


# Frailty in patients undergoing transcatheter aortic valve replacement: prognostic value of the Geriatric Nutritional Risk Index

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## Abstract

**Background** Malnutrition is a hallmark of frailty, is common among elderly patients, and is a predictor of poor outcomes in patients with severe symptomatic aortic stenosis (AS). The Geriatric Nutritional Risk Index (GNRI) is a simple and well-established screening tool to predict the risk of morbidity and mortality in elderly patients. In this study, we evaluated whether GNRI may be used in the risk stratification and management of patients undergoing transcatheter aortic valve replacement (TAVR).

**Methods** Patients with symptomatic severe AS ( $n = 953$ ) who underwent transfemoral TAVR at the University Hospital Schleswig-Holstein Kiel, Germany, between 2010 and 2019 (development cohort) were divided into two groups: normal GNRI  $\geq 98$  (no nutrition-related risk;  $n = 618$ ) versus low GNRI  $< 98$  (at nutrition-related risk;  $n = 335$ ). The results were validated in an independent (validation) cohort from another high-volume TAVR centre ( $n = 977$ ).

**Results** The low-GNRI group had a higher proportion of female patients (59.1% vs. 52.1%), higher median age (82.9 vs. 81.8 years), prevalence of atrial fibrillation (50.4% vs. 40.0%), median logistic EuroSCORE (17.5% vs. 15.0%) and impaired left ventricular function ( $< 35\%$ : 10.7% vs. 6.8%), lower median estimated glomerular filtration rate (50 vs. 57 mL/min/1.73 m<sup>2</sup>) and median albumin level (3.5 vs. 4.0 g/dL) compared with the normal-GNRI group. Among peri-procedural complications, Acute Kidney Injury Network (AKIN) Stage 3 was more common in the low-GNRI group (3.6% vs. 0.6%,  $p = 0.002$ ). After a mean follow-up of 21.1 months, all-cause mortality was significantly increased in the low-GNRI group compared with the normal-GNRI group ( $p < 0.001$ ). This was confirmed in the validation cohort ( $p < 0.001$ ). Low GNRI  $< 98$  was identified as an independent risk factor for all-cause mortality (hazard ratio 1.44, 95% CI 1.01–2.04,  $p = 0.043$ ). Other independent risk factors included albumin level  $<$  median of 4.0 g/dL, high-sensitive troponin T in the highest quartile ( $> 45.0$  pg/mL), N-terminal pro-B-type natriuretic peptide in the highest quartile ( $> 3595$  pg/mL), grade III–IV tricuspid regurgitation, pulmonary arterial hypertension, life-threatening bleeding, AKIN Stage 3 and disabling stroke.

**Conclusions** Low GNRI score was associated with an increased risk of all-cause mortality in patients undergoing TAVR, implying that this vulnerable group may benefit from improved preventive measures.

**Keywords** Aortic stenosis; geriatric; Geriatric Nutritional Risk Index; transcatheter aortic valve replacement

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## Introduction

As a hallmark of frailty, malnutrition is common among elderly patients<sup>1–5</sup> and is a predictor of poor outcomes in patients with severe aortic stenosis (AS).<sup>5–9</sup> Various methods have been used to evaluate the nutritional status of patients undergoing transcatheter aortic valve replacement (TAVR), although no single tool is considered standard in the routine clinical practice setting.<sup>5,10–15</sup>

Whereas some nutritional assessment strategies can be time consuming and cumbersome,<sup>16</sup> the Geriatric Nutritional Risk Index (GNRI) is a simple and well-established nutritional screening tool that may help predict the risk of morbidity and mortality in elderly patients.<sup>17–19</sup> However, the prognostic value of the GNRI in patients undergoing TAVR has only been assessed in a few studies,<sup>15,20–22</sup> and additional data are needed to clarify its role in this context.

We performed a study to evaluate whether the GNRI might be helpful in risk stratification of patients undergoing TAVR and validated our results in an independent cohort from another high-volume TAVR centre. The underlying hypothesis was that patients with a low GNRI would have a significantly higher rate of all-cause mortality.

## Methods

### Study design

Patients undergoing transfemoral TAVR at our institution (University Hospital Schleswig-Holstein Kiel, Germany) for symptomatic severe AS between March 2010 and October 2019 were identified from our TAVR database (development cohort). Mitral and tricuspid regurgitation were assessed in a pre-procedural echocardiography. In patients with a complete dataset, the GNRI was calculated based on serum albumin level and body mass index (BMI) obtained on admission, following Kinugasa's method:  $\text{GNRI} = 14.89 \times \text{serum albumin (g/dL)} + 41.7 \times \text{BMI}/22$ . BMI/22 was defined as one in patients with a BMI > 22 kg m<sup>-2</sup>.<sup>23</sup> Patients were stratified into two groups, in accordance with previously described cut-offs for GNRI: normal GNRI  $\geq 98$  (no nutritional-related risk) versus low GNRI < 98 (at nutritional-related risk).<sup>24</sup> The primary objective of our study was to determine all-cause mortality in both groups. Our results were validated in an independent validation cohort from another high-volume TAVR centre (Heart Center Bonn, Germany).

### Data collection

Informed consent was obtained from each participant. The study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee at

the University of Kiel. Blood samples and baseline patient data were collected 1–3 days prior to TAVR. Patient outcomes were analysed following the Valve Academic Research Consortium 2 (VARC-2) system.<sup>23</sup>

Acute Kidney Injury Network (AKIN) Stage 3 (but not 1 or 2) was assessed in our study as it is an important endpoint after TAVR. AKIN Stage 3 is defined by an increase in serum creatinine to  $\geq 300\%$  (>3× increase compared with baseline) or serum creatinine of  $\geq 4.0$  mg/dL ( $\geq 354$  mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) or urine output < 0.3 mL/kg/h for  $\geq 24$  h or anuria for  $\geq 12$  h.

Follow-up after discharge from hospital usually included an in-person visit at our cardiology outpatient clinic 1–3 months after TAVR and an annual phone call follow-up with the patient or their general practitioner and cardiologist.

### Statistical analyses

Continuous variables were expressed as median and interquartile ranges (IQR); categorical data were presented as counts (percentages). Data were analysed using Mann–Whitney *U* test and the chi-squared test. In case of few observations (frequency less than 10 for an individual cell), Fisher's exact test was used. Survival data were presented as Kaplan–Meier curves and compared using log-rank tests. For the Cox regression model, all pre-procedural variables that had been found to be significantly associated with survival were included. Backward selection was based on the likelihood ratio criteria. For each covariable, the proportional hazards assumption was approved by testing for interactions between Schoenfeld residuals and the log-transformed time using the function *cox.zph()* of the 'R (*survival*)' package'. Results were presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI). In addition, receiver operating characteristic (ROC) curve analysis was used to further assess the diagnostic ability of GNRI. Statistical analyses were performed using the statistical software GraphPad Prism 8 and RStudio, Version 1.3.959-1.

## Results

A total of 953 TAVR patients with a complete dataset were available for analysis using the TAVR database of the University Hospital Schleswig-Holstein Kiel, Germany (development cohort). Among this cohort, 618 had normal GNRI  $\geq 98$  (no nutritional-related risk), and 335 had low GNRI < 98 (at nutritional-related risk). ROC analysis revealed an AUC of 0.70 for GNRI, 0.72 for high-sensitive troponin T (hs-TNT), 0.67 for *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) and 0.64 for the log. EuroSCORE (all *p*-values < 0.001) (*Figure S1*). The independent validation

**Table 1** Baseline characteristics of patients undergoing transfemoral transcatheter aortic valve replacement (development cohort and validation cohort)

	Development cohort (University Hospital Schleswig-Kiel)			Validation cohort (Heart Center Bonn)		
	Total (n = 953)	GNRI ≥ 98 (n = 618)	GNRI < 98 (n = 335)	Total (n = 977)	GNRI ≥ 98 (n = 602)	GNRI < 98 (n = 375)
Age (years)	82.1 (78.6–85.9)	81.8 (78.5–85.0)	82.9 (78.9–87.3)	82 (78–85)	81 (78–84)	82 (79–86)
Female, n (%)	520 (54.6)	322 (52.1)	198 (59.1)	493 (50.5)	322 (53.5)	171 (45.6)
BMI (kg/m <sup>2</sup> )	26.1 (23.8–29.4)	26.2 (24.0–29.7)	26.0 (22.9–29.4)	26.1 (23.6–29.3)	26.6 (24.0–29.4)	25.2 (22.3–28.7)
CAD, n (%)	627 (65.8)	407 (65.9)	220 (65.7)	594 (60.8)	373 (62.0)	221 (58.9)
COPD, n (%)	161 (16.9)	108 (17.5)	53 (15.8)	158 (16.2)	88 (14.6)	70 (18.7)
CVD, n (%)	173 (18.2)	107 (17.3)	66 (19.7)	—	—	—
Diabetes mellitus, n (%)	278 (29.2)	172 (27.8)	106 (31.6)	274 (28.0)	180 (29.9)	94 (25.1)
Dyslipidaemia, n (%)	496 (52.0)	341 (55.2)	155 (46.3)	733 (75.0)	477 (79.2)	256 (68.3)
History of AF, n (%)	416 (43.7)	247 (40.0)	169 (50.4)	431 (44.1)	257 (42.7)	174 (46.4)
Hypertension, n (%)	860 (90.2)	558 (90.3)	302 (90.1)	837 (85.7)	509 (84.6)	328 (87.5)
PAD, n (%)	131 (13.7)	77 (12.5)	54 (16.1)	—	—	—
PAH, n (%)	181 (19.0)	108 (17.5)	73 (21.8)	—	—	—
LVEF						
<35%, n (%)	78 (8.2)	42 (6.8)	36 (10.7)	—	—	—
35%–45%, n (%)	98 (10.3)	59 (9.5)	39 (11.6)	—	—	—
45%–54%, n (%)	193 (20.3)	119 (19.3)	74 (22.1)	—	—	—
≥55%, n (%)	584 (61.3)	398 (64.4)	186 (55.5)	660 (67.6)	414 (68.8)	246 (65.6)
eGFR (mL/min/1.73 m <sup>2</sup> )	55 (41–62)	57 (45–65)	50 (36–61)	56 (42–70)	59 (45–70)	50 (38–66)
Log. ES (%)	16.1 (10.3–23.5)	15.0 (9.6–22.0)	17.5 (12.1–25.3)	13.8 (9.0–22.7)	13.1 (8.6–21.0)	15.7 (9.7–26.2)
Prev. cardiac surgery, n (%)	158 (16.6)	108 (17.5)	50 (14.9)	146 (14.9)	101 (16.8)	45 (12.0)
Chronic haemodialysis, n (%)	11 (1.2)	5 (0.8)	6 (1.8)	—	—	—
Iron deficiency anaemia, n (%)	237 (24.9)	118 (19.1)	119 (35.5)	—	—	—
Albumin (g/dL)	4.0 (3.7–4.3)	4.2 (4.0–4.4)	3.5 (3.2–3.7)	3.9 (3.6–4.2)	4.1 (4.0–4.3)	3.5 (3.1–3.7)
hs-TNT (pg/mL)	25.2 (15.8–45.0)	21.3 (14.0–34.8)	37.7 (22.1–69.4)	—	—	—
NT-proBNP (pg/mL)	1930 (885–3595)	1466 (704–2791)	2790 (1284–6577)	—	—	—
AVA (cm <sup>2</sup> )	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.7 (0.6–0.8)
MPG (mmHg)	40 (31–50)	40 (31–50)	40 (31–50)	—	—	—
MR III–IV	124 (13.0)	75 (12.1)	49 (14.6)	—	—	—
TR III–IV	43 (4.5)	25 (4.0)	18 (5.4)	—	—	—

Values are presented as counts (percentages) or median (IQR).

AF, atrial fibrillation; AVA, aortic valve area; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; hs-TNT, high-sensitive troponin T; Log. ES, logistic EuroSCORE; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; MR, mitral valve regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAD, peripheral artery disease; PAH, pulmonary arterial hypertension; TR, tricuspid valve regurgitation

cohort comprised 977 patients recruited from the Heart Center Bonn, Germany.

In the development cohort, the low-GNRI group had a higher proportion of female patients (59.1% vs. 52.1%,  $p = 0.038$ ) and a slightly higher median age (82.9 vs. 81.8 years,  $p = 0.004$ ) compared with the normal-GNRI group (Table 1). The low-GNRI group revealed a higher prevalence of atrial fibrillation (50.4% vs. 40.0%,  $p = 0.002$ ) and impaired left ventricular function (44.5% vs. 35.6%,  $p = 0.007$ ), a lower median estimated glomerular filtration rate (50 vs. 57 mL/min/1.73 m<sup>2</sup>,  $p < 0.001$ ) and a higher median logistic EuroSCORE (17.5 vs. 15.0,  $p < 0.001$ ). The low-GNRI group displayed a lower median albumin level than the normal-GNRI group (3.5 vs. 4.2 g/dL,  $p < 0.001$ ) and higher median levels of iron deficiency anaemia (35.5% vs. 19.1%,  $p < 0.001$ ), hs-TNT (37.7 vs. 21.3 pg/mL,  $p < 0.001$ ) and NT-proBNP (2790 vs. 1466 pg/mL,  $p < 0.001$ ). The prevalence of dyslipidaemia was lower in the low-GNRI group (46.3% vs. 55.2%,  $p = 0.009$ ).

The only significant difference between the groups with respect to peri-procedural outcomes was that a higher proportion of patients in the low-GNRI group had AKIN Stage 3 compared with the normal-GNRI group (3.6% vs. 0.6%,  $p = 0.002$ ) (Table 2).

After a mean follow-up of 21.1 months, the rate of all-cause mortality was significantly higher in the group of patients with low GNRI (<98) compared to those with normal GNRI ( $p < 0.001$ ) (Figure 1). This finding was confirmed in the validation cohort. Available baseline characteristics of the validation cohort are presented in Table 1.

Pre-procedural factors that were associated with all-cause mortality according to the log-rank test are shown in Table 3. A significant association between GNRI < 98 and mortality was found ( $p < 0.001$ ).

The results of univariable and multivariable Cox regression analyses of factors associated with all-cause mortality are shown in Table 4. Of the 10 factors significantly associated

with mortality in univariable analysis, one factor (logistic EuroSCORE above the median) lost significance in the multivariable analysis. GNRI < 98 was a significant risk factor for all-cause mortality, increasing the risk by 44% (HR 1.44, 95% CI 1.01–2.04,  $p = 0.043$ ). Other factors significantly associated with an increased risk of mortality were albumin level below the median of 4.0 g/dL (associated with a 44% increase in risk); hs-TNT value in the top quartile, that is, > 45.0 pg/mL (45% increased risk); NT-proBNP in the top quartile, that is, > 3595 pg/mL (46% increased risk); grade III–IV tricuspid regurgitation (78% increased risk); pulmonary arterial hypertension (35% increased risk); life-threatening bleeding (3.42-fold increase in risk); AKIN Stage 3 (4.96-fold increase in risk); and disabling stroke (6.25-fold increase in risk).

## Discussion

Our study found that a low GNRI < 98 is associated with an increased risk of all-cause mortality in patients undergoing transfemoral TAVR for severe AS.

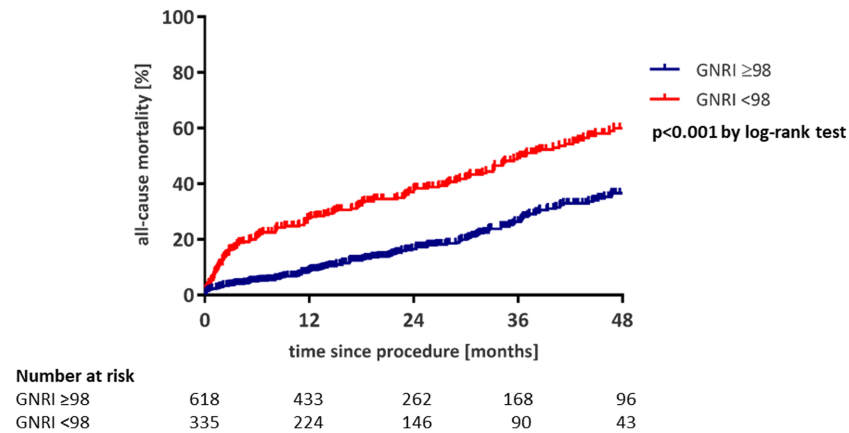
Frailty is associated with worse outcomes in patients with severe AS,<sup>24</sup> and poor nutrition is an important contributor to frailty.<sup>25</sup> Poor nutritional status has been shown to increase the risk of adverse outcomes after TAVR.<sup>5–9</sup> Analysis of more than 100,000 patients undergoing TAVR for severe AS found that malnutrition was an independent predictor of increased mortality (adjusted odds ratio [OR] 2.68,  $p < 0.001$ ), complications (adjusted OR 2.09,  $p < 0.001$ ) and 30-day readmission (adjusted OR 1.34,  $p < 0.001$ ).<sup>7</sup> Assessment of patients' nutritional status might aid in pre-procedural risk stratification and identify those who may benefit from nutritional interventions before or after an intervention. Although there is a lack of sufficient data in the context of patients undergoing TAVR, a correction of nutritional deficiency is recommended in patients undergoing

**Table 2** Procedural variables and outcomes

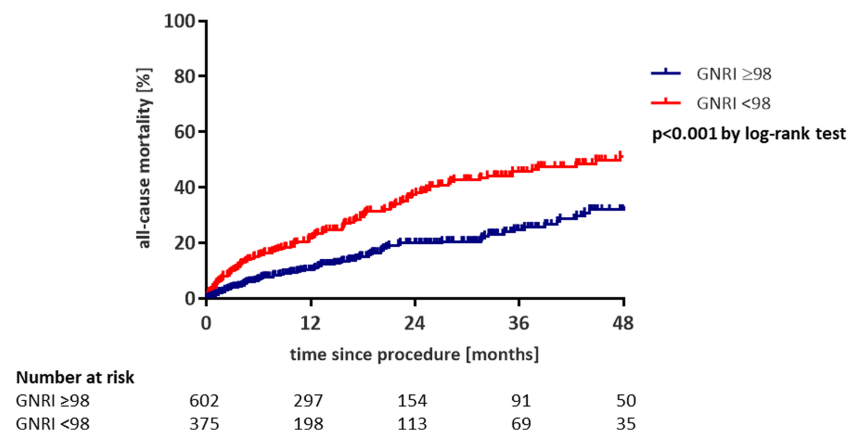
	Total (n = 953)	GNRI ≥ 98 (n = 618)	GNRI < 98 (n = 335)	p-Value
Procedural duration (min)	50 (40–63)	50 (40–62)	52 (41–65)	0.199
Contrast medium (mL)	85 (70–107)	85 (68–106)	85 (70–109)	0.473
VARC-2				
Conversion to open surgery (%)	5 (0.5)	3 (0.5)	2 (0.6)	>0.999
New pacemaker, n (%)	115 (12.1)	66 (10.7)	49 (14.6)	0.074
Myocardial infarction, n (%)	8 (0.8)	5 (0.8)	3 (0.9)	>0.999
AKIN Stage 3, n (%)	16 (1.7)	4 (0.6)	12 (3.6)	0.002
Life-threatening bleeding, n (%)	27 (2.8)	13 (2.1)	14 (4.2)	0.065
Disabling stroke, n (%)	7 (0.7)	4 (0.6)	3 (0.9)	0.702
Major vascular access complication, n (%)	19 (2.0)	10 (1.6)	9 (2.7)	0.331
Severe residual AR	5 (0.5)	4 (0.6)	1 (0.3)	0.662

Values are presented as counts (percentages) or median (IQR).

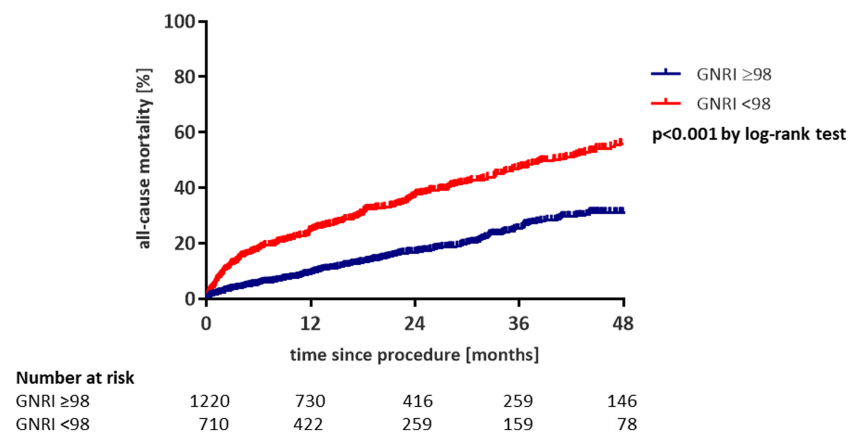
AKIN, Acute Kidney Injury Network; AR, aortic regurgitation; GNRI, Geriatric Nutritional Risk Index; VARC-2, Valve Academic Research Consortium 2



A



B



C

**Figure 1** Low Geriatric Nutritional Risk Index (GNRI) score ( $< 98$ ) is associated with adverse outcome in patients undergoing transfemoral transcatheter aortic valve replacement: (A) development cohort from Kiel, Germany, with a 21.1-month follow-up; (B) validation cohort from Bonn, Germany, with a 16.5-month follow-up; (C) pooled data from Bonn and Kiel, Germany. Note: Patients at both centres had an annual follow-up.

cardiac surgery.<sup>26</sup> In addition, a high-calorie nutritional supplement has previously demonstrated beneficial effects in patients with chronic heart failure and cachexia.<sup>27,28</sup>

Furthermore, iron deficiency has been shown to impact the further course of patients with heart failure<sup>27</sup> as well as patients undergoing TAVR.<sup>29</sup> Whether a correction of iron

**Table 3** Factors associated with all-cause mortality (log-rank test)

	p-Value
GNRI < 98	<0.001
Albumin < median (4.0 g/dL)	<0.001
Age > median (82.1 years)	0.002
NT-proBNP Q4 (>3595 pg/mL)	<0.001
hs-TNT Q4 (>45.0 pg/mL)	<0.001
BMI < median (26.1 kg/m <sup>2</sup> )	0.007
COPD	0.007
History of AF	<0.001
Dyslipidaemia	0.018
eGFR < median (55 mL/min)	<0.001
Log. ES > median (16.1%)	<0.001
LVEF < 55%	<0.001
PAD	<0.001
PAH	0.005
MR III–IV	0.007
TR III–IV	0.005
AKIN Stage 3	<0.001
Disabling stroke	<0.001
Life-threatening bleeding	<0.001
Major access complication	<0.001
Myocardial infarction	0.011

AF, atrial fibrillation; AKIN, Acute Kidney Injury Network; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; hs-TNT, high-sensitive troponin T; Log. ES, logistic EuroSCORE; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAD, peripheral artery disease; PAH, pulmonary arterial hypertension; Q, quartile; Q4, upper quartile; TR, tricuspid valve regurgitation

deficiency or iron deficiency anaemia impacts prognosis after TAVR remains to be investigated in future studies.

Apart from the cardiovascular context in general, several nutritional factors are discussed to have an impact on frailty. Studies seem to indicate a protective role of protein supplementation. However, it is well established that excess protein intake can also be harmful.<sup>30</sup> Other discussed nutritional factors are, for example, vitamin D, omega-3 fatty acids and medium-chain triglycerides.<sup>30</sup> A Mediterranean diet also seems to have a preventive effect against frailty.<sup>30,31</sup> Hsieh et al.<sup>32</sup> performed a randomized controlled trial to

investigate individualized home-based exercise and nutrition interventions to improve frailty in older adults. In their study, 319 pre-frail or frail patients were randomized and followed up for 3 months. They showed that exercise and nutrition interventions are effective tools in improving frailty and physical performance.<sup>32</sup> Two important components of the GNRI are serum albumin and BMI. In case of chronic malnutrition, as a lack of protein and amino acid supply, the formation of albumin and serum albumin, among other protein reserves, is reduced. In particular, an optimized diet with sufficient/supplemented protein intake might influence serum albumin. In addition, if the diet is accompanied by weight gain, ideally in muscle mass, the BMI is elevated, and in consequence, the GNRI increases. It seems intuitive that a prehabilitation approach including a nutrition intervention may improve outcomes in a subgroup of TAVR patients.

The GNRI is a well-established screening tool for nutrition-related risk in the elderly.<sup>17,18</sup> It is simple to use and combines two nutritional indicators, serum albumin and the discrepancy between ideal and actual bodyweight.<sup>17</sup> Scores above 98 indicate no nutrition-related risk, whereas lower GNRI scores imply an increased risk of nutrition-related morbidity and mortality.<sup>17</sup> In our study, the rate of all-cause mortality was significantly higher among patients with GNRI < 98 compared with those with GNRI ≥ 98. Multivariable analysis confirmed GNRI < 98 as an independent risk factor for increased all-cause mortality after TAVR, and it was associated with a 44% increase in risk compared with a higher GNRI score.

Our results are consistent with other studies evaluating the GNRI in TAVR patients, which found a significantly higher mortality rate at 3 months<sup>20</sup> or 1 year<sup>15,21,22</sup> among patients with a low baseline GNRI compared to those with a high GNRI. These studies also confirmed a low GNRI to be an independent risk factor for all-cause mortality in multivariable analyses.<sup>15,21,22</sup> In a study involving 412 patients that used the same GNRI cut-off as our study, GNRI ≤ 98 was associated with an adjusted HR of 3.77 (1.54–9.20) for all-cause

**Table 4** Cox regression analysis of factors associated with all-cause mortality

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
GNRI < 98	2.46 (1.95–3.11)	<0.001	1.44 (1.01–2.04)	0.043
Albumin < median (4.0 g/dL)	2.43 (1.90–3.10)	<0.001	1.44 (1.00–2.07)	0.048
hs-TNT Q4 (>45.0 pg/mL)	2.08 (1.62–2.66)	<0.001	1.45 (1.10–1.90)	0.007
NT-proBNP Q4 (>3595 pg/mL)	2.18 (1.69–2.82)	<0.001	1.46 (1.10–1.94)	0.009
Life-threatening bleeding	5.47 (2.80–10.70)	<0.001	3.42 (1.70–6.88)	<0.001
AKIN Stage 3	11.1 (4.89–25.10)	<0.001	4.96 (2.09–11.78)	<0.001
Disabling stroke	9.07 (3.36–24.50)	<0.001	6.25 (2.26–17.25)	<0.001
Log. ES > median (16.1%)	1.38 (1.09–1.75)	0.007	1.16 (0.90–1.48)	0.249
TR III–IV	1.8 (1.07–3.02)	0.028	1.78 (1.05–3.03)	0.034
PAH	1.41 (1.08–1.84)	0.012	1.35 (1.02–1.79)	0.033

Results are presented as adjusted hazard ratio (HR) with 95% confidence interval (CI).

AKIN, Acute Kidney Injury Network; BMI, body mass index; GNRI, Geriatric Nutritional Risk Index; hs-TNT, high-sensitive troponin T; Log. ES, logistic EuroSCORE; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; Q, quartile; Q4, upper quartile; TR, tricuspid valve regurgitation

mortality at 1 year.<sup>21</sup> One study found that addition of the GNRI to conventional surgical risk models (logistic EuroSCORE or Society of Thoracic Surgeons score) resulted in improved predictive ability for mortality.<sup>21</sup> Our study adds to the body of evidence supporting the GNRI as an appropriate risk stratification tool for use in patients being considered for TAVR.

Several other nutritional indices, such as the Mini-Nutritional Assessment-Short Form (MNA-SF), the Controlling Nutritional Status (CONUT), the Prognostic Nutritional Index (PNI) and the original Nutritional Risk Index (NRI), have also been shown to predict outcomes in TAVR patients in a limited number of studies.<sup>5,10,13,14</sup> Of these, the MNA-SF involves self-reporting of nutritional status by patients, whereas the PNI and CONUT, like the GNRI (and NRI), are objective indices based on easily measurable parameters. Whereas the GNRI assesses serum albumin and weight loss,<sup>17</sup> the PNI assesses serum albumin and lymphocyte count,<sup>10</sup> and the CONUT assesses serum albumin, lymphocyte count and total cholesterol.<sup>13</sup> Two small studies have compared the value of the GNRI, PNI and CONUT for predicting 1-year mortality in TAVR patients, with conflicting results. One found that the CONUT and PNI were superior to the GNRI,<sup>33</sup> whereas the other found that the GNRI had better predictive value than the CONUT or PNI.<sup>22</sup> Additional studies are needed to clarify whether any of these indices is better than the others for predicting outcomes in TAVR patients.

Serum albumin level is often reduced in frail patients<sup>25</sup> and in patients with AS<sup>34–36</sup> hence its inclusion in frailty and nutritional indices used in this patient population. In our study, we found that a reduced albumin level (below the median of 4.0 g/dL) is an independent risk factor for all-cause mortality. This is consistent with previous studies that have shown that hypoalbuminaemia is associated with an increased risk of mortality after TAVR.<sup>37,38</sup>

We also identified hs-TNT and NT-proBNP levels as significant predictors of mortality. This finding is in line with two meta-analyses, which concluded that an elevated baseline level of NT-proBNP and hs-TNT is associated with mortality after TAVR.<sup>39</sup> Notably, patients with a low GNRI had significantly elevated cardiovascular biomarkers and a higher prevalence of chronic heart failure compared with the normal-GNRI group. Our data reflect the crucial interplay between frailty, cachexia and heart failure.<sup>38,39</sup>

### Limitations

This was a retrospective single-centre study with the focus on all-cause mortality. Both measured and unmeasured confounding factors may limit the conclusions that can be drawn from our analysis. However, the main outcome was confirmed in a separate validation cohort that included patients from another high-volume TAVR centre. The development and validation cohort together involved more than 1900

patients. The observed rates of MR and TR were based on a pre-procedural echocardiographic examination. Although it is known that especially MR severity may significantly improve after TAVR,<sup>40,41</sup> this has not been systematically assessed in our study. We consider this justified as (1) the association between poor nutritional status and higher rates of significant MR and TR stresses the relationship between poor nutritional status and heart failure, (2) it can be expected that a significant number of patients had an improvement in terms of MR and TR severity, and (3) even if patients with MR/TR IV were excluded from the analysis, GNRI still would remain a statistically significant factor. Taken together, our study supports the relevance of GNRI as a predictive biomarker for all-cause mortality after TAVR. Further work is necessary to determine the prognostic impact of nutritional interventions in a subgroup of TAVR patients.

### Conclusions

A low GNRI (<98) was associated with an increased risk of all-cause mortality in patients undergoing transfemoral TAVR. The GNRI is a simple objective tool for assessing nutritional-related risk that could aid in risk stratification of patients with severe AS being considered for TAVR: In addition, our findings may pave the way for future intervention studies targeting malnutrition as a modifiable risk factor.

### Ethical standards

The study was performed in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki. The study and the combination of both datasets were approved by the Ethics Committee at the University of Kiel under the numbers A174/09 and D529/16 and the Bonn University under the number 077/14. Informed consent was obtained from all participants.

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## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** ROC Analysis for the prognostic impact of GNRI, hs-TNT, NT-proBNP and the logistic EuroSCORE.

*Legend:* AUC, Area Under the Curve.

## Conflicts of Interest

Hatim Seoudy, Baravan Al-Kassou, Jasmin Shamekhi, Atsushi Sugiura, Johanne Frank, Mohammed Saad, Anna Katharina Seoudy, Thomas Puehler, Dominik Schulte and Matthias Laudes declare no conflict of interest for this study. Peter Bramlage received research funding and honoraria for his advisory role from Edwards Lifesciences and Abbott. Georg

Lutter is consultant for Medtronic and Abbott. Georg Nickenig received lecture fees from Edwards Lifesciences. Norbert Frey received lecture fees from Edwards Lifesciences. Jan-Malte Sinning has received research funding and speaker honoraria from Medtronic, Boston Scientific, Abbott, Abiomed and Edwards Lifesciences. Derk Frank is consultant for Edwards Lifesciences and Medtronic and received research funding from Edwards Lifesciences.

## Contributors

Study conception and design: HS, DF. Acquisition of data and/or analysis and interpretation of data: HS, BAK, JS, AS, JF, MS, PB, AKS, TP, GL, DS, ML, GN, NF, JMS, DF. Drafting of manuscript: HS, PB, DF. Critical revision: BAK, JS, AS, JF, MS, AKS, TP, GL, DS, ML, GN, NF, JMS. Final approval: all.

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