

# Nutritional status in tricuspid regurgitation: implications of transcatheter repair

Christian Besler<sup>1†</sup>, Matthias Unterhuber<sup>1†</sup>, Karl-Philipp Rommel<sup>1</sup>, Elisabeth Unger<sup>1</sup>, Philipp Hartung<sup>1</sup>, Maximilian von Roeder<sup>1</sup>, Thilo Noack<sup>2</sup>, Markus Zachäus<sup>3</sup>, Ulrich Halm<sup>3</sup>, Michael Borger<sup>2</sup>, Steffen Desch<sup>1</sup>, Holger Thiele<sup>1</sup>, and Philipp Lurz<sup>1\*</sup>

<sup>1</sup>Department of Internal Medicine/Cardiology, Heart Center Leipzig, University of Leipzig, Leipzig, Germany; <sup>2</sup>Department of Heart Surgery, Heart Center Leipzig, University of Leipzig, Leipzig, Germany; and <sup>3</sup>Department of Internal Medicine and Gastroenterology, Park-Klinikum Leipzig, Leipzig, Germany

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## Aims

To characterize the prevalence and clinical relevance of malnutrition in patients undergoing transcatheter tricuspid valve edge-to-edge repair (TTVR).

## Methods and results

Overall, 86 consecutive patients (mean age  $78 \pm 7$  years) with moderate-to-severe tricuspid regurgitation (TR) at prohibitive surgical risk were analysed. Mini Nutritional Assessment (MNA), quality of life assessment, 6-min walk test distance and laboratory analyses were performed before and 1 month after TTVR. A total of 43 patients (50%) underwent concomitant transcatheter mitral valve repair. According to MNA, 81 patients (94%) were malnourished or at risk of malnutrition before TTVR. Following TTVR, MNA improved in 64 patients (74%). As compared to patients without MNA improvement, patients with increased MNA score had greater reductions in TR [regurgitation volume  $-17.0$  (interquartile range, IQR  $-25.0; -7.0$ ) mL vs.  $-26.4$  (IQR  $-40.3; -14.5$ ) mL,  $P < 0.001$ ] and inferior vena cava diameter. Only patients with increased MNA score displayed a decrease in N-terminal pro-brain natriuretic peptide levels [ $-320$  (IQR  $-1294; 105$ ) pg/mL vs.  $+708$  (IQR  $-342; 2708$ ) pg/mL,  $P = 0.009$ ], improvements in cholinesterase levels ( $0.0 \pm 11.9$   $\mu\text{mol/L}$  vs.  $+10.9 \pm 16.7$   $\mu\text{mol/L}$ ,  $P < 0.001$ ) and renal function during follow-up. Beneficial effects on quality of life scores and 6-min walk test distance following TTVR were observed exclusively in patients with improvement in MNA. During a median follow-up of 6 months, patients with worsened MNA had an increased risk of death and rehospitalization for heart failure.

## Conclusion

Nutritional impairment is common and of prognostic importance in patients undergoing TTVR. Hepatorenal function modestly improves after successful TTVR. Further study of extracardiac implications of TR-associated right heart failure is warranted to improve care in this vulnerable patient population.

## Keywords

Right heart failure • Tricuspid regurgitation • Malnutrition • Transcatheter tricuspid valve edge-to-edge repair • Renal function • Liver function

## Introduction

Moderate-to-severe tricuspid regurgitation (TR) is a common valvular disease with foremost prevalence among the elderly population.<sup>1,2</sup> The most frequent aetiology is functional TR secondary to left-sided valvular or myocardial disease and pulmonary

hypertension.<sup>2</sup> Functional TR is observed in a substantial number of patients with heart failure with reduced left ventricular ejection fraction (LVEF) and is associated with worse survival.<sup>3</sup> Patients with clinically significant TR often present late in the natural history of the disease with symptoms and signs of right ventricular failure, repeat heart failure hospitalizations, various comorbidities

\*Corresponding author: Department of Internal Medicine/Cardiology, Heart Center Leipzig, University of Leipzig, Strümpellstraße 39, 04289 Leipzig, Germany. Tel: +49 341 865252022, Fax: +49 341 8651471, Email: philipp.lurz@medizin.uni-leipzig.de

<sup>†</sup>These authors contributed equally to this manuscript.

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and frailty.<sup>4</sup> Several transcatheter therapies are currently in early clinical testing as an alternative treatment option for severe TR in elderly patients at high or prohibitive surgical risk and persisting symptoms of right heart failure despite optimal medical therapy.<sup>5</sup>

Malnutrition and impairment of hepatic or renal function may complicate the clinical course of patients currently evaluated for transcatheter tricuspid valve therapies. However, the prevalence and clinical relevance of malnutrition as well as periprocedural changes in nutritional status or hepatorenal function in these patients have to date not been studied. Of note, right atrial pressure independently predicts malnutrition in patients with advanced chronic heart failure, and malnutrition is associated with increased mortality in these patients.<sup>6</sup> Right ventricular failure and elevated right atrial pressure have been suggested as important activators of catabolic pathways in patients with advanced heart failure with reduced LVEF.<sup>7</sup> The present study aimed to characterize the prevalence, clinical characteristics, laboratory features and outcome of malnourished patients with symptomatic predominantly functional TR at high surgical risk currently considered for transcatheter tricuspid valve edge-to-edge repair (TTVR).

## Methods

### Patients

Overall, 86 patients with New York Heart Association (NYHA) functional class  $\geq$ II despite guideline-directed medical therapy and clinically relevant TR were included in this single-centre analysis. All patients were discussed within the Heart Team and considered at high or prohibitive surgical risk. A transcatheter approach using the MitraClip™ device (Abbott Vascular, Santa Clara, CA, USA) in the tricuspid position on a compassionate use basis was favoured. Criteria for patient selection were mainly based on echocardiographic imaging as detailed previously.<sup>8–11</sup> A total of 43 patients had concomitant severe mitral regurgitation (MR) and underwent combined transcatheter mitral and tricuspid valve edge-to-edge repair (TMTVR). All procedures were performed between August 2016 and August 2018. Routine clinical assessment before and 1 month after intervention included a careful physical examination, blood sample collection, transthoracic and transoesophageal echocardiography (TOE), a 6-min walk test distance (6MWT) and quality of life assessment using Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Medical Outcomes Study Short Form 36-item questionnaire (MOS SF-36). In 72 patients, an invasive haemodynamic assessment including mean systolic pulmonary artery pressure, pulmonary wedge pressure and left ventricular end-diastolic pressure was performed prior to TTVR or TMTVR. The study was conducted in conformity with the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty of the University of Leipzig. All patients provided written informed consent prior to enrolment in the study.

### Nutritional assessment

Nutritional assessment was performed 1–3 days before TTVR or TMTVR and after 1 month of follow-up using the short form of the Mini Nutritional Assessment (MNA) and Nutritional Risk Screening 2002 (NRS). The NRS estimates undernutrition primarily in the hospital setting based on the two categories of disease severity and undernutrition [assessed by body mass index (BMI), weight loss within the last

3 months and reduced food intake].<sup>12</sup> Patients are scored in each of the two categories with a total score of 0–6. Patients with a total score  $\geq$ 3 are classified as nutritionally at risk.

The purpose of MNA is to detect the presence of undernutrition and the risk of developing undernutrition among the elderly, and is more likely to identify both at an early stage.<sup>12</sup> The MNA questionnaire evaluates changes in appetite or digestive problems, weight loss, mobility, acute illness or psychological stress, neuropsychological problems, and BMI.<sup>12</sup> Patients with an MNA short-form screening score of 12–14 are classified as having a normal nutrition status. Patients with an MNA score of 8–11 are considered at risk of malnutrition and patients with an MNA score of 0–7 are malnourished.

Both scores have previously been validated as malnutrition screening tools of prognostic importance in patients with chronic heart failure.<sup>13,14</sup> An MNA score improvement by at least one point was considered as an improvement in MNA score, and a delta equal to 0 or negative was considered as no improvement.

### Transcatheter tricuspid valve repair

The detailed protocol has been described previously.<sup>9–11,15</sup> In brief, TTVR was performed under general anaesthesia, using the MitraClip™ system and was guided by two- and three-dimensional TOE and fluoroscopy. In cases undergoing TMTVR, mitral valve repair was carried out first and the MitraClip™ system was withdrawn in the right atrium afterwards.<sup>15</sup> Transgastric imaging supported clip orientation and localization in the designed commissure. Leaflet grasping was documented using mid-to-deep transoesophageal four-chamber views corresponding to long-axis and transgastric views. More than one clip was used if satisfactory reduction of TR was not achieved after implantation of the first clip. Procedural success was considered as successful clip deployment with TR reduction of  $\geq$ 1 at 1 month.

### Echocardiography analysis and tricuspid regurgitation grading

Transthoracic echocardiography and TOE were performed according to current guidelines by the American Society of Echocardiography/European Association of Cardiovascular Imaging.<sup>16,17</sup> To take into account the 'torrential' nature of TR severity in some patients currently undergoing TTVR and to consider quantitative TR reductions in patients still exhibiting severe TR after the procedure,<sup>18</sup> one additional TR grade 4 (defined as a vena contracta diameter  $>$ 15 mm) was introduced in line with recent publications in the field.<sup>8–11</sup>

Functional TR was classified according to aetiology in a step-wise fashion: patients on chronic haemodialysis as dialysis-related TR; patients with reduced LVEF ( $<$ 50%) or MR  $\geq$ 2 as left heart disease-related TR; patients with systolic pulmonary artery pressure  $\geq$ 50 mmHg as pulmonary hypertension-related TR; the remaining patients with tricuspid annular dilatation either as atrial functional-related TR or if tricuspid annular plane systolic excursion (TAPSE)  $<$ 16 mm as right ventricular remodelling-related TR.<sup>19</sup>

### Statistical analysis

Statistical analyses were performed with R (version 3.5.2 running on MacOS X). Data were assessed for normality using Kolmogorov–Smirnov tests. Variables are expressed as mean  $\pm$  standard deviation, or median [interquartile range (IQR)] as appropriate. Categorical variables are presented as frequencies

**Table 1** Baseline characteristics of the study population according to the Mini Nutritional Assessment score

	All	MNA >8	MNA ≤8	P-value
Patients, <i>n</i>	86	49	37	
Age, years	77.9 ± 6.5	76.8 ± 7.5	79.5 ± 4.4	0.17
Female	39 (45.3)	20 (40.8)	19 (50.0)	0.33
BMI, kg/m <sup>2</sup>	27.0 ± 4.6	27.5 ± 5.3	26.3 ± 3.5	0.42
EuroSCORE II, %	6.1 [3.9–10.4]	5.5 [3.5–11.0]	6.9 [4.0–10.2]	0.60
STS mortality score, %	3.8 [2.6–6.0]	3.8 [2.5–5.8]	3.8 [2.7–11.1]	0.60
NYHA class				
II	14 (16.3)	10 (20.4)	4 (10.8)	0.23
III	50 (58.1)	27 (55.1)	23 (62.2)	0.51
IV	22 (25.6)	12 (24.5)	10 (27.0)	0.79
Lead across tricuspid valve	30 (34.9)	17 (34.7)	13 (35.1)	0.97
Previous PCI	22 (25.6)	16 (32.6)	6 (16.2)	0.08
Previous CABG	12 (14.0)	9 (18.4)	3 (8.1)	0.17
Ischaemic heart disease	19 (22.1)	11 (22.4)	8 (21.6)	1.0
HFrEF	46 (53.5)	25 (51.0)	21 (56.8)	0.60
Atrial fibrillation	78 (91)	44 (90)	34 (92)	1.0
Chronic pulmonary disease	21 (24.4)	9 (18.4)	12 (32.4)	0.13
Child–Pugh class B	3 (3)	1 (2.0)	2 (5.4)	0.08
MELD score	14.7 [10.1–18.4]	14.6 [9.1–19.1]	14.8 [11.2–17.5]	0.74
ACEI/ARB	73 (84.9)	44 (89.8)	29 (78.4)	0.22
Beta-blocker	79 (91.9)	47 (95.9)	32 (86.5)	0.11
Aldosterone antagonist	26 (30.2)	16 (32.7)	10 (27.0)	0.57
Diuretic	82 (95.3)	47 (95.9)	35 (94.6)	0.77
Furosemide dose equivalent, mg	63.2 ± 53.4	63.0 ± 61.0	63.5 ± 41.6	0.96

Values are expressed as mean ± standard deviation, *n* (%), or median [interquartile range].

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; HFrEF, heart failure with reduced ejection fraction; MELD, Model of End-stage Liver Disease; MNA, Mini Nutritional Assessment; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.

and percentages. Comparisons between groups were made using chi-square tests for categorical variables, continuous variables were compared with unpaired Student's *t*-tests or the non-parametric Mann–Whitney *U* test as appropriate. Differences between baseline and follow-up measurements were analysed using paired sample *t*-tests or Wilcoxon tests in non-normally distributed data. Within-group changes were calculated using Wilcoxon signed-rank tests. The primary endpoint was a composite of all-cause death and rehospitalization for heart failure during the entire follow-up period. Secondary endpoints were improvement in NYHA class, 6MWTD and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at follow-up. The distribution of time-to-event variables for the primary endpoint was estimated using the Kaplan–Meier method with log-rank testing for significance. Univariate binary regression analyses of clinical parameters associated with MNA improvement and with the primary endpoint were performed. For all calculations, two-sided *P*-values <0.05 were considered as statistically significant.

## Results

### Baseline characteristics

Clinical baseline characteristics of the 86 patients enrolled are summarized in Table 1. The mean age was 77.9 ± 6.5 years, with 39 patients (45%) being female. Patients were at high risk for surgery [EuroSCORE II 6.1% (IQR 3.9–10.4), Society of Thoracic

Surgeons Predicted Risk of Mortality for mitral valve repair 3.8 (IQR 2.6–6.0)] and highly symptomatic with 84% of subjects presenting in NYHA class III or IV despite optimized medical therapy including a mean furosemide equivalent dose of 63 mg per patient. Fifty-five patients (64%) were found to have peripheral oedema, 28 (33%) had pleural effusion and 19 (22%) had ascites. According to the Child–Pugh scoring system, 83 patients (96.5%) were in class A and 3 patients (3.5%) in class B. The Model for End-stage Liver Disease (MELD) scoring was comparable between patients with baseline MNA ≤8 and MNA >8 (Table 1).

### Pre-procedural findings on echocardiography and haemodynamic data

Results of pre-procedural echocardiography are displayed in Table 2. Mean LVEF was 48.2 ± 16.2% with left ventricular end-diastolic diameter being within the upper normal range (52.3 ± 8.9 mm). Severe or massive TR was present in 72 (84%) and 8 (9%) patients, respectively, with a median effective regurgitant orifice area (EROA) of 0.50 cm<sup>2</sup> (IQR 0.30–0.68) and a mean vena contracta of 9.3 ± 2.7 mm. Right ventricular function was impaired in 44 patients (51%) according to TAPSE measurements and in 28 patients (33%) according to right ventricular fractional

**Table 2** Baseline echocardiographic findings according to the Mini Nutritional Assessment score

	All (n = 86)	MNA >8 (n = 49)	MNA ≤8 (n = 37)	P-value
Left ventricular ejection fraction, %	48.2 ± 16.2	48.7 ± 16.8	47.5 ± 15.5	0.67
LVEDD, mm	52.3 ± 8.9	50.7 ± 8.9	54.4 ± 8.5	<b>0.042</b>
TAPSE <17 mm	44 (51.2)	27 (55.1)	17 (45.9)	0.40
RVFAC <35%	28 (32.6)	15 (30.6)	13 (35.1)	0.66
TV EROA (PISA), cm <sup>2</sup>	0.50 [0.30–0.68]	0.50 [0.30–0.60]	0.48 [0.34–0.73]	0.25
TR vena contracta, mm	9.3 ± 2.7	9.1 ± 2.5	9.6 ± 2.9	0.57
TV annulus diameter, mm	49.5 ± 5.1	49.5 ± 4.5	49.5 ± 5.9	0.77
sPAP, mmHg	49.0 [41.3–61.0]	49.0 [40.3–58.0]	49.0 [43.8–68.3]	0.280
IVC diameter, mm	27.0 ± 6.7	25.6 ± 5.6	28.9 ± 7.6	<b>0.009</b>
TR grade				
2	6 (7.0)	3 (6.1)	3 (8.1)	0.72
3	72 (83.7)	44 (89.8)	28 (75.7)	0.08
4	8 (9.3)	2 (4.1)	6 (16.2)	0.06
Concomitant mitral valve clipping	43 (50%)	25 (58)	18 (49)	1.0

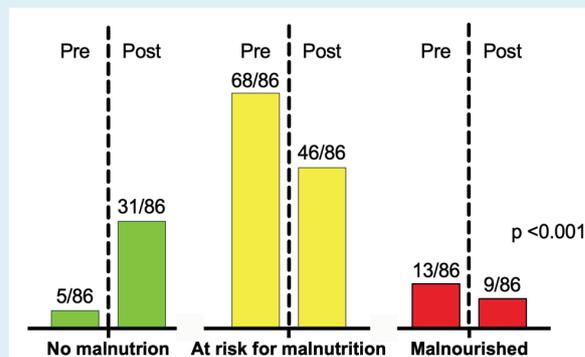
Values are expressed as mean ± standard deviation, n (%), or median [interquartile range].

EROA, effective regurgitant orifice area; IVC, inferior vena cava; LVEDD, left ventricular end-diastolic diameter; MNA, Mini Nutritional Assessment; PISA, proximal isovelocity surface area; RVFAC, right ventricular fractional area change; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV, tricuspid valve.

area change. TR was functional in 81 patients (94.2%). Out of these 81 patients, 25 presented with atrial functional-related TR, 24 with pulmonary hypertension-related TR, 24 with left heart disease-related TR, 5 with dialysis-related TR and 3 with right ventricular remodelling-related TR (online supplementary Tables S1 and S2). Distribution of putative TR causes did not differ between patients with MNA ≤8 and MNA >8 at baseline (online supplementary Table S1) or patients with and without MNA improvement at follow-up (online supplementary Table S2). A lead across the TV was present in 30 patients, but none of the patients had primarily lead-induced TR. Mean systolic pulmonary artery pressure and pulmonary wedge pressure were higher in patients undergoing TMTVR as compared to TTVR, whereas no significant differences in left ventricular end-diastolic pressure were observed (online supplementary Table S3).

### Pre-procedural status of nutrition

By applying the NRS scoring system, 44 patients (51%) were deemed at risk for malnutrition. According to pre-procedural MNA scores, 5 patients (6%) had a normal nutritional status, 68 patients (79%) were at risk for malnutrition and 13 patients (15%) were malnourished (Figure 1). Median MNA score in the present patient sample was 8, corresponding to the MNA cutoff value to differentiate between patients at risk for malnutrition and malnourished patients. There were no significant differences in baseline characteristics between patients with a median MNA score >8 as compared to patients with a median MNA score ≤8 (Table 1), including NYHA functional class distribution. On echocardiography, patients with a median MNA score ≤8 displayed a larger diameter of the inferior vena cava (IVC) and more profound left ventricular dilatation (Table 2). TR severity, TV annular diameter, right ventricular function and echocardiography-derived estimate



**Figure 1** Nutritional status according to Mini Nutritional Assessment scores at baseline and follow-up after isolated transcatheter tricuspid valve edge-to-edge repair or combined transcatheter mitral and tricuspid valve edge-to-edge repair.

of systolic pulmonary artery pressure were comparable between both groups of patients. Furthermore, no significant differences in NT-proBNP, haemoglobin or C-reactive protein levels as well as measures of renal and liver function parameters were apparent between patients with a median MNA score >8 and patients with a median MNA score ≤8 (online supplementary Table S4).

### Pre-procedural nutrition and quality of life assessment

No significant difference was observed in the SF-36 general health score as well as in the MLHFQ general and MLHFQ physical functioning domains score between patients with a pre-procedural median MNA score >8 and patients with a pre-procedural median MNA score ≤8 (online supplementary Table S5). Also, 6MWT did

**Table 3** Changes in body mass index, furosemide dose, quality of life measures and 6-min walk test distance following isolated transcatheter tricuspid valve edge-to-edge repair or combined transcatheter mitral and tricuspid valve edge-to-edge repair according to Mini Nutritional Assessment score improvement

Parameter	MNA not improved (n = 22)			MNA improved (n = 64)		
	Baseline	1-month FU	Δ	Baseline	1-month FU	Δ
Age, years	76.9 ± 7.7			78.3 ± 6.0		
BMI, kg/m <sup>2</sup>	27.8 ± 6.7	27.5 ± 6.3	-0.39 ± 2.5	26.7 ± 3.7	<b>26.0 ± 3.3<sup>a</sup></b>	-0.85 ± 2.4
Furosemide, mg	70 [35–150]	40 [35–150]	0 [-15 to 20]	40 [20–80]	40 [20–80]	0 [-20 to 10]
MLHFQ	32.0 [26.5–36.8]	34.0 [22.5–47.0]	3.0 [-5.0 to 17.0]	32.0 [23.3–42.8]	<b>24.0 [13.8–35.3]<sup>a</sup></b>	-5.0 [-14.5 to 2.0]
MLHFQ physical	22.2 ± 8.9	22.1 ± 8.7	-0.3 ± 12.5	20.8 ± 7.9	<b>14.8 ± 9.0<sup>a</sup></b>	-5.7 ± 9.2
MOS - SF-36, %	48.1 ± 16.2	44.4 ± 22.6	-4.75 ± 29.3	41.1 ± 16.0	<b>54.3 ± 20.3<sup>a</sup></b>	+14.1 ± 24.5 <sup>b</sup>
MOS - SF-36 physical, %	37.9 ± 29.1	34.3 ± 32.1	-3.0 ± 40.4	26.7 ± 25.2	<b>45.9 ± 29.8<sup>a</sup></b>	+21.6 ± 38.0 <sup>b</sup>
6MWT, m	231 ± 131	213 ± 140	-17.6 ± 97.5	258 ± 128	<b>320 ± 119<sup>a</sup></b>	+54.1 ± 68.5 <sup>b</sup>

Values are expressed as mean ± standard deviation, or median [interquartile range].

6MWT, 6-min walk test distance; BMI, body mass index; FU, follow-up; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MNA, Mini Nutritional Assessment; MOS - SF-36, Medical Outcomes Study - 36-item Short-Form questionnaire.

<sup>a</sup>Difference between baseline and 1-month FU in the MNA improved group with  $P < 0.05$ .

<sup>b</sup>Difference in changes from baseline to 1-month FU values between the MNA not improved and MNA improved groups with  $P < 0.05$ .

not differ between groups. Patients with a pre-procedural median MNA score  $\leq 8$  displayed a lower SF-36 physical role functioning score when compared to patients with a pre-procedural median MNA score  $> 8$ .

## Results of transcatheter tricuspid regurgitation treatment

A total of 43 patients (50%) underwent TTVR for isolated TR, whereas the other half underwent combined TMTVR for concomitant severe MR. In the entire cohort, the proportion of patients with TR grade  $\geq 2$  was reduced from 93% at baseline to 15% following TTVR and TMTVR. Since clip deployment was successful in all patients, procedural success was driven by TR reduction  $\geq 1$  grade at 1 month. A TR reduction  $\geq 1$  grade was achieved in 76 patients (88%) in the entire cohort. According to baseline MNA score, a TR reduction  $\geq 1$  grade was observed in 42/49 patients (86%) with MNA score  $> 8$  and in 34/37 patients (92%) with MNA score  $\leq 8$ . When stratified according to MNA improvement during follow-up, a TR reduction was evident in 58/64 patients (91%) with MNA improvement and 18/22 patients (82%) without MNA improvement. Among patients who underwent TMTVR, no patient showed an MR grade  $> 2$  at follow-up.

## Differences between patients undergoing isolated transcatheter tricuspid valve repair and combined transcatheter mitral and tricuspid valve repair

Due to differences in pathophysiology in patients with isolated TR and those with concomitant MR, separate analyses of patients undergoing isolated TTVR and combined TMTVR were carried out (online supplementary Tables S6–S15). Baseline clinical characteristics were comparable between groups (online

supplementary Tables S6 and S11). Patients with a baseline MNA score  $\leq 8$  in the TTVR cohort displayed a significantly larger IVC diameter. Likewise, a numeric increase in IVC diameter was observed in patients with an MNA score  $\leq 8$  in the TMTVR cohort (online supplementary Tables S7 and S12).

## Post-procedural changes in nutritional status

After 1 month of follow-up, MNA scores improved in 64 patients (74%) (Figure 1). According to MNA score, 31 patients (36%) were found to be in normal nutritional status, whereas 46 patients (53%) were still at risk for malnutrition and 9 patients (10%) were malnourished. Following TTVR or TMTVR, median NRS score declined from 3.0 (IQR 2.5–3.2) to 2.0 (IQR 1.8–2.4,  $P < 0.001$ ) after 1 month of follow-up (online supplementary Figure S1).

## Nutritional status and quality of life following transcatheter tricuspid regurgitation treatment

Patients without an improvement in MNA score following TTVR or TMTVR did not show an improvement in any quality of life measure after 1 month of follow-up (Table 3; online supplementary Tables S8 and S13). 6MWT did not change significantly in patients without MNA improvement (Table 3; online supplementary Tables S8 and S13). Patients with an increase in MNA score after 1 month of follow-up displayed an improvement in general quality of life domains of MLHFQ and SF-36 as well as in the physical functioning role domains of each questionnaire (Table 3; online supplementary Tables S8 and S13). In contrast to patients without improvement in MNA score, 6MWT significantly increased in patients with an improvement in MNA score, regardless of whether

**Table 4** Echocardiographic findings in patients with or without Mini Nutritional Assessment score improvement at baseline and follow-up

Parameter	MNA not improved (n = 22)			MNA improved (n = 64)		
	Baseline	1-month FU	Δ	Baseline	1-month FU	Δ
LVEF, %	42.6 ± 19.4	42.3 ± 17.8	-0.27 ± 9	50.1 ± 14.6	51.8 ± 12.5	1.2 ± 8.4
LVEDD, mm	56.5 ± 9.1	56.9 ± 7.2	0.5 ± 5.0	50.8 ± 8.4	50.5 ± 7.0	-0.05 ± 5.4
TAPSE, mm	16.5 ± 4.9	16.1 ± 4.2	-0.5 ± 4.3	16.7 ± 4.2	16.4 ± 3.9	-0.4 ± 3.9
RVFAC, %	39.3 ± 11.4	38.3 ± 9.7	-0.9 ± 10.3	38.4 ± 9.6	37.6 ± 8.9	-1.0 ± 9.0
TV EROA (PISA), cm <sup>2</sup>	0.5 [0.3–0.6]	<b>0.2 [0.1–0.5]<sup>a</sup></b>	-0.2 [-0.3 to 0.6]	0.5 [0.4–0.7]	<b>0.2 [0.1–0.3]<sup>b</sup></b>	-0.3 [-0.4 to -0.1]
TR vena contracta, mm	9.0 [7.8–11.3]	<b>6.0 [4.0–7.3]<sup>a</sup></b>	-3.0 [-5.3 to -1.0]	9.0 [7.0–10.8]	<b>5.0 [4.0–6.0]<sup>b</sup></b>	-4.0 [-5.0 to -2.8]
TV annulus diameter, mm	49.5 ± 5.6	<b>43.1 ± 7.2<sup>a</sup></b>	-6.4 ± 6.6	49.5 ± 5.0	<b>45.5 ± 5.7<sup>b</sup></b>	-4.1 ± 5.3
TR volume, mL	40.0 (33.0–57.5)	<b>22.0 (14.5–34.3)<sup>a</sup></b>	-17.0 (-25.0 to -7.0)	44.0 (30.5–64.0)	<b>18.0 (11.5–30.5)<sup>b</sup></b>	<b>-26.4 (-40.3 to -14.5)<sup>c</sup></b>
TR reduction ≥1 grade		18 (82)			48 (75)	
sPAP, mmHg	51.5 (45.5–61.5)	48.0 (35.3–55.3)	-5.0 (-14.3 to 3.3)	48.0 (38.0–61.0)	44.0 (35.5–51.5)	-4.5 (-19.3 to 16.9)
IVC diameter, mm	25.8 ± 5.7	<b>23.4 ± 7.5<sup>a</sup></b>	-2.4 ± 5.0	27.5 ± 7.1	<b>22.2 ± 6.5<sup>b</sup></b>	<b>-5.4 ± 7.1<sup>c</sup></b>

Values are expressed as mean ± standard deviation, median [interquartile range], or n (%).

EROA, effective regurgitant orifice area; FU, follow-up; IVC, inferior vena cava; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MNA, Mini Nutritional Assessment; PISA, proximal isovelocity surface area; RVFAC, right ventricular fractional area change; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV, tricuspid valve.

<sup>a</sup>Difference between baseline and 1-month FU in the MNA not improved group with  $P < 0.05$ .

<sup>b</sup>Difference between baseline and 1-month FU in the MNA improved group with  $P < 0.05$ .

<sup>c</sup>Difference in changes from baseline to 1-month FU values between the MNA not improved and MNA improved groups with  $P < 0.05$ .

patients underwent TTVR or TMTVR (Table 3; online supplementary Tables S8 and S13). Univariate binary logistic regression analysis showed an association between 6MWT improvement [odds ratio (OR) 6.3, 95% confidence interval (CI) 2.0–19.5;  $P < 0.001$ ] as well as IVC diameter reduction (OR 2.9, 95% CI 1.0–8.5;  $P = 0.05$ ) and MNA improvement (online supplementary Figure S2).

## Echocardiographic findings in patients with improved nutritional status

Both patients with an improvement in MNA score and patients without an improvement in MNA score exhibited a TR reduction following TTVR or TMTVR according to EROA and vena contracta measurements of TR (Table 4; online supplementary Tables S9 and S14). Although the numeric decrease in EROA and vena contracta measurements of TR were more pronounced in patients with improved MNA score, this between-group difference did not reach statistical significance. The decrease in TR regurgitant volume according to proximal isovelocity surface area and the decline in the IVC diameter was significantly more pronounced in patients with an improved MNA score at follow-up (Table 4). When patients with TTVR and TMTVR were analysed separately, in both groups those patients with an MNA improvement also exhibited larger reductions in IVC diameter (online supplementary Tables S9 and S14). No differences in left ventricular diameter and LVEF as well as right ventricular function were apparent between patients with and without an improvement in MNA score at follow-up (Table 4; online supplementary Tables S9 and S14).

## Changes in laboratory parameters following transcatheter tricuspid regurgitation treatment

Laboratory parameters before and 1 month after TTVR or TMTVR are summarized in Table 5 and online supplementary Tables S10 and S15. NT-proBNP levels decreased 1 month after TTVR in patients with improved MNA score on follow-up. A statistically non-significant increase in NT-proBNP levels was apparent in patients without improvement in MNA score after 1 month of follow-up.

Renal function parameters and cholinesterase enzyme levels improved significantly in the total group of patients with an increased MNA score after 1 month of follow-up. Moreover, blood urea nitrogen levels, total bilirubin, gamma-glutamyltransferase and alkaline phosphatase levels decreased, whereas total serum protein levels increased in patients with improved MNA score on follow-up. In the group of patients without MNA score improvement after 1 month of follow-up, no significant differences between baseline and follow-up laboratory parameters were observed. MELD score showed a stronger arithmetic decrease in patients with MNA improvement at 1 month without reaching statistical significance (Table 5).

## Prognostic relevance of nutritional status

During a median follow-up of 6 months, 13 patients (15%) died and 22 patients (25.6%) were readmitted to hospital for

**Table 5** Changes in laboratory parameters following isolated transcatheter tricuspid valve edge-to-edge repair or combined transcatheter mitral and tricuspid valve edge-to-edge repair according to Mini Nutritional Assessment score improvement

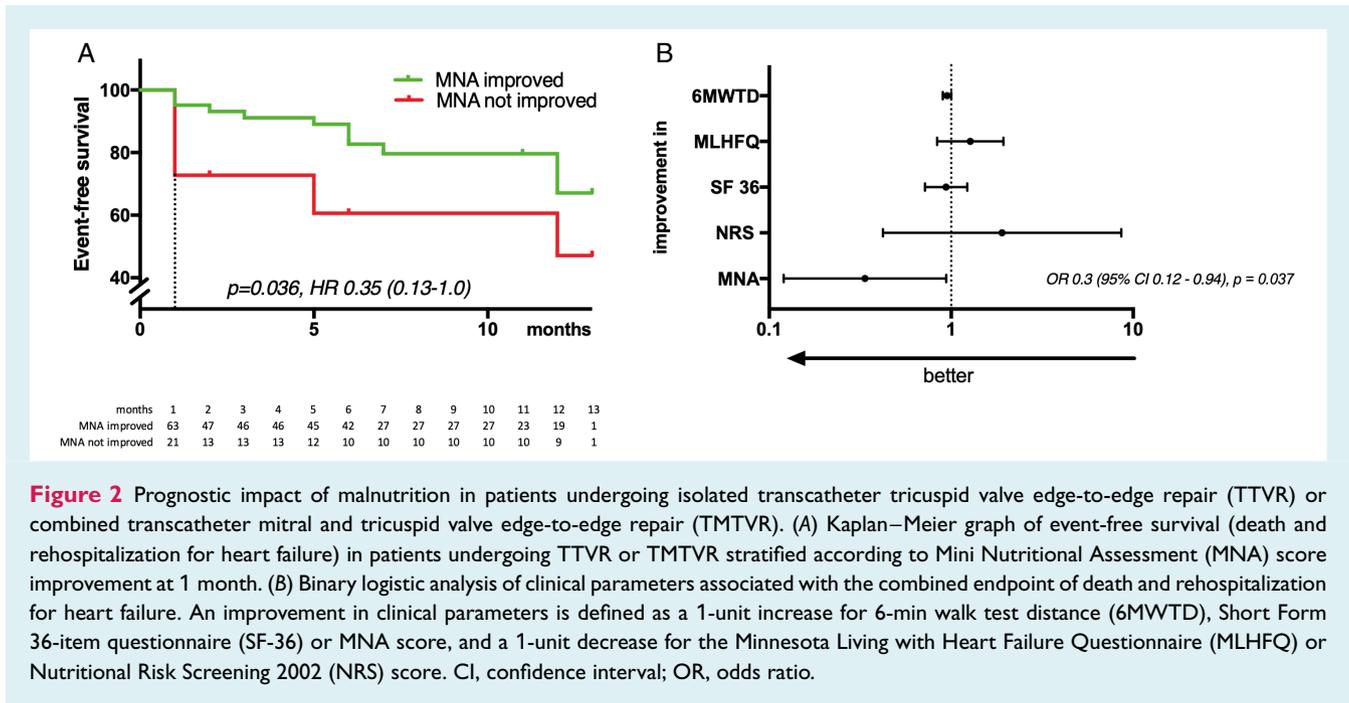
Parameter	MNA not improved (n = 22)		MNA improved (n = 64)	
	Baseline	1-month FU	Baseline	1-month FU
NT-proBNP (pg/mL)	5299 [1931–13 845]	6699 [2315–18 153]	3038 [1897–6298]	2474 <sup>a</sup> [1417–5075]
eGFR, mL/min	38.8 ± 12.7	38.3 ± 17.3	45.7 ± 17.3	49.2 ± 17.1 <sup>a</sup>
Creatinine, mg/dL	1.7 [1.3–2.3]	1.8 [1.3–2.3]	1.4 [1.1–1.6]	1.3 [1.0–1.5] <sup>a</sup>
BUN, mmol/L	14.2 [9.6–21.5]	13.7 [8.0–27.5]	10.3 [8.4–14.9]	9.4 [7.1–12.0] <sup>a</sup>
Bilirubin total, µmol/L	10.8 [5.7–14.0]	12.5 [8.8–13.9]	14.0 [9.0–19.0]	11.7 [8.6–16.7] <sup>a</sup>
AST, µmol/L	0.46 [0.41–0.52]	0.44 [0.36–0.52]	0.43 [0.36–0.51]	0.43 [0.35–0.52]
ALT, µmol/L	0.3 [0.3–0.5]	0.3 [0.3–0.4]	0.34 [0.26–0.42]	0.29 [0.23–0.40]
γGT, µmol/L	1.6 [1.0–3.3]	1.3 [0.9–2.3]	1.6 [1.0–2.5]	1.3 <sup>a</sup> [0.8–2.6]
Alcaline phosphatase, µmol/L	1.5 [1.3–1.8]	1.7 [1.4–1.9]	1.5 [1.2–2.2]	1.5 [1.1–1.9] <sup>a</sup>
Albumin, g/L	42.2 [38.5–44.2]	42.9 [38.9–45.9]	44.0 [40.0–46.0]	45.0 [42.4–46] <sup>a</sup>
Leucocytes, Gpt/L	6.9 [5.5–7.5]	6.9 [5.7–7.5]	7.1 [5.8–8.0]	6.5 [5.5–7.5]
Haemoglobin, mmol/L	7.2 ± 1.4	6.8 ± 1.1	7.7 ± 1.4	7.5 ± 0.9
CHE, µmol/L	87.1 ± 35.8	88.8 ± 31.7	87.7 ± 27.5	97.8 ± 28.0 <sup>a</sup>
Haematocrit	0.33 ± 0.06	0.35 ± 0.04	0.36 ± 0.05	0.36 ± 0.05
C-reactive protein, mg/L	6.0 [4.3–24.9]	17.0 [3.2–76.8]	3.6 [1.1–7.4]	2.9 [1.6–6.7]
Total serum protein, g/L	70.9 [62.1–75.3]	65.2 [63.3–72.9]	68.6 [64.5–72.3]	71.3 [68.2–74.6] <sup>a</sup>
MELD score	15.2 [8.7–20.4]	15.1 [7.2–21.6]	14.6 [10.9–18.1]	11.7 [9.3–14.9]
			Δ	Δ
			708 [–342 to 2708]	–320 <sup>b</sup> [–1294 to 105]
			–0.5 ± 9.4	+3.5 ± 13.1 <sup>b</sup>
			0.1 [–0.1 to 0.4]	–0.1 [–0.3 to 0.06] <sup>b</sup>
			–0.6 [–2.5 to 3.2]	–1.2 [–4.6 to 0.9]
			1.7 [–1.0 to 4.2]	–2.3 [–6.0 to 1.2]
			–0.02 [–0.1 to 0.02]	0.0 [–0.1 to 0.07]
			–0.01 [–0.1 to –0.03]	–0.04 [–0.12 to 0.06]
			–0.2 [–0.3 to –0.1]	–0.2 [–0.4 to 0.1]
			0.2 [–0.1 to 0.5]	–0.09 [–0.28 to 0.08]
			0.7 [–0.6 to 2.8]	1.0 [–1.0 to 3.5]
			0.05 [–0.9 to 1.2]	–0.4 [–1.0 to 0.4]
			–0.5 ± 1.0	–0.2 ± 1.1
			0.0 ± 11.9	+10.9 ± 16.7 <sup>b</sup>
			0.02 ± 0.05	0.0 ± 0.04
			–0.2 [–11.2 to 15.4]	–0.6 [–4.8 to 1.9]
			1.2 [–3.0 to 2.4]	5.5 [0.03–8.7]
			–0.1 [–1.3 to 1]	–2.9 [–3.3 to –0.5]

Values are expressed as mean ± standard deviation, or median [interquartile range]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CHE, cholinesterase enzyme; eGFR, estimated glomerular filtration rate (Cockcroft–Gault formula); γGT, gamma-glutamyltransferase; MNA, Mini Nutritional Assessment; MELD, Model of End-stage Liver Disease; NT-proBNP, N-terminal pro-brain natriuretic peptide.

<sup>a</sup>Difference between baseline and 1-month Follow-up of MNA improved group with P-value <0.05.

<sup>b</sup>Difference in changes from baseline to 1-month Follow-up values between MNA not improved and MNA improved groups with P-value <0.05.



**Figure 2** Prognostic impact of malnutrition in patients undergoing isolated transcatheter tricuspid valve edge-to-edge repair (TTVR) or combined transcatheter mitral and tricuspid valve edge-to-edge repair (TMTVR). (A) Kaplan–Meier graph of event-free survival (death and rehospitalization for heart failure) in patients undergoing TTVR or TMTVR stratified according to Mini Nutritional Assessment (MNA) score improvement at 1 month. (B) Binary logistic analysis of clinical parameters associated with the combined endpoint of death and rehospitalization for heart failure. An improvement in clinical parameters is defined as a 1-unit increase for 6-min walk test distance (6MWT), Short Form 36-item questionnaire (SF-36) or MNA score, and a 1-unit decrease for the Minnesota Living with Heart Failure Questionnaire (MLHFQ) or Nutritional Risk Screening 2002 (NRS) score. CI, confidence interval; OR, odds ratio.

decompensated heart failure. The combined endpoint was reached in 24 patients (27.9%). Cardiovascular death occurred in 9/13 patients (69%). The main cause of cardiac death was progressive heart failure occurring in 7/13 patients (54%). Two patients died in hospital with one patient suffering endocarditis of the mitral and aortic valve, and the other died of progressive right heart failure after TTVR or TMTVR. Three patients died from unknown cause and one patient following a major trauma. Patients with improved MNA score at 1 month had significantly longer survival free of death and heart failure hospitalization (Figure 2A). Those patients whose MNA score remained  $\leq 8$  after 1 month of follow-up had an increased risk of death or rehospitalization for heart failure during follow-up (online supplementary Figure S3). A univariate binary regression analysis for MNA improvement showed an OR of 0.3 (95% CI 0.12–0.94;  $P = 0.037$ ), a specificity of 76% and a sensitivity of 55%, a positive predictive value of 25% and a negative predictive value of 91% for the primary endpoint (Figure 2B). The absolute change in MNA score predicted the combined endpoint of rehospitalization and death for every score point increase with an OR of 0.6 (95% CI 0.5–0.8;  $P = 0.001$ ) in a binary logistic regression model.

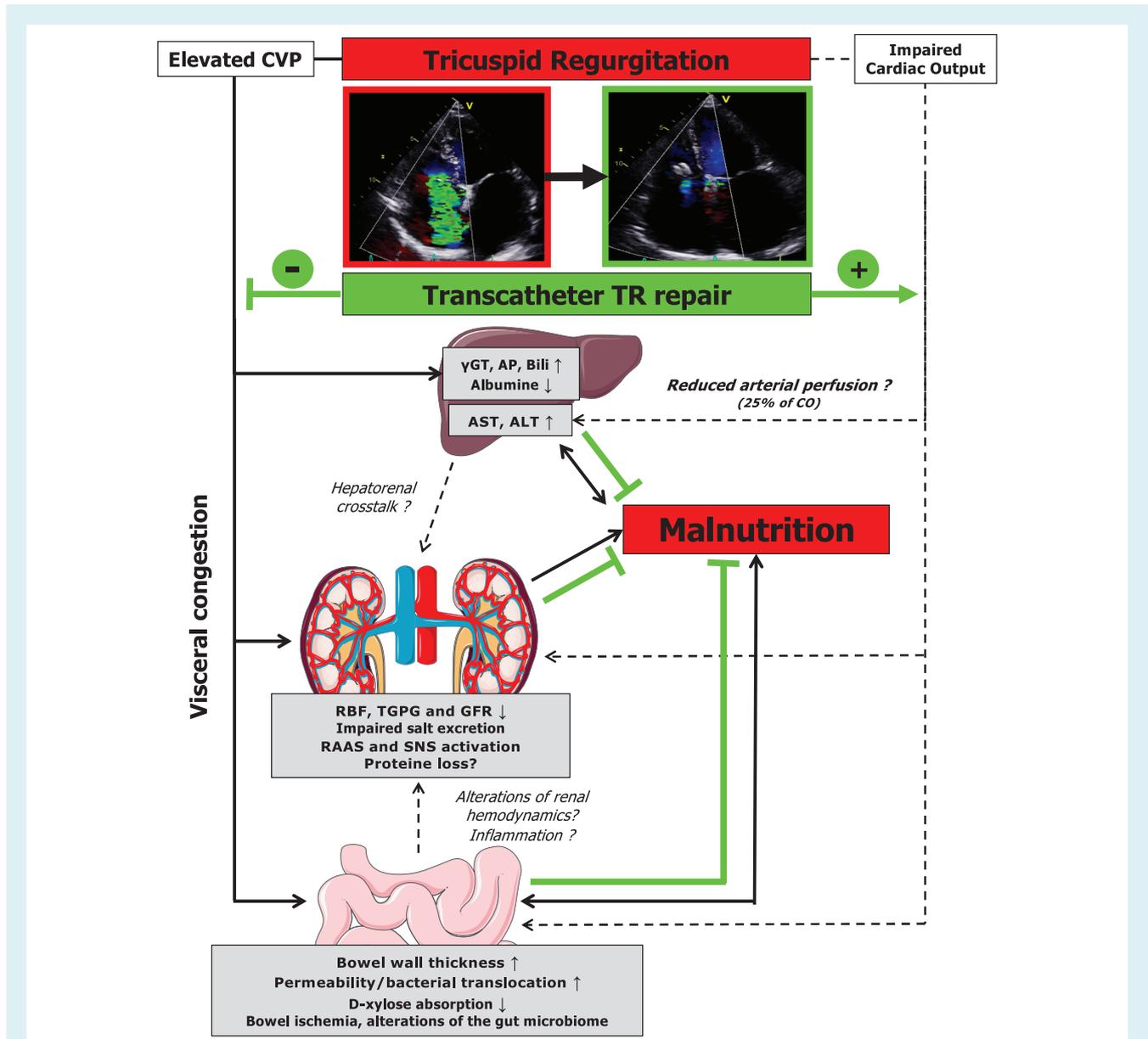
## Discussion

The findings of the present study suggest that a substantial proportion of patients undergoing TTVR or TMTVR are either at risk of malnutrition or malnourished. According to MNA score, nutritional status improves in about three quarters of patients following treatment. The improvement in nutritional status is associated with less venous congestion, lower NT-proBNP levels and laboratory evidence of a modest improvement in kidney and liver function. Only patients with enhanced nutritional status display an

improvement in quality of life measures and 6MWT on follow-up. Notably, worse nutritional status following TTVR or TMTVR is linked to poor survival and more frequent hospitalization rates for heart failure.

Patients currently evaluated for TTVR or TMTVR are in advanced age, display severe-to-massive TR and intractable symptoms of right heart failure. Often, these patients present with many comorbidities and advanced multi-organ sequelae of venous congestion. Interestingly, we did not detect any significant differences in baseline characteristics between patients with pre-procedural MNA scores below and above the median, indicating that nutritional status, although important, might not be well reflected in current measures of pre-procedural patient assessments. Overall, malnutrition has likely a multi-factorial origin, being not only the result of a single deteriorating organ system but the common final pathway of different concurring pathological evolutions. Based on previous knowledge,<sup>20–22</sup> we hypothesize that the improvement in nutritional status of our patients after TTVR could be a result of decongestion of the liver, kidney and gastrointestinal tract (Figure 3). The pathophysiological mechanisms, although intensively investigated, are still not thoroughly understood.

In TR, backward failure leads to direct pressure transduction to the hepatic sinusoids. This causes hepatocyte architecture modifications, leading to atrophy with apoptosis<sup>23</sup> and consecutive impaired perfusion, nutrient uptake and metabolic imbalances.<sup>24</sup> In patients with improved MNA, TTVR or TMTVR and thereby relief of venous congestion led to a reduction in gamma-glutamyltransferase levels and an increase in cholinesterase enzyme as well as small but significant changes in albumin and total protein, suggesting less liver congestion and improved liver synthesis. These findings are in line with other studies that support the hypothesis of reversibility of liver injury when resolving



**Figure 3** Beneficial effects of transcatheter tricuspid regurgitation (TR) repair on extracardiac implications of TR. ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; Bili, bilirubin; CO, cardiac output; CVP, central venous pressure; GFR, glomerular filtration rate;  $\gamma$ GT, gamma-glutamyltransferase; RAAS, renin–angiotensin–aldosterone system; RBF, renal blood flow; SNS, sympathetic nervous system; TGPG, transglomerular pressure gradient.

the underlying cause of right heart failure,<sup>25</sup> if liver disease is not advanced.<sup>26</sup> Accordingly, hepatic function was in the normal range for the majority of patients (96.5%) when assessed by the Child–Pugh classification. This enforces the hypothesis that liver injury in TR is slow, progressive and likely reversible when tissue damage has not yet reached the point of no return.

At baseline, our patients had moderately reduced kidney function. Formerly, worsening renal function has mainly been attributed to over-diuresis and/or poor perfusion as a consequence of reduced cardiac output.<sup>27</sup> However, recent studies suggest mechanisms directly related to venous congestion, which correlate

with estimated glomerular filtration rate decrease and higher mortality.<sup>28</sup> We hypothesize the improvement in renal function following TTVR or TMTVR being a result of less renal vein congestion, which again was seen only in patients with improved MNA.

In the last decade, the role of the gut in patients with heart failure has increasingly been an object of interest.<sup>29</sup> Currently known pathophysiology is based on findings of intestinal malfunction due to liver cirrhosis<sup>30</sup> and patients who underwent Fontan operations. These include intestinal dysmotility, small intestinal bacterial overgrowth, dysbiosis, protein losing enteropathy and intestinal malabsorption, also called 'leaky gut'.<sup>29,30</sup> In case of

an underlying right heart disease such as TR, increased venous pressure translates in higher lymphatic pressure, causing protein losing enteropathy, whereas in patients with isolated portal hypertension it does not. Reports show reversibility if the underlying cause can be treated.<sup>31,32</sup> The observed increase in total serum protein in patients with improved nutrition score could be a consequence of less splanchnic venous congestion with positive effects of the above-mentioned mechanisms. Interestingly, mean BMI was 27 kg/m<sup>2</sup> even in malnourished patients and did not differ significantly across MNA score groups (Table 3; online supplementary Figure S4). This underlines the limitations of BMI as a measure of body composition and nutritional status. A normal BMI must not imply a normal nutrition status.

Transcatheter tricuspid valve edge-to-edge repair or TMTVR also impacts on cardiac output and reduces forward failure, as shown previously<sup>33</sup> and supported by improvements in 6MWT and NT-proBNP levels in our cohort. This itself might have contributed to the improved renal and liver function as well as patients' quality of life, indicating a general improvement of the patient's subjective wellbeing.

To date, several studies have shown the association between right heart disease and impaired nutritional status, including cardiac cachexia.<sup>7,20</sup> The observed improvement in MNA score following TTVR or TMTVR is likely to be multifactorial, whereas the individual contribution and exact mechanism remain speculative. Potential explanations for the increased albumin and total protein levels include increased liver synthesis as well as less urinary and intestinal loss. In addition, improved cardiac output following TTVR<sup>33</sup> and a less catabolic state, leading to more dietary intake and less muscle wasting, might have contributed. Lastly, less abdominal discomfort with less liver congestion after TTVR or TMTVR could have improved appetite in our patients.

Despite all unknowns, the link between nutritional status change and outcome is remarkable. A superior nutritional status after TTVR or TMTVR reflects in increased functional parameters and better quality of life, whereas no improvement and low post-procedural MNA scores pose patients at higher risk for death or rehospitalization for heart failure. These promising results need confirmation in larger cohorts to evaluate the potential role of MNA for predicting outcome of TTVR or TMTVR beyond currently applied risk stratifications.

## Limitations

First, the sample size in the present analysis is limited. Second, the observed changes at 1 month of follow-up need to be observed over a longer period of time in order to determine potential late changes in nutritional status, laboratory findings and prognosis. Also, changes in liver and renal function were small and the clinical relevance remains to be determined. Third, both groups, despite including a comparable ratio of patients concomitantly treated for MR, could be confounded. Forth, mechanisms linking reduced venous congestion to improvements in nutritional status and functional parameters following TTVR or TMTVR remain speculative. Fifth, the number of tests performed increase the risk of a type

1 error. Overall, findings should be considered as hypothesis generating at present. In addition, future studies are needed to compare the diagnostic and prognostic benefit of different malnutrition screening tools in this patient population. In addition, further analyses are needed to address changes in nutritional status over time in more detail, as the current assessment was limited to 1 month.

## Conclusion

This study suggests that a substantial part of elderly patients undergoing TTVR or TMTVR are either at risk for malnutrition or malnourished. At 1 month after TTVR or TMTVR, three-quarter of patients showed an improved nutritional status along with better quality of life and increased exercise capacity, accompanied by ameliorated central venous pressure, renal and hepatic function parameters. Patients with poor nutritional status after TTVR or TMTVR had a higher risk of rehospitalization for heart failure or death. The underlying mechanisms are still insufficiently understood; nonetheless, nutritional status can be used as a new patient-centred marker to judge procedural success and to monitor outcome during follow-up. This could be important for future trial design but also now, as many new transcatheter techniques for transcatheter treatment of TR are being evaluated.

## Supplementary Information

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

**Table S1.** Putative causes of tricuspid regurgitation according to baseline MNA score above or below median in the patient sample.

**Table S2.** Putative causes of tricuspid regurgitation according to MNA improvement after 1 month of follow-up in the patient sample.

**Table S3.** Invasive haemodynamic data at baseline in the patient sample.

**Table S4.** Baseline laboratory findings according to MNA score.

**Table S5.** Quality of life and 6-min walk test distance according to MNA score.

**Table S6.** Baseline characteristics of patients undergoing isolated transcatheter tricuspid valve edge-to-edge repair.

**Table S7.** Baseline echocardiographic findings in patients undergoing isolated transcatheter tricuspid valve edge-to-edge repair.

**Table S8.** Changes in body mass index, furosemide dose, quality of life measures and 6-min walk test distance in patients undergoing isolated transcatheter tricuspid valve edge-to-edge repair.

**Table S9.** Echocardiographic findings at baseline and after 1 month of follow-up in patients undergoing isolated transcatheter tricuspid valve edge-to-edge repair.

**Table S10.** Laboratory findings in patients undergoing isolated transcatheter tricuspid valve edge-to-edge repair at baseline and after 1 month of follow-up.

**Table S11.** Baseline characteristics of patients undergoing combined transcatheter mitral and tricuspid valve edge-to-edge repair.

**Table S12.** Baseline echocardiographic findings in patients undergoing combined transcatheter mitral and tricuspid valve edge-to-edge repair.

**Table S13.** Changes in body mass index, furosemide dose, quality of life measures and 6-min walk test distance in patients undergoing combined transcatheter mitral and tricuspid valve edge-to-edge repair.

**Table S14.** Echocardiographic findings at baseline and after 1 month of follow-up in patients undergoing combined transcatheter mitral and tricuspid valve edge-to-edge repair.

**Table S15.** Laboratory findings in patients undergoing combined transcatheter mitral and tricuspid valve edge-to-edge repair at baseline and after 1 month of follow-up.

**Figure S1.** Nutritional status according to NRS scores at baseline and follow-up after isolated transcatheter tricuspid valve edge-to-edge repair or combined transcatheter mitral and tricuspid valve edge-to-edge repair.

**Figure S2.** Binary logistic regression analysis of clinical parameters associated with MNA improvement.

**Figure S3.** Kaplan–Meier graph of event-free survival (death and rehospitalization for heart failure) in patients undergoing isolated transcatheter tricuspid valve edge-to-edge repair or combined transcatheter mitral and tricuspid valve edge-to-edge repair stratified according to median MNA score at 1 month.

**Figure S4.** Median (interquartile range) MNA scores according to patient body mass index at baseline and follow-up.

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