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RESEARCH ARTICLE

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Tumor necrosis factor alpha—an underestimated risk predictor in patients undergoing transcatheter aortic valve replacement (TAVR)?

Moritz Mirna[1] | Mario Holnthoner[1] | Albert Topf[1] | Peter Jirak[1] | Dzeneta Fejzic[1] | Vera Paar[1] | Jörg Kellermair[2] | Hermann Blessberger[2] | Christian Reiter[2] | Jürgen Kammler[2,3] | Lukas J. Motloch[1] | Christian Jung[4] | Daniel Kretzschmar[5] | Marcus Franz[5] | Brunilda Alushi[6] | Alexander Lauten[6] | Uta C. Hoppe[1] | Clemens Steinwender[2,3] | Michael Lichtenauer[1]

[1]Department of Internal Medicine II, Division of Cardiology, Paracelsus Medical University of Salzburg, Salzburg, Austria

[2]Department of Cardiology, Kepler University Hospital, Medical Faculty, Johannes Kepler University Linz, Linz, Austria

[3]Paracelsus Medical University of Salzburg, Linz, Austria

[4]Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University Duesseldorf, Dusseldorf, Germany

[5]Department of Cardiology, Clinic of Internal Medicine I, Universitätsherzzentrum Thüringen, Friedrich Schiller University Jena, Jena, Germany

[6]Department of General and Interventional Cardiology and Rhythmology, Helios Clinic, Erfurt, Germany

Correspondence
Moritz Mirna, Department of Internal Medicine II, Division of Cardiology, Universitätsklinikum der Paracelsus Medizinischen Universität, Müllner Hauptstraße 48, 5020 Salzburg, Austria.
Email: m.mirna@salk.at

Abstract

Background: Systemic inflammation has been identified as a major cardiovascular risk factor in patients undergoing transcatheter aortic valve replacement (TAVR), yet currently, it is not adequately portrayed in scores for pre-interventional risk assessment. The aim of this study was to investigate the predictive ability of TNF-α in TAVR.

Methods: A total of 431 patients undergoing transfemoral TAVR were enrolled in this study. Blood samples were drawn prior to intervention, 24 h post-intervention, 4, 5, and 7 days post-intervention, and 1, 3, and 6 months post-TAVR.

Results: In a univariate Cox proportional hazard analysis, plasma concentrations of TNF-α after 24 h and after 5 days were associated with mortality after 12 months (after 24 h: HR 1.002 (1.000–1.004), $p = 0.028$; after 5d: HR 1.003 (1.001–1.005), $p = 0.013$). This association remained significant even after correction for confounders in a multivariate Cox regression analysis. Additionally, cut-offs were calculated. Patients above the cut-off for TNF-α after 5d had a significantly worse 12-month mortality than patients below the cut-off (18.8% vs. 2.8%, $p = 0.046$).

Conclusion: Plasma levels of TNF-α after 24 h and 5 days were independently associated with 12-month mortality in patients undergoing TAVR. Thus, TNF-α could represent a novel biomarker for enhanced risk stratification in these patients.

KEYWORDS
biomarkers, inflammation, transcatheter aortic valve replacement, tumor necrosis factor alpha

1 | INTRODUCTION

Aortic valve stenosis constitutes the most frequent valvular heart disease in the Western world, and its prevalence is expected to increase further due to demographical changes and improved life expectancy.[1] Transcatheter aortic valve replacement (TAVR) allows causative treatment in patients at prohibitive surgical risk who were previously treated with a conservative approach only.[2] Promising results of several previous trials have resulted in a trend to expand the spectrum of patients considered suitable for TAVR to patients at lower risk,[3–6] which is why the annual number of TAVR procedures is very likely to increase unabatedly in the near future.[7]

However, various studies have reported that TAVR can also be associated with periprocedural complications such as stroke, vascular complications, or the need for a permanent pacemaker,[8,9] and according to a recent trial based on the FRANCE-TAVI registry, intrahospital mortality is currently estimated at a high 5.6% for self-expanding valves.[10] Consequently, pre-interventional risk assessment evaluated, for example, by calculating EuroSCORE[11,12] or Society of Thoracic Surgeons Score (STS-Score),[13] both of which were developed to predict mortality in patients undergoing cardiac surgery, has become an integral component of clinical practice. However, EuroSCORE and STS-Score were recently found to have suboptimal discriminatory power and calibration in patients undergoing TAVR,[14–16] which is why further identification of individual risk predictors of affected patients is urgently warranted for clinical practice.

Systemic inflammation was previously identified as a major cardiovascular risk factor and was associated with both the progression of calcific aortic valve stenosis and adverse outcomes in patients undergoing thoracic surgery.[17,18] Furthermore, a recent study by Sinning et al. reported that the presence of systemic inflammatory response syndrome (SIRS), with its concomitant increase in IL-6, IL-8, leukocyte count, C-reactive protein, and procalcitonin, was a major risk predictor for mortality after 30 days and 12 months in patients undergoing TAVR.[19] However, systemic inflammation is currently not adequately depicted in validated scoring systems, which justifies further scientific attention to this matter. Tumor necrosis factor alpha (TNF-α) constitutes a cytokine secreted by macrophages/monocytes, T lymphocytes, and natural killer (NK) cells, which plays a pivotal role in different inflammatory, apoptotic, and rheumatic processes. TNF-α binds to the membrane-bound TNFR-1 and TNFR-2 receptors, which subsequently initiate intracellular signaling pathways, such as the nuclear factor kappa B (NF-κB) pathway, thus leading to gene transcription.[20–22] Similar to other pro-inflammatory cytokines, there is increasing evidence that TNF-α is implicated in the pathophysiology of atherosclerosis and other cardiovascular diseases.[23,24] In this regard, a recent study by Yuan et al. reported an increased risk for coronary artery disease or ischemic stroke in the presence of elevated TNF-α concentrations (OR 2.25 and 2.27 per unit increase in natural log-transformed TNF-α levels).[25]

The increasing number of TAVR procedures, the suboptimal predictive ability of current scoring systems, and growing evidence of systemic inflammation as a key regulator in cardiovascular diseases further warrant an investigation of the "inflammasome" of patients undergoing TAVR. Therefore, we investigated the predictive ability of the serum concentrations of TNF-α in affected patients in this study.

2 | MATERIALS AND METHODS

The study protocol was reviewed and approved by the ethics committee of the Friedrich Schiller University, Jena, Germany (No.: 3237-09/11), the ethics committee of the state of Upper Austria (EK E-41–16), and the ethics committee of the state of Salzburg, Austria (EK 415-E/1969/5-2016) prior to enrollment. The study was conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice.

In total, 431 patients were enrolled in this study; informed consent was obtained from all participants prior to enrollment. Patients with symptomatic severe aortic valve stenosis admitted for transfemoral transcatheter aortic valve replacement (TAVR) to one of the three study centers (university hospital of the Friedrich Schiller University, Jena, Germany, university hospital of the Johannes Kepler University, Linz, Austria, or university hospital of the Paracelsus Medical Private University, Salzburg, Austria) were recruited into the study between 2010 and 2018. Diagnosis of aortic valve stenosis was confirmed by transthoracic echocardiography according to the current guidelines of the European Society of Cardiology (ESC),[26] and blood samples were collected prior to TAVR, after 24 h, at days 4, 5, and 7 after TAVR, and during the follow-up visits after 1 month, 3 months, and 6 months post-procedure.

The primary endpoint was all-cause mortality after 12 months.

2.1 | TAVR procedure

All TAVR procedures were conducted using a transfemoral approach. Transfemoral access was achieved by inserting a 14- to 21-French delivery system into the femoral artery. Then, the valve prosthesis (Medtronic CoreValve Evolut R, Edwards Sapien XT, Medtronic CoreValve, JenaValve, or SJM Portico) was implanted with prior balloon valvuloplasty (BAV) in the majority of patients (72.8%, $n = 319$). The femoral insertion site was closed by applying a closure device (ProGlide, Abbott).

Dual antiplatelet therapy with acetylic salicylic acid and clopidogrel were administered for 6 months in all patients; follow-up visits were conducted 1, 3, 6, and 12 months after the procedure.

2.2 | Laboratory tests

Biomarker concentrations of TNF-α were determined by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (DY210-05; R&D Systems). The preparation of all reagents was conducted according to the manufacturer's instructions. In brief, 96-well plates (Nunc MaxiSorp Flat-Bottom 96-Well Plate; VWR International GmbH) were coated with an appropriate capture antibody and incubated overnight at room temperature. The next day, ethylenediaminetetraacetic acid (EDTA) samples and standard samples were transferred into the plate wells and incubated for 2 h. Then, plates were washed with a phosphate-buffered saline (PBS)/Tween-20 solution (Sigma-Aldrich) and a biotin-labeled antibody was added. After another 2 h and a second washing step, streptavidin horseradish peroxidase (streptavidin-HRP), diluted to 1:40 with 1% bovine serum albumin (BSA) in PBS, was added. Lastly, tetramethylbenzidine (TMB; Sigma-Aldrich) was added, serving as the substrate to obtain a yellow color reaction. Subsequently, after 20 min of incubation time, the color reaction was stopped by addition of 2 *N* sulfuric acid (H_2SO_4). Optic density was measured at 450 nm with a microplate absorbance reader (iMark Microplate Absorbance Reader; Bio-Rad Laboratories).

2.3 | Statistical analyses

Statistical analyses were conducted using SPSS (version 22.0; SPSS Inc.,) and R (version 4.0.2.; R Core Team (2013), R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Data distribution, skew, and kurtosis were assessed visually with histograms and complemented by performing a Shapiro-Wilk test. Medians were compared by using a Mann-Whitney *U* test or a Kruskal-Wallis test, and categorical data were analyzed using Fisher's exact test. Spearman's rank correlation coefficient was used for correlation analysis, univariate Cox proportional hazard analysis was used to analyze parameters associated with increased risk after TAVR. ROC analysis and AUC measurement were calculated for TNF-α, and a cut-off was calculated by means of the Youden Index.[27] For multivariate regression, confounders with $p < 0.10$ in the univariate Cox regression were included. Multicollinearity was excluded by applying the collinearity diagnostics tool by SPSS, variance inflation factors (VIFs) are depicted in the Figure and Table Legend. A *p*-value of < 0.05 was considered to be statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

The median age of all patients enrolled was 83 years (IQR 79–86), and the majority of patients was female (51.3%). The median estimated glomerular filtration rate (eGFR) at baseline was 59.5 ml/min/1.73m² (IQR 45.2–70.0), whereas the median C-reactive protein (CRP) was 0.3 mg/dl (IQR 0.0–1.0).

At baseline, the median left ventricular (LV) systolic function was 60% (IQR 50–65) and the median mean pressure gradient (MPG) of the aortic valve was 46 mmHg (IQR 40–58; see Table 1). TAVR resulted in a significant reduction in median MPG by the 3 months follow-up visit compared with pre-procedural values (median 9 mmHg (IQR 6–11), $p < 0.0001$; see Table 1).

TABLE 1 Baseline characteristics of patients enrolled

	Median	*IQR*
Age (years)	83	79–86
BMI (kg/m²)	27.3	24.2–30.5
Hemoglobin (mmol/l)	7.8	7.0–8.6
CRP (mg/dl)	0.3	0.0–1.0
BNP (ng/l)	994.0	459.5–2468.0
Creatinine (µmol/l)	97.2	79.6–122.0
eGFR (ml/min/1.73m²)	59.5	45.2–70.0
EF (%)	60	50–65
Mean pressure gradient (mmHg)	46	40–58
	%	*n*
Female gender (total n = 318)	51.3	189
Diabetes mellitus (total n = 431)	36.0	155
Arterial hypertension (total n = 431)	86.3	372
Coronary artery disease (total n = 431)	70.3	303
-Single-vessel disease	39.7	56
-Double-vessel disease	25.5	36
-Triple-vessel disease	34.8	49
History of stroke (total n = 427)	5.4	23
Peripheral artery disease (total n = 431)	13.7	59
	%	*n*
Prior balloon valvuloplasty	72.8	310
Type of valve prosthesis		
-Medtronic CoreValve Evolut R	43.7	187
-Edwards Sapien XT	37.6	161
-SJM Portico or JenaValve	10.7	46
-Medtronic CoreValve	7.9	34

Abbreviations: BMI, Body mass index; BNP, Brain natriuretic peptide; CRP, C-Reactive protein; EF, Ejection fraction; eGFR, Estimated glomerular filtration rate.

Balloon valvuloplasty was conducted in the majority of patients (72.8%, *n* = 310). The most frequently implanted valve prosthesis was the Medtronic CoreValve Evolut R (43.7%, *n* = 187; see Table 1).

3.2 | Biomarker concentrations

TAVR resulted in a 1.6-fold increase in the mean plasma concentration of TNF-α after 5 days when compared to the respective baseline values (baseline: mean 26.8 ± 115.0 pg/ml vs. after 5 d: mean 42.0 ± 151.3 pg/ml, $p = 0.269$). Thereafter, TNF-α again decreased until 6 months after the procedure (6 months: mean 14.5 ± 55.2 pg/ml; see Table 2 and Figure 1). Notably, plasma concentrations

TABLE 2 Plasma concentrations of TNF-α throughout the study

	Pre ($n = 408$)		24 h ($n = 201$)		4 Days ($n = 73$)		5 Days ($n = 85$)		7 Days ($n = 66$)		1 Month ($n = 66$)		3 Months ($n = 151$)		6 Months ($n = 65$)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
TNF-α (pg/ml)	26.8	115.0	27.4	110.3	20.0	81.7	42.0	151.3	13.2	54.2	14.3	62.1	27.7	102.2	14.5	55.2

Abbreviations: SD, Standard deviation; TNF-α, Tumor necrosis factor alpha.

throughout the whole study remained statistically insignificant when a Kruskal-Wallis test was applied ($p = 0.183$).

3.3 | Correlation analysis

Biomarker concentrations of TNF-α after 7 days showed a significant inverse correlation with eGFR (TNF-α: after 7 d: rs: −0.312, $p = 0.011$), whereas plasma levels at 3 months correlated positively with body mass index (BMI; TNF-α: after 3 months: rs: 0.195, $p = 0.048$; see Table 3). Furthermore, TNF-α after 7 days and 1 month correlated inversely with pre-interventional New York Heart Association (NYHA) stage (TNF-α: after 7 days: rs: −0.255, $p = 0.041$, TNF-α: after 1 month: rs: −0.263, $p = 0.034$; see Table 3).

Notably, concentrations of TNF-α after 24 h, 4 days, 5 days, and 6 months did neither correlate with any of the investigated baseline laboratory or echocardiographic parameters, nor with parameters at 12 months follow-up.

3.4 | Periprocedural complications and outcomes

In-hospital mortality was 6.0% ($n = 26$), whereas mortality after 30 days was 6.3% ($n = 27$) and mortality after 3 months was 11.1% ($n = 42$). Mild vascular complications occurred in 16.1% ($n = 69$), and severe vascular complications (eg, major bleedings) occurred in 6.1% ($n = 26$). Immediately after TAVR, moderate para-/valvular leaks were documented in 11.1% ($n = 42$), whereas severe regurgitations occurred only in 3 patients (0.8%). Stroke within 30 days occurred in 18 patients ($n = 4.3\%$).

Data on mortality after 12 months were available for 319 patients (74.0%). Of these, 57 patients had died, resulting in a 12-month mortality rate of 17.9%. Echocardiographic follow-up data after 12 months were available for 156 patients only (36.2%). Of these, 6 patients had moderate para-/valvular leaks and 3 moderate or severe flow acceleration over the aortic valve as defined by the VARC-2 criteria.[28] The median MPG of the aortic valve prosthesis after 12 months was 8 mmHg (IQR 6–11).

3.5 | Cox regression analyses and TNF-α cut-offs

In univariate Cox proportional hazard analysis, plasma concentrations of TNF-α after 24 h and after 5 days were independently associated with mortality after 12 months (after 24 h: HR 1.002 (1.000–1.004), $p = 0.028$; after 5 d: HR 1.003 (1.001–1.005), $p = 0.013$). Further ROC analysis was conducted and AUC was calculated for TNF-α after 24 h and after 5 days (after 24 h: AUC 0.73; after 5 d: AUC 0.80). Optimal cut-offs for TNF-α after 24 h and after 5 days were calculated by means of the Youden Index (after 24 h: 10.74 pg/ml (sens.: 75%, spec.: 76%); after 5 d: 5.77 pg/ml (sens.: 75%, spec.: 72%)). In the following analysis, 12-month mortality rate was significantly worse in patients above the calculated cut-off for

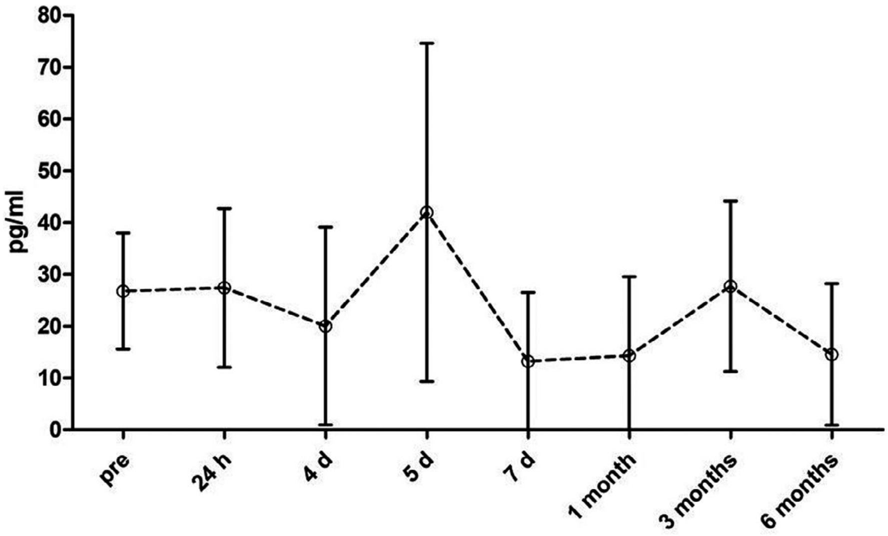

FIGURE 1 Plasma levels of TNF-α throughout the study (depicted are mean +95% CI). *Abbreviations*: *d, Days*

TNF-α after 5 days (18.8% vs. 2.8%, OR 8.07 (95% CI 0.77–84.78), $p = 0.046$) when compared to patients below the cut-off. Moreover, a higher mortality rate in patients above the calculated cut-off for TNF-α after 24 h was observed; however, this finding remained statistically insignificant (13.8% vs. 5.7%, $p = 0.134$), possible due to the low number of events in the group.

For multivariate Cox regression analysis with TNF-α concentrations after 24 h and after 5 days, we further performed univariate Cox regression analysis in possible confounders associated with mortality after TAVR. Here, baseline serum creatinine, C-reactive protein (CRP), and left ventricular (LV) systolic function, as well as the presence of peripheral artery disease and diabetes mellitus, were associated with mortality (see Table 4). We then included confounders with $p < 0.10$ in a multivariate Cox regression analysis. After correction for serum creatinine, CRP, LV systolic function, PAD, and diabetes mellitus, the association between TNF-α concentrations after 24 h and after 5 days and mortality remained statistically significant (see Table 4).

4 | DISCUSSION

Because of demographical changes and improved life expectancy, the prevalence of patients with severe aortic valve stenosis is steadily increasing.[29] On a daily basis, clinicians have to face the decision whether SAVR, TAVR, or rather a conservative approach is indicated in the individual patient. In this regard, risk stratification by established risk scores has become an integral component of pre-interventional assessment of patients undergoing TAVR. However, due to lack of TAVR-specific scoring systems for individual risk prediction, surgical scores, such as STS-Score or EuroSCORE, which do not adequately predict adverse outcomes in patients undergoing interventional valve replacement,[14–16] are currently in use in these patients.[30] With steadily increasing numbers of TAVR procedures, the need for a refinement of existing systems on peri-interventional risk stratification is evident. Given the suboptimal predictive ability of current scoring systems and growing evidence of systemic inflammation as a key regulator in cardiovascular diseases, novel predictors for improved risk evaluation are warranted for clinical practice. In this regard, the application of a risk score including underlying diseases and biomarkers has already proven its value in other disease entities such as sepsis.[31]

As inflammatory biomarkers were reported to be indicative of disease progression in aortic valve stenosis, their implementation into future scoring systems might prove valuable for individual risk evaluation in patients undergoing TAVR.[19,32] Furthermore, systemic inflammatory response syndrome was found to be an independent predictor of mortality in TAVR, emphasizing the impact of systemic inflammation in the context of valve replacement.[19] According to a previous study, peri-interventional inflammatory biomarkers may also be indicative of worse left ventricular mass index, global longitudinal strain, and ventricular recovery after TAVR, and why inflammatory biomarkers might be further helpful for the prediction of functional left ventricular response in patients with low-flow/low-gradient aortic stenosis.[33] However, established risk scores such as EuroSCORE and STS-Score do not incorporate inflammatory activity, thus leaving a blind spot in cardiovascular risk prediction in patients undergoing interventional valve replacement.

TNF-α represents one of the most extensively studied inflammatory biomarkers in humans, is currently established in clinical routine through uncomplicated laboratory analysis and rapidly available test results, and has demonstrated clinical relevance in rheumatic and autoimmunological disease entities.[34] While other inflammatory biomarkers such as CRP and leukocyte count were already shown to be associated with mortality after TAVR,[19] studies on the prognostic impact of TNF-α in affected patients are comparatively scarce. In fact, previous studies mainly reported descriptive results concerning the plasma concentration of this established inflammatory biomarker in patients undergoing interventional aortic valve replacement. For example, Sulzenko et al. recently investigated degenerative changes in patients undergoing SAVR and TAVR, and reported higher plasma levels of TNF-α in the TAVR group at baseline, as well as at one-year

TABLE 3 Correlation of biomarker concentrations with clinical and laboratory parameters

		Age	BMI, pre. (kg/m²)	NYHA stage, pre.	EF, pre. (%)	MPG, pre. (mmHg)	Hemoglobin, pre. (mmol/l)	CRP, pre. (mg/dl)	BNP, pre. (pg/ml)	eGFR, pre. (ml/min/1.73 m²)	NYHA stage, 12 months	MPG, 12 Months (mmHg)	VARC–2 - AV flow acc. after 12 Months
TNF-α, pre. (pg/ml)	r_s	−0.004	0.042	0.057	−0.052	0.013	−0.038	0.048	−0.033	−0.073	−0.011	−0.010	0.075
	p-value	0.936	0.518	0.324	0.340	0.801	0.467	0.340	0.583	0.149	0.924	0.908	0.587
TNF-α, 7 days (pg/ml)	r_s	−0.081	−0.016	−0.255	0.091	−0.194	−0.206	0.079	−0.033	−0.312	0.544	0.213	0.113
	p-value	0.518	0.899	0.041	0.552	0.130	0.100	0.529	0.851	0.011	0.456	0.555	0.757
TNF-α 1, month (pg/ml)	r_s	0.023	0.076	−0.263	0.066	−0.121	−0.146	0.070	−0.026	−0.236	0.544	0.529	0.586
	p-value	0.857	0.543	0.034	0.667	0.348	0.245	0.578	0.881	0.056	0.456	0.116	0.075
TNF-α, 3 months (pg/ml)	r_s	−0.097	0.195	−0.111	0.082	0.004	−0.068	0.065	−0.085	−0.099	−0.061	0.114	0.262
	p-value	0.237	0.048	0.260	0.380	0.959	0.411	0.428	0.392	0.228	0.686	0.328	0.147

Abbreviations: BMI, Body mass index, BNP; Brain natriuretic peptide; CRP, C-Reactive protein; EF, Ejection fraction; eGFR, Estimated glomerular filtration rate; flow acc, Flow acceleration; MPG, Mean pressure gradient; NYHA, New York Heart Association; r_s, Correlation coefficient; TNF-α, Tumor necrosis factor alpha; VARC-2, Valve Academic Research Consortium.

and two-year follow-up,[35] which, however, could in part be attributed to a higher disease burden in TAVR patients. Furthermore, TNF-α was shown to be related to postoperative inflammatory response after SAVR and TAVR, while higher levels were observed in patients post-SAVR.[36]

In concurrence with the descriptive results of former analyses, our study contributes the first outcome data on TNF-α in patients undergoing TAVR, suggesting a considerable prognostic significance of this biomarker in peri-interventional risk stratification. In our study cohort, TAVR led to a 1.6-fold increase in the plasma concentrations of TNF-α, indicating an early post-procedural inflammatory response. Additionally, elevated plasma levels of TNF-α after 24 h and 5 days were independently associated with 12-month mortality (after 5 d: HR 1.003 (1.001–1.005), $p = 0.013$), which even remained statistically significant after correction for possible confounders in a multivariate Cox regression model. When calculating cut-offs for TNF-α after 24 h and 5 days, patients above the cut-off for TNF-α after 5d (5.77 pg/ml (sens.: 75%, spec.: 72%)) again had a significantly worse 12-month mortality than patients below the cut-off (18.8% vs. 2.8%, $p = 0.046$).

Notably, although systemic inflammation has been identified as a pivotal driver of degenerative processes in prosthetic heart valves,[32,37] we did not observe a correlation of the biomarker concentrations of TNF-α with echocardiographic outcome data after 12 months in our study cohort. However, since echocardiographic data were only available for 156 patients, our study might be underpowered in this regard. Further trials on this matter are certainly warranted.

In conclusion, based on the findings of our study, TNF-α could constitute a novel independent risk predictor in patients undergoing interventional valve replacement. In this regard, our findings are in line with former studies on the prognostic impact of inflammatory biomarkers on mortality in TAVR,[19] emphasizing the prognostic impact of systemic inflammation in the context of interventional valve replacement.

5 | CONCLUSION

Plasma concentrations of TNF-α after 24 h and 5 days were associated with 12-month mortality, which even remained statistically significant after correction for possible confounders. Thus, TNF-α could represent an independent risk predictor for the refinement and enhancement of established risk scores in patients undergoing TAVR. Based on our findings, further research on this matter is certainly warranted.

5.1 | Limitations

A major limitation of this study is the incomplete follow-up, which was available from only 74% of all patients. Because of diverging group sizes at different timepoints of follow-up, as well as the relatively low

TABLE 4 Univariate and multivariate Cox proportional hazard analyses (variance inflation factors: diabetes: 1.031, EF: 1.007, PAD: 1.033, CRP: 1.015, creatinine: 1.043)

	Univariate HR			Multivariate HR		
	HR	*95% CI*	*p-value*	*HR*	*95% CI*	*p-value*
Age (years)	0.980	0.943–1.018	0.980			
BMI (kg/m²)	0.971	0.914–1.032	0.345			
Gender	1.386	0.673–2.853	0.376			
Diabetes mellitus	1.867	1.111–3.138	0.018	2.462	0.552–10.988	0.238
Peripheral artery disease	1.865	1.005–3.463	0.048	0.000	0.000–0.001	0.987
Coronary artery disease	0.872	0.503–1.513	0.626			
NYHA stage, pre.	1.106	0.725–1.689	0.640			
EF (%), pre.	0.976	0.955–0.998	0.030	0.961	0.916–1.008	0.102
CRP (mg/dl), pre.	1.080	1.022–1.140	0.006	0.056	0.001–2.804	0.149
BNP (ng/l), pre.	1.000	1.000–1.000	0.745			
Creatinine (µmol/l), pre.	1.005	1.002–1.007	0.001	1.004	0.971–1.038	0.823
eGFR (ml/min/1.73m²), pre.	0.987	0.974–1.001	0.063			
Hemoglobin (mmol/l), pre.	0.855	0.672–1.089	0.205			
Mean pressure gradient (mmHg), pre.	0.991	0.971–1.011	0.363			
TNF-α, pre. (pg/ml)	1.001	1.000–1.003	0.109			
TNF-α, after 24 h (pg/ml)	1.002	1.000–1.004	0.028	1.004	1.001–1.006	0.007
TNF-α, after 4 days (pg/ml)	0.931	0.733–1.183	0.559			
TNF-α, after 5 days (pg/ml)	1.003	1.001–1.005	0.013	1.004	1.001–1.008	0.012
TNF-α, after 7 days (pg/ml)	0.756	0.399–1.433	0.392			
TNF-α, after 1 Month (pg/ml)	0.578	0.180–1.856	0.357			
TNF-α, after 3 Months (pg/ml)	0.787	0.436–1.422	0.428			
TNF-α, after 6 Months (pg/ml)	0.982	0.898–1.073	0.688			

Abbreviations: 95% CI, 95% Confidence interval; BMI, Body mass index; BNP, Brain natriuretic peptide; CRP, C-Reactive protein; EF, Ejection fraction; eGFR, Estimated glomerular filtration rate; HR, Hazard ratio; MPG, Mean pressure gradient; NYHA, NEW York Heart Association; TNF-α, Tumor necrosis factor alpha.

number of events in groups, statistical biases cannot be excluded with certainty. In this regard, the wide 95% CIs of the ORs for the calculated cut-offs of TNF-α after 5 days and 3 months are worth mentioning.

Furthermore, we depicted mean ± SD although the Shapiro-Wilk test was significant for all groups. The reason for this was that depiction of median and IQR would have affected the readability of the article. Statistical analyses, however, were conducted with non-parametrical tests, which do not assume normal distribution.

Lastly, despite inflammation having been linked to the progression of calcific aortic valve stenosis and the degeneration of prosthetic valves,[32,37] we did not find a correlation of TNF-α levels with echocardiographic outcome data at 12 months follow-up. However, echocardiographic follow-up data were only available from 156 patients (36.2%), so our study was likely underpowered in this regard. Future trials should address this issue.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTIONS

MM, ML, UH, AL, and CS conceptualized the study design and patient recruitment. JK, HB, CR, JK, CJ, DK, MF, BA, and AL were involved in patient recruitment. MH, VP, and LJM conducted the in vitro experiments. MM conducted the statistical analyses. MM, AT, PJ, and DF wrote the article. ML, UH, AL, CS, JK, HB, CR, JK, CJ, DK, MF, BA, and AL reviewed the article prior to submission and provided substantial contributions for improvement. All authors read and approved the final version of the article prior to submission.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ORCID

Moritz Mirna https://orcid.org/0000-0001-5679-4872

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