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DEMOGRAPHIC, CLINICAL, BIOLOGICAL, AND ECHOCARDIOGRAPHIC PARAMETERS ASSOCIATED WITH CHANGE/IMPROVEMENT IN QUALITY OF LIFE IN PATIENTS UNDERGOING TAVI

PhD THESIS SUMMARY

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- **Rădulescu C,** Călin I. Transcatheter Repair in Mitral Regurgitation. In Dorobanțu FL (editor) Minimally Invasive Reconstructive Procedures in Mitral Insufficiency, Paideia Publishing House, Bucharest 2021

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LIST OF ABBREVIATIONS

LA = left atrium

AVA = aortic valve area

AVAi = indexed aortic valve area

PAD = Peripheral arterial disease

ICD = Ischemic coronary disease

CKD = Chronic kidney disease

LBBB = left bundle branch block

LAd = left atrium diameter

CO = cardiac output

LVED = left ventricular end-diastolic diameter

DM = Diabetes mellitus

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

AF = Atrial fibrillation

LVEF = left ventricular ejection fraction

Max G = Maximum transvalvular gradient

Mean G = Mean transvalvular gradient

CHF = chronic heart failure

AKI = acute kidney injury

MLHFQ = Minnesota Living with Heart Failure Questionnaire

CIN = Contrast-induced nephropathy

NYHA = New York Heart Association

PASP = Pulmonary artery systolic pressure

PW= posterior wall

QoL = quality of life

GFR = Glomerular filtration rate

MR = mitral regurgitation

PVR = paravalvular regurgitation

PRO = patient-reported outcomes

TR = tricuspid regurgitation

AS = aortic stenosis

ESC = European Society of Cardiology

IVS = interventricular septum

SAVR = surgical aortic valve replacement

TAPSE = Tricuspid Annular Plane Systolic Excursion

TAVI = Transcatheter Aortic Valve Implantation

CCT = Cardiac Computed Tomography

SV = stroke volume

RV = right ventricle

LV = left ventricle

INTRODUCTION

Aortic stenosis (AS) is the most common acquired valvular heart disease in adults, with an increasing prevalence among elderly patients. It is estimated that aortic stenosis affects approximately 5% of patients over 75 years old (1), the cause being valvular degeneration and calcification. The increase in life expectancy, earlier diagnosis, and access to new interventional treatment methods have made aortic stenosis the primary valvular disease requiring surgical or interventional correction in Europe and North America (2). Thus, transcatheter aortic valve implantation (TAVI) has become an increasingly used intervention for patients with severe symptomatic AS over 75 years old.

Conversely, in situations where patients are young, with low surgical risk, require surgical intervention for another indication, or present unfavorable anatomical/technical features for TAVI (absence of transfemoral vascular access or other vascular access sites, annular dimensions outside the limits of current prostheses, aortic bicuspidy, thrombi in the aorta/LV), surgical treatment will be preferred.

The growing number of patients with AS treated minimally invasively requires the development of specific tools for evaluating quality of life, as well as for measuring PROMs. Most questionnaires used were created to meet the need for evaluating quality of life in patients with heart failure (HF). However, there are numerous differences between patients with HF and those with AS – a large part of the causes of HF, especially with reduced EF (Heart Failure with Reduced Ejection Fraction – HFrEF) are irreversible, while AS involves a different phenotype of HF, predominantly with preserved EF (Heart Failure with Preserved Ejection Fraction – HFpEF) of reversible cause (3).

The PhD thesis titled "Demographic, Clinical, Biological, and Echocardiographic Parameters Associated with Change/Improvement in Quality of Life in Patients Who Underwent TAVI" aimed to explore the factors influencing quality of life after TAVI, considering the significant variability in patients' post-procedural response. Although previous studies have demonstrated a clear improvement in quality of life after this intervention, a significant

percentage of patients do not show optimal recovery, raising questions about the weight of comorbidities or peri-procedural complications, as well as suboptimal procedural outcomes in predicting changes in quality of life.

Through longitudinal analysis of data from a prospective cohort of patients, this study aimed to identify predictive factors for why quality of life improves less in certain categories of patients. The design was a prospective, non-randomized, longitudinal study conducted over 12 months. Patients with severe aortic stenosis indicated for valve replacement who underwent the TAVI procedure, according to inclusion criteria, were enrolled in a tertiary cardiovascular center, with demographic, clinical, laboratory, and echocardiographic data obtained at the time of the intervention, and subsequently followed at four time points up to one year after the intervention. All patients included in the study signed informed consent.

Quality of life assessment was done using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), which is a score used to evaluate the quality of life component in patients with heart failure. This choice was made because there is currently no dedicated tool for patients with aortic stenosis that captures their specificities, but this certainly represents an important direction for development in understanding the clinical evolution of these patients. The questionnaire was applied at baseline, before the intervention, and subsequently at each follow-up moment.

The obtained MLHFQ scores were correlated with echocardiographic evaluations, clinical data, and laboratory data to identify predictive factors for suboptimal trajectories of quality of life improvement post-TAVI. The primary objective of the study was the MLHFQ score, with higher scores indicating poorer quality of life. The secondary objective was the descriptive statistical analysis of the population, including clinical and echocardiographic characteristics during follow-up.

To identify potential predictors of the score values, univariate regression analyses were initially performed for each baseline variable. Predictors with a p-value <0.2 in the univariate analysis were subsequently included in the multivariate analysis. The most important predictive factors for suboptimal response at one year were peripheral arterial disease (PAD) and paravalvular regurgitation or leak (PVL).

Considering the temporal variability of scores for each patient and the types of non-linear responses that cannot be captured by traditional ANOVA analyses, mixed models statistics were used. This presents several significant advantages in a longitudinal study with repeated measurements. The mixed model allows analysis of variability both between patients and the effects of time on the same patient. This type of model is specifically designed to handle repeated data, allowing analysis of scores over time and offering greater flexibility in specifying relationships between variables. Another major advantage is that they can capture non-linear effects that are frequently encountered in patient-reported data, such as quality of life scores. Additionally, by using mixed models, a more robust estimate of statistical significance can be obtained, reducing the risk of type I or type II errors.

The final model for the present study identified certain significant predictors that influenced MLHFQ values. The presence of contrast-induced nephropathy (CIN) and PAD were associated with the most important coefficients for increasing the MLHFQ score. Among the biological parameters with statistical significance in the evolution of the MLHFQ score were hemoglobin level, serum creatinine, and natriuretic peptide values (NT-proBNP). From an echocardiographic perspective, reduced left ventricular ejection fraction (LVEF), left atrial dilation expressed by left atrial diameter (LAD), and tricuspid regurgitation (TR) greater than grade 2 were the most important factors associated with poorer quality of life after the procedure.

These results, as well as the variability of patient responses that can be influenced by multiple factors such as educational level, socio-economic status, and quality of life assessment tools, make a future patient-centered direction necessary in care.

1. Working Hypothesis and General Objectives

The general objectives that constitute the subject of this thesis are:

1. Identification of factors that can predict changes in quality of life, respectively the lack of optimal improvement in patients with severe AS treated interventionally through TAVI. These changes are objectified by MLHFQ score values, with higher values reflecting poorer quality of life, while lower values show better quality of life.

2. Determination of the temporal dynamics of quality of life through longitudinal analysis of the MLHF score.

3. Obtaining a descriptive analysis of the study population that allows characterization of the treatment response profile and establishment of evolution trajectories of quality of life.

4. Identification of subgroups of patients with different evolution trajectories of quality of life and predictive factors for belonging to a certain group.

The working hypotheses underlying the study can be summarized as follows:

1. The presence of comorbidities such as peripheral arterial disease (PAD), chronic kidney disease (CKD) defined by elevated serum creatinine/glomerular filtration rate exacerbated by contrast-induced nephropathy (CIN) are independent predictive factors of suboptimal recovery of quality of life after TAVI.

2. Paravalvular regurgitation (PVL) reflecting suboptimal long-term procedural outcome represents a strong independent factor associated with poorer quality of life post-TAVI.

2. General Methodology of Scientific Research

2.1 Study Population

This was a prospective, non-randomized, longitudinal study conducted over a period of 12 months. Of the 179 patients who underwent TAVI in a tertiary center between December 2022 and December 2023, 38 did not express consent for participation in the study, and 23 met exclusion criteria. The remaining 116 patients were followed for 12 months, with data collection at baseline – before the procedure, at 1-3 months (first control in a well-defined time interval), 6 months, and 12 months post-procedural. During follow-up, 2 losses to follow-up and 3 deaths were recorded (Supplementary Figure). The first quality of life assessment using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was performed pre-procedural (baseline). During follow-up, collected data included MLHFQ, clinical parameters, biological, and echocardiographic.

2.1.1 Inclusion Criteria

Severe Aortic Stenosis as defined by the SEC guidelines (2):

• High-gradient AS (mean gradient ≥40 mmHg, peak velocity ≥4 m/s, AVA ≤1 cm^2 or ≤0.6 cm^2/m^2) or low-gradient AS (mean gradient <40 mmHg, AVA ≤1 cm^2, LVEF <50%, indexed stroke volume ≤35 ml/m^2), or aortic valve calcium score measured in Agatston units (AU) as follows:

- for men >3000 AU and for women >1600 AU → high probability of severe AS
- for men >2000 AU and for women >1200 AU → probable severe AS
- for men <1600 AU and for women <800 AU → low probability of severe AS (4,5).

• Symptomatic patients with signs of heart failure (dyspnea, fatigue, systemic or pulmonary congestion), angina, or syncope associated with AS.

• Favorable anatomic criteria for percutaneous procedure feasibility as assessed by comprehensive echocardiographic evaluation and CT following the TAVI protocol.

2.1.2 Exclusion Criteria

Patients were excluded from the study if they presented with:

- Relative or absolute contraindications to TAVI:
  - Severe comorbidities with very limited life expectancy or with low probability of recovery of quality of life
  - Unicuspid or non-calcified aortic valve
  - Presence of other severe valvular diseases, as defined by the guidelines, requiring surgical correction
  - Active endocarditis
  - Left ventricular thrombus
  - Recent stroke or intracranial hemorrhage
  - Severe coronary artery disease that cotraindicates TAVI as a stand-alone procedure
  - Severe aorto-iliac or infra-inguinal occlusive disease preventing transfemoral vascular access

- **Need** for percutaneous coronary revascularization (PCI) during the index hospitalization

- **Valve**-in-valve procedure in a previously implanted surgical bioprosthesis or prior TAVI

- **Active** cancer or other comorbidities with a life expectancy of less than one year

2.2 Patient evaluation

All patients included in the study were evaluated by medical history, physical examination, standard 12-lead electrocardiogram, standard transthoracic echocardiography (TTE), coronary angiography, and cardiac-gated CT in a TAVI protocol for the assessment of the aortic valve area and femoral access.

The following data were recorded:

Clinical data:

- Age, sex, and place of residence
- Presence of typical symptoms (signs and symptoms of heart failure, angina, syncope)

- Cardiovascular risk factors (smoking, sedentary lifestyle, arterial hypertension, diabetes mellitus or impaired glucose tolerance, dyslipidemia, abdominal obesity)
- Presence of cardiac comorbidities (arrhythmias, coronary artery disease, etc.)
- Presence of non-cardiac comorbidities (chronic lung disease, peripheral artery disease, chronic kidney disease, significant past oncologic history)
- Paraclinical data – laboratory tests (complete blood count and coagulation profile, urea, creatinine, electrolytes, blood glucose, glycated hemoglobin, liver enzymes, NT-pro-BNP) performed prior to the procedure.
  With the exception of glycated hemoglobin, which was measured only before the procedure, all other tests were repeated during the follow-up period.

Echocardiographic data

Echocardiographic evaluations consisted of standard transthoracic echocardiograms, performed in the hospital by a team of cardiologists with expertise in the assessment of aortic stenosis (AS). The acquisition protocol included all parameters recommended by the ESC guideline (2**)** for the evaluation of AS severity.

The echocardiographic reports documented:

- Aortic valve assessment in 2D and with color Doppler to evaluate valve morphology, including the left ventricular outflow tract (LVOT) diameter and the degree of associated aortic regurgitation
- Peak transvalvular velocity obtained by continuous-wave Doppler at the aortic valve level from at least three echocardiographic windows
- Transvalvular gradients (maximum and mean)
- Aortic valve area (AVA) calculated by the continuity equation
- Left ventricular (LV) dimensions (diameters, wall thickness, LV mass)
- LV systolic function assessed by left ventricular ejection fraction (LVEF)
- LV diastolic function assessed by transmitral inflow profile and by tissue Doppler velocities of S and E′ waves
- Left atrial (LA) size (antero-posterior diameter and volume)
- Right heart chamber dimensions
- Right ventricular (RV) systolic function estimated by TAPSE
- Evaluation of mitral and tricuspid valve disease
- Estimation of pulmonary artery systolic pressure (PASP)

2.3 Follow-up of Patients

Subsequently, patients were followed up during four visits over one year as follows: the first evaluation was performed at 1–3 months, the second at 6 months, and the last visit at 12 months. All patients completed the Minnesota Living with Heart Failure Questionnaire (MLHFQ) before the intervention and at each follow-up visit. Systematic assessments included medical history, clinical examination, echocardiography, and laboratory tests comprising complete blood count, renal function tests (urea, serum creatinine), and NT-proBNP.

Echocardiographic assessment focused on: Prosthesis function parameters (peak velocity, transvalvular gradients, AVA, presence and quantification of paravalvular regurgitation), Left ventricular (LV) systolic function expressed by LVEF, Degree of mitral and tricuspid regurgitation, Right ventricular (RV) systolic function assessed by TAPSE.

2.4 Informed Consent

The study protocol was reviewed and approved by the Hospital Ethics Committee. Patients were informed about the study protocol and its objectives and signed the informed consent to participate in the study. Participation in the study did not interfere with the patients' usual in-hospital care, evaluations, or treatments.

2.5 Statistical Analysis

Continuous variables were expressed as mean ± standard deviation for data with a normal distribution, or as median and interquartile range (IQR**)** for data with a non-normal distribution. Categorical variables were presented as absolute numbers and percentages. Normality of data distribution was assessed using the Shapiro–Wilk test and histogram analysis.

Associations between the studied parameters were assessed using Pearson and Spearman correlation coefficients. The relationship between the dependent variable and the studied factors was analyzed using ANOVA for differences in clinical characteristics, Odds Ratio for the frequency of events, and regression analysis to determine the relationship between the considered variables and the event.

To identify potential predictors of the MLHFQ score, initial univariate linear regression analyses were performed for each baseline variable. Predictors with a p-value < 0.2 in the univariate analysis were subsequently included in a multivariate linear regression model to

evaluate the independent association with MLHFQ scores at baseline (short-term) and at 12 months (long-term).

Comparisons between groups (favorable vs. unfavorable outcomes, as defined in the study) for continuous variables were performed using the independent-samples t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate.

To further explore the factors influencing MLHFQ scores over time, a mixed-effects model was applied, accounting for both fixed effects (predictors) and random effects (inter-individual variability). Initially, univariate analyses were performed to identify relevant baseline and time-varying factors, using a significance threshold of $p < 0.05$ for subsequent inclusion in the final model. A backward stepwise selection procedure was then applied to derive the final multivariate model, retaining only statistically significant predictors. The magnitude of each factor's effect was expressed as estimates: positive values indicated worse quality of life, while negative values indicated improvement.

This methodological approach is superior to repeated-measures ANOVA, as it can handle missing data and appropriately accounts for the correlation structure among repeated observations.

All reported p-values are two-tailed, with a significance threshold set at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics, version 20 (IBM Corp., Armonk, NY, USA). For the mixed-effects modeling, the software R, version 4.3.2 (2023) was used: R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, with the following packages: gtsummary, effects, ggplot2, sjPlot, lme4, and lmerTest.

The lme4 package served as the main tool for estimating mixed-effects models, providing an efficient implementation of the Restricted Maximum Likelihood (REML) algorithms. Complementarily, the lmerTest package was used to perform the necessary statistical tests for evaluating the significance of fixed effects by applying Satterthwaite's degrees of freedom approximation. The gtsummary package was used to generate descriptive tables.

3. RESULTS SUMMARY

3.1 General Characteristics of the Study Population

The study included 116 patients with a mean age of 76 ± 6.5 years, of whom 66 (56.9%) were male. Most patients were non-smokers (74.1%). Among comorbidities: atrial fibrillation was present in 47 patients (40.5%), coronary artery disease in 37 patients (31.9%), peripheral artery disease in 14 patients (12.1%), diabetes mellitus in 34 patients (29.3%), chronic kidney disease (CKD) in 39 patients (33.6%). Anemia was documented in 55 patients (47.4%), with a median hemoglobin level of 12 [11–14] g/dl.

Regarding functional and geriatric status, the majority of patients were independent (82.8%), while 13.8% required assistance. At baseline, 47.4% of patients were in NYHA functional class II, 35.3% in class III, and 17.2% in class IV. The mean EuroSCORE II was 3.68 ± 4.3, and the mean estimated glomerular filtration rate (eGFR) at admission was 69.8 ± 24.9 ml/min/1.73 m^2.

Most patients had a tricuspid aortic valve (87.9%), 3.4% had a bicuspid valve, and in 8.6% the morphology could not be determined. The mean peak velocity across the aortic valve was 4.5 ± 0.5 m/s, with a median aortic valve area (AVA) of 0.7 cm^2 [0.6–0.85]. The median mean transaortic gradient was 50 mmHg [43–58], and the median peak gradient was 78 mmHg [68–91]. Aortic regurgitation was grade I in 52 patients (44.8%) and grade IV in 2 patients (1.7%). Mitral regurgitation was grade III in 12 patients (10.3%) and grade IV in 8 patients (6.9%). The median left ventricular ejection fraction (LVEF) was 55% [interquartile range 45–60%].

Regarding the TAVI procedure, the transfemoral approach was used in 98.3% of patients, while the transapical approach was used in 1.7%. The types of prosthetic valves used were: Edwards Sapien 3 (Edwards Lifesciences, Irvine, CA, USA) in 82 patients (70.7%), Evolut R (Medtronic, Minneapolis, MN, USA) in 31 patients (26.7%), Myval (Meril Life Sciences, Vapi, Gujarat, India) in 3 patients (2.6%). The mean post-procedural peak velocity was 2.1 ± 0.44 m/s, with a median mean gradient of 10.4 mmHg [8–14].

Paravalvular regurgitation (PVR) was: absent (grade 0) in 38.8%, grade I in 51.7%, grade II in 9.5%, with no cases of severe PVR. Procedural success was achieved in 94% of cases. Contrast-induced nephropathy (CIN) occurred in 6% of patients, and puncture-site

complications were reported in 8.6%. The need for permanent pacemaker implantation after the procedure was reported in 20.7% of patients.

Regarding discharge therapy after TAVI: 87% of patients were on statins, 83% were on beta-blockers, the use of ACE inhibitors/ARBs was below 60%, and MRAs were prescribed at discharge in about one-third of patients. In terms of antithrombotic therapy: 45% of patients were on oral anticoagulation (indicated for atrial fibrillation), 49% received dual antiplatelet therapy (DAPT), and 27% were discharged on single antiplatelet therapy.

3.2 Study of the Factors Influencing Quality of Life Improvement after Transcatheter Aortic Valve Implantation (TAVI)

3.2.1 Analysis of Baseline Characteristics in Relation to the MLHFQ Score

At baseline, the mean MLHFQ score was 41.1 ± 16.6, with a significant reduction to 28.8 ± 10 at the first follow-up visit ($p<0.001$), and subsequently to 23.4 ± 10 at 12 months ($p<0.001$). This indicates a progressive and statistically significant improvement in quality of life over time.

Pre-procedurally, the mean MLHFQ score was 41.12 ± 16.67 points. A substantial and significant early decrease was observed at the first follow-up (one month), where the mean MLHFQ score was 28.82 ± 10.00 points. At later visits, 6 and 12 months post-TAVI, the score continued to decline more gradually, reaching 25.36 ± 9.12 points at 6 months and 23.24 ± 10.00 points at 1 year.Rezultatele analizei de regresie liniară multivariată la primul control și la 12 luni

In the multivariate linear regression analysis evaluating short-term predictors of MLHFQ scores (at the first follow-up), several variables were significantly associated with the MLHFQ score. Each 1-point increase in baseline MLHFQ was associated with a higher MLHFQ score at 3 months. The presence of paravalvular regurgitation (PVR) and peripheral arterial disease (PAD) were both significantly associated with higher scores. In addition, each 10 mmHg increase in systolic pulmonary artery pressure (sPAP) and each 1 ml increase in left atrial volume (LAV) were correlated with higher MLHFQ scores.

In the multivariate linear regression analysis evaluating long-term predictors of MLHFQ scores (at 12 months), the same variables remained significant: PAD, PVR, LAV, sPAP, and baseline MLHFQ were all associated with the MLHFQ score at 12 months (Table 1).

Table 1. Determinants of Quality of Life after TAVI – Factors Influencing MLHFQ Scores during Post-Procedural Follow-up.

A. Follow-up 1 month				
Variable	B Coeficient	Lower CI	Upper CI	P value
PAD	7.22	3.35	11.1	<0.001
LAV	0.05	0.01	0.11	0.042
sPAP	0.11	0.03	0.25	0.017
PVR	2.50	1.49	4.50	0.015
MLHFQ baseline	0.36	0.25	0.47	<0.001
B. Follow-up 12months				
Variabile	Coeficient B	CI inferior	CI superior	Valoarea p
BAP	10.70	6.1	15.4	<0.001
Volumul AS	0.06	0.005	0.11	0.032
PAPS	0.23	0.12	0.34	<0.001
RPV	3.64	1.21	6.06	0.04
MLFHQ	0.19	0.06	0.32	0.04

3.2.3 Mixed effects statistical model

Since traditional regression analyses cannot account for repeated measures over time (e.g., MLHFQ scores) or for inter-patient variability, a mixed-effects statistical model was employed to evaluate the impact of both baseline and time-varying variables on MLHFQ scores. Because repeated measures were taken from the same patients, the observations were not independent. To evaluate the influence of predictors on quality-of-life scores, a linear mixed-effects (hierarchical/multilevel) model was applied. The dependent variable was the MLHFQ score measured at four different time points for each patient, while the independent variables included demographic, clinical, and echocardiographic parameters. Independent variables were of two types: those measured only at baseline, and those assessed repeatedly over time. Given the availability of only four measurements per patient (a total of 452 observations), a fully random-effects model (with both random slopes and intercepts) could not be applied; therefore, a partial model with random intercepts only was used.

MLHFQ scores decreased significantly throughout follow-up compared to baseline. The lowest mean score was observed at 12 months, though differences between post-procedural follow-up means were not clinically significant. The trajectory suggested a non-linear early decline up to the first follow-up, followed by a relatively stable course. Random effects varied substantially across patients, with some experiencing marked quality-of-life improvement and others reporting deterioration during the one-year follow-up. Overall, the model explained 74% of the variance in MLHFQ scores, with 47% explained by random effects.

The final model identified several significant predictors of MLHFQ scores, reflecting their impact on quality of life. Predictor selection was performed in two steps: initially, univariate mixed models were used to screen variables ($p<0.05$), and significant predictors were subsequently tested in multivariate models.

Some predictors, evaluated only at baseline, had a statistically significant impact on quality of life and its starting point. For instance, the EURO Score II, a perioperative mortality risk index in cardiac surgery, was positively associated with MLHFQ evolution: each 1-unit increase corresponded to a 1.1-point rise in MLHFQ, but only up to values of 22–23%, beyond which the association plateaued. This suggests limited discriminatory power of the score in patients with extremely high surgical risk and severely impaired baseline quality of life.

Extracardiac involvement was also positively associated with MLHFQ. Interestingly, this was not a gradual progression but rather reflected specific extracardiac phenotypes in patients with severe aortic stenosis. Statistically, however, progression from stage 1 to stage 4 translated into a 5-point increase in mean MLHFQ scores. The model explained 40% of the variance, with 27% explained by random effects.

Frailty was another important factor. In this study, frailty was assessed using the Geriatric Scale. Most patients were independent (82.8%), 14% required assistance, 2.6% had dementia, and 1% had urinary incontinence. Increasing frailty correlated with higher MLHFQ scores, each stage progression adding approximately 4 points to the mean score. This model explained 40% of the variance, with 35% attributable to random effects.

NYHA functional class at baseline was also a significant predictor. Interestingly, although patients were reclassified at each follow-up, NYHA class was significant only in univariate

analyses, not multivariate. Nonetheless, higher NYHA classes were associated with progressively worse MLHFQ scores: NYHA II patients had higher means, NYHA III patients +4 points, and NYHA IV patients +15 points, reflecting severely impaired quality of life in decompensated heart failure. This model explained 40% of the variance, with random effects contributing 25%. A possible explanation for the lack of predictive value in multivariate analysis is the limited sensitivity and specificity of NYHA classification in patients with marked post-TAVI quality-of-life improvements. Moreover, NYHA class does not always capture patient-reported outcomes.

Using backward selection, the multivariate analysis identified the strongest predictors of impaired quality of life: moderate-to-severe tricuspid regurgitation (+8.82 points), contrast-induced nephropathy (+7.42 points), paravalvular regurgitation ≥ grade 2 (+6.28 points), peripheral arterial disease (+4.47 points)

Among biomarkers, hemoglobin was inversely associated with MLHFQ (–1.72 points per 1 g/dl increase), while higher creatinine (+2.67 points per 0.5 mg/dl increase) and NT-proBNP (+0.18 points per 100 pg/ml increase) were associated with worse scores. Each 5% increase in LVEF corresponded to a 1.9-point reduction, while each 3 mm increase in left atrial diameter was associated with a 1.14-point rise **(Table 2).**

Table 2. Predictors of QoL obtained from the multivariable mixed-effects model

Predictors	**Estimates**	**Lower CI**	**Upper CI**	**P-value**
Absence of CIN	-7.42	-13.96	-0.88	0.026
Absence of PAD	-4.47	-8.97	-0.04	0.052
Hemoglobin (per 1 g/dl ↑	-1.72	-2.64	-0.81	<0.001
Creatinine (per 0.5 mg/dl ↑)	2.67	0.46	4.42	0.003
NT-proBNP (per 100 pg/ml ↑)	0.18	0.12	0.27	<0.001
LVEF (per 5 units ↑)	-1.9	-1.65	-1.05	<0.001

Left atrial diameter (per 3 mm ↑)	1.14	0.42	1.86	0.002
TR grade 2	3.37	0.88	5.86	0.008
TR grade 3/4	8.82	4.55	13.08	<0.001
PVL grade 1	1.43	-1.13	3.98	0.273
PVL grade 2	6.28	0.7	11.86	0.028

Thus, the factors influencing quality of life were as follows:

The presence of nephropathy was associated with an increase of 7.42 points in the MLHFQ score, peripheral arterial disease with a 4.47-point increase, while hemoglobin had a negative effect (each 1 g/dl increase corresponded to a 1.72-point decrease). Creatinine was positively associated with quality-of-life impairment (each 1-unit increase was associated with a 5.35-point rise in MLHFQ). NT-proBNP showed a positive association (each 100-unit increase corresponded to a 0.06-point increase). LVEF had a negative effect (each 1-unit increase corresponded to a 0.38-point decrease). Left atrial anteroposterior diameter (LAAP) was positively associated, with each 1-unit increase leading to a 0.38-point rise. Tricuspid regurgitation also showed a positive association: compared with grades 0–1, grade 2 corresponded to a 3.37-point increase, while grades 3–4 corresponded to an 8.82-point increase. Finally, paravalvular regurgitation showed a positive association: grade 1 (versus grade 0) corresponded to a non-significant 1.43-point increase, while grade 2 was associated with a 6.28-point rise. The model explained 70% of the variance in MLHFQ scores, with 20% explained by random effects.

In the multivariate regression analysis assessing short-term predictors (first follow-up at 1–3 months), several factors were significantly associated with MLHFQ scores. The baseline MLHFQ score was a strong predictor of subsequent evolution, with each 1-point increase at baseline correlating with a 0.36-point rise at the first follow-up (B=0.360, 95% CI [0.25–0.47], p<0.0001). The presence of paravalvular regurgitation was associated with a 2.5-point increase in MLHFQ at short-term follow-up (B=2.49, 95% CI [0.49–1.2], p=0.001). Another significant

predictor was peripheral arterial disease, associated with a 7.1-point increase in MLHFQ (B=7.21, 95% CI [3.35–11.07], p<0.0001). Pulmonary hypertension, reflected by systolic pulmonary artery pressure, was also a significant predictor: every 10 mmHg increase corresponded to a 1.1-point rise in MLHFQ (B=1.1, 95% CI [0.2–2], p=0.001). Left atrial dilation, expressed by left atrial volume, showed that each 1 ml increase was associated with a 0.066-point increase in MLHFQ (B=0.06, 95% CI [0.02–0.10], p<0.003).

In the multivariate regression analysis conducted at 12 months post-TAVI, several factors remained statistically significant. Peripheral arterial disease had a strong impact, associated with a 10.7-point increase (B=10.74, 95% CI [6.09–15.39], p<0.001). Paravalvular regurgitation was associated with a 3.6-point rise (B=3.64, 95% CI [1.21–6.06], p=0.04). Each 1 mmHg increase in pulmonary artery pressure correlated with a 0.23-point rise in MLHFQ (B=0.23, 95% CI [0.12–0.34], p<0.0001). Similarly, each 1 ml increase in left atrial volume corresponded to a 0.059-point increase (B=0.05, 95% CI [0.00–0.11], p=0.03). Importantly, higher baseline MLHFQ scores also predicted worse long-term outcomes: each 1-point increase at baseline corresponded to a 0.20-point rise at 12 months (B=0.19, 95% CI [0.06–0.32], p=0.04).

4. Conclusions and personal contributions

The impact of severe aortic stenosis (AS) on healthcare systems is particularly significant, as it represents the most common acquired valvular disease in adults, and treatment of these patients requires the allocation of substantial financial resources. With regard to interventional treatment methods—either surgical or transcatheter (TAVI)—clear indications are currently established by the ESC guidelines for the evaluation and management of valvular heart disease.

TAVI has become the treatment of choice for elderly patients with severe, symptomatic AS. The excellent procedural outcomes have considerably expanded its use, even among patients with low surgical risk. However, an important aspect, often overlooked, is not only the survival of these patients but also their quality of life after TAVI, which is essential for improving patient-centered care.

In this thesis, I investigated the predictors that influence quality-of-life improvement after TAVI, both in the early and long-term follow-up. The focus was on identifying factors that impact the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score. A key strength of the study was the comprehensive evaluation—including clinical, biological, and echocardiographic assessments, as well as quality-of-life scoring—performed at four time points, up to one-year post-TAVI. The study demonstrated a marked reduction in the mean MLHFQ score, particularly in the early post-procedural period, reflecting a substantial improvement in quality of life. Predictors that influenced quality of life at the first follow-up remained statistically significant at 12 months. The strongest determinants of suboptimal improvement were the presence of peripheral arterial disease, paravalvular regurgitation of grade >2, tricuspid regurgitation grade 3 or 4, pulmonary hypertension, and left atrial dilation. Among biomarkers, the greatest impact was observed with elevated natriuretic peptides, low hemoglobin, and increased serum creatinine.

Another significant finding of this study was the identification of distinct response trajectories. Patients could be classified as having a rapid positive response or a slow/absent improvement when considering the composite endpoint. Interestingly, baseline factors associated with subgroup stratification included age, NYHA functional class, geriatric status, and the presence of paravalvular regurgitation.

The results of this study highlight the importance of patient-centered care and patient-reported outcomes, contributing to the development of approaches tailored to individual patient needs. Predictor identification and analysis were performed using a rigorous methodological approach, based on mixed-effects models, which reduced the risk of type I error and enabled the evaluation of data with temporal variability.

Considering the clinical importance of assessing quality of life in patients with severe AS undergoing TAVI, this study demonstrates the need for dedicated tools specifically designed for this population, capable of capturing their unique characteristics and differentiating them from patients with heart failure. These findings, however, require further confirmation in larger studies to fully validate the results.

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