved by the Ethics Committee of Fuwai Hospital of the Chinese Academy of Medical Sciences, Shenzhen, China.

Data Collection and Definitions

The sampling procedure was performed by reviewing the electronic medical records of the Fuwai Hospital Chinese Academy of Medical Sciences and screening the population based on the inclusion and exclusion criteria. Data on basic patient demographics, clinical findings, laboratory test results, presence of complications, and medications used were extracted from the records. The eosinophil and monocyte absolute values from the first fasting blood sample during hospitalization were obtained from the hospital laboratory. Each comprehensive decompensated HF

diagnosis was made according to the standards established by the European Society of Cardiology clinical practice guidelines and based on a combination of the patient's medical history, clinical findings, cardiac color Doppler ultrasound, and N-terminal pro B-type natriuretic peptide (NT-proBNP) value.¹⁰ The eosinophil count was determined using an automatic blood cell analyzer, and the baseline EMR was calculated according to the following formula: absolute eosinophil value ($\times 10^9/L$)/absolute monocyte value ($\times 10^9/L$).⁸

Endpoints

The primary endpoint was a composite outcome of CV death or rehospitalization due to HF; the secondary endpoints were CV death and rehospitalization due to HF (evaluated individually). The first primary endpoint event that occurred during the follow-up period was used in the analysis. If the same event occurred multiple times, only the first event was used. The patients (or their family members) reported whether the patient experienced CV death or rehospitalization due to HF within 1 year of hospital discharge. The clinical outcomes of interest were confirmed by trained personnel who carefully reviewed the corresponding medical records; these personnel were not aware of any baseline characteristics through telephone contact with the patient or their family members.

Statistical Analysis

All the patients were divided into three groups according to the EMR tertiles. If a continuous variable conformed to a normal distribution, it is expressed as the mean \pm standard deviation; otherwise, it is expressed as the median and interquartile range. Categorical variables are expressed as numbers and percentages. The chi-square or Fisher's exact tests were used to analyze the differences in the categorical variables between the groups. The ANOVA or Kruskal–Wallis *H*-tests were used to analyze the differences in the continuous variables between the groups. The Kaplan–Meier method was used to draw a time-to-event curve. The difference in the event incidences among the three EMR groups was determined using the Log rank test. We performed a Cox proportional hazard regression analysis to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the clinical outcomes. The Cochran–Armitage test was used to determine the correlation between the EMR and clinical outcomes. We used the following four models to adjust for confounding factors: Model 1 was adjusted for white blood cell count, the total bilirubin, D-dimer, creatinine, potassium, sodium, HbA1c, and NT-proBNP values, ejection fraction, and left ventricular end

diastolic diameter; Model 2 was adjusted for the variables in model 1 plus sex, age, body mass index, systolic blood pressure, and heart rate; Model 3 was adjusted for the variables in model 2 plus the New York Heart Association classification, myocardial infarction (MI), atrial fibrillation, and the use of diuretics, β blockers, digoxin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors, spironolactone, and SGLT-2 inhibitors. Statistical significance was set at $P < 0.05$. The statistical analyses were performed using the “DescTools” and “survival” packages in R version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria).

Results

A patient selection flow chart is shown in Figure 1. In the present study, 2531 patients with HF were initially screened, of which 2264 patients were found to have decompensated HF. A total of 381 of these patients were excluded, as they did not have recorded eosinophil or monocyte absolute values. Finally, 1883 patients met the inclusion criteria. These patients were divided into three approximately equal groups according to the EMR tertile (T1, $EMR \leq 0.15$; T2, $0.15 < EMR \leq 0.32$; T3, $EMR > 0.32$); T1 had 627 patients, T2 had 628, and T3 had 628. The baseline characteristics of the patients are shown in Table 1. There were many significant differences between the baseline characteristics and the trends across the EMR tertiles. As the EMR increased across the tertiles, the proportions of men, age, blood pressure,

sodium level, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors increased. In contrast, higher EMRs across the tertiles also corresponded to lower heart rates, total bilirubin, D-dimer, and NT-proBNP levels, atrial fibrillation incidence, and diuretic and digoxin use.

Primary Outcome

The primary outcome survival curves of the three EMR groups are shown in Figure 2. There were significant differences in the composite outcome of CV death or HF rehospitalization event rates among the three groups (log-rank $P = 0.007$). A comparison between the groups is shown in Table 2. The results show that both the T1 group (HR: 1.50, 95% CI: 1.16–1.94, $P = 0.002$) and the T2 group (HR: 1.34, 95% CI: 1.03–1.74, $P = 0.030$) had higher risks of CV death or HF rehospitalization compared to the T3 group. The T1 group (HR: 1.43, 95% CI: 1.09–1.87, $P = 0.010$) and the T2 group (HR: 1.34, 95% CI: 1.03–1.74, $P = 0.032$) also both show higher risks of CV death or HF rehospitalization than the T3 group in adjusted model 1. In model 2, the T1 group (HR: 1.43, 95% CI: 1.08–1.88, $P = 0.011$) and the T2 group (HR: 1.36, 95% CI: 1.04–1.78, $P = 0.023$) both show higher risks of CV death or HF rehospitalization than the T3 group. In model 3, both the T1 group (HR: 1.34, 95% CI: 1.01–1.77, $P = 0.040$) and the T2 group (HR: 1.33, 95% CI: 1.02–1.74, $P = 0.035$) had higher risks of CV death or HF rehospitalization compared to the T3 group. The Cochran-Armitage

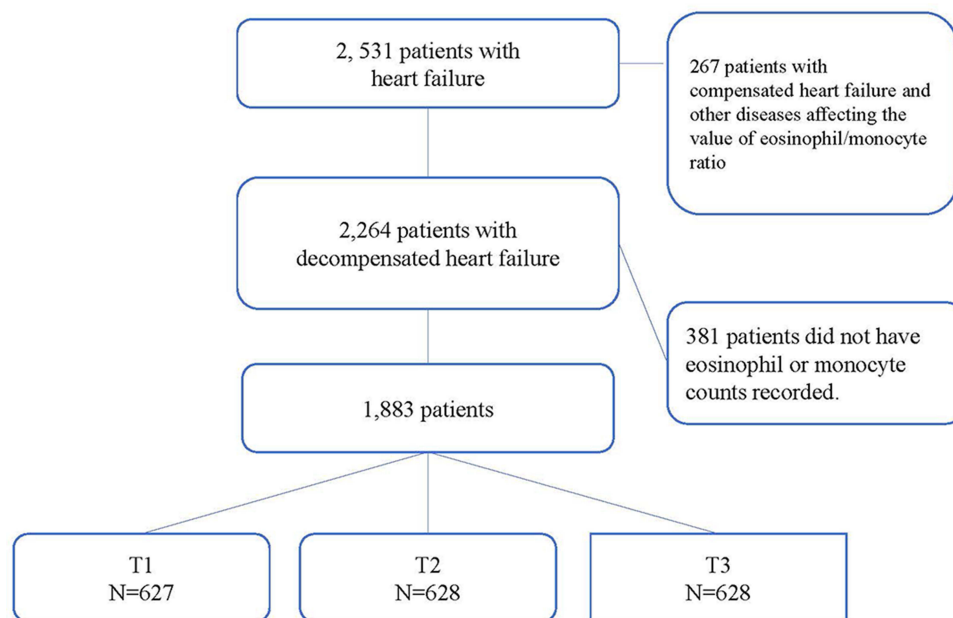


Figure 1 Flow chart of patient selection.

Table I The Characteristic of Population

	T1 (EMR≤0.15)	T2 (0.15<EMR≤0.32)	T3 (EMR>0.32)	P value
Number	627	628	628	
Age (mean (SD))	59.93 (14.51)	59.96 (14.91)	61.93 (13.86)	0.019
Male (%)	308 (49.1)	344 (54.8)	377 (60.0)	0.001
BMI (mean (SD))	20.90 (1.91)	21.01 (1.76)	21.13 (1.82)	0.078
SBP (mean (SD))	121.35 (20.53)	124.26 (20.00)	125.53 (21.68)	0.001
Heart rate (mean (SD))	85.34 (20.54)	79.87 (19.44)	78.19 (17.71)	<0.001
WBC (mean (SD))	8.78 (3.55)	7.29 (2.55)	6.67 (2.03)	<0.001
TB (mean (SD))	20.05 (16.07)	16.02 (11.45)	13.50 (9.34)	<0.001
D-dimer (mean (SD))	2.69 (4.46)	1.30 (2.61)	0.90 (1.49)	<0.001
Creatinine (mean (SD))	101.20 (58.42)	99.36 (61.77)	104.17 (68.62)	0.394
Potassium (mean (SD))	4.25 (0.36)	4.18 (0.35)	4.25 (0.38)	<0.001
Sodium (mean (SD))	139.49 (3.11)	140.38 (2.84)	140.63 (2.83)	<0.001
HbA1c (mean (SD))	5.87 (1.02)	5.92 (1.13)	5.97 (1.18)	0.262
NT-proBNP				
(median (range))	4333.41 (6422.14)	2655.52 (4835.77)	2209.65 (4392.10)	<0.001
EF (mean (SD))	42.84 (12.28)	43.67 (11.65)	43.33 (11.44)	0.461
LVEDD (mean (SD))	53.56 (11.84)	53.36 (11.82)	53.59 (10.41)	0.925
Cause of HF (%)				0.002
DCM	276 (44.0)	315 (50.2)	309 (49.2)	
ICM	110 (17.5)	109 (17.4)	96 (15.3)	
VHD	47 (7.5)	58 (9.2)	79 (12.6)	
HCM	162 (25.8)	119 (18.9)	106 (16.9)	
NYHA classification (%)				<0.001
III	36 (5.7)	86 (13.7)	108 (17.2)	
IV	190 (30.3)	241 (38.4)	274 (43.6)	
Hypertension (%)	42 (6.7)	40 (6.4)	58 (9.2)	0.106
MI (%)	54 (8.6)	63 (10.0)	67 (10.7)	0.454
AF (%)	272 (43.4)	212 (33.8)	200 (31.8)	<0.001
Diuretics (%)	489 (78.0)	405 (64.5)	371 (59.1)	<0.001
B blocker (%)	375 (59.8)	394 (62.7)	383 (61.0)	0.563
Digoxin (%)	143 (22.8)	77 (12.3)	58 (9.2)	<0.001
ACEI/ARB/ARNI (%)	243 (38.8)	318 (50.6)	329 (52.4)	<0.001
Spironolactone (%)	260 (41.5)	228 (36.3)	233 (37.1)	0.129

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; WBC, white blood cell; TB, Total bilirubin; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; HF, heart failure; NYHA, New York Heart Association; MI, myocardial infarction; AF, atrial fibrillation; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; VHD, valvular heart disease; HCM, hypertrophic cardiomyopathy.

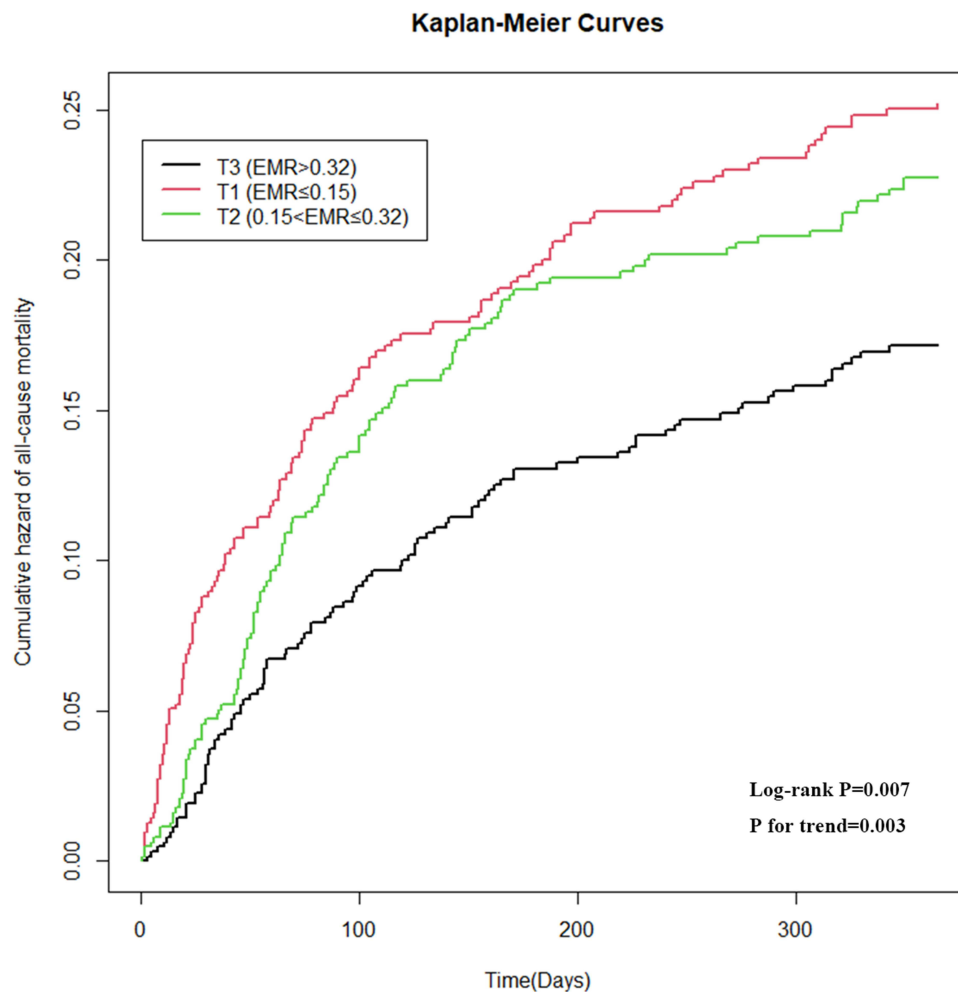


Figure 2 Kaplan–Meier survival curve for the primary endpoint event.

test for trends showed a positive correlation between the EMR and the primary outcome ($P=0.003$).

Cardiovascular Death

The CV death endpoint survival curve is shown in [Figure 3](#). There were significant differences in the risk of CV death among the three groups (log-rank $P<0.001$). A results comparison between the groups is presented in [Table 2](#). Compared with the T3 group, the T1 group had a higher risk of CV death (HR: 4.24, 95% CI: 1.86–9.67, $P<0.001$), and the T2 group had a similar risk of CV death (HR, 1.29; 95% CI: 0.48–3.46, $P=0.615$). The Cochran–Armitage test for trend showed a positive correlation between the EMR and CV death ($P<0.001$).

Heart Failure Rehospitalization

The HF rehospitalization endpoint survival curve is shown in [Figure 4](#). There were significant differences in the risk

of CV death among the three groups (log-rank $P=0.030$). A results comparison between the groups is presented in [Table 2](#). Compared with the T3 group, the T1 group had a similar risk of CV death (HR: 1.25, 95% CI: 0.95–1.64, $P=0.110$), and the T2 group had a higher risk of CV death (HR, 1.44; 95% CI, 1.10–1.88; $P=0.008$). The Cochran–Armitage test for trend showed no correlation between the EMR and HF rehospitalization ($P=0.134$).

Discussion

The results of this study show that there is a correlation between the EMR and the composite risk of death or rehospitalization for patients with decompensated HF; ie, the higher the HF ratio, the lower the composite risk of CV death or HF rehospitalization.

Resident and recruited immune cells play a role in heart damage.^{11–13} Initially, resident and infiltrating immune cells activate inflammatory pathways and tissue

Table 2 The Association Between Eosinophil/Monocyte Ratio and Clinical Outcomes in Patients with Decompensated Heart Failure

	T1 (EMR≤0.15)	T2 (0.15<EMR≤0.32)	T3 (EMR>0.32)	Log Rank Test (P value)	P for Trend
Number	627	628	628		
Primary outcome					
Events	140	128	99		
HR (95% CI)	1.50 (1.16–1.94)	1.34 (1.03–1.74)	References	0.007	0.003
Adjusted Model 1	1.43 (1.09–1.87)	1.34 (1.03–1.74)	References		
Adjusted Model 2	1.43 (1.08–1.88)	1.36 (1.04–1.78)	References		
Adjusted Model 3	1.34 (1.01–1.77)	1.33 (1.02–1.74)	References		
Cardiovascular dead					
Events	29	9	7		
HR (95% CI)	4.24 (1.86–9.67)	1.29 (0.48–3.46)	References	<0.001	<0.001
HF hospitalization					
Events	114	123	94		
HR (95% CI)	1.25 (0.95–1.64)	1.44 (1.10–1.88)	References	0.03	0.134

Abbreviations: HR, hazard ratio; CI, confidence interval; EMR, eosinophil/monocyte ratio; HF, heart failure.

repair processes that determine the course of HF development.¹⁴ Immune cells not only regulate the function of cardiomyocytes, but they also regulate the progress of interstitial fibrosis, thereby affecting heart function.¹⁵ Patients with HF often have an accompanied increase in proinflammatory cytokine levels, which becomes more obvious as heart function deteriorates.¹⁶ Therefore, inflammatory mechanisms may be involved in the HF pathophysiological process.¹⁷ Indeed, increased levels of proinflammatory cytokines and other inflammatory markers may identify patients at risk of developing HF.^{5,18}

The EMR is a new marker that can reflect the level of inflammation in the body. Deng et al conducted a retrospective study to evaluate the value of the EMR for predicting major adverse cardiovascular events in patients with MI, and their results indicated that there is a positive correlation.⁹ Another study indicated that the EMR can predict prognosis and functional outcomes in patients with ischemic stroke.^{7,8} Inflammatory factors are thought to be involved in the occurrence and progression of ischemic CV disease, and the level of inflammation is related to its prognosis.¹⁹ Clinical studies have shown that the use of inflammatory inhibitors can improve the prognosis of patients with ischemic CV disease.^{20–22} Although the EMR reflects the level of inflammation in the body, the predictive value of this ratio for the prognosis of patients with HF remains unclear. In the present study, a retrospective analysis method was used to explore this issue, and the results showed that the EMR and the prognosis of patients with chronic HF were positively correlated.

There are several possible explanations for this finding. Eosinophils may mediate myocardial tissue repair. Animal experiments have shown that eosinophil proliferation can promote the subsequent polarization of IL-4/STAT6 axis-mediated macrophages to the M2 type, thereby promoting cardiac structure and function recovery after an MI.²³ Liu et al reported that blood and cardiac eosinophil counts increased after MIs in both humans and mice; these increases were primarily in the infarcted area, and the authors established the cardioprotective effect of eosinophils in the heart post-MI.²⁴ An increase in peripheral monocytes can also occur 2–3 days after an acute infarction, indicating monocyte and macrophage infiltration into the necrotic myocardium.²⁵ Higher peak monocyte levels are associated with larger left ventricular end-diastolic volumes, lower left ventricular ejection fractions, and worse clinical outcomes.^{26–28} Additionally, a peak monocyte count >900 can independently predict HF, left ventricular aneurysm formation, and cardiac events.²⁹ Therefore, eosinophils and monocytes have opposite effects on HF; ie, higher eosinophil numbers and lower monocyte numbers both correlate with better patient prognoses.

The EMR, which directly reflects the prognosis of patients, is easy to obtain in clinical practice. In future research, the EMR can be incorporated into existing HF prognostic prediction models to improve their predictive performance. Additionally, the results of this study confirm that not all inflammatory indicators are harmful for patients with HF. For example, an increase in eosinophils during the early stages of HF may have a protective effect

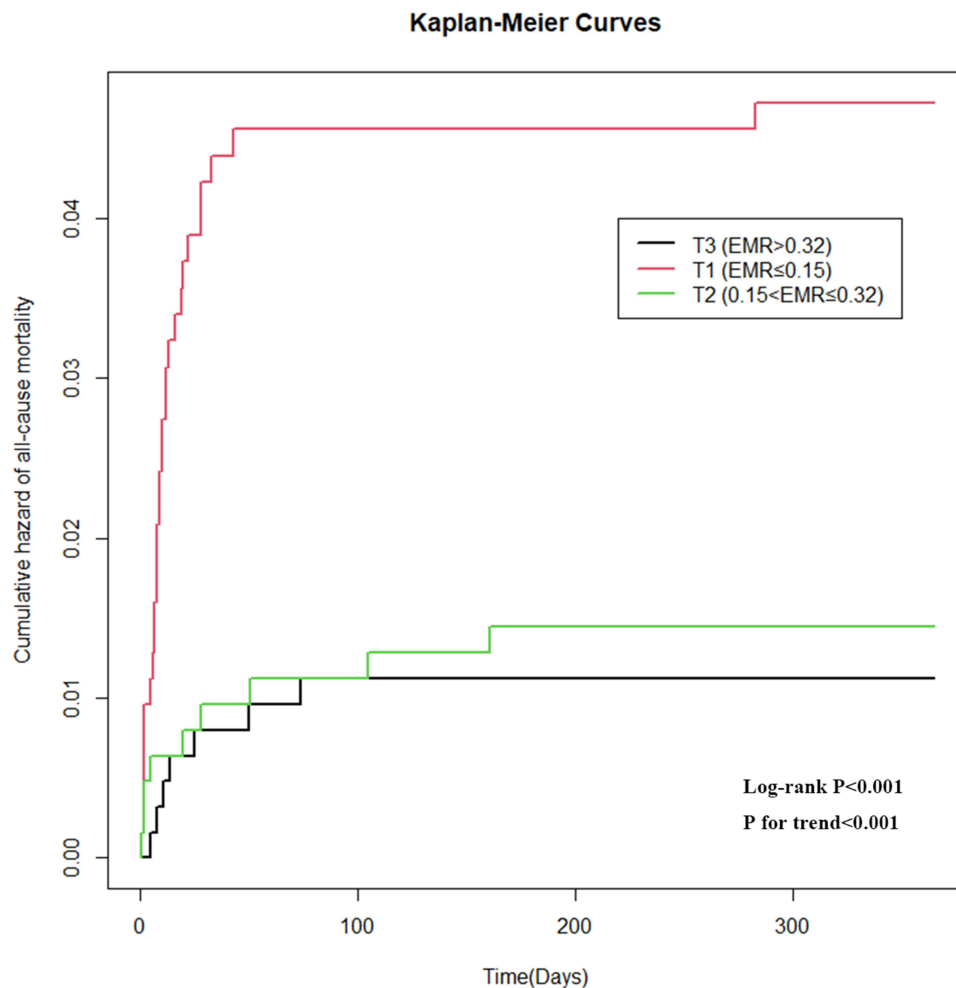


Figure 3 Kaplan–Meier survival curve for cardiovascular death.

on cardiomyocytes. However, clinical trials have failed to confirm that inflammation inhibitors can improve the prognosis of patients with HF,^{30–32} suggesting that there are multiple inflammatory pathways involved in its occurrence and progression. Further research is needed to explore the pathophysiological mechanisms underlying the influence of eosinophils on the structure and function of the heart.

Limitations

This study has several limitations. First, the follow-up time was too short; a longer follow-up period is needed to clarify the influence of the EMR on long-term prognoses. Second, causality could not be determined because this was a single-center retrospective study. Third, this study was confined to a population of Chinese patients. Further research is needed to verify whether our findings are valid for other populations. Fourth, we obtained the first EMR for each patient at admission. However, the EMR was

a time-dependent covariate. Although the proportional hazards assumption from the Cox regression model held, and we used the Cox regression model to estimate the effect of the EMR on survival, further studies using a Cox model with time-dependent covariates and data that has been organized in a counting process style are warranted.³³ Fifth, there are different pathogenesis mechanisms of preserved and reduced HF development. However, the patients in our study were not sorted according to the ejection fraction. Therefore, further studies are warranted to evaluate whether the type of HF (HF with preserved, mid-range, or reduced ejection fraction) influences the effect of the EMR on prognosis.

Conclusions

The results of this study show that the EMR is positively correlated with the prognosis of patients with decompensated HF; ie, the lower the ratio, the worse the prognosis.

Kaplan-Meier Curves

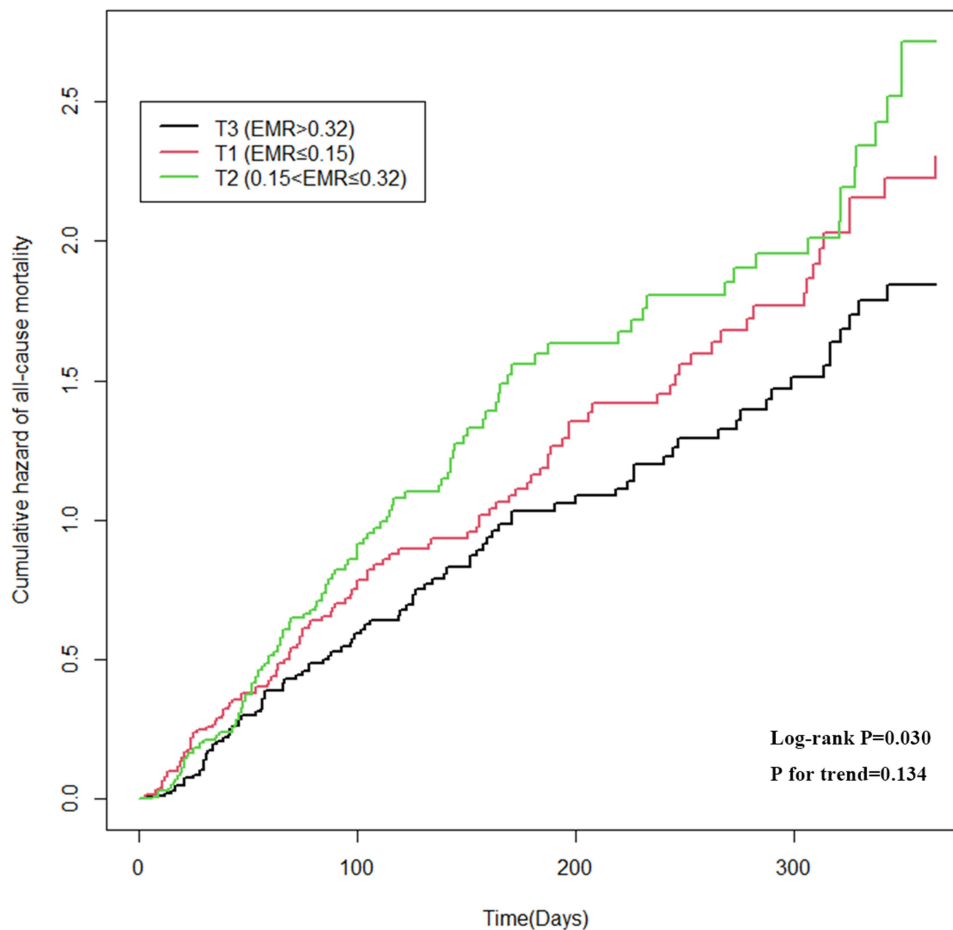


Figure 4 Kaplan–Meier survival curve for rehospitalization due to heart failure.

Further studies are needed to evaluate the impact of dynamic monitoring of the EMR on the prognosis of patients with HF.

Abbreviations

ANOVA, analysis of variance; CI, confidence interval; CV, cardiovascular; EMR, eosinophil/monocyte ratio; HBA1C, hemoglobin A1C; HF, heart failure; HR, hazard ratio; IL-4/STAT6, interleukin-4/signal transducer and activator of transcription 6; MI, myocardial infarct; NT-proBNP, N-terminal pro B-type natriuretic peptide; SGLT-2 inhibitors, sodium-glucose co-transporter-2 inhibitors; TNF- α , tumor necrosis factor-alpha.

Data Sharing Statement

All the data reported in this study are available upon request by contacting the corresponding author.

Ethical Statement

This study was approved by the Ethics Committee of Fuwai Hospital of the Chinese Academy of Medical Sciences, Shenzhen and was performed in accordance with the Declaration of Helsinki. Informed consent was waived due to this study's retrospective nature and the anonymized processing of patient data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Xiehui Chen and Weichao Huang are co-first authors for this study. The authors report no conflicts of interest in this work.

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