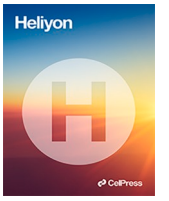
Heliyon 10 (2024) e35905

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Prognostic significance of serum secreted frizzled-related protein 5 in patients with acute aortic dissection

Mingle Zhang [a,b,1], Gaoshan Li [a,1], Kunyan Li [a,1], Zhichun Gao [a], Chun Yin [a], Fangzheng Zeng [c], Hao Yang [a], Wang Dong [a], Guiquan Zhou [a], Wenxu Pan [a], Ying Wang [a,**], Jun Jin [a,*]

[a] Department of Cardiology, The Second Affiliated Hospital (Xinqiao Hospital) of Army Medical University, Chongqing, 400037, China
[b] School of Medicine, Chongqing University, Chongqing, 400044, China
[c] Department of Emergency Medicine, The Second Affiliated Hospital (Xinqiao Hospital) of Army Medical University, Chongqing, 400037, China

ARTICLE INFO

Keywords:
Acute aortic dissection
Adipokine
Secreted frizzled-related protein 5
Prognosis

ABSTRACT

Background: Secreted frizzled-related protein 5 (SFRP5) is a novel adipokine that has been found to be closely associated with metabolic and cardiovascular diseases. We investigated serum SFRP5 levels during the acute phase and their predictive value for the prognosis of acute aortic dissection (AAD).

Methods: In total, 152 AAD patients and 164 controls were enrolled in this study. Serum SFRP5 levels were measured using an enzyme-linked immunosorbent assay (ELISA). AAD patients were divided into high-SFRP5 and low-SFRP5 groups based on the optimal cutoff value and followed up for prognosis. The primary endpoint was all-cause mortality, and the secondary endpoint focused on AAD-related events (including AAD-related mortality and unplanned reoperations).

Results: Serum SFRP5 levels were significantly higher in AAD patients than in non-AAD controls, regardless of whether they had Stanford type A or B AD. Multivariate logistic regression analysis revealed an independent association between SFRP5 and the presence of AAD (adjusted OR 1.267, 95 % CI 1.152–1.394; $p < 0.001$). The receiver operating characteristic curve demonstrated that the optimal cutoff value for SFRP5 to predict the presence of AAD was 10.26 ng/mL (AUC 0.7241, sensitivity 49.34 %, specificity 87.20 %). Notably, serum SFRP5 levels of patients in the death group were significantly higher than those in the survival group. Compared with patients in the low-SFRP5 group, those in the high-SFRP5 group exhibited a significantly increased risk of all-cause mortality (HR 9.540, 95 % CI 2.803–32.473; $p < 0.001$) and AAD-related events (HR 6.915, 95 % CI 2.361–20.254; $p < 0.001$) during the follow-up period.

Conclusion: Serum SFRP5 levels were significantly elevated in the acute phase of AAD, and high serum SFRP5 levels were independently associated with poor AAD prognosis. These results suggest that serum SFRP5 level during the acute phase may be an effective biomarker and therapeutic target for the prognosis of AAD.

* Corresponding authors.
** Corresponding author.
E-mail addresses: yingwang89@tmmu.edu.cn (Y. Wang), xqyyjinjun@163.com (J. Jin).
[1] Equal contribution.

https://doi.org/10.1016/j.heliyon.2024.e35905
Received 15 February 2024; Received in revised form 5 August 2024; Accepted 6 August 2024
Available online 12 August 2024

1. Introduction

Acute aortic dissection (AAD) is a serious disease with a high mortality rate and poor prognosis [1–4]. Exploring biomarkers that can effectively diagnose and predict the prognosis in the early stages is of great significance for improving the prognosis of AAD.

Adipose tissue plays an important role in maintaining metabolic homeostasis [5,6]. Many studies have reported a close relationship between adipokines secreted by the adipose tissue and metabolic disorders. In recent years, their correlation with cardiovascular disease (CVD) has been revealed [6–8]. Currently, research on the role of adipokines in AAD is limited.

Secreted frizzled-related protein 5 (SFRP5), a novel adipokine in the SFRP family, is highly expressed in white adipose tissues [9–14]. It shares homology with the speculated Wnt binding site found in Frizzled proteins [15]. Previous studies have shown that SFRP5 participates in various pathophysiological processes, including inflammation, adipogenesis, cell proliferation, and differentiation, by regulating the Wnt signalling pathway [16,17]. Specifically, clinical studies have consistently reported a decrease in serum SFRP5 levels in metabolic disorders such as obesity and insulin resistance [18–21]. Further basic studies have found that SFRP5 can inhibit the activation of the canonical Wnt/β-catenin signalling pathway and affect the activity of transcription factors such as peroxisome proliferator-activated receptor γ (PPAR-γ) and CCAAT/enhancer binding protein-α (C/EBPα), thereby exerting anti-inflammatory activity and affecting adipogenesis, antagonising the progression of metabolic diseases [18–22]. Additionally, several studies have reported that SFRP5 improves metabolic function and reduces adipose tissue inflammation by inhibiting the activation of non-canonical JNK by Wnt5a [23–26]. Teliewubai et al. have suggested that SFRP5 may inhibit smooth muscle cell (SMC) proliferation, migration and inflammation by suppressing the Wnt/β-catenin and p38/mitogen-activated protein kinase signaling pathways [27].

Consistently, basic research on CVD has also found that SFRP5 can have an anti-inflammatory effect by inhibiting Wnt5a-mediated activation of the non-canonical JNK signalling pathway, thereby reducing macrophage infiltration, and downregulating the expression of proinflammatory cytokines and chemokines, ultimately playing a protective role in ischemic myocardial injury, atherosclerosis etc. [13,28–33]. Collectively, these findings indicate that SFRP5 plays a protective role against CVD. However, the association between serum SFRP5 levels and the prevalence and prognosis of various CVD, as reported in clinical studies, is controversial.

Some studies on stable coronary heart disease and peripheral arterial disease have found that serum SFRP5 levels are reduced and are negatively correlated with disease progression, consistent with research on metabolic diseases [11,28,29,34,35]. Unexpectedly, a study focusing on ST-segment elevation myocardial infarction (STEMI) found a significant increase in serum SFRP5 levels during the acute phase of STEMI and gradual decrease during the non-acute phase [36]. Another study on heart failure (HF) found that serum SFRP5 levels in patients with HF were significantly higher than those in healthy controls and that patients with a poor prognosis had higher serum SFRP5 levels [37].

The aforementioned studies have identified a close correlation between serum SFRP5 levels and CVD; however, this relationship may be heterogeneous across different disease types and stages (such as the acute and chronic phases, or in a highly inflammatory state), requiring in-depth research with appropriate control populations in the context of specific diseases.

Therefore, the current study aimed to clarify the expression levels of serum SFRP5 in AAD patients during the acute phase and to explore the association between serum SFRP5 levels and the onset and prognosis of AAD.

2. Methods

2.1. Study population

This was a single-centre observational cohort study. Patients with traumatic AAD, infectious aortic disease, malignant tumors, severe chronic renal failure (estimated glomerular filtration rate (eGFR) < 15 mL/min per 1.73 m^2), and pregnancy were excluded. Controls with a history of aortic disease, infection, malignant tumors, or pregnancy were excluded. From March 2022 to September 2023, 152 eligible AAD patients who were classified according to the Stanford classification were enrolled in the emergency department upon admission [1], and 164 age- and sex-matched controls were enrolled during physical examinations at our hospital (Fig. S1). Baseline clinical data including sex, age, body mass index (BMI), current smoking status, history of hypertension, dyslipidaemia, diabetes mellitus, admission blood pressure (BP), and laboratory tests, were obtained from medical records. Written informed consent was obtained from all enrolled subjects. This study was approved by the Ethics Committee of the Second Affiliated Hospital of the Army Medical University (approve no. 202317201) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Examination of serum SFRP5 levels

The serum was isolated from blood samples collected on admission and stored at −80 °C until measurement. The concentration of serum SFRP5 was determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Wuhan ElAab Science Co., Ltd, China). The SFRP5 assay had a sensitivity of 0.98 ng/mL. This process was performed according to the manufacturer's instructions. First, prepare standard samples with concentrations of 0, 1.56, 3.12, 6.25, 12.5, 25, 50, and 100 ng/mL were prepared. Then, 100 μl standard or serum sample was added to each well and incubated at 37 °C for 2 h. The liquid was removed, and the working solution of Detection Reagent A added and incubated for 1 h. Each well was washed with washing buffer, and the working solution of Detection Reagent B was added and incubated for another hour. Each well was washed, the Substrate was added and incubated for 20 min, and then Stop Solution was added to each well. Finally, serum SFRP5 concentration was calculated based on the optical density of the samples in each well at a wavelength of 450 nm.

2.3. Outcomes

AAD Patients were followed up at regular intervals after the initial admission to assess the long-term outcomes and monitor for any potential complications. Follow-up visits were scheduled at 1 month, 6 months, and annually thereafter, allowing for the determination of survival time at each time point. Survival days of patients were calculated from the day of admission. The follow-up assessments were conducted either in person during clinic visits, via telephone interviews or questionnaire. The clinical outcomes of AAD patients in this study were defined as the primary endpoint (all-cause mortality) and secondary endpoints (AAD-related events, particularly aortic-related mortality, and unplanned reoperation). In this study, 8 (5.2 %) AAD patients were lost to final follow-up. Their survival days were counted until the last follow-up time point and treated as censored data in the survival analysis.

2.4. Statistical analysis

Continuous variables are represented by mean ± standard deviation (normal distribution) or quartiles 1st-3rd (abnormal distribution). Categorical variables were described as percentages or frequencies. The unpaired *t*-test and Mann Whitney *U* test were used to compare intergroup differences between AAD patients and controls or continuous variables. The Chi-square test was used to assess intergroup differences in categorical data. The relationship between variables and serum SFRP5 expression was investigated using Spearman correlation analysis. A logistic regression model was used to assess the association between serum SFRP5 expression and the risk of AAD. A receiver operating characteristic (ROC) curve was constructed to evaluate the diagnostic accuracy and optimal diagnostic value of serum SFRP5 in AAD. The Kaplan Meier curve was used to visualise the outcomes in groups with different SFRP5 levels. Multivariate Cox regression analysis was conducted to evaluate the effect of serum SFRP5 levels on adverse prognosis among patients with AAD. All statistical analyses were performed using SPSS (version 24.0; IBM Corp, Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics and detection of serum SFRP5 levels

The baseline characteristics of the study population are presented in Supplemental Table 1. Compared with controls, the prevalence of hypertension was higher among AAD patients. Additionally, AAD patients had a higher systolic BP, white blood cell (WBC) count, monocyte count, neutrophil (NEUT) count, creatinine level, and blood urea nitrogen level. Conversely, their haemoglobin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, red blood cell count, and platelet

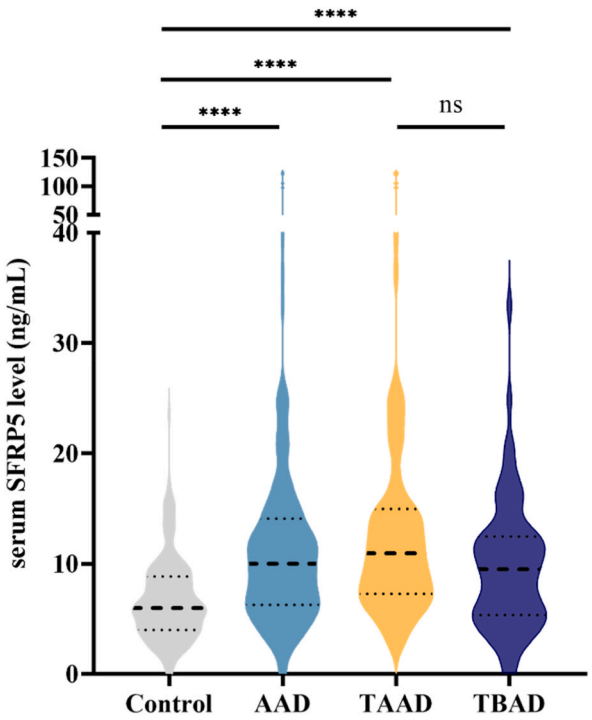


Fig. 1. Serum SFRP5 levels in AAD patients and controls. ****$p < 0.0001$, ns $p > 0.05$. AAD, acute aortic dissection; TA AD, Type A aortic dissection; TB AD, Type B aortic dissection.

count were lower. Notably, serum SFRP5 levels in patients with AAD were significantly higher in patients with AAD than in the controls (9.99 vs. 5.96, $p < 0.001$). No significant difference was observed in the serum SFRP5 levels between the two types of AAD patients classified according to the Stanford type (Fig. 1).

3.2. Association of serum SFRP5 levels with clinical characteristics of aortic dissection

We investigated the association between serum SFRP5 levels and variables using Spearman correlation analysis (Table S2). Serum SFRP5 levels were positively correlated with systolic BP, aspartate aminotransferase level, WBC count, NEUT count, and monocyte count ($p < 0.05$). Serum creatinine and blood urea nitrogen levels were also positively associated with serum SFRP5 levels. Conversely, there was a negative correlation between total cholesterol, high-density lipoprotein, low-density lipoprotein, lymphocytes, red blood cell count, haemoglobin, platelet count, and serum SFRP5 levels. However, no significant association was observed between serum SFRP5 levels and BMI or triglycerides in the current cohort. Univariate logistic regression analysis revealed that serum SFRP5 levels were associated with AAD. Furthermore, multivariate logistic regression analysis indicated that serum SFRP5 levels were independently associated with the presence of AAD after adjusting for age, sex, smoking status, history of hypertension, total cholesterol and triglycerides (OR = 1.267 95 % CI 1.152–1.394, $p < 0.001$, Table 1).

3.3. Diagnostic power of high serum SFRP5 levels for the presence of aortic dissection

To investigate the diagnostic value of serum SFRP5 in AAD, we plotted the ROC curve of serum SFRP5 levels and AAD. The ROC curve revealed that the optimal cutoff value for SFRP5 for diagnosing AAD was 10.26 ng/mL (sensitivity 49.34 %, specificity 87.20 %, AUC 0.7241; Fig. 2).

Furthermore, we categorised AAD patients into high- and low-SFRP5 groups based on the optimal cutoff values (Table 2). Compared to AAD patients in the low-SFRP5 group, those in the high-SFRP5 group were older and had a higher BMI, a higher prevalence of dyslipidaemia, elevated serum creatinine and blood urea nitrogen levels, and higher alanine aminotransferase and aspartate aminotransferase levels.

3.4. High serum Sfrp5 level is significantly associated with adverse outcomes of AAD

The median follow-up duration of the AAD cohort was 477 days. Of 152 patients, 43 (28.3 %) experienced all-cause mortality (33 with Stanford type A AD and 10 with Stanford type B AD). Additionally, 44 patients (28.9 %) experienced AAD-related events (34 with Stanford type A AD patients and 10 with Stanford type B AD). AAD patients with high serum SFRP5 levels demonstrated a significantly increased incidence of all-cause mortality (Fig. 3A and B) and AAD-related events (Fig. 3C and D) compared with those with low serum SFRP5 levels, independent of the Stanford type. In the subgroup analysis of AAD patients who underwent surgery or thoracic endovascular aortic repair (TEVAR), those with high SFRP5 levels in the Stanford type A group without surgery and the Stanford type B group without TEVAR had an increased risk of all-cause mortality and AAD-related events. Although the p value was not significant in Stanford type A patients without surgery and Stanford type B patients with TEVAR, AAD patients with high SFRP5 levels exhibited a trend toward a higher risk of all-cause mortality and AAD-related events (Figs. S2–S3). Compared to the survival group, the death group had older age, lower BMI, worse renal function, and higher WBC and NEUT levels (Table S3). The multivariate Cox regression model indicated that an increased serum SFRP5 level was a significant predictor of adverse outcomes in AAD patients (for all-cause mortality, HR 9.540; 95 % CI 2.803–32.473; $p < 0.001$; for AAD-related mortality or unplanned reoperation, HR 6.915; 95 % CI 2.361–20.254; $p < 0.001$, Fig. 4).

4. Discussion

The expression of serum SFRP5 in CVD and its association with disease prognosis remain controversial. In contrast to the bulk of research that implies that serum SFRP5 levels are lower in CVD, our data demonstrated that patients with AAD had considerably higher serum SFRP5 levels than healthy controls. Furthermore, AAD patients with high serum SFRP5 levels had a worse prognosis than their low-SFRP5 counterparts.

To date, basic research has supported SFRP5 as a specific inhibitor of the WNT signalling pathway, playing an anti-inflammatory and protective role in both metabolic and cardiovascular diseases [13,38,39]. Clinical studies have found that SFRP5 levels are reduced in metabolic disorders such as obesity and diabetes [20,40]. Consistent with this trend in metabolic diseases, serum SFRP5 levels were decreased in patients with coronary artery disease (CAD) and peripheral arterial occlusive disease [29,41]. However, several studies have reported conflicting results. Serum SFRP5 levels significantly increased during the acute phase of STEMI and then gradually decrease during the non-acute phase [36].

Table 1
Association between serum SFRP5 level and the presence of AAD.

Model	Odds Ratio (95%CI)	p value
Model 1: crude no adjustment	1.191 (1.124–1.263)	<0.001
Model 2: adjusting for age, male, smoking, history of hypertension, total cholesterol , triglyceride	1.267 (1.152–1.394)	<0.001

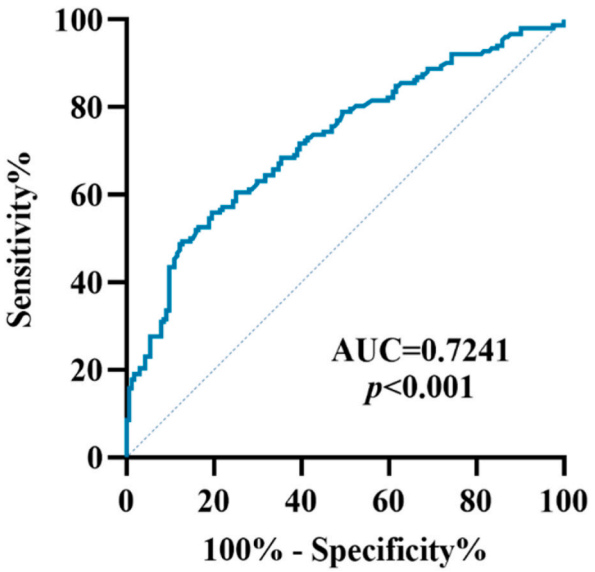


Fig. 2. Diagnostic power of serum SFRP5 levels for the presence of AAD by ROC curve. The optimal cutoff value is 10.26 ng/mL, calculated using the Jordon index. Sensitivity is 49.34 % and specificity is 87.20 %. AUC, area under the curve.

Table 2
Comparison of baseline characteristics between low-SFRP5 group and high-SFRP5 group in AAD patients.

Variables	Low-SFRP5 group (n = 77)	High-SFRP5 group (n = 75)	*p*-value
Sex	62 (80.50 %)	59 (78.70 %)	0.777
Age (years)	52.56 ± 11.97	58.32 ± 12.61	0.004
BMI (kg/m^2)	25.08 (22.70–27.42)	24.77 (22.07–27.88)	0.565
Smoking (n/%)	44 (58.70 %)	42 (56.00 %)	0.813
Hypertension (n/%)	53 (68.80 %)	55 (73.30 %)	0.617
Dyslipidemia (n/%)	24 (31.20 %)	40 (53.30 %)	0.010
Diabetes mellitus (n/%)	2 (2.60 %)	4 (5.30 %)	0.328
TAAD (n/%)	35 (45.50 %)	44 (58.70 %)	0.103
SBP (mmHg)	135.57 ± 25.61	136.61 ± 23.07	0.801
DBP (mmHg)	78.59 ± 15.98	77.38 ± 16.50	0.659
FBG (mmol/L)	6.23 (5.02–6.85)	5.78 (4.77–7.61)	0.814
HbA1c (%)	5.60 (5.15–5.90)	5.70 (5.50–5.95)	0.390
Albumin (g/L)	40.52 ± 3.49	39.24 ± 4.32	0.049
ALT (IU/L)	23.40 (13.65–35.85)	25.95 (16.28–49.73)	0.106
AST (IU/L)	22.40 (17.10–29.55)	23.05 (19.30–50.18)	0.067
Total cholesterol (mmol/L)	4.29 (3.84–4.86)	3.84 (3.44–4.37)	0.045
Triglyceride (mmol/L)	1.32 (0.92–1.84)	1.25 (0.93–2.09)	0.978
HDL-c (mmol/L)	1.11 ± 0.30	1.05 ± 0.28	0.254
LDL-c (mmol/L)	2.24 ± 0.66	2.08 ± 0.69	0.194
CRP (mg/L)	10.80 (3.45–48.55)	14.60 (3.40–75.50)	0.458
IL-6 (pg/ml)	34.42 (16.65–76.00)	25.60 (17.12–56.80)	0.423
IL-8 (pg/ml)	33.30 (9.97–573.00)	67.90 (9.10–824.75)	0.813
TNF-α (pg/ml)	8.25 (5.73–9.60)	7.10 (4.60–10.75)	0.955
White blood cell count (× 10^9/L)	11.15 ± 4.35	11.79 ± 4.60	0.383
Monocyte count (× 10^9/L)	0.83 ± 1.16	0.99 ± 1.84	0.532
Lymphocyte count (× 10^9/L)	1.65 ± 2.77	1.62 ± 2.60	0.954
Neutrophil count (× 10^9/L)	11.03 ± 12.33	11.64 ± 11.30	0.750
Red blood cell count (× 10^9/L)	4.37 (4.00–4.77)	4.29 (3.93–4.73)	0.375
Hemoglobin (g/dL)	132.51 ± 18.02	130.52 ± 20.61	0.528
Platelet (× 10^9/L)	185.35 ± 68.26	176.23 ± 79.81	0.451
Scr (umol/L)	86.43 ± 36.94	109.05 ± 92.92	0.049
BUN (mmol/L)	6.41 ± 2.24	7.54 ± 3.30	0.014
SFRP5 (ng/ml)	6.54 (4.46–8.16)	14.39 (12.09–20.31)	<0.001

Continuous values are expressed by mean ± SD or median (1st quartile−3rd quartile). AAD, acute aortic dissection; BMI, body mass index; TAAD, Type A aortic dissection; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, Glycosylated hemoglobin, Type A1C; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; CRP, C-reaction protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-alpha; IL-8, Interleukin-8; Scr, serum creatinine; BUN, blood urea nitrogen; SFRP5, secreted frizzled related protein 5.

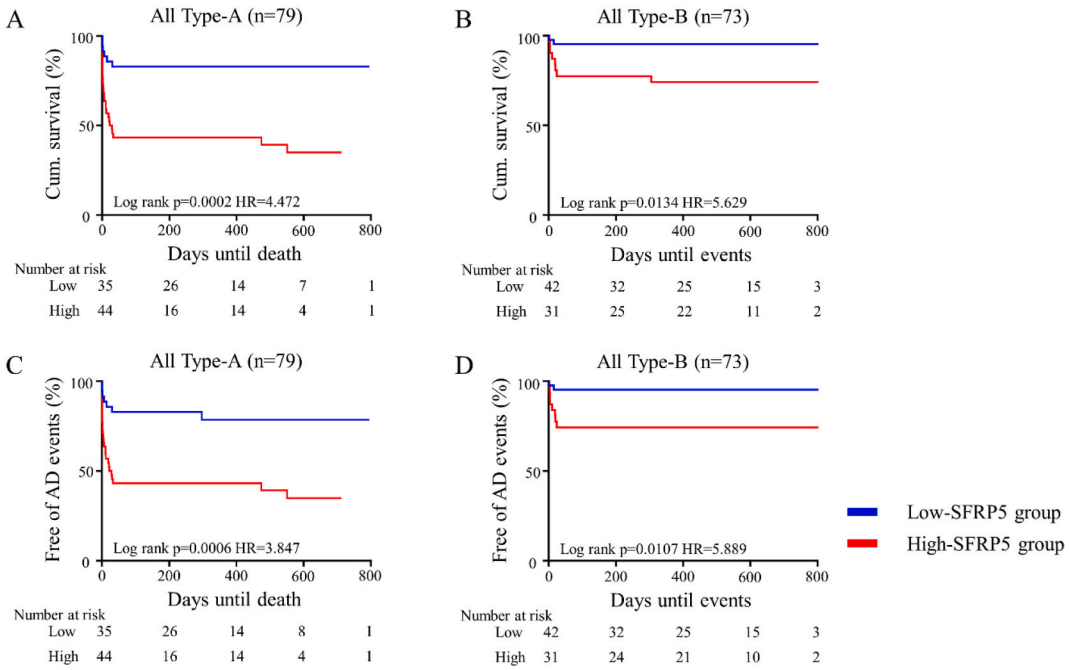


Fig. 3. Kaplan–Meier curves for serum SFRP5 levels on adverse AAD progression. (A) Cumulative all-cause survival rate in different SFRP5 levels in Stanford type A AD. (B) Cumulative all-cause survival rate in different SFRP5 levels in Stanford type B AD. (C) Free of AAD-related events rate in different SFRP5 levels in Stanford type A AD. (D) Free of AAD-related events rate in different SFRP5 levels in Stanford type B AD.

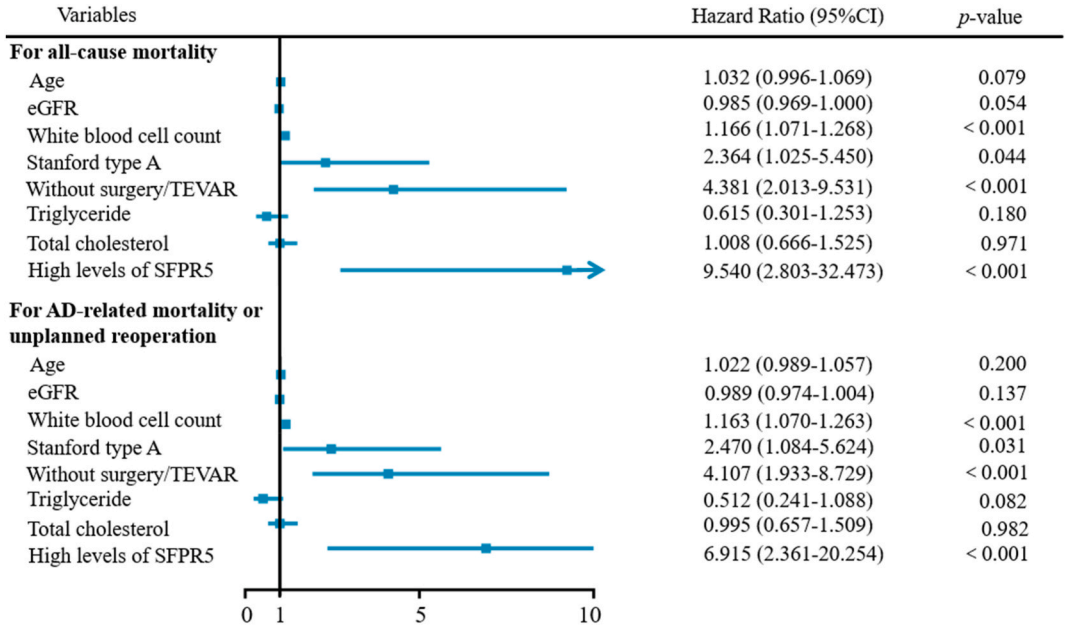


Fig. 4. Forest polt of multivariate Cox regression model for the risk of all-cause death and AAD-related events. eGFR, estimated glomerular filtration rate; TEVAR, thoracic endovascular aortic repair; SFRP5, secreted frizzled-related protein 5.

Obesity and insulin resistance are known to be associated with a chronic low-grade inflammatory state. Stable CAD and peripheral arterial disease are often in the chronic phase rather than in the acute or highly inflammatory phase of the disease, with no significant short-term fluctuations in severity. Therefore, we believe that the decrease in serum SFRP5 levels may reflect its continuous consumption counteract chronic inflammation. In contrast, STEMI represents an acute unstable phase of CAD, characterised by excessive inflammation. The transient elevation of serum SFRP5 levels during the acute phase of STEMI may indicate a high demand for SFRP5 in

response to acute inflammation, followed by a compensatory mechanism [36]. Thus, it is necessary to limit or define the disease phase of the enrolled patients when comparing serum SFRP5 levels in different populations. Another factor that should not be ignored is the control population, which is the most important reference standard. In some studies, the definition of the control population was not carefully described, and we could not determine whether the controls were patients from the same department or healthy volunteers. In the current study, we measured the serum SFRP5 levels in AAD patients during the acute phase and recruited a control group from the physical examination department of the same hospital. We found that serum SFRP5 levels in AAD patients during the acute phase were significantly higher than those in the healthy controls.

Elevated serum SFRP5 levels in AAD patients may be caused by various factors. First, as evidenced by the significant increase of peripheral blood WBCs, monocytes, and NEUTs in AAD patients compared with those in the control population, the inflammatory response is sharply upregulated during the acute phase of AAD. This upregulation is similar to that observed in STEMI, where elevated serum SFRP5 levels are considered a compensatory mechanism to enhance its anti-inflammatory effects [22]. Therefore, we inferred that increased serum SFRP5 levels in AAD patients may also follow a compensatory mechanism. Secondly, AAD has a significant impact on the haemodynamics of renal arteries [42]. A considerable proportion (approximately 40 %) of AAD patients have experience renal artery dissection, with 33.9 % showing reduced renal enhancement on computed tomography angiography [43]. Even if the dissection does not involve the renal artery, compression of the false lumen into the true lumen will still lead to reduced renal perfusion. Consequently, acute kidney injury (AKI) has emerged as a common complication in AAD patients, as documented in a report in which 36.8 % of individuals with Type B dissection developed AKI before TEVAR [44]. In our study, although we were unable to assess the incidence of preoperative AKI due to the lack of creatinine monitoring, our baseline data showed a significant negative correlation between serum SFRP5 levels and eGFR as previously reported [45,46], suggesting a certain degree of AKI incidence in the current cohort. Based on this, we speculated that renal dysfunction caused by AKI or other factors may lead to a decrease in SFRP5 excretion, which may serve as another potential cause of elevated serum SFRP5 levels in the acute phase of AAD.

Previous studies have reported that SFRP5 levels are negatively correlated with the levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol [47]. As SFRP5 levels decrease, the risk of elevated total cholesterol levels increases significantly [48]. Further research has demonstrated that the expression of PPAR-γ and C/EBPα, two genes crucial for lipid production, is downregulated by SFRP5 [49]. Consistently, in the current cohort, we found that the total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels in AAD patients were significantly lower than those in the control population.

Although Miao et al. recently published a similar study, their conclusions differed significantly from those of our current research [50]. Their study reported that SFRP5 levels in the AAD group were lower than those in controls. However, it is essential to recognize that the control group in their study were non-AAD patients with chest pain admitted to the emergency department, with the majority likely being acute myocardial infarction patients. Previous studies have reported a close association between SFRP5 and myocardial infarction [36], and serum SFRP5 levels in non-AAD patients with chest pain are different from those in healthy individuals. Importantly, the control group in our study was recruited from a relatively healthy population who underwent physical examinations at our hospital and were not in the acute phase of the disease. Therefore, the results of the current study better reflect the true changes in serum SFRP5 levels in AAD patients. Serum SFRP5 levels vary during the acute and chronic phases of the disease. The serum samples of AAD patients in this study were collected during the acute onset period when they were admitted to the emergency department, whereas the study by Miao et al. did not mention the serum sampling time. Therefore, potential differences in serum sampling time may also lead to differences in the research conclusions. The association between SFRP5 levels and CVD prognosis of remains controversial. Among patients with chronic heart failure, SFRP5 levels were significantly higher in those with a poor prognosis [37]. Individuals with higher SFRP5 levels have a higher incidence of cardiovascular events [51]. Another study focusing on acute STEMI, found that high SFRP5 levels were associated with accelerated cardiac function recovery after PCI [36]. Another important finding of this study was that AAD patients with higher serum SFRP5 levels had poorer prognoses than AAD patients with lower serum SFRP5 levels, contrary to the research findings of Miao et al. [50].

In our study, the overall mortality rate of AD patients (28.3 % vs. 27.4 %) and the mortality rate of Type A AD patients (21.7 % vs. 22 %) were comparable to the data reported by International Registry of Acute Aortic Dissection (IRAD) [3]. However, the mortality rate for Type B AD patients (6.5 % vs. 13 %) in our study was relatively lower, which we believed might be attributed to the significant advancements in endovascular stent technology that significantly improved the prognosis of patients with Type B AD. Therefore, our study population was representative of the survival outcomes of the majority of AD patients. The Stanford classification of AAD and whether patients undergo surgery are two key factors that determine the prognosis of AAD patients. In a study by Miao et al., 90.6 % of Type A patients and 91.7 % of Type B patients received surgical treatment, however, the prognostic analysis did not adjust for the important factor of whether patients underwent surgery. In the prognostic analysis of our study, we divided the patients into four subgroups based on the Stanford classification of AAD and whether they had undergone surgery. Importantly, although the differences did not reach statistical significance in a few subgroups, the predicted trend of high serum SFRP5 levels for a poor prognosis remained consistent across different groups, further enhancing the credibility of the results of our study.

Notably, in our study, the death group exhibited advanced age, lower BMI, impaired renal function, and elevated WBC and NEUT counts compared to the survival group. The high serum SFRP5 group showed a significant increase in creatinine levels, with a trend towards older age and higher levels of interleukin 8. Previous studies have shown the predictive value of elevated creatinine, advanced age, and inflammatory biomarkers for the prognosis of AAD [52–56]. Additionally, AKI was one of the reasons for increased SFRP5 levels, but it also had a significant impact on prognosis [57–60]. Therefore, the association between high SFRP5 levels and poor prognosis in AAD observed in this study may be attributed to the potential association between SFRP5 and the factors associated with poor AAD prognosis. We believe that the controversy in the relationship between serum SFRP5 levels and the prognosis of CVD may be

due to the dynamic and context-dependent expression levels of serum SFRP5, which are closely influenced by different disease types, stages of progression, and other factors.

Our study has some limitations. First, our measurements were limited to the evaluation of serum SFRP5 levels in AAD patients in the acute phase. Further investigation is needed to explore the dynamic changes in SFRP5 levels during disease progression. Second, we only measured serum SFRP5 concentrations. Future research analysing the expression of SFRP5 in the aortic wall and peripheral vascular tissues will help better understand the pathophysiological role of SFRP5 in the progression of AAD.

5. Conclusion

Our findings indicate that serum SFRP5 levels in AAD patients are significantly elevated compared to those in controls. Moreover, higher serum SFRP5 levels were associated with a poorer prognosis in AAD patients. Therefore, serum SFRP5 levels may serve as a valuable prognostic indicator for individuals diagnosed with AAD.

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Army Medical University with the approval no.202317201. All participants provided written informed consent to participate in the study.

Funding

This work was supported by the National Natural Science Foundation of China 82100288 (Y.W.), Chongqing Doctoral Research Fund CSTB2022BSXM-JCX0023 (Y.W.), Chongqing Innovation Support Program for Returned Overseas Scholars cx2020010 (Y.W.), Young Doctoral Talent Program 2022YQB009 (Y.W.), Chongqing Talent Program CQYC201903087 (J.J.), Leading medical talents in Chongqing (J.J.), and Chongqing Clinical Key Specialty Boutique Project.

Data availability statement

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

CRediT authorship contribution statement

Mingle Zhang: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Gaoshan Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Kunyan Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Zhichun Gao:** Investigation, Formal analysis. **Chun Yin:** Investigation, Formal analysis. **Fangzheng Zeng:** Methodology. **Hao Yang:** Resources. **Wang Dong:** Software. **Guiquan Zhou:** Investigation. **Wenxu Pan:** Software. **Ying Wang *:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Jun Jin:** Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35905.

References

[1] C.A. Nienaber, et al., Aortic dissection, Nat. Rev. Dis. Prim. 2 (2016) 16071.
[2] Y. Zhu, et al., Type a aortic dissection-experience over 5 decades: jacc historical breakthroughs in perspective, J. Am. Coll. Cardiol. 76 (14) (2020) 1703–1713.
[3] A. Evangelista, et al., Insights from the international registry of acute aortic dissection: a 20-year experience of collaborative clinical research, Circulation 137 (17) (2018) 1846–1860.
[4] V. Aboyans, M. Boukhris, Dissecting the epidemiology of aortic dissection, Eur Heart J Acute Cardiovasc Care 10 (7) (2021) 710–711.
[5] T. Ronti, G. Lupattelli, E. Mannarino, The endocrine function of adipose tissue: an update, Clin. Endocrinol. 64 (4) (2006) 355–365.

[6] J.M. Northcott, et al., Adipokines and the cardiovascular system: mechanisms mediating health and disease, Can. J. Physiol. Pharmacol. 90 (8) (2012) 1029–1059.
[7] H. Yamawaki, Vascular effects of novel adipocytokines: focus on vascular contractility and inflammatory responses, Biol. Pharm. Bull. 34 (3) (2011) 307–310.
[8] Z. Wang, T. Nakayama, Inflammation, a link between obesity and cardiovascular disease, Mediat. Inflamm. 2010 (2010) 535918.
[9] C. Lagathu, et al., Dact1, a nutritionally regulated preadipocyte gene, controls adipogenesis by coordinating the wnt/beta-catenin signaling network, Diabetes 58 (3) (2009) 609–619.
[10] D.M. Schulte, et al., Pro-inflammatory wnt5a and anti-inflammatory sfrp5 are differentially regulated by nutritional factors in obese human subjects, PLoS One 7 (2) (2012) e32437.
[11] M. Carstensen-Kirberg, et al., Inverse associations between serum levels of secreted frizzled-related protein-5 (sfrp5) and multiple cardiometabolic risk factors: kora f4 study, Cardiovasc. Diabetol. 16 (1) (2017) 109.
[12] S.A. Rebuffat, et al., Downregulation of sfrp5 promotes beta cell proliferation during obesity in the rat, Diabetologia 56 (11) (2013) 2446–2455.
[13] K. Nakamura, et al., Secreted frizzled-related protein 5 diminishes cardiac inflammation and protects the heart from ischemia/reperfusion injury, J. Biol. Chem. 291 (6) (2016) 2566–2575.
[14] Y.J. Kwon, et al., Secreted frizzled-related protein 5 suppresses inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes through down-regulation of c-jun n-terminal kinase, Rheumatology 53 (9) (2014) 1704–1711.
[15] D. Koutaki, et al., The emerging role of sfrp5 and wnt5a in the pathogenesis of obesity: implications for a healthy diet and lifestyle, Nutrients 13 (7) (2021).
[16] L. Recinella, et al., Adipokines: new potential therapeutic target for obesity and metabolic, rheumatic, and cardiovascular diseases, Front. Physiol. 11 (2020) 578966.
[17] M. Pashirzad, et al., Role of wnt5a in the pathogenesis of inflammatory diseases, J. Cell. Physiol. 232 (7) (2017) 1611–1616.
[18] M. Carstensen, et al., Sfrp5 correlates with insulin resistance and oxidative stress, Eur. J. Clin. Invest. 43 (4) (2013) 350–357.
[19] Z. Hu, H. Deng, H. Qu, Plasma sfrp5 levels are decreased in Chinese subjects with obesity and type 2 diabetes and negatively correlated with parameters of insulin resistance, Diabetes Res. Clin. Pract. 99 (3) (2013) 391–395.
[20] W. Hu, et al., Circulating sfrp5 is a signature of obesity-related metabolic disorders and is regulated by glucose and liraglutide in humans, J. Clin. Endocrinol. Metab. 98 (1) (2013) 290–298.
[21] Q. Xu, et al., Plasma sfrp5 levels correlate with determinants of the metabolic syndrome in Chinese adults, Diabetes Metab Res Rev 33 (6) (2017).
[22] L.B. Liu, et al., The wnt antagonist and secreted frizzled-related protein 5: implications on lipid metabolism, inflammation, and type 2 diabetes mellitus, Biosci. Rep. 38 (4) (2018).
[23] N. Ouchi, et al., Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity, Science 329 (5990) (2010) 454–457.
[24] H. Mori, et al., Secreted frizzled-related protein 5 suppresses adipocyte mitochondrial metabolism through wnt inhibition, J. Clin. Invest. 122 (7) (2012) 2405–2416.
[25] H.P. He, S. Gu, The ppar-γ/sfrp5/wnt/β-catenin signal axis regulates the dexamethasone-induced osteoporosis, Cytokine 143 (2021) 155488.
[26] M. Sun, et al., Secreted frizzled-related protein 5 (sfrp5) protects atdc5 cells against lps-induced inflammation and apoptosis via inhibiting wnt5a/jnk pathway, J. Orthop. Surg. Res. 16 (1) (2021) 129.
[27] J. Teliewubai, et al., Sfrp5 serves a beneficial role in arterial aging by inhibiting the proliferation, migration and inflammation of smooth muscle cells, Mol. Med. Rep. 18 (5) (2018) 4682–4690.
[28] C.J. Kelly, et al., Association of circulating plasma secreted frizzled-related protein 5 (sfrp5) levels with cardiac function, J Cardiovasc Dev Dis 10 (7) (2023).
[29] S. Tong, et al., Expression of sfrp5/wnt5a in human epicardial adipose tissue and their relationship with coronary artery disease, Life Sci. 245 (2020) 117338.
[30] S. Tong, et al., Sfrp5/wnt pathway: a protective regulatory system in atherosclerotic cardiovascular disease, J. Interferon Cytokine Res. 39 (8) (2019) 472–482.
[31] N. Ding, C. Zheng, Secreted frizzled-related protein 5 promotes angiogenesis of human umbilical vein endothelial cells and alleviates myocardial injury in diabetic mice with myocardial infarction by inhibiting wnt5a/jnk signaling, Bioengineered 13 (5) (2022) 11656–11667.
[32] Y.K. Cho, et al., Effect of sfrp5 (secreted frizzled-related protein 5) on the wnt5a (wingless-type family member 5a)-induced endothelial dysfunction and its relevance with arterial stiffness in human subjects, Arterioscler. Thromb. Vasc. Biol. 38 (6) (2018) 1358–1367.
[33] W. Liu, et al., Sfrp5 mediates downregulation of the wnt5a/caveolin-1/jnk signaling pathway, J. Endocrinol. 247 (3) (2020) 263–272.
[34] J. Teliewubai, et al., Association of asymptomatic target organ damage with secreted frizzled related protein 5 in the elderly: the northern shanghai study, Clin. Interv. Aging 13 (2018) 389–395.
[35] T. Miyoshi, et al., Low serum level of secreted frizzled-related protein 5, an anti-inflammatory adipokine, is associated with coronary artery disease, Atherosclerosis 233 (2) (2014) 454–459.
[36] Y. Du, et al., High serum secreted frizzled-related protein 5 levels associates with early improvement of cardiac function following st-segment elevation myocardial infarction treated by primary percutaneous coronary intervention, J Atheroscler Thromb 26 (10) (2019) 868–878.
[37] Y. An, et al., Clinical significance of sfrp5, rbp-4 and nt-probnp in patients with chronic heart failure, Am J Transl Res 13 (6) (2021) 6305–6311.
[38] Y. Ren, et al., Adipokines, hepatokines and myokines: focus on their role and molecular mechanisms in adipose tissue inflammation, Front. Endocrinol. 13 (2022) 873699.
[39] B. Li, et al., Type 2 diabetes with hypertensive patients results in changes to features of adipocytokines: leptin, irisin, lgr4, and sfrp5, Clin. Exp. Hypertens. 41 (7) (2019) 645–650.
[40] X. He, H. Ma, Correlation between circulating levels of secreted frizzled-related protein 5 and type 2 diabetic patients and subjects with impaired-glucose regulation, Diabetes Metab Syndr Obes 13 (2020) 1243–1250.
[41] B. Wang, et al., Sfrp5/wnt5a and leptin/adiponectin levels in the serum and the periarterial adipose tissue of patients with peripheral arterial occlusive disease, Clin. Biochem. 87 (2021) 46–51.
[42] J. Buech, et al., Visceral and renal malperfusion syndromes in acute aortic dissection type a: the fate of the branch vessel, J. Cardiovasc. Surg. 63 (2) (2022) 117–123.
[43] C.C. Wang, et al., Renal artery involvement in acute aortic dissection: prevalence and impact on renal atrophy in non-interventional treatment patients, J Cardiovasc Comput Tomogr 12 (5) (2018) 404–410.
[44] H.M. Ren, et al., Relationship between acute kidney injury before thoracic endovascular aneurysm repair and in-hospital outcomes in patients with type b acute aortic dissection, J Geriatr Cardiol 12 (3) (2015) 232–238.
[45] I.R. Báez, et al., Association of serum levels of secreted frizzled-related protein 5 and wnt member 5a with glomerular filtration rate in patients with type 2 diabetes mellitus and chronic renal disease: a cross-sectional study, Sao Paulo Med. J. 138 (2) (2020) 133–139.
[46] C.P. Wang, et al., Circulating secreted frizzled-related protein 5 and chronic kidney disease in patients with acute st-segment elevation myocardial infarction, Cytokine 110 (2018) 367–373.
[47] X. Tan, et al., Sfrp5 correlates with obesity and metabolic syndrome and increases after weight loss in children, Clin. Endocrinol. 81 (3) (2014) 363–369.
[48] Y. Bai, et al., Secreted frizzled-related protein 5 is associated with glucose and lipid metabolism related metabolic syndrome components among adolescents in northeastern China, Diabetes Metab Syndr Obes 14 (2021) 2735–2742.
[49] J. Zeng, et al., Sfrp5 is a target gene transcriptionally regulated by pparγ in 3t3-l1 adipocytes, Gene 641 (2018) 190–195.
[50] H. Miao, et al., Expression of secreted frizzled-related proteins in acute aortic dissection patients and the effects on prognosis, Front Cardiovasc Med 10 (2023) 1139122.
[51] Hongwei, et al., High serum level of secreted frizzled-related protein 5 (sfrp5) is associated with future cardiovascular events 2 (1) (2017) 1–7.
[52] H. Zhang, et al., The potential value of the neutrophil to lymphocyte ratio for early differential diagnosis and prognosis assessment in patients with aortic dissection, Clin. Biochem. 97 (2021) 41–47.
[53] P. Angleitner, et al., Type a acute aortic dissection presenting with cerebrovascular accident at advanced age, Semin. Thorac. Cardiovasc. Surg. 34 (3) (2022) 805–813.

[54] B. Huang, et al., Influence of age on clinical presentation, therapeutic options, and outcome in Chinese patients with acute aortic dissection, Int. Heart J. 60 (6) (2019) 1373–1380.
[55] Z.R. Luo, X.D. Chen, L.W. Chen, Age-dependent differences in the prognostic relevance of body composition-related variables in type a aortic dissection patients, J. Cardiothorac. Surg. 16 (1) (2021) 359.
[56] Z.N. Wu, et al., Does preoperative serum creatinine affect the early surgical outcomes of acute stanford type a aortic dissection? J. Chin. Med. Assoc. 83 (3) (2020) 266–271.
[57] X. Chen, et al., Outcomes and risk management in type b aortic dissection patients with acute kidney injury: a concise review, Ren. Fail. 43 (1) (2021) 585–596.
[58] J. Liu, et al., Thyroid hormone is related to postoperative aki in acute type a aortic dissection, Front. Endocrinol. 11 (2020) 588149.
[59] E. Xie, et al., Association between platelet counts and morbidity and mortality after endovascular repair for type b aortic dissection, Platelets 33 (1) (2022) 73–81.
[60] R.C. Hoogmoed, et al., Acute kidney injury in acute type b aortic dissection: outcomes over 20 years, Ann. Thorac. Surg. 107 (2) (2019) 486–492.