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Non-O Blood Group Is Associated with High Thrombus Burden and Poor Short- and Long-Term Prognosis in ST-Segment Elevation Myocardial Infarction Patients

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Highlights

- Non-O blood groups in ST-segment elevation myocardial infarction (STEMI) patients are linked to higher thrombus burden, suggesting implications for reperfusion interventions.
- Non-O blood group patients have higher mortality rates, stressing blood group's importance in STEMI care.
- Non-O blood group independently predicts high thrombus burden, highlighting its role in STEMI outcomes.
- This study underscores customizing treatment based on blood group for better outcomes in reperfusion interventions.

Keywords
ABO blood group · Thrombus burden · ST-segment elevation myocardial infarction

Abstract

Introduction: This study investigated how non-O blood groups relate to thrombus burden (TB) and prognosis in ST-segment elevation myocardial infarction (STEMI) patients, aiming to shed light on their association with thrombotic complications in cardiovascular diseases. ***Methods:*** Retrospectively, 1,180 STEMI patients undergoing primary percutaneous coronary intervention were included. The study population was divided into groups according to TB status and the groups were compared in terms of basic clinical characteristics, laboratory parameters and ABO blood group types. In addition, short-term (30 days) and long-term (12 months) clinical outcomes were assessed to evaluate the prognostic implications. ***Results:*** The analysis revealed a significant association between non-O blood groups and increased TB in STEMI patients (p = 0.001). Non-O blood group was independently associated with high TB (OR: 1.726, 95% confidence interval [CI]: 1.279–2.330, $p < 0.001$). Additionally, patients with non-O blood groups had higher

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short and long-term mortality rates (hazard ratio [HR]: 2.480, 95% CI: 1.361–4.520, p = 0.003; HR: 2.347, 95% CI: 1.433–3.844, p = 0.001; respectively). ***Conclusions:*** This study emphasizes the significance of the ABO blood group system in STEMI outcomes, associating non-O blood groups with higher TB and poorer clinical outcomes. While proposing personalized treatment strategies based on blood group status to improve reperfusion interventions and outcomes, additional trials are needed to comprehensively evaluate their impact.

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is a life-threatening condition characterized by the sudden occlusion of a coronary artery, resulting in myocardial ischemia and potential tissue damage [1]. Numerous studies have shed light on the multifactorial nature of STEMI prognosis [1, 2]. As researchers delve deeper into the factors influencing STEMI prognosis, the role of the ABO blood group system has emerged as an intriguing avenue of investigation [3] on its potential influence on thrombotic vascular disease and patient outcomes [4]. The ABO blood group system classifies individuals into four main groups based on the presence or absence of specific antigens on the surface of red blood cells: A, B, AB, and O [5]. While primarily known for its significance in blood transfusion compatibility, recent studies have revealed its potential relevance to various health conditions, including cardiovascular diseases [4, 5]. A growing body of evidence has established a correlation between non-O blood groups (A, B, and AB) and arterial and venous thrombotic complications [3, 4]. Thrombus burden (TB) reflects the extent of blood clotting in coronary arteries. Elevated TB correlates with delayed and less efficient reperfusion therapies, possibly resulting in larger infarct sizes and poorer cardiac outcomes [6]. Despite effective restoration of blood flow in STEMI patients, high thrombus burden (HTB) is an important predictor of adverse cardiovascular events and short- and long-term prognosis in these patients [7]. Genome-wide association studies have suggested that the ABO blood group locus is an inherited determinant of thrombotic complications, cardiovascular risk factors, and myocardial infarction [5, 8]. Patients with non-O blood groups may be at a higher risk of major adverse cardiac events such as recurrent myocardial infarctions, heart failure, and mortality in both short and long terms [4, 5]. Recent research indicates that non-O blood groups are linked to higher TB in STEMI patients, potentially leading to impaired blood flow, delayed reperfusion, and increased myocardial damage. Understanding this association could help in risk stratification for short and long-term clinical outcomes in these patients [4, 5] and could lead to personalized treatment and improved patient outcomes. This study aimed to uncover the association between ABO groups, TB, and short- and long-term clinical outcomes in STEMI patients.

Materials and Methods

Study Population and Data Collection

In this retrospective study, we included 1180 STEMI patients who underwent successful primary percutaneous coronary intervention (pPCI) within 12 h of symptom onset between January 2019 and March 2022. Diagnosis, treatment, and follow-up followed current guidelines. We obtained demographic, clinical, laboratory, and blood group data, as well as short and long-term clinical outcomes from hospital records and national health databases. Exclusions comprised patients with a history of CABG or myocardial infarction, those on antiplatelet/anticoagulant therapy, previous thrombolytic therapy, delayed pPCI, inflammatory/autoimmune diseases, hematological/endocrine disorders, liver/kidney failure, severe valve disease, complex coronary procedures, and missing ABO blood typing or data (Fig. 1).

Angiographic Procedure and Assessment of TB

Coronary angiography followed by standard pPCI was performed to ensure adequate blood flow in the infarct-related artery. Other coronary lesions were addressed only in cases of cardiogenic shock. Procedure decisions, including stent type, size, and adjunctive pharmacotherapy, were operator-dependent. Angiographic optimization was conducted post-stent implantation. TB in the infarct-related artery was classified into five TIMI grades. Patients with total occlusion (grade 5) were reassessed upon restoration of flow. TB was categorized as low (grades 1–3) or high (grades 4–5). Images were analyzed by two blinded cardiologists, with <5% intra- and interobserver variability. Disagreements were resolved by a third blinded cardiologist [9, 10].

Periprocedural Medication

Before pPCI, patients received 300 mg of aspirin, 600 mg clopidogrel, and unfractionated heparin (70 IU/kg intravenous). Long-term aspirin (100 mg/day) and clopidogrel (75 mg/day for bare-metal stent or balloon angioplasty for ≥1 month, and for ≥1 year for drug-eluting stent) were prescribed post-stent placement. Tirofiban use was discretionary and given as a 25 μg/kg intravenous loading dose, followed by a 0.15 μg/kg/min infusion for at least 18 h post-procedure if administered. β-Blockers and high-intensity statins were administered to all eligible patients during hospitalization.

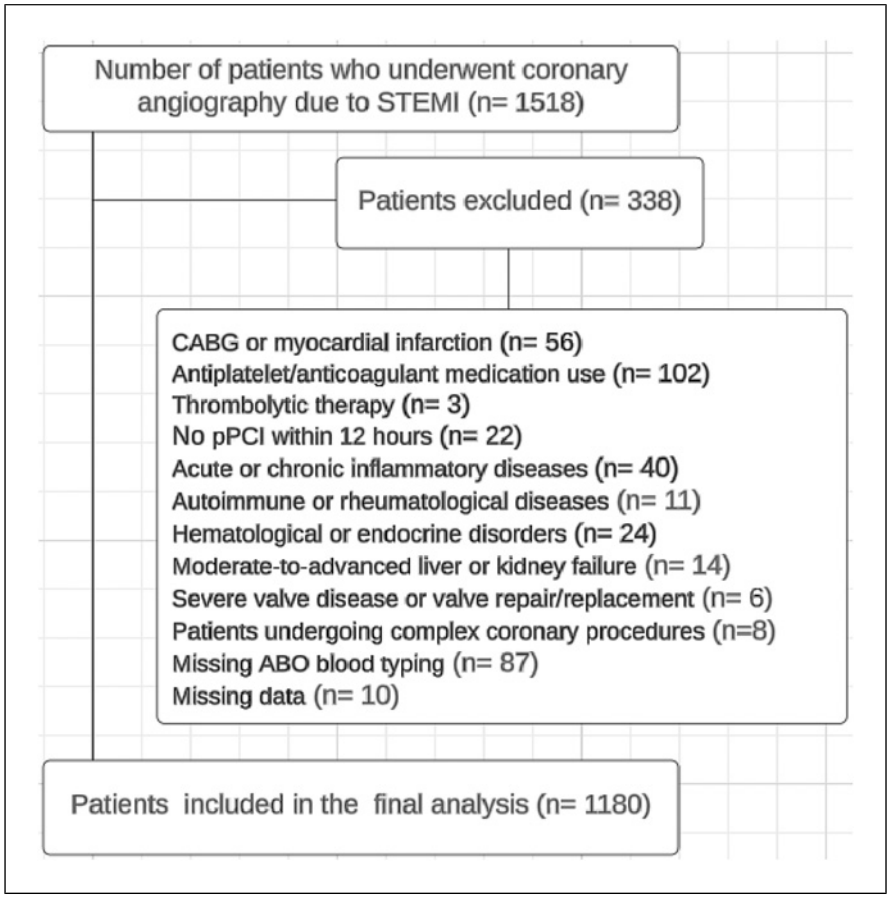

Fig. 1. Flowchart of the study population.

Follow-Up and Primary Endpoint

Short-term (30-day) and long-term (1-year) clinical follow-up results (all-cause mortality) of all patients included in the study were obtained from hospital and national health databases. All-cause mortality was determined as the primary endpoint.

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 software. Normality of continuous variables was assessed with the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or median (interquartile range) and compared using Student's *t* test or Mann-Whitney U test accordingly. Categorical variables were compared using the χ^2 test. Variables with $p < 0.10$ in univariate analysis were considered potential risk markers and included in the multivariate regression model, employing backward elimination method. Model fit was assessed with the Hosmer-Lemeshow test. Intra- and interobserver variability were calculated using Cohen's kappa value. Cox proportional hazard regression model determined risk ratios of blood groups on short- and long-term mortality, with three models created to assess potential confounding effects. Kaplan-Meier analysis evaluated all-cause mortality and survival, with statistical significance determined by the Log-rank test. Our sample size of 1,180 patients was deemed adequately powered for meaningful associations between ABO blood groups, TB, and clinical outcomes in STEMI patients, with a significant level of $p < 0.05$.

Results

Of 1,180 patients who applied for STEMI and underwent pPCI, 819 (69.4%) were male, and the mean age was 59.9 ± 11.5 years. The patients were categorized into two groups as HTB and low thrombus burden (LTB) according to their TB status, and the basic demographic, clinical and laboratory characteristics of the patients are summarized in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000538777). The presence of diabetes mellitus and dyslipidemia from comorbid features was significantly higher in the HTB group than in the LTB group (39.3% vs. 31.6%, $p = 0.008$; 50% vs. 41.4, $p = 0.005$; respectively). There was no significant difference between the periprocedural hemodynamic characteristics of the groups ($p > 0.05$; for all). Among the laboratory parameters, fasting plasma glucose, uric acid, C-reactive protein, hemoglobin, hematocrit, mean platelet volume, peak CK-MB, peak troponin I and HbA1c levels were significantly higher in the HTB group than in the LTB group, while albumin levels were

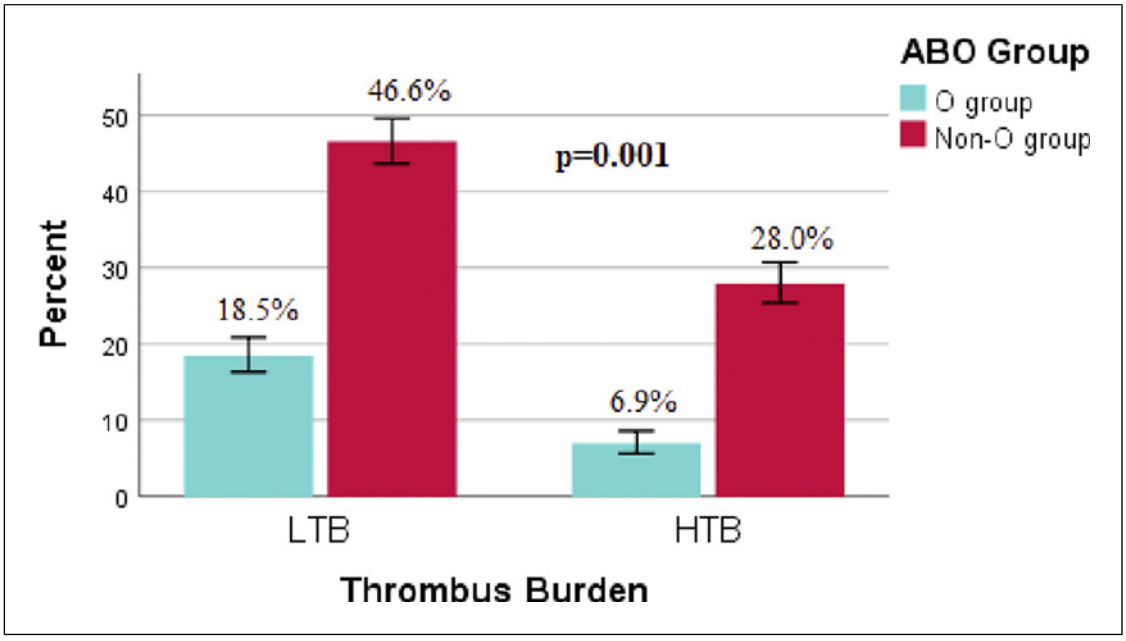

Fig. 2. Clustered bar percent of TB status by ABO group. Of the patients included in the study, 18.5% were in the LTB + O blood group, 46.6% were in the LTB + non-O blood group, 6.9% were in the HTB + O blood group, and the remaining 28.0% were in the HTB + non-O blood group. HTB, high thrombus burden; LTB, low thrombus burden.

lower ($p < 0.05$; for all). There was no significant difference between the pre-procedural medications of the study groups ($p > 0.05$; for all). Among the STEMI patients, 300 (25.4%) had blood group O, 633 (53.6%) had blood group A, 139 (11.8%) had blood group B, and 108 (9.2%) had blood group AB (online suppl. Fig. 1). 18.5% of patients in the study belonged to the LTB + O blood group, 46.6% to the LTB + non-O blood group, 6.9% to the HTB + O blood group, and the remaining 28.0% to the HTB + non-O blood group (Fig. 2). The presence of HTB was notably greater in the Non-O blood group compared to the O blood group, with HTB observed in 80.1% of Non-O blood group patients and 71.6% of O blood group patients ($p = 0.001$), despite the fact that the frequency of HTB in the O-group was lower than the frequency of LTB (19.9% vs. 28.4%, respectively) (Fig. 3). Periprocedural and angiographic features of the patients according to TB status are summarized in Table 1. The frequency of multivessel disease and SYNTAX score were significantly higher in the HTB group than in the LTB group ($p = 0.035$, $p = 0.012$; respectively). The presence of no-reflow phenomenon in the HTB group was significantly higher than in the LTB group (18.2% vs. 12.5%; $p = 0.008$). As expected, the frequency of mechanical thrombus aspiration and distal embolism in the HTB group were significantly higher than in the LTB group (10.9% vs. 4.0%, $p < 0.001$; 3.9% vs. 1.2%, $p = 0.002$; respectively). Diabetes mellitus, dyslipidemia, fasting plasma glucose, uric acid, albumin, hematocrit, troponin I, HbA1c, multivessel disease, SYNTAX Score, and non-O blood group type were determined as independent predictors for the presence of HTB in the multivariable analysis (Table 2).

The average period of follow-up was 11.0 ± 2.7 months. All-cause mortality was classified in the short- and long-term by comparing O and non-O blood groups. The Cox regression analysis for 1-year all-cause mortality related with ABO blood group types is presented in Table 3. Even after adjusting for multiple confounding factors (Model 3), non-O blood type was found to be an independent predictor of short- and long-term all-cause mortality (hazard ratio [HR] = 2.480, 95% confidence interval [CI]: 1.361–4.520, $p = 0.003$; HR = 2.347, 95% CI: 1.433–3.844; $p = 0.001$; respectively). Kaplan-Meier cumulative survival curves showed that patients with STEMI had an increased risk of short-term and long-term all-cause mortality in the presence of non-O blood group type ($p = 0.006$, $p = 0.001$; respectively) and HTB ($p < 0.001$, $p < 0.001$; respectively) (Fig. 4, 5).

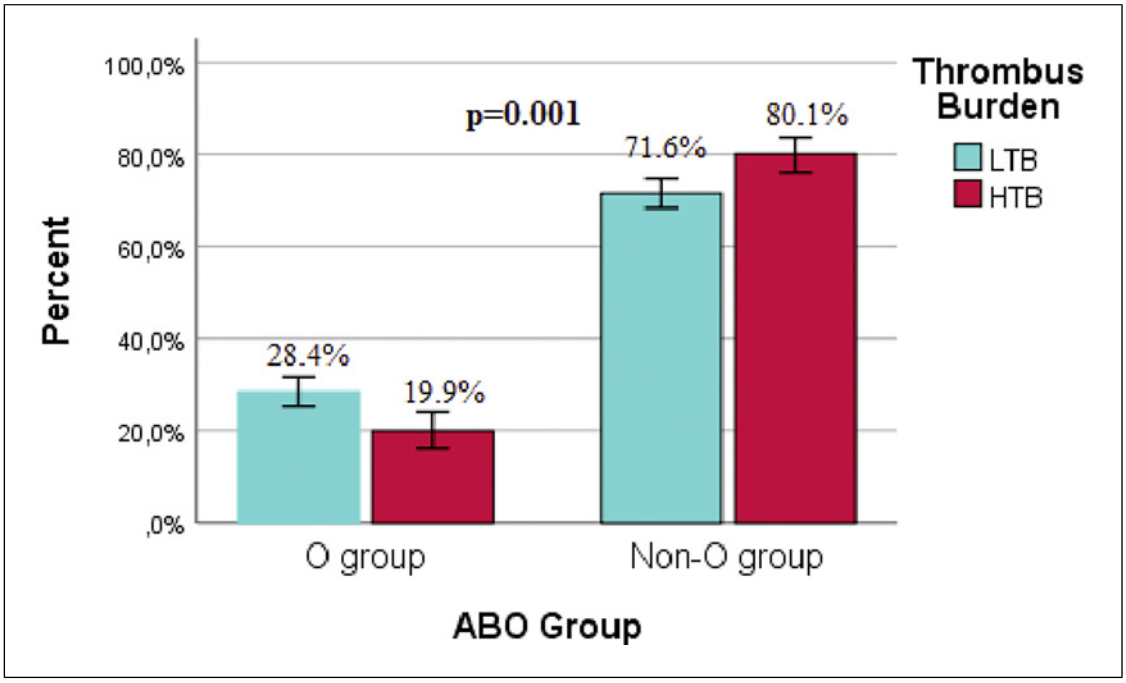

Fig. 3. Representation of the frequency of HTB and LTB according to the ABO groups in the bar graph. While the frequency of HTB in the O-group was lower than the frequency of LTB (19.9% vs. 28.4%), the incidence of HTB in the non-O group was significantly higher than the frequency of LTB (80.1% vs. 71.6%; p = 0.001). HTB, high thrombus burden; LTB, low thrombus burden.

Discussion

Our findings suggest that non-O blood groups are associated with increased TB in STEMI patients, which may affect the efficacy of reperfusion therapies. Non-O blood group individuals showed a higher prevalence of extensive thrombi and faced higher short- and long-term mortality compared to O blood group individuals. Similarly, patients with HTB had higher mortality rates than those with LTB. Non-O blood group emerged as an independent predictor of short- and long-term mortality in STEMI patients.

Many studies have investigated the relationship between the ABO blood group and coronary artery disease (CAD) [4, 5]. In a recent meta-analysis involving 17 studies, the risk of CAD was found to be significantly higher in the non-O blood group than in the O blood group [11]. In another meta-analysis, non-O blood type was shown to be an independent risk factor for CAD and myocardial infarction [12]. One meta-analysis confirmed a close association between vascular diseases and the non-O blood group, and the odds ratios were similar to those predicted by the effect of the ABO blood group on von Willebrand factor (vWF) levels [4]. According to the Framingham Heart Study, blood group A is related with the development of CAD [13] and the Northwick Park Heart Study concluded that the AB blood type is related with an increased risk of ischemic heart disease [14].

In our study, the presence of HTB was associated with short- and long-term mortality in patients with STEMI, consistent with previous reports [3–6]. The existence of a similar relationship with the non-O blood group and the presence of HTB in the non-O blood group individuals suggest that it may play an important role in the causal link between the increased short- and long-term mortality in individuals with the non-O blood group, as shown in previous studies [4]. Several potential pathways have been suggested to link non-O blood types to enhanced thrombus formation [14–19]. Mechanistic hypotheses mainly include elevated levels of vWF, platelet hyperactivity, and heightened inflammation. Subjects with non-O blood types had higher levels of factor VIII [14, 16, 17], vWF [15, 17–19], prothrombin fragment 1 + 2 [20], and lower activated partial thromboplastin time [21], implying that they have a higher prothrombotic tendency. Elevated levels of factor VIII, vWF, and prothrombin fragment 1 + 2 could lead

Table 1. Periprocedural features of the patients according to TB

Variables	Low thrombus burden (LTB) (n = 768)	High thrombus burden (HTB) (n = 412)	p value
Door to balloon time, min	57.3±8.1	56.4±8.1	0.096
SYNTAX Score	13.7±5.1	14.5±5.3	0.012
Infarct-related artery, n (%)			
LAD and/or its branches	350 (45.6)	186 (45.1)	0.283
LCx and/or its branches	163 (21.2)	106 (25.7)	
RCA and/or its branches	245 (31.9)	115 (27.9)	
LMCA	10 (1.3)	5 (1.2)	
No-reflow	96 (12.5)	75 (18.2)	0.008
Stent type, n (%)			
DES	716 (93.2)	375 (91.0)	0.171
BMS	52 (6.8)	37 (9.0)	
Maximal stent diameter, mm	3.24±0.39	3.22±0.39	0.440
Maximal stent length, mm	30.34±6.49	29.75±6.59	0.139
Procedure type, n (%)			
Only PTCA	25 (3.3)	22 (5.3)	0.160
Direct stenting	9 (1.2)	7 (1.7)	
PTCA+stenting	734 (95.6)	383 (93.0)	
Thrombus aspiration	31 (4.0)	45 (10.9)	<0.001
Distal embolization	9 (1.2)	16 (3.9)	0.002

Values are mean ± SD or n (%) unless otherwise stated. BMS, bare-metal stent; LCx, left circumflex artery; DES, drug-eluting stent, LAD, left anterior descending artery; LMCA, left main coronary artery; PTCA, percutaneous transluminal coronary angioplasty, RCA, right coronary artery.

Table 2. Univariable and multivariable regression analysis to identify independent predictors of HTB in STEMI patients

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Diabetes mellitus	1.400 (1.091–1.797)	0.008	1.348 (1.036–1.753)	0.026
Dyslipidemia	1.415 (1.112–1.800)	0.005	1.536 (1.193–1.978)	0.001
Fasting plasma glucose	1.004 (1.001–1.007)	0.020	1.003 (1.000–1.006)	0.045
Uric acid	1.082 (1.004–1.167)	0.040	1.087 (1.005–1.175)	0.037
Albumin	0.775 (0.605–0.992)	0.043	0.708 (0.540–0.929)	0.013
C-reactive protein	1.098 (0.984–1.224)	0.094	1.083 (0.966–1.215)	0.171
Hemoglobin	1.075 (1.003–1.151)	0.040	1.046 (0.934–1.171)	0.436
Hematocrit	1.022 (1.000–1.044)	0.047	1.029 (1.006–1.053)	0.015
Peak CK-MB	1.003 (1.000–1.006)	0.042	1.003 (1.000–1.006)	0.053
Peak troponin I	1.020 (1.003–1.037)	0.021	1.018 (1.001–1.036)	0.040
Mean platelet volume	1.091 (1.002–1.188)	0.046	1.075 (0.983–1.175)	0.112
HbA1c	1.121 (1.005–1.250)	0.041	1.127 (1.008–1.260)	0.035
Multivessel disease	1.305 (1.019–1.671)	0.035	1.418 (1.095–1.835)	0.008
SYNTAX Score	1.029 (1.006–1.053)	0.013	1.026 (1.002–1.050)	0.036
ABO blood group type (non-O group)	1.595 (1.196–2.128)	0.001	1.726 (1.279–2.330)	<0.001

to increased platelet adhesion and aggregation, contributing to the formation of larger and more occlusive thrombi.

Studies have suggested that non-O blood groups may be linked to heightened inflammatory response [12]. Genome wide association studies have recently identified strong

Table 3. Hazard ratios based on Cox Proportional Survival Analysis to estimate the predictive value of non-O blood group on short- and long-term mortality in STEMI patients

Variables	Short-term mortality			Long-term mortality		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Model 1	2.232	1.244–4.005	0.007	2.195	1.352–3.564	0.001
Model 2	2.234	1.626–5.294	<0.001	2.657	1.629–4.333	<0.001
Model 3	2.480	1.361–4.520	0.003	2.347	1.433–3.844	0.001

Model 1: unadjusted. Model 2: adjusted for diabetes mellitus, dyslipidemia, fasting plasma glucose, uric acid, albumin, C-reactive protein, hemoglobin, hematocrit, peak CK-MB, peak troponin I, mean platelet volume, HbA1c, multivessel disease, SYNTAX Score. Model 3: further adjusted for HTB. CI, confidence interval; HR, hazard ratio; STEMI, ST-elevation myocardial infarction.

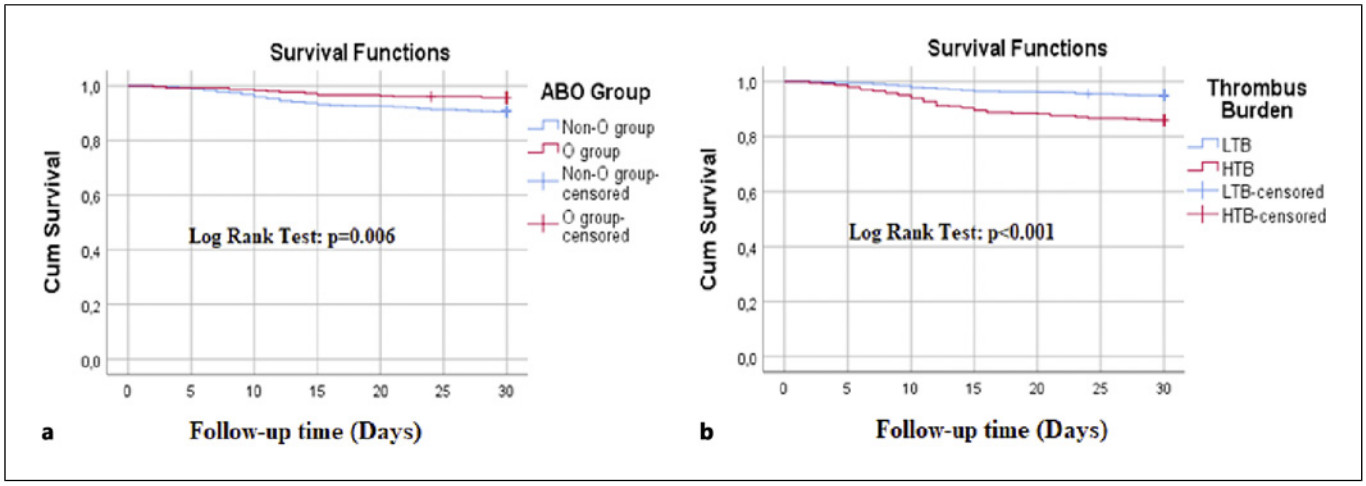

Fig. 4. Kaplan-Meier survival curves of short-term mortality in STEMI patients according to the ABO blood group (**a**) and TB (**b**) categories. LTB, low thrombus burden; HTB, high thrombus burden.

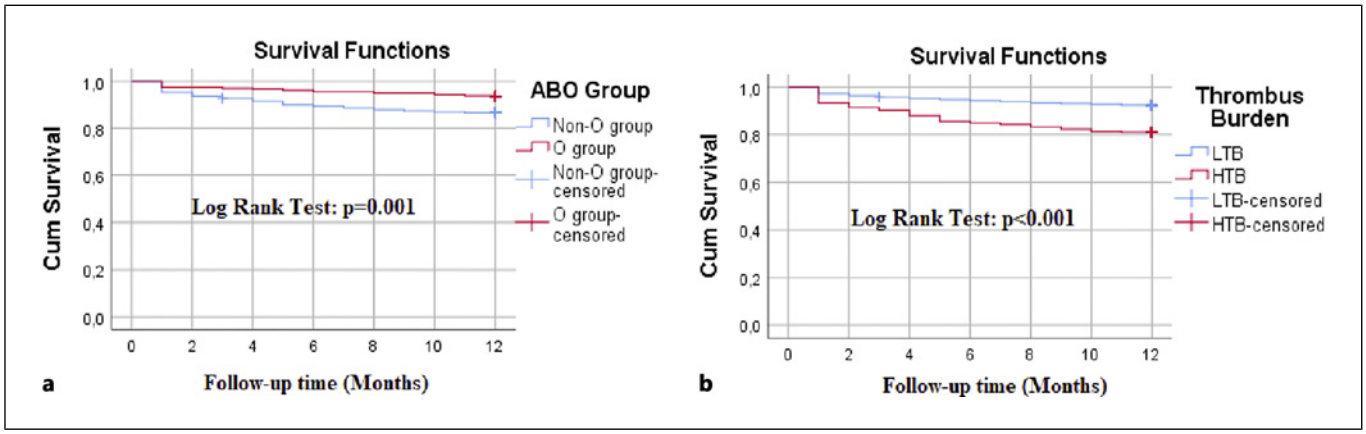

Fig. 5. Kaplan-Meier survival curves of long-term mortality in STEMI patients according to the ABO blood group (**a**) and TB (**b**) categories. LTB, low thrombus burden; HTB, high thrombus burden.

relationships of genetic polymorphisms in the ABO blood type region with levels of several inflammatory markers, including soluble levels of E-selectin, intercellular adhesion molecule 1 (ICAM1), P-selectin, tumor necrosis factor, and interleukin-6 (IL-6) [21–23]. Recently, rs8176704 in the ABO gene was discovered to have an important relationship with C-reactive protein [23], which is an acute phase reactant that reflects different degrees of inflammation and has received the most attention for its use in screening, risk prediction, and risk stratification in a variety of CAD, particularly in acute coronary syndromes [24]. Furthermore, individuals with non-O blood types, notably group A [25], were shown to have higher levels of angiotensin-converting enzyme, which promotes the inflammatory response [26]. In addition, levels of IL-10, an anti-inflammatory cytokine, are higher in the blood of patients with blood group O [27].

Inflammation plays a crucial role in the development and progression of atherosclerosis, a key factor in STEMI [24]. Increased inflammation might exacerbate thrombus formation in non-O blood group individuals with STEMI [28]. Also, non-O blood group individuals may exhibit platelet hyperactivity, characterized by increased platelet reactivity and aggregation [29]. It is known that ABO blood group loci express adhesion molecules at different levels that provide platelet and endothelial cell interaction, and it is possible that this may modulate the relationship between blood groups and thrombus load [23]. So, this heightened platelet response could contribute to the formation of larger and more occlusive thrombi. It is known that dyslipidemia predisposes to prothrombogenic environment [30] and studies have shown that individuals with the non-O blood group are prone to dyslipidemia [31]. Interestingly, one study suggests that the effect of non-O blood type on LDL-C elevation mediated roughly 10% of the effect of non-O blood type on CAD [32]. Therefore, dyslipidemic status may also contribute to increased TB in non-O group individuals.

Our study also showed that the severity of CAD was higher in the non-O blood group, which was consistent with previous studies, and revealed that the clinical outcomes were poorer in these individuals [4, 33]. HTB is known to be associated with poor clinical outcomes in patients with STEMI [13–15], and TB may be a possible link between non-O blood group and poor clinical outcomes. The evolving understanding of the relationship between the non-O blood group and TB necessitates a reevaluation of STEMI management strategies. As research continues to unravel the relationship between the non-O blood groups and STEMI prognosis, healthcare providers should consider blood groups and STEMI prognosis; healthcare providers should consider blood group information when assessing and treating patients. Tailoring treatment strategies based on a patient's blood group could potentially optimize reperfusion interventions and improve outcomes. Additionally, further investigations are needed to explore the effectiveness of personalized approaches targeting TB reduction in non-O blood group patients.

Our study had some limitations. First, the design of our study was retrospectively conducted with a relatively small sample size, which limits the ability to exclude a small difference in results based on blood groups. In addition, we did not measure the levels of vWF, factor VIII, and proinflammatory cytokines, which may have prognostic value regardless of ABO groups. Another limitation is that we did not test relationships between ABO genotypes and clinical outcomes. As the A2 genetic variant has just 20% of the activity of the A1 enzyme, there are fewer A antigens per vWF molecule and vWF levels are not considerably greater than in people with blood group O [34]. Genotyping for ABO blood group variants could provide additional prognostic insight. However, due to the retrospective design, other blood group phenotypes like Lewis (ab) were not tested. Although traditional risk factors were included in regression analysis, unmeasured confounders may have influenced results. The precise impact of treatment delays on TB could not be quantified due to limitations in study design limitations.

Conclusions

Our study underscores the significant influence of the ABO blood group on outcomes in patients with ST-segment elevation myocardial infarction (STEMI). We have established the ABO blood group as an independent predictor of both short- and long-term mortality, emphasizing its importance in risk stratification and prognostication in STEMI management. While our findings provide valuable insights, we emphasize the importance of adhering to established guidelines for optimal patient care. Healthcare providers should consider integrating the ABO blood group information into risk assessment and treatment planning within the framework of evidence-based protocols for STEMI management.

Statement of Ethics

The study adhered to the principles of the Declaration of Helsinki and received approval from the Local Ethics and Research Committee. As the study was retrospective, patient consent was not required, as determined by the Ethics Committee overseeing the study.

Conflict of Interest Statement

There were no conflicts of interest to report for all authors.

Author Contributions

Kenan Toprak, Mustafa Kaplangöray, and Muhammed Bahadır Omar: conception and design of the study. Kenan Toprak, Mustafa Kaplangöray, Muhammed Bahadır Omar, İbrahim Halil Toprak, Osman Acar, and Ayten Dursun: extraction of data and drafting of the manuscript. Kenan Toprak, Mustafa Kaplangöray, Osman Acar, Ayten Dursun, and Recep Demirbağ: analysis and interpretation of data. All authors read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the author upon request.

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