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Research article

α-HBDH is a superior to LDH in predicting major adverse cardiovascular events in patients with acute aortic dissection

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ABSTRACT

Objective: Acute aortic dissection (AAD) with a high mortality and postoperative complications remains presently no effective indicators to conjunctly predict the short-term mortality and the prognosis. This study aimed to investigate the predictive role of α-HBDH on in-hospital mortality and postoperative Major adverse cardiovascular events (MACE) in patients with AAD.

Methods: In this retrospective study, a total of 369 enrolled patients from 2015 to 2021 were divided into three groups (T1: low, T2: medium and T3: high) based on the tertiles of α-HBDH levels on admission. In terms of the preoperative, intraoperative and postoperative indicators among 3 groups, the relationship between α-HBDH and studying endpoints was determined by logistic regression models, along with the consolidation using Kaplan–Meier and restricted cubic spline (RCS) analysis for predicting the in-hospital death and MACE complications. Last, subgroup analysis further verified the predictive value of α-HBDH.

Results: Logistic regression analysis showed that α-HBDH was independently associated with in-hospital mortality of patients with AAD [OR(95CI): 4.771(1.043–21.832), P = 0.044] and MACE [OR(95CI): 9.869(2.148–45.349), P = 0.003]. Moreover, Kaplan-Meier analysis also showed an increased α-HBDH levels associated with poor survival within 30 days (log rank test, P < 0.01), especially in acute Stanford A dissection. RCS presented that 204 U/L was the optimal cut-off value of α-HBDH for in-hospital mortality and postoperative MACE, which facilitated clinical stratification of patients with AAD. Subgroup analysis confirmed a stable correlation between α-HBDH level and hospital mortality and MACE (P > 0.05).

Conclusions: α-HBDH is a predictor of the in-hospital mortality and postoperative MACE, guiding admission stratification of patients with AAD.

1. Introduction

Acute aortic dissection (AAD) is a severe aortic disease with a high morbidity and mortality [1–4]. Surgical correction of AAD should be performed as soon as possible; otherwise, patients may die from aortic rupture, pericardial tamponade, aortic insufficiency, and heart failure. Unfortunately, the occurrence of postoperative adverse events after surgical treatment still existed no matter what type of acute type A or B AAD (ATAAD or ATBAD). Especially for acute ATAAD, the perioperative mortality rate is 30%–60 % [5]. With

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Abbreviations and Acronyms

FET	frozen elephant trunk
TEVAR	thoracic endovascular aortic repair
CABG	coronary-artery-bypass-grafting
AVR	aortic valve replacement
AVP	aortic valvuloplasty
CPB	cardiopulmonary bypass
DHCA	deep hypothermic circulatory arrest
MACE	major adverse cardiovascular events

the improvement in treatments and postoperative management, the perioperative mortality rate has decreased to 13%–25 % [6], whereas the risk of early postoperative complications affecting the nervous, respiratory, digestive, and circulatory systems was still 58.3 % [7]. Furthermore, Major adverse cardiovascular events (MACE) following AAD surgery is associated with a high mortality and poor prognosis.

α-hydroxybutyrate dehydrogenase (α-HBDH) is same as the lactate dehydrogense (LDH), which is a key enzyme of anaerobic metabolism and a functional checkpoint for glucose restoration during gluconeogenesis and single-stranded DNA metabolism [8]. LDH consists of five isozymes with different combinations of H and M subunits: LDH1 (H4), LDH2 (H3M), LDH3 (H2M2), LDH4 (HM3), and LDH5 (M4), among them, α-HBDH reflects the activity of LDH1 and LDH2, which are mainly distributed in heart and enzymatic activity of heart accounts for more than half of the total enzymatic activity. Recent evidence indicates that the preoperative serum α-HBDH level is associated with in-hospital mortality and postoperative intensive care admission (unplanned intensive care unit admissions) after non-cardiac surgery [9]. Meanwhile, the predictive value of α-HBDH for cardiac infarction has been reported, which contributes to the hypothesis that it may also represent a poor prognosis following cardiac ischemia in patients with AAD [10]. However, it remains unclear whether α-HBDH is associated with the initiation and progression of AAD as well as MACE. The aim of this study was to explore the prognostic ability of α-HBDH on postoperative in-hospital mortality and MACE of patients with AAD.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the data of 369 consecutive patients with AAD seen at the cardiac surgery or emergency department, Fourth Hospital of Hebei Medical University between January 2015 and June 2021. Diagnosis of AAD in all patients (aged 18 years or

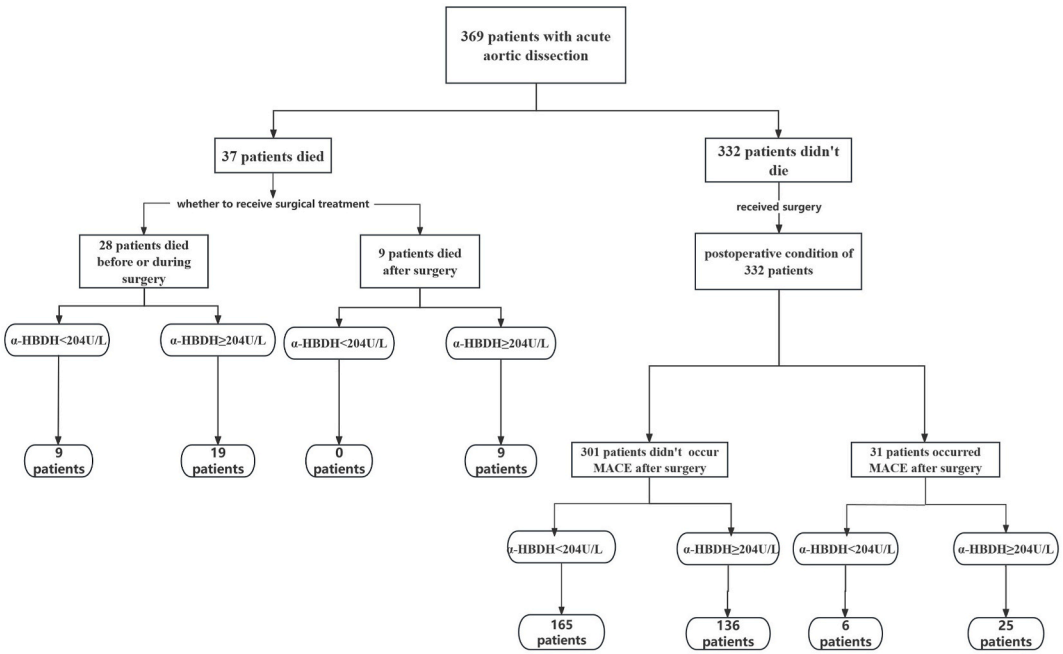

Fig. 1. Flow chart of patient AAD with α-HBDH levels.

older) was confirmed by computed tomographic angiography, with duration of onset ≤14 days as definitive diagnosis. All patients with complete data, including α-HBDH and other laboratory tests results, that were available on hospital admission as well as those who developed symptoms within 72 h were included in the study. The exclusion criteria were as follows: patients with incomplete data, Marfan's syndrome, pregnancy, traumatic dissection, and chronic aortic dissection. We classified the enrolled patients according to whether or not they died, and then again according to whether or not surgery was performed, and all surviving patients underwent surgery. To be more comprehensive, we did not exclude patients who died, and 369 patients were eventually included (Fig. 1). Using the tertiles of the α-HBDH level on admission, patients were divided into three groups: T1, ≤178 U/L (n = 126); T2, 179–259 U/L (n = 122); and T3, ≥260 U/L (n = 121).

This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (2021k7359) and have obtained informed consent from the research participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee.

2.2. Clinical data collection

Clinical variables were collected from the patients' medical records and included gender, age, past medical history (hypertension, diabetes, coronary heart disease, surgical history), cigarette smoking, alcohol intake, systolic blood pressure (SBP), diastolic blood pressure, type of AAD (type A or B), length of hospital stay, and in-hospital mortality. Cigarette smoking was defined smoking every day for more than 6 months. Drinking was defined as alcohol consumption ≥25 g per day or ≥100 g per week for more than 1 year.

2.3. Laboratory test indicators

Peripheral blood sample collection was performed prior to any surgical/endovascular treatment. Levels of α-HBDH (reference range, 72–182 U/L), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), urea (BUN), glucose, platelet count, hemoglobin, red blood cell count, white blood cell count, neutrophil count, lymphocyte count, mononuclear cell count, LDH, and serum K^+, Na^+, Cl^-, and Ca^{2+} were measured.

2.4. AAD therapy

Patients with AAD complicated with hypertension or other chronic diseases were intravenously administered hypotensive drugs or nitroglycerin preoperatively to maintain the SBP at 100–120 mmHg. The choice of surgical plan was determined by cardiologists and surgeon decides. Patients with type A AAD underwent surgical repair (Bentall, total arch replacement, hemiarch replacement, aortic valve replacement(AVR), aortic valvuloplasty (AVP) and coronary-artery-bypass-grafting(CABG)) under cardiopulmonary bypass, while patients with type B AAD underwent interventional therapy Thoracic endovascular aortic repair (TEVAR) or frozen elephant trunk (FET). Complicated type B AAD was treated with thoracic endovascular aortic repair. If cases of type B AAD with very low risk of retrograde tear and vascular risk were encountered, they were repaired with cardiopulmonary bypass.

2.5. Definition of renal insufficiency, hepatic insufficiency, and MACE

Renal insufficiency was defined as a decrease of ≥30 % in the glomerular filtration rate or effective renal plasma flow compared with baseline values [11–13]. Acute kidney injury was defined as an increase in serum creatinine levels >0.3 mg/dL or 1.5 times above baseline values within 7 days.

Hepatic insufficiency was diagnosed when ALT or AST levels were >80 U/L, or there were signs of liver failure. Infection refers to the sum of infections in the lungs and wounds.

MACE constituted a combined endpoint mainly including the following events: cardiovascular death, coronary revascularisation, unstable angina, myocardial infarction, congestive heart failure (CHF), arrhythmias, cardiac arrest, pulmonary embolism or stroke [14].

2.6. Study outcomes and follow-up

In-hospital mortality and length of hospitalization were obtained from medical records. All-cause mortality during hospitalization was defined as the primary endpoint, and the secondary endpoint was the incidence of MACE.

2.7. Statistical analysis

Data with normal distribution were expressed as mean ± standard deviation, and one-way analysis of variance was used to compare more than two groups. Non-normally distributed variables were expressed as median (P25, P75). The Kruskal-Wallis H test was used for multi-group comparison in terms of continuous variables. Categorical variables were shown as frequency (%) and compared by the Chi-square test and Fisher's exact test. Multivariate logistic regression analysis was used to determine factors associated with the postoperative prognosis in terms of the odds ratio and 95 % confidence interval. In multivariate regression analysis, potential confounders were adjusted ($P < 0.05$). Kaplan–Meier curves were created to determine the cumulative survival of each group through the log rank test for comparison. RCS was used to explore the relationship between α-HBDH and in-hospital mortality and

MACE and to determine the optimal value for stratification. Subgroup analyses for age, gender, hypertension, AST and Cr levels, smoking and drinking, type of AAD, and LDH level at baseline were performed with tests for interaction. SPSS 25.0 and R version 4.2.1 were used for all statistical analyses. $P < 0.05$ was considered statistically significant. Patient characteristics, principal results, and implications of this study are shown in Fig. 1.

3. Results

3.1. Characteristics of patients with AAD

There were 369 patients with AAD with a median age of 53.2 years; 273 (74 %) were men. The clinical features at baseline are displayed in Table 1. The median duration of hospitalization was 12 days. Characteristics of patients included hypertension (73.2 %), diabetes (1.9 %), coronary artery disease (4.1 %), drinking (58.5 %), and smoking (53.4 %). Compared to baseline values, changes in ALT, AST, creatinine, BUN, blood glucose, and LDH levels during hospitalization were all significant (all $P < 0.05$).

3.2. Intraoperative characteristics of patients with ATAAD and ATBAD

A total of 133 patients with type A dissection excluding type B dissection, preoperative death and missing data were included (Supplementary Table 1). High α-HBDH levels (Tertile III) had more likely intraoperative CABG (14 % vs 2.4 % vs 0, P = 0.014), Higher α-HBDH levels may have a longer cardiopulmonary bypass (191.00 (152.50, 240.00) minutes vs 165.50(150.25, 192.25) minutes, P <

Table 1
Baseline characteristics of patients with AAD.

Characteristic	Total (n = 369)	Tertile I (≤178 U/L) (n = 126)	Tertile II (179–259 U/L) (n = 122)	Tertile III (≥260 U/L) (n = 121)	*P*-value
Demographics					
Age(y)	53.2 (44.5, 63.0)	54.0 (47.8, 64.0)	53.0 (44.5, 64.0)	51.0 (41.0, 62.0)	0.107
Gender(male)	273.0 (74.0)	93.0 (73.8)	94.0 (77.0)	86.0 (71.1)	0.569
Comorbidities					
Hypertension	270.0 (73.2)	96.0 (76.2)	82.0 (67.2)	92.0 (76.0)	0.193
Diabetes	7.0 (1.9)	3.0 (2.4)	2.0 (1.6)	2.0 (1.6)	0.887
CHD	15.0 (4.1)	5.0 (4.1)	5.0 (4.1)	5.0 (4.1)	0.998
Smoking	197.0 (53.4)	68.0 (54.0)	73.0 (59.8)	56.0 (46.3)	0.105
Drinking	76.0 (58.5)	74.0 (58.7)	66.0 (54.1)	66.0 (54.1)	0.720
History of cardiac injury[a]	30.0(8.1)	3.0(2.4)[b]	5.0(4.1)[c]	22.0(18.2)	<0.001
History of Surgery	321.0 (87.0)	113.0 (89.7)	106.0 (86.9)	102.0 (84.3)	0.453
Type of AAD					0.198
ATAAD	216.0 (58.5)	67.0 (53.2)	71.0 (58.2)	78.0 (64.5)	
ATBAD	153.0 (41.4)	59.0 (46.8)	51.0 (41.8)	43.0 (35.5)	
Admission indictors					
SBP	136.0 ± 28.5	140.8 ± 25.5	138.7 ± 30.0	139.3 ± 29.1	0.833
DBP	81.0 ± 19.0	81.2 ± 17.6	80.5 ± 20.6	81.3 ± 18.9	0.937
ALT	22.2 (15.6, 31.5)	18.9 (13.9, 29.4)	21.2 (15.5, 31.2)[c]	25.2 (17.9, 34.9)	0.002
AST	29.9 (19.0, 49.7)	21.9 (17.8, 35.2)[b]	28.7 (20.4, 47.0)[c]	43.7 (26.1, 72.4)	<0.001
Creatinine	79.0 (62.0, 108.0)	70.0 (57.0, 92.0)	77.0 (62.0, 99.0)[c]	96.0 (73.0, 130.0)	<0.001
BUN	6.1 (4.7, 8.1)	5.6 (4.4, 7.5)	6.0 (4.9, 7.9)[c]	6.8 (5.1, 9.1)	0.002
Glucose	7.1 (6.0, 8.8)	6.8 (5.8, 8.0)	7.2 (6.1, 8.5)[c]	7.3 (6.2, 9.4)	0.044
Hematologic signatures					
Platelet	171.5 (134.0, 211.0)	177.5 (137.8, 216.5)	165.5 (133.0, 203.8)	171.5 (133.3, 213.3)	0.415
HB	128.3 ± 17.0	128.6 ± 15.2	128.0 ± 18.0	128.5 ± 18.0	0.960
RBC	4.1 ± 0.7	4.1 ± 0.5	4.1 ± 0.6	4.2 ± 0.7	0.482
WBC	11.5 (9.4, 14.2)	11.3 (9.4, 13.5)	11.7 (9.5, 14.5)	11.6 (9.3, 14.2)	0.900
NEUT	9.8 (7.5, 12.5)	9.8 (7.2, 11.9)	9.8 (7.5, 12.9)	10.0 (7.5, 12.4)	0.934
LYM	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)	0.8 (0.7, 1.2)	0.9 (0.7, 1.4)	0.051
LDH	232.9 (189, 349.3)	175.8 (156.7, 206.3)[b]	233.8 (208.8, 281.7)[c]	380.0 (293.5, 472.8)	<0.001
Electrolytes signatures					
Serum K^+	4.0 (3.4, 4.0)	4.0 (3.4, 4.0)	3.9 (3.4, 4.0)	4.0 (3.5, 4.2)	0.339
Serum Na^+	138.0(136.0,140.0)	138.0(135.7140.0)	139.0(136.0,141.0)	138.0(136.0,141.0)	0.082
Serum Cl^-	104.0 (101.0, 107.0)	138.0 (135.8, 139.3)	139.0 (136.0, 141.0)	138.0 (136.0, 141.0)	0.093
Serum Ca^{2+}	2.2 (2.1, 2.3)	2.2 (2.1, 2.3)	2.2 (2.1, 2.3)	2.2 (2.1, 2.3)	0.758

Note: ALT, Alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CHD, Coronary heart disease; DBP, diastolic blood pressure; HB, hemoglobin; LYM, lymphocyte count; LDH, lactic dehydrogenase; MONO, mononuclear cell count; NEUT, neutrophil count; RBC, red blood cell count; SBP, systolic blood pressure; WBC, white blood cell count.

[a] Patients with any one of preoperative comorbidities including pericardial effusion, tamponade, cardiac infarction, cardiac insufficiency, cardiogenic shock, heart failure etc. pericardial tamponade, pericardial effusion, and heart failure.

[b] The comparison between T1 and T3 group P < 0.05.

[c] The comparison between T2 and T3 group P < 0.05.

0.05), And a longer aortic cross clamp time (122.00 (104.50, 163.00) minutes vs 113.00 (86.75, 134.50) minutes, P < 0.05) (Supplementary Table 1). α-HBDH levels did not show difference in the interventional procedure (all P > 0.05). A total of 216 ATAAD, 153 ATBAD in 369 AAD patients, 3 in ATBAD, had severe involvement and repair under cardiopulmonary bypass, and the rest underwent TAVER or FET (Supplementary Table 2).

3.3. Short-term outcomes of patients with AAD

Table 2 shows the short-term postoperative outcomes of patients with AAD. The overall in-hospital mortality was 10 %; the mortality rates in the T1, T2, and T3 groups were 3.2 %, 8.2 %, and 19 %, respectively, showing a tendency for mortality with increased α-HBDH levels. There were statistically significant differences in the incidence of MACE among the three groups (4 %, 9 %, 27.3 %, respectively; all $P < 0.001$). However, there were no significant differences in the incidences of other conditions, including multiple organ failure, hepatic insufficiency, infection, paraplegia, among all groups (all $P > 0.05$; Supplementary Fig. 1). These results suggest that elevated levels of α-HBDH were significantly associated with MACE in patients with AAD ($P < 0.05$).

3.4. Multivariable logistic regression model of in-hospital mortality and MACE according to α-HBDH and LDH levels

As α-HBDH could better reflect levels of LDH1 and LDH2, we explored the relationship between α-HBDH and LDH (Supplementary Fig. 2). Pearson correlation showed that there was a significantly positive correlation between α-HBDH and LDH (r = 0.613, $P < 0.001$; Supplementary Fig. 2).

We constructed four logistic regression models with the main study endpoint (in-hospital mortality) and secondary study endpoints (MACE), the four models including: 1) Crude model; 2) adjusted for demographics; 3) adjusted for demographics, comorbidities, type of AAD, admission indictors; 4) Fully adjust the mode: adjusted for demographics, comorbidities, type of AAD, admission indictors and lab test. α-HBDH was set as a categorical variable, and patients were divided into three groups (T1, T2, and T3). The results showed that α-HBDH was still an independent risk factor for in-hospital mortality in the T3 group [OR(95CI): 4.771(1.043–21.832), P = 0.044], with the T1 group as reference. Regarding the secondary endpoint (MACE), In model 4, α-HBDH was set as a categorical variable; it was still an independent risk factor for postoperative MACE, the risk of MACE remained significant higher in T3 group than in the TI group[OR(95CI): 9.869(2.148–45.349), P = 0.003] (Table 3).

Similarly, LDH was adjusted in the same manner as for α-HBDH , however, in the fully-adjusted model 4 , LDH was not an independent risk factor for both the primary [OR(95CI): 1.605(0.277–9.293), P = 0.598] and secondary study endpoints[OR(95CI): 1.437(0.342–6.034), P = 0.621](Table 3).

3.5. Survival analysis of the relationship between α-HBDH and in-hospital mortality

As shown in Fig. 2A, high levels of α-HBDH on admission were associated with a poor survival rate within 30 days after surgery for patients with AAD (log rank, $P < 0.01$). Patients were further classified into ATAAD (n = 216) and ATBAD (n = 153) groups. Although there was no significant correlation between α-HBDH and the ATBAD group (log rank, $P > 0.05$; Fig. 2B), increased α-HBDH levels were significantly associated with a lower survival rate within 30 days after surgery in the acute ATAAD group (log rank, $P < 0.01$; Fig. 2C).

3.6. RCS analysis for the prediction model

After adjusting for age, gender, levels of AST, ALT, Cr, glucose, and LDH, and history of MACE with 5 %, 35 %, 65 %, and 95 % nodes in the prediction model, the results of RCS analysis showed that there was a positive linear relationship between α-HBDH and in-hospital mortality ($P = 0.543$). When the level of α-HBDH was low, the correlation between α-HBDH and in-hospital mortality did not change. However, when the level of α-HBDH increased, the correlation between α-HBDH and in-hospital mortality showed an

Table 2
Short-term outcomes of patients with AAD.

outcomes	Total (n = 369)	Tertile I (≤178 U/L) (n = 126)	Tertile II (179–259 U/L) (n = 122)	Tertile III (≥260 U/L) (n = 121)	*P*-value
In-hospital mortality	37.0 (10.0)	4.0 (3.2)	10.0 (8.2)[b]	23.0 (19.0)	<0.001
Multiple organ failure	12.0(3.3)	4.0(3.2)	2.0(1.6)	6.0(5.0)	0.345
Renal insufficiency	56.0(15.2)	12.0(9.5)	20.0(16.4)	24.0(19.8)	0.07
Hepatic insufficiency	41.0(11.1)	12.0(9.5)	12(9.8)	17(14)	0.454
Infection	10.0(2.7)	2.0(1.6)	4.0(3.3)	4.0(3.3)	0.633
Paraplegia and Stroke	7.0(1.2)	1.0(0.8)	1.0(0.8)	5.0(4.1)	0.089
MACE	49(13.2)	5.0(4.0)[a]	11.0(9.0)[b]	33.0(27.3)	<0.001
Hospital stays	12.0 (6.0, 20.0)	12.0 (5.0, 19.0)	12.0 (7.8, 21)	11.0 (3.0, 20.5)	0.311

Note: MACE: major adverse cardiovascular events.
[a] The comparison between T1 and T3 group P < 0.05.
[b] The comparison between T2 and T3 group P < 0.05.

Table 3
Multivariable Logistic Model of In-hospital mortality and MACE with α-HBDH and LDH.

	α-HBDH(U/L)					LDH(U/L)				
	Tertile I	Tertile II		Tertile III		Tertile I	Tertile II		Tertile III	
Model		OR(95%CI)	*P*	OR(95%CI)	*P*		OR(95%CI)	*P*	OR(95%CI)	*P*
In-hospital mortality										
1	1	2.723(0.830–8.930)	0.099	7.158(2.396–21.388)	<0.001	1	3.821(1.221–11.962)	0.021	5.435(1.791–16.490)	0.003
2	1	2.829(0.860–9.309)	0.087	7.673(2.544–23.146)	<0.001	1	3.966(1.262–12.467)	0.018	5.838(1.910–17.843)	0.002
3	1	2.207(0.622–7.820)	0.220	6.534(1.998–21.370)	0.002	1	3.807(1.101–13.173)	0.035	5.842(1.674–20.386)	0.006
4	1	2.326(0.521–10.381)	0.269	4.771(1.043–21.832)	0.044	1	3.188(0.724–14.040)	0.125	1.605(0.277–9.293)	0.598
MACE										
1	1	2.398(0.808–7.119)	0.115	9.075(3.406–24.176)	<0.001	1	1.101(0.466–2.599)	0.827	2.729(1.282–5.810)	0.009
2	1	2.413(0.812–7.174)	0.113	9.406(3.506–25.235)	<0.001	1	1.100(0.465–2.599)	0.828	2.741(1.283–5.853)	0.009
3	1	2.902(0.702–11.998)	0.141	7.366(1.947–27.875)	0.003	1	0.675(0.185–2.461)	0.552	2.721(0.895–8.270)	0.078
4	1	3.062(0.638–14.696)	0.162	9.869(2.148–45.349)	0.003	1	0.411(0.094–1.789)	0.236	1.437(0.342–6.034)	0.621

Note: Model 1,Crude; Model 2, Adjusted for demographics(Age and Gender); Model 3, Adjusted for demographics, comorbidities(Hypertension, Diabetes, CHD, Smoking, Drinking, History of cardiac injury, History of surgery), type of AAD(ATAAD and ATBAD), Admission indictors(SBP, DBP, Creatinine, BUN, Glucose); Model 4, Adjusted for demographics, comorbidities, type of AAD, Admission indictors and lab test(Platelet, HB, RBC, WBC, NEUT, LYM, Serum K^{+}, Serum Na^{+}, Serum Cl^{-}, Serum Ca^{2+}).

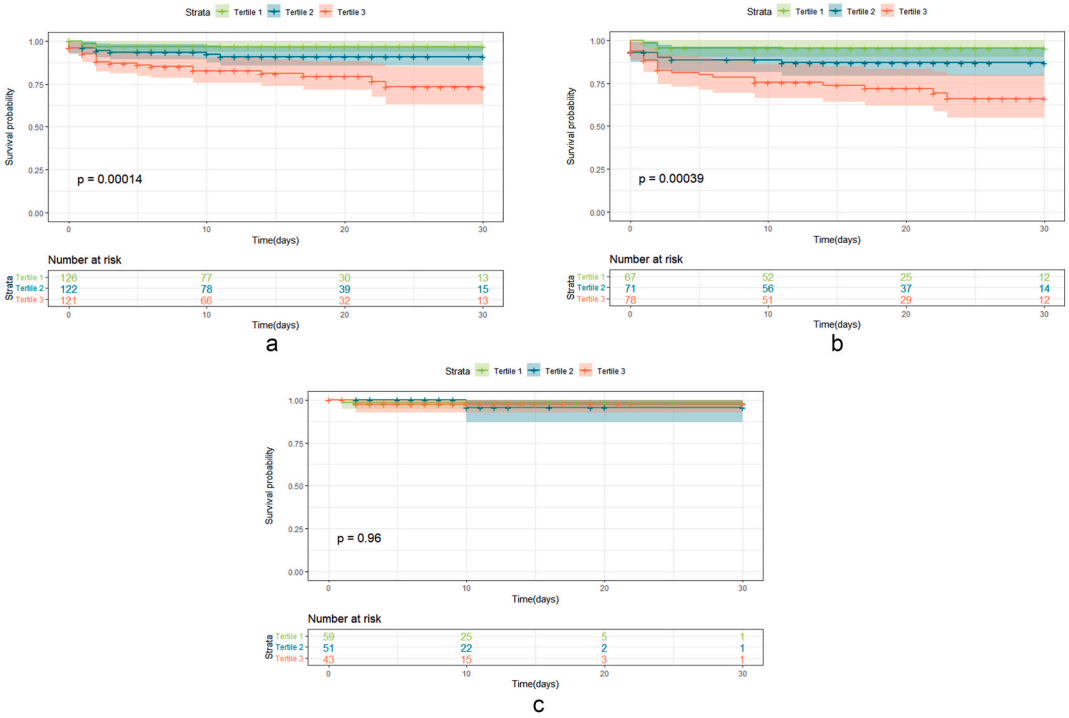

Fig. 2. Survival curves of AAD patients according to α-HBDH levels (A) Kaplan-Meier survival curves for different levels of α-HBDH in patients with AAD. **(B)** Kaplan-Meier survival curves for different levels of α-HBDH in patients with ATAAD. **(C)** Kaplan-Meier survival curves for different levels of α-HBDH in patients with ATBAD.

increasing trend ($P < 0.001$). Notably, when the α-HBDH level was <204 U/L (the cut-off point) and >204 U/L, the left and right hazard ratios were <1 and >1, respectively ($P < 0.05$), suggesting that patients with a α-HBDH level >204 U/L on admission have an increased risk for in-hospital mortality and a poor prognosis (Fig. 3A).

The relationship between α-HBDH and postoperative MACE was analyzed by the prediction model that adjusted for the above-mentioned factors and by RCS. The results showed that there was a non-linear relationship between α-HBDH and MACE ($P = 0.0012$). The risk for MACE was lower when the α-HBDH level was <204 U/L but increased remarkably when the α-HBDH level was >204 U/L; the risk stabilized when the α-HBDH level reached 401 U/L. In summary, α-HBDH level >204 U/L increases the risk of in-hospital mortality and postoperative MACE (Fig. 3B).

3.7. Subgroup analysis

We used age, gender, hypertension, smoking, drinking, type of AAD (Stanford), and AST, Cr, and LDH levels as stratification variables to observe the trends of effect sizes in these variables (Table 4). We noted that none of the interactions were observed based on the primary observation endpoint (in-hospital mortality) through our a priori specification (all $P > 0.05$), demonstrating that the relationship between α-HBDH and in-hospital mortality was stable.

Similarly, based on the secondary end point (MACE), we found no interaction (all $P > 0.05$), demonstrating that the relationship between α-HBDH and MACE was also stable.

4. Discussion

The main findings of this study show that 1) α-HBDH is independently associated with in-hospital mortality and MACE in patients with AAD; 2) α-HBDH is more specific than LDH for predicting postoperative MACE in patients with AAD; 3) high levels of α-HBDH on admission were associated with a poor survival rate within 30 days after surgery, especially in patients with ATAAD; 4) the α-HBDH level was linearly correlated with in-hospital mortality and non-linearly correlated with postoperative MACE, with a cut-off value of 204 U/L; and 5) the association between α-HBDH and in-hospital death and MACE was stable. To the best of our knowledge, this was the first study to reveal a potential correlation between α-HBDH and clinical outcomes as well as complications in other organ systems in patients with AAD.

Since the underlying mechanisms of the occurrence and development of spontaneous AAD remain unclear, screening of AAD and prevention of death of patients have been restricted [15]. Finding more indicators related to the progression and prognosis of AAD will help us to more comprehensively understand and analyze the occurrence and outcome of AAD disease. For example, preoperative

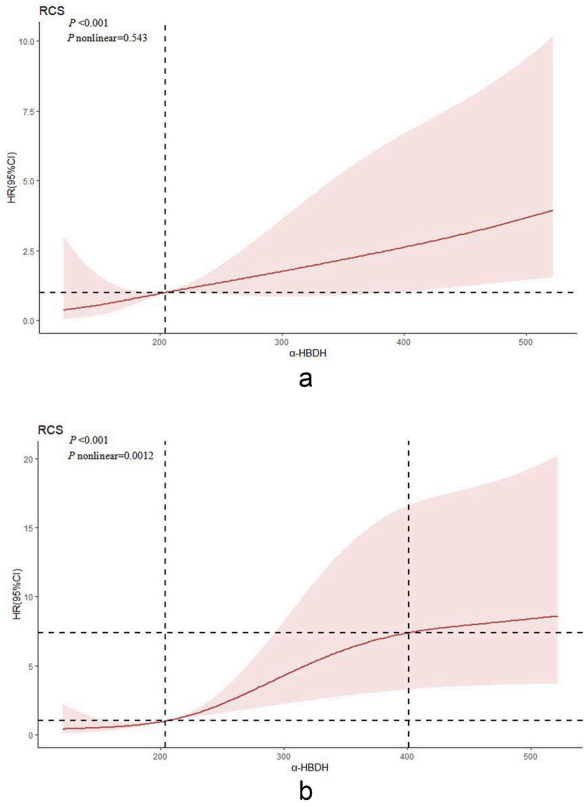

Fig. 3. Restricted cubic spline analysis for α-HBDH. (A) Restricted cubic spline for the relationship between α-HBDH and in-hospital mortality. **(B)** Restricted cubic spline for the relationship between α-HBDH and MACE.

levels of D-dimer, Cr, uric acid, serum tenascin-C, and inflammatory factors are associated with short-term mortality in AAD [16,17]. Additionally, malperfusion in multiple organs and disturbances in hemodynamics, including hypotension, shock, cardiac tamponade, insufficient pulse, and renal failure, are also associated with short-term mortality [18]. Among these indicators, an increased D-dimer level reflects the risk of thrombosis and bleeding, and elevated levels of inflammatory factors indicate local or systemic inflammation, all of which are relevant in determining the status and prognosis of patients with AAD.

α-HBDH can reflect myocardial injury and necrosis, as do myocardial enzymes such as myoglobin, cTnI, CK-MB, LDH [19–21]. As literature goes，although LDH and HBDH are less specific for cardiac injury than cTnI and CK-MB, they play a supportive role in the recognition of myocarditis or myocardial infarction [22], and myocardial infarction is a common perioperative cardiovascular complication in cardiac surgery and is independently associated with postoperative mortality [23–25]. Application of α-HBDH should not be limited to myocardial infarction, any other diseases would be associated with cardiomyocyte injury, apoptosis, hemolysis, and necrosis. The occurrence of postoperative MACE indicates the changes in the heart and vascular status, we urgently need more indicators to identify changes in this state. In MACE, fatal myocardial infarction and heart failure are the most severe, and accurate prediction and diagnosis enable providing assistance in preventing disease progression. In addition, routine in clinic, α-HBDH can be measured with only a single biochemical whole item, without the need for separate testing, which can decrease cost.

It has been reported that the relationship between LDH levels and in-hospital mortality from AAD [26,27], the high levels of LDH were positively associated with in-hospital mortality in patients with AAD, but the relationship between HBDH and hospital mortality is still unclear. Our findings may provide valuable information for preoperative α-HBDH levels predicting the prognosis and guiding hierarchical risk management of patients with AAD. Preoperative and intraoperative protection of the myocardium may be performed based on α-HBDH levels to reduce the risk of death and incidence of adverse postoperative cardiac events in patients with AAD. The main strength of this study was that we identified a novel biomarker that is associated with postoperative MACE in patients with AAD, providing an important supplement for the index of cardiac enzymes that previously only focused on LDH.

Our study had some strengths: 1) this study was an retrospective observational study, we included as many samples as possible but it is susceptible to potential confounders; however, we used strict statistical adjustments to minimize residual confounders; and 2) we handled the target independent variables as both continuous and categorical variables, which can reduce the contingency in data analysis and enhance the robustness of the results.

Table 4
Results of subgroup analysis and interaction analysis.

Characteristic	Total n	<204U/L n (%)	≥204U/L n (%)	In-hospital mortality OR (95 % CI) P	P for interaction	MACE OR (95 % CI) P	P for interaction
Age (years)					0.714		0.685
< 60	249	112(62.2)	137(72.5)	3.446(1.243,9.549) 0.017		0.748(0.369,1.518) 0.422	
≥ 60	120	68(37.8)	52(27.5)	3.349(0.970,11.567) 0.056		1.967(0.604,6.404) 0.261	
Gender					0.353		0.421
Male	273	43(23.9)	53(28.0)	4.287(1.552,11.843) 0.005		1.149(0.574,2.299) 0.695	
Female	96	137(76.1)	136(72.0	1.994(0.569,6.990) 0.280		0.647(0.192,2.177) 0.482	
Hypertension					0.818		0.558
No	99	46(25.6)	53(28.0)	2.809(0.538,14.657) 0.221		1.300(0.425,3.978) 0.646	
Yes	270	134(74.4)	136(72.0)	3.501(1.442,8.503) 0.006		0.874(0.425,1.796) 0.714	
Smoking					0.799		0.571
No	172	76(42.2)	96(50.8)	3.600(1.150,11.267) 0.028		0.821(0.341,1.980) 0.661	
Yes	197	104(57.8)	93(49.2)	2.933(0.992,8.671) 0.052		1.165(0.510,2.659) 0.778	
Drinking					0.268		0.197
No	163	75(41.7)	88(46.6)	2.176(0.792,5.980) 0.132		0.625(0.258,1.567) 0.325	
Yes	206	105(58.3)	101(53.4)	5.471(1.522,19.665) 0.009		1.414(0.626,3.190) 0.404	
Type of AAD					0.788		0.374
ATAAD	216	99(55.0)	117(61.9)	3.250(1.397,7.558) 0.006		0.778(0.363,1.667) 0.518	
ATBAD	153	81(45.0)	72(38.1)	2.286(0.203,25.751) 0.503		1.368(0.511,3.665) 0.533	
AST (μ/L)					0.194		0.064
Nomal (≤40)	240	142(78.9)	98(51.9)	4.362(1.347,14.131) 0.014		1.133(0.538,2.389) 0.742	
High (>40)	129	38(21.1)	91(48.1)	1.516(0.516,4.457) 0.449		0.770(0.277,2.141) 0.617	
Creatinine (μmol/L)					0.533		0.456
Normal (70–100)	131	64(35.6)	67(35.4)	1.210(0.310,4.722) 0.784		1.800(0.640,5.066) 0.266	
High (>100)	107	36(20.0)	71(37.6)	2.106(0.711,6.234) 0.179		0.487(0.166,1.433) 0.191	
LDH (U/L)					0.427		0.135
Normal (109–245)	193	89(49.4)	104(55)	2.562(1.073,6.114) 0.034		1.246(0.454,3.422) 0.669	
High (>245)	175	91(50.6)	84(44.4)	8.182(0.985,67.978) 0.052		0.920(0.427,1.983) 0.832	

5. Study limitations

Some limitations of this study must be mentioned. The association between α-HBDH and in-hospital mortality and short-term prognosis of patients with AAD was evaluated in single-center, the predictive efficacy of α-HBDH on the long-term prognosis of these patients should be explored. Also, it would be beneficial to reveal the underlying mechanisms by dynamically measuring the α-HBDH level. Third, as a single-center study, the results must be interpreted with caution when extrapolating them into other settings. Finally, comparison of the predictive ability of α-HBDH for cardiac injury with cTnI, cTnT, BNP was lack under the context of AAD.

6. Conclusion

α-HBDH levels in patients with AAD on admission were independently associated with in-hospital mortality and MACE, especially in adverse postoperative cardiovascular events. α-HBDH is superior to LDH in predicting MACE in patients with acute aortic dissection α-HBDH levels on admission may be used to identify high-risk patients with AAD and those with a poor prognosis.

There were 369 patients with AAD, including 332 alive and 37 deaths, in which includes 28 preoperative or intraoperative deaths and 9 postoperative deaths. Among 28 dead patients, 19 and 9 patients had high and low α-HBDH levels, respectively. Additionally, high α-HBDH levels in 9 postoperative patients died. These results suggested that the elevated α-HBDH levels were positively

associated with the mortality of patients with or without surgery. Among the 332 patients who underwent surgery, it was found that surgery may be a potential risk factor for the development of complications. In this cohort, 31 patients developed MACE after surgery, 25 of whom had high α-HBDH levels. These results showed that an elevated α-HBDH level before surgery also predicted the prognosis of patients with AAD.

There are five LDH isozymes, LDH1, LDH2, LDH3 and LDH4, LDH5. Their activity in human tissues is different (the figure shows the main activity distribution of each organ), in which LDH1 and LDH2 are mainly distributed in myocardium, and α-HBDH reflects the activity of LDH1 and LDH2.

α-HBDH is not an independent specific enzyme, but is a general term for LDH1 and LDH2 containing the H subunit (α-HBDH is determined by using α-ketoacid as the substrate to measure the activity of LDH, because the H subunit of LDH has a large affinity for this substrate, so this enzyme activity replaces the activity of LDH1 and LDH2 containing a large number of H subunits.)

When AAD occurs, the heart is involved and the myocardium is damaged and hypoxia leads to the energy metabolism of myocardium cells, the structure of myocardial membrane is destroyed, the membrane permeability is increased, and the intracellular enzyme is released in large quantities, resulting in the increase of α-HBDH level.

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Ethics declarations

This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (2021k7359) and research participants have signed written informed consent form. have obtained informed consent from the research participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee.

Data availability statement

Data associated with the study has not been deposited into a publicly available repository, the raw data supporting the findings of this study are available from the corresponding author at request.

CRediT authorship contribution statement

Yun-jing Zhang: Writing – original draft, Methodology, Formal analysis, Data curation. **Yue Sun:** Software, Resources, Project administration, Data curation. **Yong-bo Zhao:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Dong Ma:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29155.

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