Article

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The Relationship between Hematocrit Levels and Major Adverse Cardiovascular Events in Patients with Acute Myocardial Infarction

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Background: The relationship between hematocrit (HCT) levels and the occurrence of major adverse cardiovascular events (MACEs) in patients with acute myocardial infarction (AMI) remains unexplored. A better understanding of this interplay may enhance the prognosis and management of AMI patients.

Methods: Between January 2021 and August 2022, clinical data were collected from patients diagnosed with AMI at 10 tertiary healthcare institutions in China. A total of 1946 eligible participants were included and divided into three groups based on sex-specific tertiles of HCT levels upon admission: 648 patients with low HCT levels, 649 patients with intermediate HCT levels, and 649 patients with high HCT levels. Follow-up approaches included hospital outpatient visits, inpatient stays, and telephone calls for 180 days. The primary endpoint was the occurrence of MACEs. Influential factors, including general information, admission status, and supplementary examination results that differed across the cohorts, were analyzed. Cox regression analysis was employed to evaluate the 180-day MACE rates and HCT levels in patients with AMI. To assess the reliability of the findings, three sensitivity analyses and subgroup analyses were performed.

Results: During this time, 136 individuals in the low HCT group, 77 in the intermediate HCT group, and 73 in the high HCT group experienced endpoint events. With all covariates controlled, the Cox regression analysis indicated that the low HCT group had a higher risk of MACEs compared to the intermediate HCT group [hazard ratio (HR) = 1.44, 95% confidence interval (CI) = 1.07–1.95, p = 0.017]. The low HCT group also presented a higher risk of acute coronary syndrome (HR = 1.57, 95% CI = 1.06–2.32, p = 0.024). However, the high and intermediate HCT groups exhibited comparable prognoses for AMI. The limited cubic spline plot revealed that HCT values between 41.58% and 45.36% implied a protective effect against MACEs. These results were further verified by sensitivity analysis, and the subgroup analysis showed no variable interaction.

Conclusions: Our findings indicate that low HCT levels in patients with AMI increase the incidence of MACEs within 180 days, offering new insights into the prognosis and management of AMI patients.

Clinical Trial Registration: ChiCTR2200066456.

Keywords: myocardial infarction; hematocrit; major adverse cardiovascular events; short-term prognosis

Introduction

Cardiovascular diseases are characterized by high incidence, morbidity, and mortality, resulting in a substantial economic burden. The World Health Organization has designated cardiovascular disorders as one of the four most prevalent non-communicable diseases globally. Among all cardiovascular diseases, ischemic heart disease has emerged as the leading cause of mortality in the general population [1]. According to the latest statistics from the China Cardiovascular Disease Report [2], the incidence and mortality of cardiovascular disorders in China continue to rise. In patients with ischemic heart disease, acute myocardial infarction (AMI) is a critical determinant of death [3].

Hematocrit (HCT) measures the proportion of red blood cells in a given volume of whole blood, serving as a crucial factor for key physiological indicators such as blood pressure and cardiac output [4,5]. When HCT levels are low, the blood becomes more fluid and less viscous, thereby reducing the resistance to blood flow in the arteries. The resultant decreased blood pressure enables the heart to pump blood more efficiently, consequently increasing cardiac output. Conversely, when HCT levels are elevated, the

blood becomes more viscous, augmenting the resistance to flow and impeding the blood flow through small vessels, along with increased blood pressure and reduced cardiac output.

In recent years, HCT has garnered increasing attention as a prognostic indicator for various diseases [6–10]. For about 50 years, research has focused on investigating the connection between HCT levels and cardiovascular illnesses. Existing evidence suggests that HCT may affect adverse cardiovascular events, and one study has assessed the impact of HCT on the incidence and mortality of cardiovascular diseases within the general population [11]. However, there is scarce clinical data revealing how HCT affects the prognosis of patients with cardiovascular conditions, especially AMI. Consequently, this research aimed to uncover the relationship between HCT levels and the likelihood of major adverse cardiovascular events (MACEs) in AMI patients.

Materials and Methods

Study Cohort

The participants in this study were from a prospective cohort study (Clinical Trial Registration Number: ChiCTR2200066456, https://www.chictr.org.cn/historyversionpub.html?regno=ChiCTR2200066456, 6 May 2023, Chinese Clinical Trial Registry) investigating the development of Traditional Chinese Medicine (TCM) syndromes, pathogenesis, and etiology of myocardial infarction. The research protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University, in compliance with the principles outlined in the Declaration of Helsinki (Ethics Committee Approval Numbers: 2020-KL-141-IH01, 2020-KL-141-C01).

Clinical data of patients diagnosed with AMI were gathered from 10 tertiary healthcare institutions across China between January 2021 and August 2022. The collected data included basic demographic information, treatment status, comorbidities, laboratory test results, and echocardiography findings. The diagnostic criteria for myocardial infarction were based on the Fourth Universal Definition of Myocardial Infarction, published by the American College of Cardiology in 2018 [12].

The inclusion criteria for AMI were defined according to this diagnostic guideline. The exclusion criteria included: (1) patients with missing or abnormal HCT values (abnormal values were defined as those deviating from the overall mean HCT by $\pm$4 standard deviations); (2) patients with severe primary conditions, such as complicated symptoms affecting the liver, kidneys, hematological system, or malignant tumors; (3) pregnant or lactating women; and (4) patients with incomplete clinical data or unavailable information. Patients were also excluded from the final analysis if they were (1) misdiagnosed, leading to mistaken inclusion, or (2) lacked evaluable records after initial inclusion.

Patients were assigned into three groups based on the sex-specific tertiles of their initial HCT levels upon admission: low, intermediate, and high HCT groups. The cutoff values for HCT tertiles were 40.5% and 45.1% for males, and 35.5% and 39.8% for females. All patients provided written informed consent before participating in the study.

Clinical Endpoints

In this study, participants from the three cohorts were followed for 180 days, with the date of enrollment as the starting point and the occurrence of endpoint events as the termination point. There are several reasons for setting a follow-up period of 180 days. Firstly, 180 days is a common timeframe widely employed in observing cardiovascular events and clinical outcomes. Secondly, this duration is sufficient to capture significant events and changes in the majority of myocardial infarction patients, including recurrent myocardial infarction, rehospitalization, and mortality.

The primary endpoint was a combination of MACEs within 180 days, including cardiovascular mortality, secondary acute coronary syndrome, secondary congestive heart failure, or stroke. The secondary endpoints included all-cause mortality and the three major subgroups of the primary endpoint: cardiovascular mortality, recurrent acute coronary syndrome, and recurrent congestive heart failure. Stroke was not analyzed as a separate secondary endpoint due to the limited number of occurrences (9 cases) during the follow-up period and the resulting low statistical power.

Patients were followed up on the 90th and 180th days after joining the study cohort. Follow-up was conducted through hospital outpatient services, inpatient admissions, or telephone interviews. The total follow-up time for all participants, both available and unavailable for follow-up, was calculated. All follow-up staff members were trained clinical physicians. After the follow-up was completed, two professional clinical physicians randomly selected 10% of enrolled patients for verification of data, including survey questionnaires and telephone follow-up records. No interventions were performed on patients during the follow-up period.

Covariates

Covariates were selected from the following three major categories.

(1) General information, including age, sex, body mass index (BMI), occupation (whether the individual is a farmer, given the higher proportion of cardiovascular deaths in rural areas compared to urban areas in China) [2], and medical history (tobacco use, alcohol consumption, hypertension, diabetes, myocardial infarction, and cerebral infarction).

(2) Admission status, encompassing shock index [13], type of myocardial infarction (ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI)), prehospital delay (<24

h or ≥24 h), presence of cardiac arrest (CA), atrial fibrillation (AF), pulmonary infection (PI), and the presence or absence of percutaneous coronary intervention (PCI) upon admission.

(3) Auxiliary examinations, such as high-sensitivity C-reactive protein (hs-CRP), lipid profiles (triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL)), renal function (serum creatinine (SCr)), serum uric acid (SUA), homocysteine (Hcy), cardiac enzymes (lactate dehydrogenase (LDH), creatine kinase (CK), alanine aminotransferase (ALT)), coagulation parameters (prothrombin time (PT), prothrombin activity (PTA), international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen (FIB), D2-dimer), natriuretic peptides (brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP)), and echocardiography findings (left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD)). Troponin I or troponin T was not included as a covariate due to variations in evaluation methods across different centers.

Statistical Analysis

Statistical analysis was conducted independently by personnel at the Institute of Cardiovascular-Cranial Disease of Zhejiang Chinese Medical University using SPSS 25.0 software (SPSS Inc., Chicago, IL, USA) and R software (version 4.3.0, R Project for Statistical Computing; R Core Team, Vienna, Austria). Comparisons among different HCT groups were performed for general information, admission status, and auxiliary examination variables. Laboratory tests were carried out on the first batch of blood samples collected upon admission, and echocardiography results within the first three days following AMI onset were utilized.

R was employed to handle variables with missing data, eliminating those with missing data exceeding 20% and conducting multiple imputations for variables with missing data less than 20%. Categorical variables were presented as frequencies and percentages, while continuous data were expressed as mean ± standard deviation (SD) or Median (P25, P75).

To compare variables across different HCT groups, chi-square tests, analyses of variance, or the Kruskal-Wallis test were utilized. Pairwise comparisons between HCT groups were conducted using the Bonferroni method for post-hoc analysis.

To mitigate potential confounding effects, variables with $p < 0.05$ in group comparisons were selected as covariates for constructing a multivariate Cox proportional hazard model. To prevent overfitting, the model included at least 10 endpoint events per covariate. With 21 variables meeting the $p < 0.05$ criterion and a sample size allowing for at least 210 endpoint events (286 observed), all 21 covariates were included in the model to investigate the relationship between different HCT levels and the incidence of MACEs in AMI patients. Rigorous data analysis utilized log-rank tests and Kaplan-Meier curves. All statistical tests employed a two-tailed distribution, and differences with *p*-values less than 0.05 were deemed statistically significant unless specified otherwise.

Three sensitivity analyses were conducted. Firstly, to assess the impact of input data, the analysis was repeated after removing input data to validate the consistency of the results. Secondly, to enhance the robustness of prognosis assessment in different HCT groups, the analysis was re-executed excluding patients lost to follow-up. Finally, restricted cubic spline (RCS) analysis was employed to explore the sustained relationship between HCT levels and short-term MACE incidence post-AMI.

Given the influence of factors like sex, age, and smoking history on HCT levels, detailed interactions were analyzed between HCT and various covariates including sex, age (<60 or ≥60 years), smoking history, hypertension, diabetes, type of myocardial infarction (STEMI or NSTEMI), admission delay (<24 h or ≥24 h), PCI status upon admission, and LVEF (<60% or ≥60%). Subgroup analyses were subsequently conducted to explore these interactions further.

Results

The Inclusion and Clinical Characteristics Data of Study Subjects

Fig. 1 illustrates the flowchart of the research process. Initially, 2033 patients were enrolled in the trial. Among them, 32 patients lacked follow-up data and were excluded. Additionally, 20 patients had severe primary diseases (e.g., malignant tumors), 31 patients were missing HCT data, and 4 patients had abnormal HCT values. Ultimately, a total of 1946 patients were included in the study.

To ensure data integrity, we randomly selected 195 patients for further evaluation using survey questionnaires and telephone follow-up. Hospitalization information and survey responses were obtained for all patients, except 11 who could not be reached by phone.

According to the experimental design described previously, three groups were defined: the low HCT group (648 patients; HCT = 40.5% for men and 35.5% for women), the intermediate HCT group (649 patients; HCT = 40.6%–45.1% for men and 35.6%–39.8% for women), and the high HCT group (649 patients; HCT = 45.2% for men and 39.9% for women).

As depicted in Fig. 2, variables with a high number of missing data points—PTA, BNP, BMI, NT-proBNP, LVESD, LVEDD, creatine kinase-isoenzyme (CK-MB), and Hcy—were excluded from the analysis. Those included were LVEF, hs-CRP, D-Dimer, LDH, CK, PTT, TC, LDL, HDL, TG, ALT, FIB, PT, INR, SUA, and SCr.

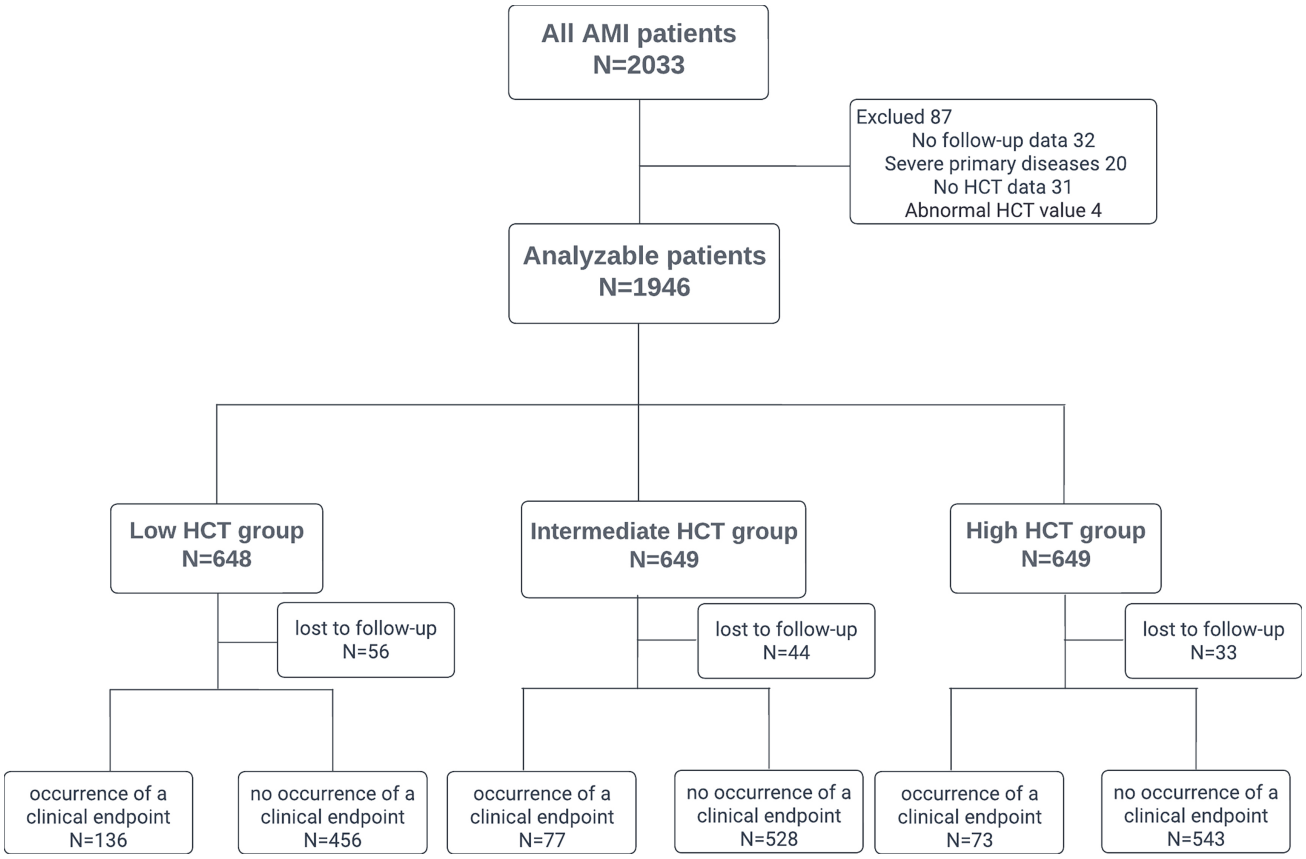

Fig. 1. Flowchart for inclusion, exclusion, grouping, and follow-up. Abbreviations: AMI, acute myocardial infarction; HCT, hematocrit.

Clinical characteristics of the three groups were collected and summarized in Table 1. There were no statistically significant differences observed for male gender, farmer occupation, alcohol history, hypertension, history of myocardial infarctions, presence of CA, SUA, PTT, and ALT among the three groups ($p > 0.05$).

In terms of general information, significant differences were noted in the proportions of patients aged $\geq$60 years, with diabetes, history of cerebral infarction, and smoking history among the three groups ($p < 0.001$).

Regarding admission status, statistically significant differences were observed in shock index, STEMI, prehospital delay $\geq$24 hours, presence of AF, presence of PI, and undergoing PCI among the three groups ($p < 0.001$).

In auxiliary examinations, significant differences were found in levels of hs-CRP, TGs, TC, LDL, HDL, SCr, PT, INR, FIB, D-Dimer, LDH, CK and LVEF ($p < 0.05$) among the three groups.

Comparisons of the Effects of HCT at Different Levels on Clinical Endpoints

Over a period of 180 days, a total of 1946 patients with AMI were monitored, during which 286 patients experienced endpoint events, and 133 were lost to follow-up. The follow-up was completed for 592 patients (with 136 experiencing endpoint events) in the low HCT group, 605 patients (with 77 experiencing endpoint events) in the intermediate HCT group, and 616 patients (with 73 experiencing endpoint events) in the high HCT group (Fig. 1).

Cox regression data presented in Table 2 (Model 1) revealed that without adjusting for covariates, patients in the low HCT group exhibited a significantly higher risk of MACEs within 180 days following AMI compared to the intermediate HCT group (hazard ratio (HR) = 1.86, 95% confidence interval (CI) 1.40–2.46, $p < 0.001$). Additionally, they showed elevated risks of all-cause mortality (HR = 2.67, 95% CI 1.55–4.61, $p < 0.001$), cardiovascular mortality (HR = 2.43, 95% CI 1.40–4.24, $p = 0.002$), and acute coronary syndrome (HR = 1.55, 95% CI 1.08–2.24, $p = 0.018$). The risk of congestive heart failure was slightly elevated but did not reach statistical significance (hazard ratio = 2.23, 95% CI = 0.95–5.20, $p = 0.065$). No significant difference in AMI prognosis was found between the high HCT group and the intermediate HCT group in the unadjusted model. Unadjusted Kaplan-Meier curves illustrating the cumulative incidence of MACEs within 180 days across different HCT groups are shown in Fig. 3A. These curves indicate a significantly higher incidence of MACEs in the low HCT group compared to the other groups ($p < 0.0001$).

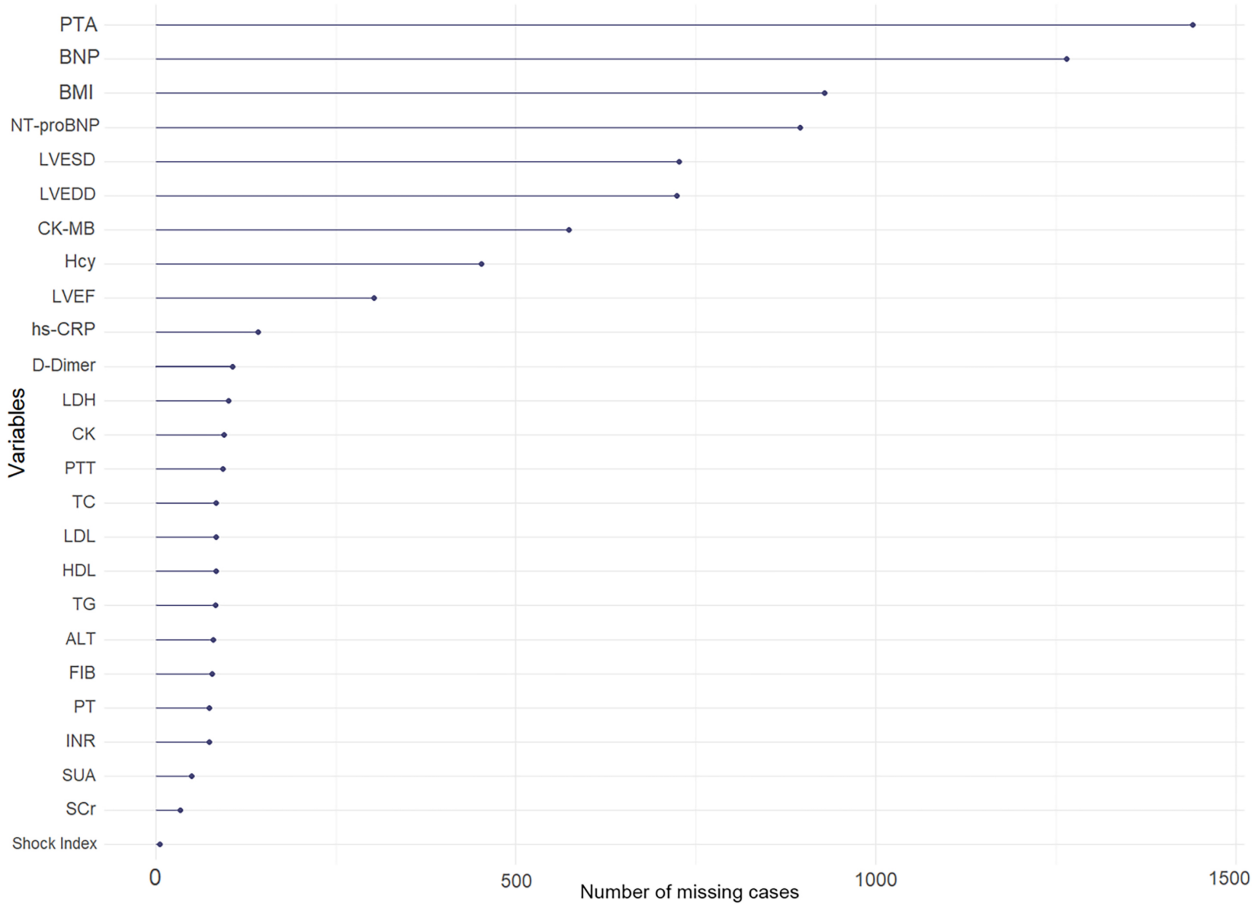

Fig. 2. Variables and the number of missing data. The following variables had missing data equal to or exceeding 20% of the total cases: BMI, Hcy, PTA, CK-MB, NT-proBNP, BNP, LVEDD, and LVESD. Abbreviations: PTA, prothrombin activity; BNP, brain natriuretic peptide; BMI, body mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; CK-MB, creatine kinase-isoenzyme; Hcy, homocysteine; LVEF, left ventricular ejection fraction; hs-CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; CK, creatine kinase; PTT, partial thromboplastin time; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; ALT, alanine aminotransferase; FIB, fibrinogen; PT, prothrombin time; INR, international normalized ratio; SUA, serum uric acid; SCr, serum creatinine.

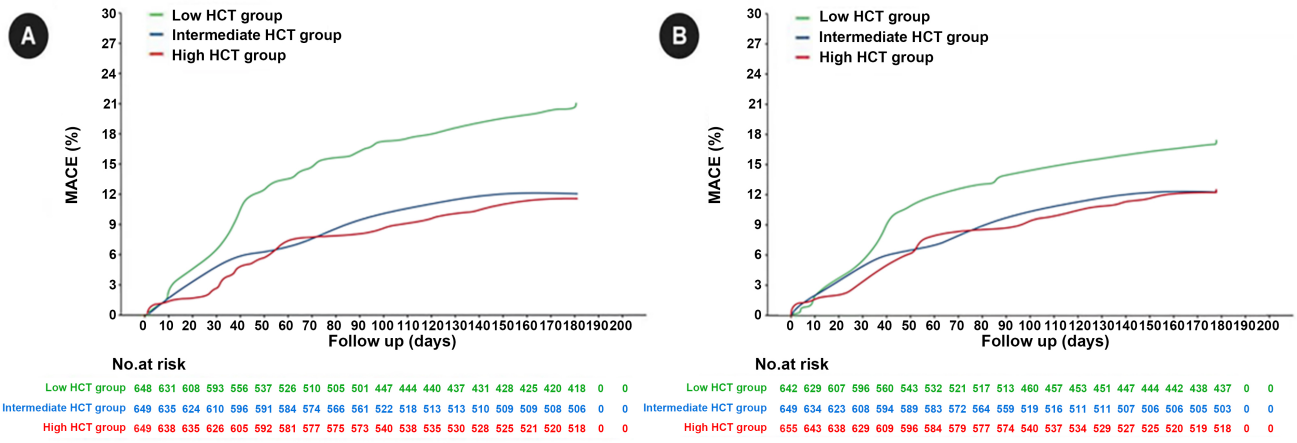

Fig. 3. The incidence of MACEs within 180 days was analyzed in a total of 1946 AMI patients according to different HCT groups. Kaplan-Meier survival curves were generated both before adjustment (A) and after inverse probability weighting adjustment (B). Abbreviations: MACEs, major adverse cardiovascular events.

Table 1. The clinical baseline features based on the three quartiles of HCT levels in AMI patients.

Item	Low HCT group (n = 648)	Intermediate HCT group (n = 649)	High HCT group (n = 649)	F/H/χ^2	*p*
General information					
Age ≥60 yr (n, %)	503 (77.6)^{ab}	350 (53.9)	280 (43.1)^{a}	165.861	<0.001
Male (n, %)	492 (75.9)	489 (75.3)	497 (76.6)	0.270	0.874
Farmer (n, %)	126 (19.4)	123 (19.0)	108 (16.6)	1.941	0.379
Smoking history (n, %)	264 (40.7)^{ab}	319 (49.2)	372 (57.3)^{a}	35.661	<0.001
Alcohol history (n, %)	161 (24.8)	164 (25.3)	189 (29.1)	3.705	0.157
Hypertension (n, %)	388 (59.9)	385 (59.3)	369 (56.9)	1.383	0.501
Diabetes (n, %)	218 (33.6)^{ab}	157 (24.2)	141 (21.7)	26.194	<0.001
History of myocardial infarctions (n, %)	29 (4.5)	27 (4.2)	27 (4.2)	0.105	0.949
History of cerebral infarction (n, %)	96 (14.8)^{ab}	60 (9.2)	39 (6.0)	28.534	<0.001
Admission status					
Shock index	0.65 ± 0.19^{ab}	0.60 ± 0.14	0.60 ± 0.16	19.581	<0.001
STEMI (n, %)	281 (43.4)^{b}	314 (48.4)	367 (56.5)^{a}	22.980	<0.001
Prehospital delay ≥24 h (n, %)	408 (63.0)^{ab}	336 (51.8)	261 (40.2)^{a}	67.191	<0.001
Presence of CA (n, %)	17 (2.6)	8 (1.2)	9 (1.4)	4.390	0.111
Presence of AF (n, %)	61 (9.4)^{ab}	33 (5.1)	18 (2.8)	27.164	<0.001
Presence of PI (n, %)	49 (7.6)^{ab}	22 (3.4)	16 (2.5)	22.383	<0.001
PCI (n, %)	357 (55.1)^{b}	396 (61.0)	448 (69.0)^{a}	26.857	<0.001
Auxiliary examination					
hs-CRP (mg/L)	7.69 (2.00, 38.30)^{ab}	2.83 (1.13, 8.50)	2.13 (0.86, 5.17)^{a}	186.675	<0.001
TGs (mmol/L)	1.19 (0.90, 1.64)^{ab}	1.42 (1.05, 2.03)	1.55 (1.15, 2.16)^{a}	92.981	<0.001
TC (mmol/L)	4.03 ± 1.21^{ab}	4.59 ± 1.20	4.70 ± 1.28	55.735	<0.001
LDL (mmol/L)	2.39 ± 0.93^{ab}	2.79 ± 0.98	3.01 ± 0.98^{a}	69.831	<0.001
HDL (mmol/L)	0.99 ± 0.31^{ab}	1.09 ± 0.39	1.14 ± 0.47	24.590	<0.001
SCr (μmol/L)	87.00 (70.93, 110.98)^{ab}	75.60 (65.00, 90.00)	73.00 (63.00, 85.20)^{a}	127.899	<0.001
SUA (μmol/L)	368.46 ± 136.68	359.24 ± 115.22	355.22 ± 113.82	1.995	0.136
PT (s)	12.48 ± 5.51^{ab}	11.54 ± 3.24	11.22 ± 1.93	18.740	<0.001
INR	1.05 (0.97, 1.14)^{ab}	0.98 (0.91, 1.05)	0.96 (0.89, 1.04)^{a}	196.130	<0.001
PTT (s)	31.59 ± 17.17	30.23 ± 15.84	30.16 ± 12.95	1.767	0.171
FIB (g/L)	3.69 ± 1.44^{ab}	3.19 ± 1.28	2.96 ± 0.89^{a}	59.661	<0.001
D-Dimer (μg/L)	663.50 (304.00, 1497.50)^{ab}	360.00 (200.00, 700.00)	280.00 (160.00, 470.00)^{a}	211.258	<0.001
LDH (U/L)	284.50 (202.00, 491.75)^{a}	239.50 (185.50, 437.00)	259.60 (193.50, 442.60)	9.425	0.009
CK (U/L)	169.00 (86.00, 621.00)^{b}	190.00 (91.00, 894.25)	218.20 (100.10, 978.00)	8.612	0.013
ALT (U/L)	42.00 (24.00, 112.25)	42.00 (25.00, 116.20)	43.00 (27.00, 115.50)	1.940	0.379
LVEF (%)	55.84 ± 12.15^{ab}	58.64 ± 10.61	58.57 ± 10.03	13.767	<0.001

Comparisons with the intermediate HCT group are denoted by the letter 'a', while comparisons with the high HCT group are denoted by the letter 'b', both indicating a significance level of $p = 0.05$. Abbreviations: STEMI, ST-segment elevation myocardial infarction.

In the model adjusted for all covariates (Model 3), the association between the risk of MACEs (HR = 1.44, 95% CI 1.07–1.95, $p = 0.017$) and acute coronary syndrome risk (HR = 1.57, 95% CI 1.06–2.32, $p = 0.024$) was slightly attenuated in the low HCT group compared to the intermediate HCT group, but remained statistically significant. However, there was no evidence supporting an association between low HCT levels and an increased risk of all-cause mortality (HR = 1.40, 95% CI 0.77–2.53, $p = 0.270$), cardiovascular mortality (HR = 1.32, 95% CI 0.72–2.40, $p = 0.367$), or congestive heart failure (HR = 1.26, 95% CI 0.50–3.18, $p = 0.621$). Furthermore, in the adjusted model, no significant difference was detected in the prognosis of AMI between the high HCT group and the intermediate HCT group. Adjusted Kaplan-Meier curves illustrating the incidence of MACEs across different HCT groups are depicted in Fig. 3B, showing that patients in the low HCT group had a higher incidence of MACEs compared to the other groups ($p = 0.0075$).

Sensitivity and Subgroup Analyses of the Effects of HCT at Different Levels

As illustrated in Table 3, the analysis excluding the input covariate data (Model A) showed that the low HCT group had an increased risk of MACEs (HR = 1.70, 95% CI 1.17–2.48, $p = 0.006$) and acute coronary syndrome (HR

Table 2. Relationship of HCT levels with the endpoint events in different HCT groups.

	N of events	N of subjects	Model 1		Model 2		Model 3	
			HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
MACEs								
Low HCT group	132	648	1.86 (1.40–2.46)	<0.001	1.60 (1.20–2.13)	0.001	1.44 (1.07–1.95)	0.017
Intermediate HCT group	77	649	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High HCT group	72	649	0.92 (0.69–1.27)	0.616	1.00 (0.72–1.38)	0.993	1.04 (0.75–1.45)	0.813
p for trend				<0.001		0.001		0.036
All-cause mortality								
Low HCT group	45	648	2.67 (1.55–4.61)	<0.001	2.22 (1.27–3.87)	0.005	1.40 (0.77–2.53)	0.270
Intermediate HCT group	18	649	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High HCT group	25	649	1.37 (0.75–2.52)	0.306	1.51 (0.82–2.76)	0.188	1.81 (0.96–3.40)	0.065
p for trend				0.004		0.084		0.504
Cardiovascular mortality								
Low HCT group	41	648	2.43 (1.40–4.24)	0.002	2.00 (1.14–3.50)	0.016	1.32 (0.72–2.40)	0.367
Intermediate HCT group	18	649	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High HCT group	24	649	1.32 (0.72–2.43)	0.377	1.45 (0.79–2.68)	0.234	1.70 (0.90–3.22)	0.103
p for trend				0.011		0.168		0.505
Acute coronary syndrome								
Low HCT group	70	648	1.55 (1.08–2.24)	0.018	1.40 (0.96–2.03)	0.081	1.57 (1.06–2.32)	0.024
Intermediate HCT group	49	649	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High HCT group	42	649	0.84 (0.56–1.27)	0.418	0.89 (0.59–1.35)	0.588	0.87 (0.57–1.32)	0.516
p for trend				0.001		0.024		0.007
Congestive heart failure								
Low HCT group	16	648	2.23 (0.95–5.20)	0.065	1.80 (0.75–4.28)	0.184	1.26 (0.50–3.18)	0.621
Intermediate HCT group	8	649	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High HCT group	4	649	0.49 (0.15–1.63)	0.246	0.56 (0.17–1.86)	0.344	0.61 (0.18–2.06)	0.422
p for trend				0.003		0.029		0.234

Model 1 was unadjusted for covariates. Model 2 was adjusted for variables from the general information section of Table 1 with $p < 0.05$. Model 3 further adjusted for variables from the admission status and laboratory examination sections of Table 1 with $p < 0.05$, building upon Model 2. Abbreviations: HR, hazard ratio. Because a small number of patients were not included due to accidents such as car accidents, the sample size of MACEs in the Low HCT group and the High HCT group was slightly missing compared to the sample size that occurred at the endpoint events.

= 2.18, 95% CI 1.30–3.64, $p = 0.003$) compared to the intermediate HCT group. However, there was no statistically significant association between low HCT levels and the risk of all-cause mortality (HR = 1.26, 95% CI 0.62–2.57, $p = 0.520$), cardiovascular mortality (HR = 1.16, 95% CI 0.56–2.38, $p = 0.694$), or congestive heart failure (HR = 1.79, 95% CI 0.58–5.53, $p = 0.309$).

Specifically, after excluding data from patients lost to follow-up (Model B), the low HCT group still showed a higher risk of MACEs (HR = 1.47, 95% CI 1.08–1.98, $p = 0.013$) and acute coronary syndrome (HR = 1.59, 95% CI 1.08–2.36, $p = 0.020$) compared to the intermediate HCT group. Similarly, there was no statistically significant association between low HCT levels and the risk of all-cause mortality (HR = 1.36, 95% CI 0.75–2.48, $p = 0.311$), cardiovascular mortality (HR = 1.30, 95% CI 0.71–2.38, $p = 0.398$), or congestive heart failure (HR = 1.29, 95% CI 0.51–3.27, $p = 0.592$). Comparison of the high HCT group with the intermediate HCT group revealed no discernible difference in prognosis, consistent with earlier models (Table 3). In the analysis of the continuous relationship between HCT and MACEs, we observed that when HCT was below 41.58%, the lower limit of the 95% CI for the HR was greater than 1, indicating an increased risk of MACEs. Between HCT levels of 41.58% and 48.01%, the upper limit of the 95% CI for the HR was less than 1, suggesting a potential protective effect against MACEs. Beyond 48.01% HCT, the upper limit of the 95% CI for the HR was greater than 1, while the lower limit was less than 1, as depicted in Fig. 4A. After adjustment for covariates, the conclusions remained largely consistent with these findings. However, the protective range for HCT narrowed to 41.58%–45.36% (Fig. 4B).

As illustrated in Fig. 5, subgroup analyses based on covariates confirmed that there was no interaction observed between the low and high HCT groups compared to the intermediate HCT group across all subgroups.

Table 3. Sensitivity analysis of the relationship between different HCT groups and endpoint events.

	N of events	N of subjects	Model A		Model B	
			HR (95% CI)	*p*	HR (95% CI)	*p*
MACEs						
Low HCT group	132	648	1.70 (1.17–2.48)	0.006	1.47 (1.08–1.98)	0.013
Intermediate HCT group	77	649	1.00 (Reference)		1.00 (Reference)	
High HCT group	72	649	1.16 (0.77–1.77)	0.478	1.04 (0.75–1.44)	0.833
p for trend				0.034		0.027
All-cause mortality						
Low HCT group	45	648	1.26 (0.62–2.57)	0.520	1.36 (0.75–2.48)	0.311
Intermediate HCT group	18	649	1.00 (Reference)		1.00 (Reference)	
High HCT group	25	649	1.70 (0.80–3.57)	0.165	1.74 (0.93–3.26)	0.086
p for trend				0.488		0.511
Cardiovascular mortality						
Low HCT group	41	648	1.16 (0.56–2.38)	0.694	1.30 (0.71–2.38)	0.398
Intermediate HCT group	18	649	1.00 (Reference)		1.00 (Reference)	
High HCT group	24	649	1.57 (0.74–3.35)	0.241	1.63 (0.86–3.08)	0.135
p for trend				0.467		0.543
Acute coronary syndrome						
Low HCT group	70	648	2.18 (1.30–3.64)	0.003	1.59 (1.08–2.36)	0.020
Intermediate HCT group	49	649	1.00 (Reference)		1.00 (Reference)	
High HCT group	42	649	1.03 (0.58–1.83)	0.915	0.88 (0.58–1.34)	0.540
p for trend				0.004		0.006
Congestive heart failure						
Low HCT group	16	648	1.79 (0.58–5.53)	0.309	1.29 (0.51–3.27)	0.592
Intermediate HCT group	8	649	1.00 (Reference)		1.00 (Reference)	
High HCT group	4	649	0.88 (0.23–3.37)	0.852	0.61 (0.18–2.07)	0.424
p for trend				0.227		0.221

In Model A, based on Model 3, the analysis was repeated after excluding input data from the covariates. In Model B, also based on Model 3, the analysis was repeated after excluding patients lost to follow-up. Abbreviation: CI, confidence interval. Because a small number of patients were not included due to accidents such as car accidents, the sample size of MACEs in the Low HCT group and the High HCT group was slightly missing compared to the sample size that occurred at the endpoint events.

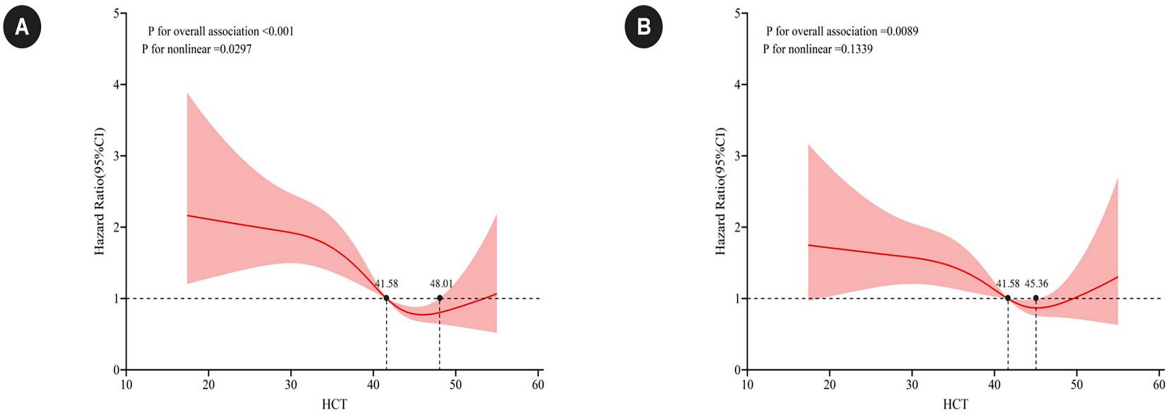

Fig. 4. The RCS plot displays the unadjusted (A) and adjusted (B) continuous relationship between HCT and MACEs. The HR value is indicated by the red line, with the 95% CI represented by the pink-shaded region. Abbreviation: RCS, restricted cubic splines.

Discussion

In this prospective observational cohort study, we followed up AMI patients treated at tertiary hospitals across various regions in China for approximately six months. The Cox proportional hazards model, initially without covariate adjustment, identified low HCT levels as a risk factor for MACEs within 180 days after AMI. Even after adjusting

Subgroup	Event/Number	HR(95%CI)	P value	P for Interaction
Age				0.257
≥60yr	168/853	1.49(1.06-2.11)	0.024	
<60yr	41/444	1.25(0.60-2.60)	0.544	
Gender				0.603
male	145/981	1.50(1.03-2.19)	0.033	
female	64/316	1.28(0.73-2.26)	0.395	
Smoking history				0.149
Yes	63/583	1.13(0.64-1.99)	0.671	
No	146/714	1.62(1.11-2.36)	0.012	
Hypertension				0.393
Yes	136/773	1.32(0.91-1.92)	0.150	
No	73/524	1.56(0.91-2.66)	0.106	
Diabetes				0.220
Yes	76/375	1.78(1.01-3.13)	0.045	
No	133/922	1.18(0.81-1.72)	0.393	
STEMI				0.922
Yes	84/595	1.44(0.88-2.37)	0.146	
No	125/702	1.37(0.92-2.03)	0.121	
Pre-hospital delay				0.935
≥24h	138/744	1.47(1.00-2.16)	0.051	
<24h	71/553	1.26(0.75-2.13)	0.382	
PCI				0.059
Yes	104/753	1.15(0.75-1.75)	0.519	
No	105/544	1.93(1.20-3.09)	0.006	
LVEF				0.312
≥60%	91/639	1.92(1.20-3.06)	0.006	
<60%	118/658	1.18(0.79-1.77)	0.417	

Subgroup	Event/Number	HR(95%CI)	P value	P for Interaction
Age				0.378
≥60yr	84/630	0.92(0.58-1.47)	0.738	
<60yr	65/668	1.11(0.66-1.89)	0.693	
Gender				0.454
male	107/986	1.02(0.68-1.53)	0.922	
female	42/312	0.87(0.44-1.69)	0.674	
Smoking history				0.635
Yes	68/691	1.16(0.68-1.97)	0.584	
No	81/607	0.87(0.55-1.37)	0.552	
Hypertension				0.254
Yes	89/754	0.81(0.52-1.27)	0.353	
No	60/544	1.10(0.63-1.91)	0.743	
Diabetes				0.064
Yes	42/298	1.33(0.68-2.61)	0.400	
No	107/1000	0.78(0.52-1.17)	0.233	
STEMI				0.919
Yes	84/595	0.86(0.51-1.44)	0.570	
No	125/702	0.92(0.58-1.47)	0.739	
Pre-hospital delay				0.998
≥24h	83/597	0.98(0.61-1.58)	0.947	
<24h	66/701	1.01(0.61-1.70)	0.957	
PCI				0.740
Yes	98/844	0.95(0.63-1.43)	0.796	
No	51/454	1.10(0.58-2.09)	0.777	
LVEF				0.122
≥60%	59/686	0.75(0.43-1.28)	0.286	
<60%	90/612	1.26(0.80-1.99)	0.321	

Fig. 5. A forest plot depicting the subgroup analysis of MACEs in the low HCT group and the intermediate HCT group is shown in panel (A), and a forest plot describing the subgroup analysis in the high HCT group and the intermediate HCT group is presented in panel (B). The red dots represent the HR values, and the red line segments represent the 95% CI.

for variables with inter-group comparisons of HCT yielding $p < 0.05$ across general information, admission status, and laboratory examination, the association between low HCT levels and increased risk of MACEs remained statistically significant.

In secondary endpoint analysis using the Cox proportional hazards model without covariate adjustment, low HCT levels emerged as risk factors for all-cause mortality, cardiovascular mortality, and secondary acute coronary syndrome within 180 days post-AMI. However, after adjusting for covariates, no significant associations were found between low HCT levels and all-cause mortality or cardiovascular mortality within six months, though the association with secondary acute coronary syndrome risk remained statistically significant. Moreover, across progressively adjusted models, the prognosis of AMI was comparable between the high and intermediate HCT groups.

Our sensitivity analysis indicated consistent results when excluding missing covariate data or data from participants lost to follow-up, affirming the reliability of our findings. Notably, a protective effect against MACEs was observed within HCT levels ranging from 41.58% to 45.36%, as depicted in the RCS. Subgroup analyses revealed no significant interactions between variables.

During the 1980s and 1990s, researchers focused on exploring the association between HCT levels and cardiovascular diseases, primarily within the general population. However, a definitive connection between HCT levels and the development or prognosis of cardiovascular diseases was not conclusively established [14–16]. According to reports [16], meaningful statistical analyses were hindered by a limited number of positive events. It has been documented that there is no correlation between HCT levels and cardiovascular disorders in males, whereas females with high HCT levels exhibit a significantly increased risk of coronary heart disease [17].

Given the significant influence of sex on HCT levels, our study categorized participants into sex-specific tertiles for grouping. Existing studies have supported a correlation between HCT levels and the risk of cardiovascular diseases, further reinforcing the potential relationship between HCT levels and the development of cardiovascular disorders [18]. While numerous studies have examined the impact of hemoglobin levels on prognosis in patients with cardiovascular problems, particularly AMI [19,20], research specifically focusing on the effect of HCT levels on prognosis remains scarce. Specifically, the link between HCT levels at the onset of treatment and the risk of MACEs in AMI patients remains largely underexplored, highlighting the significance of our study in providing new clinical data and evidence for this relationship.

Previous studies have indicated poorer prognosis for myocardial infarction among men with HCT levels >47% and women with HCT levels >46% [21]. Takaoka *et al.* [11] categorized HCT levels into five quintiles (17.3–41.5, 41.6–43.5, 43.6–45.2, 45.3–47.2, 47.3–64.3) and identified an association between high HCT levels and increased mortality risk from AMI in younger Japanese women. In contrast, our investigation revealed that low HCT levels elevate the short-term risk of MACEs in AMI patients. This discrepancy may stem from factors such as varying definitions of high HCT levels, ethnic diversity in study populations, age demographics, and differences in follow-up duration.

In previous research where high HCT levels were linked to increased MACE risk, the threshold defining high HCT levels typically used higher numerical values. In our study, high HCT levels were defined as ≥45.2% for men and ≥39.9% for women. Similarly, our sensitivity analysis examining the continuous relationship between HCT and MACEs corroborated these findings. Notably, HCT levels ranging from 41.58% to 45.36% appeared to confer a protective effect against short-term MACE occurrence in AMI patients. However, this protective effect diminished as HCT levels continued to rise beyond this range.

Although our study did not find an increased short-term risk of MACEs following AMI in the high HCT group, previous research has highlighted a direct association between higher HCT levels, increased blood viscosity, and elevated prevalence of cardiovascular diseases and related deaths in the general population [22]. According to the RCS plot in our study, maintaining an optimal HCT level post-AMI was deemed crucial [23].

Higher HCT levels in the general population have been consistently associated with an increased risk of developing or dying from coronary heart disease [24–26], myocardial infarction [27,28], and congestive heart failure [29], which contrasts with the findings of our study. This discrepancy can be attributed to the physiological implications of low hemoglobin levels resulting from decreased HCT, which lead to inadequate oxygen supply to tissues. This condition triggers various pathophysiological mechanisms, including heightened sympathetic nervous system activity and activation of the renin-angiotensin-aldosterone system, which contribute to arrhythmias, sodium-water retention, left ventricular hypertrophy, and cardiac enlargement.

In response to low hemoglobin levels, the heart compensates by increasing resting blood flow, thereby compromising coronary reserve capacity and increasing myocardial oxygen consumption [30,31]. This physiological state may explain why type 2 myocardial infarctions, arising from conditions like hypoxia due to low blood pressure, anemia, or unstable circulation, generally have a worse prognosis compared to type 1 myocardial infarctions, which typically result from partial or complete blockage of coronary arteries such as blood clot formation or rupture of an atherosclerotic plaque [32].

Low HCT levels may also be implicated in other health conditions such as bleeding disorders, malnutrition, bone marrow diseases, and immune-related abnormalities

of red blood cells [33], all of which contribute to poorer prognosis in patients with low HCT levels. Studies have demonstrated that specific increases in blood HCT concentration (HCT >1.5%) through targeted interventions before discharge can improve outcomes in patients with cardiovascular diseases [34,35]. These findings underscore the potential benefits of optimizing HCT levels through appropriate therapeutic strategies in enhancing the prognosis and overall management of these patients.

Despite the significant findings, this study has several limitations. Firstly, it was conducted in tertiary hospitals across diverse regions in China, which inherently carries the limitations of a non-randomized design. Secondly, the grouping of patients into three HCT level categories was based on measurements from the first batch of blood samples collected upon admission. HCT levels can fluctuate due to various factors such as seasonal variations, diurnal rhythms, and the acute onset of AMI. It was not feasible to ensure uniformity in the timing of blood collection or confirm whether patients were fasting, which could introduce potential confounding factors. To mitigate these issues, we included numerous covariates in our multivariable Cox regression analysis. Thirdly, to ensure balanced group sizes, we used sex-specific tertiles for grouping criteria. Despite adjusting for covariates, we observed worse prognosis in the low HCT group, whereas outcomes in the high and intermediate HCT groups were minimally affected.

Notwithstanding these limitations, our study underscores the clinical relevance of HCT levels upon admission in predicting outcomes for patients with AMI.

Conclusions

In conclusion, our study confirms a correlation between low HCT levels and an increased risk of MACEs in the short term among patients with AMI, suggesting that HCT could serve as an independent prognostic indicator in this context. These findings hold implications for clinical practice, highlighting the potential for individualized analyses to define optimal HCT levels and establish risk classification and management strategies for AMI patients. This could lead to more timely diagnoses and the implementation of comprehensive interventions and preventive measures aimed at improving patient outcomes.

Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author upon reasonable request.

Author Contributions

Substantial contributions to conception and design: YHS, BX. Data acquisition, data analysis and interpretation: JHY, XXZ, HFZ, JWY, ZSD, HTW. Drafting the article or critically revising it for important intellectual content: all authors. Final approval of the version to be published: all authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved: all authors.

Ethics Approval and Consent to Participate

Every patient signed a form of informed consent. The Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University gave its permission to the research protocol, which complied with the standards specified in the Declaration of Helsinki (Ethics Committee approval number: 2020-KL-141-IH01, 2020-KL-141-C01).

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Conflict of Interest

The authors declare no conflict of interest.

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