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Research article

Association between red blood cell distribution width-platelet ratio (RPR) and mortality in patients with heart failure from the MIMIC IV database: A retrospective cohort study

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ABSTRACT

The association between the red blood cell distribution width-platelet ratio (RPR) and mortality in heart failure patients remains unclear. We aimed to investigate the potential non-linear relationship between RPR and 1-year mortality risk. A retrospective cohort study was conducted involving 6982 participants from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. Multivariable Cox regression and restricted cubic spline analyses were performed to evaluate the association between RPR and 1-year mortality, adjusting for potential confounders. We observed 1091 patients died in hospital and 2535 patients died during 1 year follow-up period. The prevalence or incidence of mortality did not show statistically significant differences among RPR groups in the overall study population. However, a positive association between RPR and the risk of mortality was noted after adjusting for multiple variables (HR = 1.38, 95 % CI = 1.06–1.81, $P = 0.018$). Analysis using restricted cubic splines indicated a U-shaped relationship between RPR levels and the risk of mortality (P nonlinearity <0.05), with the point of lowest risk at 0.104. Compared to this level, lower RPR (<0.104) was associated with increased mortality (HR = 0.046, 95 % CI: 0.004–0.546), as was higher RPR (>0.104) (HR = 2.656, 95 % CI: 1.692–4.170).This U-shaped association was consistent across subgroup analyses (all interaction P values > 0.05). RPR exhibits a U-shaped association with 1-year mortality in heart failure patients, suggesting both low and high RPR levels are linked to increased risk. RPR may serve as a relevant biomarker for risk stratification in this population. We incorporated RPR into the SOFA (AUC 0.731) and SAPS II (AUC 0.746) models, which significantly improved their predictive ability for in-hospital mortality. For 1-year mortality prediction, RPR + SAPS II (AUC 0.683) showed significantly improved accuracy, while RPR + SOFA (AUC 0.626) did not improve significantly.

1. Introduction

Red blood cell distribution width-platelet ratio (RPR) is a vital hematologic biomarker that offers valuable insights into human physiology and overall health [1–3]. Its measurement serves as a sensitive indicator of the intricate homeostatic mechanisms within

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the body, providing real-time information on internal changes. As an integral component of routine health assessments, RPR levels play a significant role in understanding various metabolic processes and organ functions. These values are influenced by a complex interplay of genetic factors, lifestyle choices, and environmental influences. Abnormal RPR levels outside the established reference range can indicate underlying health issues, prompting further clinical investigation and intervention [4–6].

The clinical relevance of RPR extends to its utility in the diagnosis and management of a wide range of acute and chronic conditions. Its dynamic nature makes it a valuable tool for monitoring disease progression, assessing treatment effectiveness, and customizing personalized healthcare strategies. Ongoing research efforts aim to elucidate the physiological factors that influence RPR levels, thereby enhancing our understanding of its significance in health and disease. This knowledge contributes to the development of innovative diagnostic and therapeutic approaches, as well as the identification of individuals at risk for specific health conditions [7, 8].

In summary, RPR is a versatile and essential hematologic parameter that provides a dynamic assessment of human health. Regular measurement and interpretation of RPR are crucial for timely diagnosis, effective management, and personalized care in diverse clinical settings.

Regarding the current state of evidence on the relationship between RPR and the mortality of heart failure patients, there is a lack of sufficient data. There is no established evidence specific to the study population in question. Therefore, it is imperative to conduct a retrospective cohort study to investigate the potential association between RPR and the mortality of heart failure patients. The secondary objectives of this study include exploring the potential non-linear dose-response relationship between RPR and the 1-year mortality in heart failure patients, as well as identifying threshold levels of RPR that may impact mortality in patients with heart failure. The study involved a retrospective cohort analysis of 6982 participants from the MIMIC IV database.

2. Materials and methods

2.1. Study design and setting

A retrospective cohort study using patient data from patients hospitalized for heart failure was conducted. Data were gathered from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (version:2.2), included critical care information of 76,540 patients who had been admitted to intensive care units and treated in hospitals at the Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2008 to 2019 [9]. The database is accessible to anybody who has passed the Collaborative Institutional Training Initiative exam (Certification number 52219361 for Tang and 60071489 for Zhang). After obtaining permission, we downloaded the database to the local database and used Structured Query Language (SQL) with PostgreSQL (version 13.0) and Navicat software (version 16.0) to identify the cohort and extract the relevant clinical information. Specifically, for clinical parameters with multiple outcomes during a patient's hospitalization, only the initial outcome was included. Moreover, each variable extraction underwent double-checking by two individuals to ensure data accuracy and reliability.Considering that this was a retrospective study and all patients in this study were extracted from a public database, informed consent was waived. This cohort study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

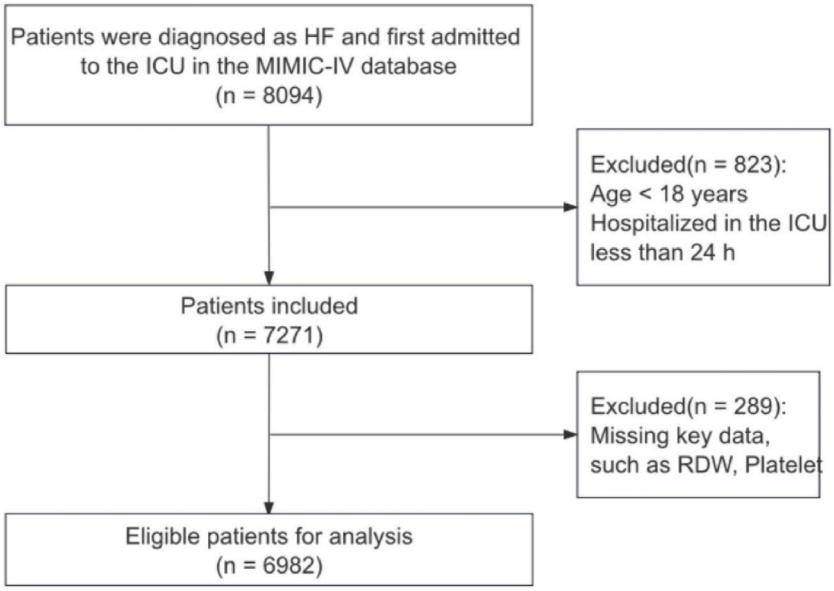

Fig. 1. The flowchart of patients' selection.
Abbreviations: ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV; RDW, red blood cell distribution width.

2.2. Patients

Patients first admitted to the intensive care unit were identified in the MIMIC-IV database from 2008 to 2019. The inclusion criteria were as follows: adult patients with heart failure admitted to the ICU (age ≥18 years); heart failure defined as International Classification of Disease (ICD), Ninth or Tenth Revision (Supplementary Table 1). Of the 8094 patients extracted from the MIMIC-IV database, 823 were excluded because of hospitalized in the ICU less than 24 h. In addition, 289 patients were excluded because of missing key data, such as red blood cell distribution width (RDW) and platelet. Finally, 6982 patients with heart failure were included in this study (Fig. 1). Survival information was extracted from a table named 'patients' from the MIMIC-IV database. Data regarding the length of hospital stay were extracted from the table named 'admissions' of the MIMIC-IV database.

2.3. Covariates

Our variable selection was based on the recommendations from Refs. [6,10,11] and clinical practice experience, aiming to comprehensively reflect patients' demographic characteristics, clinical manifestations, comorbidities, laboratory test results, and treatment conditions, laying a solid data foundation for subsequent analyses. RPR, the main factor we intended to study, was calculated as follows: RPR=RDW (%)/platelet count (K/uL). The baseline RDW and platelet count obtained was the first time value measured within 24 h of ICU admission in the MIMIC-IV database. The baseline RDW and platelet count used to calculate RPR were the first recorded values measured simultaneously within 24 h of ICU admission in the MIMIC-IV database, cross-verified by two independent reviewers.

We included the following variables of enrolled participants in the database based on published literature and clinical experience: 1) demographic characteristics: age, sex, ethnicity, marital status, insurance, body mass index (BMI) [the calculation formula for BMI is: weight(kg)/height(m)2] 2) Physical examination: heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP). 3) Comorbidities: myocardial infarct, atrial fibrillation, hypertension, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease (CKD), diabetes, cancer. 4)Laboratory tests measured the first time within 24 h of ICU admission: hemoglobin, RDW, white blood cell (WBC), platelet, prothrombin time (PT), creatinine, potassium, sodium, chloride, PH. 5) Medications: angiotensin converting enzyme inhibitor/angiotension receptor antagonists(ACEI/ARB), beta-blockers, aspirin, warfarin, vasoactive drugs(including dobutamine, dopamine, vasopressin, phenylephrine, norepinephrine, nitrate, nesiritide, epinephrine).6)Treatments: coronary artery bypass graft (CABG), PCI(percutaneous coronary intervention), mechanical ventilation, hemodialysis).

Another factor to consider is the first 24-h Sequential Organ Failure Assessment (SOFA) score, the Simplified Acute Physiology Score II(SAPSII) score, as well as Charlson comorbidity index. SOFA score was designed to objectively assess the organ function from six aspects: respiration, coagulation, liver, cardiovascular, central nervous system, and renal. Each item was scored 0–4 points, and the higher the score, the more severe the organ dysfunction was reflected [12]. SAPSII score was assessed based on age, 12 physiological variables (heart rate, SBP, body temperature, PaO2/FiO2 ratio, urinary output, serum urea or serum urea nitrogen level, WBC count, serum potassium level, serum sodium level, serum bicarbonate level, bilirubin level, and Glasgow Coma Scale score), type of admission, and 3 chronic diseases (acquired immuno-deficiency syndrome, haematological malignancy, and metastatic cancer).The higher score indicated the more severe condition [13]. Charlson Comorbidity Index (CCI) consisted of 19 items corresponding to different medical comorbid conditions is a tool used to predict mortality by classifying or weighting comorbid conditions. It assigns a score to various pre-existing medical conditions, with higher scores indicating a greater comorbidity burden [14].

2.4. Outcome

The outcome of this study was 1-year mortality from the moment of admission to the ICU.

2.5. Statistical analysis

Histogram distribution, Q-Q plot, and Kolmogorov-Smirnov test were utilized to assess the normality of the variables. Normally distributed continuous variables were reported as mean ± standard deviation (SD), while skewed continuous variables were represented as median (interquartile range [IQR]). Categorical variables were expressed as frequencies and percentages (%). Statistical analysis for continuous variables between groups was conducted using either the independent samples Student's t-test or Mann-Whitney *U* test, depending on the distribution normality. Categorical data were compared using the chi-square test as deemed appropriate. We used dummy variables to indicate missing covariate values.

We adopted multi-variable Cox regression analyses and smooth curve fitting to assess the independent association between RPR and in-hospital mortality. We further applied a two-piecewise linear regression model using a smoothing curve to examine the nonlinear association between platelet count and1-year mortality. A likelihood ratio test was conducted to compare the one-line linear regression model with the two-piecewise linear model. Meanwhile, Cox proportional hazards models with robust estimators were employed to assess the relationship between RPR and 1-year mortality in the study. The selection of confounders was based on clinical relevance and existing scientific literature. Four models were constructed: Model 1 adjust for: none; Model 2 which included adjustments for covariates included in demographics; Model 3, which further adjusted for covariates included in physical examination, scores and laboratory test; Model 4, which additionally adjusted for covariates included in medications and treatments. To evaluate the role of RPR in predicting short-term and long-term prognosis, we constructed binary logistic regression models and Cox regression models to analyze the association between RPR and in-hospital mortality risk and 1-year mortality risk, respectively. We also

conducted comparative analyses with red blood cell distribution width (RDW) and platelet count (PLT) alone.

We utilized a restricted cubic spline model to construct smooth curves in order to investigate potential non-linear dose-response relationships between RPR and mortality. According to Chen 's recommendations [15], we set 3 knots during the fitting process, located at the 25th, 50th, and 75th percentiles of RPR. Non-linearity was assessed by introducing a quadratic term into the regression models. In cases where a non-linear correlation was identified, a two-piecewise regression model was employed to determine the threshold effect of RPR on mortality. We performed Kaplan-Meier survival curve analysis and log-rank tests to compare the survival curves between high RPR group and low RPR group, divided by the cutoff value of RPR, to visually present the association between RPR levels and patient survival. Additionally, we constructed ROC curves for the RPR + SOFA and RPR + SAPS II models and compared them with the ROC curves of the SOFA score and SAPS II score alone to evaluate whether RPR could enhance the predictive performance of these scoring systems.

Subgroup analysis was conducted to explore the association between RPR and mortality based on subgroup variables. In the data analysis process, we noticed missing values for some variables. To address the missing data and reduce potential bias, we employed multiple imputation methods. Specifically, we used the "mice" package in R software and performed multiple imputation using chained equations, generating 5 imputed datasets. During the imputation process, we constructed imputation models based on other complete variables and used methods such as logistic regression and predictive mean matching to estimate missing values for categorical and continuous variables, respectively (Table S2).

All statistical analyses were carried out using R Statistical Software (Version 4.2.2, http://www.R-project.org, The R Foundation) and Free Statistics analysis platform (Version 1.9, Beijing, China, http://www.clinicalscientists.cn/freestatistics). A two-tailed test was performed and $p < 0.05$ was considered statistically significant.

3. Results

We enrolled 6982 patients with a mean age of 72 ± 13.3 years. Among them, 69.5 % were of white, and 58.0 % were male. The overall prevalence of 1 year mortality was 36.31 %. Table 1 presents the general characteristics of the participants based on the presence of 1 year mortality. Participants with mortality were observed to be older, with a higher proportion of males, lower BMI, lower eGFR, higher in SAPSII, SOFA and CCI, and a higher likelihood of having atrial fibrillation, chronic pulmonary disease, chronic kidney disease, diabetes, and cancer (all $P < 0.05$). However, there were no significant differences among the two groups in terms of ethnicity, SBP, DBP, myocardial infarction, vasoactive agents, and PCI.

Tables S3 and S4 present the associations of RPR, RDW, and PLT levels with in-hospital mortality risk and 1-year mortality risk, respectively After adjusting for various confounding factors (Model 4), RPR was significantly associated with in-hospital mortality risk (OR 1.89, 95 % CI 1.06–3.39). In contrast, the predictive ability of RDW and PLT levels alone was weaker, with the OR value of RDW (1.08, 95 % CI 1.05–1.11) being significantly lower than that of RPR, and the OR value of PLT (1.00, 95 % CI 1.00–1.00) being close to 1. RPR was an independent predictor of 1-year mortality risk, with a fully adjusted HR of 1.38 (95 % CI 1.06–1.81). In comparison, the predictive ability of RDW and PLT was weaker. Univariate Cox and multivariable Cox regression analysis of risk factors for 1-year mortality in patients with heart failure is reported in Table 2. We found age, physical examination, scores, history of chronic kidney disease, history of cerebrovascular disease, eGFR, PT, ACEI/ARB, beta-blockers, warfarin, aspirin, CABG and hemodialysis were independent risk factors for in-hospital mortality in this cohort (all $P < 0.05$). In the multivariable Cox proportional hazard model, after adjusting for potential confounders as shown in Table 2, RPR was analyzed as a continuous variable (per 1 unit) and found to be inversely associated with the risk of mortality (hazard ratio [HR] = 1.38, 95 % CI = 1.06–1.81, P = 0.018) (Table 3).

In order to investigate the presence of a dose-response relationship between RPR levels and the incidence of mortality, we conducted a smoothing function analysis. We observed that the relationship between RPR and mortality was non-linear. Following adjustment for potential confounders, we identified a nonlinear association between RPR and mortality (P for nonlinearity = 0.001, as shown in Fig. 2).

Data were fit to a piecewise multivariate Cox regression model and found two different slopes. The risk of mortality was found to be positively correlated with RPR levels up to a peak at 0.104 (0.063–0.145) ($P = 0.003$). On the left side of the inflection point, the HR was 0.046(95%CI: 0.004–0.546, p = 0.0148). On the right side of the inflection point, the HR was 2.656 (95%CI: 1.692–4.17, $p < 0.001$). It suggests that the risk of 1-year mortality started to decrease by 95.4 % per RPR change until RPR of 0.104. Then the risk of 1-year mortality started to increase by 1.656 per RPR change (P-value for non-linear test was <0.001) (Table 4). The Log-rank test indicated a significant difference between the two survival curves ($p < 0.001$) (Fig. 3). Patients in the high RPR group exhibited significantly lower 1-year survival rates compared to those in the low RPR group. This finding visually demonstrates that heart failure patients with elevated RPR levels have a poorer prognosis. Incorporating RPR into the SOFA score (AUC: 0.626) and SAPS II score (AUC: 0.683) models significantly improved their predictive ability for 1-year mortality risk prediction (Fig. 4).

In several subgroups, stratified analysis was performed to assess potential effect modifications on the relationship between RPR and 1-year mortality. No significant interactions were found in any subgroups after stratifying by age, sex, BMI, eGFR, myocardial infarction, hypertension, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, diabetes, cancer and SOFA. The subgroup analysis did not reveal any evidence of effect modification or interaction based on common risk factors for mortality, as indicated by the P values for interaction, all of which were greater than 0.05 (Figure S1).

4. Discussion

In this extensive retrospective cohort study of MIMIC IV patients, we have demonstrated that red blood cell distribution width-

Table 1
Baseline characteristics of the study participants.

Variables	Total (n = 6982)	Survival (n = 4447)	Death (n = 2535)	*P-value*
Demographics				
Age (years)	72.01 ± 13.32	69.76 ± 13.51	75.96 ± 11.99	<0.001
Gender (%)				0.022
Female	2932 (41.99)	1822 (40.97)	1110 (43.79)	
Male	4050 (58.01)	2625 (59.03)	1425 (56.21)	
Ethnicity (%)				0.053
White	4855 (69.54)	3111 (69.96)	1744 (68.8)	
African American	658 (9.42)	416 (9.35)	242 (9.55)	
Others	600 (8.59)	399 (8.97)	201 (7.93)	
Unknown	869 (12.45)	521 (11.72)	348 (13.73)	
Marital status (%)				<0.001
Single	1504 (21.54)	1021 (22.96)	483 (19.05)	
Married	3231 (46.28)	2114 (47.54)	1117 (44.06)	
Divorced	531 (7.61)	347 (7.8)	184 (7.26)	
Widowed	1195 (17.12)	678 (15.25)	517 (20.39)	
Unknown	521 (7.46)	287 (6.45)	234 (9.23)	
Insurance (%)				<0.001
Medicare	4032 (57.75)	2380 (53.52)	1652 (65.17)	
Medicaid	308 (4.41)	225 (5.06)	83 (3.27)	
Others	2642 (37.84)	1842 (41.42)	800 (31.56)	
BMI (kg/m2)	30.02 ± 8.13	30.80 ± 8.19	28.63 ± 7.82	<0.001
Physical examination				
Heart rate (bpm)	87.63 ± 19.73	86.41 ± 19.04	89.79 ± 20.70	<0.001
Systolic blood pressure (mmHg)	119.56 ± 23.84	119.85 ± 23.36	119.07 ± 24.66	0.187
Diastolic blood pressure (mmHg)	64.75 ± 17.63	64.52 ± 16.76	65.16 ± 19.06	0.14
Scores				
SAPSII (score)	41.63 ± 13.73	38.56 ± 12.45	47.03 ± 14.20	<0.001
SOFA (score)	6.68 ± 3.79	6.05 ± 3.47	7.79 ± 4.06	<0.001
CCI (score)	7.40 ± 2.49	6.84 ± 2.36	8.40 ± 2.39	<0.001
Co-morbidities (%)				
Myocardial infarction	2483 (35.56)	1544 (34.72)	939 (37.04)	0.051
Atrial fibrillation	3594 (51.48)	2178 (48.98)	1416 (55.86)	<0.001
Hypertension	2015 (28.86)	1427 (32.09)	588 (23.2)	<0.001
Cerebrovascular disease	958 (13.7)	542 (12.2)	416 (16.4)	<0.001
Chronic pulmonary disease	2597 (37.20)	1604 (36.07)	993 (39.17)	<0.001
Chronic kidney disease	2628 (37.64)	1429 (32.13)	1199 (47.3)	<0.001
Diabetes	2830 (40.53)	1739 (39.11)	1091 (43.04)	<0.001
Cancer	620 (8.88)	246 (5.53)	374 (14.75)	<0.001
Laboratory test				
RPR (ratio)	0.08 (0.06, 0.11)	0.08 (0.06, 0.11)	0.08 (0.06, 0.12)	<0.001
Hemoglobin (g/dL)	10.24 ± 2.24	10.30 ± 2.31	10.13 ± 2.13	<0.001
RDW (%)	15.52 ± 2.36	15.05 ± 2.08	16.36 ± 2.59	<0.001
WBC (K/μL)	12.88 ± 8.74	12.66 ± 8.33	13.26 ± 9.41	<0.001
Platelet (K/μL)	186.0 (136.0, 251.0)	183.0 (136.5, 245.0)	192.0 (134.0, 261.5)	0.011
PT (s)	15.10 (13.20, 18.34)	15.00 (13.10, 17.50)	15.50 (13.30, 20.67)	<0.001
Creatinine(mg/dL)	1.20 (0.90, 1.90)	1.10 (0.80, 1.60)	1.50 (1.00, 2.50)	<0.001
eGFR (ratio)	55.76 (32.46, 83.68)	64.25 (40.80, 88.41)	41.52 (22.84, 65.86)	<0.001
Potassium (mmol/L)	4.29 ± 0.72	4.24 ± 0.67	4.38 ± 0.80	<0.001
Sodium (mmol/L)	138.45 ± 5.08	138.61 ± 4.54	138.18 ± 5.91	<0.001
Chloride (mmol/L)	103.03 ± 6.92	103.82 ± 6.50	101.64 ± 7.40	<0.001
PH	7.37 ± 0.09	7.38 ± 0.08	7.36 ± 0.10	<0.001
Medications (%)				
ACEI/ARB	3094 (44.31)	2339 (52.6)	755 (29.78)	<0.001
Beta-blockers	4209 (60.28)	2926 (65.8)	1283 (50.61)	<0.001
Aspirin	3835 (54.93)	2692 (60.54)	1143 (45.09)	<0.001
Warfarin	1294 (18.53)	959 (21.57)	335 (13.21)	<0.001
Vasoactive agents	5071 (72.63)	3228 (72.59)	1843 (72.7)	0.918
Treatments (%)				
CABG	1112 (15.93)	980 (22.04)	132 (5.21)	<0.001
PCI (%)	408 (5.84)	264 (5.94)	144 (5.68)	0.661
Mechanical ventilation (%)	6603 (94.57)	4183 (94.06)	2420 (95.46)	0.013
Hemodialysis (%)	927 (13.28)	389 (8.75)	538 (21.22)	<0.001
Heart failure type (%)				
AHF	2730 (39.10)	1699 (38.21)	1031 (40.67)	0.042
CHF	3328 (47.67)	2027 (45.58)	1301 (51.32)	<0.001
Length of hospitalization (days)	5.46 ± 6.34	4.76 ± 5.51	6.69 ± 7.43	<0.001

Abbreviations: BMI, body mass index; AHF, acute heart failure; CHF, Chronic heart failure; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index; RPR, cell distribution width to platelet ratio; RDW, red blood cell distribution

width; WBC, white blood cell; PT, prothrombin time; eGFR, estimate glomerular filtration rate; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotension receptor antagonists; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table 2
Univariate Cox and Multivariable Cox analysis evaluating the association between RPR and 1 year morality.

Variables	Univariate Cox analysis		Multivariable Cox analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Demographics				
Age (years)	1.03 (1.03–1.04)	<0.001	1.02 (1.02–1.03)	<0.001
Gender (Male vs Female)	0.91 (0.84–0.99)	0.022	0.95 (0.87–1.04)	0.276
Race				
White	Ref.		Ref.	
African American	1.02 (0.89–1.16)	0.805	0.95 (0.83–1.1)	0.485
Others	0.92 (0.79–1.06)	0.243	0.92 (0.79–1.07)	0.272
Unknown	1.21 (1.08–1.36)	0.001	1.12 (0.97–1.3)	0.117
Marital status				
Single	Ref.		Ref.	
Married	1.1 (0.99–1.22)	0.091	0.95 (0.85–1.06)	0.39
Divorced	1.08 (0.92–1.29)	0.349	1.09 (0.91–1.29)	0.346
Widowed	1.46 (1.29–1.65)	<0.001	0.98 (0.85–1.12)	0.746
Unknown	1.66 (1.42–1.94)	<0.001	1.25 (1.03–1.51)	0.023
Insurance				
Medicare	Ref.		Ref.	
Medicaid	0.59 (0.47–0.74)	<0.001	1.08 (0.85–1.36)	0.532
Others	0.69 (0.63–0.75)	<0.001	0.98 (0.9–1.07)	0.7
BMI	0.97 (0.96–0.97)	<0.001	0.98 (0.97–0.98)	<0.001
Physical examination				
Heart rate (bpm)	1.01 (1.01–1.01)	<0.001	1 (1~1.01)	<0.001
Systolic blood pressure (mmHg)	1 (1~1)	0.09	1 (1~1)	0.004
Diastolic blood pressure (mmHg)	1 (1~1)	0.093	1 (1~1.01)	0.006
Scores				
CCI	1.04 (1.03–1.04)	<0.001	1.01 (1.01–1.01)	<0.001
SAPSII	1.11 (1.1–1.12)	<0.001	1.05 (1.03–1.06)	<0.001
SOFA	1.21 (1.19–1.23)	<0.001	1.13 (1.1–1.16)	<0.001
Co-morbidities (%)				
Myocardial infarction	1.1 (1.01–1.19)	0.026	1.08 (0.99–1.19)	0.091
Atrial fibrillation	1.25 (1.16–1.35)	<0.001	1.04 (0.96–1.14)	0.328
Hypertension	0.69 (0.63–0.76)	<0.001	0.97 (0.87–1.08)	0.598
Diabetes	1.13 (1.04–1.22)	0.003	1 (0.92–1.1)	0.92
Chronic kidney disease	1.64 (1.51–1.77)	<0.001	0.79 (0.7–0.89)	<0.001
Chronic pulmonary disease	1.1 (1.01–1.19)	0.025	0.95 (0.87–1.04)	0.263
Cerebrovascular_disease1	1.35 (1.22–1.5)	<0.001	1.21 (1.08–1.36)	0.001
Cancer	2.16 (1.93–2.41)	<0.001	1.09 (0.95–1.26)	0.199
Laboratory test				
eGFR	0.98 (0.98–0.99)	<0.001	1 (0.99–1)	<0.001
PT (s)	1.02 (1.01–1.02)	<0.001	1.01 (1.01–1.01)	<0.001
WBC (K/μL)	1.01 (1~1.01)	<0.001	1 (1~1)	0.619
RPR	2.76 (2.27–3.36)	<0.001	1.38 (1.06–1.81)	0.018
Medications (%)				
ACEI/ARB	0.44 (0.4–0.48)	<0.001	0.6 (0.55–0.66)	<0.001
Beta-blockers	0.59 (0.54–0.63)	<0.001	0.85 (0.78–0.92)	<0.001
Warfarin	0.59 (0.53–0.67)	<0.001	0.7 (0.62–0.79)	<0.001
Aspirin	0.6 (0.55–0.65)	<0.001	0.8 (0.73–0.87)	<0.001
Vasoactive agents	1.05 (0.97–1.15)	0.238	1 (0.9–1.1)	0.939
Treatments (%)				
PCI	0.95 (0.81–1.13)	0.585	1.11 (0.93–1.33)	0.241
CABG	0.24 (0.2–0.29)	<0.001	0.31 (0.26–0.37)	<0.001
Hemodialysis	2.23 (2.03–2.45)	<0.001	1.33 (1.18–1.49)	<0.001
Mechanical ventilation	1.33 (1.11–1.61)	0.003	1.2 (0.99–1.45)	0.064

Note: Multivariable Cox analysis adjust for demographics, physical examination, Scores, laboratory test, medications and treatments.
Abbreviations: BMI, body mass index; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index; RPR, cell distribution width to platelet ratio; WBC, white blood cell; PT, prothrombin time; eGFR, estimate glomerular filtration rate; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotension receptor antagonists; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; Ref., reference.

platelet ratio (RPR) is independently associated with a 38 % increase in the risk of 1-year mortality for the first time. Notably, the analysis using restricted cubic splines indicated a U-shaped relationship between the levels of RPR and the risk of 1-year mortality (P nonlinearity <0.05), with the lowest risk observed at 0.104. We found that incorporating RPR into the SOFA and SAPS II models

Table 3
The relationship between the RPR ratio and 1 year mortality in a Cox regression model.

Models	HR (95 % CI)	*P* -value
Model 1	2.76 (2.27, 3.36)	<0.001
Model 2	2.9 (2.36, 3.56)	<0.001
Model 3	1.76 (1.35–2.31)	<0.001
Model 4	1.38 (1.06–1.81)	0.018

Note: Model 1 adjust for: none; Model 2 adjust for: covariates included in demographics; Model 3 adjust for: model 2 +covariates included in physical examination, Scores and laboratory test; Model 4 adjust for: model 3 + covariates included in medications and treatments.
Abbreviations: HR, hazard ratio; CI, confidence interval.

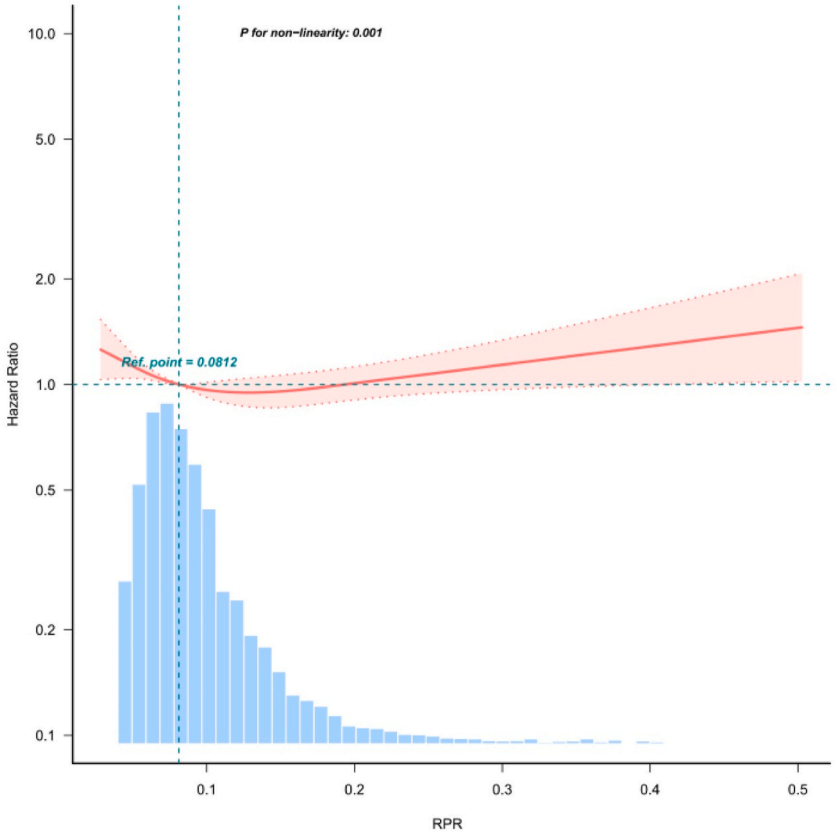

Fig. 2. Dose-response relationship between the RPR and all-cause mortality in patients with heart failure.
Note : Adjusted for demographics, physical examination, Scores, laboratory test, medications and treatments. Solid and dashed lines indicate the predicted value and 95 % CI.

Table 4
The non-linearity relationship between RPR and 1 year mortality.

Threshold of RPR	HR	95 % CI	*P*-value
<0.104	0.046	0.004–0.546	0.0148
≥0.104	2.656	1.692–4.17	<0.001
Non-linear test			<0.001

Note: Adjusted for demographics, physical examination, Scores, laboratory test, medications and treatments.
Abbreviations: HR, hazard ratio; CI, confidence interval.

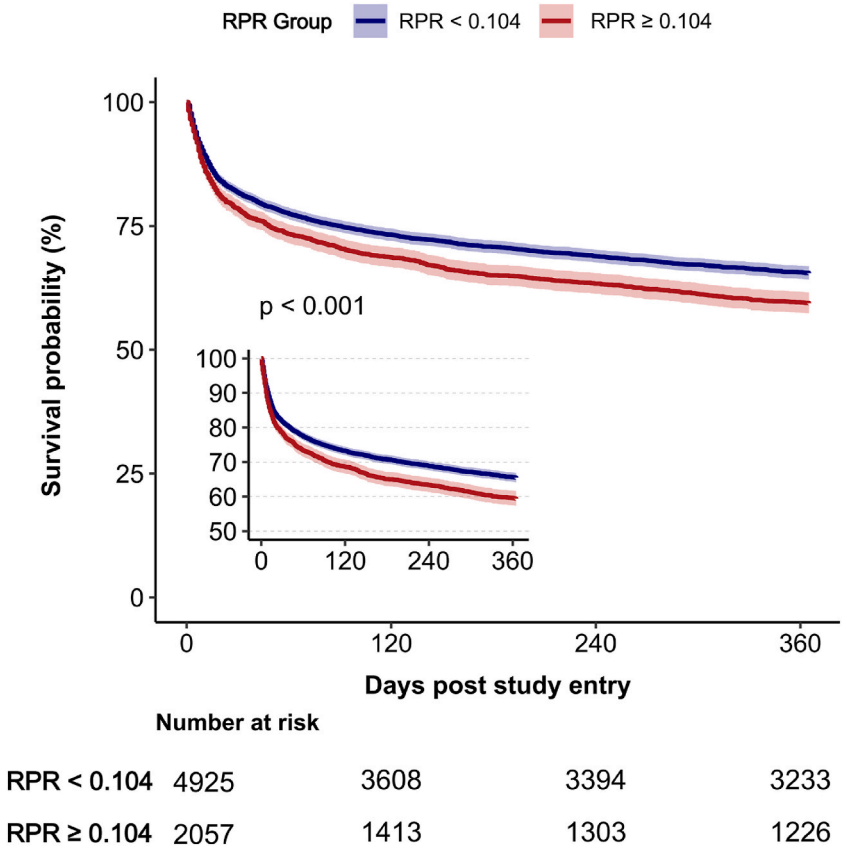

Fig. 3. K–M curve for 1-year mortality
Note: Group 1: RPR <0.104, Group 2: RPR ≥0.104.

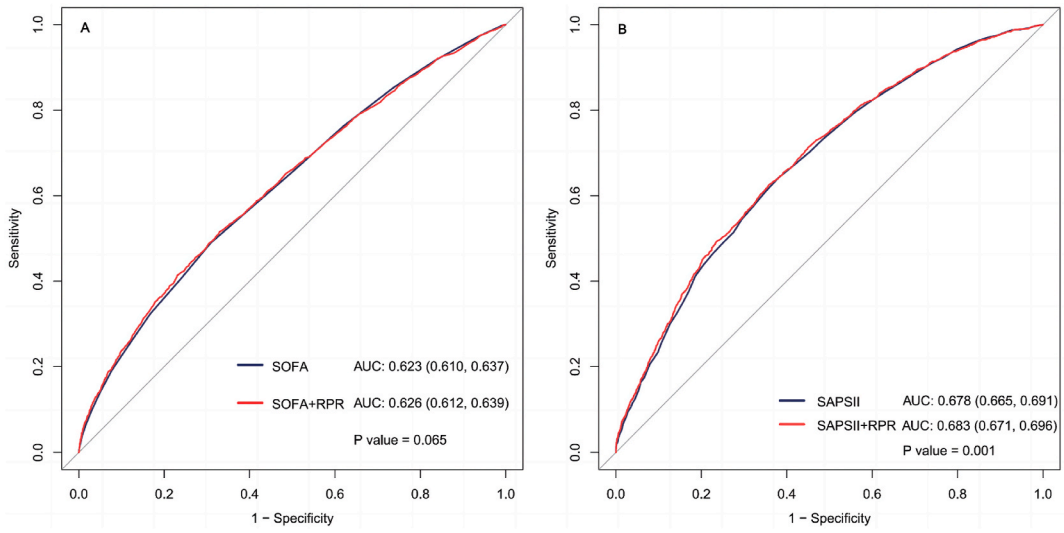

Fig. 4. Incremental effect of the RPR for predicting 1-year mortality
Abbreviations: RPR, Red cell distribution width to platelet ratio; SOFA, sequential organ failure assessment; SAPSII, simplified acute physiology score II; AUC, The area under the curve.

significantly improved their accuracy in predicting 1-year mortality risks, with the RPR + SAPS II model showing the most significant improvement. Subsequent exploratory subgroup analysis revealed no significant interactions. These findings hold significant clinical implications.

Our study investigated the nonlinear relationships of RPR with in hospital and 1-year mortality among patients with heart failure in the MIMIC IV database. Our findings align with those of other observational studies. Previous research has delved into the association between RPR and heart failure. For instance, L et al. identified a significant link between RPR and 28-day readmission in the heart failure population (OR = 1.082, 95 % CI = 1.012–1.158, P = 0.0212) [8]. Additionally, a cross-sectional study based on the National Health and Nutrition Examination Survey 1999–2020 highlighted a significant association between RPR and cardiovascular disease, the ORs with 95 % CIs across the second to fourth quartiles were 1.04 (0.92–1.17), 1.22 (1.05–1.42) and 1.64 (1.43–1.87) for the RPR compared with the lowest quartile (p for trend <0.0001), respectively [3]. Recent studies have begun to shed light on the connection between RPR and mortality. a recent prospective longitudinal cohort study involving patients with acute myocardial infarction demonstrated a noteworthy connection between RPR and 180-day in-hospital mortality (HR: 2.677, 95 % CI: 1.159–6.188, P = 0.021) [7]. Moreover, pooled analyses of prospective cohort studies investigating the relationship between RPR and mortality have affirmed these findings. Furthermore, we found that RPR can provide valuable supplementary information to the SOFA and SAPS II scoring systems, enhancing their predictive capability. Our study builds upon and reinforces these existing findings within the MIMIC IV patient cohort, revealing that a significant association between RPR and the risk of in-hospital and 1-year mortality.

The magnitudes of the significant associations between RPR and incident mortality were modest yet consistent across different event subtypes, including chronic pulmonary disease and cancer, as well as across various subgroups based on age, sex, BMI, eGFR, SOFA and cardiovascular disease risk factors such as myocardial infarction, hypertension, chronic kidney disease, and diabetes (with the exception of cerebrovascular disease: adjusted HR = 0.43, 95 % CI = 0.08–2.31). The observed significant association with mortality aligns with the current body of literature. Our research results showed that RPR not only predicted the long-term prognosis of heart failure patients but also was significantly associated with in-hospital mortality risk after adjusting for confounding factors, suggesting that RPR may also have some value in assessing early prognosis. Compared to RDW and PLT, RPR, as an indicator that comprehensively combines anemia, platelet count, and other pathological factors, exhibited a significant advantage in predicting prognosis, which may be due to its ability to more comprehensively reflect the patient's inflammatory state and disease severity. Therefore, RPR can not only be used as an auxiliary prognostic assessment indicator in clinical practice but also provide clues for further mechanistic research.

The possible mechanism between RPR and increased risk of death in heart failure patients is as follows: 1) Inflammation: Heart failure is often accompanied by a systemic inflammatory response, and an increase in RDW has been considered a marker of inflammation. Inflammation can lead to increased heterogeneity in the production and maturation of red blood cells, thereby increasing RDW [16]. Inflammation can also reduce platelet by shortening the lifespan of platelets and/or affecting their production, thus raising RPR [17]. Therefore, an increase in RPR reflects the level of inflammation in patients with heart failure, where inflammation is a key factor in the deterioration and poor prognosis of heart failure [18]. 2) Hypoxia and tissue ischemia: Heart failure leads to a reduced cardiac pumping function, which can cause insufficient oxygenation of the body's tissues and organs. Hypoxic conditions disrupt the normal production and maturation of red blood cells, leading to an increase in RDW [19]. At the same time, hypoxia can activate various platelet activation pathways, affecting platelet count and function, which may be reflected in changes in PLT [20]. Thus, an increase in RPR can partially reflect the degree of hypoxia and tissue ischemia in patients with heart failure. 3) Tendency for thrombosis: Patients with heart failure have reduced blood flow, increasing the risk of thrombosis [21]. Platelets play a key role in the formation of thrombi. A decrease in platelet count may reflect an increased consumption of platelets, a marker of thrombotic activity [22]. Therefore, an increase in RPR might reflect an increased risk of thrombosis in patients with heart failure.4) Malnutrition: Patients with heart failure may experience malnutrition, especially iron deficiency anemia, which affects the production and maturation of red blood cells, leading to an increased RDW [23,24]. Malnutrition can also affect the production of platelets [25], and these factors together may lead to an increase in RPR. 5) Cardiac remodeling and endothelial dysfunction: Heart failure can lead to remodeling of the heart's structure and function, as well as dysfunction of the vascular endothelium [26]. These changes may affect the number and function of red blood cells and platelets through various mechanisms, thereby affecting RPR. In conclusion, our study contributes to the growing body of evidence on the association between RPR and mortality, further research is needed to validate our results and delve into the intricate relationship and potential underlying mechanisms.

This study presents novel findings on the association between RPR and the risk of mortality in patients with heart failure based on data gathered from MIMIC-IV database. The research approach adopted in this study was rigorous and demonstrated both novelty and potential therapeutic implications. The study offers robust evidence on the relationship between RPR and mortality risk in patients with heart failure, accounting for potential confounders and biases meticulously.

Our study found a U-shaped association between RPR and 1-year mortality risk in heart failure patients, providing evidence-based support for the clinical application of RPR. Firstly, as a simple, economical, and readily available biochemical indicator, RPR can serve as an auxiliary tool for evaluating prognosis risk and risk stratification in heart failure patients, facilitating the development of individualized and precise medical decisions. Secondly, for patients with abnormal RPR values, clinicians should further analyze the underlying pathophysiological mechanisms, such as anemia, inflammation, and malnutrition, and provide timely interventions and corrections to improve prognosis. Dynamic monitoring of RPR can also aid in evaluating treatment efficacy and guiding individualized treatment adjustment strategies. Moreover, future clinical trials may consider utilizing RPR as an alternative efficacy evaluation indicator, exploring novel treatment strategies to improve heart failure prognosis by modulating RPR levels, thereby providing new intervention targets for pharmaceutical or non-pharmaceutical interventions. In summary, our research findings establish an evidence-based foundation for the application of RPR in secondary prevention of heart failure.

Several limitations should be acknowledged in the interpretation of the findings. Firstly, even though regression models, stratified analyses, and sensitivity analysis were performed, residual confounders potentially exist, as with all retrospective analyses. Secondly, RPR measurements were used initial blood counts on admission to minimize treatment effects, the influences of long-term medication regimens on HF outcomes still require further elucidation. Third, due to the nature of the simulation database, this study lacks some potential variables, such as the impacts of inflammation, anemia and EPO on RDW, precluding detailed analysis of the underlying mechanisms linking these factors with RDW. Moreover, as a retrospective study using the MIMIC-IV database, there is an inherent risk of selection bias, and our findings may not fully represent the outpatient heart failure population or account for potential confounders such as lifestyle and genetic factors. An important limitation is the inability to continuously measure and analyze RPR changes, which restricted our in-depth analysis of RPR change patterns and their associations with prognosis. Finally, the current findings were derived from the MIMIC-IV database, a single-center study, limiting the external validity and generalizability of our findings to other populations. Future research with multi-center, multi-ethnic cohorts is warranted to validate and expand upon the current results.

5. Conclusion

Our study revealed a non-linear, U-shaped association between RPR and 1-year mortality among heart failure patients, indicating increased risk with both low and high RPR levels. The optimal RPR cutoff of 0.104 was identified. These findings suggest RPR may be a relevant biomarker for mortality risk stratification in heart failure.

Data accessibility

Datasets were sourced from the MIMIC-IV database (version 2.2), which is available at https://physionet.org/content/mimiciv/2.2/. Authorization codes 52219361 for Tang and 60071489 for Zhang facilitated access.

Ethical considerations

Compliant with local and institutional regulations, this research on human subjects did not necessitate ethical approval or subsequent reviews. Additionally, obtaining written informed consent was not required by either national laws or institutional policies.

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CRediT authorship contribution statement

Shanshan Tang: Writing – original draft, Software, Project administration, Data curation, Conceptualization. **Zhiqiang Zhang:** Methodology, Formal analysis, Conceptualization. **Yulong Wang:** Writing – original draft, Resources. **Yongle Li:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to polish. After using this tool or service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35796.

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