



Machine Learning Prediction Models of Optimal Time for Aortic Valve Replacement in Asymptomatic Patients

Salah Alzghoul^{1,*}, Othman Smadi¹, Ali Al Bataineh², Mamon Hatmal³ and Ahmad Alamm⁴

¹Biomedical Engineering Department, The Hashemite University, Zarqa, Jordan

²Department of Electrical and Computer Engineering, Norwich University, Northfield, Vermont, 05663, USA

³Department of Biochemistry and Molecular Biology, The Hashemite University, Zarqa, Jordan

⁴National Centre for Big Data Science and Artificial Intelligence, Amman, Jordan

*Corresponding Author: Salah Alzghoul. Email: alzghoul@hu.edu.jo

Received: 08 December 2022; Accepted: 06 February 2023

Abstract: Currently, the decision of aortic valve replacement surgery time for asymptomatic patients with moderate-to-severe aortic stenosis (AS) is made by healthcare professionals based on the patient's clinical biometric records. A delay in surgical aortic valve replacement (SAVR) can potentially affect patients' quality of life. By using ML algorithms, this study aims to predict the optimal SAVR timing and determine the enhancement in moderate-to-severe AS patient survival following surgery. This study represents a novel approach that has the potential to improve decision-making and, ultimately, improve patient outcomes. We analyze data from 176 patients with moderate-to-severe aortic stenosis who had undergone or were indicated for SAVR. We divide the data into two groups: those who died within the first year after SAVR and those who survived for more than one year or were still alive at the last follow-up. We then use six different ML algorithms, Support Vector Machine (SVM), Classification and Regression Tree (C and R tree), Generalized Linear (GL), Chi-Square Automatic Interaction Detector (CHAID), Artificial Neural Network (ANN), and Linear Regression (LR), to generate predictions for the best timing for SAVR. The results showed that the SVM algorithm is the best model for predicting the optimal timing for SAVR and for predicting the post-surgery survival period. By optimizing the timing of SAVR surgery using the SVM algorithm, we observed a significant improvement in the survival period after SAVR. Our study demonstrates that ML algorithms generate reliable models for predicting the optimal timing of SAVR in asymptomatic patients with moderate-to-severe AS.

Keywords: Aortic stenosis; aortic valve replacement; machine learning; survival period enhancement; artificial intelligence in cardiology



This work is licensed under a Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

1 Introduction

1.1 Background

AS is one of the most common valvular heart and cardiovascular disease in North America and Europe [1].

Elderly asymptomatic patients with moderate-to-severe AS (effective orifice area is less than 1.5 cm²) may suffer from reduced systemic arterial compliance (SAC) with preserved ejection fraction (EF) [2–5]. Therefore, in such cases, the paradoxical pairing of measurements and clinical symptoms in these patients may present doubts regarding the validity of the Doppler results even though these patients are frequently symptomatic [4]. This difficulty may be exacerbated by the fact that many asymptomatic patients are referred for catheterization, where concomitant hypertension may shadow the symptoms of AS severity [6]. Patients with severe symptomatic aortic stenosis (SAS) have a low overall survival rate without aortic valve replacement (AVR), which is the preferred treatment method whether surgical or transcatheter [1,7,8].

Cardiologists are frequently confronted with the dilemma of whether to perform surgery on asymptomatic SAS patients. Lowering operational risk by completing valve replacement sooner, avoiding sudden cardiac death, and preventing irreversible myocardial damage are the prognostic factors for suggesting surgical intervention for asymptomatic patients. Unfortunately, for elderly patients, the risk of surgery may outweigh its benefits [1,7]. Thus, medical treatment is recommended for individuals at excessively high risk for any operation or for whom hemodynamic parameters are less likely to improve after valve replacement [8]. Medications used for heart failure, lifestyle adjustments, and general care are part of the medical management of patients with symptomatic SAS [7].

SAVR and transcatheter aortic valve replacement (TAVR) are surgical treatment procedures for patients [9]. By using a balloon or self-expandable valve via catheterization, TAVR is less invasive than SAVR [10]. Many studies have shown TAVR to be a more convenient operation, especially for intermediate- and high-risk patients [9–16]. Overall, the choice of type of operation is challenging [17,18]. In addition, the duration of the intervention (surgery or catheterization) is different for each patient. For example, SAVR is recommended for symptomatic SAS patients. However, deciding on SAVR for asymptomatic SAS patients is balanced by the likelihood of a poor outcome and the decision-making process is not straightforward [6].

Because many patients are examined as outpatients, the delay between the cardiologist's recommendation for SAVR and the actual operation date may put the patient at risk of heart failure progression or death. Furthermore, specific individuals may postpone SAVR until their symptoms worsen or new technology becomes available [19].

Almost half of all patients with severe aortic stenosis are asymptomatic at the time of diagnosis. It remains uncertain and challenging to determine the optimal timing of intervention to minimize early morbidity and mortality in these patients. Numerous techniques for optimizing valve replacement surgery time in asymptomatic individuals with AS have been developed for this purpose [20–22].

Kang et al. recently published the results of an eight-year follow-up study in which patients with asymptomatic, very severe aortic stenosis were randomly assigned to surgical aortic valve replacement or conservative therapy. The researchers discovered that the patients who underwent early surgical aortic valve replacement had a much lower incidence of morbidity and/or mortality compared to those assigned for conservative therapy [23].

With the progress and enhancement of artificial intelligence (AI) and ML algorithms over the years, these technologies have evolved from concepts to practice. Numerous applications of AI have

been demonstrated in medicine. AI technology has emerged as a significant component that may influence the growth of the medical industry and enhance the quality of healthcare services. AI can assist doctors in disease diagnosis and improve therapeutic quality. When integrated into standard medical processes, AI has the potential to minimize misdiagnoses and enhance diagnostic effectiveness. Currently, AI technologies are used in cardiology for purposes such as precision medicine, clinical forecasting, cardiac imaging assessment, and intelligent robotics. The application of AI in cardiovascular therapy has promising potential [24–30].

Clinicians often deal with binary outcomes in which patient-specific cases are not generally considered. This issue is so prevalent in the biomedical literature that statisticians refer to it as “dichomania”. In essence, dichotomizing continuous data leads to the loss of critical information regarding the strength of associations. It is better to estimate an individual patient’s probability rather than to generate binary categories. ML algorithms may provide clinical benefits by delivering more accurate predictions of the outcome likelihood [31].

Many studies have used ML algorithms in cardiology over the last decade, such as in forecasting the fatality rate of coronary artery disease, utilizing an SVM for the forecasting and computation of the American College of Cardiology and American Heart Association risk scores, implementing ML algorithms for echocardiographic variables to differentiate hypertrophic cardiomyopathy from physiological hypertrophy in athletes, evaluating left ventricular diastolic dysfunction, and estimating 12 kinds of heart rhythms [32].

1.2 Contribution

To enhance the reliability of the decision-making on the best SAVR timing for asymptomatic patients with moderate-to-severe AS, several ML algorithms were tested in the current study using 24 parameters representing patients’ clinical characteristics, Doppler echocardiographic data of the left ventricle (LV) geometry and function, and systematic arterial indexes.

The main contribution of this study is to optimize SAVR time, which will help asymptomatic AS patients live longer. In other words, the patient may live longer if the surgery is performed at the right time.

Different combinations of two ML models were created in a novel way to accomplish our goal. Six ML algorithms were used in the first ML model to predict the best time for SAVR for the patient population. We then applied a second ML model (which also contained six ML algorithms) on the predicted SAVR to determine how the optimized SAVR timing affected patients’ ability to survive longer after surgery.

To our knowledge, this is the first study to investigate the connection between the prediction of SAVR operation time and the impact of the predicted SAVR timing on a patient’s survival period. The significance of this study lies in its potential to improve decision-making and enhance patient outcomes after the surgical operation of valve replacement. By using ML algorithms to predict the optimal timing for SAVR, we have developed a more accurate and objective approach that has the potential to overcome the limitations of traditional methods based on clinical biometric records and healthcare professional judgment. Our findings have important implications for patients, healthcare professionals, and the broader scientific community as they demonstrate the potential of ML algorithms to improve patient outcomes and optimize medical decision-making.

2 Materials and Methods

2.1 Data Source

The data in this study were retrospectively collected and reviewed for 1,154 individuals referred to the Quebec Heart Institute echocardiographic laboratory between August 1999 and March 2005 for AS examination [4,5]. Only 176 asymptomatic patients with moderate-to-severe aortic stenosis (peak aortic jet velocity ≥ 2.5 m/s) who underwent SAVR or had their operation postponed by a cardiology specialist were retrospectively analyzed, and the follow-up period was up to seven years. Patients were 66.4 ± 12.4 -years-old on average, with 64 percent being male. The data included clinical and echocardiographic information (patient characteristics, medical records, symptoms, and medical test results). The exclusion criteria were moderate or severe aortic insufficiency or mitral valve disease, left ventricular ejection fraction (LVEF) of 50%, and symptoms at baseline.

The data were divided into two groups based on the survival period after SAVR. Patients who underwent SAVR and survived for more than one year were included in the modeling group (111 patients). In contrast, those who died less than one year after SAVR were included in the implementation group (65 patients).

As shown in Fig. 1, there was a significant difference in survival rates between the two selected subgroups (the modeling group vs. the implementation group, p -value < 0.001).

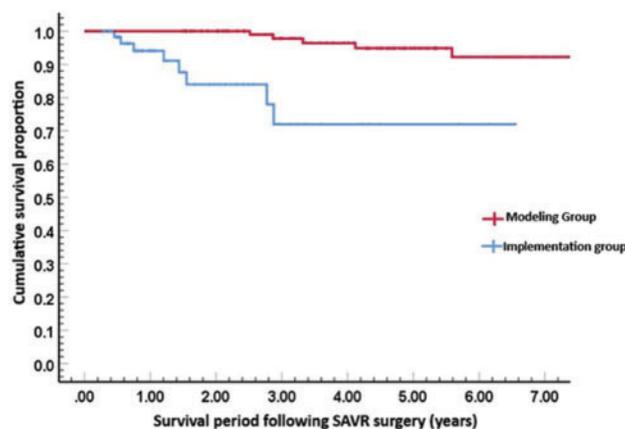


Figure 1: Overall survival function between the modeling group (red) vs. the implementation group (blue)

2.2 Study Design

The modeling group was initially separated into a training set (70 percent of the data) and a testing set (the remaining 30 percent of the data). Then, the modeling group was applied into six different machine learning algorithms to predict the optimal time of SAVR (ML model 1). In parallel, the same modeling group was applied into ML model 2 (which also contained six ML algorithms) to predict the survival period after SAVR.

The ML algorithm with the best correlation from model 1 was applied to the implementation group ($n = 65$) and the resulting SAVR operation time was labeled as the new optimal SAVR operation time. Then, the implementation group was updated by replacing the old SAVR operation time with

the predicted optimal SAVR operating time. The updated implementation group was then fed into the ML model 2 to estimate the survival period after applying the new SAVR operation.

Finally, the impact ratio (the ratio of the number of patients with updated SAVR times (Q) to the total sample number (n)) and the survival period enhancement ratio (the number of patients with a predicted time of death one year longer than the actual time of death divided by the number of patients with updated SAVR times (Q)) was calculated.

The central illustration in [Fig. 2](#) depicts the various data extraction methods and the production of modeling and implementation groups of the machine learning algorithms.

2.3 Feature Ranking

The dataset used in this study contained 26 variables; those with more than 20% of missing values were excluded from the ML algorithms. These variables included diabetes and dyslipidemia. The IBM Statistical Package for the Social Sciences (SPSS) Modeler was used to perform the feature ranking method.

Extracting or ranking features is an effective method to reduce the complexity and difficulty of ML algorithms. ML applications often include hundreds if not thousands of categories that can be utilized as inputs. Consequently, considerable time and effort were expended to determine the categories or variables to be included in the algorithm. The Feature Selection technique in the IBM SPSS Modeler was used to identify the most essential fields. The IBM SPSS Modeler disabled this stage for the SVM algorithm.

2.4 Predictor Variables

The data were then divided into different categories. The first category included clinical characteristics such as age, sex, body surface area (BSA), obesity (Body Mass Index (BMI) >30 (kg/m^2)), hypertension (blood pressure greater than 140/90 mm Hg), and the presence of CAD.

The second category included Doppler echocardiographic and systematic arterial indices such as aortic valve area (AVA), peak transvalvular pressure gradient (PG), mean transvalvular pressure gradient (MG) less than 30 mm Hg, systolic arterial pressure, diastolic arterial pressure, heart rate (HR), SAC as calculated by dividing the stroke volume index over the pulse pressure of the branchia, and systemic vascular resistance, which is the ratio of mean arterial pressure multiplied by 80 over the cardiac output (CO).

The third group is Doppler echocardiographic data of LV geometry and function, such as relative wall thickness (RWTH), which was calculated by multiplying 2 by the ratio of posterior wall thickness over left ventricle diastolic diameter, LV mass (The American Society of Echocardiography's revised formula was used to determine LV mass, which was then indexed for body surface area), CO, stroke volume (SV), mean volume flow rate (Q_{mean}), overall EF as a parameter to assess how much blood the left ventricle of the heart pumps into the body for each heartbeat, paradoxical low-flow (PLF) as defined by a low-flow condition of the normal left ventricle ejection fraction (stroke volume index ≤ 35 mL/m^2), transaortic peak instantaneous velocity (V_{max}), LV hypertrophy (defined as an LV mass index greater than 134 g/m^2 for males and an LV mass index greater than 110 g/m^2 for females), and valvuloarterial impedance (Z_{va}) (which was calculated by adding systolic arterial pressure to the mean transvalvular gradient and the result divided by the stroke volume index).

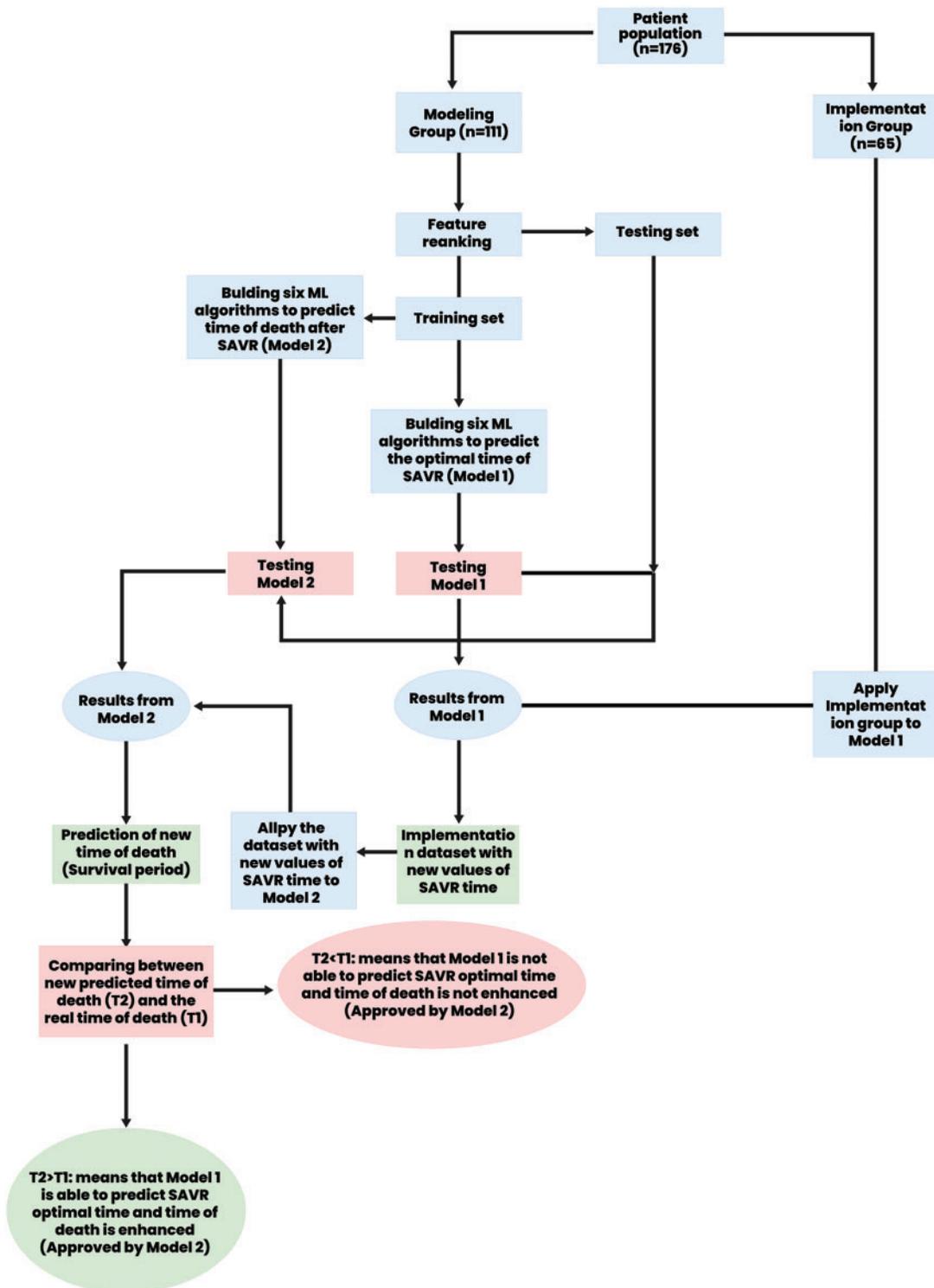


Figure 2: Central illustration of building the ML algorithms

Patients in the implementation group appeared to have a significantly higher Vmax, PG, MG, systemic vascular resistance, and LV mass. However, there were no significant differences among the other variables used in this study (Table 1).

Table 1: Clinical characteristics of the 176 patients

No.	Variable	Overall population <i>n</i> = 176	Implementation group <i>n</i> = 65	Modeling group <i>n</i> = 111	<i>p</i> -value
Clinical characteristics					
1	Age (years)	66.4 ± 12.4	66.6 ± 12.4	66.3 ± 12.4	NS
2	Gender (female/male)	176 (63/113)	(22/43)	(41/70)	NS
3	Body surface area (BSA), m ²	1.86 ± 0.21	1.88 ± 0.2	1.84 ± 0.19	NS
4	Obesity (BMI > 30)	54	23	31	NS
5	Coronary artery disease (CAD)	113	40	73	NS
6	Hypertension	70	26	44	NS
Doppler echocardiographic and systematic arterial indexes					
7	Aortic valve area (AVA), cm ²	0.93 ± 0.3	0.87 ± 0.23	0.96 ± 0.31	NS
8	Peak gradient (PG), mm Hg	60 ± 21.1	64.9 ± 23.9	57.1 ± 20.6	<0.001
9	Mean gradient (MG), mm Hg	35.7 ± 14	38.8 ± 15.4	33.8 ± 12.8	<0.001
10	Systolic arterial pressure, mm Hg	133.5 ± 21.6	133.4 ± 20.1	133.5 ± 22.4	NS
11	Diastolic arterial pressure, mm Hg	73.2 ± 10.9	73.3 ± 11	73.2 ± 10.9	NS
12	Heart rate (HR), (beats per minute)	66.9 ± 11	65.9 ± 9.9	67.6 ± 11.8	NS
13	Systemic arterial compliance (SAC), mL.m ⁻² .mmHg ⁻¹	1.41 ± 0.47	1.4 ± 0.46	1.42 ± 0.47	NS
14	Systemic vascular resistance (RESISTvao), dyne.s.cm ⁻⁵	197.1 ± 907	2211 ± 1078	1871 ± 766	0.016
Doppler echocardiographic data of LV geometry and function					
15	Relative wall thickness, %	46.3 ± 10.5	47 ± 10	46.0 ± 10.9	NS
16	LV mass, g	217.5 ± 67.8	233 ± 77.5	208.9 ± 60.4	0.029
17	Cardiac output, L.min ⁻¹	5.13 ± 1.2	5.1 ± 1.16	5.15 ± 1.34	NS
18	Left ventricle hypertrophy	97	36	61	NS
19	Stroke volume, mL	79 ± 17.5	78.9 ± 16.9	79.1 ± 18	NS
20	Qmean, mL/s	248.7 ± 59.3	245.56 ± 56.3	250.6 ± 61.3	NS
21	Overall ejection fraction, %	66.5 ± 6.6	65.6 ± 6.1	66 ± 7.01	NS
22	Paradoxical low-flow	33	13	20	NS
23	Transaortic peak instantaneous velocity, m/s	3.79 ± 0.69	3.95 ± 0.72	3.7 ± 0.65	<0.008
24	Valvuloarterial impedance (<i>Z_{va}</i>), mmHg.mL ⁻¹ m ²	4.13 ± 1	4.23 ± 1	4.05 ± 1	NS

2.5 Machine Learning Algorithms

The six most frequently supervised ML models were selected to predict the optimal operation time and the expected survival period after optimizing SAVR operation time. These algorithms include regression, CHAID, SVM, ANN, C and R trees, and GL.

The regression algorithm aims to directly describe the relationship between the input variables and outputs, mainly in mathematical functions with variables derived from the data. These methods are often very effective in predicting the correlations between specific inputs and outputs.

CHAID algorithms are based on two or more category criteria variables and those algorithms involve both descriptive and predictive analyses. The number of independent variable categories is determined by the chi-squared test findings. The most significant independent variable appears in the first node of the classification of the resultant tree. When there is no significant association between the variables, the node generation and segment construction procedures are complete [33].

SVM is a group of linked supervised learning methods used to solve regression and classification tasks. Owing to its robust theoretical underpinning, SVM has grown in popularity since its launch a quarter-century ago [34]. SVM discovers the best equation such that the output classifications match the results as closely as possible, with minimum misclassification. The SVM algorithm assumes that future cases originate from the same population and the generated model can categorize them according to their characteristics [24].

ANN algorithms have recently gained popularity in various fields as valuable models for categorization, segmentation, pattern classification, and forecasting. ANN are now commonly used for general function approximation in quantitative approaches owing to their excellent qualities of self-learning, adaptability, reliability, nonlinearity, and improvement in input-to-output modeling [35].

C and R trees are well-known statistical learning approaches that have been used in many applications owing to their model precision, adaptability to large datasets, and link to guideline decisions. These characteristics are regarded as a need for patient care in domains such as healthcare. The C and R trees begin by systematically splitting the object dataset and assigning a forecast feature for classification models or an actual value to each division of the regression models [36].

It is possible to utilize GL in the linear case and with a nonlinear probabilistic output such as logistic regression. Although GL is theoretically simple to understand and apply, determining its variables without using computational equipment becomes increasingly difficult as the number of variables increases [37].

In this study, a number of existing methods have been integrated in order to combine their strengths and address specific challenges or problems that were not well-solved by the individual methods such as giving a guidance to decision-making and enhance patient outcomes after the surgical operation of valve replacement. To prove the effectiveness of the integrated methods, simulations were conducted to evaluate the performance of the integrated system on a specific task or set of tasks. Also, the performance of the integrated system to the performance of the individual components or methods that make up the system was compared.

2.6 Statistical Analyses

The two-tailed Student's t-test was used to examine continuous variables. Statistical analyses were performed using IBM SPSS version 25 and a p -value < 0.05 was considered to be statistically significant.

3 Results

3.1 Training and Testing Using Several ML Algorithms (Modeling Group)

For ML model 1, six machine learning algorithms were used for the patient modeling group as listed in Table 2.

Table 2: Model 1 ML algorithms comparison (modeling group)

ML algorithm	Correlation coefficient (R)	Number of used variables	Mean absolute error (MAE)
SVM	0.81	24	0.45
CHAID	0.77	8	0.58
GL	0.64	24	0.77
Regression	0.64	23	0.77
C and R tree	0.58	15	0.75
ANN	0.5	24	0.88

The SVM algorithm used 24 variables and showed the highest correlation ($R = 0.81$) with a minimum MAE of 0.45. The CHAID algorithm used only eight variables and had a correlation coefficient of 0.77. However, the MAE was relatively higher (MAE = 0.58). Finally, the rest of the algorithms in Table 2 show R-values less than 0.65.

Fig. 3 shows the relationship between the actual and predicted SAVR times for the six ML algorithms. The SVM algorithm provided the best linear relationship between the predicted and actual SAVR times using the linear regression equation, Y (predicted time) = $0.553 \times$ (actual time) + 0.4934 shown in Fig. 3A. However, the other five ML algorithms exhibit weak linear behavior.

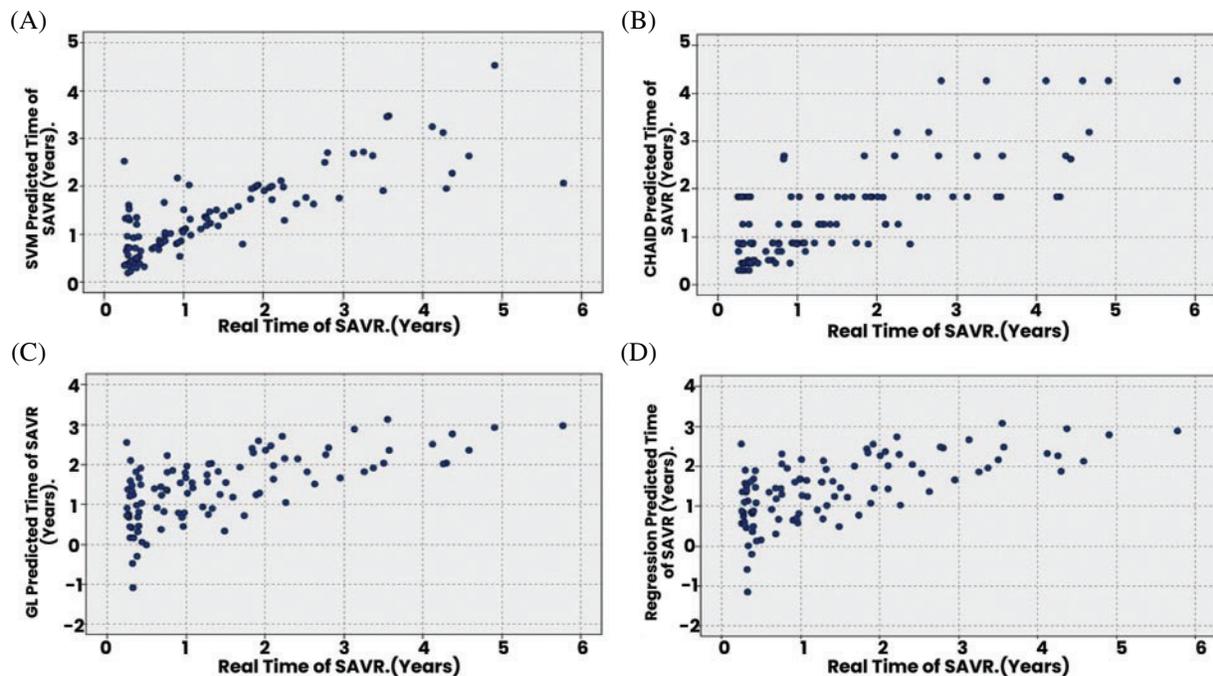


Figure 3: (Continued)

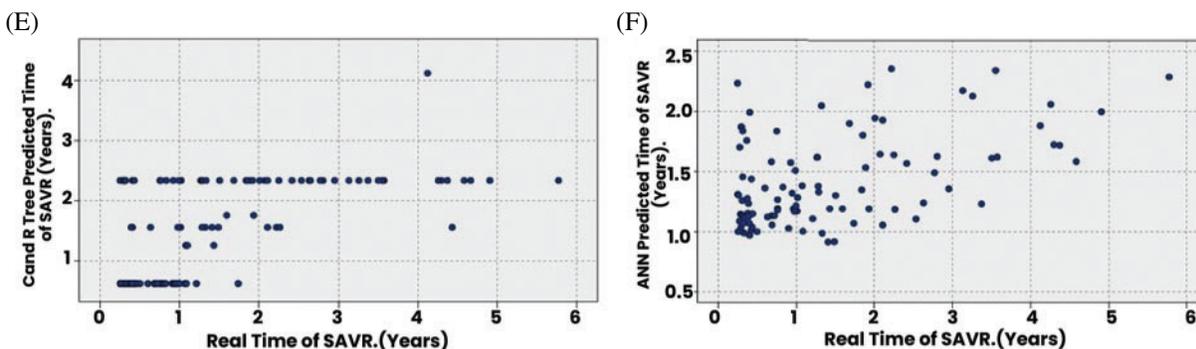


Figure 3: ML model 1 algorithm results of SAVR time prediction vs. real SAVR time for the modeling group. (A) SVM algorithm results. (B) CHAID algorithm results. (C) GL algorithm results. (D) Regression algorithm results. (E) C and R tree algorithm results. (F) ANN algorithm results

ML model 2 (Table 3) was created using the same algorithms. The results show that the SVM algorithms gave the highest correlation coefficient value ($R = 0.8$) with the lowest MAE, with a value of 0.67. In addition, SVM uses 24 variables to create the model, which shows more linear characteristics, whereas the CHAID algorithm uses only three variables to create a high-correlation model. All other methods yielded the lowest values.

Table 3: Model 2 ML algorithms comparison (modeling group)

ML algorithm	Correlation coefficient (R)	Number of used variables	MAE
SVM	0.80	24	0.67
CHAID	0.74	3	0.95
GL	0.7	24	1
Regression	0.69	23	1.05
ANN	0.63	23	1.09
C and R tree	0.0	24	1.57

Fig. 4 shows the relationship between the actual and predicted survival periods after SAVR according to the six ML algorithms. Like ML model 1, the SVM algorithm provided the best linear relationship between the predicted and actual survival periods, with a linear regression equation of Y (predicted survival period) = $0.564 \times$ (actual survival) + 2.12 shown in Fig. 3A. However, the other five ML algorithms exhibit weak linear behavior. Finally, the C and R tree algorithm results provided a constant predicted survival time for all patients (4.62 years as shown in Fig. 4F).

3.2 The Impact of Using the SVM Algorithm on Enhancing Survival Period After SAVR

The SVM algorithm was used to generate the optimal SAVR time (ML model 1) and to predict the survival period following SAVR surgery (ML model 2).

After applying the dataset of the implementation group to ML model 1, the SVM algorithm predicted the new time of SAVR and the average of the predicted times for SAVR was earlier than the average of the actual times for SAVR (the average of actual SAVR time = 1.5 years \pm 1.46 years. The average of predicted SAVR time = 1.2 years \pm 0.76 years). The results showed that this algorithm

could predict a new SAVR time for 89 percent of patients, which means that 58 patients will have a revised SAVR operation schedule.

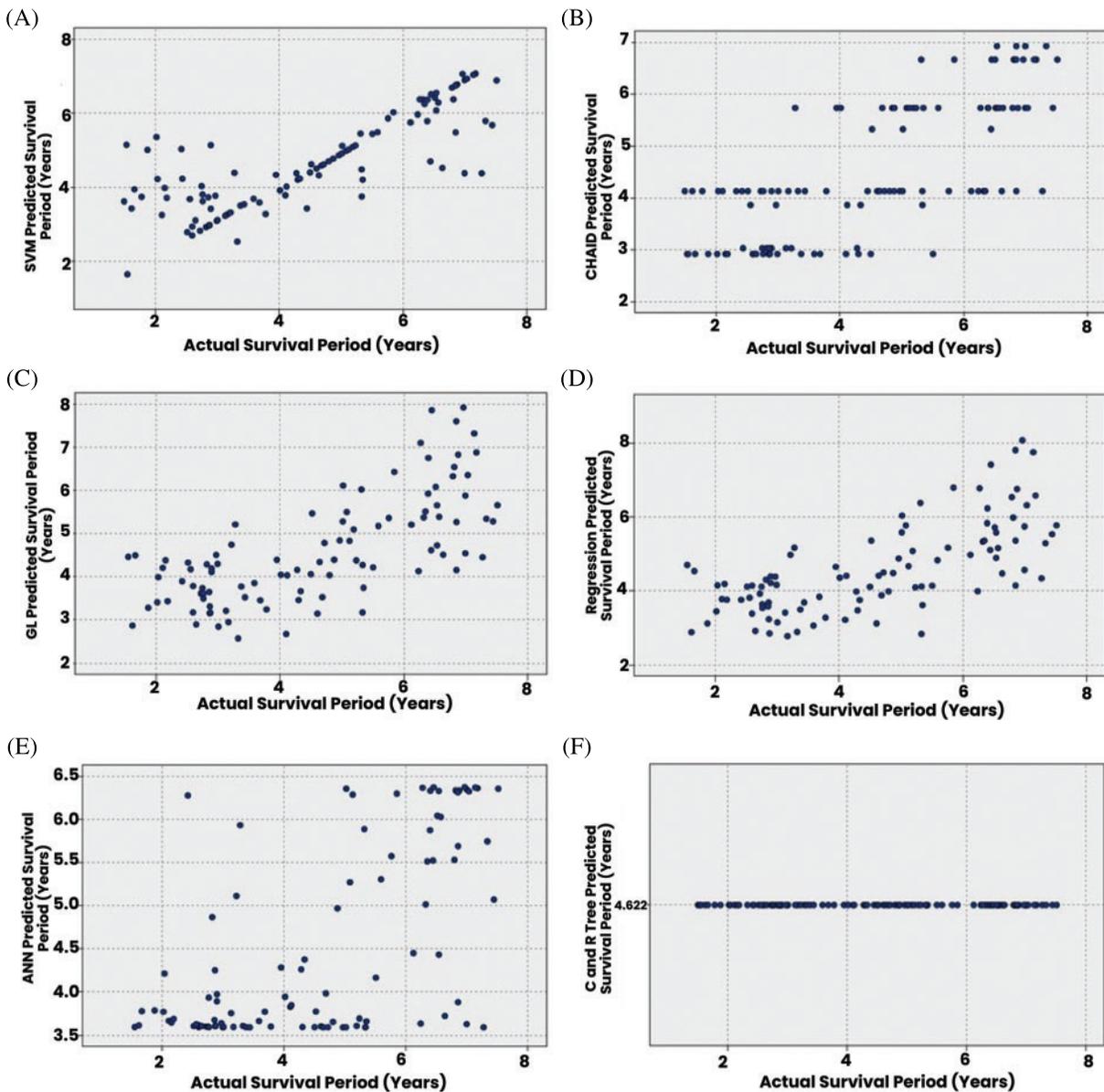


Figure 4: ML model 2 algorithm’s predictions of the survival period after SAVR vs. the actual survival period after SAVR for the modeling group. (A) SVM algorithm results. (B) CHAID algorithm results. (C) GL algorithm results. (D) Regression algorithm results. (E) ANN algorithm results. (F) C and R tree algorithm results

To confirm that the revised SAVR time predicted by ML model 1 was the best time for surgery, ML model 2 used to estimate the survival period after the intervention time for the 58 patients was revised.

As shown in Table 4, the SVM ML algorithm of ML model 2 outcomes shows that 93 percent of the 58 patients (54 patients) have a significantly more extended survival period and will die at a significantly older age (the average of the actual survival period is $0.18 \text{ years} \pm 0.38$, the average of the predicted time of survival period is $3.15 \text{ years} \pm 0.97$, 95% CI for the difference (2.87, 3.41), p -value < 0.001). The results suggest that the ML model 1 can forecast the best time for SAVR and that by optimizing the SAVR time, patients' survival periods are increased, and they might live longer.

Table 4: Overall comparison of models

Overall model number	ML algorithm in Model 1	ML algorithm in Model 2	Survival period enhancement ratio (= number of patients with predicted time of death more than the actual time of death)/total number of patients	Average enhancement time (years)	Is the enhancement ratio of Overall model 1 significant from the other Overall models? (p -value)
1	SVM	SVM	93%	3.15	
2	SVM	CHAID	88%	2.51	No (0.131)
3	SVM	GL	69%	2.21	Yes (<0.001)
4	SVM	Regression	69%	2.23	Yes (<0.001)
5	SVM	ANN	69%	1.95	Yes (<0.001)
6	CHAID	SVM	90%	2.67	No (0.349)
7	CHAID	CHAID	77%	2.51	Yes (<0.001)
8	CHAID	GL	69%	2.21	Yes (<0.001)
9	CHAID	Regression	69%	2.25	Yes (<0.001)
10	CHAID	ANN	69%	1.95	Yes (<0.001)
11	GL	SVM	69%	2.81	Yes (<0.001)
12	GL	CHAID	77%	2.51	Yes (<0.001)
13	GL	GL	69%	2.25	Yes (<0.001)
14	GL	Regression	69%	2.22	Yes (<0.001)
15	GL	ANN	69%	1.89	Yes (<0.001)
16	Regression	SVM	77%	2.21	Yes (<0.001)
17	Regression	CHAID	69%	2.23	Yes (<0.001)
18	Regression	GL	77%	2.62	Yes (<0.001)
19	Regression	Regression	69%	2.29	Yes (<0.001)
20	Regression	ANN	69%	1.95	Yes (<0.001)
21	ANN	SVM	69%	2.02	Yes (<0.001)
22	ANN	CHAID	64%	2.32	Yes (<0.001)
23	ANN	GL	69%	2.32	Yes (<0.001)
24	ANN	Regression	69%	2.33	Yes (<0.001)
25	ANN	ANN	69%	2.01	Yes (<0.001)

Fig. 5 shows the significant difference in survival rates between the actual and predicted survival periods (p -value < 0.007).

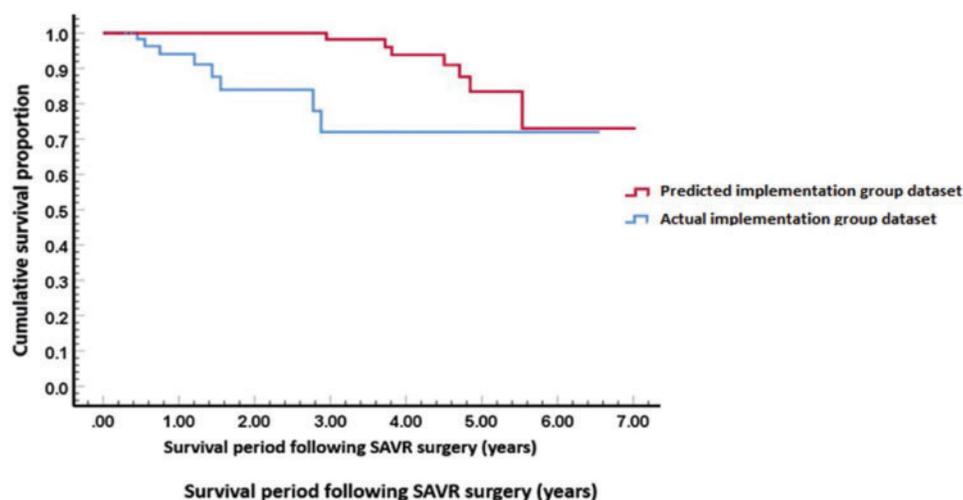


Figure 5: Overall survival function between the SVM group (red) vs. the actual implementation group (blue)

4 Discussion

According to recent research, ML algorithms may effectively predict mortality after cardiac procedures such as transcatheter aortic valve replacement (AVR). In 2018, Hernandez-Suarez et al. predicted in-hospital deaths following an AVR operation with an Area Under Curve (AUC) value of 0.92 [38].

This study describes the ML algorithms used in the verification and validation of the enhanced survival period based on predicting the optimal SAVR operation time for moderate-to-severe asymptomatic AS patients.

By using different ML algorithms, a modeling group (training and testing) was created to evaluate the potential of different ML algorithms to predict the actual time of SAVR and actual survival period. After selecting the ML algorithm with the best correlation, the implementation group was tested to explore the effect of the newly predicted SAVR time on the enhancement of the survival period.

In the modeling group, SVM, CHAID, and GL had the most potent capacity to predict the actual SAVR operational time (ML model 1), utilizing 24, 8, and 24 variables, respectively. The SVM algorithm is preferred over the CHAID and GL algorithms because it has the highest correlation coefficient value, can also be used for linear and nonlinear ML regression, and uses all important AS predictor variables.

Moreover, despite having a high correlation coefficient, CHAID utilizes a lower number of variables, which may affect the accuracy of the resulting model when new patients are evaluated because the unused variables may carry out key elements that strengthen the forecasting results [33,36].

For predicting the actual survival period in the modeling group (ML model 2), among the other methods, SVM also had the highest correlation coefficient and utilized 24 variables. Therefore, it was selected as the preferred method to predict survival.

To evaluate the potential of the ML algorithms in predicting the optimal time of the SAVR operation, different combinations of the proposed ML algorithms were tested on an implementation group to predict the time of SAVR and the related enhancement in the survival period. We found that

using the SVM algorithm for both models 1 and 2 had a significant improvement in the survival period following the new predicted time of SAVR compared to other combinations.

One factor that can impact the complexity of ML algorithms is the number of variables or features used in the model. The number of variables can affect the accuracy and efficiency of the resulting model as more variables can provide more information and increase the complexity of the model, but may also increase the risk of overfitting. For example, although CHAID had a high correlation coefficient, it used a lower number of variables, which may affect the accuracy of the resulting model when new patients are evaluated as the unused variables may carry out key elements that strengthen the forecasting results.

This suggests that the SVM algorithm may be effective at predicting survival outcomes while also being able to handle a relatively large number of variables. In general, the number of variables used in the ML algorithms can impact the complexity and performance of the resulting models.

5 Conclusion

Several models have been proposed and developed using ML methods and algorithms to estimate the best timing for SAVR in asymptomatic patients with moderate-to-severe AS (ML model 1) and forecast the survival period for the same patients following the newly predicted SAVR operation time (ML model 2). Using the SVM algorithm to utilize models 1 and 2 yielded the most promising results in forecasting the optimal timing of SAVR among several tested ML algorithms (ML model 1). The postoperative survival time was significantly longer as demonstrated by the ML model 2. The results showed that ML algorithms have a great potential to help clinicians make decisions that will help patients with complicated cases live longer.

Acknowledgement: We would like to express our most tremendous appreciation to Dr. Philippe Pibarot (Canada Research Chair in Valvular Heart Diseases and Head of Cardiology Research at the Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), Université Laval) for granting access to the institute's dataset.

Funding Statement: The authors received no specific funding for this study.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

References

- [1] H. Baumgartner, "Aortic stenosis: Medical and surgical management," *Heart*, vol. 91, no. 11, pp. 1483–1488, 2005.
- [2] R. O. Bonow, B. A. Carabello, K. Chatterjee, A. C. De Leon, D. P. Faxon *et al.*, "ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease," *Circulation*, vol. 114, no. 5, pp. e1–e148, 2006.
- [3] J. G. Dumesnil, P. Pibarot and B. Carabello, "Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: Implications for diagnosis and treatment," *European Heart Journal*, vol. 31, no. 3, pp. 281–289, 2010.
- [4] Z. Hachicha, J. G. Dumesnil, P. Bogaty and P. Pibarot, "Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival," *Circulation*, vol. 115, no. 22, pp. 2856–2864, 2007.

- [5] Z. Hachicha, J. G. Dumesnil and P. Pibarot, "Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis," *Journal of the American College of Cardiology*, vol. 54, no. 11, pp. 1003–1011, 2009.
- [6] C. M. Otto, "Valvular aortic stenosis," *Journal of the American College of Cardiology*, vol. 47, no. 11, pp. 2141–2151, 2006.
- [7] G. S. Gheorghe, A. S. Hodoroagea, A. C. D. Gheorghe, I. T. Nanea and A. Ciobanu, "Medical management of symptomatic severe aortic stenosis in patients non-eligible for transcatheter aortic valve implantation," *Journal of Geriatric Cardiology*, vol. 17, no. 11, pp. 704–709, 2020.
- [8] C. Dubois, M. Coosemans, F. Rega, G. Poortmans, A. Belmans *et al.*, "Prospective evaluation of clinical outcomes in all-comer high-risk patients with aortic valve stenosis undergoing medical treatment, transcatheter or surgical aortic valve implantation following heart team assessment," *Interactive Cardio Vascular and Thoracic Surgery*, vol. 17, no. 3, pp. 492–500, 2013.
- [9] H. Möllmann, K. Bestehorn, M. Bestehorn, K. Papoutsis, E. Fleck *et al.*, "In-Hospital outcome of transcatheter vs. surgical aortic valve replacement in patients with aortic valve stenosis: Complete dataset of patients treated in 2013 in Germany," *Clinical Research in Cardiology*, vol. 105, no. 6, pp. 553–559, 2016.
- [10] S. V. Arnold, M. R. Reynolds, K. Wang, E. A. Magnuson, S. J. Baron *et al.*, "Health status after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis at increased surgical risk," *Journals of the American College of Cardiology: Cardiovascular Interventions*, vol. 8, no. 9, pp. 1207–1217, 2015.
- [11] S. M. Pio, M. R. Amanullah, S. C. Butcher, K. Y. Sin, N. A. Marsan *et al.*, "Discordant severity criteria in patients with moderate aortic stenosis: Prognostic implications," *Open Heart*, vol. 8, no. 1, pp. e001639, 2021.
- [12] A. Ler, Y. J. Ying, F. Sazzad, A. M. T. L. Choong and T. Kofidis, "Structural durability of early-generation transcatheter aortic valve replacement valves compared with surgical aortic valve replacement valves in heart valve surgery: A systematic review and meta-analysis," *Journal of Cardiothoracic Surgery*, vol. 15, no. 1, pp. 127–139, 2020.
- [13] F. Fang, J. Tang, Y. Zhao, J. He, P. Xu *et al.*, "Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients at low and intermediate risk: A risk specific meta-analysis of randomized controlled trials," *PLoS One*, vol. 14, no. 9, pp. e0221922, 2019.
- [14] S. Ellahham, H. Ibrahim and M. Hassan, "Transcatheter aortic valve replacement patient selection: A frailty-centered approach," *Journal of Clinical and Experimental Cardiology*, vol. 11, no. 651, pp. 2, 2016.
- [15] P. Nardi and M. Russo, "The treatment of aortic valve stenosis in patients at intermediate-high risk," *Interventional Cardiology Journal*, vol. 2, no. 2, pp. 1–9, 2016.
- [16] G. M. Deeb, M. J. Reardon, S. Chetcuti, H. J. Patel, P. M. Grossman *et al.*, "3-year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement," *Journal of the American College of Cardiology*, vol. 67, no. 22, pp. 2565–2574, 2016.
- [17] K. Booth, R. Beattie, M. McBride, G. Manoharan, M. Spence *et al.*, "High risk aortic valve replacement- the challenges of multiple treatment strategies with an evolving technology," *Ulster Medical Journal*, vol. 85, no. 1, pp. 18–22, 2016.
- [18] S. Elmariah, I. F. Palacios, T. McAndrew, I. Hueter, I. Inglessis *et al.*, "Outcomes of transcatheter and surgical aortic valve replacement in high-risk patients with aortic stenosis and left ventricular dysfunction," *Circulation: Cardiovascular Interventions*, vol. 6, no. 6, pp. 604–614, 2013.
- [19] S. C. Malaisrie, E. McDonald, J. Kruse, Z. Li, E. C. McGee *et al.*, "Mortality while waiting for aortic valve replacement," *The Annals of Thoracic Surgery*, vol. 98, no. 5, pp. 1564–1571, 2014.
- [20] B. A. Carabello, "Aortic valve replacement should be operated on before symptom onset," *Circulation*, vol. 126, no. 1, pp. 112–117, 2012.
- [21] P. K. Shah, "Severe aortic stenosis should not be operated on before symptom onset," *Circulation*, vol. 126, no. 1, pp. 118–125, 2012.
- [22] R. J. Everett, M. A. Clavel, P. Pibarot and M. R. Dweck, "Timing of intervention in aortic stenosis: A review of current and future strategies," *Heart*, vol. 104, no. 24, pp. 2067–2076, 2018.

- [23] D. Kang, S. J. Park, S. A. Lee, S. Lee, D. Kim *et al.*, “Early surgery or conservative care for asymptomatic aortic stenosis,” *New England Journal of Medicine*, vol. 382, no. 2, pp. 111–119, 2020.
- [24] F. Jiang, Y. Jiang, H. Zhi, Y. Dong, H. Li *et al.*, “Artificial intelligence in healthcare: Past, present and future,” *Stroke and Vascular Neurology*, vol. 2, no. 4, pp. 230–243, 2017.
- [25] A. Kilic, A. Goyal, J. K. Miller, E. Gjekmarkaj, W. L. Tam *et al.*, “Predictive utility of a machine learning algorithm in estimating mortality risk in cardiac surgery,” *The Annals of Thoracic Surgery*, vol. 109, no. 6, pp. 1811–1819, 2020.
- [26] D. Dey, P. J. Slomka, P. Leeson, D. Comaniciu, S. Shrestha *et al.*, “Artificial intelligence in cardiovascular imaging,” *Journal of the American College of Cardiology*, vol. 73, no. 11, pp. 1317–1335, 2019.
- [27] J. M. Kwon, S. Y. Lee, K. H. Jeon, Y. Lee, K. H. Kim *et al.*, “Deep learning-based algorithm for detecting aortic stenosis using electrocardiography,” *Journal of the American Heart Association*, vol. 9, no. 7, pp. e014717, 2020.
- [28] Y. Yan, J. W. Zhang, G. Y. Zang and J. Pu, “The primary use of artificial intelligence in cardiovascular diseases: What kind of potential role does artificial intelligence play in future medicine?,” *Journal of Geriatric Cardiology*, vol. 16, no. 8, pp. 585–591, 2019.
- [29] R. R. Lopes, M. S. van Mourik, E. V. Schaft, L. A. Ramos, J. Baan *et al.*, “Value of machine learning in predicting tavi outcomes,” *Netherlands Heart Journal*, vol. 27, no. 9, pp. 443–450, 2019.
- [30] R. Thalappillil, P. Datta, S. Datta, Y. Zhan, S. Wells *et al.*, “Artificial intelligence for the measurement of the aortic valve annulus,” *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 34, no. 1, pp. 65–71, 2020.
- [31] K. W. Johnson, J. T. Soto, B. S. Glicksberg, K. Shameer, R. Miotto *et al.*, “Artificial intelligence in cardiology,” *Journal of the American College of Cardiology*, vol. 71, no. 23, pp. 2668–2679, 2018.
- [32] N. Kagiya, S. Shrestha, P. D. Farjo and P. P. Sengupta, “Artificial intelligence: Practical primer for clinical research in cardiovascular disease,” *Journal of the American Heart Association*, vol. 8, no. 17, pp. e012788, 2019.
- [33] J. Barbier, F. Krzakala, N. Macris, L. Miolane and L. Zdeborová, “Optimal errors and phase transitions in high-dimensional generalized linear models,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 116, no. 12, pp. 5451–5460, 2019.
- [34] A. Y. Ng, “Feature selection, L 1 vs. L 2 regularization, and rotational invariance,” in *Proc. of the Twenty-First Int. Conf. on Machine Learning*, Banff, Canada, pp. 354–361, 2004.
- [35] F. M. Díaz-Pérez and M. Bethencourt-Cejas, “CHAID algorithm as an appropriate analytical method for tourism market segmentation,” *Journal of Destination Marketing & Management*, vol. 5, no. 3, pp. 275–282, 2016.
- [36] O. Maimon and L. Rokach, “Classification trees,” in *Data Mining and Knowledge Discovery Handbook*, 2nd ed., New York, USA: Springer, Chapter 9, Section 9.8.3, pp. 164, 2010.
- [37] O. I. Abiodun, A. Jantan, A. E. Omolara, K. V. Dada, N. A. Mohamed *et al.*, “State-of-the-art in artificial neural network applications: A survey,” *Heliyon*, vol. 4, no. 11, pp. e00938, 2018.
- [38] D. F. Hernandez-Suarez, Y. Kim, P. Villablanca, T. Gupta, J. Wiley *et al.*, “Machine learning prediction models for in-hospital mortality after transcatheter aortic valve replacement,” *Journals of the American College of Cardiology: Cardiovascular Interventions*, vol. 12, no. 14, pp. 1328–1338, 2019.