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ORIGINAL RESEARCH

Multiorgan Dysfunction and its Association With Congestion and Outcome in Aortic Stenosis Treated With TAVI

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ABSTRACT

BACKGROUND Degenerative severe aortic stenosis (AS) is treated by valve replacement to improve outcome. Despite diagnostic advancements, many AS patients are still diagnosed late with advanced heart failure.

OBJECTIVES The aim of the study was to assess multiorgan dysfunction in severe AS using blood biomarkers and their association with quantitative fluid levels and clinical outcomes after transcatheter aortic valve implantation (TAVI).

METHODS Consecutive AS patients undergoing TAVI received comprehensive preinterventional assessment with serum biomarker profiles reflecting organ dysfunction and quantitative fluid overload (FO) using bioelectrical impedance spectroscopy. FO by bioelectrical impedance spectroscopy was defined according to a previously established cut-off (≥1.0 L). Time to first heart failure hospitalization or death served as composite primary endpoint.

RESULTS Among 880 patients (age 81 ± 7 years, 47% female), 41% had FO and 89% had biomarker abnormalities of at least one domain. Ascending fluid levels were independently associated with distorted biomarkers across domains of myocyte stress, hepatic dysfunction, renal dysfunction, inflammation, and anemia. After 2.4 ± 1.0 years of follow-up, 27% had reached the primary endpoint (29 heart failure hospitalization, 194 deaths, 13 both). Biomarkers across all domains were individually and independently associated with outcomes. In a multidomain approach, every affected extra-cardiac domain was associated with a 71% increase in event hazard (adjusted HR: 1.71; 95% CI: 1.39-2.11). Also, for each domain, the combination of distorted biomarkers and FO had the highest event risk.

CONCLUSIONS Biomarker abnormalities are highly prevalent in severe AS, influenced by congestion, and associated with impaired prognosis post-TAVI. Multiorgan dysfunction faces a particularly dismal outcome. (JACC Adv. 2025;4:101544)

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

BIS = bioelectrical impedance spectroscopy

FO = fluid overload

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal prohormone of brain natriuretic peptide

TAVI = transcatheter aortic valve implantation

Degenerative aortic stenosis (AS) represents the most frequent acquired valvular heart disease and warrants treatment by valve replacement if symptomatic or associated with worsening left ventricular function.[1] Increased afterload due to outflow tract obstruction causes a remodeling response of the myocardium that aims at preserving cardiac function. If left untreated, compensatory mechanisms exhaust over time, resulting in both forward and backward failure. Improvements in the understanding of adverse remodeling and its unfavorable impact on prognosis have resulted in efforts to intervene earlier, even in the absence of symptoms. Nevertheless, a considerable proportion of AS patients are still treated late with advanced decompensated heart failure and significant fluid overload (FO).[2,3]

Clinical signs of congestion have been shown to lack accuracy in the assessment of FO.[4] Bioelectrical impedance spectroscopy (BIS) represents a noninvasive tool to quantify FO and ascending levels of congestion by BIS in AS have been associated with an incremental hazard of unfavorable postinterventional clinical outcomes, improving risk stratification compared to conventional congestion signs.[2,3,5]

Chronic heart failure is a complex process that involves neurohormonal activation and systemic inflammation. Systemic congestion results from backward failure, and consequences include congestive cirrhosis, impaired intestinal absorption, and subsequent iron deficiency and anemia.[6,7] Forward failure causes coronary and systemic hypoperfusion. Biomarkers reflecting organ dysfunction have been linked to impaired prognosis in chronic heart failure.[8-10] Despite their well-established prognostic importance in the general heart failure population, the role of these biomarkers as well as their association with fluid overload remains poorly studied in the setting of AS. Furthermore, the cumulation of affected extra-cardiac organs with biomarker distortions is likely to impact outcomes in AS but has never been described.

It was therefore the aim of the present study to: 1) assess multiorgan dysfunction by blood biomarkers in patients with severe AS scheduled for transcatheter aortic valve implantation (TAVI); 2) determine the association of these biomarkers with fluid levels by BIS; and 3) evaluate their relationship with clinical outcomes post-TAVI.

METHODS

STUDY DESIGN AND POPULATION. This large-scale, single-center, observational study was conducted between 2017 and 2021 at the Vienna General Hospital, a university-affiliated tertiary center, prospectively enrolling consecutive adult patients with severe degenerative AS scheduled for TAVI. The center performs approximately 250 to 300 TAVIs per year, with numbers continuously increasing over the last years (including the study period). Eligibility and decision for TAVI were confirmed by the local multidisciplinary heart team. Written informed consent was obtained from each patient. The study was conducted in accordance with the Declaration of Helsinki's institutional policies and approved by the Ethics Committee of the Medical University of Vienna (EK no. 2218/2016).

CLINICAL MEASURES AND BLOOD BIOMARKERS. Each patient underwent a comprehensive pre-TAVI work-up, encompassing clinical examination, electrocardiogram, transthoracic echocardiography, and laboratory analysis. Assessment of blood biomarkers incorporated a full blood count and serum biochemistry profile assessing cardiac, renal, and hepatic function as well as inflammation (C-reactive protein) and anemia. Renal dysfunction was assessed using the following biomarkers and cut-offs: creatinine (>1.2 mg/dL in men, >0.9 mg/dL in women) and blood urea nitrogen (BUN) (>23 mg/dL). Anemia was defined by decreased hemoglobin levels (<13.5 g/dL for men, <12.0 g/dL for women). Normal values of biomarkers were defined according to reference ranges of the local laboratory (Supplemental Table 1).

ECHOCARDIOGRAPHY. All patients underwent clinical transthoracic echocardiography, as per local protocols and international imaging guidelines, to evaluate ventricular function, the severity of AS, and other valve pathologies. Echocardiography was performed by board-certified cardiologists using commercially available equipment (Vivid E95, GE Healthcare, and Acuson Sequoia, Siemens). Cardiac morphology was assessed according to recent recommendations.[11] Left ventricular ejection fraction was measured using Simpson's biplane method. Left ventricular mass was determined using the formula from Devereux et al.[12] Valvular stenosis and regurgitation were quantified and evaluated as none, mild, moderate, or severe according to the corresponding recommendations.[13,14] AS was considered severe

when transvalvular velocity exceeded 4 m/s, mean transvalvular gradient was ≥40 mm Hg, and aortic valve area was <1 cm^2. "Classical" low-flow, low-gradient was defined as an aortic valve area ≤1.0 cm2, with a left ventricular ejection fraction (LVEF) <50%, an indexed stroke volume <35 ml/m^2, a peak aortic valve velocity <4 m/s, and a mean gradient <40 mm Hg; conversely "paradoxical" low-flow, low-gradient was defined as an LVEF ≥50%, but an indexed stroke volume <35 ml/m^2, peak velocity <4 m/s, and mean gradient <40 mm Hg.[14] Where equivocal, AS severity was adjudicated using low-dose dobutamine stress echocardiography (in classical low-flow low-gradient AS) and the computed tomography-derived aortic valve calcium score (using sex-specific cut-off values according to current guidelines).[15]

ASSESSMENT OF FLUID STATUS. Quantitative assessment of fluid status was conducted in all patients using a portable whole-body BIS device (Body Composition Monitor, Fresenius Medical Care). Previous work has described the underlying principles of BIS [2,16] and proven its reproducibility.[17] Briefly, patients are in supine position, and electrodes are placed on the nondominant hand and ipsilateral foot. Measurements take around 2 minutes. BIS is based on the principle that the body acts as a circuit with a given resistance (opposition of current flow through extracellular and intracellular solutions) and reactance (capacity of cells for energy storage), where the total body fluid volume is largely reflected in the resistance. The device measures impedance at 50 frequencies over a range from 5 to 1,000 kHz to determine the electrical resistance of total body water and extracellular water (ECW). FO, as assessed by BIS, is expressed as an absolute value in liters or as a relative value in %, calculated as the ratio between FO and the content of ECW (relative FO = FO/ECW × 100). In particular, we have previously applied this technique to subjects with heart failure and AS and shown its significant prognostic value in these patient samples.[2,3,5,18,19] In the present study, we defined FO according to previously established and prespecified cut-off values in AS patients: no FO (<1.0 L), mild FO (1.0-3.0 L), and severe FO (>3.0 L).[2,3,20]

DEFINITION OF ENDPOINTS. The primary outcome was defined as a composite of all-cause mortality and/or hospitalization for heart failure (HHF). Three sources—the patient records of the Medical University of Vienna, the Vienna-Health-Association database, and the national electronic health records—were used to determine HHF, including hospitalizations in all Austrian hospitals. Heart failure hospitalization was defined as an acute deterioration of the clinical status with symptoms and signs of heart failure requiring hospital admission for inpatient intravenous decongestive treatment. Mortality data were retrieved via the Austrian Death Registry. Clinical follow-up was carried out at 3 months, 12 months, and every year thereafter. Minimum follow-up period was 12 months. Maximum follow-up period was 5 years.

TAVI OUTCOMES. Periprocedural complications were captured according to updated Valve Academic Research Consortium 3 criteria.[21]

STATISTICAL METHODS. Statistical analyses were performed using SPSS 29 (IBM SPSS) and R version 4.3.2 (Foundation for Statistical Computing). Categorical variables were reported as % (n). Continuous variables were expressed as median (IQR). Differences between groups were analyzed with the Wilcoxon rank sum and Kruskal-Wallis test, as appropriate. Chi-square tests or Fisher's exact tests were used for categorical variables. To assess associations of quantitative fluid levels with blood biomarkers, multiple linear regression analysis was performed with adjustment for a clinical confounder model (age, sex, body mass index, LVEF, estimated systolic pulmonary artery pressure). Univariate and multivariable Cox regression analyses were conducted to assess the association of blood biomarkers with the primary outcome. A clinical confounder model was used for multivariable adjustment (age, sex, EuroSCORE II, and quantitative fluid levels). To facilitate comparison among continuous variables within the multivariable model, scaled hazard ratios (Z-scores) were generated by subtracting the mean from individual values and then dividing them by the respective standard deviation. A multidomain approach was used to calculate the prognostic impact of the number of affected extra-cardiac domains with one point assigned for each domain with distorted biomarker levels (kidney: elevated creatinine and/or BUN; inflammation: elevated C-reactive protein (CRP); anemia: low hemoglobin; cholestatic liver dysfunction: elevation of at least 2 out of 3 cholestasis markers [bilirubin, γGT, and/or AP]; ischemic liver dysfunction: elevation of both transaminases [AST/ALT]). The independent prognostic value of the multidomain approach was tested by Cox regression using a stepwise forward selection for multivariable adjustment, including all significant variables on univariable testing. To assess whether FO provided

incremental prognostic information to high-risk biomarker constellations, blood biomarkers were stratified according to tertiles with the highest/lowest tertile, respectively, representing patients at high risk. FO was then added, yielding 4 groups that were compared with respect to event-free survival using Kaplan-Meier estimates. A two-sided P value ≤0.05 was considered statistically significant.

RESULTS

PATIENT SAMPLE. Among 945 consecutive patients undergoing TAVI, 65 patients (6.9%) had to be excluded for various reasons (Supplemental Figure 1). The remaining 880 patients with valid BIS data and complete serum biomarker profiles formed the final study sample, which was stratified according to the presence of no (59%, n = 520/880), mild (31%, n = 274/880), or severe FO (10%, n = 86/880). Detailed patient characteristics are shown in **Table 1**. Median age was 80.8 years (IQR: 77.5-85.5 years) and 47.4% were female.

CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS. In patients with no, mild, and severe FO, quantitative fluid levels were −0.1 L (−1 to 0.5), 1.8 L (1.3-2.3), and 4.1 L (3.3-5.2), respectively. Patients with FO were more likely to be male (no vs mild vs severe FO: 47.3 vs 56.2 vs 73.3%, $P < 0.001$), with a lower body mass index ($P < 0.001$), and higher surgical risk scores (EuroSCORE II: 4.1 [3.9-4.7] vs 4.2 [3.9-4.8] vs 4.3 [4.0-5.2], $P = 0.012$). The distribution of cardiovascular comorbidities was similar between groups, except for diabetes mellitus (25.0% vs 25.6% vs 37.6%, $P = 0.047$) and atrial fibrillation (27.1% vs 31.1% vs 40.0%, $P = 0.044$), which were more prevalent in patients with FO. On echocardiography, ascending levels of FO were associated with an increase in cardiac damage. Patients with more severe FO presented with more severe left ventricular hypertrophy, larger left atria, lower LVEF, and had a higher prevalence of significant mitral and tricuspid regurgitation (P for all <0.05). Baseline characteristics with stratification according to the number of affected extra-cardiac domains are displayed in Supplemental Table 5. On average, an increase in the number of affected domains was associated with higher fluid levels, more symptoms, and more severe cardiac decompensation on echocardiography.

BLOOD BIOMARKERS AND STAGES OF FLUID OVERLOAD. Stages of FO differed significantly with respect to biomarker risk profiles (**Figure 1**, Supplemental Table 2). Overall, an increase in FO was associated with a higher prevalence of anemia (no vs mild vs severe FO: 54.0% vs 77.7% vs 84.7%, $P < 0.001$), thrombocytopenia (13.0% vs 17.5% vs 22.4%, $P = 0.041$), hyperkalemia (1.7% vs 4.4% vs 7.0%, $P = 0.01$), renal impairment (elevated creatinine: 50.8% vs 48.9% vs 64.0%, $P = 0.044$), cholestasis (elevated γGT: 28.9% vs 34.7% vs 54.8%, $P < 0.001$; hyperbilirubinemia: 6.7% vs 8.8% vs 22.1%), impaired liver synthetic function (hypoalbuminemia: 11.6% vs 15.2% vs 36.9%, $P < 0.001$; low cholinesterase: 11.7%, 25.2% vs 58.1%, $P < 0.001$), and systemic inflammation (elevated C-reactive protein: 49.4% vs 55.1% vs 75.6%). Similar differences between groups were observed with respect to blood biomarkers expressed as continuous values (**Table 1**). Furthermore, a stepwise increase in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) serum levels was observed from no FO to mild FO to severe FO (1,601 pg/mL [674-3,160] vs 1,967 [951-5,099] vs 5,047 [1,923-12,333], $P < 0.001$). Reference ranges of blood biomarkers are displayed in Supplemental Table 1.

ASSOCIATION OF BLOOD BIOMARKERS WITH CONGESTION. By univariable logistic regression, blood biomarkers across domains of kidney function, liver function, inflammation, anemia, and myocyte stress showed significant associations with quantitative fluid levels by BIS (Supplemental Table 3). After adjustment for clinical confounders, lower hemoglobin and hematocrit, higher creatinine, lower albumin and cholinesterase, higher alkaline phosphatase, γGT and total bilirubin, higher C-reactive protein, and higher NT-proBNP (all $P \leq 0.02$) were significantly associated with more congestion.

ASSOCIATION OF BLOOD BIOMARKERS WITH OUTCOMES. During a median follow-up of 2.3 years (1.6-3.3), 27% ($n = 236/880$) of patients experienced an event (194 deaths, 29 HHF, and 13 both). By univariable Cox regression analysis, most blood biomarkers were associated with clinical outcomes (**Table 2**). After multivariable adjustment, lower hemoglobin and hematocrit, lower sodium, higher potassium, higher creatinine and BUN, lower albumin, lower cholinesterase, higher alkaline phosphatase, γGT and bilirubin, higher C-reactive protein, and higher NT-proBNP (all $P < 0.02$) remained significantly linked to poor postinterventional outcomes (**Figure 2**). In a multidomain approach, we evaluated the prognostic impact of the number of extra-cardiac domains with distorted biomarker levels. By multivariable Cox regression, the multidomain approach

TABLE 1 Baseline Characteristics

	All Patients (N = 880)	No FO (n = 520, 59%)	Mild FO (n = 274, 31%)	Severe FO (n = 86, 10%)	*P* Value
Demographics					
Age, y	80.8 (77.7-85.5)	81.1 (77.5-85.6)[b]	81.3 (78.5-85.7)[c]	79.6 (76.3-83.6)	0.031
Male, %	52.6	47.3[a,b]	56.2[c]	73.3	**<0.001**
BMI, kg/m^2	26.8 (23.8-30.1)	27.5 (24.5-30.5)[a,b]	25.6 (22.8-30.5)	24.8 (22.8-29.1)	**<0.001**
FO by BIS, L	0.7 (−0.4-1.8)	−0.1 (−1 to 0.5)[a,b]	1.8 (1.3-2.3)[c]	4.1 (3.3-5.2)	**<0.001**
Clinical parameters					
EuroSCORE II	4.2 (3.9-4.7)	4.1 (3.9-4.6)[a,b]	4.2 (3.9-4.8)	4.3 (4.0-4.8)	**0.012**
CAD, %	51.9	51.3	52.4	54.1	0.880
Diabetes mellitus, %	26.4	25.0[b]	25.6[c]	37.6	**0.047**
Hypertension, %	59.5	61.0[b]	60.1	48.2	0.083
Atrial fibrillation, %	29.6	27.1[b]	31.1	40.0	**0.044**
AS phenotype, %					**<0.001**
D1: high gradient	77.8	79.6	77.7	67.4	
D2: LFLG, LVEF ≥50%	12.5	13.8	10.6	10.5	
D3: LFLG, LVEF <50%	9.5	6.5	11.7	20.9	
Symptoms					
Asymptomatic, %	3.1	3.3	3.3	1.2	0.559
NYHA functional class, %					0.062
I	5.9	5.6	7.3	2.3	
II	50.1	51.5	47.1	51.2	
III	38.2	38.8	37.6	36.0	
IV	5.9	4.0[a,b]	8.0	10.5	
CCS ≥ II, %	18.1	19.3	17.5	12.8	0.337
Syncope, %	15.3	15.1	14.2	19.8	0.451

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was significantly associated with outcome (adjusted HR: 1.71; 95% CI: 1.39-2.11, $P < 0.001$; log-rank, $P < 0.001$, **Table 3**). A stepwise increase in event hazard was observed with an increase in the number of affected domains from one (vs no domain: adjusted HR: 0.93; 95% CI: 0.42-2.09; $P = 0.9$) to 2 (vs no domain: adjusted HR: 2.16; 95% CI: 1.04-4.50; $P = 0.038$), to 3 (vs no domain: adjusted HR: 2.98; 95% CI: 1.43-6.20; $P = 0.003$), to 4 or more domains (vs no domain: adjusted HR: 5.21; 95% CI: 2.25-12.06; $P < 0.001$) (**Figure 3**, **Central Illustration**). Results remained consistent when assessing high-gradient (log-rank, $P < 0.001$) and low-gradient AS (log-rank, $P = 0.004$) (Supplemental Figure 2) separately. Finally, ascending levels of FO were associated with a stepwise increase in event hazard (log-rank, $P < 0.001$) (Supplemental Figure 3) and these results remained unchanged for high-gradient and low-gradient AS (Supplemental Figure 4). Addition of FO to high-risk biomarker constellations (highest/lowest tertile depending on respective biomarker and low hemoglobin) yielded 4 groups: biomarker-/FO-, biomarker+/FO-, biomarker-/FO+, and biomarker+/FO+. Survival curves across domains of anemia (hemoglobin), kidney (creatinine) and hepatic function (cholinesterase, bilirubin), inflammation (C-reactive protein), and myocyte stress (NT-proBNP) demonstrated the highest risk for patients in the group of biomarker+/FO+ (**Figure 4**).

TAVI OUTCOMES. Periprocedural characteristics are displayed in Supplemental Table 4. Procedure-associated complications occurred at the same rate across groups of FO (all $P > 0.05$). On postinterventional echocardiography predischarge, patients with severe FO displayed slightly more favorable transprosthetic hemodynamics compared to patients with no/mild FO (lower mean and peak transprosthetic gradients, $P < 0.05$ for both).

DISCUSSION

In this large-scale prospective cohort study encompassing 880 patients with severe AS undergoing TAVI, we sought to explore the role of multiorgan dysfunction and its association with congestion and clinical outcomes. Overall, the prevalence of distorted blood biomarkers was high and increased in

TABLE 1 Continued

	All Patients (N = 880)	No FO (n = 520, 59%)	Mild FO (n = 274, 31%)	Severe FO (n = 86, 10%)	*P* Value
Blood biomarkers					
Hemoglobin, g/dL	12.0 (10.7-13.2)	12.4 (11.1-13.5)[a,b]	11.7 (10.5-13.0)[c]	10.6 (9.2-12.3)	**<0.001**
Hematocrit, %	36.1 (32.2-39.4)	37.1 (33.5-40.4)[a,b]	34.9 (31.6-38.7)[c]	32.0 (27.9-37.0)	**<0.001**
WBC count × 10^9/L	7.08 (5.89-8.56)	7.12 (5.93-8.66)	7.12 (5.87-8.34)	6.48 (5.71-8.18)	0.271
Platelets × 10^9/L	206 (169-251)	209 (171-250)	203 (167-258)	197 (160-252)	0.612
Sodium, mmol/L	139 (137-141)	139 (137-141)	139 (137-141)	139 (136-141)	0.212
Potassium, mmol/L	4.2 (3.9-4.5)	4.2 (3.9-4.4)	4.2 (3.9-4.5)	3.9 (3.9-4.6)	0.518
Creatinine, mg/dL	1.1 (0.9-1.4)	1.1 (0.9-1.4)[b]	1.1 (0.9-1.4)[c]	1.3 (1.0-1.7)	**<0.001**
eGFR, mL/min/1.73 m^2	61 (46-77)	61.8 (47.7-76.6)[b]	62.3 (44.1-78.2)[c]	56.6 (34.5-75.6)	0.058
BUN, mg/dL	20.7 (16.0-29.1)	20.6 (15.8-27.8)	20.7 (16.1-30.1)	23.4 (16.2-30.9)	0.235
Albumin, g/L	40.3 (36.9-42.8)	40.9 (38.0-43.3)[a,b]	39.7 (36.3-42.5)[c]	36.8 (32.8-40.2)	**<0.001**
Cholinesterase, kU/L	6.2 (5.0-7.5)	6.6 (5.5-7.9)[a,b]	5.9 (4.9-6.8)[c]	4.6 (3.7-5.5)	**<0.001**
ALP, U/L	71 (57-89)	69 (57-88)[b]	73 (59-90)[c]	77 (63-105)	**0.009**
γGT, U/L	33 (19-67)	29 (18-57)[a,b]	33 (21-74)[c]	62 (39-103)	**<0.001**
Total bilirubin, mg/dL	0.54 (0.37-0.78)	0.53 (0.37-0.75)[b]	0.54 (0.38-0.78)[c]	0.63 (0.40-1.13)	**0.050**
AST, U/L	23 (19-29)	23 (19-29)	23 (18-29)	23 (18-31)	0.942
ALT, U/L	19 (15-26)	19 (15-26)	18 (14-25)	20 (14-33)	0.351
C-reactive protein, mg/dL	0.56 (0.19-2.37)	0.48 (0.19-1.53)[b]	0.62 (0.16-3.30)[c]	1.68 (0.47-8.76)	**<0.001**
NT-proBNP, pg/mL	1,820 (812-4,479)	1,601 (674-3,160)[a,b]	1,967 (951-5,099)[c]	5,047 (1,923-12,333)	**<0.001**
Echocardiographic parameters					
Aortic valve					
AV PPG, mm Hg	71 (64-81)	71 (64-81)[b]	71 (64-84)[c]	70 (49-81)	0.038
AV MPG, mm Hg	44 (38-51)	44 (39-51)[b]	44 (38-53)[c]	44 (31-49)	0.066
AV Vmax, m/s	4.2 (3.9-4.6)	4.2 (4.0-4.6)	4.3 (3.8-4.6)	4.1 (3.4-4.7)	0.137
Cardiac structure and function					
LV EF, %	58 (51-66)	58 (53-67)[b]	58 (50-64)[c]	55 (41-60)	**<0.001**
LV mass index, g/m^2	134 (113-158)	132 (111-153)[a,b]	138 (115-159)	145 (121-171)	**0.002**
LA volume index, ml/m^2	41 (35-50)	41 (34-48)[a,b]	43 (36-54)	44 (38-57)	**<0.001**
MR ≥ moderate, %	19.5	16.2[b]	21.0[c]	34.6	**<0.001**
TR ≥ moderate, %	18.8	14.8[b]	20.7[c]	37.2	**<0.001**
RV dysfunction ≥ moderate, %	5.7	4.6[a,b]	6.4	10.7	0.097
sPAP, %					0.138
<31 mm Hg	42	45.0[a]	35.8	44.2	
31-55 mm Hg	29.8	28.7	31.8	30.2	
>55 mm Hg	28.2	26.3	32.5	25.6	

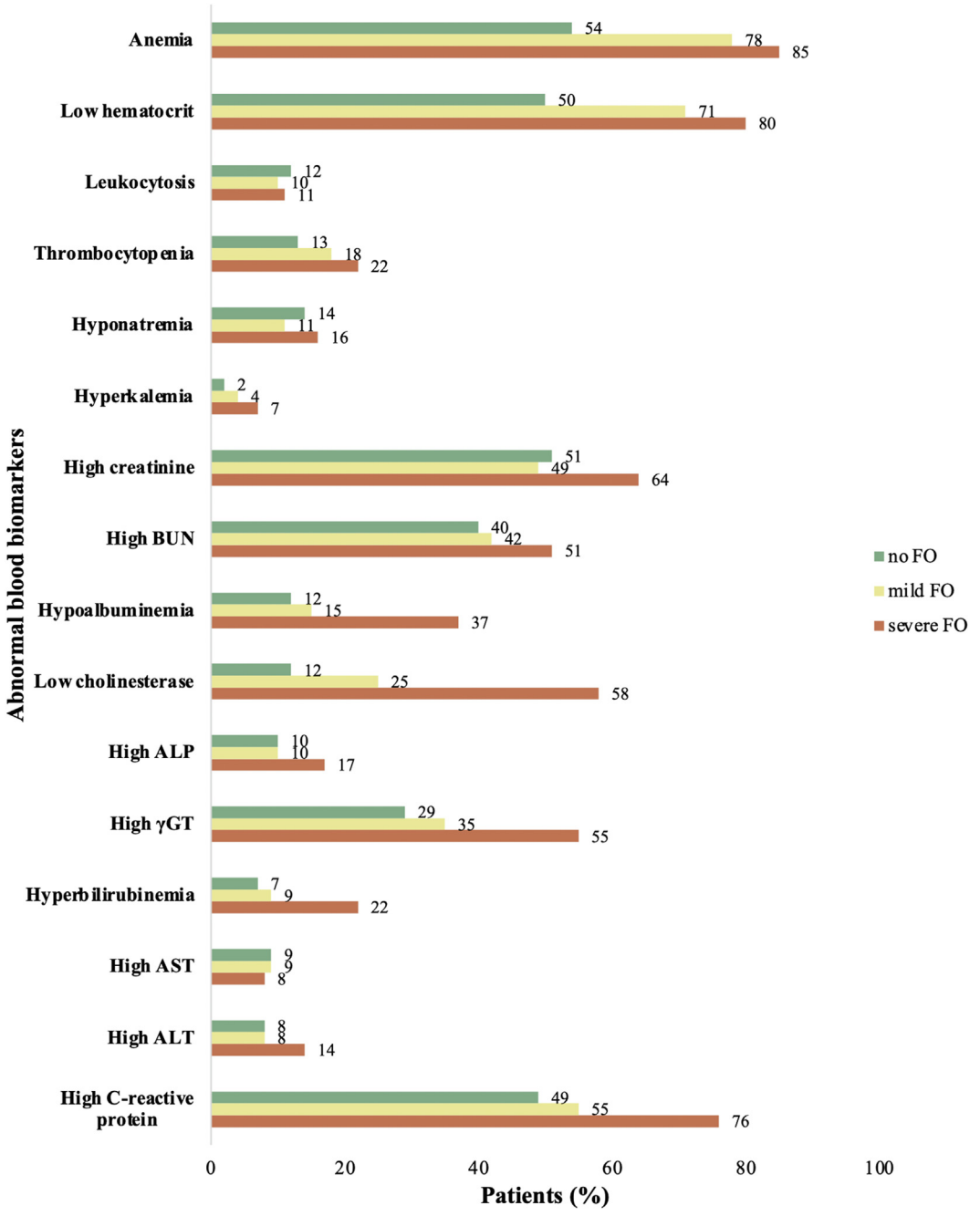
Values are median (IQR) or %. A statistically significant value of $P < 0.05$ is shown in bold font. [a]Indicates $P \leq 0.05$ for no FO group vs mild FO group. [b]Indicates $P \leq 0.05$ for no FO group vs severe FO group. [c]Indicates $P \leq 0.05$ for mild FO group vs severe FO group.

γGT = gamma-glutamyltransferase; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; AV = aortic valve; BMI = body mass index; BIS = bioimpedance spectroscopy; BUN = blood urea nitrogen; CAD = coronary artery disease; EF = ejection fraction; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FO = fluid overload; LA = left atrium; LV = left ventricle; MPG = mean pressure gradient; MR = mitral regurgitation; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PPG = peak pressure gradient; RV = right ventricle; TR = tricuspid regurgitation; Vmax = maximum velocity; WBC = white blood cell; sPAP = systolic pulmonary artery pressure.

severity with ascending fluid levels. Blood biomarkers reflecting organ dysfunction were independently predictive of worse postinterventional outcomes. The event hazard increased with an ascending number of affected domains/organs, and patients with both significant fluid overload and biomarker distortion had the most unfavorable prognosis. These findings illustrate AS and its hemodynamic sequelae as a multifaceted systemic disease process with potential implications for refined risk stratification and therapeutic interventions beyond valve replacement.

PREVALENCE OF BIOMARKER ABNORMALITIES IN AORTIC STENOSIS. In heart failure forms not attributable to AS, various pathophysiological pathways have been described to play a crucial role in the pathogenesis and disease progression.[22] Most

FIGURE 1 Prevalence of Blood Biomarker Abnormalities According to Levels of Fluid Overload



γGT = gamma-glutamyltransferase; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; FO = fluid overload.

intuitively, increasing myocyte stress has been demonstrated to be measurable by serum levels of NT-proBNP, which represents the pre-prohormone of brain natriuretic peptide and is released by the ventricular myocytes in response to volume and pressure overload. Due to its diagnostic and prognostic capabilities, measurement of NT-proBNP levels has been adopted by heart failure guidelines.[23] In

TABLE 2 Univariable and Multivariable Cox Regression Analyses Assessing the Association of Blood Biomarkers With Mortality/Hospitalization for Heart Failure

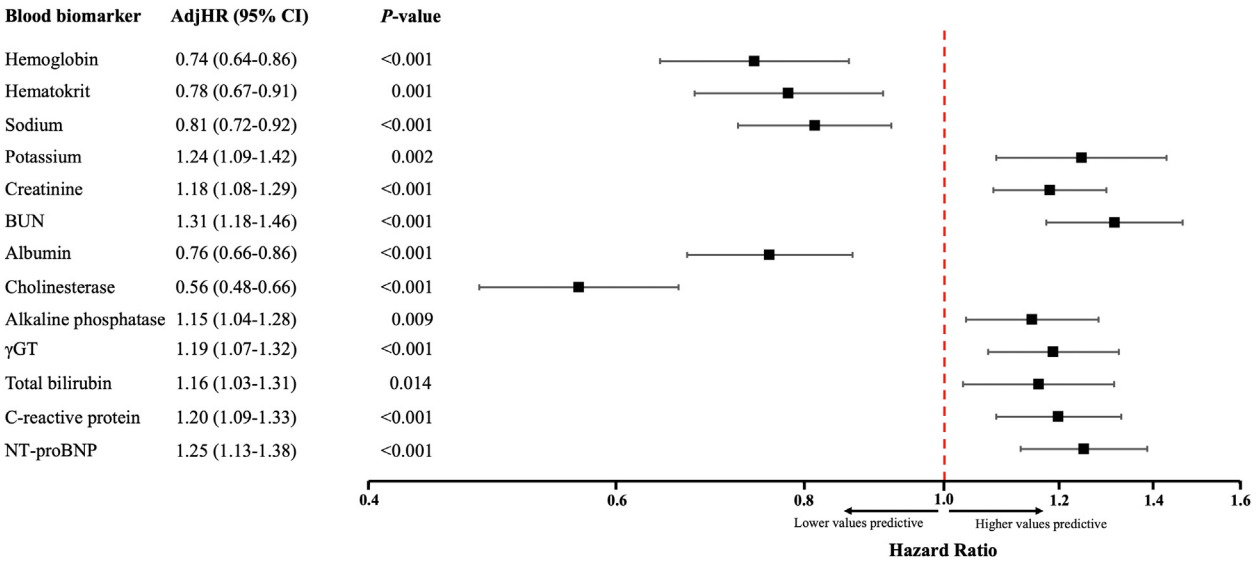
Blood Biomarker	Crude HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value
Hemoglobin	0.731 (0.640-0.836)	**<0.001**	0.739 (0.636-0.859)	**<0.001**
Hematocrit	0.759 (0.664-0.868)	**<0.001**	0.780 (0.672-0.907)	**0.001**
WBC	1.037 (0.918-1.172)	0.559	1.074 (0.932-1.237)	0.326
Platelets	0.990 (0.870-1.127)	0.877	1.037 (0.909-1.183)	0.588
Sodium	0.802 (0.717-0.898)	**<0.001**	0.814 (0.720-0.919)	**<0.001**
Potassium	1.216 (1.074-1.377)	**0.002**	1.244 (1.086-1.424)	**0.002**
Creatinine	1.213 (1.121-1.312)	**<0.001**	1.183 (1.081-1.294)	**<0.001**
BUN	1.359 (1.234-1.496)	**<0.001**	1.311 (1.176-1.461)	**<0.001**
Albumin	0.723 (0.645-0.810)	**<0.001**	0.757 (0.664-0.864)	**<0.001**
Cholinesterase	0.516 (0.450-0.591)	**<0.001**	0.559 (0.477-0.655)	**<0.001**
Alkaline phosphatase	1.113 (1.026-1.207)	**0.010**	1.150 (1.035-1.278)	**0.009**
γGT	1.172 (1.077-1.275)	**<0.001**	1.189 (1.072-1.320)	**0.001**
Total bilirubin	1.260 (1.133-1.401)	**<0.001**	1.162 (1.030-1.310)	**0.014**
AST	1.054 (0.972-1.142)	0.203	1.047 (0.952-1.153)	0.344
ALT	0.992 (0.866-1.136)	0.904	0.987 (0.851-1.146)	0.867
C-reactive protein	1.220 (1.109-1.342)	**<0.001**	1.199 (1.086-1.325)	**<0.001**
NT-proBNP	1.349 (1.232-1.478)	**<0.001**	1.249 (1.129-1.381)	**<0.001**

A statistically significant value of $P < 0.05$ is shown in bold font. [a]Adjusted for age, sex, EuroSCORE II, and fluid levels.

Abbreviations as in Table 1.

the present study, NT-proBNP was significantly elevated in the overall sample with a median level of 1,800 pg/mL, reflecting the deleterious effect of increased afterload and preload on the ventricles in AS. The heart and kidneys are functionally interconnected through various mechanisms, among which renal venous hypertension and limited organ perfusion are believed to be of particular importance in chronic cardiorenal syndrome.[24] The adverse effects of elevated markers reflecting kidney dysfunction have been extensively described for the general heart failure population;[24] and also in the present AS cohort, kidney dysfunction was highly prevalent and seen in half of patients. The liver is particularly vulnerable to damage in the presence of heart failure with congestive hepatopathy, cardiogenic ischemic hepatitis, malnutrition, and systemic inflammation as underlying pathophysiological mechanisms. Previous heart failure studies have linked elevated bilirubin and lower cholinesterase levels to unfavorable invasive hemodynamics (elevated central venous pressure, lower cardiac output). Hypoalbuminemia is also prevalent in heart failure and mainly influenced by nutritional status and systemic inflammation, whereas elevation of transaminases (due to ischemia) is much less common.[25,26] In AS patients from the current study, hyperbilirubinemia (1/10), hypoalbuminemia (15%), low cholinesterase levels (1/5), and elevation of at least one cholestasis marker (~40%) were observed in a significant proportion of patients. Conversely, elevated transaminases were only present in ~5%, suggesting that the cholestatic

FIGURE 2 Association of Blood Biomarkers With Clinical Outcomes



γGT = gamma-glutamyltransferase; adjHR = adjusted HR; BUN = blood urea nitrogen; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

TABLE 3 Univariable and Multivariable Cox Regression Analyses Assessing the Association of Clinical Variables With Mortality/Hospitalization for Heart Failure

	Univariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, per year increase	1.038 (1.017-1.060)	**<0.001**	1.047 (1.018-1.077)	**0.001**
Male	1.529 (1.178-1.986)	**0.001**	1.490 (1.035-2.143)	**0.032**
BMI, per kg/m^2 increase	0.976 (0.949-1.003)	0.078		
FO by BIS, per L increase	1.174 (1.101-1.252)	**<0.001**	1.170 (1.068-1.282)	**<0.001**
EuroSCORE II, per point increase	1.010 (0.991-1.028)	0.307		
CAD	1.346 (1.039-1.743)	**0.024**		
Diabetes mellitus	1.270 (0.960-1.680)	0.094		
Hypertension	1.001 (0.770-1.301)	0.993		
Atrial fibrillation	1.694 (1.305-2.200)	**<0.001**		
NT-proBNP, per quartile increase	1.445 (1.284-1.626)	**<0.001**		
AV MPG, per mm Hg increase	0.979 (0.970-0.988)	**<0.001**	0.989 (0.977-1.000)	0.054
LV EF	0.981 (0.972-0.990)	**<0.001**		
LV mass index, per g/m^2 increase	1.004 (1.001-1.008)	**0.016**		
LA volume index, per ml/m^2 increase	1.017 (1.007-1.026)	**<0.001**		
Significant MR	1.605 (1.353-1.903)	**<0.001**	1.288 (1.014-1.634)	**0.038**
Significant TR	1.444 (1.262-1,651)	**<0.001**		
RV dysfunction	1.578 (1.313-1.897)	**<0.001**		
sPAP[a]	1.147 (0.981-1.342)	0.085		
Affected extra-cardiac domains, per domain increase	1.663 (1.447-1.911)	**<0.001**	1.714 (1.394-2.108)	**<0.001**

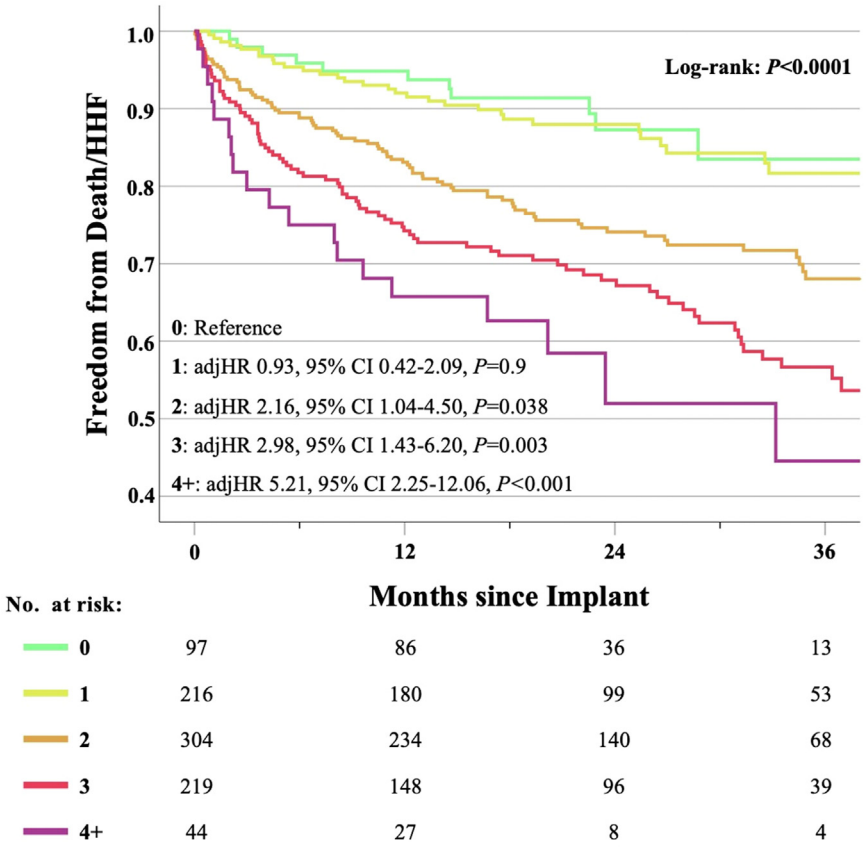
A statistically significant value of $P < 0.05$ is shown in bold font. [a]sPAP was graded into <31 mm Hg, 31 to 55 mm Hg, and >55 mm Hg.
Abbreviations as in Table 1.

type II cardiohepatic syndrome due to chronic congestion rather than the ischemic type I is the predominant cause of liver dysfunction in AS.[8] Inflammation is known to be important for the pathogenesis and progression of many forms of heart failure, and CRP was detected in 3 of 4 patients with congestive heart failure in a landmark study in 1956.[27,28] In line with these first observations, CRP elevation was observed in more than half of AS patients in the present study, highlighting a high prevalence of low-grade inflammation in this population.[27] Finally, anemia has been described as a common comorbidity in heart failure. Fluid overload with a hemodilution effect and impaired erythropoiesis resulting from chronic inflammation and/or iron deficiency due to anorexia/malabsorption are among the main pathophysiological causes.[10] Anemia was present in two-thirds of patients in the present AS cohort, which is significantly higher compared to proportions reported for congestive heart failure (median 18%).[9]

BIOMARKERS AND CONGESTION. As detailed above, volume overload is believed to represent a key pathophysiological mechanism in the development of multiorgan dysfunction in heart failure, but this association has never been investigated in AS. Assessment of fluid overload is limited by the low accuracy of physical congestion signs, and quantitative and reliable measures are therefore highly desirable. We have previously investigated a portable device in AS, which enables noninvasive and accurate quantification of fluid overload using bioelectrical impedance. Higher fluid levels were associated with higher cardiac damage markers on echocardiography, myocardial edema and fibrosis on cardiac magnetic resonance imaging, and worse post-TAVI outcomes.[2,3,5] The present study shows for the first time that quantitative fluid levels were independently associated with biomarker abnormalities across domains of kidney dysfunction, liver dysfunction/malnutrition, systemic inflammation, anemia, and myocyte stress. These data suggest that AS with progressive cardiac decompensation and congestion represents a multifaceted disease process that cannot be reduced to pump failure alone.

BIOMARKERS AND OUTCOMES. Laboratory abnormalities reflecting dysfunction of extracardiac organs have been linked to worse outcomes in heart failure,[8-10] whereas only limited data are available for

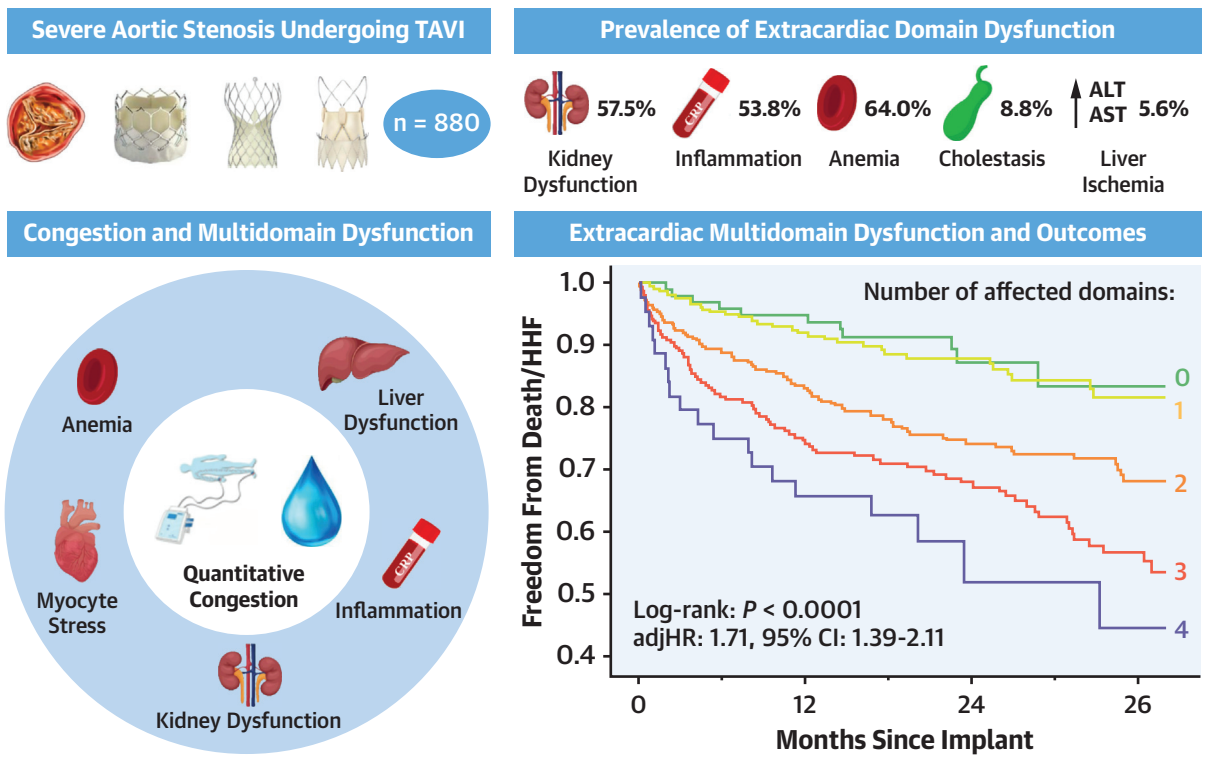
FIGURE 3 Kaplan-Meier Curves Stratified According to Number of Extracardiac Domains With Distorted Biomarker Levels



adjHR = adjusted HR; HHF = hospitalization for heart failure.

AS patients undergoing valve replacement. Among blood biomarkers that have been reported to portend worse prognosis post-TAVI are preinterventional hemoglobin, serum creatinine, and albumin.[29-31] In the present study, distorted biomarker levels from all organs investigated were associated with a higher event hazard post-TAVI, even after adjustment for established risk factors. In an attempt to assess the prognostic role of multiorgan dysfunction, we selected a multidomain approach. If 2 or more systems were affected, an increase in the number of extracardiac domains with distorted biomarker levels was associated with an incremental event hazard post-intervention. The 1-year event hazard for patients with 4+ affected domains was >30%, compared to 5% for patients without domain dysfunction. On average, for every additional affected domain, there was a ~70% increase in event hazard. Of note, patients with only one affected domain performed similarly to patients with no biomarker abnormalities. However, as detailed above, the prevalence of biomarker distortions was high, and the number of patients with no affected extracardiac domain was very low (11%). Furthermore, we investigated the additive role of fluid overload in biomarker distortions. Across all domains studied, patients with both distorted biomarkers and fluid overload had the worst prognosis. These results are intriguing on different levels. First, the multidomain approach can be used for comprehensive risk stratification in TAVI recipients to guide postdischarge management strategies, with high-risk candidates potentially deriving benefit from more

CENTRAL ILLUSTRATION **Multiorgan Dysfunction and Congestion in Patients With Severe Aortic Stenosis**



Halavina K, et al. JACC Adv. 2025;4(2):101544.

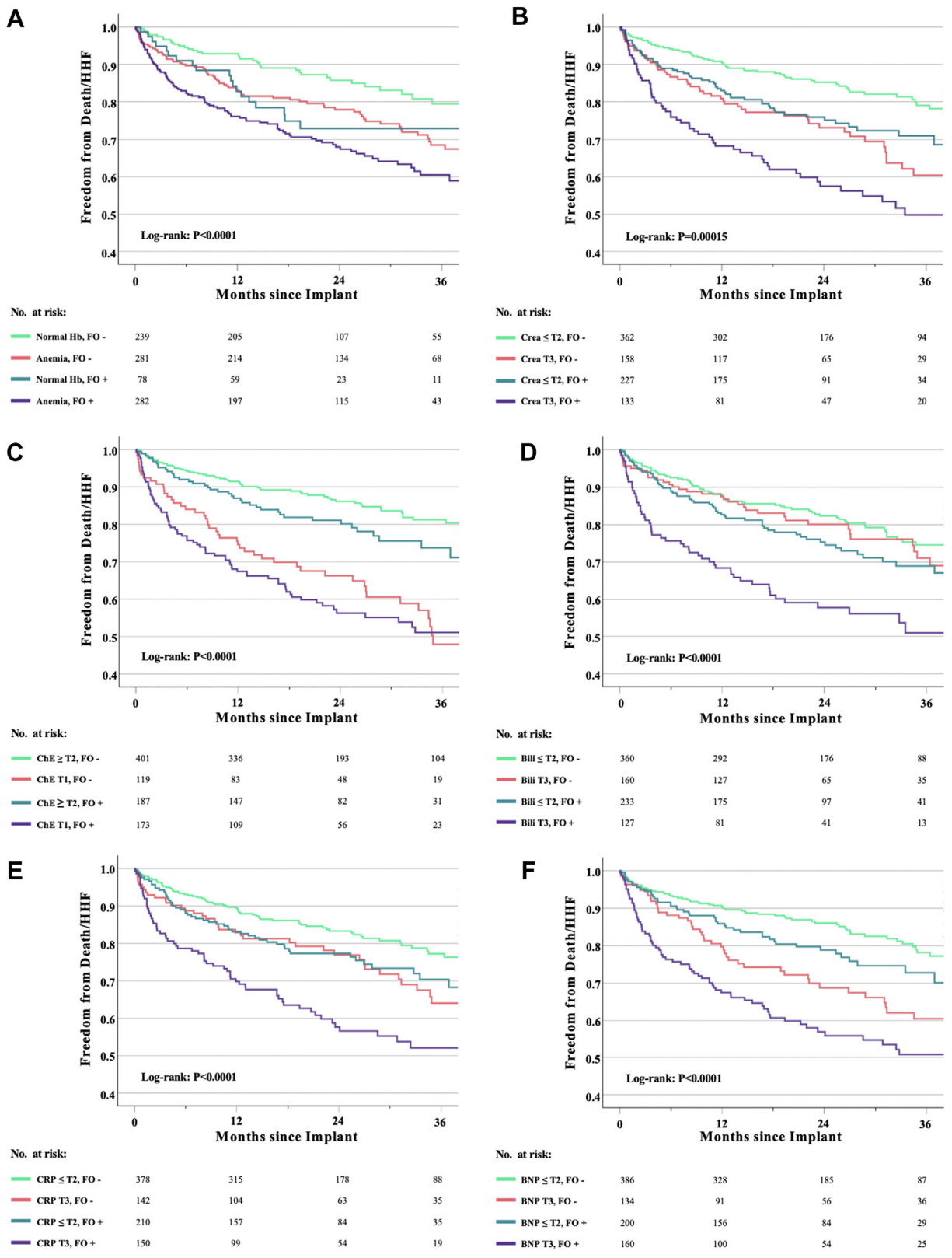
ALT = alanine transaminase; AST = aspartate transaminase.

intensified follow-up. Second, assessment of biomarker abnormalities might help identify patients who may benefit from additional interventions, such as nutritional supplementation, as already shown to be effective in older adults with cardiovascular disease.[32] Third, fluid overload represents a potentially modifiable risk factor. Individualized decongestive treatment has been demonstrated to improve outcomes post-TAVI [19] and might thus help to correct biomarker distortions. Recent evidence suggests benefit of early TAVI in patients with severe asymptomatic AS.[33] The current multidomain approach may potentially identify patients with severe AS but no symptoms at elevated risk of adverse outcomes to guide treatment strategies.

In conclusion, biomarker abnormalities are highly prevalent in patients with severe AS, influenced by congestion, and associated with impaired prognosis post-TAVI. Patients who exhibit multiorgan dysfunction, as illustrated by the multidomain approach, face a particularly dismal outcome.

STUDY LIMITATIONS. The present report is subject to limitations that warrant consideration. Firstly, the single-center setting potentially introduced a selection and referral bias that may limit the generalizability of our findings. However, the study design allowed for the implementation of identical protocols for FO and laboratory assessment, echocardiographic examination, and TAVI throughout the investigation, resulting in comprehensive data collection and consistency. Moreover, the predominantly Caucasian patient population of this study hinders the assessment of potential ethnicity-specific differences.

FIGURE 4 Kaplan-Meier Curves Stratified According to Biomarker Constellation and Fluid Overload



Patients with distorted biomarkers and fluid overload experienced the most unfavorable prognosis across domains of anemia (A), kidney dysfunction (B), liver dysfunction (C and D), inflammation (E), and myocyte stress (F). Bili = total bilirubin; BNP = brain natriuretic peptide; ChE = cholinesterase; Crea = creatinine; CRP = C-reactive protein; FO = fluid overload; Hb = hemoglobin; HHF = hospitalization for heart failure; T = tertile.

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KEY WORDS anemia, inflammation, kidney, liver, TAVR, volume overload

APPENDIX For supplemental tables and figures, please see the online version of this paper.