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RESEARCH ARTICLE

Cardio-hepatic syndrome in patients undergoing mitral valve transcatheter edge-to-edge repair

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Aims The impact of the cardio-hepatic syndrome (CHS) on outcomes in patients undergoing mitral valve transcatheter edge-to-edge repair (M-TEER) for relevant mitral regurgitation (MR) is unknown. The objectives of this study were three-fold: (i) to characterize the pattern of hepatic impairment, (ii) to investigate the prognostic value of CHS, and (iii) to evaluate the changes in hepatic function after M-TEER.

Methods and results Hepatic impairment was quantified by laboratory parameters of liver function. In accordance with existing literature, two types of CHS were distinguished: ischaemic type I CHS (elevation of both transaminases) and cholestatic type II CHS (elevation of two out of three parameters of hepatic cholestasis). The impact of CHS on 2-year mortality was evaluated using a Cox model. The change in hepatic function after M-TEER was assessed by laboratory testing at follow-up. We analysed 1083 patients who underwent M-TEER for relevant primary or secondary MR at four European centres between 2008 and 2019. Ischaemic type I and cholestatic type II CHS were observed in 11.1% and 23.0% of patients, respectively. Predictors for 2-year all-cause mortality differed by MR aetiology. While in primary MR cholestatic type II CHS was independently associated with 2-year mortality, ischaemic CHS type I was an independent mortality predictor in secondary MR patients. At follow-up, patients with MR reduction ≤2+ (obtained in 90.7% of patients) presented with improved parameters of hepatic function (median reduction of 0.2 mg/dl, 0.2 U/L and 21 U/L for bilirubin, alanine aminotransferase and gamma-glutamyl transferase, respectively, $p < 0.01$).

Conclusions The CHS is frequently observed in patients undergoing M-TEER and significantly impairs 2-year survival. Successful M-TEER may have beneficial effects on CHS.

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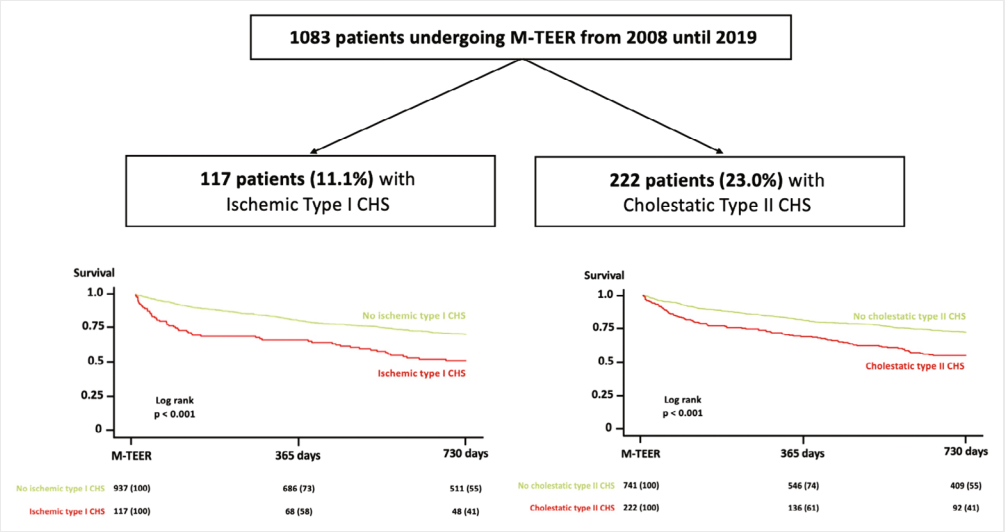
Graphical Abstract



Cardio-hepatic syndrome (CHS) in patients with primary or secondary mitral regurgitation undergoing transcatheter edge-to-edge repiar M-TEER, mitral valve transcatheter edge-to-edge repair.

Keywords Cardio-hepatic syndrome • Heart failure • MitraClip • PASCAL • Mitral valve transcatheter edge-to-edge repair

Introduction

Mitral regurgitation (MR) is one of the most common valve disorders worldwide and leads to high rates of morbidity, mortality, and hospitalization for heart failure.[1,2] Most patients, particularly those with heart failure, are at high risk when treated with surgical valve repair or replacement due to age or comorbidities. Transcatheter treatment techniques have therefore emerged as a therapeutic alternative.[3] The most commonly used technique is mitral valve transcatheter edge-to-edge repair (M-TEER) with safety, efficacy and prognostic benefit documented in randomized controlled trials and registries.[4–7]

Previous studies have shown the negative impact of reduced left ventricular ejection fraction (LVEF) on hepatic function in patients with chronic heart failure and identified the prognostic importance of liver dysfunction in patients with chronic heart failure.[8,9] Furthermore, right heart diseases including severe tricuspid regurgitation (TR) and right ventricular dysfunction (RVD) can lead to kidney and liver dysfunction by means of systemic venous congestion.[10] Recently, RVD has been identified as an important prognostic factor in patients undergoing M-TEER for treatment of secondary MR (SMR).[11] While the impact of the cardio-renal syndrome on survival has been previously described in patients undergoing M-TEER,[12,13] the significance of a cardio-hepatic syndrome (CHS) remains unclear. Besides the known prognostic implications and beneficial influence of transcatheter tricuspid valve repair on hepatic function that have recently been demonstrated, no data exist on the change in liver function after M-TEER.[14,15] Different types of CHS are described in the literature. Ischaemic type I CHS is attributable to a decrease in systemic and thus hepatic perfusion and most commonly presents with elevated transaminases.[16] Cholestatic type II CHS is the result of chronic congestion and leads to an increase in cholestasis parameters when transaminases are often normal.[16]

This study was conducted to investigate the hepatic function in patients with severe MR and M-TEER treatment and to characterize the pattern of hepatic dysfunction. Based on these findings, we sought to apply an easy laboratory-based definition of CHS and investigate its impact on procedural results, symptoms, and mortality after M-TEER. Finally, this study also evaluated the evolution of hepatic function after M-TEER.

Methods

Study population and procedural technique

Patients who underwent M-TEER for primary (PMR) or SMR at four European heart valve centres (Munich, Bern, Hamburg, and Paris) between November 2008 and December 2019 were included in this study. Only patients with available laboratory evaluation of liver function at baseline were considered. Due to the known impact of tricuspid valve transcatheter edge-to-edge repair (T-TEER) on hepatic function,[14] patients who underwent concomitant T-TEER were excluded.

M-TEER was performed according to the standard of care at each centre in line with international guidelines.[3,17] Patients were treated with a commercially available system for mitral leaflet approximation (either MitraClip [Abbott, Santa Clara, CA, USA] or PASCAL [Edwards Lifesciences, Irvine, CA, USA]).

The procedural technique of edge-to-edge mitral valve repair has previously been described. After induction of general anaesthesia, the M-TEER device is implanted under fluoroscopy and transoesophageal echocardiography guidance by access through the femoral vein and puncture of the interatrial septum.[18]

The study was approved by the respective local ethics committees and conforms to the principles outlined in the Declaration of Helsinki.

Study design and endpoints

Hepatic function

Patients underwent laboratory tests at baseline (maximum 100 days prior to M-TEER) including bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP). To assess the impact of M-TEER on CHS, laboratory hepatic follow-up was included if assessed a minimum of 180 days after intervention. For AST, ALT, GGT and AP, we defined abnormal values by sex-specific cut-offs: AST and ALT (female [f] >34 U/L, male [m] >49 U/L), GGT (f > 39 U/L, m > 59 U/L), AP (f > 105, m > 130). Bilirubin levels were considered abnormal when exceeding 1.2 mg/dl independent of sex. The Model for End-Stage Liver Disease (MELD) XI score was calculated as follows: MELD XI = 5.11 × ln (bilirubin [mg/dl]) ± 11.76 × ln (creatinine [mg/dl]) ± 9.44.[19] The MELD-XI score was chosen in preference to the conventional MELD score because of the high prevalence of atrial fibrillation in the study cohort, which confounded international normalized ratio values by oral anticoagulation. Ischaemic type I CHS was defined as an elevation of both transaminases (AST/ALT). Cholestatic type II CHS was defined as an elevation of two out of three parameters of hepatic cholestasis (bilirubin, GGT and/or AP).[15,16]

Each patient was retrospectively evaluated regarding hepatic comorbidities. Those included chronic alcohol abuse, chronic or active hepatitis, liver cysts, malignancies (primary or metastatic), biliary cirrhosis, hemangiomas, cholangitis, steatosis hepatis, cholelithiasis, prior liver transplant, schistosomiasis, and cryptogenic liver cirrhosis.

Follow-up procedures

Patients attended regular follow-up visits at each centre's outpatient clinics according to the respective schedule. Completeness of follow-up was improved in cooperation with the patient's treating general practitioners, the national civil register and via telephone interview with the patients or the next of kin.

Symptomatic status

Heart failure symptoms were assessed according to New York Heart Association (NYHA) functional class at baseline and latest available follow-up.

Endpoints

The primary endpoint was all-cause mortality at 2 years. Secondary endpoints were MR reduction ≤2+, long-term development of MR, NYHA functional class improvement and change in hepatic function after M-TEER.

Echocardiography

Echocardiography was performed in line with guidelines of the European Association of Cardiovascular Imaging (EACVI) by experienced investigators at each participating centre.[3,20,21] MR severity was expressed using a four-grade scale: mild (1+), moderate (2+), moderate to severe (3+) and severe (4+); MR was quantified before and immediately after the M-TEER procedure before exiting the cardiac catheterization lab, as well as at latest available follow-up. Systolic pulmonary artery pressure (sPAP) was approximated by addition of maximum systolic tricuspid valve pressure gradient with estimated right atrial pressure derived from the inferior vena cava width. We applied a four-grade scale for quantification of TR severity: none (0+), mild (1+), moderate (2+), severe (3+) and massive/torrential (4+).

Statistical analysis

Normality of data was assessed by Kolmogorov–Smirnov and Shapiro–Wilk test. Continuous data are shown as mean ± standard deviation or median with interquartile range (IQR). Between group differences were analysed using Pearson's Chi^2 or Mann–Whitney U test, as appropriate. Comparison of dependent samples was performed by Wilcoxon test. A proportional hazard Cox regression model was used for survival analysis. Parameters showing statistical significance in a univariate analysis were included into a multivariate backward selection model to adjust for possible confounders. Results are depicted as hazard ratio (HR) with 95% confidence interval (CI) and *p*-value. For all analyses, the level of statistical significance was set to $p < 0.05$. Statistical analyses were performed using SPSS (version 25, IBM Corp., Armonk, NY, USA) and R (version 4.0.4).

Results

Baseline study characteristics

This study included 1083 patients (mean age 74.7 ± 10.6 years, 39.3% female) who underwent M-TEER for treatment of symptomatic high-grade MR with available baseline laboratory liver parameters. Aetiology of MR was primary in 37.9% ($n = 408$) and secondary in 62.1% ($n = 669$). The majority (93.6%, $n = 995$) of patients were highly symptomatic with NYHA functional class III (69.5%, $n = 739$) or IV (24.1%, $n = 256$). Renal function was moderately impaired with a mean estimated glomerular filtration rate (eGFR) of 51.4 ± 22.4 ml/min. Seventy percent of all patients ($n = 692$) presented with an eGFR <60 ml/min. At baseline, the mean MELD-XI score was 13.5 ± 6.1. Complete baseline data are depicted in online supplementary *Table S1*.

Among the overall study population, 6.2% of patients ($n = 67$) presented with hepatic comorbidities; among them 37.3% ($n = 25$) with alcohol abuse, 16.4% ($n = 11$) with a history of hepatitis, 16.4% ($n = 11$) with hepatic steatosis, 7.5% ($n = 5$) with liver cysts and 6.0% ($n = 4$) with hepatic tumours. Drug induced liver injury, schistosomiasis, prior liver transplant and cholangitis were observed in <4 patients. Mean LVEF was moderately impaired to 42.8 ± 15.5% (online supplementary *Table S1*). Most patients suffered from severe MR (grade 4+, 58.4%, $n = 627$) or moderate to severe MR (grade 3+, 40.7%, $n = 437$). MR was successfully reduced by M-TEER to ≤1+ in 60.1% ($n = 645$) and ≤2+ in 90.7% ($n = 974$) patients ($p < 0.01$) (online supplementary *Table S2*).

Hepatic function and cardio-hepatic syndrome

Baseline liver enzymes were measured at a median of 2 days (IQR 1–5 days) before the procedure. At baseline, GGT and AP were significantly elevated in the entire cohort with median levels of 69.0 (35.0–137.0) U/L and 90.5 (69.0–121.3) U/L, respectively, whereas median bilirubin level (0.9 [0.6–1.4] mg/dl) was within the normal range (online supplementary *Table S1*). Abnormal levels of bilirubin, GGT, and AP were present in 28.1% ($n = 209$), 60.5% ($n = 575$), and 26.1% ($n = 129$), respectively. Patients with at least one abnormal elevated parameter of cholestasis presented with reduced 2-year survival rates (online supplementary *Figure S1A–C*). Median transaminases were within normal range (AST: 27.0 [21.0–36.0] U/L; ALT: 21.0 [15.0–33.0] U/L). Only 19.2% ($n = 202$) of patients presented with elevated baseline levels of AST and 16.7% ($n = 177$) with elevated levels of ALT. Elevated transaminases were also associated with impaired 2-year survival (online supplementary *Figure S1D,E*).

Ischaemic type I CHS was present in 117 patients (11.1%), while cholestatic type II CHS was observed more frequently (222 patients; 23.0%). *Table 1* depicts baseline differences when comparing patients with and without ischaemic type I CHS. The latter was associated with younger age, female sex, worse biventricular function, and more severe heart failure symptoms. Left atrial dilatation, impaired biventricular function, concomitant TR and higher sPAP were associated with cholestatic type II CHS (*Table 2* and online supplementary *Figure S2*). Of note, among patients with type II CHS, MR was more frequently secondary than primary (70.2% vs. 58.7%) but showed no sex-specific prevalence differences.

Prognostic implications of the cardio-hepatic syndrome

Patients with ischaemic or cholestatic CHS had a significantly increased mortality after M-TEER. The estimated survival rates were 65.1% vs. 79.5% at 1 year and 49.4% vs. 69.3% at 2 years for patients with vs. without ischaemic type I CHS (both $p < 0.01$; *Figure 1*). For cholestatic type II CHS, survival rates were 67.5% vs. 80.2% at 1 year and 52.9% vs. 71.0% at 2 years.

Within the overall study population, a multivariate Cox regression analysis (*Table 3* and online supplementary *Table S3*) revealed LVEF (per 10% decrease: HR 1.18, 95% CI 1.01–1.38, $p = 0.04$), tricuspid annular plane systolic excursion (TAPSE) (per mm decrease: HR 1.05, 95% CI 1.01–1.10, $p = 0.02$), eGFR (per 10 ml/min decrease: HR 1.16, 95% CI 1.07–1.27, $p < 0.01$), history of stroke or transient ischaemic attack (TIA) (HR 2.06, 95% CI 1.31–3.33, $p < 0.01$), NYHA functional class IV (HR 1.58, 95% CI 1.09–2.30, $p = 0.02$), residual MR ≥2+ (HR 2.28, 95% CI 1.44–3.61, $p < 0.01$) and ischaemic type II CHS (HR 1.49, 95% CI 1.05–2.12, $p = 0.03$, *Figure 2*) as independent predictors of 2-year all-cause mortality. The inclusion of the MELD-XI score in the multivariable Cox regression analysis as another indicator of impaired liver and renal function was not identified as independent predictor when included instead of CHS.

Aetiology-stratified sub-analysis revealed differences in predictors for 2-year all-cause mortality in patients with PMR vs. SMR. In patients with PMR, TAPSE (per mm decrease: HR 1.08, 95% CI 1.03–1.13, $p < 0.01$), post-procedural MR severity ≥3+ (HR 2.61, 95% CI 1.54–4.42, $p < 0.01$) and cholestatic type II CHS (HR 2.13, 95% CI 1.28–3.55, $p < 0.01$, *Table 3*, online supplementary *Table S4*, *Figures 2* and *3*). When including only patients with SMR into the multivariate Cox regression model, TAPSE (per mm decrease: HR 1.08, 95% CI 1.02–1.13, $p < 0.01$), eGFR (per 10 ml/min decrease: HR 1.28, 95% CI 1.16–1.43, $p < 0.01$), history of stroke or TIA (HR 2.59, 95% CI 1.19–2.92, $p < 0.01$), NYHA functional class IV (HR 1.86, 95% CI 1.09–2.30, $p = 0.02$), TR severity ≥3+ (HR 1.67, 95% CI 1.05–2.66, $p = 0.03$) and ischaemic type I CHS (HR 2.73, 95% CI 1.48–5.06, $p < 0.01$) were independently associated with 2-year all-cause mortality (*Table 3*, online supplementary *Table S5*, *Figures 2* and *4*).

While cholestatic type II CHS was associated with a higher degree of post-procedural MR (≥3+ in 13.5% vs. 8.3% of patients with vs. without cholestatic type II CHS), this trend was no longer observed at latest available follow-up (online supplementary *Table S2* and *Figure S4*). Although patients with both types of CHS (ischaemic and cholestatic) presented with more severe NYHA functional class at baseline, symptomatic improvement was comparable irrespective of hepatic function (*Table 2* and online supplementary *Figure S5*).

Changes in hepatic function after mitral valve transcatheter edge-to-edge repair

Repeat analysis of hepatic function during follow-up was available in a subgroup of patients with a median time to follow-up of 363 days (208–741 days) (online supplementary *Table S6* depicts baseline and follow-up characteristics in patients with and without available laboratory hepatic follow-up). A significant decrease in levels of bilirubin (0.9 to 0.7 mg/dl, $p < 0.01$, 221 paired values), AST (27.0 to 26.0 U/L, $p = 0.04$, 439 paired values), ALT (22.0 to 21.0 U/L, $p = 0.02$, 452 paired values) and GGT (76.0 to 49.0 U/L, $p < 0.01$, 403 paired samples) was observed (online supplementary *Table S7A*). In contrast, AP levels remained unchanged (84.0 to 83.0 U/L, $p = 0.75$). In an exploratory analysis we addressed the change in liver function in patients with or without successful M-TEER. As depicted in *Figure 5*, the above-described improvement in hepatic function was observed only in patients with successful procedural MR reduction to ≤2+ (online supplementary *Table S7*). Further, a time-phased sub-analysis showed that the decongestive effect of M-TEER occurred within the first year after treatment, while reduction of transaminases took more time (online supplementary *Table S8*).

Within the subgroup of patients who initially presented with CHS, all parameters of hepatic function (bilirubin, AST, ALT, GGT and AP) were significantly reduced at follow-up evaluation (online supplementary *Table S7*). In 70.2% of these patients, a normalization of the impaired liver function parameters was observed at follow-up. Among patients with normal pre-procedural hepatic function, 9.0% suffered from CHS at follow-up examination.

Table 1 Baseline characteristics by ischaemic type I cardio-hepatic syndrome

	Overall population ($n = 1083$)	Ischaemic type I CHS ($n = 117$)	No ischaemic type I CHS ($n = 938$)	*p*-value*
Clinical characteristics				
Age, years	74.7 ± 10.6	69.1 ± 15.3	75.4 ± 9.7	**<0.001**
Female sex	432 (39.3)	57 (48.7)	365 (38.9)	**0.041**
MR aetiology				**0.008**
PMR	408 (37.9)	31 (26.5)	365 (39.2)	
SMR	669 (62.1)	86 (73.5)	567 (60.8)	
Previous MI	300 (27.9)	41 (35.0)	252 (27.1)	0.070
Previous stroke or TIA	141 (13.1)	14 (12.0)	122 (13.1)	0.727
Atrial fibrillation or flutter	738 (68.5)	83 (70.9)	636 (68.2)	0.543
Coronary artery disease	413 (48.9)	57 (56.4)	347 (48.2)	0.121
ICD/CRT	310 (32.0)	37 (34.3)	269 (32.2)	0.670
eGFR, ml/min	51.4 ± 22.4	54.9 ± 24.3	50.6 ± 21.6	0.143
Creatinine, mg/dl	1.6 ± 1.2	1.5 ± 0.5	1.7 ± 1.2	0.232
NT-proBNP, ng/L	3498 [1494–7245]	6453 [2229–14 636]	3356 [1471–6763]	**<0.001**
MELD-XI score	13.5 ± 6.1	14.7 ± 6.1	13.5 ± 5.8	0.093
Known hepatic disease	67 (6.5)	6 (5.1)	62 (6.6)	0.539
Hepatic function				
Bilirubin, mg/dl	0.9 [0.6–1.4]	1.2 [0.7–2.2]	0.8 [0.6–1.2]	**<0.001**
AST, U/L	27.0 [21.0–36.0]	68.0 [51.0–134.5]	25.0 [20.0–28.0]	**<0.001**
ALT, U/L	21.0 [15.0–33.0]	87.0 [53.5–189.0]	20.0 [14.0–28.0]	**<0.001**
GGT, U/L	69.0 [35.0–137.0]	137.0 [77.3–304.5]	62.0 [32.0–120.0]	**<0.001**
AP, U/L	90.5 [69.0–121.3]	107.0 [80.0–168.0]	86.0 [67.0–116.5]	**<0.001**
Albumin, g/dl	3.3 [2.9–3.7]	3.2 [2.8–3.6]	3.2 [2.9–3.7]	0.125
Medication				
ACEi/ARB	697 (68.1)	38 (36.5)	607 (68.0)	0.353
Beta-blocker	856 (83.3)	79 (75.2)	755 (84.3)	0.019
Diuretics	929 (90.8)	93 (89.4)	812 (90.9)	0.616
Aldosterone antagonists	406 (40.3)	45 (43.3)	355 (40.5)	0.584
Echocardiographic characteristics				
MR EROA PISA, cm^2	0.35 ± 0.29	0.32 ± 0.20	0.36 ± 0.30	0.188
MR volume PISA, ml	47.3 ± 35.3	40.0 ± 24.5	48.4 ± 36.7	**0.049**
MR vena contracta, cm	0.75 ± 0.24	0.78 ± 0.26	0.75 ± 0.24	0.312
LVEF, %	42.8 ± 15.5	36.0 ± 15.1	43.4 ± 15.5	**<0.001**
LVEDV, ml	162.3 ± 76.5	174.5 ± 85.9	161.4 ± 75.7	0.247
LVESV, ml	100.7 ± 70.5	116.2 ± 73.2	99.5 ± 70.4	**0.023**
LVEDD, mm	59.1 ± 11.2	58.4 ± 11.9	59.3 ± 11.2	0.522
LVESD, mm	48.9 ± 11.9	49.2 ± 12.4	48.9 ± 11.9	0.838
LA volume, ml	118.6 ± 59.0	106.9 ± 46.2	120.0 ± 59.8	**0.073**
MV mean PG, mmHg	2.2 ± 1.2	2.1 ± 1.2	2.2 ± 1.2	0.446
TAPSE, mm	17.8 ± 5.2	16.4 ± 5.0	18.0 ± 5.2	**0.003**
RV EDA, cm^2	23.1 ± 7.6	24.6 ± 10.0	23.0 ± 7.3	0.257
RV ESA, cm^2	15.4 ± 5.9	16.6 ± 5.9	15.3 ± 6.0	0.060
RV FAC	0.34 ± 0.11	0.32 ± 0.09	0.34 ± 0.11	0.057
sPAP, mmHg	46.6 ± 15.6	46.2 ± 15.0	46.6 ± 15.8	0.857
Severity of MR, TR and NYHA functional class				
MR severity				0.087
2+	10 (0.9)	3 (2.6)	7 (0.8)	
3+	437 (40.7)	41 (35.0)	383 (41.2)	
4+	627 (58.4)	73 (62.4)	539 (58.0)	

Table 1 (Continued)

	Overall population ($n = 1083$)	Ischaemic type I CHS ($n = 117$)	No ischaemic type I CHS ($n = 938$)	*p*-value*
TR severity				0.404
0+	34 (3.4)	6 (5.6)	27 (3.1)	
1+	430 (42.7)	38 (35.5)	375 (42.9)	
2+	311 (30.9)	38 (35.5)	269 (30.8)	
3+	196 (19.4)	20 (18.7)	171 (19.6)	
4+	37 (3.7)	5 (4.7)	32 (3.7)	
NYHA functional class				**<0.001**
II	68 (6.4)	3 (2.6)	62 (6.7)	
III	739 (69.5)	61 (53.0)	655 (71.2)	
IV	256 (24.1)	51 (44.3)	203 (22.1)	

Data are presented as mean ± standard deviation, *n* (%), or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; AP, alkaline phosphatase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; CHS, cardio-hepatic syndrome; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EDA, end-diastolic area; ESA, end-systolic area; EROA, effective regurgitant orifice area; FAC, fractional area change; GGT, gamma-glutamyl transferase; ICD, implantable cardioverter-defibrillator; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PG, pressure gradient; PISA, proximal isovelocity surface area; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack; TR, tricuspid regurgitation.
*CHS vs. no CHS.

In a landmark survival analysis of patients following their latest available laboratory results, patients who presented with cholestatic type II CHS at both baseline and follow-up ($n = 33$, 6.7%) had the worst survival (1-year post follow-up survival 43.6%, $p < 0.001$) (online supplementary *Figure S5A*). In contrast, patients without type II cholestatic CHS at baseline or follow-up ($n = 366$, 84.4%) and patients whose baseline type II cholestatic CHS ameliorated at follow-up ($n = 34$, 6.7%) had comparably good survival prognosis (1-year post follow-up survival 82.3% and 83.7%, respectively). The subgroup of patients who presented without type II cholestatic CHS at baseline and developed type II cholestatic CHS at follow-up ($n = 76$, 14.9%) presented with an intermediate prognosis (1-year post follow-up survival 67.0%). Patients with maintained or *de novo* type II cholestatic CHS had comparable post-procedural MR to those without follow-up type II cholestatic CHS ($p = 0.97$). The two groups differed merely in serum levels of AST (30.0 [23.0–44.0] U/L vs. 26.0 [20.0–35.90] U/L; $p = 0.020$), AP (98.0 [80.0–140.0] U/L vs. 81.0 [62.0–110.1] U/L; $p = 0.039$) and bilirubin (1.0 [0.6–1.9] mg/dl vs. 0.8 [0.5–1.3] mg/dl; $p = 0.019$).

A similar trend was observed when looking at ischaemic type I CHS (online supplementary *Figure S5B*). Patients with ischaemic type I CHS at baseline and follow-up had worst survival rates (1-year post follow-up survival 51.9%, $p = 0.006$). Further, patients who developed ischaemic type I CHS over time presented with intermediate survival prognosis (1-year post follow-up survival 68.2%). Alike in case of cholestatic type II CHS, patients without ischaemic type I CHS or those with recovery from baseline to follow-up presented with best survival rates (1-year post follow-up survival 79.5% and 79.2%, respectively).

Discussion

Main findings

This large multicentre study is the first to evaluate the relationship of liver function and MR in a large cohort of patients undergoing M-TEER. The three main findings of this study were: (i) ischaemic type I CHS – defined as an elevation of both transaminases – is associated with increased 2-year all-cause mortality in SMR patients undergoing M-TEER; (ii) cholestatic type II CHS – defined as an elevation of two out of three laboratory parameters of hepatic cholestasis – is associated with increased 2-year all-cause mortality in PMR patients undergoing M-TEER; and (iii) successful M-TEER is associated with an improvement in hepatic function at follow-up (*Graphical Abstract*).

Pathophysiologic considerations

Impaired left ventricular function is an important factor contributing to morbidity and mortality in patients with MR. Heart failure with reduced ejection fraction (HFrEF) is often accompanied by left ventricular and atrial dilatation with subsequent increase of pulmonary pressures. Right ventricular function and pulmonary pressures have a close interdependent relationship, known as right ventricular to pulmonary artery coupling.[11,22–24] Under physiological conditions, the right ventricle can adjust its contractility to the afterload determined by varying pulmonary pressure conditions. In a significant proportion of MR patients, right ventricular function can no longer adequately adapt to increasing afterload leading to uncoupling of the cardiopulmonary system. This transition from left-sided to biventricular heart failure may represent the

Table 2 Baseline characteristics by cholestatic type II cardio-hepatic syndrome

	Overall population ($n = 1083$)	Cholestatic type II CHS ($n = 222$)	No cholestatic type II CHS ($n = 861$)	*p*-value*
Clinical characteristics				
Age, years	74.7 ± 10.6	71.6 ± 12.3	75.3 ± 10.1	**<0.001**
Female sex	432 (39.3)	79 (35.6)	302 (40.7)	0.172
MR aetiology				**0.003**
PMR	408 (37.9)	65 (29.5)	300 (40.7)	
SMR	669 (62.1)	155 (70.5)	438 (59.3)	
Previous MI	300 (27.9)	65 (29.4)	213 (28.9)	0.892
Previous stroke or TIA	141 (13.1)	32 (14.5)	97 (13.2)	0.625
Atrial fibrillation or flutter	738 (68.5)	165 (74.7)	491 (66.6)	**0.024**
Coronary artery disease	413 (48.9)	104 (52.5)	250 (46.8)	0.170
ICD/CRT	310 (32.0)	79 (42.7)	194 (29.0)	**<0.001**
eGFR, ml/min	51.4 ± 22.4	51.3 ± 22.8	51.2 ± 22.1	0.950
Creatinine, mg/dl	1.6 ± 1.2	1.7 ± 1.8	1.6 ± 0.9	0.742
NT-proBNP, ng/L	3498 [1494–7245]	5449 [2556–11 323]	1332 [3170–6456]	**<0.001**
MELD-XI score	13.5 ± 6.1	16.6 ± 6.0	12.2 ± 5.7	**<0.001**
Known hepatic disease	67 (6.5)	21 (9.5)	40 (5.4)	**0.029**
Hepatic function				
Bilirubin, mg/dl	0.9 [0.6–1.4]	1.6 [1.2–2.3]	0.7 [0.5–1.0]	**<0.001**
AST, U/L	27.0 [21.0–36.0]	34.0 [25.0–51.0]	25.0 [20.0–34.0]	**<0.001**
ALT, U/L	21.0 [15.0–33.0]	27.0 [18.0–49.0]	21.0 [14.0–30.0]	**<0.001**
GGT, U/L	69.0 [35.0–137.0]	149.0 [82.5–300.0]	51.0 [29.0–100.0]	**<0.001**
AP, U/L	90.5 [69.0–121.3]	139.0 [109.0–180.3]	77.0 [60.0–95.0]	**<0.001**
Albumin, g/dl	3.3 [2.9–3.7]	3.4 [2.9–3.9]	3.2 [2.9–3.6]	**0.079**
Medication				
ACEi/ARB	697 (68.1)	144 (68.6)	469 (66.4)	0.563
Beta-blocker	856 (83.3)	177 (83.5)	594 (83.9)	0.888
Diuretics	929 (90.8)	195 (92.0)	634 (90.1)	0.402
Aldosterone antagonists	406 (40.3)	102 (48.6)	257 (37.0)	**0.003**
Echocardiographic characteristics				
MR EROA PISA, cm^2	0.35 ± 0.29	0.36 ± 0.32	0.36 ± 0.27	0.584
MR volume PISA, ml	47.3 ± 35.3	45.0 ± 36.6	47.7 ± 34.8	0.350
MR vena contracta, cm	0.75 ± 0.24	0.74 ± 0.20	0.75 ± 0.25	0.983
LVEF, %	42.8 ± 15.5	39.5 ± 14.6	43.8 ± 15.8	**<0.001**
LVEDV, ml	162.3 ± 76.5	170.8 ± 82.1	160.5 ± 75.7	0.128
LVESV, ml	100.7 ± 70.5	108.8 ± 68.3	99.0 ± 72.4	**0.021**
LVEDD, mm	59.1 ± 11.2	60.0 ± 11.3	58.9 ± 11.3	0.186
LVESD, mm	48.9 ± 11.9	50.4 ± 11.7	48.2 ± 12.1	**0.021**
LA volume, ml	118.6 ± 59.0	128.3 ± 73.4	116.6 ± 53.8	**0.049**
MV mean PG, mmHg	2.2 ± 1.2	2.1 ± 1.3	2.3 ± 1.2	**0.017**
TAPSE, mm	17.8 ± 5.2	16.6 ± 4.9	18.2 ± 5.3	**0.001**
RV EDA, cm^2	23.1 ± 7.6	24.3 ± 8.7	22.7 ± 7.3	**0.046**
RV ESA, cm^2	15.4 ± 5.9	16.3 ± 5.8	15.0 ± 6.0	**0.010**
RV FAC	0.34 ± 0.11	0.32 ± 0.11	0.35 ± 0.12	**0.064**
sPAP, mmHg	46.6 ± 15.6	49.1 ± 17.1	45.7 ± 15.4	0.062
Severity of MR, TR and NYHA functional class				
MR severity				0.946
2+	10 (0.9)	2 (0.9)	8 (1.1)	
3+	437 (40.7)	92 (41.4)	297 (40.5)	
4+	627 (58.4)	128 (57.7)	428 (58.4)	
TR severity				**0.005**
0+	34 (3.4)	5 (2.3)	24 (3.6)	
1+	430 (42.7)	70 (32.7)	300 (44.4)	
2+	311 (30.9)	74 (34.6)	203 (30.0)	

Table 2 (Continued)

	Overall population ($n = 1083$)	Cholestatic type II CHS ($n = 222$)	No cholestatic type II CHS ($n = 861$)	*p*-value*
3+	196 (19.4)	59 (27.6)	122 (18.0)	
4+	37 (3.7)	6 (2.8)	27 (4.0)	
NYHA functional class				**<0.001**
II	68 (6.4)	7 (3.2)	53 (7.3)	
III	739 (69.5)	131 (59.8)	522 (71.8)	
IV	256 (24.1)	81 (37.0)	152 (20.9)	

Data are presented as mean ± standard deviation, *n* (%), or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; AP, alkaline phosphatase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; CHS, cardio-hepatic syndrome; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EDA, end-diastolic area; ESA, end-systolic area; EROA, effective regurgitant orifice area; FAC, fractional area change; GGT, gamma-glutamyl transferase; ICD, implantable cardioverter-defibrillator; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PG, pressure gradient; PISA, proximal isovelocity surface area; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack; TR, tricuspid regurgitation.
*CHS vs. no CHS.

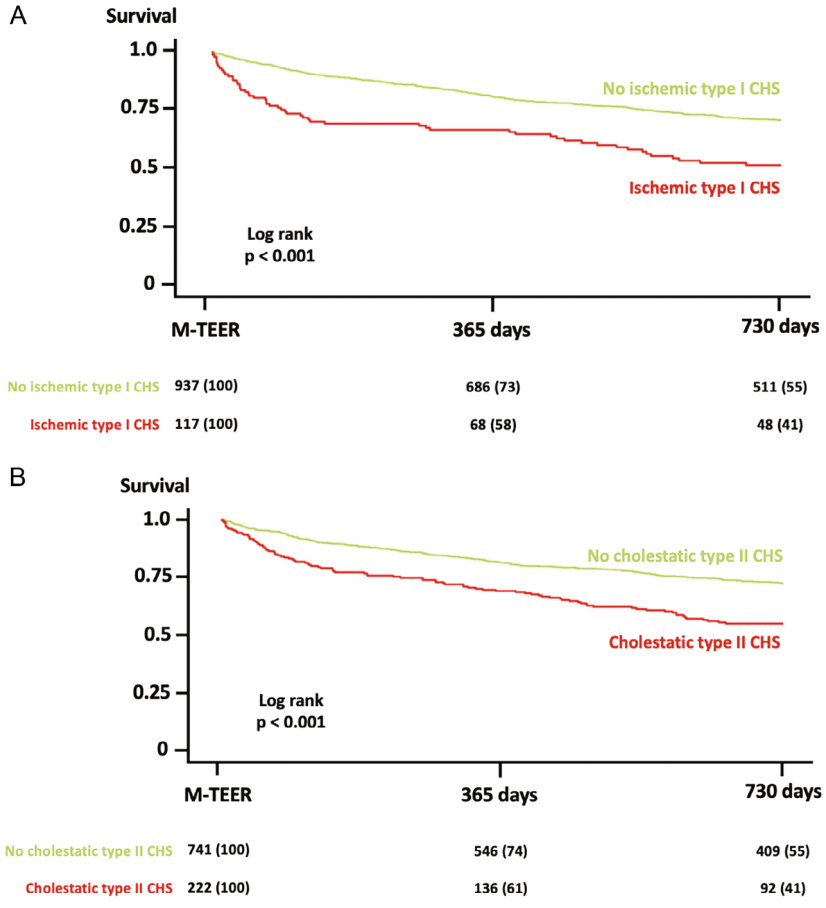


Figure 1 Impact of cardio-hepatic syndrome (CHS) on survival after mitral valve transcatheter edge-to-edge repair (M-TEER). (*A*) Impact of ischaemic type I CHS on survival after M-TEER. (*B*) Impact of cholestatic type II CHS on survival after M-TEER. Ischaemic type I CHS was defined as an elevation of both transaminases. Cholestatic type II CHS was defined as an elevation of at least two out of three laboratory parameters of liver function. Both types of CHS were associated with significantly worsened 2-year survival rates within the overall study population.

Table 3 Predictors of 2-year all-cause mortality

	Univariate			Multivariate		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Overall study cohort (PMR and SMR)						
LVEF, per 10% decrease	1.184	1.097–1.278	<0.001	1.179	1.006–1.382	0.042
TAPSE, per mm decrease	1.065	1.036–1.094	<0.001	1.047	1.007–1.098	0.021
eGFR, per 10 ml/min decrease	1.126	1.066–1.189	<0.001	1.164	1.066–1.271	0.001
Previous stroke or TIA	1.614	1.220–2.134	0.001	2.056	1.305–3.325	0.002
NYHA functional class IV	1.708	1.351–2.160	<0.001	1.581	1.087–2.297	0.016
MR severity post ≥3+	1.938	1.419–2.648	<0.001	2.280	1.439–3.614	<0.001
Cholestatic type II CHS	1.893	1.485–2.413	<0.001	1.490	1.045–2.123	0.027
PMR						
TAPSE, per mm decrease	0.935	0.896–0.976	0.002	1.075	1.026–1.126	0.003
MR severity post ≥3+	2.807	1.811–4.325	<0.001	2.606	1.538–4.417	<0.001
Cholestatic type II CHS	2.654	1.723–4.090	<0.001	2.133	1.281–3.550	0.004
SMR						
TAPSE, per mm decrease	0.943	0.910–0.978	0.001	1.075	1.020–1.132	0.007
eGFR, per 10 ml/min decrease	0.989	0.983–0.996	0.001	1.284	1.157–1.425	<0.001
Previous stroke or TIA	1.703	1.228–2.363	0.001	2.587	1.451–4.610	0.001
NYHA functional class IV	0.578	0.437–0.765	<0.001	1.860	1.187–2.915	0.007
TR severity ≥3+	1.441	1.070–1.939	0.016	1.668	1.047–2.657	0.031
Ischaemic type I CHS	1.542	1.146–2.074	0.004	2.732	1.477–5.056	0.001

CHS, cardio-hepatic syndrome; CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack; TR, tricuspid regurgitation.

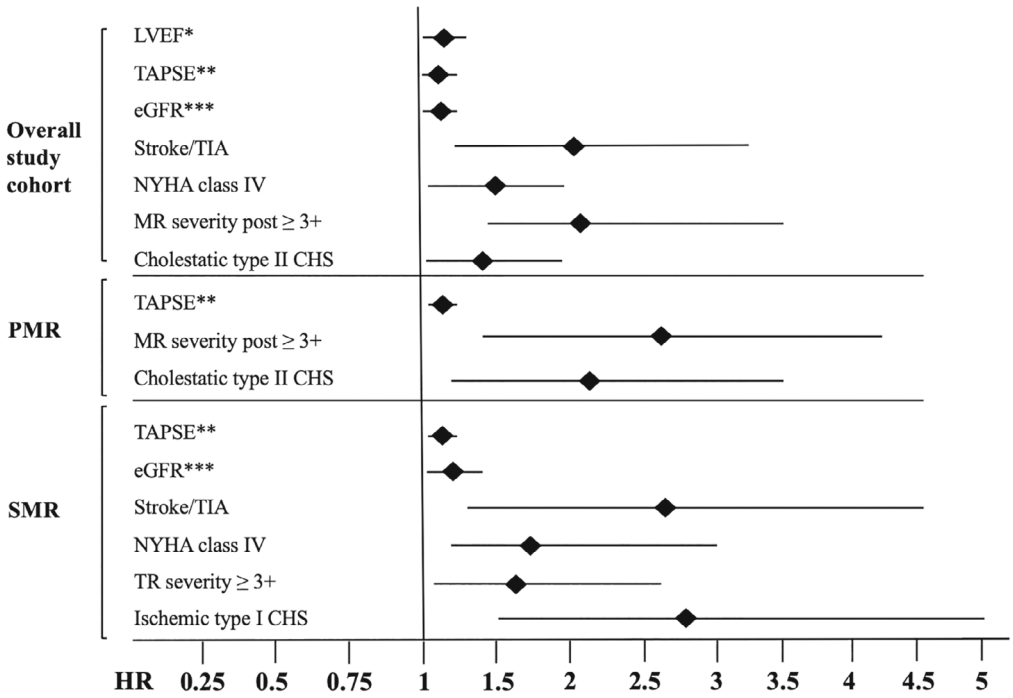


Figure 2 Multivariate predictors for 2-year all-cause mortality. Multivariate predictors of 2-year all-cause mortality after mitral valve transcatheter edge-to-edge repair are depicted as hazard ratio (HR) with 95% confidence interval. CHS, cardio-hepatic syndrome; MR, mitral regurgitation; NYHA, New York Heart Association; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TIA, transient ischaemic attack. *Per 10% decrease in left ventricular ejection fraction (LVEF); **per mm decrease in tricuspid annular plane systolic excursion (TAPSE); ***Per 10 ml/min decrease in estimated glomerular filtration rate (eGFR).

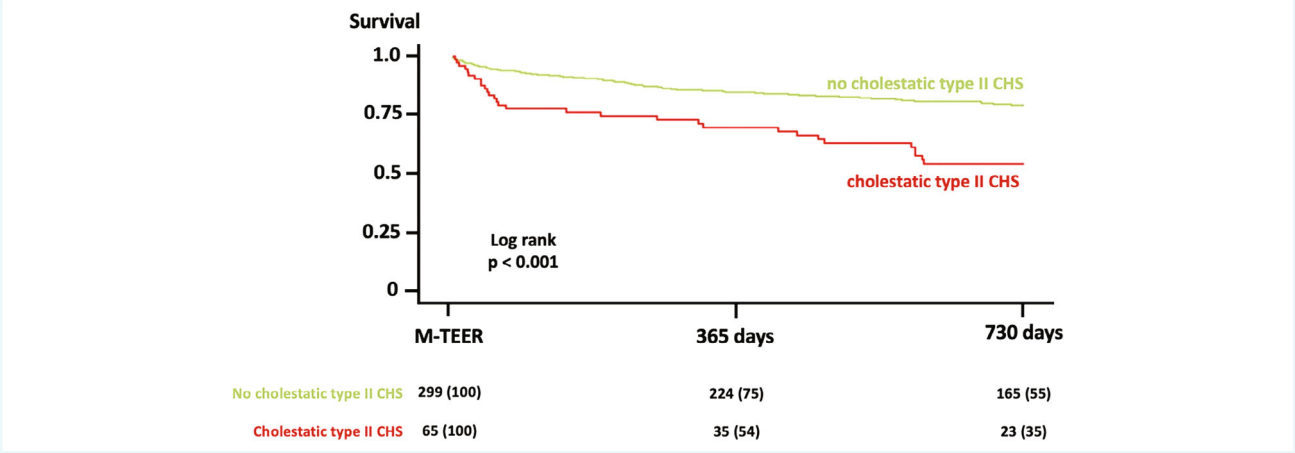


Figure 3 Impact of cholestatic type II cardio-hepatic syndrome (CHS) on 2-year all-cause mortality in patients with primary mitral regurgitation. Cholestatic type II CHS was associated with increased 2-year all-cause mortality in patients who underwent mitral valve transcatheter edge-to-edge repair (M-TEER) for severe primary mitral regurgitation.

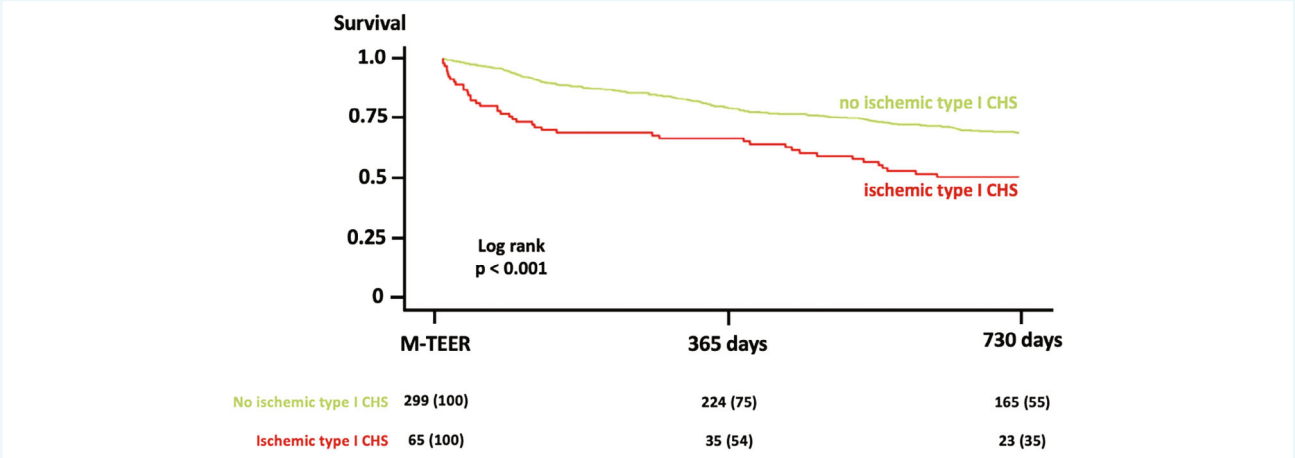


Figure 4 Impact of ischaemic type I cardio-hepatic syndrome (CHS) on 2-year all-cause mortality in patients with secondary mitral regurgitation. Ischaemic type I CHS was associated with increased 2-year all-cause mortality in patients who underwent mitral valve transcatheter edge-to-edge repair (M-TEER) for severe secondary mitral regurgitation.

main underlying pathophysiologic mechanism for the development of CHS. A recent study outlined the importance of biventricular heart failure for predicting all-cause mortality using data from a large multinational registry of HFrEF patients with secondary MR, who were treated by M-TEER.[11] Similar results were found in a sub-analysis of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial.[25] Beyond that, left heart failure-related pulmonary congestion and pulmonary hypertension, may lead to secondary TR with worsening volume overload. In patients with biventricular heart failure, congestion within the venous system conducts back into the hepatic central veins and leads to histologically evidence of pericentrovenous atrophy and necrosis, as well as sinusoidal degeneration and signs of cholestasis.[26,27] In contrast to patients with isolated TR, patients with MR and concomitant left and right ventricular dysfunction or TR could suffer from severe systemic hypoperfusion due to biventricular forward and backward failure which could further aggravate CHS in the setting of MR.[9,28] According to recent literature, different types of CHS can be distinguished.[16] As outlined above, ischaemic type I CHS is believed to be the consequence of decreased systemic and hepatic perfusion, leading to elevated transaminases.[16] Cholestatic type II CHS is considered to be the result of chronic venous congestion and leads to an increase in cholestasis parameters.[16]

Cardio-hepatic syndrome

Our study demonstrated that severe MR is more often associated with cholestatic type II compared to ischaemic type I CHS (23% vs. 11%). These findings were consistent with previous studies which

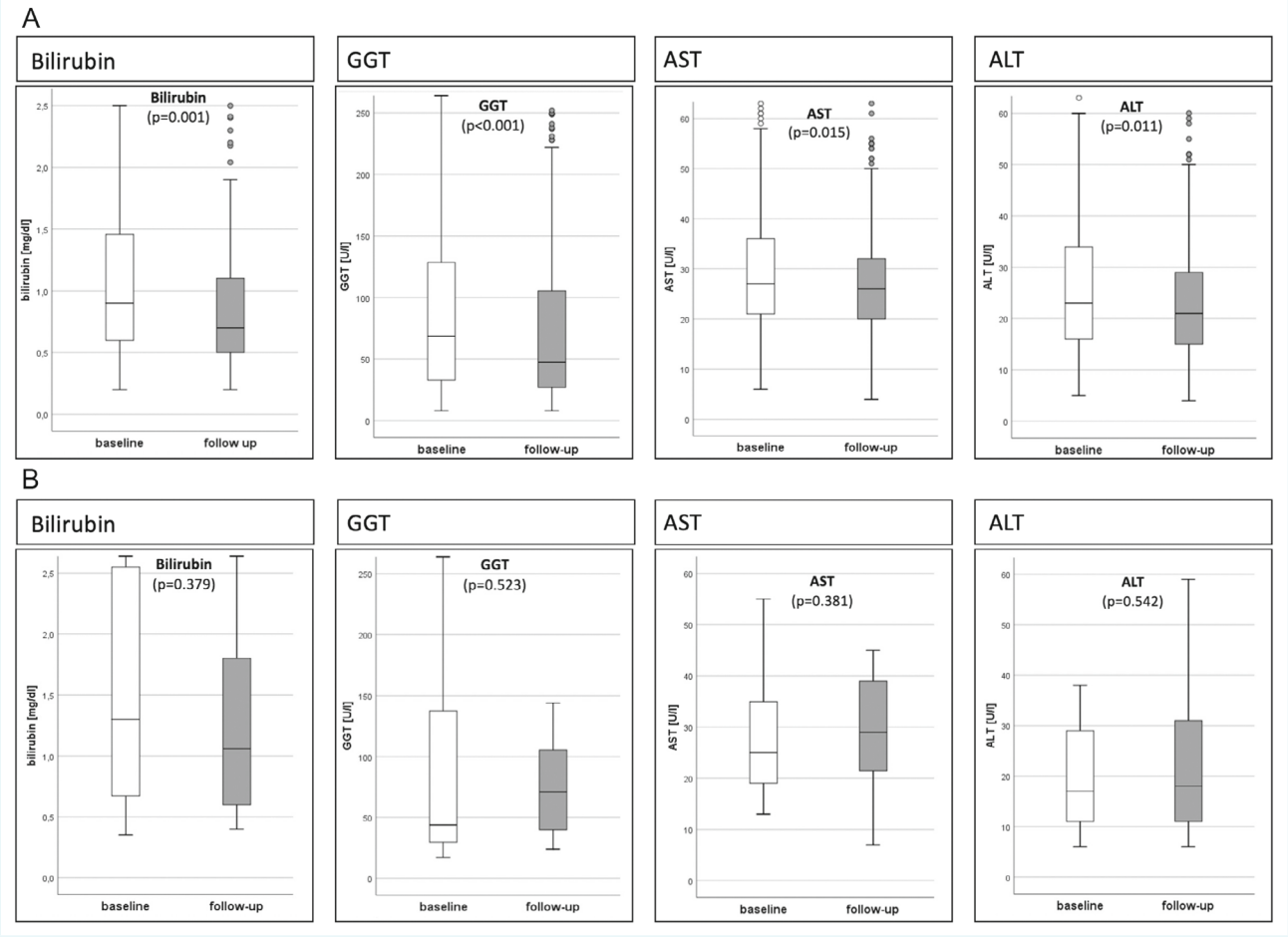


Figure 5 Change in hepatic function after mitral valve transcatheter edge-to-edge repair depending on successful mitral regurgitation reduction. In patients with successful reduction of mitral regurgitation to <3+ (*A*), hepatic function significantly improved after mitral valve transcatheter edge-to-edge repair. In case of persisting mitral regurgitation ≥3+ (*B*) after intervention, no improvement was observed. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

have reported only mild elevation of transaminases in chronic HFrEF patients but significant elevation of cholestatic parameters[10,16,29] and might represent the distribution of PMR and SMR within the study population. Transaminases are believed to play a more important role in the setting of reduced left ventricular function with a decrease of cardiac output.[10]

Cholestatic type II CHS was defined as an elevation of two out of three parameters indicating cholestasis (bilirubin, GGT, or AP) above the upper limit of normal.[15,16] According to this definition, cholestatic type II CHS was frequently observed in patients undergoing M-TEER. In line with the pathophysiologic considerations above, cholestatic type II CHS was associated with impairment of left and right ventricular function, left ventricular and left atrial dilatation, concomitant TR, and pulmonary hypertension. The prevalence of cholestatic type II CHS in the presence of significant MR was lower compared to TEER-treated TR patients (23% vs. 45%).[15] As hypothesized above, RVD and associated TR may be a key contributor to CHS. If one considers that the prevalence of RVD in TR patients is significantly higher than in MR patients,[11,30] the before-mentioned difference in prevalence seems plausible. Multivariate Cox regression analyses have shown that cholestatic type II CHS is an independent mortality predictor in PMR, but not in SMR patients. The other way around, ischaemic type I CHS has only shown predictive value within patients suffering from SMR. As stated above, PMR patients commonly present with heart failure with preserved ejection fraction, while SMR is often associated with reduced ejection fraction. The subsequent reduction in forward stroke volume in SMR patients leads to hepatic malperfusion and the development of ischaemic type I CHS. Further, SMR is associated with a significant proportion of concomitant TR and RVD which both lead to chronic venous congestion and cholestatic type II CHS. In contrast to T-TEER, concomitant TR remains in a significant proportion of MR patients even after M-TEER. We assume that this is the reason why cholestatic type II CHS is a mortality predictor in T-TEER but not in SMR patients undergoing M-TEER.

In our study, the estimated probability of survival at 2-year follow-up was almost 20% lower in patients with type I or II CHS. It

is important to realize that the independent predictive value of type I or II CHS in the respective study population was observed in addition to the reduced glomerular filtration rate, which may reflect the presence of a cardio-renal syndrome. Overall, it remains important to emphasize that all pathophysiological processes mentioned should not be considered individually but represent a functional unit. Impairment of hepatic function as represented by CHS stands at the end of a complicated chain of mechanistic interdependencies and could consequently be a marker of multiple malfunctions within this continuum. Although venous congestion might be considered as one of the main pathomechanisms for both, renal and hepatic dysfunction, the current results indicate that the presence of CHS exhibits an incremental risk of mortality over kidney dysfunction, especially in PMR patients. The underestimation of CHS for prognosis prediction becomes also evident when considering current surgical risk calculators. While the impact of liver function is not included in the EuroSCORE I and II risk calculators, the Society of Thoracic Surgeons' risk calculator for mitral valve repair only vaguely defines the presence of liver disease, e.g. by cirrhosis, portal hypertension, esophageal varices, liver transplant, or 'congestive hepatopathy', but without using any laboratory cut-offs for a better definition of CHS. Accordingly, the results of the current study indicate that a better characterization and understanding of the CHS is needed in patients undergoing mitral and probably other valvular interventions. Due to the absence of current and clear definitions of what liver impairment in the setting of heart failure is, our easily applicable definition of CHS could be implemented into current scoring systems.

Change in hepatic function after mitral valve transcatheter edge-to-edge repair

At long-term follow-up, all liver parameters significantly decreased, except for AP. Thus, we cannot exclude that elevated AP levels at baseline reflected liver impairment, but they might also be increased by iso-enzymes pointing to osteoporosis, which might have been present in this cohort. These findings were only observed in patients who successfully underwent M-TEER with reduction of MR severity to ≤2+. Patients with residual severe MR (≥3+) did not show reduced levels of bilirubin, ALT, AST and GGT at follow-up. This observation is in line with previous reports on improvement of the cardio-renal syndrome after M-TEER. The underlying mechanism for the observed improvement in hepatic function is likely to be a reduction of the venous congestive stress on the liver as a consequence of reduced secondary pulmonary hypertension and backflow into the venous system. Analogous results were recently published for T-TEER-treated TR patients.[14,15]

Interestingly, detailed sub-analyses have shown that patients who presented with normal hepatic function at baseline but developed CHS after treatment, had impaired survival prognosis after follow-up examination, in both type I and II CHS. We believe that *de novo* CHS after M-TEER might be an indicator for progressing heart failure and hence 'retrospectively' identifies patients who benefit less from M-TEER treatment. Nevertheless, some patients might also have developed any kind of non-cardiac liver impairment and will fall under the definition of new-onset CHS.

Besides the improvement in liver function, M-TEER resulted in a significant symptomatic improvement. Importantly, this symptomatic improvement was not jeopardized by the presence of CHS, and therefore M-TEER should be considered a valid treatment option in this population. However, the presence of CHS may be another parameter of interest when discussing individual treatment concepts for relevant MR in the Heart Team.

This study is the first to provide detailed data on the cardio-hepatic interactions in M-TEER-treated MR patients. Nevertheless, some limitations must be kept in mind when interpreting these results. As analysis of CHS was conducted retrospectively, not all laboratory and echocardiographic parameters were available in every patient. Furthermore, no core laboratory assessment of the echocardiographic images was performed, but a high echocardiographic experience was available in the participating heart valve centres. Patients had to be excluded if laboratory liver parameters were missing. As such laboratory follow-up was not complete in the minority of patients. Exclusion of patients without available laboratory liver parameters may lead to selection bias. Of note, especially our landmark analysis on survival after latest available follow-up depending on the development of CHS has limited power due to a relatively low number of cases. Even though having adjusted our analysis for hepatic comorbidities, we cannot rule out that other secondary effects or drug therapy for comorbidities (e.g. amiodarone, oral anticoagulation therapy) might have influenced changes in hepatic function from baseline to follow-up laboratory evaluation. Even though >90% of baseline liver laboratory blood samples were collected within 10 days before M-TEER, we cannot rule out that secondary effects might have influenced laboratory liver parameters between baseline evaluation and date of M-TEER. Due to the retrospective nature of this study, no comprehensive liver imaging data (e.g. abdominal ultrasound, elastography) are available to correlate with laboratory findings. Further, the study included patients over a period of 11 years, and we cannot present data on exact medication dosage and its changes after M-TEER. The results of this retrospective analysis need to be confirmed in larger randomized controlled prospective trials of M-TEER with parallel liver function evaluation.

In conclusion, with a prevalence of 23%, CHS is a frequent finding in patients undergoing M-TEER for severe MR. In patients with and without CHS, MR reduction and symptomatic improvement were comparable after M-TEER. Our study also indicates that M-TEER will improve hepatic function at follow-up if MR is successfully reduced. However, the presence of CHS significantly decreases the 2-year survival estimate by 18%. Accordingly, CHS could be an important indicator of disease progression and might facilitate optimal treatment timing.

Supplementary Information

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

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