

Original Article



Evaluation of risk factors in patients with calcific aortic valve disease who underwent aortic valve replacement from 2011 to 2021

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Summary

Introduction: The incidence of aortic valve diseases, especially valve stenosis, is increasing and this disease is related to various factors. This project aims to determine the risk factors leading to aortic valve replacement by examining the risk factors of the calcified aortic valve.

Methods: This study was done retrospectively. The data for all the patients who underwent valve replacement surgery at Seyed Al-Shohdai hospital in Urmia between 2011 and 2021 were taken. The patients who underwent valve replacement due to calcified aortic valve were examined and demographic information was obtained. Patients' background risk factors including age, sex, body mass index (BMI), smoking status, diabetes, hypertension, hyperlipidemia, serum C-reactive protein (CRP) level, serum calcium, and phosphorus levels were extracted from the patients' files and entered into the checklist. Additionally, echocardiography findings were incorporated into the data, which was then analyzed in SPSS 27 software according to the study's objectives.

Findings: A total of 119 patients were included in our study, of which 78 (65.5%) were men and 41 (34.5%) were women. The average age of the patients was 61 years. The severity of calcified aortic valve stenosis leading to replacement procedure has no significant relationship with gender, high blood pressure, diabetic status, dyslipidemia, and CRP level of patients ($P > 0.05$); however, a significant relationship with age, smoking, BMI, glomerular filtration rate (GFR), serum phosphorus level and serum calcium status of patients was found ($P < 0.05$).

Conclusion: In conclusion, based on our findings we observed no significant association between gender and the disease. Notably, we found a significant relationship between patients' GFR and serum calcium levels and the severity of aortic valve stenosis. We recommend conducting more extensive studies across various hospitals and medical centers to better identify risk factors and high-risk individuals.

Keywords: Aortic valve disease, Risk factor, Valve stenosis

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Introduction

The root of the aorta is a complex structure, each of its components plays an important role in the functioning of the aortic valve, and the opening and closing of the valve is also done by these components. For many years, aortic valve replacement has been the standard treatment to correct its problems.¹

The incidence of aortic valve diseases, especially valve stenosis, is increasing and this is related to various factors that will be mentioned below. Calcified aortic valve disease (CAVD) is one of the most common indications for surgery, and so far no drug treatment or lifestyle changes have been found to prevent the onset or slow the progression of this disease.²

It is important to note that, despite valve abnormalities, a person may remain asymptomatic for a long period. However, once symptoms appear, subsequent symptoms tend to develop more rapidly. While medical treatments can provide some relief or temporarily alleviate symptoms,

they do not address the underlying issue of the faulty valve. Recent advances in surgery have created a good prognosis for patients. Meanwhile, for some patients, the importance of quick surgery is very high and it can save them from immediate death. Identifying individuals classified as high-risk based on the reviewed criteria can assist in prioritizing care and preparing for complications, ultimately contributing to improved surgical outcomes.³

Based on previous studies the main risk factors for aortic stenosis (AS) include age, male sex, obesity, hypertension, diabetes, metabolic syndrome, dyslipidemia, renal dysfunction, smoking, the level of calcium and phosphorus, and importantly baseline calcium score.⁴⁻⁷

This project aims to identify the risk factors associated with aortic valve replacement by evaluating those linked to CAVD. By determining these risk factors, we can identify at-risk individuals, potentially slow disease progression, and help prevent patients from advancing to the stage of requiring aortic valve replacement.



Methods

Participants

This cross-sectional study was conducted retrospectively. Records of all patients who underwent valve replacement surgery at Seyed Al-Shohdai hospital in Urmia from 2011 to 2021 were retrieved from the archive. Patients who had valve replacement due to a calcified aortic valve were selected based on inclusion (all patients with CAVD underwent aortic valve replacement between 2011 and 2021) and exclusion criteria (incomplete file information and non-satisfaction to participate in the study), and their demographic data were gathered. Risk factors-including age, sex, body mass index (BMI), smoking status, diabetes, hypertension, hyperlipidemia, serum C-reactive protein (CRP) level, and serum calcium and phosphorus levels-were collected from the patient's files and recorded on a checklist. Additionally, echocardiographic findings were included. Finally, the collected data were coded into Excel and analyzed using SPSS 27 software according to the study's objectives.

Data analysis

Quantitative variables were reported as mean \pm standard deviation and qualitative variables as numbers (percentage) in the form of appropriate tables and graphs. Chi-score test (chi-square, if necessary, Fisher test) was used to analyze and check the relationship between qualitative variables with aortic valve calcification (AVC) severity, and an independent t-test was used to check the relationship between quantitative variables with AVC severity. Data analysis was done by using SPSS 27 software and a significance level of less than 0.05 is considered.

Results

According to the results of our study, the descriptive data for risk factors in CAVD patients are mentioned in Table 1.

As mentioned in Table 2 for risk factors affecting the severity of AS in CAVD patients, our analytic data showed the severity of calcified aortic valve stenosis had no significant relationship with the gender of the patients ($P=0.233$). The severity of calcified aortic valve stenosis has a significant relationship with the age of patients. The average age of patients with severe valve stenosis is higher than the average age of patients with moderate valve stenosis ($P=0.034$). The severity of calcified aortic valve stenosis had a significant relationship with the patient's BMI, and the mean BMI of patients with severe valve stenosis was higher than the mean BMI of patients with moderate valve stenosis ($P=0.031$). The severity of calcified aortic valve stenosis had a significant relationship with the patients' smoking status ($P=0.024$). The severity of calcified aortic valve stenosis was closely linked to patients' glomerular filtration rate (GFR), with those experiencing severe valve stenosis showing a lower average GFR than those with moderate stenosis

Table 1. Descriptive data for risk factors of CAVD patients

| Risk factors | | Data |
|------------------------------|-------------|-------------------|
| Age | Range | 16-87 |
| | Average | 61.43 \pm 14.23 |
| | Median | 61 |
| BMI | Range | 15.4-42.7 |
| | Average | 29.21 \pm 4.01 |
| | Median | 28 |
| EF | Range | 15-65 |
| | Average | 44.87 \pm 12.68 |
| | Median | 50 |
| Smoking, No. (%) | Smoker | 72 (60.5) |
| | Non- Smoker | 47 (39.5) |
| | Total | 119 (100) |
| Gender, No. (%) | Male | 78 (65.5) |
| | Female | 41 (34.5) |
| | Total | 119 (100) |
| High blood pressure, No. (%) | Yes | 58 (48.7) |
| | No | 61 (51.3) |
| | Total | 119 (100) |
| Diabetes, No. (%) | Yes | 19 (16) |
| | No | 100 (84) |
| | Total | 119 (100) |
| Dyslipidemia | Yes | 8 |
| | No | 111 |
| | Total | 119 |
| Metabolic Syndrome | Yes | 10 |
| | No | 109 |
| | Total | 119 |
| Aortic Stenosis | Severe | 105 |
| | Moderate | 14 |
| | Total | 119 |

BMI: Body mass index, EF: Ejection fraction
Data presented as Mean \pm SD and Percentage.

($P=0.003$). The severity of calcified aortic valve stenosis did not have a significant relationship with the CRP of the patients ($P=0.114$). Interestingly, there is a strong link between the severity of calcified aortic valve stenosis and patients' serum phosphorus levels, with patients suffering from severe stenosis having a higher average serum phosphorus level than those with moderate stenosis ($P=0.003$). The severity of calcified aortic valve stenosis is closely associated with patient's serum calcium levels, with those facing severe stenosis showing a higher average serum calcium level than those with moderate stenosis ($P=0.015$).

Discussion

The incidence of aortic valve diseases, especially valve stenosis, is increasing and this disease is related to

Table 2. Risk factors affecting severity of aortic stenosis in calcified aortic valve disease patients

| Variable | | Moderate AS | Severe AS | Total |
|------------------|------------|-------------|-------------|-------------|
| Gender | Male | 11 (78.6%) | 67 (63.8%) | |
| | Female | 3 (21.4%) | 38 (36.2%) | |
| | P value | 0.233 | 0.233 | |
| Age | Mean±SD | 51.14±11.45 | 62.80±14.04 | 61.43±14.23 |
| | P value | 0.034 | 0.034 | |
| BMI | Mean±SD | 25.07±5.13 | 29.76±3.52 | 29.21±4.01 |
| | P value | 0.031 | 0.031 | |
| Smoking | Smoker | 4 (28.6%) | 68 (64.7%) | |
| | Non-Smoker | 10 (71.4%) | 37 (35.3%) | |
| | P value | 0.024 | 0.024 | |
| CRP | Mean±SD | 7.59±4.5 | 9.36±6.15 | 9.15±5.99 |
| | P value | 0.114 | 0.114 | |
| Serum phosphorus | Mean±SD | 2.09±0.33 | 3.11±0.43 | 2.98±0.53 |
| | P value | 0.043 | 0.043 | |
| Serum calcium | Mean±SD | 8.17±0.19 | 9.07±0.55 | 8.97±0.60 |
| | P value | 0.015 | 0.015 | |
| EF | Mean±SD | 48.57±9.28 | 44.38±13.03 | 44.87±12.68 |
| | P value | 0.039 | 0.039 | |

BMI: Body mass index, CRP: C-reactive protein, EF: Ejection fraction

various factors.² The aim of this project is to determine the risk factors leading to aortic valve replacement by examining the risk factors of calcified aortic valve. Our study included 119 patients, with 78 men (65.5%) and 41 women (34.5%) and the majority of patients had severe aortic valve stenosis.

In the study by Kronenberg in 2021 in Australia, the results showed that the variables of age, previous atherosclerotic disease, LDL, lipoprotein (Lp-a) and high blood pressure were associated with CAVD leading to valve replacement.⁸ In this study it was the same as the severity of calcified aortic valve stenosis had a significant relationship with the age of the patients. However, most of the studied patients did not have dyslipidemia and metabolic syndrome in this study.

In the study of Sherzad et al in 2022 in Kabul, sedentary lifestyle, diabetes mellitus, high BMI (≥ 30 kg/m²), social status and good economy, and high blood pressure were independent risk factors for CAVD in the Afghan population.⁹ In our study, we found that similar to this study's findings, the severity of calcified aortic valve stenosis was significantly associated with patients' BMI. However, unlike this study, most of our participants did not have high blood pressure or diabetes. Previous study claimed that obesity is associated with hypertension and dyslipidemia.¹⁰ Investigations also report a positive association between hypertension as well as LDL and a risk of CAVD.^{11,12} Obesity, particularly excess visceral adiposity, is associated with an inflammatory state,¹⁰ but whether inflammation contributes to the development of

AVS remains unclear.

The 2018 study conducted by Hisamatsu et al in Japan found that serum magnesium was inversely associated with the progression of AORTIC valve calcification (AVC), while higher serum phosphorus and calcium levels were positively linked to the prevalence and incidence of AVC. Similarly, in our study, we observed that the severity of calcified aortic valve stenosis was significantly related to patients' serum phosphorus and calcium levels.¹³ This could be due to the importance of osteogenic and apoptotic pathways for the development of CAVD.^{14,15} Transformation of aortic valvular interstitial cells into osteoblast-like phenotypes is suggested to be dependent on Uptake of phosphate via the Pit-1 receptor in multiple cell lines.¹⁶⁻¹⁸

The 2023 study by conducted by Massera et al in the United States found that age, male sex, diabetes, coronary heart disease, and lipoprotein-associated phospholipase-A2 activity were positively correlated with the incidence of moderate to severe AS. In contrast, Black race and creatinine-based estimated GFR were inversely associated with moderate to severe AS.¹⁹ Consistent with these conclusions, our research also found an inverse link between severity and GFR and a direct correlation between age and the degree of calcified aortic valve stenosis. However, unlike Massera's findings, our study did not find significant associations between stenosis severity and patient gender, diabetes, or dyslipidemia. Higher levels of AVC were found to be independently associated with decreased renal function (low GFR) in a 2015 study conducted in Germany by Guerraty et al. In line with Guerraty and colleagues' findings, we also found in our study that patients' GFR and the degree of calcified aortic valve stenosis were inversely correlated.²⁰

Age, obesity, known CVD, hypertension, and serum phosphate were all substantially linked to the severity of AVC in the Danish study by Khurrami et al in 2021, whereas smoking, diabetes, hyperlipidemia, Serum calcium, and estimated glomerular filtration did not significantly correlate. According to our research, the severity of aortic valve stenosis was significantly correlated with the patient's age, BMI, and serum phosphorus level; hyperlipidemia and diabetes did not significantly correlate with the severity of aortic valve stenosis. Contrary to the findings of this investigation, however, we found no significant correlation between high blood pressure and the severity of aortic valve stenosis and the patients' GFR, smoking, or serum calcium levels.²¹

AVC was found to be substantially correlated with plasma Lp (a) level, age, body mass index, blood pressure, length of statin treatment, year cholesterol score, and CAC score in the 2015 Australian study by Vongprommek et al.²² Consistent with the findings of this investigation, our study found a strong correlation between the patient's age and BMI and the degree of aortic valve stenosis. However, in contrast to the study's findings, we found

no significant correlation between dyslipidemia and high blood pressure.

Conclusion

In this study, we evaluated the risk factors for aortic valve replacement in patients with calcified aortic valve stenosis. While most previous studies reported findings similar to ours, our results differed in a few notable ways. Unlike the existing literature, we found no significant association between gender and calcified aortic valve stenosis as a risk factor. Additionally, contrary to prior studies, our findings revealed a significant relationship between both GFR and serum calcium levels and the severity of aortic valve stenosis.

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Authors' Contribution

Conceptualization: Hadi Haddadi, Ali Soleimani, Ozra Asham.

Data curation: Ali Soleimani.

Formal analysis: Hadi Haddadi.

Funding acquisition: Ali Soleimani.

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Methodology: Hadi Haddadi, Ozra Asham.

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Visualization: Ali Soleimani.

Writing-original draft: Hadi Haddadi.

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Competing Interests

We declare no conflict of interests.

Ethical Approval

The ethical code was obtained from ethical committee number IR.UMSU.REC.1402.018. All patients' file information remained confidential and was extracted without mentioning any identifiable information and the ethical issues regarding patient rights and confidentiality of patient information were observed.

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