Nutritional status in tricuspid regurgitation and implications of transcatheter tricuspid edge-to-edge valve repair: Malnutrition in TR - associated right heart failure

Dissertation

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Contents

1 Introduction

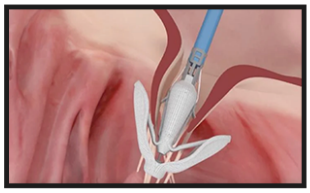
1.1 Tricuspid regurgitation

Significant tricuspid regurgitation (TR) is a valvular disease with increasing prevalence as population is constantly ageing, affecting over 4% of over 75-aged individuals worldwide. [1, 2]. It is associated with multimorbidity and with a poor survival [3]. The most prevalent form of TR in the elderly population is functional (secondary). Common causes can be long standing atrial fibrillation, right ventricular (RV) and atrial (RA) dilation with tricuspid annulus dilation, left heart disease, pulmonary hypertension, atrial septal defects etc. This leads to a coaptation gap between tricuspid leaflets, impairing systolic valve closure. Irrespective of its etiology, TR leads to volume overload and increased wall stress, both negatively influencing remodelling and consequently worsening TR. Previously, TR was considered mainly as a consequence of left-heart disease rather than a relevant disease entity itself and has been long underestimated. Attention was mostly focused on treating underlying other conditions, leaving tricuspid treatment options seen as positive side effect of left-hearted valve disease and heart failure therapies [4–6]. Patients often suffer non-specific symptoms for heart failure, frequently overshadowed by various comorbidities and frailty with consecutive recurrent hospitalizations, low quality of life and poor nutritional status. [7, 8]. Mostly, referral causes are signs of heart failure with fatigue, exercise intolerance, dyspnoea, persistent oedema and ascites. The physical examination has to be accurate to not oversee subtle signs. Frequent findings are systolic murmur, jugular venous congestion and pulse (Lancisi's sign) with hepato-jugular reflux. The most common diseases associated with TR are left-sided heart disease and surgery, atrial fibrillation, pre-capillary pulmonary hypertension, and the presence of RV leads due to cardiac implanted electronic devices [5].

1.2 Tanscatheter edge-to-edge valve leaflet repair

As patients usually present late in the natural history of the disease, frailty and comorbidities prevail and surgical therapy is often deemed at too high risk. Due to the increasing incidence of TR and lacking treatment options, transcatheter tricuspid valve interventions (TTVI) developed with the first in-man successful annuloplasty using the Mitralign (Mitralign Inc., Tewksbury, MA) device (originally designed for transcatheter mitral valve repair) reported in 2015 [9] and the first cases of successful transcatheter edge-to-edge tricuspid valve repair (TTVR) using the MitraClip (Abbott Vascular, Santa Clara, CA, USA) in 2016 [10]. Afterwards, the use of TTVI increased worldwide, in the beginning mostly in the setting of compassionate off-label use or in trials [11–15]. To date, the most frequently adopted device is the MitraClip device [14], which had been initially designed for transcatheter mitral valve repair use. As the TTVR procedure proved to be feasible and safe, more and more devices gained CE- approval in Europe, including the TriClip (Abbott), Pascal and Cardioband (Edwards Lifesciences, Irvine, California) devices [11,13,16,17]. The two transcatheter edge-to-edge repair systems are shown in *Figure 1.*

Figure 1: The currently CE-approved edge-to-edge TTVR devices.



Pascal Device
Edwards

TriClip Device
Abbott

Edge-to-edge TTVR systems rely on the surgical repair idea proposed by Ottavio Alfieri in 1991 [18], where mitral valve regurgitation is repaired using a stitch between the leaflets to clamp the edges, thus creating a double orifice mitral valve.
For TTVR, patients are under general anaesthesia as simultaneous transoesophageal echocardiography is crucial for device placement. The device is introduced through the right femoral vein, entering the right atrium and passing through the tricuspid valve in closed position. Once passed through and beyond the valve, the clip arms are opened and the leaflets grasped according to the regurgitation jet. Once pulled backwards, the clip is closed. Since usually the anteroseptal or posteroseptal commissure are grasped in lateral position, TTVR has the peculiarity of reducing the coaptation gap without necessarily creating two orifices, although tricuspid valve anatomy can vary substantially. Due to different morphologies, device selection for TTVI is crucial. The classical 3-leaflet configuration amounts to approximately 50% of cases, whereas 2- to 5- leaflet configurations are possible.

1.3 Clinical predictors of outcome after TTVR

Evidence continues to grow at a fast pace and currently affirms the feasibility and safety of the TTVR procedure. Propensity score matching analyses and observational data show a trend towards an improved prognosis of patients after TTVR with different TR aetiologies and comorbidities [13, 15, 19–22]. The largest study so far comparing TTVR versus conservative treatment comprises data from the international transcatheter tricuspid valve therapies (TriValve) registry to conservatively treated patients from twenty-two tertiary care centres in Europe and the USA. In this study TTVR was associated with a decrease in both mortality, as well as rates of heart failure rehospitalizations [15]. Thus, it is of paramount importance to identify parameters with positive influence on procedural success and outcome of patients undergoing TTVR.

Left ventricular function

TR can present with reduced, normal, or hyperdynamic left ventricular (LV) contractility. Both reduced and hyperdynamic states have shown to be associated with a higher mortality in comparison to a normal cardiac output [23, 24]. This finding was consistent with later studies of the natural history of severe TR, in which a low or high cardiac output was an independent predictor of mortality [25]. Normal cardiac output patients had significantly better survival than low- and high cardiac output groups in a U-shaped manner. Besides primary LV diseases, LV function can be influenced by RV volume changes due to the limited space in the pericardium [26] and reacts with impaired filling due to impaired distensibility, resulting in heart failure with different expressions of forward and backward failure. Impaired left ventricular ejection fraction showed to be an important prognostic marker, being associated with higher risk for the composite endpoint of heart failure re-hospitalization and death after TTVR compared to patients with preserved ejection fraction [21]. In terms of cardiac output, patients with low and high cardiac output prior to TTVR had worse outcomes after TTVR in comparison to patients with a mid-range cardiac output [27].

Right ventricular function

Assessment of RV function is challenging, as classical RV function parameters e.g.echocardiographically derived tricuspidal annular anterior systolic motion (TAPSE) can be limited by RV loading conditions. Methods including RV free wall strain and magnetic resonance imaging modalities have shown to be accurate in both in natural history of TR [28] and as prognostic marker for TTVR outcomes [29, 30].

Pulmonary artery pressures

RV function was shown to significantly influence outcome, and Right ventricular - pulmonary artery (RV-PA) coupling can help to determine whether RV function is adequately compensated for specific loading conditions. Estimation of RV-PA coupling might be feasible by the derived quotient of echocardiographic TAPSE/PASP, which was shown to be associated with all-cause mortality in patients undergoing TTVR [31, 32].

Hepatic function

TR often is associated with elevated liver enzymes and liver function impairment. Studies have shown a significant improvement in hepatic function after TTVR. Moreover, successful TTVR was significantly associated with liver function score improvement. [33, 34]

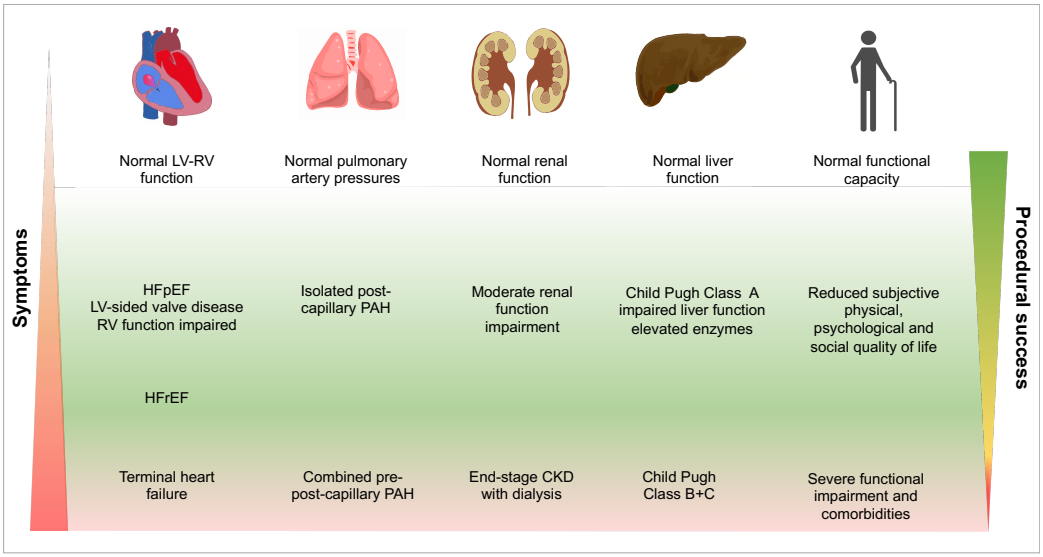


Figure 2: Clinical and physiological features suggesting a favourable outcome after TTVR. LV=Left ventricle; RV=right ventricle; HFpEF=Heart failure with preserved ejection fraction; HFrEF=Heart failure with reduced ejection fraction; PAH=Pulmonary arterial hypertension; CKD=Chronic kidney disease. Adapted from [35].

1.4 Malnutrition in heart failure

Cachexia is a common and serious complication of heart failure and involves severe body fat and muscle loss. Depending on the study design and heart failure stage, the prevalence of cachexia ranges from 13% to 80% and is associated with a high mortality [7, 8, 36]. Heart failure is a summarisation of many pathophysiological alterations. Forward heart failure is the inability of the heart to provide the necessary tissue perfusion due to a decreased output. This leads to weakness, fatigue, cyanosis and hypotension. The activated mechanisms which lead to wasting are complex and seem to

involve inflammatory and neuroendocrine pathways, proteolysis and malabsorption [37–40]. Backwards failure is characterized by an increase in volume and pressure in the ventricle, which in turn translates into a higher atrial pressure. From the RV, this leads to direct pressure transduction to the hepatic sinusoids. One major cause of malnourishment is thought to be congestive hepatopathy, which summarizes the manifestations resulting from passive hepatic congestion due to an increased central venous pressure [41]. This causes hepatocyte architecture modifications, leading to atrophy with apoptosis [42]. The consequences are impaired perfusion, nutrient uptake and metabolic dysbalances leading to fibrosis in the most vulnerable perivenular zone 3 [43]. Typically, impaired liver function parameters are found in these patients [44]. The currently most known mechanisms are based on findings regarding intestinal malfunction due to liver cirrhosis [45, 46]. These include intestinal dysmotility, small intestinal bacterial overgrowth, dysbiosis and intestinal malabsorption, otherwise called 'leaky gut'. There seems to be a fundamental difference between the two causes of intestinal malfunction: in liver cirrhosis, intestinal congestion is due to primary portal hypertension, as in right- hearted disease following elevated central venous pressures lead also to congestion of the superior vena cava, where the thoracic lymph duct flows into the anonym vein. In the case of underlying right-hearted disease due to TR, the increased pressure translates in an increased lymphatic pressure, causing often not overt protein-losing enteropathy [46]. This condition has been studied in patients with right-sided heart disease, mostly constrictive pericarditis or after Fontan procedures [47–50], and various reports show reversibility if the underlying cause can be treated [51–54]. On the contrary, in patients with isolated portal hypertension due to primary hepatic disease this phenomenon could not be observed [55]. Recently, there has been a strong body of evidence suggesting a correlation between the heart-kidney-liver axis in patients with severe TR with liver function parameters, mimicking a hyperdynamic state and being of prognostic value in the patients undergoing

TTVR [27, 34].
The aim of this study was to further investigate the role of TR in this intricate interplay and to explore the heart-liver-kidney axis in function to nutritional status improvement of patients undergoing TTVR.

2 Objective and Methods

The present study aimed to characterize the prevalence, clinical characteristics, laboratory features and outcome of malnutrition in the context of symptomatic severe TR as well as generate the hypothesis for the role of TTVR in the complex mechanism of cardio-renal-hepatic interaction.

2.1 Patient inclusion

Between August 2016 and August 2018, eighty-six 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 previously discussed within the Heart Team, which consisted of an expert joint committee comprising cardio-thoracic surgeons and cardiologists. To be eligible for a transcatheter approach, the patient was required to be 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 state-of-the art clinical and echocardiographic imaging criteria [10, 14, 56]. Fourty-three patients had concomitant severe mitral regurgitation (MR) and underwent combined transcatheter mitral and tricuspid valve edge-to-edge repair (TMTVR). Routine clinical assessment before and 1 month after intervention included a careful physical examination with assessment of peripheral edema, ascites, blood sample collection, transthoracic and transoesophageal echocardiogra-

phy (TOE), a 6-minute walking test distance (6MWTD) and quality of life assessment. 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.

2.2 Nutritional assessment

Nutritional status is associated with age, comorbidities, social, physiological, psychological and environmental factors. As body composition changes over the time, older adults show a shift in nutritional and lifestyle behaviors, resulting in considerable muscle mass loss and a reduction in metabolic resting rate [57]. Malnutrition and impairment of hepatic or renal function are common findings in patients with severe TR and, specifically, in the subgroup of patients undergoing TTVR. Both MNA and NRS scores were evaluated at baseline and at 1-month follow-up in all patients.

2.3 Mini Nutritional Assessment (MNA)

The Mini nutritional assessment questionnaire was developed for older adults, which are especially prone to malnutrition. In many circumstances, malnutrition is undetected and is often erroneously accepted as a bystander of the normal ageing process. To account for this possible problem, joint commissions of hospitals increasingly emphasized the necessity a state-of-the-art algorithms to assess nutrition status fast and easy at first patient contact. By using a standardized algorithm for assessment, nutrition disorders of the elderly can be quickly recognized in order to avoid underfeeding and to provide further nutrition-centred care during and after the hospital stay. Guigoz

et al. [58] developed the Mini Nutritional Assessment score to overcome this need using biometric data and patient history. The MNA short form comprises a six-question screening, suitable to decide if further assessment is needed. Starting from appetite or swallowing difficulties, it assesses weight loss and mobility of the patient, asking ultimately for physical stress, neuropsychological problems and body- mass index. A total score from 0 to 7 points indicates a malnourished patient, a score from 8 to 11 points suggest a patient to be at risk for malnutrition. A score of 12 to 14 points designates patients with normal nutrition status. The form used for this study is shown in *Table 1.* The MNA - Long Form is a more thorough assessment, investigating aforementioned nutritional habits in a more detailed way with a maximum score of 30 points.

Table 1: The MNA form used in this study.

Screening
Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties? 0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake
Weight loss during the last 3 months 0 = weight loss greater than 3kg 1 = does not know 2 = weight loss between 1 and 3kg 3 = no weight loss
Mobility 0 = bed or chair bound 1 = able to get out of bed / chair but does not get out 2 = goes out
Has suffered psychological stress or acute disease in the past 3 months? 0 = yes 2 = no
Neuropsychological problems 0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems
Body Mass Index (BMI) in kg/m^2 0 = BMI less than 19 1 = BMI 19 to 21 2 = BMI 21 to 23 3 = BMI 23 or greater

Table 2: Nutritional Risk Screening assessment adapted from *Kondrup et al.* [60]

	Nutritional status	Severity of disease
Absent Score 0	Normal nutritional status	Normal nutritional requirements
Mild Score 1	Weight loss > 5% in 3 months Or Food intake below 60% of normal requirement in preceding week	Hip fracture Chronic patients, in particular with acute complications: cirrhosis, COPD, Chronic hemodialysis, diabetes, oncologic diseases
Moderate Score 2	Weight loss > 5% in 2 months Or BMI 18.5-20.5 + impaired general condition Or food intake < 25% of normal requirement in preceding week	Major abdominal surgery Stroke Severe pneumonia, hematologic malignancy
Severe Score 3	Weight loss > 5% in 1 month Or BMI 18.5 + impaired general condition Or food intake <25% of normal requirement in preceding week	Head injury Bone marrow transplantation Intensive care patients

Calculate the total score:

1. Find score for nutritional status (only one: choose the variable with highest score) and severity of disease (stress metabolism, i.e. increase in nutritional requirements)
2. Add the two scores (=total score)
3. If age >70 years: add 1 to the total score to correct for frailty of elderly
4. If age-corrected total ≥3: start nutritional support

2.4 Nutritional risk score (NRS)

The purpose of the NRS is to uncover the presence of malnutrition and the risk of developing in in hospital settings, containing a grading of disease severity as a reflection of increased nutritional awareness need. It is meant to cover the most frequent disease categories which happen to be present in hospitals [59]. *Table 2* shows the screening system. Patients are scored in each of the two components - nutritional status and disease severity, according to whether they are absent, mild, moderate or severe. Subsequently, these two compartments are added giving a total score of 0-6 [60], a higher score indicating a worse nutrition status.

Quality Of Life (QoL)

As QoL is an important endpoint in health and medicine, especially in a field exploring a relatively new intervention as TTVR. Two QoL questionnaires were used to assess the baseline and follow-up patient's wellbeing.

The SF-36 and the MLHFQ scores were evaluated at baseline and at 1-month follow-up in all patients.

Short Form - 36

The Short-Form 36 Questionnaire (SF-36) comprises 8 subscales which are scored by 36 questionnaires for health-related QoL evaluation. Physical component summary and mental component summary were reported separately, where a higher score indicates a better QoL. The SF-36 questionnaire used in this study is represented in *Figure 4* in the appendix.

Minnesota Living with Heart Failure Questionnaire

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) consists of 21 questions (0 to 5 points in each section), reflecting physical, emotional and socioeconomic conditions. Each of these conditions can be differently influenced by HF. A higher MLHFQ score is a marker for worse QoL associated to heart failure and directly linked to outcome [61]. The MLHFQ used in this study is depicted in *Figure 5* in the appendix.

2.5 Transcatheter tricuspid valve repair procedure

TTVR was performed under general anaesthesia, using the Abbott MitraClip system and was guided by two- and three-dimensional TOE and fluoroscopy. In cases undergoing TMTVR, mitral valve repair was carried out first by performing transseptal puncture and and deploying the device in the mitral valve commissure. Afterwards, the MitraClip system was withdrawn in

the right atrium. Transgastric imaging supported clip orientation and localization in the designed commissure to place the clip system in the most suitable position. Leaflet grasping was documented using mid-to-deep transoesophageal four-chamber views corresponding to long-axis and transgastric views, using the combined X-plane grasping view. More than one clip was used if satisfactory reduction of TR was not achieved after implantation of the first clip. In this study, procedural success was considered as successful clip deployment with TR reduction of $\geq$1 at 1 month.

2.6 Echocardiographic analysis and TR grading

Transthoracic echocardiography and TOE were performed according to current guidelines by the American Society of Echocardiography/European Association of Cardiovascular Imaging [62–64]. 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, one additional TR grade was introduced in line with recent publications [65].

Functional TR was classified according to aetiology in a stepwise 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.

2.7 Statistical analysis

Statistical analyses were performed with R (version 3.5.2, R Foundation for Statistical Computing, Vienna). Data were assessed for normality us-

ing Kolmogorov-Smirnov tests. Variables are expressed as mean ± standard deviation, or median [interquartile range (IQR)] as appropriate. Categorical variables are presented as frequencies 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. To assess whether the association between outcome and nutritional status was of a causal nature, a mediation analysis was performed.

ESC European Society of Cardiology

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RESEARCH ARTICLE

Nutritional status in tricuspid regurgitation: implications of transcatheter repair

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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 ± 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 ± 11.9 μmoL/L vs. +10.9 ± 16.7 μmoL/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.[1,2] The most frequent aetiology is functional TR secondary to left-sided valvular or myocardial disease and pulmonary hypertension.[2] 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.[3] 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 and frailty.[4] Several transcatheter therapies are currently in early clinical testing as an alternative treatment option for severe TR in

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elderly patients at high or prohibitive surgical risk and persisting symptoms of right heart failure despite optimal medical therapy.[5]

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.[6] 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.[7] 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 ≥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.[8–11] 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 (6MWTD) 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].[12] Patients are scored in each of the two categories with a total score of 0–6. Patients with a total score ≥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.[12] The MNA questionnaire evaluates changes in appetite or digestive problems, weight loss, mobility, acute illness or psychological stress, neuropsychological problems, and BMI.[12] 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.[13,14] 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.[9–11,15] 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.[15] 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 ≥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.[16,17] 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,[18] one additional TR grade 4 (defined as a vena contracta diameter >15 mm) was introduced in line with recent publications in the field.[8–11]

Functional TR was classified according to aetiology in a stepwise fashion: patients on chronic haemodialysis as dialysis-related TR; patients with reduced LVEF (<50%) or MR ≥2 as left heart disease-related TR; patients with systolic pulmonary artery pressure ≥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.[19]

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 ± standard deviation, or median [interquartile range (IQR)] as appropriate. Categorical variables are presented as frequencies and percentages. Comparisons between groups were made using

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

	All	MNA >8	MNA ≤8	*P*-value
Patients, *n*	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^2	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.

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^2 (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 area change. TR was functional in 81 patients (94.2%). Out of

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	**0.042**
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^2	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	**0.009**
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.

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 of systolic pulmonary artery pressure were comparable between

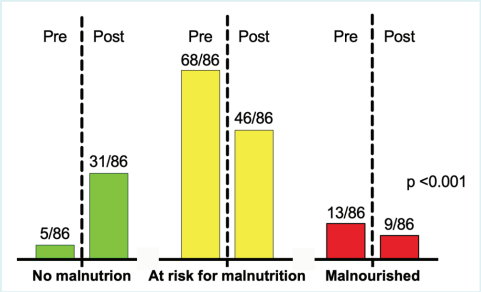

Figure 1 Nutritional status according to Mini Nutritional Assessment scores at baseline and follow-up after isolated transcatheter tricuspid valve edge-to-edge repair or combined transcatheter mitral and tricuspid valve edge-to-edge repair.

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, 6MWTD did not differ between groups. Patients with a pre-procedural median

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^2	27.8 ± 6.7	27.5 ± 6.3	−0.39 ± 2.5	26.7 ± 3.7	**26.0 ± 3.3**[a]	−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]	**24.0 [13.8–35.3]**[a]	−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	**14.8 ± 9.0**[a]	−5.7 ± 9.2
MOS - SF-36, %	48.1 ± 16.2	44.4 ± 22.6	−4.75 ± 29.3	41.1 ± 16.0	**54.3 ± 20.3**[a]	+**14.1 ± 24.5**[b]
MOS – SF-36 physical, %	37.9 ± 29.1	34.3 ± 32.1	-3.0 ± 40.4	26.7 ± 25.2	**45.9 ± 29.8**[a]	+**21.6 ± 38.0**[b]
6MWTD, m	231 ± 131	213 ± 140	−17.6 ± 97.5	258 ± 128	**320 ± 119**[a]	+**54.1 ± 68.5**[b]

Values are expressed as mean ± standard deviation, or median [interquartile range].
6MWTD, 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.
[a]Difference between baseline and 1-month FU in the MNA improved group with $P < 0.05$.
[b]Difference in changes from baseline to 1-month FU values between the MNA not improved and MNA improved groups with $P < 0.05$.

MNA score ≤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 ≥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 ≥1 grade at 1 month. A TR reduction ≥1 grade was achieved in 76 patients (88%) in the entire cohort. According to baseline MNA score, a TR reduction ≥1 grade was observed in 42/49 patients (86%) with MNA score >8 and in 34/37 patients (92%) with MNA score ≤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 ≤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 ≤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 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*). 6MWTD 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, 6MWTD 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^2	0.5 [0.3–0.6]	**0.2 [0.1–0.5]**[a]	−0.2 [−0.3 to 0.6]	0.5 [0.4–0.7]	**0.2 [0.1–0.3]**[b]	−0.3 [−0.4 to −0.1]
TR vena contracta, mm	9.0 [7.8–11.3]	**6.0 [4.0–7.3]**[a]	−3.0 [−5.3 to −1.0]	9.0 [7.0–10.8]	**5.0 [4.0–6.0]**[b]	−4.0 [−5.0 to −2.8]
TV annulus diameter, mm	49.5 ± 5.6	**43.1 ± 7.2**[a]	−6.4 ± 6.6	49.5 ± 5.0	**45.5 ± 5.7**[b]	−4.1 ± 5.3
TR volume, mL	40.0 (33.0–57.5)	**22.0 (14.5–34.3)**[a]	−17.0 (−25.0 to −7.0)	44.0 (30.5–64.0)	**18.0 (11.5–30.5)**[b]	**−26.4 (−40.3 to −14.5)**[c]
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	**23.4 ± 7.5**[a]	−2.4 ± 5.0	27.5 ± 7.1	**22.2 ± 6.5**[b]	**−5.4 ± 7.1**[c]

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.
[a]Difference between baseline and 1-month FU in the MNA not improved group with $P < 0.05$.
[b]Difference between baseline and 1-month FU in the MNA improved group with $P < 0.05$.
[c]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 6MWTD 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	Δ	Baseline	1-month FU	Δ
NT-proBNP (pg/mL)	5299 [1931–13 845]	6699 [2315–18 153]	708 [−342 to 2708]	3038 [1897–6298]	**2474[a] [1417–5075]**	**−320[b] [−1294 to 105]**
eGFR, mL/min	38.8 ± 12.7	38.3 ± 17.3	−0.5 ± 9.4	45.7 ± 17.3	**49.2 ± 17.1[a]**	**+3.5 ± 13.1[b]**
Creatinine, mg/dL	1.7 [1.3–2.3]	1.8 [1.3–2.3]	0.1 [−0.1 to 0.4]	1.4 [1.1–1.6]	**1.3 [1.0–1.5][a]**	**−0.1 [−0.3 to 0.06][b]**
BUN, mmol/L	14.2 [9.6–21.5]	13.7 [8.0–27.5]	−0.6 [−2.5 to 3.2]	10.3 [8.4–14.9]	**9.4 [7.1–12.0][a]**	−1.2 [−4.6 to 0.9]
Bilirubin total, µmol/L	10.8 [5.7–14.0]	12.5 [8.8–13.9]	1.7 [−1.0 to 4.2]	14.0 [9.0–19.0]	**11.7 [8.6–16.7][a]**	−2.3 [−6.0 to 1.2]
AST, µmol/L	0.46 [0.41–0.52]	0.44 [0.36–0.52]	−0.02 [−0.1 to 0.02]	0.43 [0.36–0.51]	0.43 [0.35–0.52]	0.0 [−0.1 to 0.07]
ALT, µmol/L	0.3 [0.3–0.5]	0.3 [0.3–0.4]	−0.01 [−0.1 to −0.03]	0.34 [0.26–0.42]	0.29 [0.23–0.40]	−0.04 [−0.12 to 0.06]
γGT, µmol/L	1.6 [1.0–3.3]	1.3 [0.9–2.3]	−0.2 [−0.3 to −0.1]	1.6 [1.0–2.5]	1.3[a] [0.8–2.6]	−0.2 [−0.4 to 0.1]
Alcaline phosphatase, µmol/L	1.5 [1.3–1.8]	1.7 [1.4–1.9]	0.2 [−0.1 to 0.5]	1.5 [1.2–2.2]	**1.5 [1.1–1.9][a]**	−0.09 [−0.28 to 0.08]
Albumin, g/L	42.2 [38.5–44.2]	42.9 [38.9–45.9]	0.7 [−0.6 to 2.8]	44.0 [40.0–46.0]	**45.0 [42.4–46][a]**	1.0 [−1.0 to 3.5]
Leucocytes, Gpt/L	6.9 [5.5–7.5]	6.9 [5.7–7.5]	0.05 [−0.9 to 1.2]	7.1 [5.8–8.0]	6.5 [5.5–7.5]	−0.4 [−1.0 to 0.4]
Haemoglobin, mmol/L	7.2 ± 1.4	6.8 ± 1.1	−0.5 ± 1.0	7.7 ± 1.4	7.5 ± 0.9	−0.2 ± 1.1
CHE, µmol/L	87.1 ± 35.8	88.8 ± 31.7	0.0 ± 11.9	87.7 ± 27.5	**97.8 ± 28.0[a]**	**+10.9 ± 16.7[b]**
Haematocrit	0.33 ± 0.06	0.35 ± 0.04	0.02 ± 0.05	0.36 ± 0.05	0.36 ± 0.05	0.0 ± 0.04
C-reactive protein, mg/L	6.0 [4.3–24.9]	17.0 [3.2–76.8]	−0.2 [−11.2 to 15.4]	3.6 [1.1–7.4]	2.9 [1.6–6.7]	−0.6 [−4.8 to 1.9]
Total serum protein, g/L	70.9 [62.1–75.3]	65.2 [63.3–72.9]	1.2 [−3.0 to 2.4]	68.6 [64.5–72.3]	**71.3 [68.2–74.6][a]**	5.5 [0.03–8.7]
MELD score	15.2 [8.7–20.4]	15.1 [7.2–21.6]	−0.1 [−1.3 to 1]	14.6 [10.9–18.1]	11.7 [9.3–14.9]	−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); γ GT, gamma-glutamyltransferase; MNA, Mini Nutritional Assessment; MELD, Model of End-stage Liver Disease; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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

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

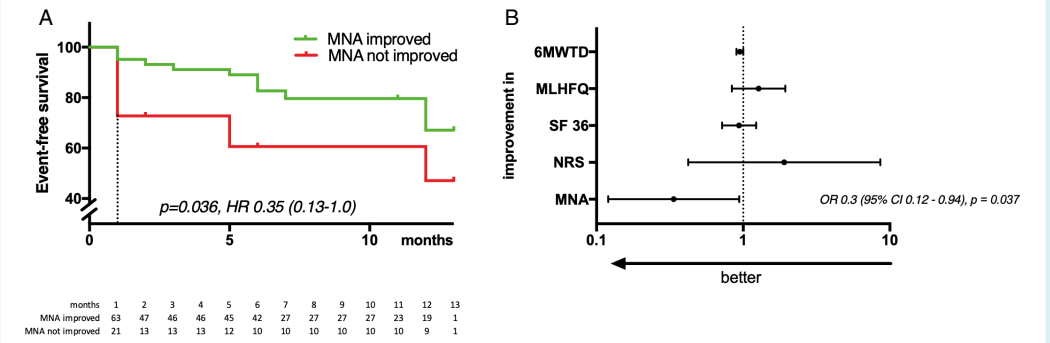

Figure 2 Prognostic impact of malnutrition in patients undergoing isolated transcatheter tricuspid valve edge-to-edge repair (TTVR) or combined transcatheter mitral and tricuspid valve edge-to-edge repair (TMTVR). (*A*) Kaplan–Meier graph of event-free survival (death and rehospitalization for heart 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 (6MWTD), 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 ≤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 6MWTD 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 evolvements. Based on previous knowledge,[20–22] 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[23] and consecutive impaired perfusion, nutrient uptake and metabolic imbalances.[24] 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

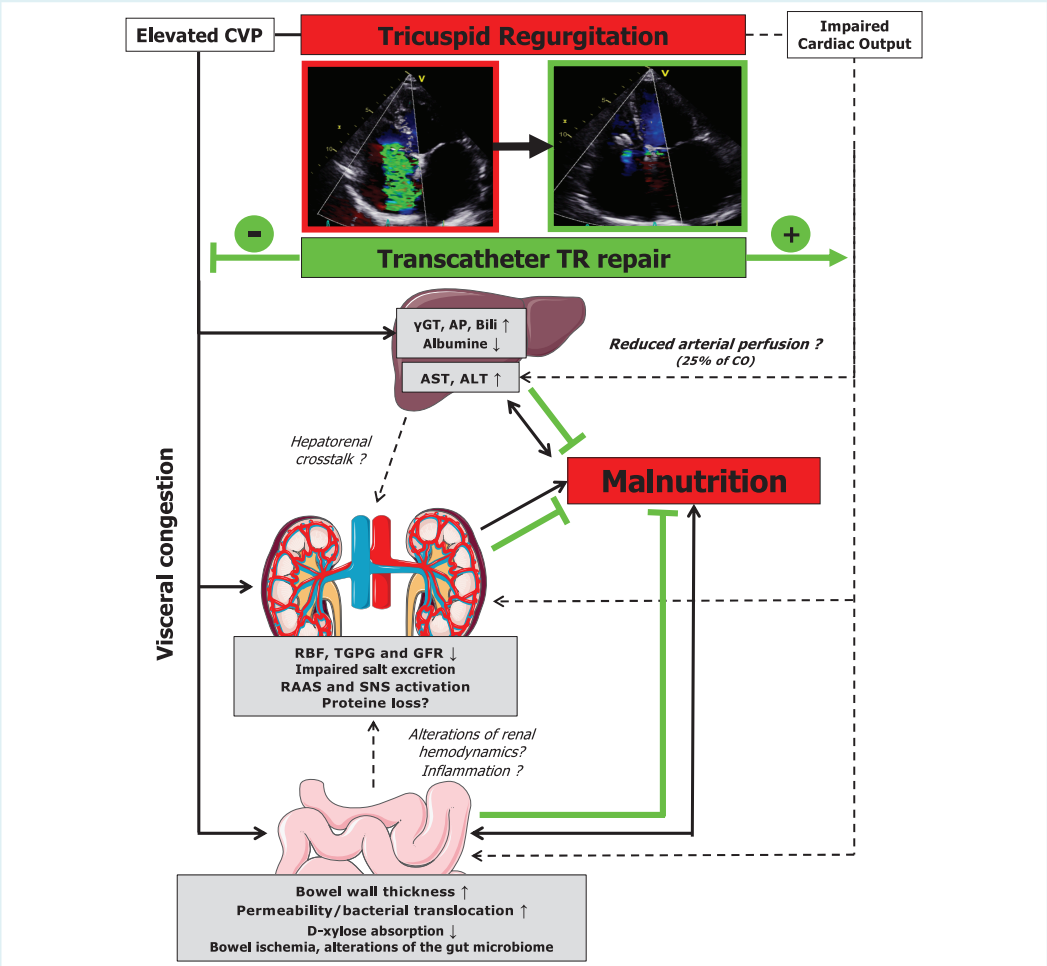

Figure 3 Beneficial effects of transcatheter tricuspid regurgitation (TR) repair on extracardiac implications of TR. ALT, alanine aminotransferase; AP, alcaline phosphatase; AST, aspartate aminotransferase; Bili, bilirubin; CO, cardiac output; CVP, central venous pressure; GFR, glomerular filtration rate; γGT, 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,[25] if liver disease is not advanced.[26] 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.[27] However, recent studies suggest mechanisms directly related to venous congestion, which correlate with estimated glomerular filtration rate decrease and higher mortality.[28] 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.[29] Currently known pathophysiology is based on findings of intestinal malfunction due to liver cirrhosis[30] 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'.[29,30] 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.[31,32] 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^2 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[33] and supported by improvements in 6MWTD 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.[7,20] 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[33] 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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Zusammenfassung der Arbeit

Dissertation zur Erlangung des akademischen Grades *Dr. med.*

Titel: *Nutritional status in tricuspid regurgitation: implications of transcatheter repair*

eingereicht von: Matthias Unterhuber

angefertigt am Herzzentrum Leipzig

betreut von Prof. Dr. Dr. med. Philipp Lurz

März 2022

This study aimed to characterize the prevalence and clinical relevance of malnutrition in patients undergoing transcatheter tricuspid valve edge-to-edge repair. Eighty-six patients (mean age 78 ± 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. The findings of this study can be summarized as follows:

1. A substantial part of elderly patients with severe TR and chronic venous congestion undergoing TTVR are either at risk for malnutrition or malnourished

2. One month after TTVR, three-quarter of patients showed an improved nutritional status and reduced venous congestion along with better quality of life, increased exercise capacity, accompanied by ameliorated central venous pressures, renal and hepatic function parameters

3. MNA score improvement showed to be a significant independent predictor for outcome in patients undergoing TTVR. Patients with no improvement in nutritional status after intervention had a higher risk of rehospitalization for heart failure or death.

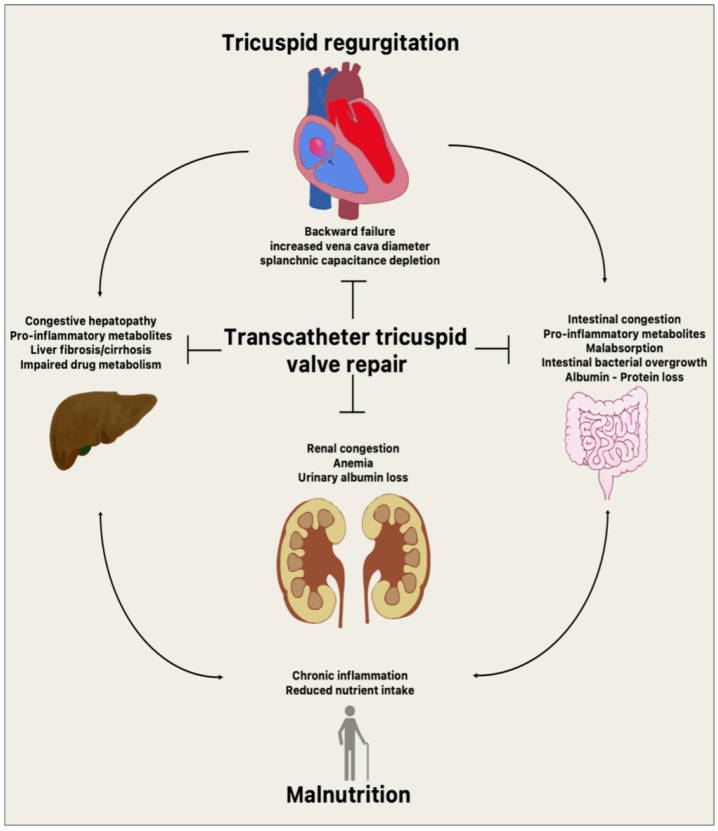
TTVR leads to a reduction in RV volume overload. It improves RV performance and LV filling by enhancing bi-ventricular interaction and improving cardiac output [66, 67].

Therefore, the procedure provides a unique model, as organ functionality changes can be noticed by regular assessments before and after intervention. By reducing TR and thus relieving venous congestion, direct observation of the differences following afterwards in the involved other systems is possible, allowing for mechanistic insights which could not be easily obtained before. We hypothesize that nutritional status impairment in patients undergoing TTVR could be due to the consequences of venous congestion and that the improvement in nutritional status after TTVR could be attributable to the reduction of venous pressure on liver, kidneys and gastrointestinal tract. The proposed mechanisms are displayed in *Figure 3*.

The most likely mechanism of nutritional impairment in TR is presumably a combination between visceral congestion leading to hepatorenal and intestinal malfunction as well as a a catabolic metabolic state. These conditions are linked to postprandial fullness, loss of appetite, nausea and abdominal discomfort. The cause is thought to involve mucosal dysfunction throughout the gastrointestinal tract, with increased wall thickness, congestion and hypoperfusion [8]. This causes a proinflammatory state with consequent malabsorption, activation of catabolic and inhibition of anabolic pathways, leading to dysmotility, small intestinal bacterial overgrowth and dysbiosis [7]. In addition, drug metabolism is impaired [68].

These conditions together end in reduced dietary intake, nutrient absorption, muscle wasting, reduced mobility and increased frailty. In this study, all patients had symptomatic TR with consequent backward failure and venous congestion. According to MNA scores, 94% of the patients were at risk for malnutrition or malnourished. After TTVR, nutritional status improved in 74% of the patients. The group with lower MNA values (i.e. worse nutritional status) had significantly larger vena cava inferior diameters compared

Figure 3: Proposal of the underlying mechanisms involving TR.



to patients with higher MNA values, suggesting a higher central venous pressure. After TTVR, we observed an effective decrease in inferior vena cava diameter in all patients.

Interestingly, the group with improved nutrition scores showed the greatest decrease in vena cava inferior diameters from baseline to one month of follow-up. Moreover, these patients experienced an increase in albumin and total protein levels levels at follow-up. Possible explanations include an improved dietary intake along with better nutrient absorption, relief of a sub-

clinical protein-loss enteropathy or urinary protein loss, or less catabolism due to reduced inflammatory triggers. Further, a greater reduction of GGT levels and an increase in cholinesterase enzyme in the group with increased nutritional status strengthens the hypothesis that reducing venous pressure can lead to a reversal of liver function impairment when addressing the underlying cause of right heart failure. [69–71]. On average, baseline renal function was reduced (GFR $43,3 \pm 16,3 ml/m^2$). An impaired kidney function was previously thought to be solely due to poor perfusion following reduced cardiac output. On the contrary, recent studies [72] suggested that there are mechanisms of kidney disfunction which are directly correlated to venous congestion and its mechanical consequences with a significant impact on mortality. Among normal central venous pressure ranges, an increase in venous pressure leads to an increase in GFR as indicator of increased preload and subsequent augmented renal perfusion due to the Frank-Starling mechanism [73]. When central venous pressure increases further exceeding the cardiac output optimum, GFR decreases [72, 74–77], presumably as expression of increased renal venous congestion leading to kidney dysfunction. An amelioration in renal function following TTVR could be observed in the patients with improved MNA at follow up. This may be the result of a combination of less venous congestion and improvement in cardiac output, both of which have been observed after TTVR [66].

A BMI within normal value ranges does not imply a normal nutritional status. In fact, mean BMI was $27 kg/m^2$ even in malnourished patients and did not differ significantly across MNA score groups (*Table 3* and *Figure S4* in the supplementary material). At follow-up, the patient group with improved MNA displayed a significant BMI reduction. At first glance this finding could appear counter-intuitive. Instead, it indicates that isolated BMI values could not reflect the nutritional status in a reliable manner in this patient cohort.

The MNA scoring system relies on assessment of behavior, multimorbidity

and dietary intake, and BMI does not reflect multiple domains of the patient's daily activities, nor can it define body composition. In this study, different intravasal volume status due to different diuretics dosages were ruled out, as there were no furosemide equivalent differences across MNA score groups and hematocrit values did not differ (*Table 3* in the paper).

Notably, patients with improved MNA scores at one month had a significantly higher event-free survival rate compared to patients without MNA improvement. According to a binary logistic analysis, MNA improvement remained the only significant predictor for death or heart failure rehospitalization(*Figure 2* in the paper).

Quality of Life

TTVR provided clinical benefits on QoL measured by SF-36 and MLHFQ. The main goal in patients with heart failure ideally is to gain an improvement in daily life activity abilities with regard to physical and psychosocial aspects. A mere prolongation of life duration might not be as favourable if QoL is severely impaired and progressive age, frailty, social isolation and cognitive deficits cast a shadow above life expectancy. [66, 78]

The present study demonstrated that after TTVR, QoL scores in physical and general domains of both MLHFQ and SF-36 questionnaires improved in patients with an increased MNA score. Improvements in SF-36 and MLHFQ score values at one month failed to predict significantly the composite outcome of heart failure rehospitalization or death during the follow-up period. This could be due to the solely subjective domain of the questionnaires, indicating the need for a combined assessment of objective measurable parameters and subjective wellbeing in combination with behavioral aspects, as reflected by the MNA scoring system.

Conclusions

New pathomechanistic insights could be achieved into TR-associated multi-organ involvement by observing the cardio-metabolic and functional changes after TTVR. Nutritional status can be used as a new patient-centered, non-invasive marker to judge procedural success and to monitor outcome during follow-up. Malnutrition, as observed in the present study, is a multifactorial condition and can be a disease trigger but also the common final pathway involving multiple deteriorating organ systems. However, the chronological order of organ involvement as well as the roles played by each different system are still to be exactly defined.

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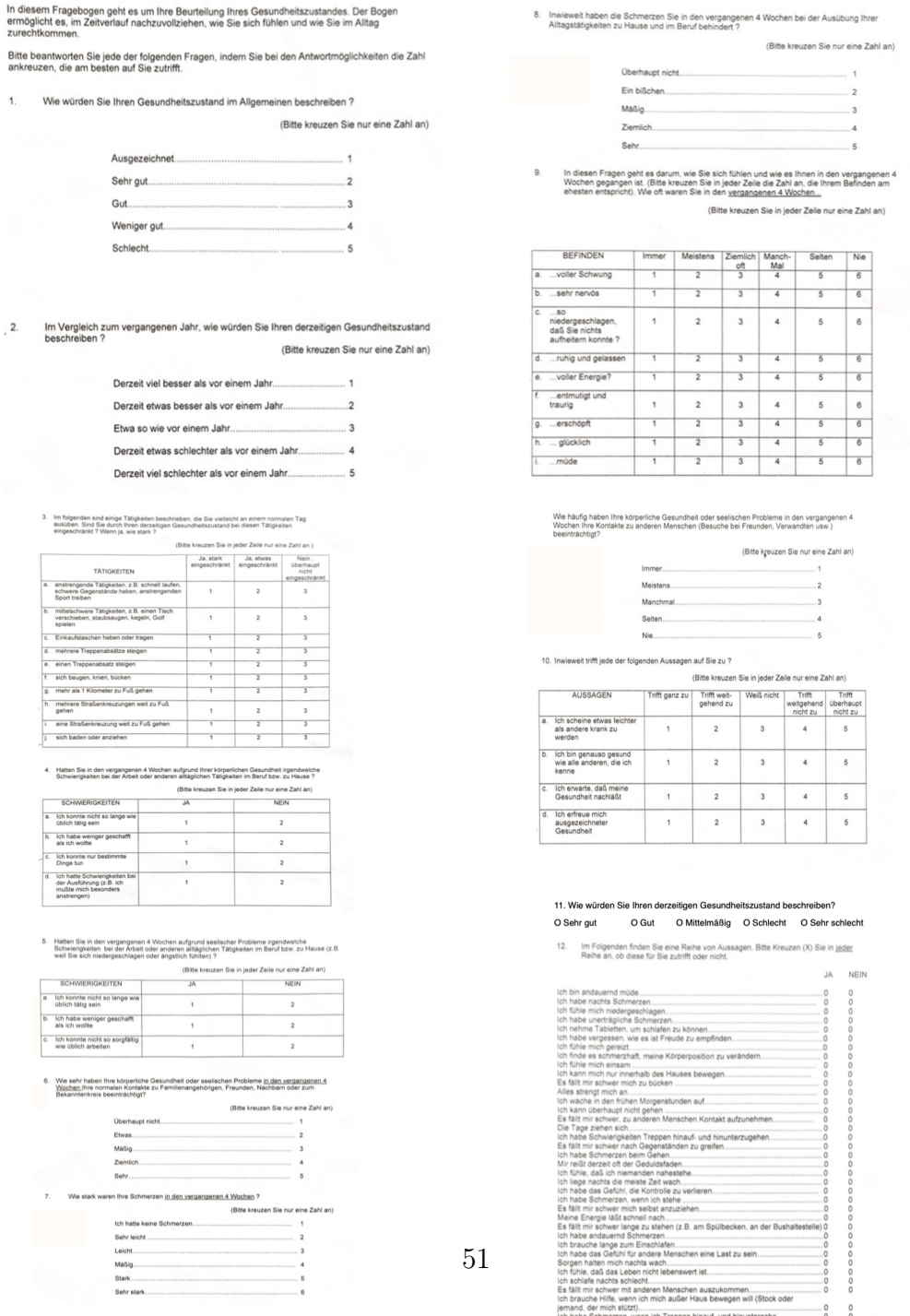
5 Figures

Figure 4: The Short Form 36 Questionnaire used in this study.



In diesem Fragebogen geht es um Ihre Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

Bitte beantworten Sie jede der folgenden Fragen, indem Sie bei den Antwortmöglichkeiten die Zahl ankreuzen, die am besten auf Sie zutrifft.

1. Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben ?

(Bitte kreuzen Sie nur eine Zahl an)

Ausgezeichnet 1
Sehr gut 2
Gut 3
Weniger gut 4
Schlecht 5

2. Im Vergleich zum vergangenen Jahr, wie würden Sie Ihren derzeitigen Gesundheitszustand beschreiben ?

(Bitte kreuzen Sie nur eine Zahl an)

Derzeit viel besser als vor einem Jahr 1
Derzeit etwas besser als vor einem Jahr 2
Etwa so wie vor einem Jahr 3
Derzeit etwas schlechter als vor einem Jahr 4
Derzeit viel schlechter als vor einem Jahr 5

3. Im folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt ? Wenn ja, wie stark ?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

TÄTIGKEITEN	Ja, stark eingeschränkt	Ja, etwas eingeschränkt	Nein , überhaupt nicht eingeschränkt
a. anstrengende Tätigkeiten, z.B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben	1	2	3
b. mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen	1	2	3
c. Einkaufstaschen heben oder tragen	1	2	3
d. mehrere Treppenabsätze steigen	1	2	3
e. einen Treppenabsatz steigen	1	2	3
f. sich beugen, knien, bücken	1	2	3
g. mehr als 1 Kilometer zu Fuß gehen	1	2	3
h. mehrere Straßenkreuzungen weit zu Fuß gehen	1	2	3
i. eine Straßenkreuzung weit zu Fuß gehen	1	2	3
j. sich baden oder anziehen	1	2	3

4. Hatten Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause ?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

SCHWIERIGKEITEN	JA	NEIN
a. Ich konnte nicht so lange wie üblich tätig sein	1	2
b. Ich habe weniger geschafft als ich wollte	1	2
c. Ich konnte nur bestimmte Dinge tun	1	2
d. Ich hatte Schwierigkeiten bei der Ausführung (z.B. ich mußte mich besonders anstrengen)	1	2

5. Hatten Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten) ?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

SCHWIERIGKEITEN	JA	NEIN
a. Ich konnte nicht so lange wie üblich tätig sein	1	2
b. Ich habe weniger geschafft als ich wollte	1	2
c. Ich konnte nicht so sorgfältig wie üblich arbeiten	1	2

6. Wie sehr haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre normalen Kontakte zu Familienangehörigen, Freunden, Nachbarn oder zum Bekanntenkreis beeinträchtigt?

(Bitte kreuzen Sie nur eine Zahl an)

Überhaupt nicht 1
Etwas 2
Mäßig 3
Ziemlich 4
Sehr 5

7. Wie stark waren Ihre Schmerzen in den vergangenen 4 Wochen ?

(Bitte kreuzen Sie nur eine Zahl an)

Ich hatte keine Schmerzen 1
Sehr leicht 2
Leicht 3
Mäßig 4
Stark 5
Sehr stark 6

8. Inwieweit haben die Schmerzen Sie in den vergangenen 4 Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert ?

(Bitte kreuzen Sie nur eine Zahl an)

Überhaupt nicht 1
Ein bißchen 2
Mäßig 3
Ziemlich 4
Sehr 5

9. In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen 4 Wochen gegangen ist. (Bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht). Wie oft waren Sie in den vergangenen 4 Wochen...

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

BEFINDEN	Immer	Meistens	Ziemlich oft	Manch-Mal	Selten	Nie
a. ...voller Schwung	1	2	3	4	5	6
b. ...sehr nervös	1	2	3	4	5	6
c. ...so niedergeschlagen, daß Sie nichts aufheitern konnte ?	1	2	3	4	5	6
d. ...ruhig und gelassen	1	2	3	4	5	6
e. ...voller Energie?	1	2	3	4	5	6
f. ...entmutigt und traurig	1	2	3	4	5	6
g. ...erschöpft	1	2	3	4	5	6
h. ... glücklich	1	2	3	4	5	6
i. ...müde	1	2	3	4	5	6

Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den vergangenen 4 Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?

(Bitte kreuzen Sie nur eine Zahl an)

Immer 1
Meistens 2
Manchmal 3
Selten 4
Nie 5

10. Inwieweit trifft jede der folgenden Aussagen auf Sie zu ?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

AUSSAGEN	Trifft ganz zu	Trifft weitgehend zu	Weiß nicht	Trifft weitgehend nicht zu	Trifft überhaupt nicht zu
a. Ich scheine etwas leichter als andere krank zu werden	1	2	3	4	5
b. Ich bin genauso gesund wie alle anderen, die ich kenne	1	2	3	4	5
c. Ich erwarte, daß meine Gesundheit nachläßt	1	2	3	4	5
d. Ich erfreue mich ausgezeichneter Gesundheit	1	2	3	4	5

11. Wie würden Sie Ihren derzeitigen Gesundheitszustand beschreiben?

O Sehr gut O Gut O Mittelmäßig O Schlecht O Sehr schlecht

12. Im Folgenden finden Sie eine Reihe von Aussagen. Bitte Kreuzen (X) Sie in jeder Reihe an, ob diese für Sie zutrifft oder nicht.

	JA	NEIN
Ich bin andauernd müde	0	0
Ich habe nachts Schmerzen	0	0
Ich fühle mich niedergeschlagen	0	0
Ich habe unerträgliche Schmerzen	0	0
Ich nehme Tabletten, um schlafen zu können	0	0
Ich habe vergessen, wie es ist Freude zu empfinden	0	0
Ich fühle mich gereizt	0	0
Ich finde es schmerzhaft, meine Körperposition zu verändern	0	0
Ich fühle mich einsam	0	0
Ich kann mich nur innerhalb des Hauses bewegen	0	0
Es fällt mir schwer mich zu bücken	0	0
Alles strengt mich an	0	0
Ich wache in den frühen Morgenstunden auf	0	0
Ich kann überhaupt nicht gehen	0	0
Es fällt mir schwer, zu anderen Menschen Kontakt aufzunehmen	0	0
Die Tage ziehen sich	0	0
Ich habe Schwierigkeiten Treppen hinauf- und hinunterzugehen	0	0
Es fällt mir schwer nach Gegenständen zu greifen	0	0
Ich habe Schmerzen beim Gehen	0	0
Mir reißt derzeit oft der Geduldsfaden	0	0
Ich fühle, daß ich niemanden nahestehe	0	0
Ich liege nachts die meiste Zeit wach	0	0
Ich habe das Gefühl, die Kontrolle zu verlieren	0	0
Ich habe Schmerzen, wenn ich stehe	0	0
Es fällt mir schwer mich selbst anzuziehen	0	0
Meine Energie läßt schnell nach	0	0
Es fällt mir schwer lange zu stehen (z.B. am Spülbecken, an der Bushaltestelle)	0	0
Ich habe andauernd Schmerzen	0	0
Ich brauche lange zum Einschlafen	0	0
Ich habe das Gefühl für andere Menschen eine Last zu sein	0	0
Sorgen halten mich nachts wach	0	0
Ich fühle, daß das Leben nicht lebenswert ist	0	0
Ich schlafe nachts schlecht	0	0
Es fällt mir schwer mit anderen Menschen auszukommen	0	0
Ich brauche Hilfe, wenn ich mich außer Haus bewegen will (Stock oder jemand, der mich stützt)	0	0
Ich habe Schmerzen, wenn ich Treppen hinauf- und hinuntergehe	0	0
Ich wache deprimiert auf	0	0
Ich habe Schmerzen, wenn ich sitze	0	0

Minnesota Living with Heart Failure

Leben mit Herzinsuffizienz

Diese Fragen sollen darüber Aufschluss geben, wie Ihre Herzinsuffizienz Sie im vergangenen Monat an der von Ihnen gewünschten Lebensweise gehindert hat. Die unten aufgelisteten Punkte beschreiben verschiedene Arten von Beeinträchtigungen. Wenn Sie sicher sind, dass ein Punkt nicht auf Sie zutrifft oder in keinem Zusammenhang mit Ihrer Herzinsuffizienz steht, kreuzen Sie „0" („Nein") an und beantworten Sie dann die nächste Frage. Wenn ein Punkt Sie betrifft, kreuzen Sie die Zahl an, die widerspiegelt, wie stark Sie an der von Ihnen gewünschten Lebensweise gehindert wurden.

Hat Ihre Herzinsuffizienz Sie im vergangenen Monat an der von Ihnen gewünschten Lebensweise gehindert, dadurch dass ...

	Nein	*Sehr wenig*				*Sehr stark*
1. Schwellungen Ihrer Knöchel, Beine etc. auftraten?	0	1	2	3	4	5
2. Sie sich tagsüber hinlegen oder setzen mussten, um sich auszuruhen?	0	1	2	3	4	5
3. Sie beim Gehen oder Treppensteigen Schwierigkeiten hatten?	0	1	2	3	4	5
4. Sie bei der Haus- oder Gartenarbeit Schwierigkeiten hatten?	0	1	2	3	4	5
5. Sie Schwierigkeiten hatten, außer Haus zu gehen?	0	1	2	3	4	5
6. Sie Schwierigkeiten hatten nachts zu schlafen?	0	1	2	3	4	5
7. Sie Schwierigkeiten hatten, mit Familie oder Freunden Kontakt zu halten?	0	1	2	3	4	5
8. Sie Schwierigkeiten hatten, Ihren Lebensunterhalt zu verdienen?	0	1	2	3	4	5
9. Sie bei Freizeitbeschäftigungen, Sport oder Hobbys Schwierigkeiten hatten?	0	1	2	3	4	5
10. Sie in Ihrem Sexualleben beeinträchtigt waren?	0	1	2	3	4	5
11. Sie weniger von dem essen konnten, was Sie mögen?	0	1	2	3	4	5
12. Sie unter Kurzatmigkeit litten?	0	1	2	3	4	5
13. Sie müde, erschöpft oder energielos waren?	0	1	2	3	4	5
14. Sie im Krankenhaus bleiben mussten?	0	1	2	3	4	5
15. Sie Geld für Ihre medizinische Versorgung bezahlen mussten?	0	1	2	3	4	5
16. Sie unter Nebenwirkungen Ihrer Medikamente litten?	0	1	2	3	4	5
17. Sie sich als Belastung für Ihre Familie oder Freunde empfanden?	0	1	2	3	4	5
18. Sie das Gefühl hatten, weniger Kontrolle über Ihr Leben zu haben?	0	1	2	3	4	5
19. Sie sich Sorgen machten?	0	1	2	3	4	5
20. Sie Schwierigkeiten hatten, sich zu konzentrieren oder sich an etwas zu erinnern?	0	1	2	3	4	5
21. Sie sich deprimiert fühlten?	0	1	2	3	4	5

Figure 5: The Minnesota Living with Heart Failure Questionnaire used in this study.

SUPPLEMENTAL MATERIAL

Nutritional Status and in Tricuspid Regurgitation: Implications of Transcatheter Repair

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Supplemental Tables

Supplemental Table 1

	All	MNA > 8	MNA ≤ 8	p-value
N	81	46	35	
AF-related TR, n (%)	25 (31)	13 (28)	12 (34)	.62
PH-related TR, n (%)	24 (30)	15 (33)	9 (26)	.77
Left heart disease- related TR, n (%)	24 (30)	12 (26)	12 (34)	.56
Dialysis-related TR, n (%)	5 (6)	4 (9)	1 (3)	.54
RV remodeling-related TR, n (%)	3 (3)	2 (4)	1 (3)	1.0

***Supplemental Table 1*:** Putative causes of TR according to baseline MNA score above or below median in the patient sample.

AF = atrial fibrillation, PH = pulmonary hypertension. RV = right ventricular.

Supplemental Table 2

	All	MNA improved	MNA not improved	p-value
N	81	59	22	
AF-related TR, n (%)	25 (31)	21 (36)	4 (18)	.22
PH-related TR, n (%)	24 (30)	18 (31)	6 (27)	.99
Left heart disease- related TR, n (%)	24 (30)	15 (25)	9 (41)	.19
Dialysis-related TR, n (%)	5 (6)	3 (5)	2 (9)	.82
RV remodeling-related TR, n (%)	3 (3)	2 (3)	1 (5)	1.0

***Supplemental Table 2*:** Putative causes of TR according to MNA improvement after 1 month of follow-up in the patient sample.

AF = atrial fibrillation, PH = pulmonary hypertension. RV = right ventricular.

Supplemental Table 3

	All	TMTVR	TTVR	p-value
N	72	31	41	
sPAP, mmHg	48 (40-58)	50 (45-65)	43 (35-50)	.01
Wedge pressure, mmHg	22±7.3	24±7.4	19±6.0	.01
LVEDP, mmHg	16±6.0	17±6.2	16±5.8	.50

***Supplemental Table 3*:** Invasive hemodynamic data at baseline in the patient sample.

LVEDP = left ventricular end-diastolic pressure, sPAP = systolic pulmonary artery pressure.

Supplemental Table 4

	All	MNA > 8	MNA ≤ 8	p-value
n	86	49	37	
NT-proBNP (pg/mL)	3224 (1932-6680)	2851 (1709-6530)	4331 (2346-7989)	.12
eGFR, ml/min	43.3±16.3	42.8±15.2	43.9±17.8	.76
Creatinine, mg/dl	1.4 (1.2-1.8)	1.4 (1.1-1.8)	1.4 (1.2-1.6)	.85
BUN mmol/l	10.8 (8.5-17.3)	11.6 (8.5-17.3)	10.7 (8.5-18.7)	.78
Bilirubin total, µmol/l	13.7 (8.8-18.6)	12.2 (8.3-17.8)	14.7 (9.4-18.9)	.39
AST, µmol/l	0.44 (0.38-0.52)	0.47 (0.39-0.59)	0.43 (0.35-0.58)	.24
ALT, µmol/l	0.33 (0.26-0.43)	0.33 (0.27-0.48)	0.31 (0.21-0.40)	.14
γGT, µmol/l	1.6 (1.0-2.5)	1.6 (1.0-2.2)	1.6 (0.9-2.9)	.91
Alcaline phosphatase, µmol/l	1.5 (1.2-2.2)	1.4 (1.2-1.7)	1.8 (1.3-2.6)	.029
Albumin, g/l	43.2 (39.3-45.0)	43.2 (39.6-45.6)	43.3 (39.0-45.0)	.91
Leucocytes, Gpt/l	7.0 (5.8-7.8)	7.0 (5.9-7.8)	7.0 (5.5-7.7)	.87
Haemoglobin, mmol/l	7.5±1.4	7.5±1.3	7.6±1.5	.59
Cholinesterase enzyme, µmol/l	87.6±29.4	87.6±31.3	87.6±27.3	.99
Haematocrit	0.35±0.05	0.35±0.05	0.35±0.05	.92
C-Reactive Protein, mg/l	4.4 (1.2-11.2)	4.8 (1.0-15.1)	3.7 (1.6-6.7)	.47
Total serum protein, g/l	69.3 (64.5-72.7)	69.6 (64.0-73.6)	69.3 (62.9-72.3)	.59

Supplemental Table 4: Baseline laboratory findings according to MNA score.

AST = aspartate aminotransferase, ALT = alanine aminotransaminase, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate (Cockcroft-Gault formula), GGT = gamma glutamyl transferase, NT-proBNP = N-terminal pro-brain natriuretic peptide.

Supplemental Table 5

	All	MNA > 8	MNA ≤ 8	p-value
n	86	49	37	
MLHFQ	32.0 (24.0-40.0)	33.0 (23.0-43.5)	32.0 (26.5-36.8)	.94
MLHFQ physical	21.2±8.1	21.0±8.5	21.6±7.6	.80
MOS-SF-36	42.8±16.2	44.8±17.7	40.2±14.0	.28
MOS-SF-36 physical	29.5±26.5	33.8±27.4	22.0±21.8	**.035**
6MWD, m	251±128	268±125	227±131	.15

Supplemental Table 5: Quality of life and 6MWD according to MNA score.

MNA = Mini Nutritional Assessment score, MLHFQ = Minnesota Living with Heart Failure Questionnaire, MOS-SF-36 = Medical Outcomes Study – 36-Item Short-Form health survey, 6MWD = six minute walk test distance.

Supplemental Table 6

	All	MNA > 8	MNA ≤ 8	p-value
n	43	24	19	
Age (years)	**78±4.0**	**77±4.0**	**80±3.4**	**.017**
Female, n (%)	18 (42)	8 (33)	10 (53)	.34
BMI, kg/m²	27±4.39	27±5	27±3.6	.93
EuroSCORE II, %	5.8 (2.8-10.7)	4.5 (2.5-11.4)	6 (3.9-9.6)	.53
STS mortality score, %	3.4 (2.5-6.4)	3.3 (2.4-4.9)	4.9 (2.93-8.0)	.29
NYHA II, n (%)	14 (33)	10 (42)	4 (21)	.27
NYHA III, n (%)	22 (51)	11 (46)	11 (58)	.63
NYHA IV, n (%)	7 (16)	3 (12)	4 (21)	.73
Lead across tricuspid valve, n (%)	11 (26)	6 (25)	5 (26)	1.0
Previous PCI, n (%)	12 (28)	7 (29)	5 (26)	1.0
Previous CABG, n (%)	8 (19)	5 (21)	3 (16)	.98
HFrEF, n (%)	19 (44)	11 (46)	8 (42)	1.0
Chronic pulmonary disease, n (%)	12 (28)	5 (21)	7 (37)	0.41
Child-Pugh class B, (%)	1 (2)	0 (0)	1 (5)	0.30
Beta-blocker, n (%)	41 (95)	23 (96)	18 (95)	1.0
Aldosterone antagonist, n (%)	10 (23)	6 (25)	4 (21)	1.0
Diuretic, n (%)	39 (91)	22 (92)	17 (89)	1.0
Furosemide dosis equivalent, mg	40 (25-80)	40 (22.5-95)	40 (22-80)	1.0

Supplemental Table 6: Baseline characteristics of patients undergoing isolated TTVR.

BMI = body mass index, CABG = coronary artery bypass grafting, HFrEF = heart failure with reduced ejection fraction, NYHA = New York Heart Association functional class, PCI = percutaneous coronary intervention, STS = Society of Thoracic Surgeons. Values are expressed in mean ± SD or median (IQR) where appropriate. Counts are expressed in n (%).

Supplemental Table 7

	All	MNA > 8	MNA ≤ 8	p-value
n	43	24	19	
LVEF, %	54±13	53±14	54±12	.77
LVEDD, mm	49±6	48±6	49±6	.49
TAPSE <17mm, n (%)	12 (28)	7 (29)	5 (26)	1.0
RV-FAC <35%, n (%)	12 (28)	7 (29)	5 (26)	1.0
TV EROA (PISA), cm^2	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.5 (0.4-0.7) | 18	.79
TR vena contracta, mm	9 (7.5-11)	9 (7-11.2)	9 (8-11)	.97
TV annulus diameter, mm	50±5	49±5	50±6	.68
sPAP, mmHg	48±15	46±13	50±18	.49
IVC diameter, mm	**27±7**	**25±6**	**30±7**	**<0.01**
TR Grade 2, n (%)	0	0	0	
TR Grade 3, n (%)	40 (93)	24 (100)	16 (84)	.16
TR Grade 4, n (%)	3 (7)	0	3 (16)	.16

Supplemental Table 7: Baseline echocardiographic findings in patients undergoing isolated TTVR.

EROA = effective regurgitant orifice area, IVC = inferior vena cava, LVEDD = left ventricular end-diastolic diameter, LVLEF = left ventricular ejection fraction, MNA = Mini Nutritional Assessment score, PISA = proximal isovelocity surface area, RV-FAC = right ventricular fractional area change, sPAP= systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, TR = tricuspid regurgitation, TV = tricuspid valve. Values are expressed in mean ± SD or median (IQR) where appropriate. Counts are expressed in n (%).

Supplemental Table 8

	MNA not improved n = 7			MNA improved n = 36		
Parameter	Baseline	1-Month FU	Δ	Baseline	1-Month FU	Δ
Age, years	77±5.11			79±3.75		
BMI, kg/m^2	25±5.24	25±4.08	-0.12±2.77	27±4.19	27±3.7	0 ± 1.4
Furosemide, mg	40 (25-80)	40 (30-80)	0 (-10-20)	40 (30-80)	40 (20-80)	0 (-20-10)
MLHFQ	12±8.96	35±11.79	23±6	29±11.52	26±18.67	-3±8
MLHFQ physical	10±7.55	20±5.29	-0.3±12.5	19±6.92	15±9.18	-4±9.2
MOS - SF-36, %	64 (57.5-70.5)	52 (44.2-58)	-8 (-23.8--7)	40 (34-51.5)	**60 (36-76)†**	**12 (-1.5-33.5)‡**
MOS - SF-36 physical, %	62.5 (52.5-80)	42.5 (31.2-50)	-20 (-48.8--2.5)	15 (5-37.5)	**50 (15-72.5)†**	**20 (-10-55)‡**
6MWD, m	345 (296.2-383.2)	352 (197.5-393.2)	7 (-124-15)	277 (134.8-388.5)	**326 (252.5-416.2)†**	**49 (23-74.5)‡**

Supplemental Table 8: Changes in BMI, furosemide dose, QoL measures and 6MWT distance in patients undergoing isolated TTVR.

BMI = Body Mass Index, FU = Follow-Up, MLHFQ =Minnesota Living with Heart Failure Questionnaire, MOS - SF-36 = Medical Outcomes Study – 36-Item Short-Form health survey, 6MWD = six minute walk test distance.

Supplemental Table 9

	MNA not improved n = 7			MNA improved n = 36		
Parameter	Baseline	1-Month FU	Δ	Baseline	1-Month FU	**Δ**
LVEF, %	48±17.6	49±16.47	0.86±5.84	55±11.76	56±9.11	1.1±9.02
LVEDD, mm	52±7.34	54±4.79	2.4±5.19	48±5.68	49±5.35	1.3±4.48
TAPSE, mm	19±5.65	16±4.11	-2.3±2.93	16±3.95	16±3.55	-0.72±4.17
RVFAC, %	44±8.83	40±10.02	-3.5±5.43	40±10.11	38±9.01	-2.2±8.79
TV EROA (PISA), cm²	0.5 (0.5-0.75)	**0.2 (0.1-0.4)***	-0.4 (-0.5- -0.25)	0.5 (0.4-0.6)	**0.2 (0.1-0.3)**†	-0.3 (-0.5--0.2)
TR Vena contracta	11 (9-12)	**6 (5-8)***	-4 (-7- -4)	9 (8-11)	**5 (4-6)**†	-4 (-5--3)
TV ann. diameter, mm	52±7	49±7	-2.9±3	50±6	**46±6**†	-2.7±4.46
TR Regurgitant volume, ml	57.5 (49-61)	**15 (14-30)***	-30 (-34 - -22)	45 (35-53)	**19 (12-25.5)**†	-27 (-37 - -18)
sPAP, mmHg	50±11.92	47±12.39	-2.9±5.98	47±15.66	48±14.89	-0.21±15.79
IVC diameter, mm	26±5.06	24±3.9	-2±2.36	28±6.77	**21±6.35**†	**-7±6.67**‡

Supplemental Table 9: Echocardiographic findings at baseline and after one month of follow-up in patients undergoing isolated TTVR.

EROA = effective regurgitant orifice area, IVC = inferior vena cava, LVEDD = left ventricular end-diastolic diameter, LVLEF = left ventricular ejection fraction, MNA = Mini Nutritional Assessment score, PISA = proximal isovelocity surface area, RV-FAC = right ventricular fractional area change, sPAP= systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, TR = tricuspid regurgitation, TV = tricuspid valve. Values are expressed in mean ± SD or median (IQR) where appropriate. Counts are expressed in n (%).

Supplemental Table 10

	MNA not improved n = 7			MNA improved n = 36		
Parameter	Baseline	1-Month FU	Δ	Baseline	1-Month FU	Δ
NT-proBNP (pg/mL)	5307.5 (2183.2-10515.2)	6166 (2077-8689.8)	859 (-350-1765)	3164 (2150-6555)	**2508 (1612-5906)***	-250 (-1290-90)
eGFR, ml/min	43±14.26	44±18.39	1.0±5.42	45±19.37	47±18.14	2.0±4.52
Creatinine, mg/dl	1.4 (1.3-1.7)	2.1 (1.3-2.2)	0.7 (-0.1-1.4)	1.3 (1.1-1.7)	1.4 (1-1.5)	1 (-0.3-2)
BUN mmol/l	13.4 (8-26)	13.7 (6.4-25)	0.3 (-2.2-2.2)	11 (8.2-17.8)	9.6 (7-12.3)	-1.4 (-4.8- -2.2)
Bilirubin total, µmol/l	12.8 (8.7- 14.9)	13.0 (12.4-14.5)	0.2 (-0.3-4.3)	14 (8.8-18.6)	13 (9.1-16.3)	-1.0 (-4.9-1.2)
AST, µmol/l	0.41 (0.4-0.4)	0.47 (0.4-0.5)	0.06 (-0.05-0.1)	0.46 (0.4-0.5)	0.46 (0.3-0.6)	0 (-0.07- 0.08)
ALT, µmol/l	0.41 (0.3 - 0.5)	0.48 (0.4 - 0.5)	0.07 (-0.1-0)	0.34 (0.3-0.4)	0.46 (0.3 - 0.6)	0.12 (-0.1-0.2)
γGT, µmol/l	1.29 (0.9-1.6)	1.29 (1-1.5)	0 (-0.3-0.3)	1.6 (0.8-2.4)	1.5 (1.2-2)	-0.1 (-0.4-0.1)
Alcaline phosphatase, µmol/l	1.61 (1.3-1.7)	1.67 (1.4-1.8)	0.06 (-0.1-0.2)	1.5 (1.2-2)	1.6 (1.2-2)	-0.1 (-0.3-0.1)
Albumin, g/l	42 (40.8-45)	45 (41-46.8)	3 (0-0.8)	45 (41-47)	45 (44-46.5)	0 (-2-2)
Leucocytes, Gpt/l	6.81 (6.1-7)	6.18 (5.8-7.1)	-0.7 (-0.7-0.5)	7 (5.8-7.9)	6.3 (5.5-7.3)	-0.7 (-1.3-0.3)
Haemoglobin, mmol/l	7.5 (6.5-8)	7.4 (6.6-7.8)	-0.1 (-0.5-0.3)	7.7 (7-8.5)	7.8 (6.6-8.3)	0.1 (-0.6-0.2)
CHE, µmol/l	93±30	96±26	3±13	93±29	100±28	7±15.07
Haematocrit	0.36±0.04	0.36±0.04	0±0.05	0.36±0.05	0.36±0.05	0±0.001
C-Reactive Protein, mg/l	2.6 (1.2-4.3)	4.3 (2.6-6.6)	1.7 (-1.0 -3)	3.7 (0.8-5)	2.1 (1.7-5.4)	-1.6 (-2.6-2.5)
Total serum protein, g/l	75.5 (74.2-76.8)	75 (75.2-77.8)	-0.5 (-4.5--0.2)	70.8 (68.8-74.7)	69.2 (66.3-72.7)	-1.6 (-0.1-6.7)

Supplemental Table 10: Laboratory findings in patients undergoing isolated TTVR at baseline and after one month of follow-up.

Supplemental Table 11

	All	MNA > 8	MNA ≤ 8	p-value
n	43	25	18	
Age (years)	78 (74.5-82)	80 (74-82)	80 (72-83)	1.0
Female, n (%)	21 (49)	12 (48)	9 (50)	1.0
BMI, kg/m²	26 (23.9-28.4)	26 (24.9-28.7)	24.75 (23.4-27.7)	.14
EuroSCORE II, %	7.4 (4.4-9.7)	6.2 (4.4-9.3)	7.4 (4.5-9.7)	.87
STS mortality score, %	4.1 (2.8-5.9)	4.3 (3.2-5.9)	3.6 (2.7-5.8)	.61
NYHA II, n (%)	0	0	0	
NYHA III, n (%)	28 (65)	16 (64)	12 (67)	1.0
NYHA IV, n (%)	15 (35)	9 (36)	6 (33)	1.0
Lead across tricuspid valve, n (%)	19 (44)	11 (44)	8 (44)	1.0
Previous PCI, n (%)	10 (23)	9 (36)	1 (6)	**.049**
Previous CABG, n (%)	4 (9)	4 (16)	0	.21
HFrEF, n (%)	27 (63)	14 (56)	13 (72)	.44
Chronic pulmonary disease, n (%)	9 (21)	4 (16)	5 (28)	.58
ACEI / ARB, n (%)	35 (83)	22 (88)	13 (76)	.57
Child-Pugh class B, (%)	2 (5)	0 (0)	2 (11)	0.30
Beta-blocker, n (%)	38 (88)	24 (96)	14 (78)	.17
Aldosterone antagonist, n (%)	16 (37)|	10 (40)	6 (33)	.90
Diuretic, n (%)	43 (100)	25 (100)	18 (100)	1.0
Furosemide dosis equivalent, mg	40 (22.5-80)	40 (20-80)	60 (40-100)	0.11

Supplemental Table 11: Baseline characteristics of patients undergoing combined TMTVR.

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, NYHA = New York Heart Association functional class, PCI = percutaneous coronary intervention, STS = Society of Thoracic Surgeons. Values are expressed in mean ± SD or median (IQR) where appropriate. Counts are expressed in n (%).

Supplemental Table 12

	All	MNA > 8	MNA ≤ 8	p-value
n	43	25	18	
LVEF, %	43 (25.5-60.5)	48 (25-61)	34.5 (30-51.5)	.57
LVEDD, mm	57 (48.5-65)	49 (44-59)	59 (55.5-67.2)	**.03**
TAPSE <17mm, n (%)	20 (47)	14 (56)	6 (33)	.25
RV-FAC <35%, n (%)	16 (37)	8 (32)	8 (44)	.61
TV EROA (PISA), cm²	0.44 (0.3-0.6)	0.45 (0.3-0.5)	0.55 (0.4-0.8)	.09
TR vena contracta, mm	9 (7-10)	9 (7-10)	9 (7-11)	.42
TV annulus diameter, mm	49±5.13	50±4.47	49±6.06	0.74
sPAP, mmHg	54±16.89	52±11.64	58±23.45	.41
IVC diameter, mm	28 (24.2-30)	25.5 (22.8-29)	30 (25.2-31.8)	.23
TR Grade 2, n (%)	6 (14)	3 (12)	3 (17)	1.0
TR Grade 3, n (%)	32 (74)	20 (80)	12 (67)	.53
TR Grade 4, n (%)	5 (12)	2 (8)	3 (17)	.69

***Supplemental Table 12**:* Baseline echocardiographic findings in patients undergoing combined TMTVR.

EROA = effective regurgitant orifice area, IVC = inferior vena cava, LVEDD = left ventricular end-diastolic diameter, LVLEF = left ventricular ejection fraction, MNA = Mini Nutritional Assessment score, PISA = proximal isovelocity surface area, RV-FAC = right ventricular fractional area change, sPAP= systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, TR = tricuspid regurgitation, TV = tricuspid valve. Values are expressed in mean ± SD or median (IQR) where appropriate. Counts are expressed in n (%).

Supplemental Table 13

	MNA not improved n = 15			MNA improved n = 28		
Parameter	Baseline	1-Month FU	Δ	Baseline	1-Month FU	Δ
Age, years	78 (74-82.5)			78.5 (75-82)		
BMI, kg/m^2	28 (25.2-32.1)	28 (24-33)	0 (-1.6-0.9)	26 (23.8-26.9)	25 (24-26)	-1 (-1.4- 0.3)
Furosemide, mg	60 (40-150)	60 (40-190)	0 (-10-10)	40 (20-70)	40 (20-50)	0 (-15-5)
MLHFQ	36 (34.5-37.8)	34 (21.5-43.5)	-2 (-5-11)	33 (25.5-44.5)	**23 (15-33.5)†**	-10 (-19.5--1)
MLHFQ physical	25±6.28	23±9.58	-2 (-4-7)	22±8.54	**15±9†**	-7 (-12.2--3)
MOS - SF-36, %	43±11.91	42±25.94	-1±30	38±15.12	**52±15.57†**	14±25.2
MOS - SF-36 physical, %	17 (5-35)	20 (0-52.5)	3 (-18.8-23.8)	15 (7.5-42.5)	**45 (17.5-65)†**	30 (-5-45)
6MWD, m	169±98.69	177±128.56	8±97.5	247±118.01	**311±127.02†**	64±80.01

Supplemental Table 13: Changes in BMI, furosemide dose, quality of life measures and 6MWT distance in patients undergoing combined TMTVR.

BMI = Body Mass Index, FU = Follow-Up, MLHFQ =Minnesota Living with Heart Failure Questionnaire, MOS - SF-36 = Medical Outcomes Study – 36-Item Short-Form health survey, 6MWD = six minute walk test distance.

Supplemental Table 14

	MNA not improved n = 15			MNA improved n = 28		
Parameter	Baseline	1-Month FU	Δ	Baseline	1-Month FU	**Δ**
LV-EF, %	30 (24.5-62)	33 (25.5-49.5)	3 (-6.5-6.5)	44 (31-59.5)	49 (32.5-56)	5 (-4-5.5)
LVEDD, mm	59 (51-65.5)	57 (53.5-64)	-2 (-3.5--0.5)	54 (45.5-59)	51 (46.5-57)	-3 (-5.5-3)
TAPSE, mm	16±4.41	16±4.33	0±4.7	17±4.49	17±4.27	0±3.56
RVFAC, %	37±12.06	37±9.78	0±12	36±8.49	37±8.99	1±9
TV EROA (PISA), cm²	0.4 (0.3-0.6)	**0.2 (0.1-0.4)***	-0.2 (-0.3-0)	0.5 (0.3-0.6)	**0.2 (0.1-0.4)†**	-0.3 (-0.3--0.1)
TR Vena contracta	9 (8-9.5)	**6 (4.5-7)***	-3 (-5--1)	9 (6.8-10)	**5 (4-7.2)†**	-4 (-5--1)
TV annulus diameter, mm	48±4.79	**40±5.42***	-8.1±7.23	50±5.31	**44±5.85†**	-5.9±5.85
sPAP, mmHg	53 (46-59)	48 (36-55.5)	-5 (-15-5.5)	53 (46-67)	**43 (36.2-46.5)†**	-10 (-25--1.8)
TR Regurgitant volume,ml	36 (30.5-41.5)	**23 (16.5-33)***	-13 (-21.5--1.5)	44 (30-69)	**17 (12.5-37.5)†**	-27 (-43.5--11)
IVC diameter, mm	27 (24-29)	24 (18.5-29)	-3 (-6-2)	28 (24.5-30.5)	**22 (19-28)†**	-6 (-9--1)

Supplemental Table 14: Echocardiographic findings at baseline and after one month of follow-up in patients undergoing combined TMTVR.

EROA = effective regurgitant orifice area, IVC = inferior vena cava, LVEDD = left ventricular end-diastolic diameter, LVLEF = left ventricular ejection fraction, MNA = Mini Nutritional Assessment score, PISA = proximal isovelocity surface area, RV-FAC = right ventricular fractional area change, sPAP= systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, TR = tricuspid regurgitation, TV = tricuspid valve. Values are expressed in mean ± SD or median (IQR) where appropriate. Counts are expressed in n (%).

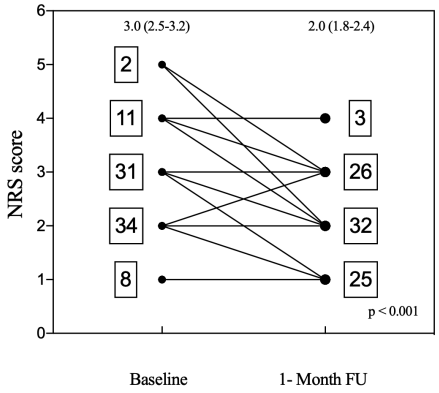
Supplemental Table 15

	MNA not improved n = 15			MNA improved n = 28		
Parameter	Baseline	1-Month FU	Δ	Baseline	1-Month FU	Δ
NT-proBNP (pg/mL)	6521 (2510.5-13720.5)	7292 (2730.5-18153.2)	1166 (-235.5-2577.5)	2663 (1965-5728.8)	**2344 (1292.8-4763)†**	**-370 (-1218.2-319.5) ↓ 26**
eGFR, ml/min	35 (26.5-48)	35 (25-36)	-2.5 (-9.8-0.5)	46 (34.8-54.2)	**54 (42-60.8)†**	**8 (-2.8-12.8)**
Creatinine, mg/dl	1.67 (1.4-2)	1.78 (1.4-2.1)	0.11 (-0.1-0.3)	1.41 (1.1-1.5)	**1.12 (1-1.3)†**	**-0.3 (-0.2-0.1)**
BUN mmol/l	14.2 (11.8-18.5)	13.95 (11.2-23.1)	-0.3 (-2.2-5.9)	10.25 (8.7-13.1)	9.2 (7.2-11.7)	-1.0 (-3.3-1.2)
Bilirubin total, µmol/l	10.75 (6.6-18.1)	10.15 (7.7-13.2)	0.25 (-2.5-0.8)	15.45 (11.6-18.6)	**11.15 (8.6-17.2)†**	-4.3 (-7.4--0.3)
AST, µmol/l	0.49 (0.4-0.6)	0.415 (0.4-0.5)	-0.09 (-0.1-0)	0.43 (0.3-0.5)	0.4 (0.3-0.4)	-0.01 (-0.1-0.1)
ALT, µmol/l	0.3 (0.2-0.6)	0.2 (0.2-0.3)	-0.1 (-0.2--0.1)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	-0.07 (-0.1-0)
γGT, µmol/l	1.8 (1.2-4)	1.6 (1-3.8)	-0.2 (-0.6--0.1)	1.6 (1.1-2.4)	1.3 (1-2.4)	-0.3 (-0.6-0.1)
Alcaline phosphatase, µmol/l	1.59 (1.3-1.8)	1.82 (1.5-2.4)	0.2 (0-0.4)	1.38 (1.2-2.3)	**1.41 (1.1-1.8)†**	**-0.3(-0.4-0)**
Albumin, g/l	40.8 (37.1-42.8)	40.6 (38.9-43.9)	-0.5 (-1.4-2.8)	42.7 (39-44.6)	**45 (41.4-46)†**	2 (0.2-3.2)
Leucocytes, Gpt/l	6.94 (5.7-7.6)	7.04 (6-7.5)	0.1 (-0.6-2.1)	7.34 (5.8-7.9)	6.905 (5.8-7.9)	-0.7 (-1-0.5)
Haemoglobin, mmol/l	7.2 (6.4-8.2)	6.3 (5.9-7.2)	-0.7 (-1.2-0)	7.7 (7-8.2)	7.5 (7.2-7.9)	**-0.1 (-0.4-0.2)**
CHE, µmol/l	66 (57.2-80.2)	65.5 (59.8-86)	0.5 (-2-5.8)	80 (58-91)	**92 (68-115)†**	12 (2-26)
Haematocrit	0.34±0.04	0.34±0.04	0.013±0.04	0.38±0.04	0.38±0.04	0.0079±0.04
C-Reactive Protein, mg/l	6 (4.4-21.4)	4.9 (3.4-57)	-1 (-8.5-9.7)	3.6 (1.8-8.9)	3.3 (1.6-7.4)	-0.3 (-4.7-0)
Total serum protein, g/l	65.0 (62-72.5)	65.0 (62.3-65.2)	0.2 (-0.2-0-1.9)	66.6 (60-72)	**71.8 (68-74)†**	5.2 (2.1-9.1)

Supplemental Table 15: Laboratory findings in patients undergoing combined TMTVR at baseline and after one month of follow-up.

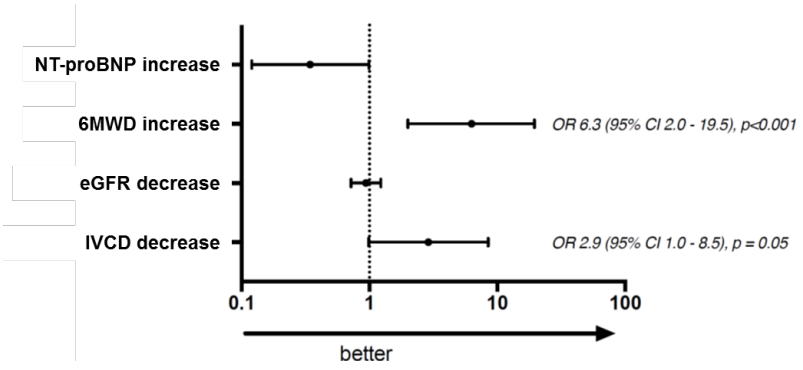
Supplemental Figures

Supplemental Figure 1



Supplemental Figure 1. Nutritional status according to NRS scores at baseline and follow-up after TTVR or TMTVR.

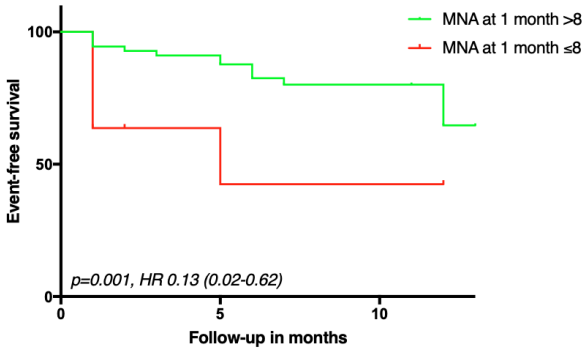
Supplemental Figure 2



***Supplemental Figure 2*:** Binary logistic regression analysis of clinical parameters associated with MNA improvement.

eGFR = estimated glomerular filtration rate (Cockcroft-Gault formula), IVCD = inferior vena cava diameter, 6MWD = six minute walk test distance.

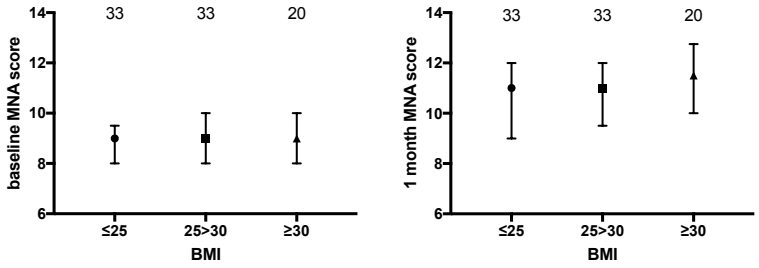
Supplemental Figure 3



FU in months	0	1	2	3	4	5	6	7	8	9	10	11	12	13
MNA at 1 month >8	74	73	56	55	55	54	50	34	34	34	34	30	26	2
MNA at 1 month ≤8	12	11	4	4	4	3	3	3	3	3	3	3	2	2

Supplemental Figure 3. Kaplan-Meier graph of event-free survival (death and rehospitalization for heart failure) in patients undergoing TTVR or TMTVR stratified according to median MNA score at 1 month.

Supplemental Figure 4

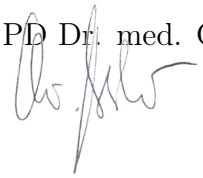


Supplemental Figure 4: Median (IQR) MNA scores according to patient BMI at baseline and follow-up.

7 Darstellung des eigenen Beitrages und geteilte Erstautorenschaft

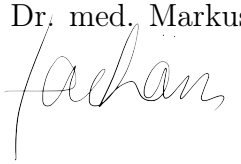
Die vorliegende Studie wurde von Matthias Unterhuber in enger Zusammenarbeit mit Christian Besler in geteilter Erstautorenschaft erstellt. Die Mitwirkung von Matthias Unterhuber erstreckte sich von der Konzeption, Erarbeitung, Datenerhebung, statistische Auswertung und Analyse bis hin zur Interpretation und Manuskripterstellung. Alle Schritte waren für die Verfassung des vorliegenden Papers von entscheidender Rolle und wurden von den beiden Erstautoren in gleichem, wesentlichem Maße ausgeführt.

PD Dr. med. Christian Besler

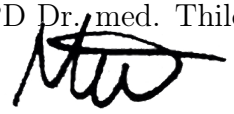


PD Dr. med. Karl-Philipp Rommel

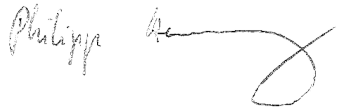
Dr. med. Markus Zachäus



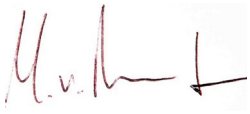
PD Dr. med. Thilo Noack



Dr. med. Philipp Hartung

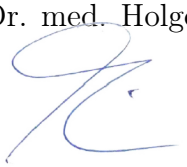


Dr. med. Maximilian von Roeder

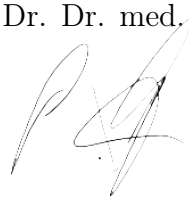


Prof. Dr. med. Steffen Desch

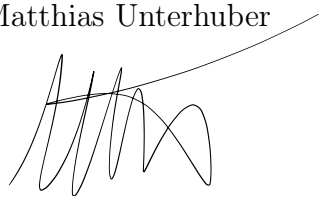
Prof. Dr. med. Holger Thiele



Prof. Dr. Dr. med. P. Lurz



Matthias Unterhuber



8 Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

Leipzig, im März 2022

Matthias Unterhuber

Curriculum vitae

Matthias Unterhuber

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E-Mail: matthias.unterhuber@gmail.com

Studium

- *2013*
  Abschluss des Studiums der Humanmedizin, Medizinische Universität Innsbruck
  Arbeit: Outcome von Patienten mit Perkutaner Coronarer Intervention am Hauptstamm, Tutor Priv.-Doz. Matthias Frick
- *2007*
  Abitur am Realgymnasium Albert Einstein, Meran
- *2002*
  Mittelschulabschluss P. Rossegger, Meran

Zertifizierungen

- *2018*
  Echokardiographie Grundkurs Leipzig, Prof. Hagendorff
- *2018*
  Good Clinical Practice GCP-ISO14155-Kombi-Schulung absolviert
- *2015*
  Notarztdiplom in Bad Hofgastein (Österreich)
- *2015*
  Diploma in Mountain and High Altitude Medicine (Deutsche Gesellschaft für Berg- und Expeditionsmedizin BExMed, Österreichische Gesellschaft für Alpin- und Höhenmedizin, IKAR Medcom, UIAA)
- *2014*
  GIMSI Syncope Expert Zertifikat (Interdisziplinäre Synkopenforschungsgruppe Italien)
- *2005*
  Nachweis über die entsprechende Kenntnis der deutschen und italienischen Sprache bezogen auf das Doktorat, Doppelsprachigkeitsnachweis A
- *2006*
  ECDL, European Computer Driving License

Erfahrungen und Tätigkeiten

- *Seit Januar 2017*
  Arzt in Weiterbildung am Herzzentrum Leipzig, Innere Medizin und Kardiologie. Tätigkeit auf Normalstation, Intermediate Care und kardiologischer Intensivstation, Ambulanzen, Tagesklinik und Funktionsproben:

  01.01.2017 bis 01.09.2017 unter Chefarzt Prof. Dr. G. Schuler und Prof. Dr. Axel Linke

  ab 01.09.2017 unter Chefarzt Prof. Dr. H. Thiele

- vom 01.08.2020 bis 01.08.2021 Innere Medizin in der Helios Klinik Schkeuditz, Chefarzt Dr. S. Sack

- *Oktober 2013-Dezember 2016*
  Arzt in Weiterbildung an der kardiologischen Abteilung im Krankenhaus Bozen (Lehrkrankenhaus der Universität Verona, weiterbildungsberechtigt zur Facharztausbildung für Innere Medizin und Kardiologie). Hauptschwerpunkte Rhythmologie mit Monitorisierungs- und Pacing-Geräten, klinischer und instrumenteller Diagnostik, Therapie sowie Syncope Unit. Insgesamt 30 Monate Tätigkeit auf Normalstation und Intensivstation mit Betreuung kardiologischer und internistischer Patienten.

- *2012-2016*
  Vizestellenleiter, ärztlicher Leiter und aktives Mitglied der Bergrettung im CNSAS, Sektion Meran mit Abhaltung von Erste Hilfe Kursen und Zertifizierungen zum Gebrauch automatischer externer Defibrillatoren für die Freiwilligen und über 200 Stunden jährlich freiwilliger Dienst in der Bergrettung mit Einsätzen als Notarzt in unwegsamen Gelände mit Ausbildung in Seiltechnik und fortgeschrittenen Bergungstechniken im Gebirge, hochalpinen Gelände, Gletscher und Höhle sowie Hubschrauberbergung.

- Medizinische Unterstützung bei verschiedenen sportlichen Events:
  - 2015 Südtiroler Herzstiftung
  - 2014-2016 Ultraskyrace Hufeisentour
  - 2014-2016 Merano Air Festival
  - 2016 Seiser Alm Halbmarathon

  etc.

- *Jan- März 2014*
  Notarztdienst und Bergrettungsdienst auf Filmset des Hollywood- Blockbusters ≪Everest≫, Baltasar Kormakur. USA, 2015
- *2012*
  Klinische Erfahrung im Studium (KPJ):
  - Innere Medizin, Krankenhaus Lienz (A)
  - Neurologie an der Wagner - Jauregg Neurologie Klinik, Linz (A)
  - Allgemeinchirurgie im Krankenhaus Feldkirch (A)
  - Anästhesie am AKH Linz (A)

Publikationen und Studien

Als Erst- Korrespondenz-, oder Letztautor:

Unterhuber, Matthias, Karl-Philipp Rommel, Karl-Patrik Kresoja, Julia Lurz, Jelena Kornej, Gerhard Hindricks, Markus Scholz, Holger Thiele, and Philipp Lurz (Sept. 2021). "Deep learning detects heart failure with preserved ejection fraction using a baseline electrocardiogram". en. In: *European Heart Journal - Digital Health*, ztab081. ISSN: 2634-3916. DOI: 10.1093/ehjdh/ztab081. URL: https://academic.oup.com/ehjdh/advance-article/doi/10.1093/ehjdh/ztab081/6371868 (visited on 09/23/2021).

Manfrin, Massimiliano, Giacomo Mugnai, Werner Rauhe, Vedran Velagic, and Matthias Unterhuber (July 2021). "Left Atrial Pressure as a Predictor of Success in Catheter Ablation of Atrial Fibrillation in a Real-Life Cohort." eng. In: *Journal of clinical medicine* 10.15. ISSN: 2077-0383. DOI: 10.3390/jcm10153208.

Unterhuber, Matthias, Karl-Patrik Kresoja, Christian Besler, Karl-Philipp Rommel, Mathias Orban, Maximilian von Roeder, Daniel Braun, Lukas Stolz, Steffen Massberg, Jonel Trebicka, Markus Zachäus, Jörg Hausleiter, Holger Thiele, and Philipp Lurz (July 2021). "Cardiac output states in patients with severe functional tricuspid regurgitation: impact on treatment success and prognosis." eng. In: *European journal of heart failure*. Place: England. ISSN: 1879-0844 1388-9842. DOI: 10.1002/ejhf.2307.

Donazzan, Luca, Francesca Baessato, Roberto Cemin, Giacomo Mugnai, and Matthias Unterhuber (Sept. 2021). "Atrial thrombosis during Tako-tsubo cardiomyopathy: chance or plausible risk?" eng. In: *Clinical research in cardiology : official journal of the German Cardiac Society* 110.9. Place: Germany, pp. 1523–1524. ISSN: 1861-0692 1861-0684. DOI: 10.1007/s00392-021-01883-2.

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Unterhuber, Matthias, Marco Tomaino, and Michele Brignole (June 2018). "[Do we need syncope units? : Experience from Bolzano, South Tyrol (Italy)]." ger. In: *Herzschrittmachertherapie & Elektrophysiologie* 29.2. Place: Germany, pp. 199–203. ISSN: 1435-1544 0938-7412. DOI: 10.1007/s00399-018-0561-3.

Unterhuber, M., W. Rauhe, P. Sgobino, F. Pescoller, M. Manfrin, and M. Tomaino (Sept. 2016). “Implantable Loop Recorder: Diagnostic Yield And Possible Therapeutic Effect In Patients With Neurally Mediated Reflex Syncope.” eng. In: *Journal of atrial fibrillation* 9.2, p. 1398. ISSN: 1941-6911. DOI: 10.4022/jafib.1398.

Als Co-Autor:

Kresoja, Karl-Patrik, Karl-Philipp Rommel, et al. (July 2021). “Right Ventricular Contraction Patterns in Patients Undergoing Transcatheter Tricuspid Valve Repair for Severe Tricuspid Regurgitation.” eng. In: *JACC. Cardiovascular interventions* 14.14. Place: United States, pp. 1551–1561. ISSN: 1876-7605 1936-8798. DOI: 10.1016/j.jcin.2021.05.005.

Higuchi, Satoshi et al. (June 2021). “Impact of Residual Mitral Regurgitation on Survival After Transcatheter Edge-to-Edge Repair for Secondary Mitral Regurgitation.” eng. In: *JACC. Cardiovascular interventions* 14.11. Place: United States, pp. 1243–1253. ISSN: 1876-7605 1936-8798. DOI: 10.1016/j.jcin.2021.03.050.

Schlotter, Florian, Mizuki Miura, et al. (July 2021). “Outcomes of transcatheter tricuspid valve intervention by right ventricular function: a multicentre propensity-matched analysis.” eng. In: *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 17.4. Place: France, e343–e352. ISSN: 1969-6213 1774-024X. DOI: 10.4244/EIJ-D-21-00191.

Park, Sang-Don et al. (Apr. 2021). “Sex-Related Clinical Characteristics and Outcomes of Patients Undergoing Transcatheter Edge-to-Edge Repair for Secondary Mitral Regurgitation.” eng. In: *JACC. Cardiovascular interventions* 14.8. Place: United States, pp. 819–827. ISSN: 1876-7605 1936-8798. DOI: 10.1016/j.jcin.2020.12.042.

Karam, Nicole, Mathias Orban, et al. (May 2021). “Impact of effective regurgitant orifice area on outcome of secondary mitral regurgitation transcatheter repair.” eng. In: *Clinical research in cardiology : official journal of the German Cardiac Society* 110.5, pp. 732–739. ISSN: 1861-0692 1861-0684. DOI: 10.1007/s00392-021-01807-0.

Muntané-Carol, Guillem, Maurizio Taramasso, Mizuki Miura, Mara Gavazzoni, Alberto Pozzoli, Hannes Alessandrini, Azeem Latib, Adrian Attinger-Toller, Luigi Biasco, Daniel Braun, Eric Brochet, Kim A. Connelly, Horst Sievert, et al. (July 2021). “Transcatheter Tricuspid Valve Intervention in Patients With Previous Left Valve Surgery.” eng. In: *The Canadian journal of cardiology* 37.7. Place: England, pp. 1094–1102. ISSN: 1916-7075 0828-282X. DOI: 10.1016/j.cjca.2021.02.010.

Karam, Nicole, Lukas Stolz, et al. (Apr. 2021). "Impact of Right Ventricular Dysfunction on Outcomes After Transcatheter Edge-to-Edge Repair for Secondary Mitral Regurgitation." eng. In: *JACC. Cardiovascular imaging* 14.4. Place: United States, pp. 768–778. ISSN: 1876-7591. DOI: 10.1016/j.jcmg.2020.12.015.

Muntané-Carol, Guillem, Maurizio Taramasso, Mizuki Miura, Mara Gavazzoni, Alberto Pozzoli, Hannes Alessandrini, Azeem Latib, Adrian Attinger-Toller, Luigi Biasco, Daniel Braun, Eric Brochet, Kim A. Connelly, Sabine de Bruijn, et al. (Feb. 2021). "Transcatheter Tricuspid Valve Intervention in Patients With Right Ventricular Dysfunction or Pulmonary Hypertension: Insights From the TriValve Registry." eng. In: *Circulation. Cardiovascular interventions* 14.2. Place: United States, e009685. ISSN: 1941-7632 1941-7640. DOI: 10.1161/CIRCINTERVENTIONS.120.009685.

Blazek, Stephan et al. (Jan. 2021). "Biventricular Physiology of Iatrogenic Atrial Septal Defects Following Transcatheter Mitral Valve Edge-to-Edge Repair." eng. In: *JACC. Cardiovascular interventions* 14.1. Place: United States, pp. 54–66. ISSN: 1876-7605 1936-8798. DOI: 10.1016/j.jcin.2020.10.032.

Lurz, Philipp et al. (Jan. 2021). "Closure of Iatrogenic Atrial Septal Defect After Transcatheter Mitral Valve Repair: The Randomized MITHRAS Trial." eng. In: *Circulation* 143.3. Place: United States, pp. 292–294. ISSN: 1524-4539 0009-7322. DOI: 10.1161/CIRCULATIONAHA.120.051989.

Orban, Mathias, Nicole Karam, et al. (Apr. 2021). "Impact of Proportionality of Secondary Mitral Regurgitation on Outcome After Transcatheter Mitral Valve Repair." eng. In: *JACC. Cardiovascular imaging* 14.4. Place: United States, pp. 715–725. ISSN: 1876-7591. DOI: 10.1016/j.jcmg.2020.05.042.

Kresoja, Karl-Patrik, Alexander Lauten, et al. (Oct. 2020). "Transcatheter tricuspid valve repair in the setting of heart failure with preserved or reduced left ventricular ejection fraction." eng. In: *European journal of heart failure* 22.10. Place: England, pp. 1817–1825. ISSN: 1879-0844 1388-9842. DOI: 10.1002/ejhf.1975.

Orban, Mathias, Karl-Philipp Rommel, et al. (Apr. 2020). "Transcatheter Edge-to-Edge Tricuspid Repair for Severe Tricuspid Regurgitation Reduces Hospitalizations for Heart Failure." eng. In: *JACC. Heart failure* 8.4. Place: United States, pp. 265–276. ISSN: 2213-1787 2213-1779. DOI: 10.1016/j.jchf.2019.12.006.

Taramasso, Maurizio et al. (Mar. 2020). "Outcomes of TTVI in Patients With Pacemaker or Defibrillator Leads: Data From the TriValve Registry." eng. In: *JACC. Cardiovascular interventions* 13.5. Place: United States, pp. 554–564. ISSN: 1876-7605 1936-8798. DOI: 10.1016/j.jcin.2019.10.058.

Lurz, Julia et al. (Oct. 2019). "Safety and Efficacy of Transcatheter Edge-to-Edge Repair of the Tricuspid Valve in Patients With Cardiac Implantable Electronic Device

Leads." eng. In: *JACC. Cardiovascular interventions* 12.20. Place: United States, pp. 2114–2116. ISSN: 1876-7605 1936-8798. DOI: 10.1016/j.jcin.2019.05.034.

Schlotter, Florian, Mathias Orban, et al. (Sept. 2019). "Aetiology-based clinical scenarios predict outcomes of transcatheter edge-to-edge tricuspid valve repair of functional tricuspid regurgitation." eng. In: *European journal of heart failure* 21.9. Place: England, pp. 1117–1125. ISSN: 1879-0844 1388-9842. DOI: 10.1002/ejhf.1547.

Praz, Fabien et al. (July 2019). "Edge-to-Edge Mitral Valve Repair With Extended Clip Arms: Early Experience From a Multicenter Observational Study." eng. In: *JACC. Cardiovascular interventions* 12.14. Place: United States, pp. 1356–1365. ISSN: 1876-7605 1936-8798. DOI: 10.1016/j.jcin.2019.03.023.

Tomaino, M. et al. (May 2016). "Combined Diagnostic Yield of Tilt Table Test And Implantable Loop Recorder to Identify Patients Affected by Severe Clinical Presentation of Neurally-Mediated Reflex Syncope who Could Respond to Cardiac Pacing." eng. In: *Journal of atrial fibrillation* 8.6, p. 1397. ISSN: 1941-6911. DOI: 10.4022/jafib.1397.

Solari, Diana et al. (Mar. 2017). "Stop vasodepressor drugs in reflex syncope: a randomised controlled trial." eng. In: *Heart (British Cardiac Society)* 103.6. Place: England, pp. 449–455. ISSN: 1468-201X 1355-6037. DOI: 10.1136/heartjnl-2016-309865.

Brignole, Michele, Regis Guieu, et al. (Feb. 2017). "Mechanism of syncope without prodromes with normal heart and normal electrocardiogram." eng. In: *Heart rhythm* 14.2. Place: United States, pp. 234–239. ISSN: 1556-3871 1547-5271. DOI: 10.1016/j.hrthm.2016.08.046.

Brignole, Michele, Fabrizio Ammirati, et al. (June 2015). "Assessment of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncopes." eng. In: *European heart journal* 36.24. Place: England, pp. 1529–1535. ISSN: 1522-9645 0195-668X. DOI: 10.1093/eurheartj/ehv069.

Barisonzo, Riccardo et al. (Feb. 2013). "Length of stay as risk factor for inappropriate hospital days: interaction with patient age and co-morbidity." eng. In: *Journal of evaluation in clinical practice* 19.1. Place: England, pp. 80–85. ISSN: 1365-2753 1356-1294. DOI: 10.1111/j.1365-2753.2011.01775.x.

Mitarbeit an internationalen Journals

- 2020 Guest Editor in Special Issue ≪State of the Art in Management of Atrial Fibrillation≫im *Journal of Clinical Medicine*
- Aktiver Reviewer für folgende Journals:

  Journal of Clinical Medicine

  Membranes

  Pediatric Reports

  European Heart Journal - Digital Health

Preise, Vorträge und faculty member an Kongressen

- 2021: 1. Preis *Young Investigator Award* in Herzinsuffizienz Session mit dem Abstract: "Deep learning detects heart failure with preserved ejection fraction using a baseline electrocardiogram in patients at risk"
- *2020*
  DoloMeeting Arrhythmias, Bozen
  Organisation und Mitglied des Steering Committee≫
  www.dolomeeting-arrhythmias.com
- *2018*
  DoloMeeting Arrhythmias, Bozen
  Organisation und Mitglied des Steering Committee (ca. 200 Teilnehmer), Vortrag in engl. Sprache: ≪Utility of an organized program of Training to act the Isometric Counterpressure Maneuvres≫
  www.dolomeeting-arrhythmias.com
- *2017*
  GIMSI Congress, Mailand
  Faculty Member und Vortrag in ital. Sprache: Der Zusammenhang zwischen Emotionen und Synkope
- *2016*
  XVII Edition of Progress in Clinical Pacing, Rom
  Faculty Member und Vortrag in engl. Sprache: ILR in AV- and Intraventricular Conduction Disturbances
- *2016*
  GIMSI Congress, Bergamo

Faculty Member und Vortrag:
≪Nicht-elektrische Therapie: Isometrische Gegendruckmaneuver und Neuigkeiten≫

- *2016*
  DoloMeeting Arrhythmias, Bozen: Organisator und Steering Committee (ca. 150 Teilnehmer). Vortrag in engl. Sprache:
  ≪Implantable Loop Recorder: Placebo Effect or regression to the mean≫

- *2016*
  Cardiology Congress, Tigullio (S. Margherita Ligure, Genua)
  Faculty member und Vortrag:
  ≪Sublinguales Coffein in vasovagalen Synkopen≫

- *2015*
  1st IMREST Meeting am Regionalkrankenhaus Bozen, Vortrag in engl. Sprache
  ≪Combined diagnostic Yield of Tilt Table Test in patients undergoing pacemaker implantation selected by implantable loop recorder≫

Abstracts

- *2019*
  Abstract DGK Mannheim: Hepatocellular damage and nutrition status in patients with severe tricuspid regurgitation undergoing transcatheter tricuspid valve repair. M. Unterhuber, C. Besler, K.-P. Rommel, P. Hartung, F. Schlotter, T. Noack, M. A. Borger, J. Ender, S. Desch, H. Thiele, P. Lurz.

- *2019*
  Abstract ESC Athen: Malnutrition in patients undergoing tricuspid valve edge-to-edge repair: incidence, clinical features and prognostic importance. M. Unterhuber, C.Besler, K.- P. Rommel, M. Roeder, T. Noack, M. Borger, J. Ender, H. Thiele, P. Lurz

- *2018*
  Abstract in ANMCO Kongress, Rimini: Complication rate of VDD and DDD implants. A single centre 16 years experience. L. Donazzan, M. Unterhuber,F. Baessato, W. Rauhe, M. Massimiliano.

- *2018*
  Abstract in ANMCO Kongress, Rimini: The neutrophil-to- lymphocyte ratio in the

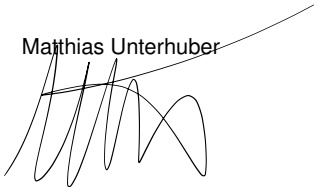
clinical scenario of tako-tsubo-syndrome: the role of periperal inflammation.
F. Baessato, M. Manfrin M , M. Unterhuber, L. Donazzan

- *2015*
  AIAC Bologna, Postervorstellung in ital. Sprache:
  ≪Eignung des Tilt Table Test zur Abschätzung des Rezidivrisikos in Patienten mit neuromediierten Synkopen nach Schrittmacherimplantation≫
- *2015*
  Venice Arrhythmias, Postervorstellung in engl. Sprache:
  ≪Possible placebo effect on loop recorder implantation≫

Hiermit bestätige ich die Richtigkeit der in diesem Schreiben festgehaltenen Informationen und Daten.

Leipzig, im März 2022

Matthias Unterhuber



10 Danksagung

Ich möchte mich bei allen, die mich während der Entstehungszeit dieser Arbeit begleitet und unterstützt haben, bedanken. Ein Dank geht an die Ko-Autoren des Papers, dessen Qualität nur durch ihre Unterstützung erreicht werden konnte.

Mein besonderer Dank geht an Prof. Dr. Dr. Philipp Lurz, welcher mir die Möglichkeit gegeben hat diese Arbeit zu verfassen und mich in meiner beruflichen sowie wissenschaftlichen Entwicklung unterstützt, geprägt und gefördert hat.

Ein großer Dank geht an meine Eltern und meine Schwestern, die mich zu dem gemacht haben, was ich heute bin.

Danke an Gabriel, Mia und Sara, die mich unermüdlich unterstützen und zur Seite stehen.

Ihr seid meine Welt.