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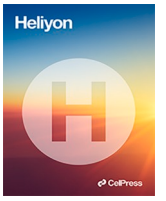

Research article

Adenosine deaminase is a risk factor for mortality after discharge in patients with acute myocardial infarction: Long-term clinical follow-up

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ABSTRACT

Background: Variations in adenosine deaminase (ADA) activity have been detected in numerous cardiovascular diseases (CVDs), but there is limited research on its role in the prognosis of CVDs. In this study, we explored the role of ADA in the prognosis of patients with acute myocardial infarction (AMI).

Method: In this study, a total of 1,574 patients with a first diagnosis of acute myocardial infarction (AMI) were followed up for a median (interquartile range [IQR]) of 77.0 (50.0, 95.0) months after discharge. Cox proportional hazards regression models were used to identify factors that are substantially valuable for patient prognosis.

Results: During the follow-up period, the mortality rate of AMI was 12.5 %. The 3-year and 5-year overall survival (OS) rates of AMI patients were 93.8 % and 91.0 %, respectively. Multivariate Cox regression analysis revealed that serum ADA (hazard ratio [HR] = 1.166, 95 % confidence interval [CI]: 1.006–1.352) was an independent risk factor for 5-year OS after discharge in AMI patients. When serum ADA was assessed in quartiles, compared with the reference group (Quartile 1), the adjusted HR for death was 2.498 (95 % CI: 1.344–4.642) in Quartile 4 for 5-year OS and 2.508 (95 % CI: 1.145–5.496) in Quartile 4 for 3-year OS.

Conclusions: Serum ADA levels at admission are a risk factor that affects the long-term prognosis of AMI patients after hospital discharge.

1. Introduction

Acute myocardial infarction (AMI) is the leading cause of death among all cardiovascular diseases (CVDs) [1]. The prevalence and mortality of AMI are high worldwide, particularly among high-risk groups such as individuals with hypertension, diabetes, hyperlipidemia and middle-aged and elderly people [2–6]. Creatine kinase and troponin are classic serum markers for the clinical diagnosis of AMI, enhancing the accuracy and efficiency of diagnosis. Additionally, percutaneous coronary intervention (PCI) and drug therapy have significantly reduced in-hospital mortality rates for AMI patients [7]. Effective monitoring and improvement of outcomes in AMI patients is another current clinical challenge. Several prognostic markers are available, such as C-reactive protein [8], interleukin-6

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(IL-6) [9], brain natriuretic peptide (BNP) [10], and microRNAs [7]; these markers are essential for the rational assessment and management of CVDs. However, there are few molecular markers that can effectively evaluate the long-term prognosis of AMI patients. Exploring molecular markers for the long-term prognosis of AMI holds important clinical significance for the standardized and personalized care of post-discharge AMI patients.

Adenosine deaminase (ADA, EC 3.5.4.4), also known as adenosine aminohydrolase, is a key enzyme involved in purine metabolism. It irreversibly converts adenosine to inosine or 2′deoxyadenosine to 2′deoxyinosine [11]. In addition to its enzymatic function, the ADA protein mediates cell-to-cell interactions involved in lymphocyte co-stimulation and endothelial activation [12]. Furthermore, elevated serum levels of ADA have been discovered in certain infectious diseases [13]. Patil et al. proposed that serum ADA activity is a marker of AMI-related inflammation [14], while Kutryb-Zajac et al. discussed the therapeutic potential of ADA inhibition in CVDs [12]. While these studies highlight the significance of ADA in CVDs, there has been limited research on the role of ADA in the prognosis of these diseases. In this study, we conducted follow-ups of AMI patients over 55 years old for a maximum of 10 years after discharge to explore the prognostic role of ADA in patients with AMI.

2. Methods

2.1. Patient population

In this study, we included 1574 patients who visited our hospital between 2012 and 2018. This was a survey study focused on middle-aged and elderly people, we initially included only AMI patients aged ≥55 years. Clinically, ADA levels are used to monitor liver function, patients with abnormal liver function often have elevated ADA levels, and the activity of ADA is also regulated by T lymphocytes, therefore, we exclude abnormal liver function and Acquired Immune Deficiency Syndrome (AIDS) patients. As shown in Fig. 1, 1859 patients with AMI over the age of 55 were treated and discharged. Initially, 39 AMI patients with a history of cancer were excluded, as were 58 patients with abnormal liver function. In addition, 1 patient with AIDS was excluded. Furthermore, 187 patients with significantly missing clinical information and laboratory data were excluded. Ultimately, 1574 AMI patients were enrolled in the study. The median follow-up time for these patients was 77.0 (IQR: 50.0, 95.0) months from discharge to the conclusion of follow-up. Clinical information and laboratory test data for AMI patients were retrieved and recorded from the hospital's electronic medical records; this information was collected retrospectively. Patients were followed up regarding their survival status by telephone. This study was approved by the Ethical Committee of Taizhou Hospital of Zhejiang Province (#K20230923).

2.2. Data collection

First, we gathered the fundamental laboratory examination information from patients with AMI after their admission to the hospital. All blood samples were collected at 6 a.m. from patients who had fasted overnight. Additionally, serum samples were obtained by centrifugation at 3500 rpm for 5 min. The concentration of BNP in the plasma was detected using an Abbott Alinity i automatic immunoassay analyzer. A Beckman DxI 800 automated chemiluminescence analyzer was also used to analyze the concentration of cardiac troponin I (cTnI) in the serum. Furthermore, a Beckman Coulter AU5800 autoanalyzer was used to detect the

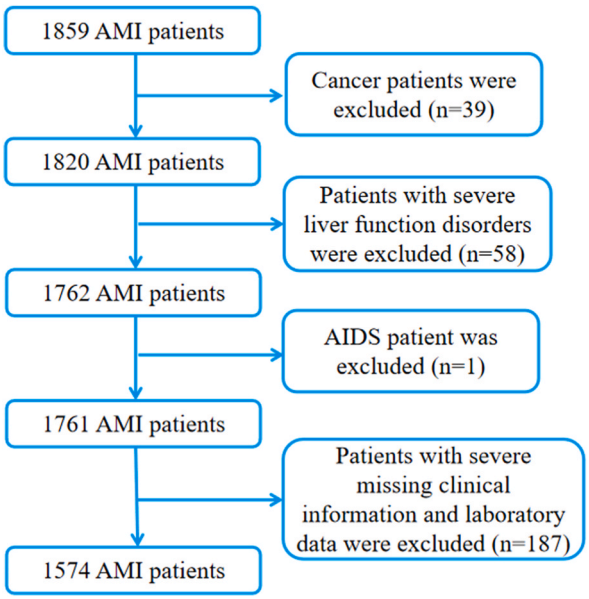

Fig. 1. Included and excluded AMI patients.

serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), ADA, triglycerides (TG), total cholesterol (TC), glucose (GLU), and C-reactive protein (CRP). A Sysmex 2100D routine hematology analyzer tested the white blood cell (WBC), platelet (PLT), and red blood cell (RBC) counts. The diagnosis of AMI was made according to the relevant guidelines established by the Chinese Medical Association [15,16]. Patients with AMI were classified into either the ST-segment elevation myocardial infarction (STEMI) group or the non-ST-segment elevation myocardial infarction (NSTEMI) group. Additionally, we also recorded the comorbidities and complications of the patients, including atrial fibrillation, heart failure, arrhythmia, pulmonary infection, chronic obstructive pulmonary disease (COPD), renal dysfunction, stroke, hypertension, and diabetes. Post-admission treatment and medication use were also recorded, including percutaneous coronary intervention (PCI), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), beta-blockers, statins, aspirin, $P2Y_{12}$ receptor antagonists, diuretics. The AMI patients were then divided into four quartiles based on serum ADA concentration: Q1: <7.0 U/L; Q2: 7.0–8.0 U/L; Q3: 8.1–10.0 U/L; Q4: >10.0 U/L. All laboratory data were the results of the first blood test after admission.

2.3. Statistical analysis

Normally distributed data were presented as mean ± standard deviation (SD), while abnormally distributed data were reported as median (interquartile range [IQR]), and categorical variables as numbers (percentages). Various parameters grouped by ADA quartiles were compared using one-way ANOVA, and differences among categorical variables were evaluated using the Chi-squared test. To intuitively evaluate the non-linear relationships between ADA levels and post-discharge mortality, as well as the risk of mortality, we applied a restricted cubic spline curve. Additionally, the Kaplan-Meier method was used to estimate the cumulative survival of AMI patients after discharge based on ADA quartiles. A Cox proportional hazards regression model was employed to estimate the correlation between ADA levels and AMI mortality rate. The regression results were reported as a 1 SD increase in ADA, treated as a continuous variable. The lowest quartile (Q1) was used as a reference and reported as a categorical variable according to ADA quartile. To further explore the relationship between ADA and mortality after discharge, we conducted a stratified analysis by subgroup variables and presented the results in the form of a forest plot. The cubic spline curve and the forest plot were obtained through statistical operations using R software. One-way ANOVA, Chi-squared test, Kaplan-Meier, and Cox proportional hazards regression were performed using statistical operations in SPSS software. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Patient population

In this cohort, there were 1,574 AMI patients with a median age of 69 years (IQR: 62–76 years), and the median follow-up time was 77.0 months (IQR: 60.0–95.0 months). During the follow-up period, 196 (12.5 %) patients died. The 3-year and 5-year overall survival (OS) rates of AMI patients were 93.8 % (95 % CI: 92.6 %–95.0 %) and 91.0 % (95 % CI: 89.6 %–92.4 %), respectively. Furthermore, the median ADA level was 8 U/L (IQR: 7–10 U/L). The characteristics of the study population are presented in Table 1. The AMI patients were divided into four groups based on their ADA concentrations. There were significant differences in age, ALP, GGT, GLU, cTnI, and BNP among the four groups (all $P < 0.05$). There were significant differences in the rate of male patients, pulmonary infection, COPD, renal dysfunction, and diabetes among the four groups (all $P < 0.05$). There were also significant differences in the percentages of AMI patients treated with PCI, ACEI/ARB, and diuretics (all $P < 0.05$).

3.2. Univariate and multivariate Cox regression analysis

We explored the relevant factors that influenced 5-year OS in AMI patients after discharge using univariate and multivariate Cox regression analyses. The univariate Cox regression revealed that age, GGT, ADA, BNP, CRP, atrial fibrillation, heart failure, pulmonary infection, COPD, renal dysfunction, and treatment with diuretics were risk factors for 5-year OS. Conversely, RBC, TG, TC, male sex, and treatment with PCI, statins, aspirin, and $P2Y_{12}$ receptor antagonists were protective factors (Table 2). By incorporating these indicators into the multivariate Cox regression, we discovered that age (HR = 1.698, 95 % CI: 1.403–2.055), ADA (HR = 1.166, 95 % CI: 1.006–1.352), BNP (HR = 1.252, 95 % CI: 1.115–1.407), and renal dysfunction (HR = 2.418, 95 % CI: 1.528–3.828) were independent risk factors, while PCI (HR = 0.530, 95 % CI: 0.346–0.813), statins (HR = 0.533, 95 % CI: 0.286–0.993), $P2Y_{12}$ receptor antagonists (HR = 0.367, 95 % CI: 0.151–0.892) were protective factors (Table 2).

3.3. ADA and mortality

Elevated ADA expression was associated with increased all-cause mortality, and the cumulative incidence of all-cause mortality during this follow-up was 6.1 %, 9.2 %, 13.3 %, and 23.9 % for patients with ADA levels in the Q1, Q2, Q3, and Q4 groups, respectively (Fig. 2; Log Rank, $P < 0.001$). The restricted cubic spline curves showed that ADA concentration had an S-shaped relationship with HR of OS in this follow-up (Fig. 3). We analyzed the correlation between baseline ADA levels and 3-year and 5-year OS (Table 3). Based on the results presented in Table 2, we constructed three adjusted models using Cox proportional hazards regression. Specifically, Model I adjusted for age, Model II adjusted for both age and BNP, while Model III adjusted for age, BNP, renal dysfunction, PCI, statins and $P2Y_{12}$ receptor antagonists. As Table 3 indicates, in the unadjusted model, a 1 standard deviation increase in ADA resulted in

Table 1
Patient characteristics by quartiles of ADA at baseline.

Variables	Total (n = 1574)	ADA Q1: <7.0 U/L	ADA Q2: 7.0–8.0 U/L	ADA Q3: 8.1–10.0 U/L	ADA Q4: >10.0 U/L	P Value
		n = 343	n = 534	n = 383	n = 314	
Age, Year	69 ± 7	67 ± 8	69 ± 8	71 ± 9	71 ± 9	<0.001
WBC, 10^9/L	8.3 (6.8, 10.4)	8.5 (6.9, 10.5)	8.6 (7.0, 10.5)	8.2 (6.5, 10.0)	8.1 (6.5, 10.7)	0.080
PLT, 10^9/L	202 (168, 242)	197 (169, 236)	203 (173, 241)	208 (170, 242)	199 (159, 255)	0.484
RBC, 10^{12}/L	4.22 ± 0.54	4.21 ± 0.48	4.23 ± 0.53	4.22 ± 0.57	4.24 ± 0.58	0.924
AST, U/L	91 (38, 218)	90 (39, 200)	100 (36, 231)	75 (38, 198)	93 (40, 228)	0.388
ALT, U/L	33 (21, 53)	32 (20, 49)	33 (21, 53)	33 (21, 53)	37 (22, 56)	0.147
ALP, U/L	86 (72, 102)	79 (69, 92)	85 (72, 100)	88 (75, 106)	93 (78, 113)	<0.001
GGT, U/L	25 (18, 40)	23 (17, 34)	24 (17, 37)	26 (18, 39)	29 (19, 55)	<0.001
TG, mmol/L	1.33 (0.96, 1.85)	1.33 (0.95, 1.86)	1.26 (0.94, 1.78)	1.35 (0.96, 1.91)	1.40 (0.99, 1.96)	0.119
TC, mmol/L	4.46 (3.77, 5.12)	4.42 (3.77, 5.15)	4.47 (3.86, 5.15)	4.52 (3.73,5.05)	4.36 (3.65, 5.13)	0.483
GLU, mmol/L	6.0 (5.3, 7.4)	5.7 (5.1, 6.7)	6.0 (5.3, 7.1)	6.0 (5.2, 7.6)	6.6 (5.5, 9.2)	<0.001
cTnI, ng/mL	15 (3, 50)	17 (6, 45)	17 (4, 59)	11 (3, 40)	13 (3, 53)	0.040
BNP, pg/mL	279 (141, 587)	203 (114, 461)	267 (147, 506)	305 (158, 625)	362 (153, 783)	<0.001
CRP, mg/L	9.2 (4.1, 25.2)	9.8 (4.1, 42.6)	8.7 (3.9, 20.1)	9.3 (4.0, 24.1)	10.5 (4.2, 24.9)	0.247
Sex, n (%)						<0.001
Male	1121 (71.2)	283 (82.5)	401 (75.1)	251 (65.5)	186 (59.2)	
Female	453 (28.8)	60 (17.5)	133 (24.9)	132 (34.5)	128 (40.8)	
STEMI, n (%)						0.793
Yes	1208 (76.7)	268 (78.1)	407 (76.2)	297 (77.5)	236 (75.2)	
No	366 (23.3)	75 (21.9)	127 (23.8)	86 (22.5)	78 (24.8)	
Atrial fibrillation, n (%)						0.155
Yes	111 (7.1)	18 (5.2)	34 (6.4)	29 (7.6)	30 (9.6)	
No	1463 (92.9)	325 (94.8)	500 (93.6)	354 (92.4)	284 (90.4)	
Heart failure, n (%)						0.985
Yes	23 (1.5)	5 (1.5)	7 (1.3)	6 (1.6)	5 (1.6)	
No	1551 (98.5)	338 (98.5)	527 (98.7)	377 (98.4)	309 (98.4)	
Arrhythmias, n (%)						0.456
Yes	88 (5.6)	16 (4.7)	26 (4.9)	24 (6.3)	22 (7.0)	
No	1486 (94.4)	327 (95.3)	508 (95.1)	359 (93.7)	292 (93.0)	
Pulmonary infection, n (%)						0.018
Yes	143 (9.1)	35 (10.2)	38 (7.1)	29 (7.6)	41 (13.1)	
No	1431 (90.9)	308 (89.8)	496 (92.9)	354 (92.4)	273 (86.9)	
COPD, n (%)						0.020
Yes	57 (3.6)	7 (2.0)	16 (3.0)	14 (3.7)	20 (6.4)	
No	1517 (96.4)	336 (98.0)	518 (97.0)	369 (96.3)	294 (93.6)	
Renal dysfunction, n (%)						0.024
Yes	98 (6.2)	18 (5.2)	31 (5.8)	18 (4.7)	31 (9.9)	
No	1476 (93.8)	325 (94.8)	503 (94.2)	365 (95.3)	283 (90.1)	
Stroke, n (%)						0.189
Yes	169 (10.7)	34 (9.9)	48 (9.0)	51 (13.3)	36 (11.5)	
No	1405 (89.3)	309 (90.1)	486 (91.0)	332 (86.7)	278 (88.5)	
Diabetes, n (%)						<0.001
Yes	369 (23.4)	294 (85.7)	104 (19.5)	96 (25.1)	120 (38.2)	
No	1205 (76.6)	49 (14.3)	430 (80.5)	287 (74.9)	194 (61.8)	
Hypertension, n (%)						0.677
Yes	893 (56.7)	186 (54.2)	312 (58.4)	218 (56.9)	177 (56.4)	
No	681 (43.3)	157 (45.8)	222 (41.6)	165 (43.1)	137 (43.6)	
PCI, n (%)						0.002
Yes	1439 (91.4)	317 (92.4)	495 (92.7)	357 (93.2)	270 (86.0)	
No	136 (8.6)	26 (7.6)	39 (7.3)	26 (6.8)	44 (14.0)	
ACEI/ARB, n (%)						0.014
Yes	392 (24.9)	100 (29.2)	109 (20.4)	106 (27.7)	77 (24.5)	
No	1182 (75.1)	243 (70.8)	425 (79.6)	277 (72.3)	237 (75.5)	
Beta-blockers, n (%)						0.341
Yes	409 (26.0)	97 (28.3)	145 (27.2)	96 (25.1)	71 (22.6)	
No	1165 (74.0)	246 (71.7)	389 (72.8)	287 (74.9)	243 (77.4)	
Statins, n (%)						0.686
Yes	1463 (92.9)	320 (93.3)	501 (93.8)	352 (91.9)	290 (92.4)	
No	111 (7.1)	23 (6.7)	33 (6.2)	31 (8.1)	24 (7.6)	
Aspirin, n (%)						0.611
Yes	1525 (96.9)	335 (97.7)	518 (97.0)	371 (96.9)	301 (95.9)	
No	49 (3.1)	8 (2.3)	16 (3.0)	12 (3.1)	13 (4.1)	
$P2Y_{12}$ receptor antagonists, n (%)						0.220
Yes	1527 (97.0)	335 (97.7)	520 (97.4)	373 (97.4)	299 (95.2)	
No	47 (3.0)	8 (2.3)	14 (2.6)	10 (2.6)	15 (4.8)	
Diuretics, n (%)						0.043
Yes	686 (43.6)	142 (41.4)	221 (41.4)	164 (42.8)	159 (50.6)	
No	888 (56.4)	201 (58.6)	313 (58.6)	219 (57.2)	155 (49.4)	

Abbreviations: no. (%), number; Adenosine deaminase, ADA; White blood cell count, WBC; Platelet count, PLT; Red blood cell count, RBC; Aspartate aminotransferase, AST; Alanine aminotransferase, ALT; Alkaline phosphatase, ALP; γ-glutamyl transpeptidase, GGT; Triglycerides, TG; Total cholesterol, TC; Glucose, GLU; Cardiac troponin I, cTnI; Brain natriuretic peptide, BNP; C-reactive protein, CRP; ST-segment elevation myocardial infarction, STEMI; Chronic obstructive pulmonary disease, COPD; Percutaneous coronary intervention, PCI; Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers, ACEI/ARB.

Table 2
Univariate and multivariate Cox regression analyses of risk factors for AMI patients after discharge.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Age, Year	2.416 (2.055, 2.842)	<0.001	1.698 (1.403, 2.055)	<0.001
WBC, 10^9/L	0.941 (0.793, 1.118)	0.491		
PLT, 10^9/L	0.956 (0.807, 1.133)	0.605		
RBC, 10^{12}/L	0.645 (0.555, 0.750)	<0.001	0.837 (0.698, 1.004)	0.055
AST, U/L	0.977 (0.825, 1.158)	0.790		
ALT, U/L	0.871 (0.673, 1.126)	0.292		
ALP, U/L	1.077 (0.951, 1.220)	0.244		
GGT, U/L	1.138 (1.012, 1.278)	0.030	0.984 (0.840, 1.152)	0.839
ADA, U/L	1.456 (1.296, 1.636)	<0.001	1.166 (1.006, 1.352)	0.041
TG, mmol/L	0.745 (0.596, 0.932)	0.010	0.906 (0.714, 1.150)	0.417
TC, mmol/L	0.823 (0.690, 0.982)	0.030	0.984 (0.832, 1.164)	0.855
GLU, mmol/L	1.081 (0.931, 1.256)	0.308		
cTnI, ng/mL	0.981 (0.830, 1.160)	0.824		
BNP, pg/mL	1.601 (1.481, 1.730)	<0.001	1.252 (1.115, 1.407)	0.000
CRP, mg/L	1.177 (1.031, 1.343)	0.016	0.995 (0.840, 1.179)	0.957
Sex (Male)	0.639 (0.455, 0.896)	0.010	0.935 (0.629, 1.388)	0.738
STEMI	0.817 (0.564, 1.185)	0.287		
Atrial fibrillation	1.729 (1.027, 2.908)	0.039	0.823 (0.475, 1.424)	0.486
Heart failure	2.765 (1.133, 6.749)	0.026	2.205 (0.867, 5.610)	0.097
Arrhythmias	1.476 (0.797, 2.730)	0.215		
Pulmonary infection	3.021 (2.029, 4.499)	<0.001	1.292 (0.801, 2.085)	0.294
COPD	2.592 (1.435, 4.682)	0.002	1.730 (0.906, 3.303)	0.097
Renal dysfunction	5.294 (3.570, 7.851)	<0.001	2.418 (1.528, 3.828)	<0.001
Stroke	1.473 (0.927, 2.341)	0.101		
Diabetes	1.116 (0.764, 1.628)	0.571		
Hypertension	1.117 (0.799, 1.560)	0.518		
PCI	0.215 (0.148, 0.310)	<0.001	0.530 (0.346, 0.813)	0.004
ACEI/ARB	1.219 (0.848, 1.752)	0.286		
Beta-blockers	0.689 (0.456, 1.042)	0.078		
Statins	0.462 (0.285, 0.749)	0.002	0.533 (0.286, 0.993)	0.047
Aspirin	0.400 (0.210, 0.761)	0.005	1.969 (0.724, 5.352)	0.184
$P2Y_{12}$ receptor antagonists	0.477 (0.234, 0.973)	0.042	0.367 (0.151, 0.892)	0.027
Diuretics	2.131 (1.521, 2.987)	<0.001	1.020 (0.990, 1.051)	0.185

Abbreviations: no. (%), number; Acute myocardial infarction, AMI; Adenosine deaminase, ADA; White blood cell count, WBC; Platelet count, PLT; Red blood cell, RBC; Aspartate aminotransferase, AST; Alanine aminotransferase, ALT; Alkaline phosphatase, ALP; γ-glutamyl transpeptidase, GGT; Triglycerides, TG; Total cholesterol, TC; Glucose, GLU; Cardiac troponin I, cTnI; Brain natriuretic peptide, BNP; C-reactive protein, CRP; ST-segment elevation myocardial infarction, STEMI; Chronic obstructive pulmonary disease, COPD; Percutaneous coronary intervention, PCI; Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers, ACEI/ARB.

corresponding unadjusted HR values of 1.396 (95 % CI: 1.205–1.617) and 1.458 (95 % CI: 1.296–1.636) for 3-year and 5-year OS, respectively. In Model III, for every 1 standard deviation increase in baseline ADA level, the risk of death increased by 1.167 (95 % CI: 1.026–1.327) for 5-year OS; this trend was also observed in 3-year OS (HR = 1.075, 95 % CI: 0.920–1.255) but was not statistically significant. The AMI patients were divided into four groups based on their ADA concentration, in the unadjusted model, increased ADA levels were associated with an increase in the mortality risk ratio for 3-year and 5-year OS (Table 3); this association still remained in Models I, II, and III. Specifically, in Model III, the 3-year and 5-year mortality risks in the Q4 group were more than double those of the Q1 group, with HR values of 2.508 (95 % CI: 1.145–5.496) and 2.498 (95 % CI: 1.344–4.642), respectively.

3.4. Serum ADA risk analysis in the AMI subgroup

Based on the 5-year OS, we analyzed the impact of serum ADA on the all-cause mortality in AMI patients after discharge according to different age subgroups (defined by the median age of 69 years), gender, and various complications/comorbidities. The adjustment factors are the same as those in Model III of Table 3, Fig. 4 reveals that serum ADA was a risk factor in the age ≥69 years subgroup (HR = 1.160, 95 % CI: 1.014–1.328), but it was not significant in the age <69 years subgroup (HR = 1.216, 95 % CI: 0.801–1.845). Furthermore, serum ADA emerged as a risk factor for 5-year OS across various subgroups, including those with NSTEMI, no atrial fibrillation, no heart failure, no arrhythmias, no pulmonary infection, no COPD, no renal dysfunction, no hypertension, and those

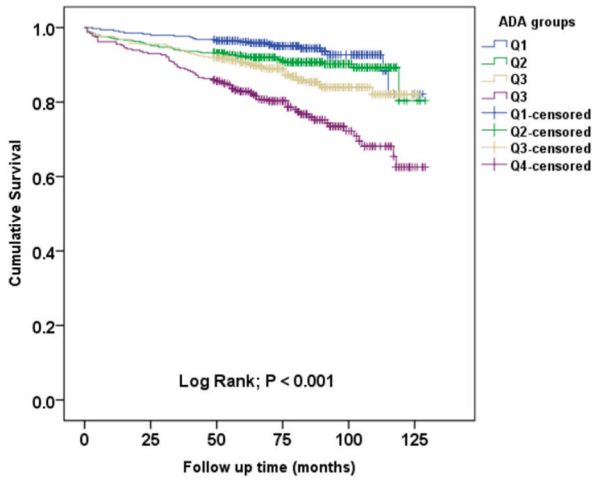

Fig. 2. Kaplan-Meier survival analysis of cumulative survival curves in this follow-up according to ADA quartile level. The AMI patients were divided into four quartiles according to serum ADA concentration: Q1: <7.0 U/L; Q2: 7.0–8.0 U/L; Q3: 8.1–10.0 U/L; Q4: >10.0 U/L. Abbreviations: Adenosine deaminase, ADA.

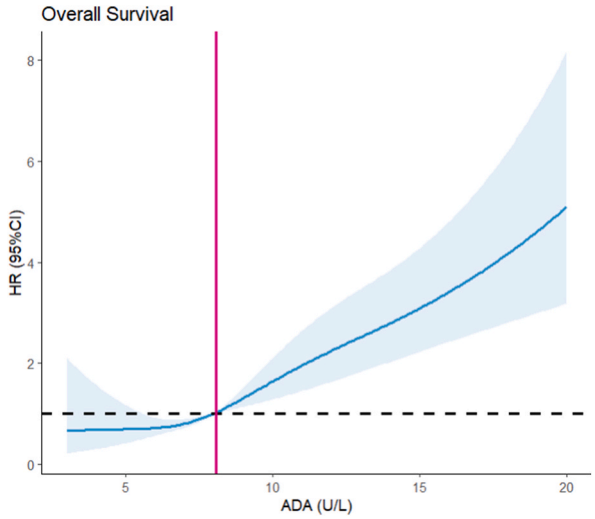

Fig. 3. Restricted cubic spline fitting for the association between ADA level and HR of overall survival in the follow-up. The shaded area represents the 95 % CI. Abbreviations: Adenosine deaminase, ADA; Hazard ratio, HR.

treated with PCI, beta-blockers, statins, aspirin and $P2Y_{12}$ receptor antagonists, as well as the no diuretics therapy subgroup.

4. Discussion

In this study, we conducted a long-term follow-up for first-time AMI patients after discharge. We found that age, ADA, BNP and renal dysfunction were independent risk factors for 5-year OS in AMI patients after discharge, while PCI, statins and $P2Y_{12}$ receptor antagonist were independent protective factors.

ADA is a housekeeping enzyme involved in purine metabolism, in addition to exercising the catalytic function of its enzymes, ADA is also involved in the regulation of various immune cells such as lymphocytes and neutrophils through the adenosine receptor pathway [17]. Furthermore, serum ADA activity has been recognized as a marker of AMI-related inflammation [14], and ADA activity in STEMI patients is substantially higher than that in NSTEMI patients [18]. Elevated ADA activity stimulates superoxide radical-induced reperfusion injuries due to reduced protective adenosine levels and elevated inosine-producing superoxide radical levels [12]. Additionally, ADA significantly attenuates the coronary vasodilatory response to exogenous adenosine and 20-s ischemia [19]. Inhibiting ADA expression and activity is expected to become an effective cardioprotective therapy and ADA has become a potential target for the treatment of CVDs [12].

To date, there has been little research on the prognosis of CVDs in relation to ADA. A 12-month follow-up study on acute coronary

Table 3
HRs or ORs (95 % CIs) associated with ADA for outcomes in AMI patients after discharge.

Models	ADA Q1: <7.0 U/L	ADA Q2: 7.0–8.0 U/L	ADA Q3: 8.1–10.0 U/L	ADA Q4: >10.0 U/L	1-SD increase in ADA
3-year OS					
Unadjusted	1	2.706 (1.250, 5.858)	2.626 (1.175, 5.872)	4.826 (2.234, 10.425)	1.396 (1.205, 1.617)
model I	1	2.142 (0.987, 4.649)	1.709 (0.757, 3.859)	3.142 (1.444, 6.835)	1.258 (1.080, 1.466)
model II	1	2.234 (1.030, 4.844)	1.488 (0.654, 3.384)	2.502 (1.143, 5.477)	1.096 (0.938, 1.280)
model III	1	2.434 (1.122, 5.282)	1.956 (0.857, 4.464)	2.508 (1.145, 5.496)	1.075 (0.920, 1.255)
5-year OS					
Unadjusted	1	2.097 (1.124, 3.913)	2.493 (1.319, 4.711)	4.759 (2.595, 8.730)	1.458 (1.296, 1.636)
model I	1	1.650 (0.882, 3.084)	1.599 (0.839, 3.048)	3.044 (1.49, 5.619)	1.310 (1.162, 1.478)
model II	1	1.664 (0.891, 3.111)	1.427 (0.745, 2.733)	2.502 (1.347, 4.650)	1.184 (1.042, 1.345)
model III	1	1.789 (0.957, 3.343)	1.728 (0.901, 3.314)	2.498 (1.344, 4.642)	1.167 (1.026, 1.327)

Unadjusted model adjusted for: none.
Model I, adjusted for: age.
Model II, adjusted for: age, BNP.
Model III, adjusted for: age, BNP, renal dysfunction, PCI, statins, $P2Y_{12}$ receptor antagonists.
Abbreviations: Acute myocardial infarction, AMI; Overall survival, OS; Brain natriuretic peptide, BNP; Adenosine deaminase, ADA; Percutaneous coronary intervention, PCI; Hazard ratio HR; Odds ratio, OR; Confidence interval, CI; Standard deviation, SD.

syndromes (ACS) revealed that the polymorphism of the ADA gene rs73598374 did not affect the long-term prognosis of ACS patients receiving dual antiplatelet therapy with acetylsalicylic acid and ticagrelor [20]. In our study, we divided ADA concentrations into four quartiles and found that increasing ADA levels corresponded to a higher AMI mortality rate. Therefore, AMI patients with higher ADA concentrations at admission should be closely monitored after discharge to prevent adverse outcomes.

ADA is an enzyme that catalyzes adenosine to inosine. At present, medical discussions on ADA mainly focus on its inflammatory regulatory function, and some ADA inhibitors have been developed as anti-inflammatory drugs [21]. The research on ADA in cardiovascular diseases is gradually increasing [22–24], and studies have shown that adenosine can alleviate ischemia/reperfusion injury and increase coronary artery blood flow during active stress and hypoxia. High levels of ADA rapidly metabolize adenosine, and the advantages of adenosine will be lost. Finally, adenosine is catalyzed to inosine, which can generate superoxide radicals and exacerbate ischemia/reperfusion injury [24]. Therefore, ADA inhibitors may have important potential functions in improving CVDs. The clinical drug dipyridamole, which has been developed, can inhibit the reuptake of adenosine, leading to platelet inhibition and vasodilation [25]. At present, only dipyridamole is well applied in clinical practice, and the development of more ADA inhibitors to improve CVDs is of great clinical significance [21,25].

We also found that age, BNP and renal dysfunction were independent risk factors of mortality in AMI patients after discharge, while the treatment with PCI, statins and $P2Y_{12}$ receptor antagonists were independent protective factors. A previous study reported that plasma BNP is a reliable predictor of cardiovascular mortality [10]. Moreover, the follow-up BNP level soon after discharge was a powerful prognostic marker for death in AMI patients [26]. Renal dysfunction is a common concomitant illness in patients with AMI. A 4-year follow-up study revealed that patients with AMI were at a higher risk of death due to acute worsening in renal function (WRF) [27]. Additionally, the severity of acute kidney injury (AKI) evaluated during the first week of hospitalization was an independent predictor of 2-year mortality in AMI patients after discharge [28]. In elderly patients with AMI, age and the estimated glomerular filtration rate (eGFR) quartile, a renal function index, were associated with death [29]. PCI is the routine treatment for AMI, and long-term follow-up studies have shown that those who underwent PCI can effectively reduce the mortality in AMI patients, which is consistent with our findings [30,31]. Statins are classic and effective lipid-lowering drugs, widely used in the treatment of hyperlipidemia; they have been associated with a reduced risk of all-cause death in a 24-month of follow-up study [32]. $P2Y_{12}$ receptor blockers are platelet aggregation inhibitors used to prevent recurrent ischemic events and restore coronary artery perfusion in AMI; these antagonists can prevent heart failure in patients with AMI [33].

Advantages and Limitations: Advantages: At present, there are few reports indicating that ADA is an independent risk factor for death in AMI patients after discharge. Our research results provide new reference indicators for patients with AMI to facilitate healthcare decisions after discharge. Moreover, the longest follow-up period in this study was 129 months, fully demonstrating the long-term prognostic effect of ADA on AMI patients. Limitations: The patients in this study were all over the age of 55, so our research findings only represent the status of the middle-aged and elderly populations. In future studies, we will expand the sample size to include younger populations and explore the impact of ADA on the prognosis of younger and middle-aged AMI patients.

In summary, we have determined through long-term follow-up that ADA is an independent risk factor for death after discharge in first-time AMI patients. We suggest assessing ADA levels when AMI patients are first admitted and including them in the prognostic evaluation indicators after discharge to provide proactive preventive care for AMI patients. The predictive effect of ADA on AMI prognosis may vary across different age groups, comorbidities, and treatments. As a result, the application of ADA in predicting the prognosis of AMI patients should be considered comprehensively in conjunction with the patient's clinical information.

Research funding

None declared.

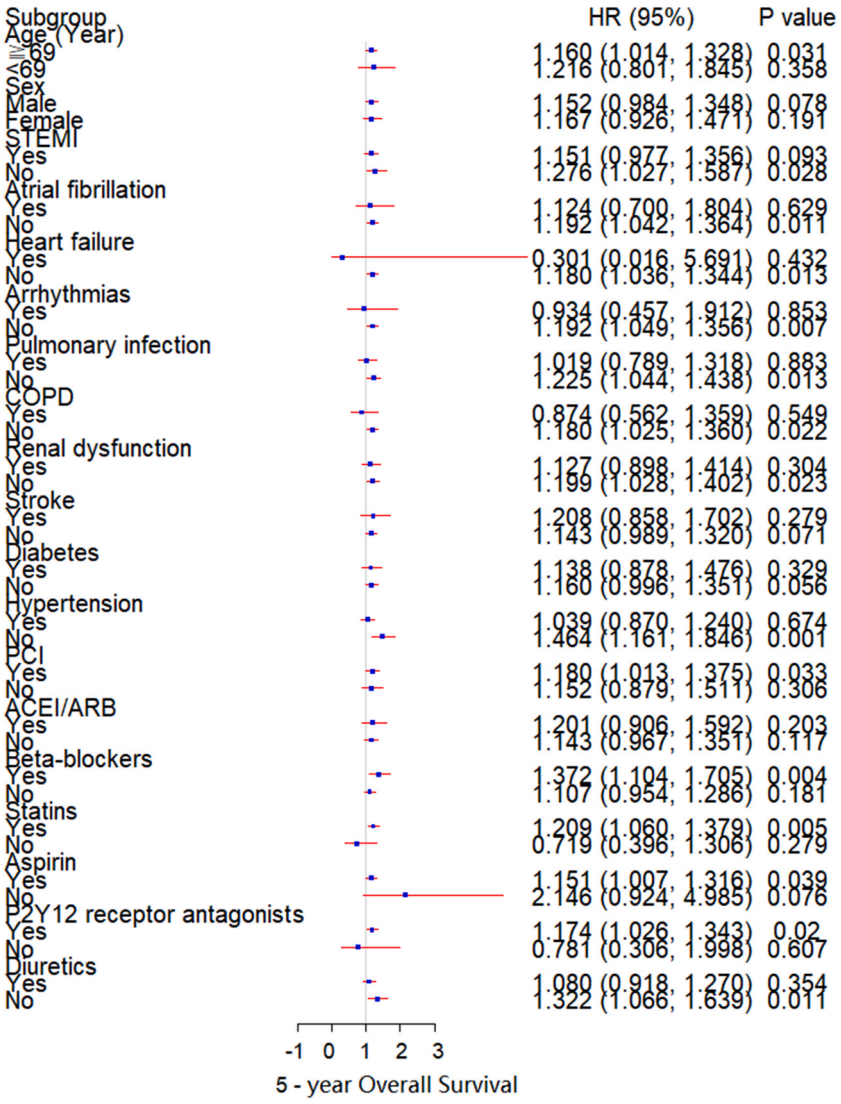

Fig. 4. Stratified analysis of HRs in 5-year overall survival follow-up of AMI patients. Abbreviations: Acute myocardial infarction, AMI; Adenosine deaminase, ADA; ST-segment elevation myocardial infarction, STEMI; Chronic obstructive pulmonary disease, COPD; Percutaneous coronary intervention, PCI; Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers, ACEI/ARB; Hazard ratio, HR.

Ethical approval and informed consent

This research did not affect the patients' health and privacy. All procedures performed in the studies involving human participants accorded with the ethical standards of the Medical Ethics Committee of Taizhou Hospital of Zhejiang Province (#K20230923).

Availability of data and materials

Dataset used during the current study is available from the corresponding author on request.

CRediT authorship contribution statement

Xiaoli Zhu: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Yijun Chen:** Software, Resources, Investigation. **Yangjun Cai:** Software, Project administration, Methodology. **Jinxi Hu:** Writing – review & editing, Resources, Methodology, Investigation.

Declaration of competing interest

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. The authors declare that they have no competing interests.

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