International Journal of Cardiology 277 (2019) 54–59

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Insulin like growth factor binding protein 2 (IGFBP-2) for risk prediction in patients with severe aortic stenosis undergoing Transcatheter Aortic Valve Implantation (TAVI)☆

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ARTICLE INFO

Article history:
Received 18 July 2018
Received in revised form 26 August 2018
Accepted 24 September 2018
Available online 2 October 2018

Keywords:
IGFBP-2
Aortic stenosis
TAVI
Biomarker

ABSTRACT

Introduction: Severe aortic stenosis (AS) caused by degenerative calcification is the most frequent acquired valvular heart disease worldwide and mortality rates are considerably high. Transcatheter Aortic Valve Implantation (TAVI) is a well-established method for valve replacement in high risk patients with AS. However, there is a lack of reliable predictors for patients undergoing TAVI since commonly used scores were developed for surgical populations.
Materials and methods: 208 patients subjected to TAVI were included in this study. Plasma samples were obtained before TAVI and were evaluated for IGFBP-2 using commercially available ELISA kits. IGFBP-2 levels were analyzed for their ability for risk prediction after TAVI.
Results: IGFBP-2 levels measured before TAVI correlated significantly with left ventricular ejection fraction, EUROSCORE and other functional and prognostic parameters like the 6-minute walking test. When patients were retrospectively divided in two groups with a cut-off of serum IGFBP-2 levels of 275 ng/ml, IGFBP-2 was a strong predictor for 30-day and one-year mortality (3% vs. 11%, $p = 0.05$ and 18.2% vs. 46.2%; $p < 0.001$ respectively). Compared to an EUROSCORE above 20 or an STS score cut-off above 8, IGFBP-2 plasma levels above 275 ng/ml outperformed the established risk score for prediction of one-year mortality as assessed by NRI (0.65 95% CI 0.37–0.94; $p < 0.001$ and 0.54 95% CI 0.25–0.82; $p < 0.001$, respectively).
Conclusions: Our results indicate that IGFBP-2 could serve as new outcome predictor for patients undergoing TAVI procedure. By providing additional information to the commonly used EUROSCORE, IGFPB-2 analysis could further assist Heart Team decision making.

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1. Introduction

Degenerative stenosis of the aortic valve (aortic stenosis, AS) is the leading valvular heart disease in elderly patients in the western world. Even though cardiac surgery with operative valve replacement remains the gold standard for severe symptomatic AS, up to 30% of patients with symptomatic AS are not eligible for surgical valve replacement due to high age, frailty or comorbidities. The prevalence of severe AS is expected to rise further with increasing age in the population.

Previous studies have shown that mortality rates are substantially high among patients not undergoing valve replacement. About 50% of these patients die within the following three years [1]. Transcatheter Aortic Valve Implantation (TAVI) is a well-established method for valve replacement in patients suffering from AS at too high risk for conventional aortic valve replacement [2]. According to recent ESC and AHA/ACC guidelines TAVI is currently indicated in high

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
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https://doi.org/10.1016/j.ijcard.2018.09.091
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(and nowadays also in medium) risk patients suffering from severe degenerative AS [3]. In order to better judge whether a surgical or interventional approach is better suitable, the so-called "Heart Team" has been implemented as a central decision-making committee. This approach is also recommended in the European and American guidelines for the treatment of AS [3,4].

For risk assessment the EUROSCORE or the STS score have routinely been applied to estimate the risk for peri-interventional mortality in patients undergoing aortic valve replacement or TAVI. Nonetheless, decision making often remains very challenging, especially in high risk patients. Furthermore, the available risk stratification scores are based on surgical populations. Thus, they might overestimate the risk for patients undergoing TAVI procedure which is very likely to carry risks different from those of conventional aortic valve replacement [5]. Due to the above mentioned reasons the recent ESC guidelines for the management of valvular heart disease emphasizes the major limitations of both scoring systems for prediction of mortality in the vulnerable group of patients undergoing TAVI procedure [3]. We therefore sought to evaluate Insulin like growth factor binding protein 2 (IGFBP-2) as a potential biomarker for a better determination of the patient's peri-interventional risk when undergoing TAVI procedure.

Insulin-like growth factors (IGFs) are central peptide hormones that are involved in metabolic signaling, regulating glucose up-take, lipogenesis, glycogen storage and suppression of protein degradation and are expressed in most mammalian tissues [6]. So far six insulin-like growth factor binding proteins (IGFBPs) have been identified [7]. IGFBPs can coordinate and regulate IGFs biological activity affecting transportation of IGF, regulating clearance and modulating interaction and binding with IGF receptors. Furthermore, IGFPBs can mediate IGF-independent effects through integrin binding [7]. IGFBP-2 has been shown to exert differential effects via binding IGFs or modulation of IGF receptor signaling. In humans plasma levels of IGFBP-2 are only subjected to minimal circadian changes. Elevated IGFBP-2 levels seem to be protective against the development of diabetes as IGFBP-2 inhibits adipogenesis and can modulate insulin sensitivity [8]. Consistently, in obese patients levels of IGFBP-2 are decreased and low IGFBP-2 levels are associated with the development of diabetes [9]. However, in cardiovascular research, IGFBP-2 is regarded as a rather novel candidate as a biomarker as comparably few studies have investigated its use for risk assessment in patients suffering from heart disease. So far it has been shown that elevated IFGBP-2 concentrations were associated with long-term cardiovascular mortality in patients with peripheral artery disease and that IGFBP-2 levels were associated with left ventricular stroke volume in patients with AS [10,11]. Moreover IGFBP-2 was confirmed as a stroke risk marker [12].

In this study we sought to investigate whether IGFBP-2 can serve as a useful biomarker for risk prediction in patients undergoing TAVI procedure and how IGFBP-2 concentrations are associated with clinical parameters.

2. Methods

The protocol for this study was approved by the local Ethics Committee of the Friedrich Schiller University Jena, Germany. Written informed consent was obtained from all patients before being enrolled. The study was conducted in accordance to the principles of the 1975 Declaration of Helsinki and Good Clinical Practice.

2.1. Study protocol

All patients suffering from symptomatic severe AS that were admitted for TAVI to the university hospital of the Friedrich Schiller University Jena, Germany in the years 2010 to 2013 were enrolled in this study with a total number of 208 patients. Plasma samples were obtained before TAVI and analyzed for IGFBP-2 concentrations. Patients were followed-up over one year with clinical visits after three and six months. Before patients were enrolled in this study, the diagnosis of severe AS was confirmed accordingly to the current guidelines of the European Society of Cardiology. Transthoracic echocardiography was utilized to measure mean and peak pressure gradients (MPG and PPG), maximum velocity (Vmax) and aortic valve area (AVA) by continuity equation before TAVI implantation according to the current guidelines of the European Society of Cardiology. Furthermore, ECG, laboratory parameters, transesophageal echocardiography and coronary angiography was performed before patients underwent TAVI procedure.

Then, the patients' results were presented in the interdisciplinary Heart Team. Those patients that were considered not eligible for surgical valve replacement underwent transfemoral TAVI procedure.

Transfemoral TAVI was performed using a 14–21 French delivery sheath that was inserted in the femoral artery, depending on size and type of TAVI-device. In those patients that not already had an implanted pacemaker, a temporary pacemaker was introduced transcutaneously via transjugular access for peri-procedural rapid pacing. Balloon valvuloplasty was performed during rapid pacing. In the next step, implantation of the valve prosthesis (either Edwards Sapien XT, Corevalve, JenaValve, SJM Portico) was conducted. The artery access was closed with a closure device (Proglide; Abbott USA). The pharmacological regimen comprised of acetylsalicylic acid (100 mg) and clopidogrel (75 mg) for six months. After six month a monotherapy of 100 mg of acetylsalicylic acid was continued.

Functional parameters of the aortic valve implant determined by echocardiography at the follow-up visits after three months, six months and one year were not addressed in this study.

2.2. ELISA analysis of IGFBP-2

Plasma levels of IGFBP-2 were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Duoset DY674; R&D Systems, USA) according to the manufacturer's protocol. In short, serum samples and standard protein was added to the wells and incubated for 2 h. After this incubation period plates were washed three times. Then, a biotin-labelled secondary antibody was added and plates were incubated for another 2 h. Later, plates were washed again and Streptavidin-horseradish-peroxidase was added. Colour reaction was achieved using tetramethylbenzidine (TMB; Sigma Aldrich, USA). Optical density values were measured at 450 nm on an ELISA plate-reader (Bio-Rad Laboratories, Austria).

2.3. Statistical analysis

Statistical analysis was performed using SPSS (22.0, SPSS Inc., USA) and R (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/. Pearson correlation analysis was used to analyze the association of IGFBP-2 plasma levels with clinical, echocardiographic and laboratory patient parameters. Normally distributed data is given in mean ± standard error of the mean (SEM) and compared by Student's *t*-test. Non-normally distributed data is given as median ± inter-quartile-range (IQR) and compared by the Wilcoxon Matched-pairs test.

Survival was depicted using Kaplan-Meier method. Univariate Cox proportional hazards analysis was used to identify factors associated with an increased risk of death in patients undergoing TAVI procedure. Relevant candidate variables were analyzed in a univariate Cox regression model after review of available literature. ROC analysis was performed, AUC calculated and an optimal cut-off calculated by means of the Youden-Index. Patients were retrospectively divided in two cohorts: those above the optimal cut-off and those beyond this value. Short-term, i.e., 30-day-mortality, and mid-term, i.e., one-year-mortality were analyzed by chi-square test. For the multivariate regression model, confounders with a p-value < 0.10 in the univariate analysis were included, then a backward variable elimination was performed. Due to missing values, we only could use a total of 150 patients in the multivariate regression model which has to be stated as a major limitation. Elimination criterion was a p-value of >0.10. Continuous net reclassification index was calculated using package *predictABEL* function reclassification in R. A p-value of <0.05 was considered statistically significant.

3. Results

Patient characteristics are shown in Table 1. To investigate the role of IGFBP-2 for risk prediction in patients with AS undergoing TAVI procedure we performed ELISA analysis of plasma samples of all patients that underwent transfemoral TAVI in the years 2010 to 2013 in the University hospital of the Friedrich Schiller University Jena, Germany. Median plasma concentration in these patients was 227 ng/ml (IQR 150–381 ng/ml). The association of IGFBP-2 levels with other laboratory parameters is depicted in Supplemental Table 1.

IGFBP-2 levels correlated significantly with STS-Score and EUROSCORE ($r = 0.22$, $p < 0.001$ and $r = 0.22$ and $p < 0.001$, respectively), CRP and BNP ($r = 0.27$, $p < 0.001$ and $r = 0.41$ and $p < 0.001$, respectively), and inversely with left ventricular ejection fraction ($r = -0.16$, $p = 0.03$). Also, significant correlations were found for maximum velocity, mean gradients, pulmonary arterial pressure (PAP), left ventricular end-diastolic diameter (LVEDD) and tricuspid annular plane systolic excursion (TAPSE) before TAVI. Moreover, significant negative correlations

Table 1
Patient characteristics before TAVI procedure in the overall cohort and those with low or high IGFBP-2 levels.

Parameter	IGFBP2 >275 ng/ml		IGFBP2 <275 ng/ml		Overall cohort		
	Mean	SEM (±)	Mean	SEM (±)	Mean	SEM (±)	p value
Age (years)	80.93	0.52	80.66	1.11	80.85	0.49	0.80
Euroscore	20.86	1.14	26.22	1.79	22.55	0.98	0.01
STS score	3.56	0.20	4.20	0.34	3.76	0,17	0.09
LVEDD (mm)	48.61	0.68	48.60	1.14	48.61	0.58	0.99
LV ejection fraction (%)	57.57	1.52	54.46	2.37	56.67	1.28	0.27
Diabetes (%)	46		53		48		0.37
Arterial hypertension (%)	94		88		92		0.17
Coronary artery disease (%)	69		69		69		0.01
1VD	23		23		23		0.99
2VD	16		9		14		0.28
3VD	17		14		16		0.69
Myocardial infarction (%)	13		16		14		0.67
Stroke (%)	41		14		13		0.82
Peripheral artery disease (%)	22		19		21		0.71
COPD (%)	24		30		26		0.39
Major vascular complications (%)	9		8		9		0.50
Mitral valve insufficiency (MINS)							
MINS I (%)	55		53		55		0.88
MINS II (%)	37		34		36		0.75
MINS III (%)	7		10		8		0.57
Tricuspide valve insufficiency (TRINS)							
TRINS I (%)	56		48		54		0.41
TRINS II (%)	29		31		30		0.72
TRINS III (%)	14		20		16		0.38
Aortic valve insufficiency (AINS)							
AINS I (%)	59		47		55		0.13
AINS II (%)	17		19		18		0.85
AINS III (%)	3		5		3		0.68
NYHA stage							
NYHA I (%)	1		0		1		0.99
NYHA II (%)	15		11		14		0.51
NYHA III (%)	74		43		64		<0.001
NYHA IV (%)	10		46		22		<0.001

Patients were divided into two groups according to their IGFBP-2 serum levels with a cut-off of 275 ng/ml. Data are presented as absolute numbers or percentages as indicated. LVEDD: left ventricular end diastolic diameter. LV: left ventricular. VD: vessel disease.

were found for IGFBP-2 with results from 6-minute walk test (6MWT) one and six months after TAVI as shown in Table 2.

In order to analyze IGFBP-2 as a potential biomarker for prediction of 1-year mortality after TAVI, a Cox regression analysis was performed. IGFBP-2 plasma concentration was found to be associated with increased 1-year mortality (changes per ng/ml IGFBP-2 concentration; HR 1.002 95% (1.002 (1.001–1.003); $p < 0.001$). Further ROC analysis was conducted and AUC was calculated for IGFBP-2 plasma concentration (0.66 95% CI (0.58–073) and compared to EUROSCORE (0.61 95% CI (0.52–0.69) $p = 0.48$ vs. IGFBP-2) and STS score (0.53 95% CI (0.45–0.62), $p = 0.09$ vs. IGFBP-2), both established scores for prediction of mortality in patients undergoing aortic valve replacement. An optimal cut-off for our cohort of patients undergoing TAVI by means of the Youden-Index was calculated to be 275 ng/ml and patients were retrospectively divided in two cohorts in those above and those beyond this concentration. Mortality of both groups was then compared after 30 days and one year. One-month mortality was significantly higher in those patients with IGFBP-2 plasma levels above 275 ng/ml (3% vs. 11%, $p = 0.05$). Also after one year patients with IGFBP-2 levels above the optimal cut-off evidenced a significantly worsened outcome (18.2% vs. 46.2% mortality; $p < 0.001$) (Fig. 1). Compared to an EUROSCORE above 20, IGFBP-2 plasma levels above 275 ng/ml outperformed the established risk score for prediction of 1-year mortality as assessed by NRI (0.65 95% CI 0.37–0.94; $p < 0.001$) (Supplemental Fig. 1). Compared to an STS score cut-off above 8, IGFBP-2 plasma levels above 275 ng/ml outperformed the established risk score for prediction of 1-year mortality as assessed by NRI (0.54 95% CI 0.25–0.82; $p < 0.001$) (Supplemental Fig. 1).

Table 2
Correlation analysis of IGFBP-2 plasma levels with clinical and laboratory parameters.

Parameter	r	p-Value
STS score	0.22	<0.001
EUROSCORE	0.22	<0.001
CRP	0.27	<0.001
BNP	0.41	<0.001
EF	−0.16	0.03
LVEDD	0.01	0.86
PAP	0.22	0.01
TAPSE	0.41	0.03
Age	0.13	0.06
mPG pre TAVI	0.03	0.71
AVA pre TAVI	−0.01	0.84
Vmax pre TAVI (m/sec.)	−0.02	0.79
6MWT pre TAVI	−0.29	<0.001
6MWT after 1 month	−0.28	<0.001
6MWT after 6 month	−0.40	0.72

The correlation of IGFBP-2 plasma levels with clinical and laboratory parameters is shown. EF: ejection fraction. LVED: left ventricular end diastolic diameter. PAP: pulmonary artery pressure. mPG: mean pressure gradient. AVA: aortic valve area. 6MWT: 6 minute walking test.

We also sought to analyze potential confounders for association with one year mortality in a univariate analysis which is shown in Table 3. We then included confounders with $p < 0.10$ in the univariate analysis in a multivariate Cox regression analysis. Troponin I and sPAP were excluded from the multivariate analyses due to missing values. After correction for EUROSCORE (points), creatinine (in mM/l), CRP (in mg/dl) and six minute walking test (in m), IGFBP-2 plasma levels remained associated with 1-year mortality (HR 1.002 (1.001–1.003) $p = 0.001$ per ng/ml increase).

4. Discussion

This study shows that pre-interventional IGFBP-2 plasma levels represent a prognostic value for 30-day and one-year mortality in patients with severe aortic valve stenosis undergoing TAVI procedure. Furthermore, we could show that pre-interventional IGFBP-2 plasma concentrations inversely correlated with functional parameters like the 6 minute walking test before as well as 1 and 6 month after TAVI.

The EUROSCORE is a well-established score that is used by the heart team to calculate the peri-interventional risk for patients that are planned for TAVI procedure. However, the model was established for patients undergoing cardiac surgery. Thus there is some evidence that the EUROSCORE overestimates the peri-interventional risk for patients undergoing TAVI procedure [13,14]. Congruently, in our patient cohort, the EUROSCORE predicted a mortality rate of 23%. However, the observed 30-day mortality in our cohort was as low as 6%. Hence there is the need for a more precise prediction tool for post-TAVI outcome [5]. Accordingly, our study revealed that in comparison to an EUROSCORE above 20, or an STS score cut-off above 8, IGFBP-2 plasma levels above 275 ng/ml outperformed the established risk score for prediction of one-year mortality as assessed by NRI.

Due to the abovementioned heart-team decision process, the patient collective included in our study comprised a cohort of very old patients with a high burden of comorbidities since only high risk patients were subjected to TAVI-Implantation during recruitment to the current study, whereas intermediate or low risk patients were subjected to surgical aortic valve replacement. Thus, the cohort of patients analyzed in this study was quite homogenous in terms of age, pre-interventional aortic valve area and pressure gradients, left ventricular ejection fraction and comorbidities such as coronary artery disease. Hence, in

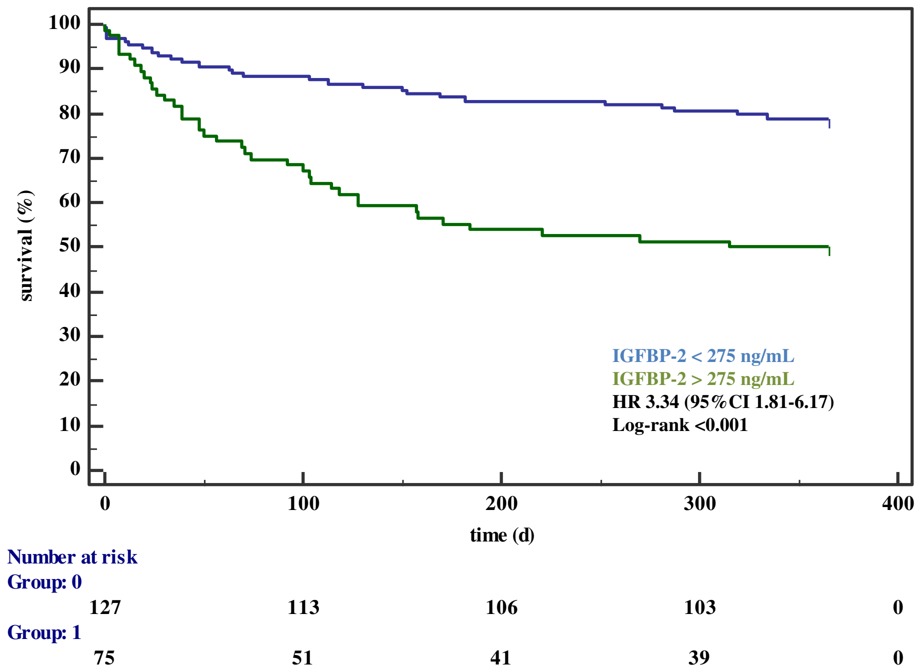

Fig. 1. Kaplan-Meier survival analyses. Kaplan-Meier curve showing a significantly heightened mortality rate in patients with IGFBP-2 levels above a cut-off of 275 ng/ml. Number of events (death): 65, number censored: 139. Mean follow-up: 278 days, 95% CI: 259–297 days. Group 0: IGFBP-2 < 275 ng/ml, Group 1: IGFBP-2 > 275 ng/ml.

our patient collective the IGFBP-2 plasma levels showed a higher predictive power than the above mentioned historical hard predictors.

In view of the limited applicability of traditional scores like the EUROSCORE for the selected patient collective undergoing TAVI procedure new prognostic indices of survival among AS patients like the assessment of myocardial fibrosis have been recommended. It has been shown that measurement of myocardial fibrosis by cardiovascular magnetic resonance using myocardial LGE prior to aortic valve replacement for AS is a promising risk predictor [15,16]. However, cardiovascular magnetic resonance is a cost intensive tool not applicable for every patient due to several contraindications. In contrast, determination of IGFBP-2 plasma levels is less cost intensive and can be applied in all patients.

IGFBP-2 is the second most abundant circulating IGFBP [17] mediating its biological effects through IGF dependent as well as through IGF independent pathways [18–20]. Previous studies have shown that IGFBP-2 levels correlate with insulin sensitivity and that decreased IGFPB-2 concentrations are a marker for the metabolic syndrome

Table 3
Results of the univariate and the multivariate regression analysis models.

Pre-interventional values	Univariate HR [95% CI]	p-Value	n	Multivariate HR [95% CI]	p-Value	n
EUROSCORE	1.03 [1.01–1.05]	0.01	149	1.02 [1.00–1.04]	0,054	130
STS score	1.06 [0.95–1.19]	0.29	146			
Creatinine (mM/l)	1.003 [1.000–1.006]	0.04	148	0.999 [0.994–1.003]	0,54	
CRP (mg/dl)	1.006 [1.000–1.013]	0.06	144	1.006 [0.998–1.014]	0,13	
LVEDD (mm)	1.04 [1.00–1.08]	0.045	111			
Coronary artery disease	0.84 [0.45–1.66]	0.66	150			
Hypertension	22.16 [0.09–5645.22]	0.27	150			
Diabetes mellitus	1.36 [0.74–2.50]	0.33	150			
Age (years)	0.98 [0.95–1.02]	0.32	150			
Hemoglobin (mmol/l)	0.88 [0.66–1.17]	0.37	144			
LV ejection fraction (%)	0.99 [0.97–1.003]	0.11	142			
Major vascular complication	1.52 [0.60–3.87]	0.38	149			
Troponin I (ng/ml)	1.28 [1.07–1.54]	0.01	64			
BNP (pg/ml)	1.00 [1.00–1.00]	0.25	70			
sPAP (mm Hg)	1.02 [1.00–1.05]	0.03	115			
AVA (cm^2)	0.29 [0.04–2.00]	0.21	135			
COPD	1.53 [0.81–2.88]	0.19	150			
pAVK	1.50 [0.77–2.93]	0.24	150			
Stroke	1.36 [0.60–3.06]	0.46	150			
Mitral valve insufficiency III	0.73 [0.23–2.38]	0.61	138			
Tricuspide valve insufficiency III	1.38 [0.63–3.04]	0.42	131			
Mean pressure gradient	0.99 [0.97–1.01]	0.22	142			
Six minute walking test (m)	0.997 [0.993–1.000]	0.054	135	1.00 [0.996–1.015]	0,98	
IGFBP-2 (pg/ml)	1.002 [1.001–1.003]	<0.001	149	1.002 [1.001–1.003]	0,001	

Analysis of different parameters with one-year mortality in a univariate analysis is shown in the left part of the table. Parameters with p < 0.10 in the univariate analysis were included in a multivariate Cox regression analysis. Troponin I and sPAP were excluded from the multivariate analyses due to missing values. After correction for potential confounders IGFBP-2 plasma levels remained associated with one-year mortality (HR 1.002 (1.001–1.003) p = 0.001 per ng/ml increase). Impact of the factors on one-year mortality is presented as Hazard Ratio (HR) and 95% Confidence Interval (95% CI). LVEDD: left ventricular end diastolic diameter. LV: left ventricular. sPAP: systolic pulmonary artery pressure. AVA: aortic valve area.

[9,21,22]. Consistently, overexpression of human IGFBP-2 in mice leads to a reduced susceptibility to obesity and improved insulin sensitivity [8]. However, a newer study suggests that higher IGFBP-2 levels in diabetics are associated with a longitudinal decline in renal function thus Narayanam and colleges suggest IGFBP-2 as a marker for deterioration in renal function in patients with type 2 diabetes. More recently, IGFBP-2 was confirmed as new risk marker in the setting of cardiovascular diseases. Thus, elevated IGFBP-2 levels were associated with a higher stroke risk in postmenopausal women as well as with cardiovascular mortality in patients with lower-extremity peripheral artery disease.

Recently, IGFPB-2 was suggested as predictor in patients with mild to moderate AS [11]. Carter et al. reported that lower IGFBP-2 levels were correlated with a lower cardiac stroke volume index, which is considered as a predictor of worse outcome in the mild to moderate AS population. However, a correlation of IGFBP-2 levels with relevant clinical parameters as the 6-minute walk test or mortality rates was not shown [11]. To our best knowledge our study is the first analysis revealing that pre-interventional IGFBP-2 plasma levels are a predictor of short-term and 1-year mortality in patients with severe AS undergoing TAVI. While the above mentioned study reported a correlation of lower IGFBP-2 levels with a predictor of worse outcomes in patients with AS we could show that higher IGFBP-2 levels are directly correlated to short-term and 1-year mortality in a AS population. The divergent results might be caused by the fact that Carter et al. analyzed a patient cohort showing mild to moderate AS whereas we explored the data of a cohort of patients with severe AS [11]. Furthermore we showed a correlation of IGFBP-2 levels with the heard endpoint of death whereas Carter and colleagues only reported a correlation between the IGFBP-2 levels and the cardiac stroke volume index as a marker for worse outcome in patients with AS.

4.1. Limitations

Our study is single-centered and of retrospective nature. We do not have functional data of our patients in the follow-up over more than one year, therefore a composite endpoint evaluation of e.g. re-hospitalization and death is lacking. Moreover, some laboratory and echocardiographic parameters were missing in some patients. Furthermore, functional parameters of the prosthetic valve like the aortic valve area and the pressure gradients determined at the follow-up visits were not taken into account for this study. Previous studies showed that the use of the continuity equation may not accurately assess aortic valve area among TAVI patients and the usual definition of patient-prosthesis mismatch (PPM) may not be adequate [23]. Nonetheless, a large body of evidence supports the relevant and significant predictive role played by the hemodynamic performance of the prosthesis implanted among severe AS patients, with specific regards to PPM [24,25]. Thus, the lacking of the analysis of PPM in this study might represent a relevant confounder with regard to the analyzed 1-year mortality.

Nonetheless, we think that our study proposes a novel biomarker for risk stratification in patients evaluated for TAVI. Prospective and multi-centered studies to evaluate novel cardiovascular biomarkers in patients with aortic stenosis and TAVI are warranted.

5. Conclusion

In conclusion, in the analysis of pre-TAVI IGFBP-2 levels in a large cohort of patients, IGFBP-2 was a strong predictor of 30-day and one-year mortality. Based on these results we assume that IGFBP-2 could serve as very helpful indicator for assessing the patient's cardiovascular risk before undergoing TAVI procedure. We think that determining plasma IGFBP-2 levels in patients planned to undergo TAVI could further assist Heart Team decision making. In high risk patients, IGFBP-2 could also be of importance for a better estimation whether TAVI procedure would be feasible. However, further prospective studies are warranted in order to substantiate this hypothesis. Nevertheless, we think that IGFBP-2 could be considered as a useful clinical biomarker in patients with AS undergoing TAVI procedure.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.091.

Conflict of interest

All authors declare to have no conflict of interest.

Acknowledgments

J.M., M.L. and B.W. prepared the manuscript, V.P. performed ELISA assays, B.W. and V.R. and G.Z. performed statistical analysis. M.K., L.B., P.C.S, M.F., P.R., H-R.F. and A.L. revised the manuscript and supported the realization of the study. C.J., M.K., M.F., U.H., H.F. provided infrastructure and gave advice for the planning of the study. C.J. and U.H. provided funding. A.L. performed TAVI procedure, implemented the concept for the study and enrolled patients. G.Z. provided helpful suggestions concerning the NRI analyses. All authors carefully red and approved the final manuscript.

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