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MALT1 Positively Relates to T Helper 1 and T Helper 17 cells, and Serves as a Potential Biomarker for Predicting 30-Day Mortality in Stanford Type A Aortic Dissection Patients

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Mucosa-associated lymphoid tissue 1 (MALT1) regulates inflammation and T helper (Th) cell differentiation, which may participate in the progression of Stanford type A aortic dissection (TAAD). This study intended to assess the association of MALT1 expression with prognosis in TAAD patients. In this prospective study, MALT1 expression was measured by reverse transcription-quantitative polymerase chain reaction assay from peripheral blood samples in 100 TAAD patients and 100 non-AD controls (non-AD patients with chest pain) before treatment. Besides, Th1, Th2, and Th17 cells of TAAD patients before treatment were measured by flow cytometry assay, and their 30-day mortality was recorded. MALT1 expression was ascended in TAAD patients vs. non-AD controls ($P < 0.001$). In TAAD patients, elevated MALT1 expression was linked with hypertension complication ($P = 0.009$), increased systolic blood pressure ($r = 0.291$, $P = 0.003$), C-reactive protein (CRP) ($r = 0.286$, $P = 0.004$), and D-dimer ($r = 0.359$, $P < 0.001$). Additionally, MALT1 expression was positively correlated with Th1 cells ($r = 0.312$, $P = 0.002$) and Th17 cells ($r = 0.397$, $P < 0.001$), but not linked with Th2 cells ($r = -0.166$, $P = 0.098$). Notably, the 30-day mortality of TAAD patients was 28.0%. MALT1 expression [odds ratio (OR) = 1.936, $P = 0.004$], CRP (OR = 1.108, $P = 0.002$), D-dimer (OR = 1.094, $P = 0.003$), and surgery timing (emergency vs. selective) (OR = 8.721, $P = 0.024$) independently predicted increased risk of death within 30 days in TAAD patients. Furthermore, the combination of the above-mentioned independent factors had an excellent ability in predicting 30-day mortality with the area under curve of 0.949 (95% confidence interval: 0.909-0.989). MALT1 expression relates to increased Th1 cells, Th17 cells, and 30-day mortality risk in TAAD patients.

Keywords: 30-day mortality; inflammation; mucosa-associated lymphoid tissue 1; Stanford type A aortic dissection; T helper cells
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Introduction

Aortic dissection (AD) is an acute disease characterized by a separation of the aortic wall layers, which forms pseudolumen to squeeze the true lumen and causes a rupture of the aorta (Sayed et al. 2021; Sen et al. 2021). AD is classified into Stanford type A when the ascending aortic thoracic tract and/or the arch are involved, and Stanford type B when the descending thoracic aorta and/or aortic abdominal tract are involved (Cifani et al. 2015; Sayed et al. 2021). Notably, Stanford type A aortic dissection (TAAD) accounts for about two-thirds of AD, which has a rapid onset and high mortality (Evangelista et al. 2018; Zhu et al. 2020; Sayed et al. 2021). The main risk factors of TAAD include inflammation dysregulation, abnormal differentiation of T helper (Th) cells, hypertension, atherosclerosis, dyslipidemia, and connective tissue diseases (Ye et al. 2018; Sayed et al. 2021; Zhou et al. 2022). Therefore, searching for

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potential biomarkers that are involved in inflammation, Th cell differentiation, and hypertension may contribute to the early identification and timely treatment of TAAD patients.

Mucosa-associated lymphoid tissue 1 (MALT1) is one of the immune proteases in humans, which participates in the regulation of the above-mentioned TAAD-related risk factors, including the inflammation process, the differentiation of Th cells, and hypertension (Staal et al. 2011; Wilck et al. 2017; Wang et al. 2022; Wang et al. 2023). For example, one study shows that MALT1 promotes inflammation by the activation of the nuclear factor-κB (NF-κB) signaling pathway (Wang et al. 2023). Meanwhile, another study also illustrates that MALT1 inhibits Th2 differentiation and induces Th17 differentiation through the c-Jun N-terminal kinase (JNK) and NF-κB signaling pathways (Wang et al. 2022). In addition, the promotion of Th17 cell differentiation by MALT1 may further lead to hypertension (Wilck et al. 2017). The above contents suggest that MALT1 may be involved in the pathogenesis of TAAD. However, the clinical value of MALT1 in TAAD is still unclear.

Therefore, the present study intended to assess MALT1 expression, as well as its relation with T helper cells and prognosis in TAAD patients.

Materials and Methods

Participants

One hundred TAAD patients who visited our hospital between February 2018 and October 2022 were enrolled in this prospective study. The inclusion criteria were: i) diagnosed with AD by clinical and imaging examinations; ii) with Stanford type A classified by Stanford classification of aortic dissection 1970 (Daily et al. 1970); iii) aged ≥18 years. The exclusion criteria were: i) had a history of other cardiopulmonary diseases; ii) obvious severe tissue perfusion defects; iii) systemic autoimmune and inflammatory diseases (such as rheumatoid arthritis, primary Sjögren syndrome, Kawasaki disease, etc.), which were commonly associated with dysregulated immune cells; iv) hematologic malignancies (such as acute myelogenous leukemia) that affected cell cycles of multi types of cells; v) pregnant or lactating female. During the same period, the study included one hundred patients who did not have AD but suffered from chest pain. These patients were matched by age and sex to the TAAD patients. The age range was 45 to 80, and the female to male ratio was 3 to 7. These participants served as non-AD controls. The inclusion criteria were: i) with non-AD disease whose primary symptom was chest pain; ii) willing to cooperate with this study. The exclusion criteria of TAAD patients were also suitable for non-AD controls. This study gained approval from the Ethics Committee, and all participants or their guardians gave informed consent.

Data and samples

Demographics, chronic comorbidities, blood biochemical indexes, surgery-related information, and hospital stays were collected from TAAD patients. Surgery types contained trunk stent implantation, total aortic arch replacement, ascending aorta replacement, aortoventriculoplasty, Bentall procedure, etc., which were conducted according to the patient's actual conditions. Besides, 30-day mortality was recorded for analysis. For patients who were died during hospitalization, the hospital stays were recorded as the duration from admission to mortality; while for patients with a duration of hospital stay of more than 30, the hospital stays were recorded as the actual duration of stay. Patients were closely monitored during the hospitalization, and received telephone follow-ups once every two days after discharge until the 30th day after admission. For sample collection, peripheral blood (PB) samples were gained from TAAD patients before treatment initiation; while PB samples from non-AD controls were also collected before treatment initiation. PB samples from TAAD patients were divided into two parts, one part was used for separating PB mononuclear cells (PBMCs) for MALT1 expression detection, which was conducted by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assay; and the other part was used for testing Th1 cells, Th2 cells, and Th17 cells by flow cytometry (FCM) assay within 24 hours. Meanwhile, PB samples were collected from non-AD controls, and the PBMCs were separated for MALT1 expression detection by RT-qPCR assay.

RT-qPCR assay

Total RNA was isolated using PureZOL RNA isolation reagent (No. Cat. 7326880, Bio-Rad, Hercules, CA, USA), and cDNA was synthesized using iScript™ cDNA Synthesis Kit (with random primer) (No. Cat. 1708891, Bio-Rad). After that, qPCR was conducted via TB Green™ Fast qPCR Mix (No. Cat. RR430S, TAKARA, Dalian, China). Relative quantification was calculated according to the $2^{-\Delta\Delta Ct}$ method. GAPDH was set as a control. The primer of MALT1 was: forward, 5′-AGTGTTGATGGCGTCTC TGAA-3′; reverse, 5′-TCTACCTTCTTGCTATCTT GACTGT-3′. The primer of GAPDH was: forward, 5′-TG ACCACAGTCCATGCCATCAC-3′; reverse, 5′-GCCTGC TTCACCACCTTCTTGA-3′ (Chen et al. 2021).

FCM assay

The CD4$^+$ T cells were isolated from the PB samples using a Dynabeads™ FlowComp™ Human CD4 kit (No. Cat. 11361D, Thermo Fisher Scientific, Waltham, MA, USA). Then the Th1, Th2, and Th17 cell ratios in CD4$^+$ T cells were determined by FCM assay, using a commercial human Th1/Th2/Th17 phenotyping kit (No. Cat. 560751, BD, Franklin Lakes, NJ, USA). All test steps were performed in strict accordance with the kit's instructions.

Statistics

SPSS 26.0 (IBM, Armonk, NY, USA) and GraphPad Prism 7.0.1 (GraphPad Software, San Diego, CA, USA) were used for data processing and picture plotting, respec-

tively. The student *t*-test and the χ^2 test were used to compare age and sex between two groups, respectively. The Spearman test was utilized for correlation analysis. Univariate and multivariate logistics regression models were constructed for finding factors related to 30-day mortality in TAAD patients. The forward stepwise method was used in the multivariate model. Receiver operating characteristic (ROC) curves were performed to show the distinguished ability of MALT1 expression between groups and the prognosis ability of the multivariate model. $P < 0.05$ indicated statistical significance.

Results

Characteristics of TAAD patients

The 100 TAAD patients had a mean age of 61.0 ± 6.9 years (mean ± standard deviation, SD), including 29 (29.0%) females and 71 (71.0%) males. There were 32 (32.0%) patients with cerebrovascular disease. Meanwhile, the median [interquartile range (IQR)] values of C-reactive protein (CRP) and D-dimer in TAAD patients were 17.2 (10.0-22.5) mg/L and 5.1 (3.0-20.7) μg/mL. Additionally, the median (IQR) values of Th1 cells, Th2 cells, and Th17 cells in TAAD patients were 18.9 (15.2-21.6)%, 7.9 (6.9-9.7)%, and 4.1 (3.2-5.5)%, respectively. The 100 non-AD controls had a mean age of 62.8 ± 9.0 years, including 30 (30.0%) females and 70 (70.0%) males. There was no difference in age ($P = 0.112$) or sex ($P = 0.877$) between TAAD patients and non-AD controls. More detailed clinical information on TAAD patients was exhibited in Table 1.

Surgery-related information of TAAD patients

Twenty-seven (27.0%) patients underwent selective surgery and 73 (73.0%) patients received emergent surgery. Furthermore, there were 89 (89.0%) patients who underwent trunk stent implantation, 69 (69.0%) patients who were treated with total aortic arch replacement, 67 (67.0%) patients who experienced ascending aorta replacement, 30 (30.0%) patients who received aortoventriculoplasty, and 15 (15.0%) patients who underwent Bentall procedure (Table 2). In addition, the median (IQR) hospital stays in TAAD patients was 16.0 (10.0-22.8) days.

Comparison of MALT1 expression between TAAD patients and non-AD controls

It was noticed that the MALT1 expression was ascended in TAAD patients compared with non-AD controls [median (IQR): 2.700 (2.068-4.073) vs. 1.015 (0.740-1.548)] ($P < 0.001$) (Fig. 1A). Moreover, MALT1 expres-

Table 1. The clinical characteristics of Stanford type A aortic dissection (TAAD) patients and non-aortic dissection (non-AD) controls.

Characteristics	TAAD patients (N = 100)	Non-AD controls (N = 100)	*P* value
Age (years), mean ± SD	61.0 ± 6.9	62.8 ± 9.0	0.112
Sex, No. (%)			0.877
Female	29 (29.0)	30 (30.0)	
Male	71 (71.0)	70 (70.0)	
BMI (kg/m^2), mean ± SD	25.4 ± 3.4	(-)	(-)
Smoking, No. (%)	37 (37.0)	(-)	(-)
Hypertension, No. (%)	79 (79.0)	(-)	(-)
Diabetes, No. (%)	18 (18.0)	(-)	(-)
Cerebrovascular disease, No. (%)	32 (32.0)	(-)	(-)
SBP (mmHg), mean ± SD	145.2 ± 11.7	(-)	(-)
DBP (mmHg), mean ± SD	80.9 ± 9.8	(-)	(-)
FBG (mmol/L), median (IQR)	5.9 (5.0-7.0)	(-)	(-)
Scr (μmol/L), median (IQR)	90.7 (83.6-97.0)	(-)	(-)
SUA (μmol/L), median (IQR)	355.7 (307.2-413.4)	(-)	(-)
TG (mmol/L), median (IQR)	1.7 (1.1-2.3)	(-)	(-)
TC (mmol/L), median (IQR)	4.3 (3.6-5.4)	(-)	(-)
LDL-C (mmol/L), median (IQR)	2.8 (2.2-3.7)	(-)	(-)
HDL-C (mmol/L), median (IQR)	0.9 (0.8-1.1)	(-)	(-)
CRP (mg/L), median (IQR)	17.2 (10.0-22.5)	(-)	(-)
D-dimer (μg/mL), median (IQR)	5.1 (3.0-20.7)	(-)	(-)
Th1 cells (%), median (IQR)	18.9 (15.2-21.6)	(-)	(-)
Th2 cells (%), median (IQR)	7.9 (6.9-9.7)	(-)	(-)
Th17 cells (%), median (IQR)	4.1 (3.2-5.5)	(-)	(-)

SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting plasma glucose; IQR, interquartile range; Scr, serum creatinine; SUA, serum uric acid; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; Th, T helper; (-), not available.

Table 2. Surgery-related information.

Items	TAAD patients (N = 100)
Surgery timing, No. (%)	
Selective	27 (27.0)
Emergency	73 (73.0)
Surgery type, No. (%)	
Trunk stent implantation	89 (89.0)
Total aortic arch replacement	69 (69.0)
Ascending aorta replacement	67 (67.0)
Aortoventriculoplasty	30 (30.0)
Bentall procedure	15 (15.0)

TAAD, Stanford type A aortic dissection.

sion exhibited a good ability to differentiate TAAD patients from non-AD controls with the area under curve (AUC) of 0.887 [95% confidence interval (CI) = 0.843-0.931]. Sensitivity and specificity were 0.880 and 0.760 respectively when the best cut-off value of MALT1 was 1.570 (Fig. 1B).

Linkage of MALT1 expression with clinical features and T helper cells in TAAD patients

Increased MALT1 expression was linked with hypertension complication (P = 0.009), elevated systolic blood pressure (r = 0.291, P = 0.003), ascended CRP (r = 0.286, P = 0.004), and rising D-dimer (r = 0.359, P < 0.001) (Tables 3, 4). There was no relationship of MALT1 expression with

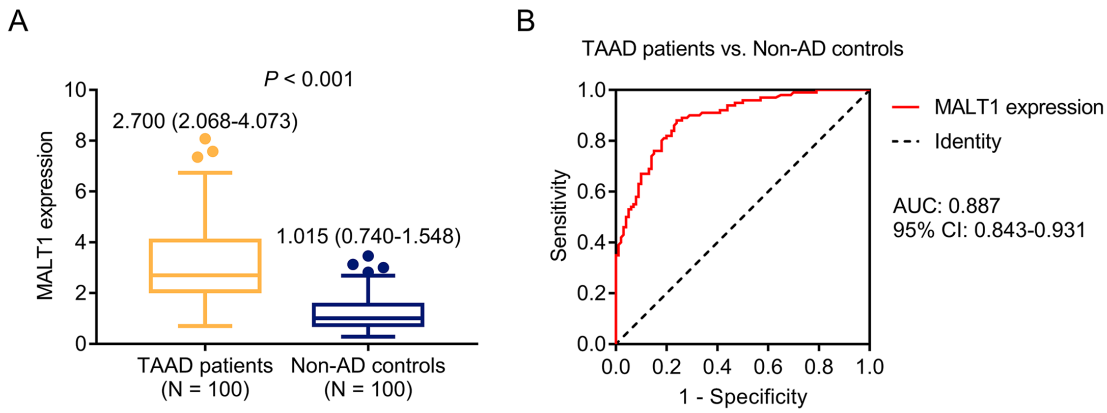

Fig. 1. Mucosa-associated lymphoid tissue 1 (MALT1) expression in Stanford type A aortic dissection (TAAD) patients and non-aortic dissection (non-AD) controls.
(A) The comparison of MALT1 expression between TAAD patients and non-AD controls. (B) Receiver operating characteristic (ROC) curve showed the ability of MALT1 expression in distinguishing TAAD patients from non-AD controls.

Table 3. Correlation of mucosa-associated lymphoid tissue 1 (MALT1) expression with categorical clinical characteristics among Stanford type A aortic dissection (TAAD) patients.

Characteristics	MALT1 expression, median (IQR)	P value
Sex		0.298
Female	3.130 (2.250-4.340)	
Male	2.670 (1.910-3.850)	
Smoking		0.342
No	2.840 (2.300-3.850)	
Yes	2.350 (1.840-4.410)	
Hypertension		0.009
No	2.360 (1.630-2.755)	
Yes	3.000 (2.110-4.310)	
Diabetes		0.100
No	2.670 (1.918-3.685)	
Yes	3.955 (2.105-5.875)	
Cerebrovascular disease		0.057
No	2.565 (1.873-3.638)	
Yes	3.300 (2.155-4.555)	

IQR, interquartile range.

Table 4. Correlation of mucosa-associated lymphoid tissue 1 (MALT1) expression with continuous clinical characteristics among Stanford type A aortic dissection (TAAD) patients.

Characteristics	*r*	*P* value
Age	0.143	0.156
BMI	0.107	0.290
SBP	0.291	0.003
DBP	0.116	0.251
FBG	0.172	0.088
Scr	0.132	0.190
SUA	0.146	0.147
TG	0.117	0.245
TC	0.142	0.158
LDL-C	0.141	0.162
HDL-C	−0.021	0.838
CRP	0.286	0.004
D-dimer	0.359	< 0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting plasma glucose; Scr, serum creatinine; SUA, serum uric acid; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

other clinical characteristics of TAAD patients (all $P > 0.05$).

MALT1 expression was positively related to Th1 cells ($r = 0.312$, $P = 0.002$) (Fig. 2A), but it was not linked with Th2 cells ($r = -0.166$, $P = 0.098$) in TAAD patients (Fig. 2B). Moreover, MALT1 expression was positively related to Th17 cells in TAAD patients ($r = 0.397$, $P < 0.001$) (Fig. 2C).

Linkage of MALT1 expression with 30-day mortality in TAAD patients

The 30-day mortality of TAAD patients was 28.0% (Fig. 3A). Besides, the MALT1 expression was increased in TAAD patients who died within 30 days vs. those who survived within 30 days [median (IQR): 4.005 (3.150-5.293) vs. 2.415 (1.790-3.125)] ($P < 0.001$) (Fig. 3B). Interestingly, MALT1 expression also showed a good utility to distinguish TAAD patients who died within 30 days from those who survived within 30 days with the AUC of 0.811 (95% CI = 0.721-0.900). Sensitivity and specificity were 0.786 and 0.764 respectively when the best cut-off value of MALT1 was 3.135 (Fig. 3C).

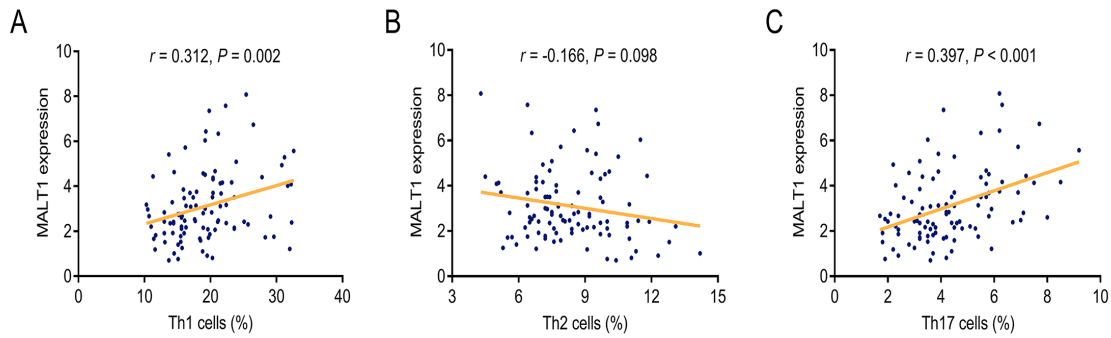

Fig. 2. Relation of mucosa-associated lymphoid tissue 1 (MALT1) expression with the proportion of T helper cells in Stanford type A aortic dissection (TAAD) patients.
The correlation of MALT1 expression with Th1 cells (A), Th2 cells (B), and Th17 cells (C) in TAAD patients.

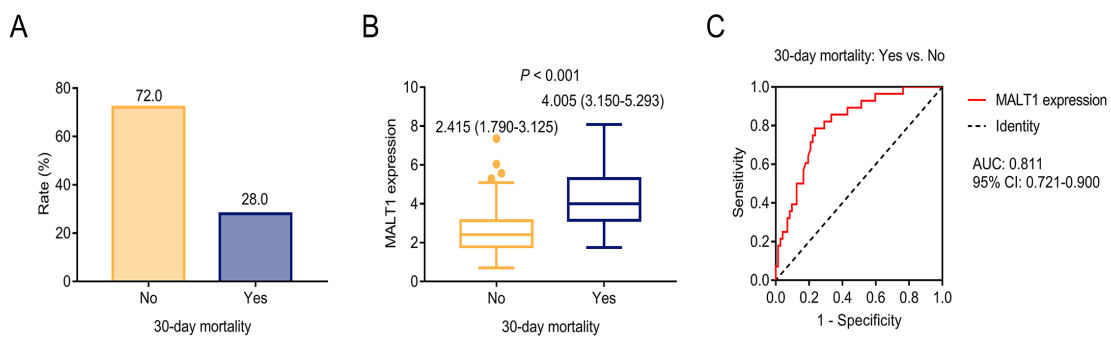

Fig. 3. Mucosa-associated lymphoid tissue 1 (MALT1) expression in Stanford type A aortic dissection (TAAD) patients who died within 30 days and those who survived within 30 days.
(A) The occurrence of 30-day mortality in TAAD patients. (B) The comparison of MALT1 expression between TAAD patients who died within 30 days and those who survived within 30 days. (C) Receiver operating characteristic (ROC) curve exhibited the ability of MALT1 expression in distinguishing TAAD patients who died within 30 days from patients who survived within 30 days.

Factors linked with 30-day mortality in TAAD patients

The univariate analysis suggested that MALT1 expression [odds ratio (OR) = 2.088, $P < 0.001$], Th17 cells (OR = 1.631, $P = 0.001$), diabetes (yes vs. no) (OR = 4.444, $P = 0.006$), fasting plasma glucose (OR = 1.523, $P = 0.029$), serum creatinine (OR = 1.070, $P = 0.003$), serum uric acid (OR = 1.008, $P = 0.024$), CRP (OR = 1.105, $P < 0.001$), D-dimer (OR = 1.104, $P < 0.001$), surgery timing (emergency vs. selective) (OR = 6.915, $P = 0.013$), and total aortic arch replacement (yes vs. no) (OR = 5.303, $P = 0.011$) were associated with enhanced risk of death within 30 days in TAAD patients (Fig. 4A). Next, the multivariate analysis revealed that MALT1 expression (OR = 1.936, $P = 0.004$), CRP (OR = 1.108, $P = 0.002$), D-dimer (OR = 1.094, $P = 0.003$), and surgery timing (emergency vs. selective) (OR = 8.721, $P = 0.024$) independently estimated elevated risk of death within 30 days in TAAD patients (Fig. 4B).

Prognostic value of combination of independent factors that related to 30-day mortality in TAAD patients

Notably, ROC curve analysis found the combination of the above-mentioned independent factors (including MALT1 expression, CRP, D-dimer, and surgery timing) disclosed an excellent value to discriminate TAAD patients who died within 30 days from those who survived within 30 days with the AUC of 0.949 (95% CI = 0.909-0.989) (Fig. 5).

Discussion

MALT1 is a paracaspase with the ability to regulate vascular inflammation, which is expressed abnormally in cardiovascular diseases, such as acute ischemic stroke (Chen et al. 2021; Zhang et al. 2022). Similarly, our study found that MALT1 expression was ascended in TAAD patients vs. non-AD controls, and exhibited a good value in

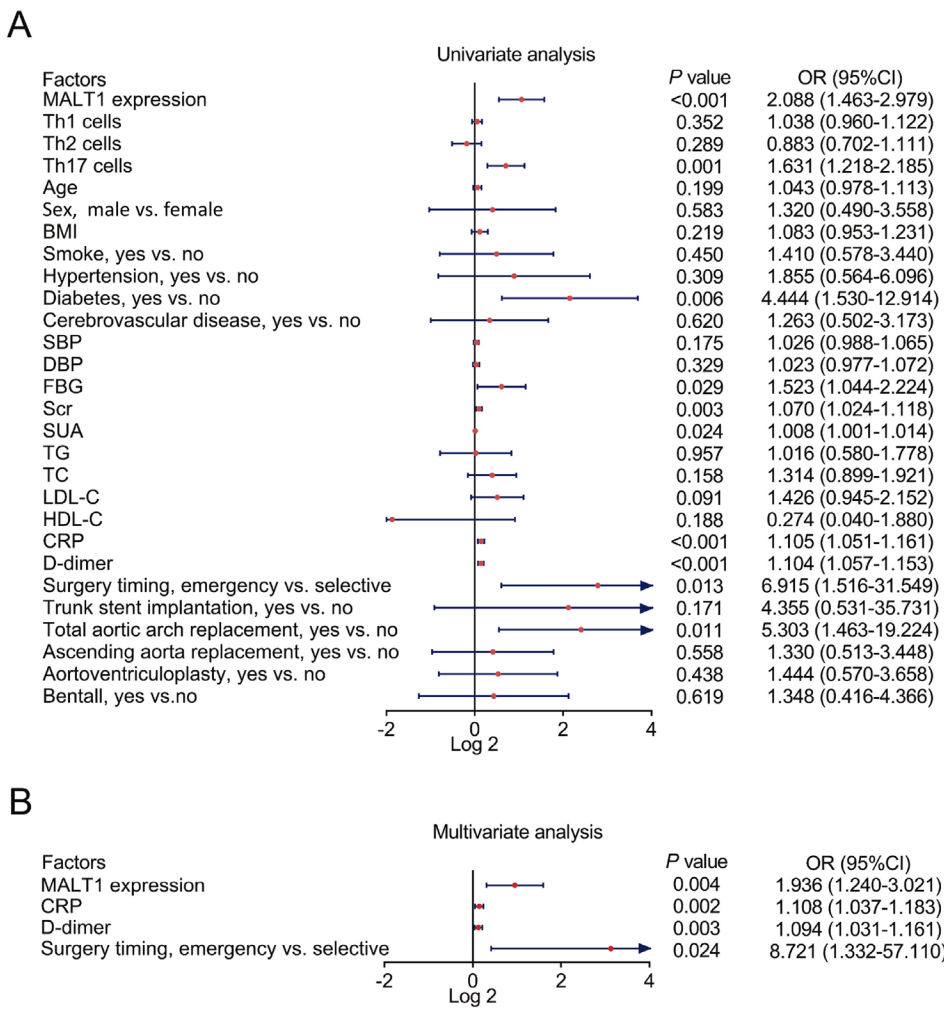

Fig. 4. The univariate and multivariate analyses for 30-day mortality in Stanford type A aortic dissection (TAAD) patients. (A) The univariate analysis of factors associated with 30-day mortality in TAAD patients. (B) The multivariate analysis of independent factors associated with 30-day mortality in TAAD patients. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting plasma glucose; Scr, serum creatinine; SUA, serum uric acid; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

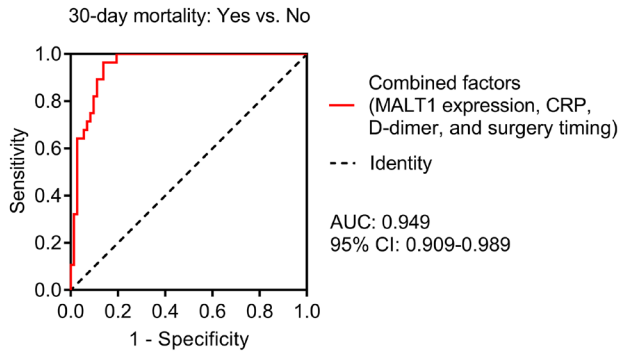

Fig. 5. Combination of mucosa-associated lymphoid tissue 1 (MALT1) expression, C-reactive protein (CRP), D-dimer, and surgery timing predicted 30-day mortality in Stanford type A aortic dissection (TAAD) patients.

differentiating TAAD patients from non-AD controls. Several probable explanations were provided: (1) MALT1 induced immune imbalance by facilitating the differentiation of Th1 cells and Th17 cells, which played a key role in TAAD etiology (Ye et al. 2018; Dumont et al. 2020; Liu et al. 2022). (2) The inflammation was exacerbated in TAAD patients (del Porto et al. 2010); meanwhile, MALT1 was positively associated with inflammation (Wang et al. 2022; Wu and Bi 2022). (3) MALT1 promotes macrophage infiltration and matrix metalloproteinase production, which might participate in the pathology of TAAD (Cifani et al. 2015; Lee et al. 2017; Wang et al. 2023). Thus, MALT1 expression was ascended in TAAD patients and could differentiate them from non-AD controls. However, our study did not verify the ability of MALT1 expression in distinguishing TAAD patients from other types of AD, such as Stanford type B aortic dissection. Thus, further studies with a disease control were required for verification.

In addition to the abnormal expression of MALT1, our study also observed that increased MALT1 expression was linked with hypertension complications, elevated systolic blood pressure, CRP, and D-dimer in TAAD patients. It might be because: (1) MALT1 promoted the differentiation of Th17 cells and increased interleukin-17A levels (Wang et al. 2022); meanwhile, interleukin-17A induced the water-sodium retention and restrained the production of endothelial nitric oxide synthase, consequently leading to elevation of blood pressure (Nguyen et al. 2013; Davis et al. 2021). Therefore, MALT1 expression was positively linked with hypertension complications and systolic blood pressure in TAAD patients. (2) MALT1 activated oxidative stress by the NF-κB signaling pathway (Wang et al. 2023); meanwhile, oxidative stress caused the elevation of blood pressure (Zhang et al. 2023). Thus, there was a positive linkage of MALT1 expression with hypertension complications and systolic blood pressure in TAAD patients. (3) MALT1 activated the NF-κB signaling pathway, which was related to the elevation of various proinflammatory cytokines and enhanced inflammatory response (Lawrence 2009; Staal et al. 2011). Thus, MALT1 was positively linked with CRP in TAAD patients. (4) MALT1 promoted thromboinflammation and deep vein thrombosis, which might be associated with the increase of D-dimer (Schutte et al. 2016; Kondreddy et al. 2022). Thus, MALT1 was correlated with elevated D-dimer in TAAD patients. Furthermore, in our study, MALT1 expression was associated with increased Th1 cells and Th17 cells in TAAD patients. This might be because MALT1 regulated the differentiation of Th1 cells and Th17 cells. The specific contents were as follows: MALT1 activated NF-κB pathways and JNK pathways, as well as cleaved roquin and regnase-1, thereby inducing the differentiation of Th1 cells and Th17 cells (Jeltsch et al. 2014; Cui et al. 2017; Wang et al. 2022). Thus, there was a positive relationship of MALT1 expression with Th1 cells and Th17 cells in TAAD patients.

TAAD is a catastrophic cardiovascular disease that often leads to death if untreated (Liu et al. 2022). Previous studies reveal that the 30-day mortality of TAAD patients ranges from 22.0% to 26.3% (Chen et al. 2020; Obel et al. 2022; Song et al. 2022). These results were similar to our study, which showed that the 30-day mortality of TAAD patients was 28.0%. Therefore, it is momentous to find new potential biomarkers for the assessment of death risks, thus promoting early intervention in TAAD patients. In our study, MALT1 expression was independently linked with 30-day mortality in TAAD patients. It might be due to the fact that: MALT1 promoted atherogenesis by activating NF-κB pathways, which might cause multiple organ pathologies (McAllister-Lucas et al. 2010; Keeter et al. 2022). Therefore, MALT1 expression was independently related to high 30-day mortality in TAAD patients. A hypothesis was proposed according to the above findings of our study that the predictive values of MALT1 expression in the prognosis of TAAD patients might also be attributed to its correlation with systolic blood pressure, CRP, and D-dimer. Notably, CRP, D-dimer, and surgery timing were also independently associated with an elevated risk of death within 30 days in TAAD patients. This might be because: CRP elevation was related to TAAD complications (such as impaired oxygenation and pleural effusion) (Hata et al. 2002; Sugano et al. 2005); D-dimer elevation was linked with organ dysfunction and increased inflammation (Zhang et al. 2021); emergency surgery reflected more severe disease conditions for patients. Thus, TAAD patients with elevated CRP, increased D-dimer, or emergency surgery had higher 30-day mortality risks.

Meanwhile, our study showed that the combination of MALT1 expression, CRP, D-dimer, and surgery timing exhibited an excellent ability in predicting 30-day mortality in TAAD patients, which might be more suitable for assessing patients' survival. The above findings of our study revealed that MALT1 was a potential biomarker for timely monitoring the progression of disease conditions and predicting the mortality, and its combination with CRP, D-dimer, and surgery timing had an excellent prediction

effect, which paved the way for early active intervention of TAAD patients.

Notably, among patients who visited our hospital between February 2018 and October 2022, we included all patients who met the inclusion criteria and did not meet the exclusion criteria in our study. In addition, due to the short follow-up period, there were no patients who lost follow-up in our study.

There were still some limitations in our research: (1) The sample size of our study was small (N = 100), which might cause insufficient statistical power, and further studies with larger sample sizes were needed for investigation. (2) Our study did not evaluate the longitudinal variation of MALT1 expression, and future studies should measure MALT1 expression at multiple time points to further explore its clinical value in TAAD patients. (3) Further exploration was needed to investigate the specific mechanism of MALT1 involvement in the progression of TAAD. (4) Further studies should be considered to add another cohort for validation.

In summary, MALT1 expression positively links with Th1 cells and Th17 cells, and also shows good utility in predicting 30-day mortality, which may serve as a potential biomarker for predicting disease risk and prognosis in TAAD patients. Especially, the combination of MALT1 expression, CRP, D-dimer, and surgery timing exhibits an excellent ability in predicting 30-day mortality in TAAD patients.

Author Contributions

Junqing Zong, Lingbo Yang and Dong Wang contributed to conceptualization, data curation, formal analysis, writing – original draft, supervision, validation and writing – review & editing. Lei Wei contributed to formal analysis, investigation, methodology, validation and writing – review & editing. Xuening Wang and Zhongjie Zhang contributed to investigation, resources, validation, writing – original draft. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare no conflict of interest.

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