

Research Article

Prognostic Value of Endothelial Progenitor Cells in Acute Myocardial Infarction Patients

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Objective. To determine prognostic role of endothelial progenitor cells (EPCs) in intensive care patients with acute myocardial infarction (AMI). **Materials and Methods.** From December 2018 to July 2021, a total of 91 eligible patients with AMI were consecutively examined in a single intensive care unit (ICU) in China. Patients with a history of acute coronary artery disease were excluded from the study. Samples were collected within 24 hr of onset of symptoms. EPCs, defined as coexpression of CD34+/CD133+ cells or CD133+/CD34+/KDR+, were studied using flow cytometry and categorized by quartiles. Based on the 28-days mortality outcome, the patients were further divided into two groups: death and survival. The study incorporated various variables, including cardiovascular risk factors such as body mass index, hypertension, diabetes, hypercholesterolemia, atherosclerotic burden, and medication history, as well as clinical characteristics such as APACHEII score, central venous-arterial carbon dioxide difference (GAP), homocysteine, creatinine, C-reactive protein, HbA1c, and cardiac index. Cox regression analysis was employed to conduct a multivariate analysis. **Results.** A total of 91 patients with AMI who were admitted to the ICU were deemed eligible for inclusion in the study. Among these patients, 23 (25.3%) died from various causes during the follow-up period. The counts of EPCs were found to be significantly higher in the survival group compared to the death group ($P < 0.05$). In the univariate analysis, it was observed that the 28-days mortality rate was associated with the several factors, including the APACHEII score ($P = 0.00$), vasoactive inotropic score ($P = 0.03$), GAP ($P = 0.00$), HCY ($P = 0.00$), creatinine ($P = 0.00$), C-reactive protein ($P = 0.00$), HbA1c ($P = 0.00$), CI ($P = 0.01$), quartiles of CD34+/CD133+ cells ($P = 0.00$), and quartiles of CD34+/CD133+/KDR+ cells ($P = 0.00$). CD34+/CD133+/KDR+ cells retained statistical significance in Cox regression models even after controlling for clinical variables (HR: 6.258×10^{-10} and $P = 0.001$). Nevertheless, no significant correlation was observed between CD34+/CD133+ cells and all-cause mortality. **Conclusions.** The decreased EPCs levels, especially for CD34+/CD133+/KDR+ cells subsets, were an independent risk factor for 28-days mortality in AMI patients.

1. Introduction

Acute myocardial infarction (AMI), a prime example of endothelial injury, is further compounded by the occurrence of superimposed thrombosis [1]. Subsequent to endothelial damage resulting from a heart attack, endothelial progenitor

cells (EPCs) are released from the bone marrow and play a role in the development of neovascularization in adults [2]. The levels of EPCs have been linked to cardiovascular disease, with their modulation believed to be influenced by the presence of vascular risk factors and the efficacy of medication in managing these risk factors [3–7]. The association

between elevated levels of EPCs and the probability of future cardiovascular events in individuals diagnosed with stable coronary artery disease has been established [8, 9].

There is increasing evidence indicating a correlation between EPCs levels and the outcomes of patients with AMI [10]. However, due to significant heterogeneity among studies, the precise role of EPCs in predicting prognosis in AMI remains uncertain [11–17]. Consequently, our objective was to assess the relationship between EPCs levels and the outcome of AMI.

2. Materials and Methods

2.1. Ethics Statement. A prospective trial was conducted at a tertiary hospital in China, adhering to the principles outlined in the Declaration of Helsinki. The study protocol received approval from the Ethics Review Board for Clinical Studies of Ningbo Medical Centre Lihuli Hospital (Approval Number: KY2019PJ044). Informed consent was obtained from all patients, their legal representatives, and agents involved in the study.

2.2. Study Population. The diagnosis of AMI involved the presence of self-reported chest pain, accompanied by evidence of ischemia on a 12-lead electrocardiogram (EKG) or significantly elevated levels of cardiac enzymes exceeding twice the upper limit of normal as observed in angiography. Based on the EKG findings, patients with AMI were categorized into two subtypes: ST-elevation myocardial infarctions (STEMIs) or non-ST-elevation myocardial infarctions (NSTEMIs). STEMI was defined as ST elevation of 0.1 mV or more in at least two contiguous leads, while NSTEMI required the presence of ischemic changes, such as ST-segment deviation or T-wave inversion. Between December 2018 and June 2021, the intensive care unit (ICU) of Ningbo Medical Centre Lihuli Hospital admitted patients diagnosed with STEMI and NSTEMI. Consistent with prevailing guidelines, all patients underwent appropriate therapeutic interventions [18–21].

The study employed specific inclusion and exclusion criteria. Inclusion criteria encompassed the diagnostic criteria for AMI as defined by the American College of Cardiology (ACC), American Heart Association (AHA), and the European Heart Association (ECH) [18–21]. Additionally, patients admitted to ICU within 24 hr and aged 16 years or older were included. Conversely, exclusion criteria consisted of patients with previously documented acute coronary artery disease, donors, those using statins, angiotensin-converting enzyme inhibitors, activated protein C, or experiencing hemorrhagic shock, chronic obstructive pulmonary disease, hydrocortisone, or isolated acute respiratory distress syndrome.

2.3. Blood Sampling and Isolation of Peripheral Blood Mononuclear Cells (PBMCs). Twenty milliliters of blood were collected from either the central venous catheter or peripheral veins within 24 hr of symptom onset and processed within 1 hr. PBMCs were isolated from the peripheral blood using Ficoll gradient centrifugation. The Ficoll solution (Tianjin Haoyang Biological Products, China) was gently poured over the peripheral blood diluted 1:1 in

phosphate-buffered saline (PBS). Initially, the cells in the interphase were centrifuged at room temperature for 25 min at 700 G, followed by aspiration and centrifugation at 300 G for 10 min. Following the removal of the supernatant, the pellet underwent an incubation period of 8 min with erythrocyte lysis buffer. Furthermore, the cells were subjected to two washes with PBS, followed by centrifugation at 300 G for 8 min, and subsequently analyzed using flow cytometry.

2.4. Flow Cytometry. We employed a double- or three-color immunofluorescence staining technique to assess the expression of cell-surface antigens on EPCs. PBMCs, consisting of 1 million cells, were incubated at a temperature of 4°C for a duration of 30 min with 5 μ L of PE-conjugated anti-human vascular endothelial growth factor (VEGFR-2) (BioLegend, USA), FITC-conjugated anti-human CD34 (BioLegend, USA), and APC-conjugated anti-human CD133 (BioLegend, USA). Subsequently, the cells were subjected to three washes at 300 G for 5 min and then resuspended in 500 μ L of PBS. Flow cytometry analysis was conducted using a FACS Calibur flow cytometer (BD Biosciences, USA) and FlowJo version 10.4 software (FlowJo, LLC, Ashland, OR, USA). The EPCs counts were quantified as percentages relative to the total PBMCs in each participant of the study.

2.5. Variables Analyzed. All patients were assessed for the following traditional cardiovascular risk factors: age, sex, body mass index (BMI), hypertension, diabetes, hypercholesterolemia, atherosclerotic burden (AB), and previous medication use. Additionally, data on demographics, clinical variables, plasma biomarkers, medical history, medication use, and behavior were collected. Plasma biomarkers consisted of cardiac troponin I (cTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP). Vasoactive inotropic score (VIS) and central venous-arterial carbon dioxide difference (P(cv-a) CO₂, GAP) were also calculated for each patient. The primary outcome measure for patients diagnosed with AMI was all-cause mortality, assessed after a period of 28 days from admission.

2.6. Data Analysis. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL). Kolmogorov–Smirnov tests were utilized to assess the presence of normal and non-Gaussian distributions. Both nonparametric and parametric methods were employed. Multivariate logistic regression analysis was conducted to identify the independent factors influencing the prognosis of patients with AMI, and statistically significant variables from the univariate analysis were included as independent variables in the multivariate analysis. The significance level for the examination was set at $\alpha = 0.05$, and a P -value of less than 0.05 was considered statistically significant.

3. Results

3.1. Study Population. Between December 2018 and June 2021, a cohort of 186 patients diagnosed with AMI were admitted to ICU. Ultimately, a total of 91 AMI patients were included in the final analysis, with 69 experiencing STEMI and 22 experiencing NSTEMI. All patients underwent coronary angiography, with

the exception of AB distribution, no significant differences were observed between the baseline characteristics or clinical variables of STEMI and NSTEMI patients. The demographic and clinical characteristics can be found in Table S1 and S2.

EPCs (CD34+/CD133+ cells) were partitioned equally into four quartiles, namely Q1 (0–0.288%), Q2 (0.288%–0.425%), Q3 (0.430%–0.555%), and Q4 (>0.555%), based on their relative numbers. Similarly, the EPCs (CD34+/CD133+/KDR+ cells) were also categorized into quartiles: Q1 (0–0.129%), Q2 (0.129%–0.170%), Q3 (0.170%–0.230%), and Q4 (>0.230%). The APACHE II score, GAP, homocysteine (HCY), creatinine, C-reactive protein, HbA1c, cardiac index (CI), and AB exhibited significant variations among the four groups of EPCs (CD34+/CD133+ cells). Additionally, a negative correlation was observed between basal EPCs (CD34+/CD133+ cells) levels and the following parameters: APACHE II score ($P = 0.00$), GAP ($P = 0.04$), HCY ($P = 0.01$), creatinine ($P = 0.01$), C-reactive protein ($P = 0.04$), HbA1c ($P = 0.04$), AB ($P = 0.01$), and CI ($P = 0.01$). Regarding EPCs (CD34+/CD133+/KDR+ cells), there was a significant association between lower basal EPCs (CD34+/CD133+/KDR+ cells) levels and higher APACHEII score ($P = 0.00$), higher creatinine ($P = 0.03$), higher HbA1c ($P = 0.04$), higher Killip classifications ($P = 0.04$), higher AB ($P = 0.02$), and a lower CI ($P = 0.03$). A comprehensive overview of the univariate analysis can be found in Tables 1 and 2.

3.2. Incidence of Outcomes of AMI Patients. Among a cohort of 91 patients who presented with AMI, a total of 23 individuals (25.3%) experienced mortality from various causes during a 28-days follow-up period. This group, referred to as the “death group,” comprised 16 deaths that transpired within the initial 7 days of hospital admission, while the remaining seven deaths occurred between the 7th and 28th days of admission. The remaining 68 patients (74.7%) successfully survived the aforementioned time frame, as the “survival group”.

A statistically significant increases EPCs counts CD34+/CD133+ cells quartiles ($P = 0.00$), and CD34+/CD133+/KDR+ cells were observed in the survival group compared with the death group ($P < 0.05$). Univariate analysis revealed that 28-days mortality was associated with the several factors, including APACHEII score ($P = 0.00$), VIS ($P = 0.03$), GAP ($P = 0.00$), HCY ($P = 0.00$), creatinine ($P = 0.00$), C-reactive protein ($P = 0.00$), HbA1c ($P = 0.00$), CI ($P = 0.01$), CD34+/CD133+ cells quartiles ($P = 0.00$), and CD34+/CD133+/KDR+ cells quartiles ($P = 0.00$). The detailed analysis can be found in Table 3.

To explore potential correlations between survival trajectory and quartiles of EPCs, we categorized 28-days mortality into three subgroups: the survival group, the death group within 7 days, and the death group from the 7th to 28th days. Notably, both quartiles of CD34+/CD133+ cells and CD34+/CD133+/KDR+ cells exhibited significant differences across these three groups (Figures 1 and 2). Moreover, the survival group exhibited the highest EPCs count.

In Cox regression models (also known as the proportional hazards model, is a semiparametric regression model), the significance of CD34+/CD133+/KDR+ cells persisted even

after controlling for various clinical variables including age, gender, BMI, APACHEII score, ST-AMI, VIS, GAP, HCY, creatinine, C-reactive protein, HbA1c, and CI (HR: 6.258×10^{-10} and $P < 0.01$). However, no significant association was observed between CD34+/CD133+ cells and all-cause mortality ($P > 0.05$), as indicated in Table 4.

4. Discussion

In accordance with our research, a lower count of EPCs exhibited a correlation with increased mortality within 28 days among individuals diagnosed with AMI. These findings are consistent with the previous studies conducted on AMI patients, which have yielded comparable outcomes. Based on the findings of the procell study, it has been determined that basal EPCs levels possess the ability to forecast forthcoming vascular events in a cohort of 100 patients diagnosed with AMI within the initial 6 months of posttreatment monitoring. Through the utilization of a multivariate Cox regression analysis, it has been established that there exists an independent correlation between EPCs counts within the lowest quartile (HR: 10.33 and $P = 0.032$) and the occurrence of new vascular events, encompassing new acute coronary syndrome, transient ischemic attack, stroke, or any hospitalization or death resulting from the cardiovascular causes [11]. In a separate investigation involving 529 individuals diagnosed with acute coronary syndrome, it was found that subjects with low levels of EPCs exhibited a 2.46-fold increase in the likelihood of all-cause mortality (95% CI 1.18–51.3) [22].

In this study, our inclusion criteria were limited to patients diagnosed with AMI, due to their critical condition and elevated mortality risk. Consequently, our research concentrated on individuals who were admitted to the hospital within 24hr of the initial event, and we monitored them for a brief duration subsequent to their admission. It is imperative to acknowledge that our study's focus solely on AMI patients admitted to our ICU may result in the exclusion of numerous AMI patients who did not require ICU treatment due to their less severe condition. Consequently, this limitation may pose challenges when attempting to extrapolate our findings to a broader population.

AMI leads to a time-dependent increase in the mobilization of EPCs from the bone marrow to the peripheral circulation [14, 17]. This mobilization process initiates shortly after an AMI, reaches its peak after several days, and returns to baseline levels within 60 days [23]. The occurrence of myocellular necrosis triggers an acute inflammatory response, resulting in the upregulation of hypoxia-inducible factor 1-alpha (HIF-1 α). Consequently, the expression of stromal cell-derived factor-1 Alpha (SDF-1 α) is stimulated, acting as a chemotactic signal for the recruitment of EPCs to ischemic tissues [24, 25].

In our study, we did not investigate the potential correlation between peripheral and bone marrow progenitor cells in patients with AMI. Despite the aforementioned findings, it remains uncertain whether the reduced levels of EPCs observed in AMI patients are a result of diminished progenitor cell reserves in the bone marrow or impaired mobilization

TABLE 1: Comparison of study variables among EPCs (CD34+/CD133+cells) quartiles (M (Q25 and Q75) or M ± SD).

	Q1 N = 23 (0–0.288%)	Q2 N = 23 (0.288%–0.425%)	Q3 N = 23 (0.430%–0.555%)	Q4 N = 22 (>0.555%)	t/F/χ ²	P
Male (n (%))	17 (73.9)	16 (69.6)	18 (78.3)	18 (81.8)	1.04	0.79
Age (years)	70.3 ± 11.7	67.3 ± 14.4	64.7 ± 15.2	60.9 ± 17.2	1.67	0.17
BMI (kg/m ²)	22.5 ± 2.4	22.3 ± 2.5	22.1 ± 2.1	21.9 ± 2.4	0.34	0.80
APACHEII score (points)	25.8 ± 7.9	18.2 ± 6.8	14.7 ± 3.8	15.8 ± 5.6	14.67	0.00
STEMI (n (%))	17 (73.9)	15 (65.2)	19 (82.6)	18 (86.4)	3.42	0.33
cTnI (μg/L)	66.8 (42.4, 85.2)	48.5 (38.6, 76.6)	48.5 (37.1, 79.3)	43.5 (32.8, 75.5)	2.76	0.43
NT-proBNP (ng/L)	9920.9 (6483.4, 19339.0)	9999.4 (8659.3, 14098.3)	8882.9 (7208.2, 13822.9)	7824.7 (5870.9, 13802.9)	2.33	0.51
VIS (points)	15.7 ± 3.0	15.0 ± 3.1	14.9 ± 2.6	15.3 ± 3.3	0.30	0.82
GAP (mmHg)	6.1 ± 1.4	5.5 ± 1.0	5.3 ± 0.7	5.4 ± 0.7	2.95	0.04
HCY (μmol/L)	29.4 (19.2, 58.6)	17.9 (11.9, 30.8)	21.6 (15.9, 37.4)	16.4 (10.2, 29.5)	10.7	0.01
Creatinine (μmol/L)	95.8 (83.3, 119.2)	69.5 (60.5, 85.2)	88.6 (65.4, 98.3)	73.8 (59.7, 98.6)	11.09	0.01
C-reactive protein (mg/L)	43.4 (20.3, 60.0)	21.2 (4.9, 44.5)	13.9 (7.5, 36.6)	17.4 (8.6, 43.7)	8.19	0.04
HbA1c (%)	6.6 ± 2.0	5.9 ± 1.5	6.3 ± 1.8	5.2 ± 0.8	2.99	0.04
CI (L/min/m ²)	2.2 ± 0.8	2.8 ± 0.7	2.6 ± 0.7	2.3 ± 0.5	4.19	0.01
Killip classifications (n (%))					5.74	0.12
Level I–II	3 (13.0)	10 (43.5)	9 (39.1)	7 (31.8)		
Level III–IV	20 (87.0)	13 (56.5)	14 (60.9)	15 (68.2)		
AB (n (%))					2.49	0.01
Three territories	7 (30.4)	5 (21.7)	3 (13.0)	2 (9.1)		
Two territories	8 (30.8)	5 (21.7)	1 (4.3)	5 (22.7)		
One territory	8 (30.8)	13 (56.5)	19 (82.6)	15 (68.2)		

AMI, indicates acute myocardial infarction; BMI, body mass index; STEMI, ST-elevation MI; VIS, vasoactive inotropic score; GAP, central venous-arterial carbon dioxide difference; HCY, homocysteine; CI, cardiac index; AB, atherosclerotic burden.

TABLE 2: Comparison of study variables among EPCs (CD34+/CD133+/KDR+ cells) quartiles (M (Q25 and Q75) or M ± SD).

	cEPCs Q1 N = 23 (0-0.129%)	cEPCs Q2 N = 23 (0.129%-0.170%)	cEPCs Q3 N = 23 (0.170%-0.230%)	cEPCs Q4 N = 22 (>0.230%)	t/F/x ²	P
Male (n (%))	16 (69.6)	15 (65.2)	21 (91.3)	17 (77.3)	4.94	0.18
Age (years)	68.3 ± 14.2	69.7 ± 12.1	62.3 ± 14.4	63.0 ± 17.9	1.46	0.23
BMI (kg/m ²)	22.6 ± 2.5	22.2 ± 2.4	21.4 ± 1.9	22.6 ± 2.5	1.19	0.32
APACHEII score (points)	24.0 ± 8.8	18.9 ± 7.2	15.9 ± 4.8	15.6 ± 5.9	7.33	0.000
STEMI (n (%))	19 (82.6)	15 (65.2)	18 (78.3)	17 (77.3)	2.09	0.55
cTnl (μg/L)	54.4 (38.6, 80.2)	75.1 (42.4, 80.2)	58.9 (37.0, 76.6)	42.8 (32.8, 62.9)	5.47	0.14
NT-proBNP (ng/L)	8882.9 (6029.1, 19098.3)	13822.9 (8659.3, 18100.7)	8949.4 (6823.8, 13822.9)	8916.2 (6371.6, 13156.9)	4.84	0.18
VIS (points)	16.3 ± 2.9	14.5 ± 3.4	15.0 ± 2.9	15.0 ± 2.6	1.45	0.23
GAP (mmHg)	5.9 ± 1.5	5.7 ± 0.9	5.5 ± 0.8	5.0 ± 0.7	1.69	0.18
HCY (μmol/L)	27.5 (16.4, 49.3)	29.1 (20.3, 34.2)	17.7 (10.8, 24.3)	15.0 (11.3, 30.9)	11.76	0.008
Creatinine (μmol/L)	92.2 (74.3, 121.6)	84.5 (70.2, 91.0)	65.5 (58.7, 88.6)	76.5 (59.9, 102.3)	8.73	0.03
C-reactive protein (mg/L)	40.5 (10.6, 49.3)	21.2 (9.9, 60.0)	12.8 (6.9, 30.4)	23.4 (9.8, 53.9)	6.02	0.11
HbA1c (%)	6.6 ± 1.8	5.7 ± 1.5	5.6 ± 1.4	6.1 ± 1.8	1.73	0.17
CI (L/min/m ²)	2.2 ± 0.7	2.3 ± 0.6	2.7 ± 0.7	2.6 ± 0.6	3.18	0.03
Killip classifications (n (%))					8.24	0.04
Level I-II	4 (17.4)	10 (43.5)	11 (47.8)	4 (18.2)		
Level III-IV	19 (82.6)	13 (56.5)	12 (52.2)	18 (81.8)		
AB (n (%))					2.40	0.02
Three territories	7 (30.4)	7 (30.4)	3 (13.0)	0 (0.0)		
Two territories	8 (30.8)	2 (8.7)	6 (26.1)	3 (13.6)		
One territory	8 (30.8)	14 (60.9)	14 (60.9)	19 (86.4)		

AMI, indicates acute myocardial infarction; BMI, body mass index; STEMI, ST-elevation MI; VIS, vasoactive inotropic score; GAP, central venous-arterial carbon dioxide difference; HCY, homocysteine; CI, cardiac index; AB, atherosclerotic burden.

TABLE 3: Comparison of study variables between survival group and death group (M (Q25 and Q75) or M ± SD).

	Survival group (N=68)	Death group (N=23)	t/U/ χ^2	P
Male (n (%))	52 (76.5)	17 (73.9)	0.06	0.80
Age (years)	65.1 ± 15.3	68.1 ± 13.5	0.84	0.41
BMI (kg/m ²)	22.2 ± 2.4	22.1 ± 2.3	0.20	0.84
APACHEII score (points)	15.5 ± 5.0	28.0 ± 5.8	9.94	0.00
STEMI (n (%))	52 (76.5)	17 (73.9)	0.06	0.80
cTnI (µg/L)	47.8 (37.1, 76.6)	75.1 (47.0, 129.0)	2.20	0.03
NT-proBNP (ng/L)	8949.4 (6950.2, 13822.9)	13822.9 (6483.4, 19339.0)	1.41	0.16
VIS (points)	14.8 ± 2.9	16.4 ± 2.9	2.24	0.03
GAP (mm Hg)	5.3 ± 0.8	6.2 ± 1.3	3.94	0.00
HCY (µmol/L)	17.8 (12.0, 30.2)	40.3 (22.2, 58.6)	4.41	0.00
Creatinine (µmol/L)	72.9 (60.1, 91.7)	95.8 (88.4, 119.2)	4.35	0.00
C-reactive protein (mg/L)	14.3 (6.7, 35.2)	49.3 (40.5, 68.9)	5.17	0.00
HbA1c (%)	5.7 ± 1.5	6.9 ± 1.9	3.25	0.00
CI (L/min/m ²)	2.6 ± 0.6	2.2 ± 0.8	2.53	0.01
CD34+/CD133+ cells (%)	0.50 ± 0.17	0.37 ± 0.18	19.56	0.00
CD34+/CD133+/KDR+ cells (%)	0.19 ± 0.06	0.14 ± 0.02	28.96	0.00
CD34+/CD133+ cells quartiles (n (%))			49.77	0.00
Q1	5 (21.7)	18 (78.3)		
Q2	21 (91.3)	2 (8.7)		
Q3	23 (100.0)	0 (0.0)		
Q4	20 (90.9)	2 (9.1)		
CD34+/CD133+/KDR+ cells quartiles (n (%))			44.04	0.00
Q1	6 (26.1)	17 (73.9)		
Q2	17 (73.9)	6 (26.1)		
Q3	23 (100.0)	0 (0.0)		
Q4	22 (100.0)	0 (0.0)		

AMI, indicates acute myocardial infarction; STEMI, ST-elevation MI; BMI, body mass index; VIS, vasoactive inotropic score; GAP, central venous-arterial carbon dioxide difference; HCY, homocysteine; CI, cardiac index; AB, atherosclerotic burden.

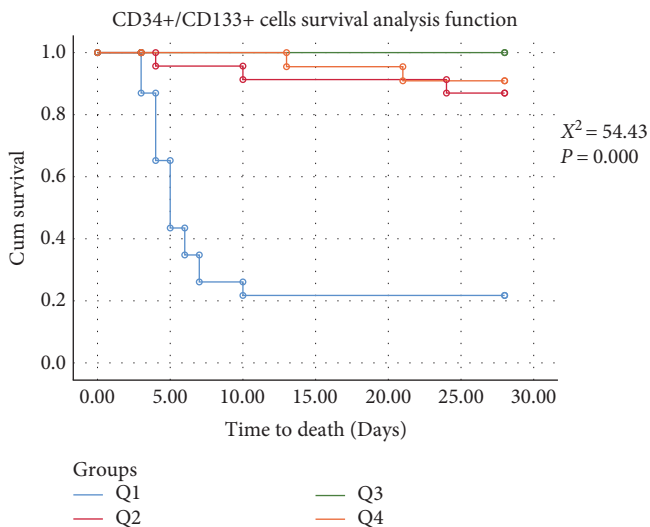


FIGURE 1: Kaplan–Meier survival curve according to CD34+/CD133+ cells (%) quartiles.

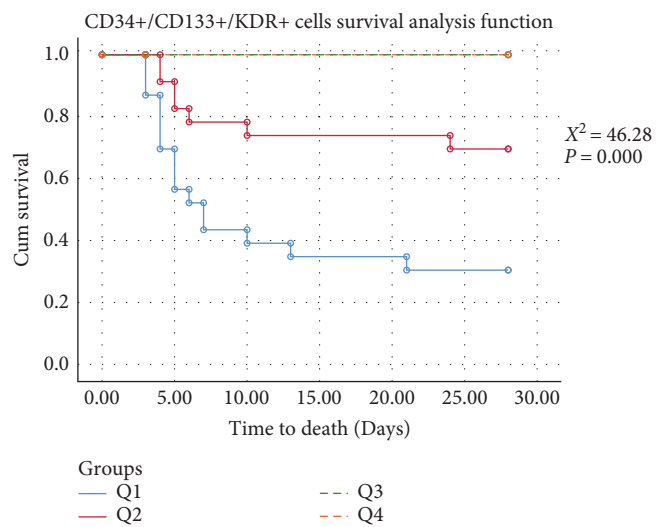


FIGURE 2: Kaplan–Meier survival curve according to CD34+/CD133+/KDR+ cells (%) quartiles.

of progenitor cells from the bone marrow [26–28]. Moreover, although the mechanism by which EPCs repair the endothelium remains incompletely understood [29–31], the application of stem cell therapy for vascular system diseases

has demonstrated encouraging outcomes. However, it is imperative to conduct larger-scale trials to assess the therapeutic effectiveness and identify the most suitable patient population.

TABLE 4: Association between EPCs counts and all-cause death in AMI patients.

	β	S_x	Wald	P value	HR	HR (95% CI)
CD34+/CD133+ cells	-4.677	2.425	3.721	0.054	0.009	8.00×10^{-4} -1.078
CD34+/CD133+/KDR+ cells	-21.192	6.270	11.423	0.001	6.258×10^{-10}	2.878×10^{-15} - 1.36×10^{-4}

Currently, two distinct strategies may be employed for the application of EPCs-based cellular therapy, particularly in the treatment of AMI, acute cerebral infarction, limb ischemia, and similar conditions [32]. One therapeutic strategy entails the administration of stem cells or endothelial progenitors via local injection directly into the ischemic tissue. Another viable approach to substitute exogenous administration is the endogenous stimulation of EPCs [33, 34]. In the presence of ischemia, the expression of VEGF, stromal cell-derived factor 1 (SDF-1), hepatocyte growth factor (HGF), and endothelin 1 (ET-1) is increased, thereby stimulating the recruitment of EPCs to the ischemic sites [32]. Furthermore, the identical factors that facilitate the mobilization of EPCs, such as VEGF and SDF-1, alongside various pharmaceutical agents including statins and erythropoietin (EPO), significantly contribute to the migration, viability, and specialization of EPCs [35–37].

In the future study, our focus was on EPCs obtained from individuals diagnosed with AMI. These cells will be divided into two distinct groups: the experimental group, which will be cultured in the endothelial cell growth medium-2 containing factors such as VEGFR, SDF-1, ET-1 etc.; and the control group, which will be cultured in the regular fetal bovine serum medium. In this study, we aim to assess the directional differentiation, proliferation, and migration capacity of two different states of EPCs. The objective is to establish a solid groundwork for subsequent drug investigations targeting AMI.

5. Conclusions

Our study demonstrates that lower EPC levels, especially for CD34+/CD133+/KDR+ cells subsets, were associated with higher mortality in the patients with AMI. These results contribute to the advancement of knowledge regarding the inherent regenerative responses following AMI and are expected to inspire the formulation of innovative approaches for cell-based therapies.

Data Availability

Data supporting the findings of this study can be obtained from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

The experiments were conceived and designed by Gongjie Ye and Jianqing Zhou. The execution of the experiments and analysis of the data were carried out by Xiaodan Chen, Yinchao Zhou, and Yongfei Song. Lei Yang and Xiaoyong

Yang provided materials and analysis tools. The paper was written by Gongjie Ye and Lei Yang. All authors have reviewed and approved the final version of the article for publication.

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Supplementary Materials

Table S1: baseline characteristics among subjects with AMI. Table S2: baseline clinical variables among subjects with AMI (M (Q25 and Q75) or $M \pm SD$). (*Supplementary Materials*)

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