Risk stratification using growth differentiation factor 15 in patients undergoing transcatheter aortic valve implantation

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Aims. Growth differentiation factor 15 (GDF15) shows potential predictive value in various cardiac conditions. We investigated relationships between GDF15 and clinical or procedural outcomes in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) in order to propose clinically useful predictive risk stratification model.

Methods. This prospective single-center registry enrolled 88 consecutive patients with severe symptomatic aortic stenosis treated with TAVI. Clinical parameters were collected and biomarkers including GDF-15 were measured within 24 h before TAVI. All relevant clinical outcomes according to the Valve Academic Research Consortium-2 were collected over the follow-up period.

Results. The cohort included 52.3% of females. The mean age of study participants was 81 years; the mean Society of Thoracic Surgeons (STS) score and logistic EuroSCORE were 3.6% and 15.4%, respectively. The mortality over the entire follow-up period was 10.2%; no death was observed within the first 30 days following TAVI. Univariate analysis showed significant associations between GDF15 and mortality (*P*=0.0006), bleeding (*P*=0.0416) and acute kidney injury (*P*=0.0399). A standard multivariate logistic regression model showed GDF-15 as the only significant predictor of mortality (*P*=0.003); the odds ratio corresponding to an increase in GDF15 of 1000 pg/mL was 1.22. However, incremental predictive value was not observed when the STS score was combined with GDF15 in this predictive model.

Conclusions. Based on our observations, preprocedural elevated GDF15 levels are associated with increased mortality and demonstrate their additional value in predicting adverse clinical outcomes in a TAVI population.

Key words: transcatheter valve implantation (TAVI), risk stratification, biomarker, growth differentiation factor 15 (GDF15)

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INTRODUCTION

Aortic stenosis (AS) is the most prevalent valvular heart disease in adults in Western countries, closely associated with ageing[1,2]. Transcatheter aortic valve implantation (TAVI) has been well established as a method of choice for patients with severe AS at high or prohibitive risk for surgical aortic valve replacement[3,4]. Despite the continuous development of TAVI aiming to improve the safety of this treatment strategy, mortality remains significant and so does the occurrence of serious clinical events associated with TAVI, especially in high-risk populations. Moreover, we observe further expansion of TAVI indications to include intermediate and low surgical risk patient groups[5]. For more comprehensive patient characterization and risk stratification associated with short- and long-term mortality and morbidity following TAVI, the Valve Academic Research Consortium-2 (VARC-2) has endorsed the selection and definitions of TAVI clinical endpoints[6]. This has led to improved comparability and interpretability of TAVI study results. TAVI-specific risk stratification models are still lacking and surgical risk scores have brought conflicting results in TAVI populations[7–9]. Therefore, various clinical measures and biomarkers have been proposed and investigated to improve risk stratification.

One of the most widely used clinical measures is frailty score assessment. Frailty is a biological syndrome characterized by increased vulnerability to stressors[10]. Frailty instruments vary across studies, resulting in a wide range of frailty prevalences. However, a high frailty score has been proven as a strong factor of worse 1-year outcome. Although guidelines suggest using frailty measures when selecting patients for TAVI (ref.[3,4]), a standard and objective method is lacking. Therefore, further research combining various frailty parameters for better results and outcomes consistency may help to identify specific risks among candidates for TAVI procedure[11,12].

Another way of improving risk stratification is to integrate an information derived from assessment of various circulating biomarkers. Biomarkers are biological parameters that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention and they have a great potential to be used as markers of diagnosis and prognosis[13]. Cardiac biomarkers can be classified according to the causal process as inflammatory markers, ischemia markers or markers of necrosis. Besides other biomarkers, high sensitivity cardiac troponin T (Hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have shown a diagnostic and prognostic potential in patients undergoing TAVI, specifically in view of their periprocedural dynamic changes[14,15]. Growth differentiation factor 15 (GDF15) represents an emerging biomarker which has shown its efficacy in assessing outcomes in various cardiovascular diseases such as heart failure and acute coronary syndromes[16,17]. GDF15 is a cytokine belonging to the transforming growth factor family that participates in inflammation and apoptosis[18]. The expression of this marker is upregulated by stress and tissue damage and it is associated with inflammatory conditions in various tissues, including the myocardium[19]. GDF15 levels are increased in patients with AS. This may indicate functional and structural ventricular changes induced by progressive pressure overload, with potential implications in terms of reverse remodeling. Circulating GDF15 levels may reflect the systemic conditions underlying a frail patient phenotype, in addition to comorbidities[20]. Elevated GDF15 correlates with lack of reverse remodelling and increased mortality following TAVI, improves mortality risk prediction when added to the Society of Thoracic Surgeons (STS) (ref.[21]) and provides additional prognostic information[22]. Although the prognostic value of GDF15 in a TAVI patient cohort has already been proven in a prospective single-centre registry[22], we investigated the relationship between GDF15 and all clinical or procedural outcomes according to the VARC-2 criteria in patients with severe symptomatic AS undergoing TAVI. Moreover, we studied whether there is any group of procedural outcomes according to the VARC-2 criteria with stronger relationship to elevated GDF15 in order to create a clinically useful model for risk stratification before TAVI. Therefore, we designed three different composite endpoints – (1) **Overall VARC-2 Endpoint** (containing all possible VARC-2 endpoints observed in our cohort, i.e. vascular complications, stroke, new pacemaker implant, death from any cause, bleeding complications and acute kidney injury), and two more specific endpoints according to their causal relationship: (2) **Structural Endpoint** (vascular complications, stroke, new pacemaker implant) associated with the direct mechanical interaction between the patient`s anatomical structure and any part of the TAVI system itself, and (3) **Systemic Endpoint** (mortality, bleeding complications, acute kidney injury) more dependent on systemic pathology. Given the prospective design of our study, we did not modify our endpoint definitions based on the VARC-2 criteria even though in the meantime, a new document with updated VARC-3 criteria was published[23].

SUBJECTS AND METHODS

Study design and patients

This study was designed as prospective single-center registry. We enrolled 88 consecutive patients undergoing TAVI over a continuous period of 11 months between December 2019 and October 2020. Patients were treated with Portico™ (Abbott Cardiovascular, Plymouth, USA), Sapien XT™ or Sapien3™ (Edwards Lifesciences, Irvine, USA) TAVI systems. The Portico™ valve is a self-expanding bovine pericardium tissue TAVI system designed for transfemoral or subclavian delivery; it is available in 23-, 25-, 27- and 29-mm sizes. The Sapien XT™ and Sapien3™ (S3) are balloon expandable TAVI valves also made of bovine pericardium, available in 20-, 23-, 26- and 29-mm sizes. They are suitable for transfemoral, transapical and transaortic access. The transfemoral access route was used in all patients in our registry. TAVI system selection was performed according to local practice concerning sizing and valve morphology. This means that all patients with bicuspid morphology were selected for Sapien XT™ or S3™ valves. All patients who presented with tricuspid AS were initially considered for Portico™ valve according to native valve computed tomography (CT) angiography measurements and only those who exceeded sizing ranges for Portico™ valve were then selected for the Sapien XT™ or S3™ valves. Since the end of February 2020, a new delivery system for Portico™ valves with an integrated sheath has been commercially available. Therefore, in all patients treated with Portico™ valves since February 29 the new FlexNav™ delivery system was used. Therefore, the delivery system insertion profile was reduced from 18 to 14 French (Fr) for Portico™ 23 and 25 and from 19 to 15 Fr for Portico™ 27 and 29. TAVI indication was approved by a heart team consisting of two cardiac surgeons and two interventional cardiologists according to a position paper of the Czech Society of Cardiology. All subjects underwent transthoracic echocardiography those with suspected low flow/low gradient AS were assessed by dobutamine echocardiography to confirm severe AS. Coronary angiography was performed as a part of routine assessment and patients with flow-limiting coronary artery disease underwent percutaneous coronary intervention at least three to four weeks before TAVI. CT angiography and carotid duplex sonography were added to routine imaging assessment. Electrocardiography was performed, clinical parameters were collected and biomarkers were measured one day prior to TAVI. The TAVI procedural details were recorded and classified in accordance with the VARC-2 definition. Similarly, all relevant clinical outcomes post-TAVI were classified according to the VARC-2 definition and collected over the entire follow up period. This study adhered to ethical guidelines and was approved by the institutional review board and ethics committee. Written informed consent was obtained from all participants before entering the study.

Biomarker data collection

Blood samples were collected within 24 h before the procedure and processed immediately. Biomarker measurements were performed at our institution`s laboratory facility.

Serum GDF15 levels were detected using an electrochemiluminescence immunoassay (Elecsys, Cobas 6000 e601, Roche Diagnostics, Mannheim, Germany).

Serum NT-proBNP levels were measured with an electrochemiluminescence immunoassay (Elecsys proBNP gen 2, Cobas 8000 e602, Roche Diagnostics). The lower limit of detection was 5 ng/L, intra-assay coefficient of variation (CV) <1.8%, and interassay CV <3.1%.

Hs-cTnT was assessed using an electrochemiluminescence immunoassay (Elecsys Tropo T, Cobas 8000 e602, Roche Diagnostics). The lower limit of detection was 5 ng/L, CV at 13 ng/L was 10%, intra-assay CV <4.8%, and interassay CV <5.2%. The upper reference limit was set at 14 ng/L.

Statistical analysis

To assess the association between an outcome (e.g. Overall VARC-2 Endpoint) and a continuous parameter (e.g. GDF15 level), the Kruskal-Wallis test was used. The Kruskal–Wallis test (or one-way ANOVA on ranks) is a non-parametric method for testing whether samples originate from the same distribution. It does require the assumption of normality. To assess the association between an outcome (e.g. Overall VARC-2 Endpoint) and a discrete parameter (e.g. diabetes status), the chi-square test in contingency table was used. If the number of patients in the respective groups was not sufficient, the Fisher's exact test was used instead. All test were performed at 0.05 significance level. The analysis was performed in MATLAB™, Statistics Toolbox, version 7.5.0.342 (R2007b). For the prediction models, standard logistic regression models were fitted. For the comparison of several models, receiver operating characteristic (ROC) analysis was used.

Table 1. Baseline cohort characteristics.

	All (n = 88)	Self-expanding (n = 66)	Balloon-expandable (n = 22)
Age (years)	81	82	78
Female	46 (52.3%)	43 (65.2%)	3 (13.6%)
BMI (kg/m^2)	28.3	27.7	30.2
NYHA classification			
I	0	0	0
II	17 (19.9%)	11 (16.4%)	6 (27.3%)
III	71 (80.1%)	55 (83.3%)	16 (72.7%)
IV	0	0	0
STS score (mean)	3.6%	3.6%	3.6%
< 4%	48 (54.5%)	34 (51.5%)	14 (63.6%)
4-8%	35 (39.8%)	27 (40.9%)	8 (36.4%)
> 8%	5 (5.7%)	5 (7.5%)	0
LogES (mean)	15.4%	16.0%	11.1%
≤ 15%	42 (47.7%)	29 (43.9%)	13 (59.1%)
> 15%	46 (52.3%)	37 (56.1%)	9 (40.9%)
History of CAD	53 (60.2%)	42 (63.6%)	11 (50.0%)
Previous cardiac surgery	19 (21.6%)	16 (24.2%)	3 (13.6%)
Atrial fibrillation	41 (46.6%)	33 (50.0%)	8 (36.4%)
Diabetes	44 (50.0%)	35 (53.0%)	9 (40.9%)
diet-controlled	5 (5.7%)	2 (3.0%)	3 (13.6%)
oral-controlled	26 (29.5%)	25 (37.9%)	1 (4.6%)
Insulin-controlled	13 (14.8%)	8 (12.1%)	5 (22.7%)
Heart failure	33 (37.5%)	27 (40.9%)	6 (27.3%)
Pulmonary hypertension	34 (38.6%)	26 (39.4%)	8 (36.4%)
Peripheral vascular disease incl. cerebrovascular	26 (29.5%)	18 (27.3%)	8 (36.4%)
Chronic renal failure	19 (21.6%)	16 (24.2%)	3 (13.6%)
LVEF (mean)	55%	60%	55%
< 35%	7 (8.0%)	5 (7.6%)	2 (9.1%)
35-50%	22 (25.0%)	15 (22.7%)	7 (31.8%)
> 50%	59 (67.0%)	46 (69.7%)	13 (59.1%)

BMI, body mass index; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons Score; LogES, logistic EuroSCORE; CAD, coronary artery disease; LVEF, left ventricular ejection fraction.

RESULTS

Baseline characteristics

Baseline characteristics of the cohort are presented in Table 1. A total of 88 consecutive patients with a mean age of 81 years (range, 45-90 years) undergoing TAVI for symptomatic AS in center were analyzed. The median follow-up was 307 days (range, 161–486 days). The follow-up period was partially affected partially by COVID-19 as the TAVI program had to be interrupted for almost 2 months. Just over one half of the study subjects were females and the median BMI was 28.3 (range, 19.9-49.0). The majority of the patients presented with symptoms consistent with New York Heart Association class III. Almost half of the subjects had chronic atrial fibrillation/flutter; 60% of patients experienced significant coronary artery disease and over 20% underwent previous cardiac surgery. Fifty percent of our patients were diabetics, most of them controlled with oral medications, whereas almost a third of diabetics were treated with insulin. Nearly 40% of the subjects had a history of congestive heart failure and a similar proportion of patients presented with significant signs of pulmonary hypertension defined by estimated systolic pulmonary artery pressure > 50 mmHg. Approximately 33% of the subject presented with reduced left ventricular (LV) function, with 8% of the entiry cohort having severe LV systolic dysfunction. Just over two out of 10 patients presented with significant chronic renal failure defined as estimated glomerular filtration rate < 45 mL/min/1.73m^2. The mean baseline STS score was 3.6% (STS < 4% in 54.5%, 4–8% in 39.8% and > 8% in 5.7% of the subjects), whereas the mean baseline logistic EuroSCORE was 15.4%. The mean pre-TAVI NT-proBNP level was 1194 ng/L (range, 112.4–21407 ng/L) and the mean pre-TAVI GDF15 level was 3370 pg/mL (range, 1373–20000 pg/mL).

Procedural variables and outcomes

The TAVI-related variables for the cohort are summarized in Table 2. The mean contrast agent volume used was 90 mL per procedure. The 15Fr delivery system insertion profile was most frequently used for all procedures.

Table 2. Overview of TAVI variables.

	All (n = 88)	Self-expanding (n = 66)	Balloon-expandable (n = 22)
Procedural time (min.)	52	54	46
Contrast agent (mL)	90	90	92
Insertion profile (ID equivalent)			
14 Fr	12 (13.6%)	10 (15.1%)	2 (9.1%)
15 Fr	39 (44.3%)	39 (59.1%)	–
16 Fr	7 (8.0%)	–	7 (31.8%)
18 Fr	9 (10.2%)	6 (9.1%)	3 (13.6%)
19 Fr	11 (12.5%)	11 (16.7%)	–
20 Fr	10 (11.4%)	–	10 (45.5%)
Post-dilation	7 (8.0%)	6 (9.1%)	1 (4.6%)
PVL >2	4 (4.6%)	4 (6.1%)	0

ID, internal diameter; Fr, French; PVL, paravalvular leak.

Table 3. Overview of outcomes.

		All (n = 88)	*P*
Mortality		9 (10.2%)	0.0006
Stroke		3 (3.4%)	NS
Bleeding	– total	11 (12.5%)	0.0416
	– major	7	–
	– minor	4	–
Vascular complications	– total	10 (11.4%)	NS
	– major	4	–
	– minor	6	–
Acute kidney injury		5 (5.7%)	0.0399
New pacemaker		10 (11.4%)	NS
Overall VARC2 Endpoint		36 (40.9%)	0.0016
Systemic Endpoint		23 (26.1%)	<0.0001
Structural Endpoint		23 (26.1%)	NS

The *P*-values in the last column are related to difference in GDF15 levels between the group experiencing the outcome and the group not experiencing the outcome. P-values were not calculated separately for major or minor vascular complications and major or minor bleeding events respectively.
NS, not significant.

Table 4. Univariate analysis of associations between predictors and endpoints.

Predictor	Overall		*P*	Systemic		*P*	Structural		*P*
	0	1		0	1		0	1	
Age (years)	80.00	82.50	0.4289	80.00	84.00	0.0662	82.00	79.00	0.0669
BMI (kg/m^2)	28.60	28.10	0.8591	28.40	28.65	0.8720	28.15	29.50	0.1122
LogES	13.35	16.85	0.2644	14.00	16.30	0.5215	15.60	15.70	0.6014
STS score	3.34	5.11	**0.0064**	3.51	5.52	**0.0013**	3.63	3.67	0.9357
GDF15 (pg/mL)	2986.00	4436.00	**0.0016**	2980.00	5127.00	**<0.0001**	3205.00	3775.00	0.7182
NT-proBNP (ng/L)	1206.00	1142.00	0.7433	1193.50	1382.00	0.6896	1545.00	589.20	**0.0231**
Hs-cTnT (ng/L)	22.50	30.00	**0.0251**	25.00	27.00	0.1516	25.00	27.00	0.3455
GFR (mL/s/1.73 m^2)	1.15	1.13	0.2553	1.15	0.95	0.1273	1.10	1.26	0.4674
Creatinine (μmol/L)	76.50	84.50	0.1664	78.00	81.00	0.2169	78.00	81.00	0.9886
Contrast (mL)	90.00	100.00	0.5300	90.00	100.00	0.2139	90.00	90.00	0.7199
LVEF (%)	55.00	60.00	**0.0460**	55.00	60.00	**0.0506**	55.00	60.00	0.2368
Sheath size (Fr)	15.00	15.00	0.3332	15.00	15.00	0.5295	15.00	16.00	0.1579

Overall – 1 represents the group of patients that experienced the Overall VARC-2 Endpoint.
Overall – 0 represents the group of patients that did not experience the Overall VARC-2 Endpoint.
The values in the table show the median of the parameters in the respective groups. *P*-values of the Kruskal-Wallis test are given.
GFR, estimated glomerular filtration rate/creatinine clearance; sheath size, delivery system insertion profile (internal diameter equivalent); LVEF, left ventricular ejection fraction.

Only a minority of the patients required post-dilation even though the self-expanding system was more frequently used. Pre-dilation is used as a default strategy in all patients in our center when the self-expanding system is implanted. There was no procedure requiring a second valve ("TAVI in TAVI"). With regard to post-TAVI paravalvular leak, the majority of the patients had no or mild aortic regurgitation.

All procedural outcomes according to the VARC-2 criteria including composite endpoints and their relationship to GDF15 are presented in Table 3. There was no patient death within 30 days after TAVI in our cohort. Therefore, the data represent mortality over the entire follow-up period. All strokes were non-disabling with good patient recovery. We observed no fatal or life-threatening bleeding complications. The majority of vascular complications were minor based on the VARC-2 definition. All patients with acute kidney injury were managed medically; dialysis was not used.

Analysis of individual risk factors for TAVI-associated outcomes

We analyzed the associations between predictors and the Overall VARC-2, Systemic and Structural Endpoints by means of univariate analysis. Table 4. summarizes the results of univariate exploratory analysis.

We observed significant associations of the Overall VARC-2 Endpoint with the STS score and GFD15 (*P*=0.0016 for GDF15; *P*=0.0064 for the STS score). Similarly, for the Systemic Endpoint, significant associations with the STS score and GDF15 were observed (*P*<0.0001 for GDF15; *P*=0.0013 for the STS score). Another significant factor for the Overall VARC-2 and Systemic Endpoints in the cohort was left ventricular ejection fraction (LVEF), but with a paradoxical relationship. Those who experienced either Overall VARC-2 or Systemic Endpoints presented with a higher LVEF compared to those who did not (*P*=0.046 for the Overall VARC-2 Endpoint, *P*=0.0506 for the Systemic Endpoint). In fact, the difference in absolute numbers was very low (60% vs. 55%) and in both cases remained within range for preserved left ventricular systolic function. There was no clinically relevant factor significantly associated with the Structural Endpoint found in our cohort.

Prediction of TAVI-associated outcomes and mortality

Next, we wanted to find predictors for the Overall VARC-2, Systemic and Structural Endpoints, and for 1-year mortality. We used the standard multivariate logistic regression model. As a benchmark, we use the STS score and we evaluate the performance of each predictive model by comparing its ROC curve to the ROC curve of the logistic model containing only the STS score predictor.

For the Overall VARC-2 Endpoint, the STS score is a significant predictor (*P*=0.007), the corresponding odds ratio (OR) is 1.37 (i.e. an increase of 1 point in the STS score is associated with 1.37 times higher odds of the Overall VARC-2 Endpoint). The level of GDF15 is a significant predictor of the Overall VARC-2 Endpoint (*P*=0.005), the OR corresponding to an increase in GDF15 of 1000 pg/mL is 1.3. Prediction of the Overall VARC2 Endpoint by means of GDF15 has a slightly better performance (blue curve in Fig. 1) than the prediction by means of the STS score (green curve in Fig. 1). If we combine the STS score and GDF15 in a multivariate logistic regression model, the STS score becomes insignificant (*P*=0.08), GDF15 remains significant (*P*=0.02), the effect size of GDF15 slightly decreases (OR=1.22 for a 1000 pg/mL increase in GDF15, red curve in Fig. 1).

For the Systemic Endpoint, the STS score is a significant predictor (*P*=0.002) with the corresponding OR=1.47 (green ROC curve in Fig. 2). GDF15 is a significant predictor (*P*=0.001), the OR corresponding to an increase in

GDF15 of 1000 pg/mL is 1.4 (blue curve in Fig. 2). In this case, the combination of the STS score and GDF15 does not yield a better predictor (see the red curve in Fig. 2).

In case of the Structural Endpoint, neither the STS score nor GDF15 are significant predictors. The ROC analysis becomes meaningless as none of the models fares better than chance (shown in Fig. 3).

For mortality, the STS score is not a significant predictor (P=0.07; OR=1.28). However, GDF15 is a significant predictor (P=0.003), the OR corresponding to an increase in GDF15 of 1000 pg/mL is 1.22 (blue curve in Fig. 4). Combination of the two predictors does not yield a better model; in this case, all the predictive power lies in the GDF-15 variable.

DISCUSSION

The present study prospectively analyzed 88 patients undergoing transfemoral TAVI to investigate the prognostic role of the biomarker GDF15 and compare its efficacy with various clinical factors, circulating biomarkers and clinical risk scores.

Effective and clinically useful risk stratification is very complex and has a meaningful role to improve TAVI-associated clinical outcomes and reduce mortality. In the context of risk stratification before TAVI, the most widely used tools are various surgical risk scores such as the STS score, logistic EuroSCORE or EuroSCORE II. Current evidence shows that risk stratification using surgical scoring systems is not always accurate in TAVI populations[24,25] and their predictive performance is inconsistent[26]. In accordance with these data, our results show significant

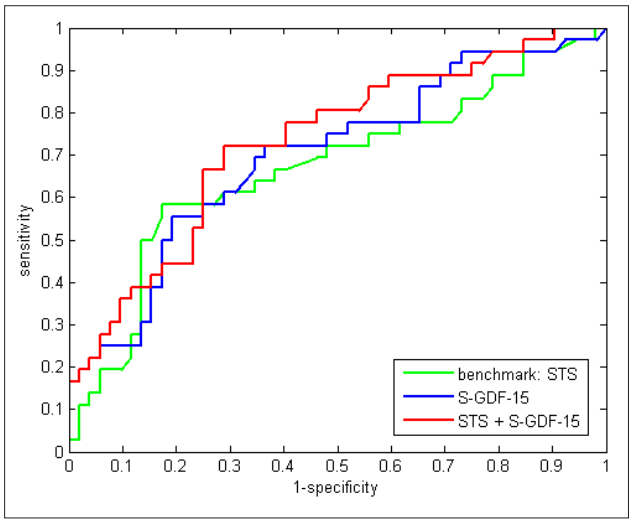

Fig. 1. Comparison of three logistic models predicting the Overall VACR-2 Endpoint.

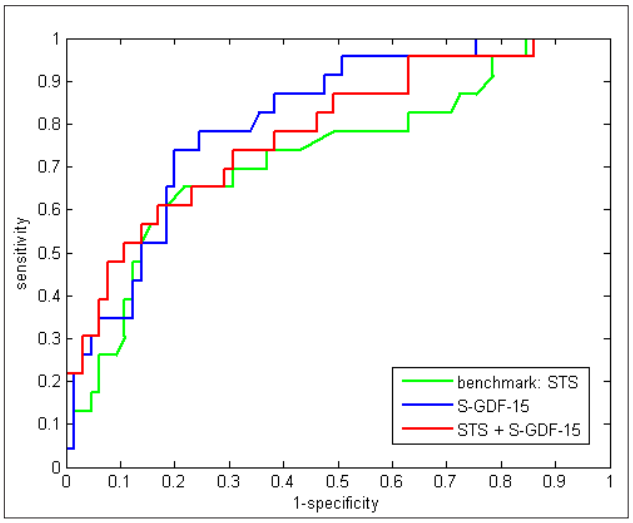

Fig. 2. Comparison of three logistic models for predicting the Systemic Endpoint. Prediction with GDF15 outperforms other two models.

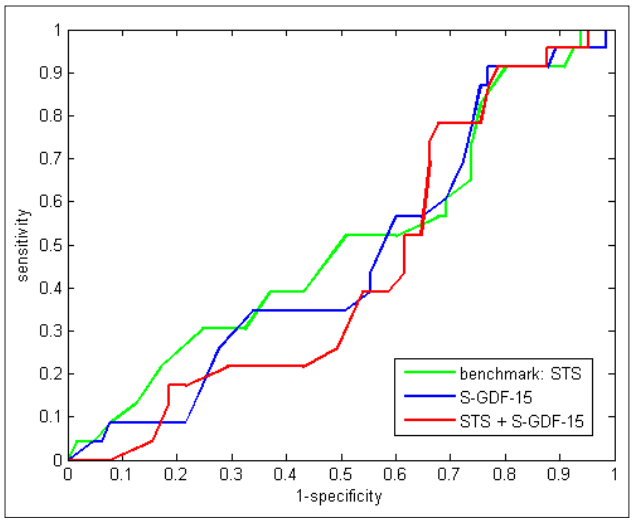

Fig. 3. Comparison of three logistic models for predicting the Structural Endpoint. None of the predictors is significant and none of the three models has any predictive power.

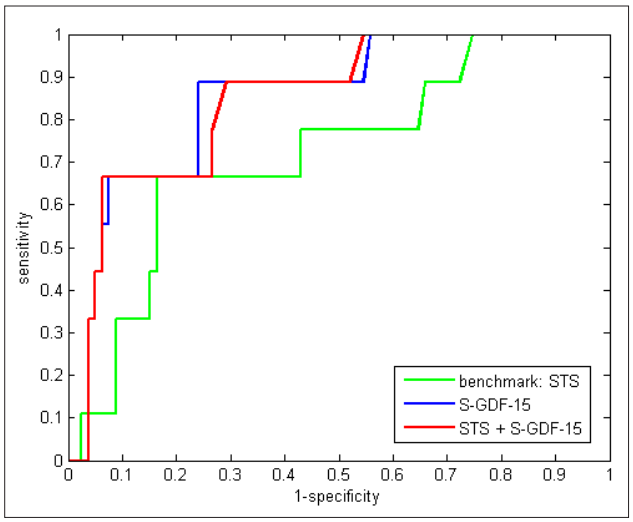

Fig. 4. Comparison of three logistic models for predicting of 1-year mortality. GDF15 is an excellent predictor in this case.

correlations between the STS score and adverse clinical outcomes following TAVI (Overall VARC-2 Endpoint, Systemic Endpoint), but no correlation with TAVI-related mortality, potentially due to significantly lower mortality rate in our cohort compared to previously published data. Results regarding the logistic EuroSCORE do not show any relationship to either the composite endpoint or mortality in our patient population. In view of these data, current clinical scoring systems require further optimization and modification in order to demonstrate more relevant predictive value, specifically in TAVI populations. Multiple clinical parameters for better risk stratification have already been identified such as the body mass index, pulmonary hypertension, the mean transvalvular gradient or left atrial diameter[27,28]. Another clinically based possibility of risk stratification before TAVI with proven value is frailty assessment[29-31]. However, data from recently published meta-analyses indicated need for further modification and standardization of this assessment concept for more consistent risk prediction[11,12].

Various circulating biomarkers have shown their potential for risk stratification in TAVI populations[32]. Periprocedural dynamic changes of Hs-cTnT and NT-proBNP levels could be associated with a worse prognosis based on data from small studies[33]. However, this strategy cannot be used for preprocedural risk prediction. The data regarding high baseline NT-proBNP are conflicting[34,35]. In the present study, we did not observe any association between baseline NT-proBNP levels and adverse clinical outcomes.

GDF15 has shown its potential for risk of mortality prediction in TAVI populations[21,22,36] and appears to be the most powerful prognostic predictor when added to the surgical scoring systems[22,36]. No studies have evaluated the role of GDF15 in predicting TAVI-related adverse outcomes such as bleeding or acute kidney injury. Our results show excellent predictive value of GDF15 with regard to the risk of mortality. This finding is consistent with data from previously published studies[21,22,36]. Moreover, this is the first study showing the potential role of GDF15 in predicting other adverse TAVI-related outcomes such as bleeding or acute kidney injury based on a significant relationship between GDF15 and the Systemic Endpoint. This was proven not only for the composite endpoint but also for its separate components in our patient cohort. These results are in agreement with studies reporting an association between elevated GDF15 and a risk of bleeding in patients following acute coronary syndrome[37,38]. In contrast to previously published data, we did not observe any incremental value of GDF15 and the STS score or logistic EuroSCORE combination in our predictive models. Based on the observed data, the present study supports a potential role of GDF15 in mortality and other adverse clinical outcomes such as bleeding complications or acute kidney injury prediction following TAVI.

Limitations

Our study has some limitations. The main limitation is the small sample size, partially caused by the COVID-19 pandemic as our TAVI program had to be interrupted for two months. Moreover, it was conducted in a single center and may have been affected by potential bias. Therefore, further integration of the GDF15 based predictive model into clinically useful risk stratification to improve TAVI-related mortality and morbidity requires additional verification in a larger multicenter trial.

CONCLUSIONS

In TAVI populations, preprocedural elevated GDF15 levels are associated with increased mortality and demonstrate their additional value in predicting adverse clinical outcomes such as bleeding and acute kidney injury. The STS score did not show any incremental prognostic value when added to a GDF15 based predictive model in this patient cohort.

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