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

Lukas Stolz, MD[a], Mathias Orban, MD,[a,b], Nicole Karam, MD, [c], Edith Lubos, MD,[d], Mirjam Wild, MD,[a], Ludwig Weckbach, MD [a,b], Thomas J. Stocker, MD [a,b], Fabien Praz, MD,[e], Daniel Braun, MD,[a], Kornelia Löw, MD, [a], Sebastian Hausleiter,[a], Konstantin Stark, MD,[a,b], Philipp Doldi, MD,[a,b] Noemie Tence, MD,[c], Martin Orban, MD,[a,b], Satoshi Higuchi, MD, [a], Magda Haum, [a],MD, Stephan Windecker, MD,[e], Christian Hagl, MD,[f], Julia Mayerle, MD,[g] Michael Näbauer, MD,[a,b], Daniel Kalbacher, MD,[d,h], Steffen Massberg, MD,[a,b], Jörg Hausleiter, MD,[a,b]

AFFILIATIONS:

[a] Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Munich, Germany
[b] German Center for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany
[c] Paris University, PARCC, INSERM, F-75015, European Hospital Georges Pompidou, Paris, France
[d] Universitäres Herz- und Gefäßzentrum Hamburg, Klinik für Kardiologie, Hamburg, Germany
[e] Department of Cardiology, Inselspital, University of Bern, Bern, Switzerland
[f] Herzchirurgische Klinik und Poliklinik, Klinikum der Universität München, Munich, Germany
[g] Medizinische Klinik und Poliklinik II, Ludwig-Maximilians-Universität München, München, Bayern, Germany
[h] German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Lübeck/Kiel, Germany

ADDRESS FOR CORRESPONDENCE:

Prof. Dr. med. Jörg Hausleiter
Marchioninistr. 15
D-81377 München, Germany
Joerg.Hausleiter@med.uni-muenchen.de
Phone: +49 89 4400 72361
Fax: +49 89 4400 78870

TOTAL WORD COUNT: 4226

ABSTRACT

AIMS:

The impact of the cardio-hepatic syndrome (CHS) on outcomes in patients undergoing 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: Ischemic 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 two-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 analyzed 1083 patients who underwent M-TEER for relevant primary or secondary MR at four European centers between 2008 and 2019. Ischemic type I and cholestatic type II CHS were observed in 11.1% and 23.0% of patients, respectively. Predictors for two-year all-cause mortality differed by MR etiology. While in primary MR cholestatic type II CHS was independently associated with two-year mortality, ischemic CHS type I was an independent mortality predictor in SMR 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 0.2mg/dl, 0.2U/l and 21U/l for bilirubin, ALT and GGT, respectively, $p<0.01$).

CONCLUSIONS:

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

KEYWORDS:

cardio-hepatic syndrome; Heart failure; MitraClip; PASCAL; transcatheter edge-to-edge mitral valve 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 co-morbidities. Transcatheter treatment techniques have therefore emerged as a therapeutic alternative[3]. The most commonly used technique is the mitral valve transcatheter edge-to-edge repair (M-TEER) with safety and 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 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[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 of liver function after M-TEER[14,15]. Different types of CHS are described in the literature. Ischemic 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 cardio-hepatic syndrome

(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 or secondary MR (PMR and SMR) at four European heart valve centers (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 transcatheter edge-to-edge tricuspid valve 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 center in line with international guidelines[3,17]. Patients were treated with a commercially available system for mitral leaflet approximation (either MitraClip [Abbott, Santa Clara, California, 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 anesthesia, the M-TEER device is implanted under fluoroscopy and transesophageal echocardiography (TEE) guidance by access through the femoral vein and puncture of the interatrial septum[18].

The study has been 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] >34U/l, male [m] >49U/l), GGT (f >39U/l, m >

59U/l), AP (f >105, m >130). Bilirubin levels were considered abnormal when exceeding 1.2mg/dl independent of sex. The Model for End-Stage Liver Disease (MELD) XI score was calculated as follows: MELD XI = 5.11 x ln (bilirubin[mg/dL]) ± 11.76 x 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 INR values by oral anticoagulation. Ischemic type I CHS was defined as elevation of both transaminases (AST/ALT). Cholestatic type II CHS was defined as 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 center'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 functional class (NYHA) at baseline and latest available follow-up.

Endpoints: Primary endpoint was all-cause mortality at two years. Secondary endpoints were MR reduction ≤2+, long-term development of MR, NYHA functional class improvement and change of 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 center[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 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 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 (sd) or median with interquartile range (IQR). Between group differences were analyzed 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, 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. Etiology 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 < 60ml/min. At baseline, the mean MELD XI score was 13.5 ± 6.1. Complete baseline data are depicted in Supplemental Table 1.

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 tumors. Drug induced liver injury, schistosomiasis, prior liver transplant and cholangitis were observed in less than four patients. Mean LVEF was moderately impaired to 42.8 ± 15.5% (Supplemental Table 1). 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, Supplemental Table 2).

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 (Supplemental Table 1). 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 two-year survival rates (Supplemental Figures 1A-C). Median transaminases were within normal range (median AST: 27.0 [21.0-36.0]U/l and ALT: 21.0 [15.0-33.0] U/l). Only 19.2% (n=202) 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 two-year survival (Supplemental Figures 1D and E).

Ischemic 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 ischemic type I CHS. The latter was associated with younger age, female sex, worse biventricular function Further and more severe heart failure symptoms. Left atrial dilation, impaired biventricular function, concomitant TR and higher sPAP were associated with cholestatic type II CHS (Table 2, Supplemental Figure 2). Of note, among patients with type II CHS, MR was more frequently secondary than primary (70.2% vs 58.7% in PMR) but showed no sex-specific prevalence differences.

PROGNOSTIC IMPLICATIONS OF THE CARDIO-HEPATIC SYNDROME

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

Within the overall study population, a multivariate Cox regression (Table 3A, Supplemental Table 3) analysis revealed LVEF (per 10% decrease: HR= 1.18, CI: 1.01-1.38, p=0.04), TAPSE (per mm decrease: HR= 1.05, CI: 1.01-1.10, p=0.02), eGFR (per 10ml/min decrease: HR= 1.16, CI: 1.07-1.27, $p<0.01$), history of stroke or TIA (HR= 2.06, CI: 1.31-3.33, $p<0.01$), NYHA functional class IV (HR= 1.58, CI: 1.09-2.30, p=0.02), residual MR ≥2+ (HR= 2.28, CI: 1.44-3.61, $p<0.01$) and ischemic type II CHS (HR=1.49, 1.05-2.12, p=0.03, Figure 2A) as independent predictors for two-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.

Etiology-stratified subanalysis revealed differences in predictors for two-year all-cause mortality in patients with PMR vs. SMR. In patients with PMR, TAPSE (per mm decrease: HR= 1.08, CI: 1.03-1.13, p<0.01), postprocedural MR severity ≥3+ (HR= 2.61, CI: 1.54-4.42, p<0.01) and cholestatic type II CHS (HR= 2.13, CI: 1.28-3.55, p<0.01, Table 3B, Supplemental Table 4, Figure 2B, Figure 3). When including only patients with SMR into the multivariate cox regression model, TAPSE (per mm decrease: HR= 1.08, CI: 1.02-1.13, p<0.01), eGFR (per 10ml/min decrease: HR= 1.28, CI: 1.16-1.43, p<0.01), history of stroke or TIA (HR= 2.59, CI: 1.19-2.92, p<0.01), NYHA functional class IV (HR= 1.86, CI: 1.09-2.30, p=0.02), TR severity ≥3+ (HR= 1.67, CI: 1.05-2.66, p=0.03) and ischemic type I CHS (HR= 2.73, CI: 1.48-5.06, p<0.01) were independently associated with two-year all-cause mortality (Table 3C, Supplemental Table 5, Figure 2C, Figure 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 for with vs. without cholestatic type II CHS), this trend was no longer observed at latest available follow-up (Supplemental Table 2, Supplemental Figure 4). Even though patients with both types of CHS (ischemic and cholestatic) presented with more severe NYHA functional class at baseline, symptomatic improvement was comparable irrespective of hepatic function (Table 2, Supplemental Figure 5).

CHANGES IN HEPATIC FUNCTION AFTER M-TEER

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]. Supplemental Table 6 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 0.7mg/dl, $p<0.01$, 221 paired values), AST (27.0 to 26.0U/l, $p=0.04$, 439 paired values), ALT (22.0 to 21.0U/l, $p=0.02$, 452 paired values) and GGT (76.0 to 49.0U/l, $p<0.01$, 403 paired samples) was observed (Supplemental Table 7A). In contrast, AP levels remained unchanged (84.0 to 83.0U/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 Figures 5A and 5B the above-described improvement in hepatic function was observed only in patients with successful procedural MR reduction to ≤2+ (Supplemental Table 7). Further, a time-phased subanalysis showed that the de-congestive effect of M-TEER occurred within the first year after treatment, while reduction of transaminases took more time (Supplemental Table 8).

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 (Supplemental Table 7). 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.

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% of patients) had the worst survival (one-year post follow-up survival 43.6%, $p<0.001$) (Supplemental Figure 5A). 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 (one-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 (one-year post follow-up survival 67.0%). Patients with maintained or "de novo" developed type II cholestatic CHS had comparable postprocedural MR to those without follow-up type II cholestatic CHS (p=0.974). 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 ischemic type I CHS (Supplemental Figure 5B). Patients with ischemic type I CHS at baseline and follow-up had worst survival rates (one-year post follow-up survival 51.9%, p=0.006). Further, patients who developed ischemic type I CHS over time presented with intermediate survival prognosis (one-year post follow-up survival 68.2%). Alike in case of cholestatic type II CHS, patients without ischemic type I CHS or those with recovery from baseline to follow-up presented with best survival rates (one-year post follow-up survival 79.5% and 79.2%, respectively).

DISCUSSION

MAIN FINDINGS

This large multicentric study is the first to evaluate the relationship of liver function and mitral regurgitation in a large cohort of patients undergoing M-TEER. The three main findings of this study were:

I. Ischemic type I CHS – defined as elevation of both transaminases – is associated with increased two-year all-cause mortality in SMR patients undergoing M-TEER

II. Cholestatic type II CHS – defined as elevation of two out of three laboratory parameters of hepatic cholestasis – is associated with increased two-year all-cause mortality in PMR patients undergoing M-TEER

III. Successful M-TEER is associated with an improvement in hepatic function at follow-up

PATHOPHYSIOLOGIC CONSIDERATIONS

Impaired left ventricular function is an important factor contributing to morbidity and mortality in patients with MR. HFrEF is often accompanied by left ventricular and atrial dilation with subsequent increase of pulmonary pressures. RV function and pulmonary pressures have a close interdependent relationship, known as right ventricular to pulmonary artery coupling (RVPAc)[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 bi-ventricular heart failure may represent the main underlying pathophysiologic mechanism for the development of CHS. A recent study outlined the importance of bi-ventricular 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 subanalysis of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trail[25]. Beyond that, left heart failure-related pulmonary congestion and pulmonary hypertension, may lead to secondary TR with worsening volume overload. In patients with bi-ventricular 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 LV and RV dysfunction or TR could suffer from severely depressed 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, ischemic 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 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 ischemic type I CHS (11% vs. 23%). These findings were consistent with previous studies which 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 LV function with a decrease of cardiac output[10].

Cholestatic type II CHS was defined as 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 pathophysiological considerations above, cholestatic type II CHS was associated with impairment of left and right ventricular function, LV and LA dilation, 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, ischemic type I CHS has only shown predictive value within patients suffering from SMR. As stated above, PMR patients commonly present with HFpEF, 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 ischemic 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 two-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 STS risk calculator for MV 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 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 M-TEER

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 profit 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 centers. Patients had to be excluded if laboratory liver parameters were missing. As such laboratory FU 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 more than 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 character of this study, no comprehensive liver imaging data (e.g., abdominal ultrasound, elastography) is available to correlate with laboratory findings. Further, the study included patients over a period of eleven 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 two-year survival estimate by 18%. Accordingly, CHS could be an important indicator of disease progression and might facilitate optimal treatment timing.

ACKNOWLEDGEMENT:

We thank Diana Rösler, Andrea Englmaier and Tobias Reithmayer for their extensive support over the course of this study.

FUNDING:

No funding.

CONFLICT OF INTEREST:

Nicole Karam has received consultant fees from Abbott Vascular. Michael Näbauer, Edith Lubos, Daniel Kalbacher and Daniel Braun have received speaker honoraria from Abbott Vascular. Mathias Orban received speaker fees from Abbott Vascular and Tomtec Imaging Systems. Martin Orban received speaker honoraria from SedanaMedical, AstraZeneca and Bayer Vital. Stephan Windecker reports research and educational grants to the institution from Abbott, Amgen, Astra Zeneca, BMS, Bayer, Biotronik, Boston Scientific, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Johnson & Johnson, Medicure, Medtronic, Novartis, Polares, OrPha Suisse, Pfizer, Regeneron, Sanofi-Aventis, Sinomed, Terumo, V-Wave. Stephan Windecker serves as unpaid advisory board member and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sinomed, V-Wave and Xeltis, but has not received personal payments by pharmaceutical companies or device manufacturers. He is also member of the steeringing/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. Daniel Kalbacher has received proctor fees from Edwards Lifesciences. Satoshi Higuchi has received lecture fees from Medtronic Japan Co., Ltd., Daiichi Sankyo Co., Ltd, and Ono Pharmaceutical Co., Ltd. Jörg Hausleiter has received speaker honoraria and research support from and serves as consultant for Abbott Vascular and Edwards Lifesciences. The other authors have no conflicts of interest to declare.

REFERENCES:

1. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nature reviews. Cardiology* 2011;**8**:162-172. doi: 10.1038/nrcardio.2010.202
2. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. *J Am Coll Cardiol* 2015;**65**:1231-1248. doi: 10.1016/j.jacc.2015.02.009
3. Otto CM, Nishimura RA, Bonow RO*, et al.* 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2020. doi: 10.1016/j.jacc.2020.11.018
4. Stone GW, Lindenfeld J, Abraham WT*, et al.* Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *The New England journal of medicine* 2018;**379**:2307-2318. doi: 10.1056/NEJMoa1806640
5. Whitlow PL, Feldman T, Pedersen WR*, et al.* Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *J Am Coll Cardiol* 2012;**59**:130-139. doi: 10.1016/j.jacc.2011.08.067
6. Kalbacher D, Schafer U, RS VB*, et al.* Long-term outcome, survival and predictors of mortality after MitraClip therapy: Results from the German Transcatheter Mitral Valve Interventions (TRAMI) registry. *Int J Cardiol* 2019;**277**:35-41. doi: 10.1016/j.ijcard.2018.08.023
7. Stolz L, Orban M, Braun D*, et al.* Anatomy and Outcome of Secondary Mitral Regurgitation Subtypes Undergoing Transcatheter Mitral Valve Edge-to-Edge Repair. *JACC Cardiovasc Interv* 2021;**14**:110-111. doi: 10.1016/j.jcin.2020.09.035
8. Laribi S, Mebazaa A. Cardiohepatic syndrome: liver injury in decompensated heart failure. *Current heart failure reports* 2014;**11**:236-240. doi: 10.1007/s11897-014-0206-8
9. Samsky MD, Patel CB, DeWald TA*, et al.* Cardiohepatic interactions in heart failure: an overview and clinical implications. *J Am Coll Cardiol* 2013;**61**:2397-2405. doi: 10.1016/j.jacc.2013.03.042
10. Poelzl G, Ess M, Mussner-Seeber C*, et al.* Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. *European journal of clinical investigation* 2012;**42**:153-163. doi: 10.1111/j.1365-2362.2011.02573.x
11. Karam N, Stolz L, Orban M*, et al.* Impact of Right Ventricular Dysfunction on Outcomes After Transcatheter Edge-to-Edge Repair for Secondary Mitral Regurgitation. *JACC Cardiovasc Imaging* 2021. doi: 10.1016/j.jcmg.2020.12.015
12. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;**52**:1527-1539. doi: 10.1016/j.jacc.2008.07.051
13. Shah B, Villablanca PA, Vemulapalli S*, et al.* Outcomes After Transcatheter Mitral Valve Repair in Patients With Renal Disease. *Circ Cardiovasc Interv* 2019;**12**:e007552. doi: 10.1161/circinterventions.118.007552
14. Karam N, Braun D, Mehr M*, et al.* Impact of Transcatheter Tricuspid Valve Repair for Severe Tricuspid Regurgitation on Kidney and Liver Function. *JACC Cardiovasc Interv* 2019;**12**:1413-1420. doi: 10.1016/j.jcin.2019.04.018
15. Stolz L, Orban M, Besler C*, et al.* Cardiohepatic Syndrome Is Associated With Poor Prognosis in Patients Undergoing Tricuspid Transcatheter Edge-to-Edge Valve Repair. *JACC Cardiovasc Interv* 2022;**15**:179-189. doi: 10.1016/j.jcin.2021.10.033
16. Poelzl G, Auer J. Cardiohepatic syndrome. *Current heart failure reports* 2015;**12**:68-78. doi: 10.1007/s11897-014-0238-0
17. Baumgartner H FV, Bax J, De Bonis M, Hamm C, Holm P, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano J. E. S. C. Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739-2791. doi: 10.1093/eurheartj/ehx391

18. Boekstegers P, Hausleiter J, Baldus S*, et al.* Percutaneous interventional mitral regurgitation treatment using the Mitra-Clip system. *Clin Res Cardiol* 2014;**103**:85-96. doi: 10.1007/s00392-013-0614-x
19. Heuman DM, Mihas AA, Habib A*, et al.* MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 2007;**13**:30-37. doi: 10.1002/lt.20906
20. Nishimura RA, Otto CM, Bonow RO*, et al.* 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;**135**:e1159-e1195. doi: 10.1161/cir.0000000000000503
21. Lang RM, Badano LP, Mor-Avi V*, et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1-39 e14. doi: 10.1016/j.echo.2014.10.003
22. Matsumoto T, Nakamura M, Yeow WL*, et al.* Impact of pulmonary hypertension on outcomes in patients with functional mitral regurgitation undergoing percutaneous edge-to-edge repair. *Am J Cardiol* 2014;**114**:1735-1739. doi: 10.1016/j.amjcard.2014.08.044
23. Tigges E, Blankenberg S, von Bardeleben RS*, et al.* Implication of pulmonary hypertension in patients undergoing MitraClip therapy: results from the German transcatheter mitral valve interventions (TRAMI) registry. *Eur J Heart Fail* 2018;**20**:585-594. doi: 10.1002/ejhf.864
24. Asch FM, Grayburn PA, Siegel RJ*, et al.* Echocardiographic Outcomes After Transcatheter Leaflet Approximation in Patients With Secondary Mitral Regurgitation: The COAPT Trial. *J Am Coll Cardiol* 2019;**74**:2969-2979. doi: 10.1016/j.jacc.2019.09.017
25. Brener MI, Grayburn P, Lindenfeld J*, et al.* Right Ventricular-Pulmonary Arterial Coupling in Patients With HF Secondary MR: Analysis From the COAPT Trial. *JACC Cardiovasc Interv* 2021;**14**:2231-2242. doi: 10.1016/j.jcin.2021.07.047
26. Sherlock S. The liver in heart failure; relation of anatomical, functional, and circulatory changes. *British heart journal* 1951;**13**:273-293. doi: 10.1136/hrt.13.3.273
27. EDWARD W. BOLAND MDFAW, M.D. CHANGES IN THE LIVER PRODUCED BY CHRONIC PASSIVE CONGESTION. *Arch Intern Med* 1938:723-739. doi: doi:10.1001/archinte.1938.00180160002001
28. Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart Failure and Liver Disease: Cardiohepatic Interactions. *JACC Heart Fail* 2019;**7**:87-97. doi: 10.1016/j.jchf.2018.10.007
29. Kubo SH, Walter BA, John DH, Clark M, Cody RJ. Liver function abnormalities in chronic heart failure. Influence of systemic hemodynamics. *Arch Intern Med* 1987;**147**:1227-1230. doi:
30. Brener MI, Lurz P, Hausleiter J*, et al.* Right Ventricular-Pulmonary Arterial Coupling and Afterload Reserve in Patients Undergoing Transcatheter Tricuspid Valve Repair. *J Am Coll Cardiol* 2022;**79**:448-461. doi: 10.1016/j.jacc.2021.11.031

LEGENDS:

Figure 1. Impact of Cardio-hepatic syndrome on survival after M-TEER

Figure 1A. Impact of ischemic type I CHS on survival after M-TEER

Figure 1B. Impact of cholestatic type II CHS on survival after M-TEER

Ischemic type I CHS was defined as elevation of both transaminases. Cholestatic type II CHS was defined as elevation of at least two out of three laboratory parameters of liver function. Both types of CHS were associated with significantly worsened two-year survival rates within the overall study population.

CHS = Cardio-hepatic syndrome; MR = Mitral regurgitation; M-TEER = Transcatheter mitral valve edge-to-edge

Figure 2. Multivariate predictors for two-year all-cause mortality

Multivariate predictors of two-year all-cause mortality after M-TEER are depicted as hazard ratio with 95% confidence interval. Hazard ratios are depicted per 10% decrease in LVEF, per mm decrease in TAPSE and per 10 ml/min decrease in eGFR. Figure 2A represents the overall study cohort, while 2B and 2C depict results for PMR and SMR patients, respectively.

CHS = Cardio-hepatic dysfunction; eGFR = estimated glomerular filtration rate; HR = Hazard ratio; LVEF = Left ventricular ejection fraction; MR = Mitral regurgitation; NYHA = New York Heart Association; TAPSE = Tricuspid annular plane systolic excursion; TIA = Transient ischemic attack; M-TEER = Transcatheter mitral valve edge-to-edge repair; PMR = Primary mitral regurgitation; SMR = Secondary mitral regurgitation

Figure 3. Impact of cholestatic type II CHS on two-year all-cause mortality in patients with primary mitral regurgitation

Cholestatic type II CHS was associated with increased two-year all-cause mortality in patients who underwent M-TEER for severe PMR.

CHS = Cardio-hepatic dysfunction; M-TEER = Transcatheter mitral valve edge-to-edge repair; PMR = Primary mitral regurgitation

Figure 4. Impact of ischemic type I CHS on two-year all-cause mortality in patients with secondary mitral regurgitation

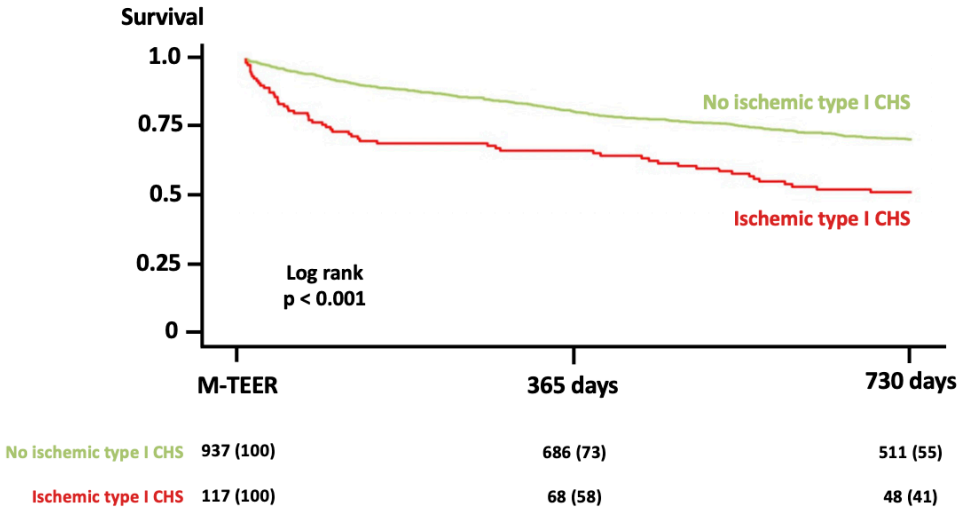
Ischemic type I CHS was associated with increased two-year all-cause mortality in patients who underwent M-TEER for severe SMR.

CHS = Cardio-hepatic dysfunction; M-TEER = Transcatheter mitral valve edge-to-edge repair; SMR = Secondary mitral regurgitation

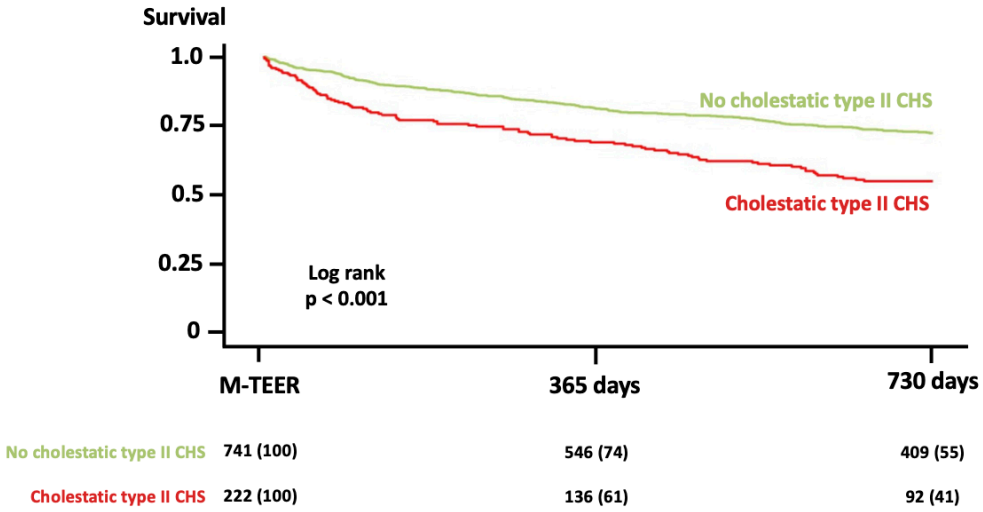
Figure 5. Change in hepatic function after M-TEER depending on successful MR reduction

In patients with successful reduction of MR to <3+ (5A), hepatic function significantly improved after M-TEER treatment. In case of persisting MR ≥3+ (5B) after intervention, no improvement was observed.

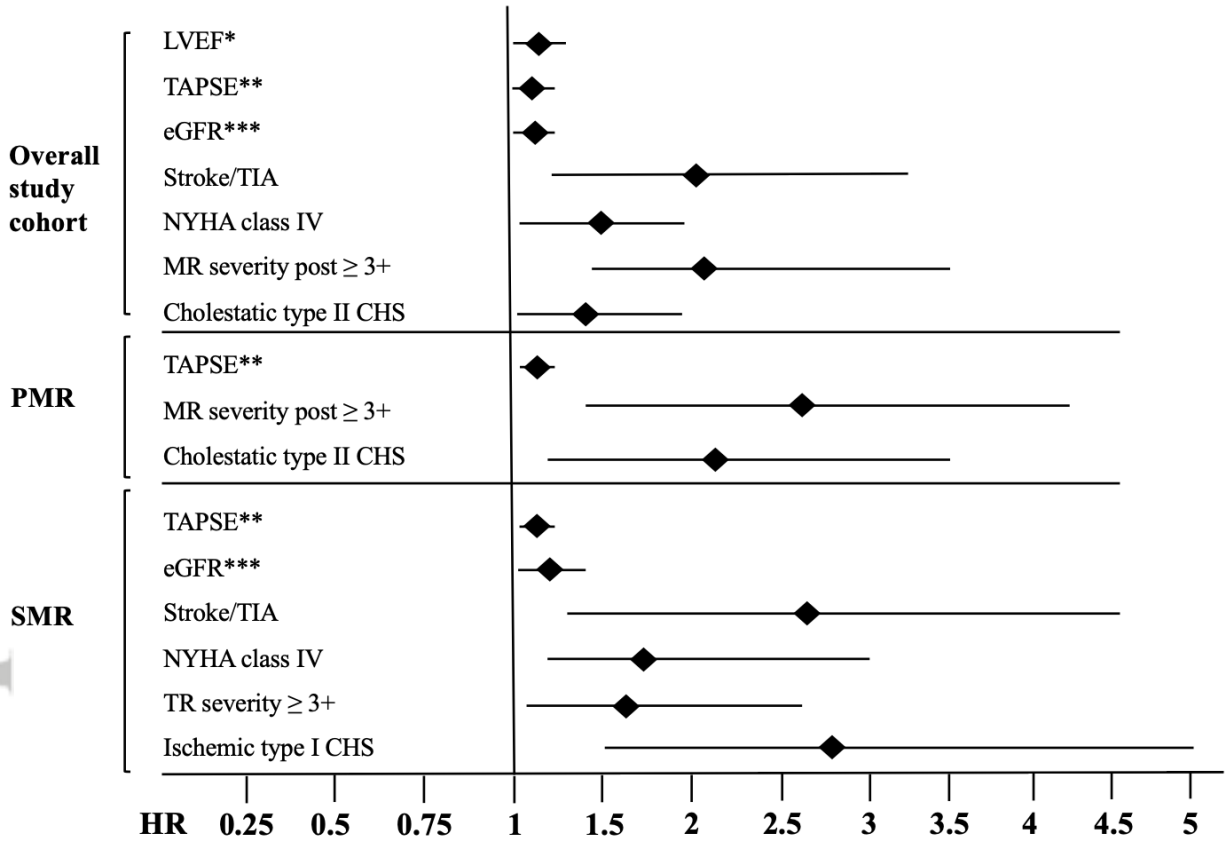
ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; γGT = Gamma glutamyl transferase; MR = Mitral regurgitation; PMR = primary mitral regurgitation; SMR = secondary mitral regurgitation; M-TEER = Transcatheter mitral valve edge-to-edge repair



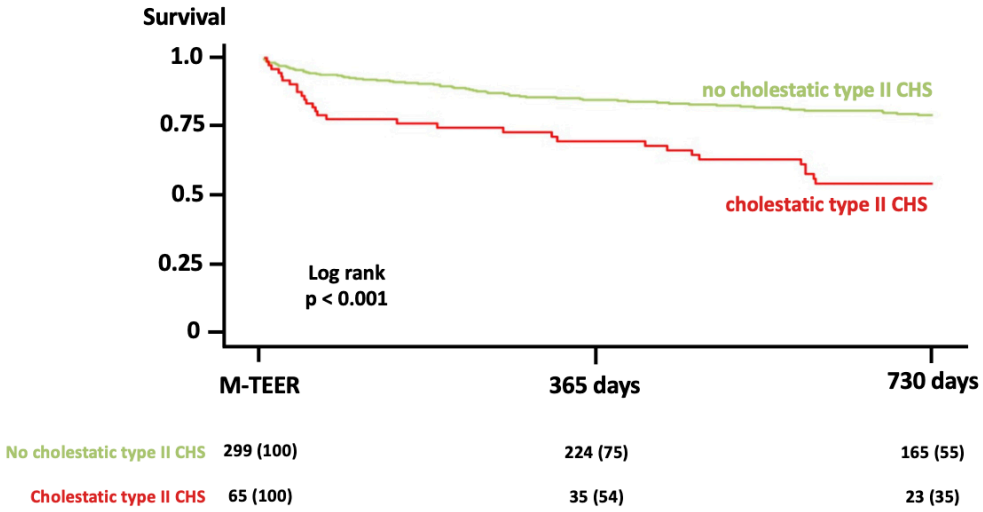
EJHF_2842_Figure 1A.tiff



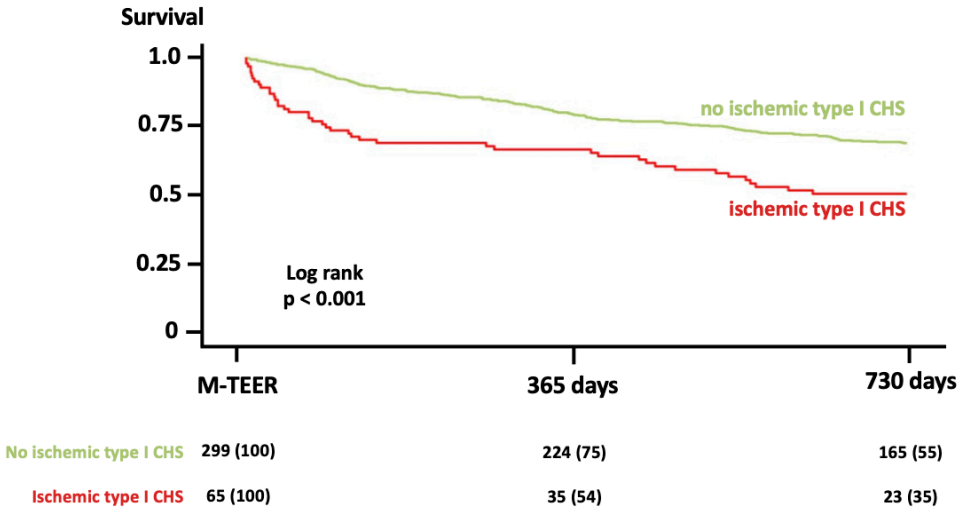
EJHF_2842_Figure 1B.tiff



EJHF_2842_Figure 2.tiff



EJHF_2842_Figure 3.tiff



EJHF_2842_Figure 4.tiff

Table 1 – Baseline characteristics by ischemic type I CHS				
1A. Clinical characteristics				
	Overall population (n=1083)	Ischemic type I CHS (n=117)	No ischemic type I CHS (n=938)	p-value*
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 etiology				
PMR	408 (37.9)	31 (26.5)	365 (39.2)	**0.008**
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 [2229-14636]	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
1B. 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
1C. Medication				
ACE/ARB	697 (68.1)	38 (36.5)	607 (68.0)	0.353
ß 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
1D. Echocardiographic characteristics				
MR EROA PISA, cm²	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, cm²	23.1 ± 7.6	24.6 ± 10.0	23.0 ± 7.3	0.257
RV ESA, cm²	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
Echo-sPAP, mmHg	46.6 ± 15.6	46.2 ± 15.0	46.6 ± 15.8	0.857
1E. Severity of MR, TR and NYHA functional class				
MR Severity				
2+ 3+	10 (0.9) 437 (40.7)	3 (2.6) 41 (35.0)	7 (0.8) 383 (41.2)	0.087

4+	627 (58.4)	73 (62.4)	539 (58.0)	
TR Severity				
0+ 1+ 2+ 3+ 4+	34 (3.4) 430 (42.7) 311 (30.9) 196 (19.4) 37 (3.7)	6 (5.6) 38 (35.5) 38 (35.5) 20 (18.7) 5 (4.7)	27 (3.1) 375 (42.9) 269 (30.8) 171 (19.6) 32 (3.7)	0.404
NYHA functional class				
II III IV	68 (6.4) 739 (69.5) 256 (24.1)	3 (2.6) 61 (53.0) 51 (44.3)	62 (6.7) 655 (71.2) 203 (22.1)	**<0.001**

Data are presented as mean ± standard deviation, median [Interquartile range (IQR)] or number (%)

* CHS vs no CHS

ACE = Angiotensin converting enzyme; 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; NYHA = New York Heart Association functional class; PG = Pressure gradient; PISA = Proximal isovelocity surface area; RV = Right ventricle; sPAP = Systolic pulmonary artery pressure; TAPSE = Tricuspid annular plane systolic excursion; TIA = Transient ischemic attack; TR = Tricuspid regurgitation

Table 2 – Baseline characteristics by cholestatic type II CHS				
2A. Clinical characteristics				
	Overall population (n=1083)	Cholestatic type II CHS (n=222)	No Cholestatic type II CHS (n=861)	p-value*
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 etiology				
PMR	408 (37.9)	65 (29.5)	300 (40.7)	**0.003**
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 [2556-11323]	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**
2B. 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**
2C. Medication				
ACE/ARB	697 (68.1)	144 (68.6)	469 (66.4)	0.563
ß 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**
2D. Echocardiographic characteristics				
MR EROA PISA, cm²	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, cm²	23.1 ± 7.6	24.3 ± 8.7	22.7 ± 7.3	**0.046**
RV ESA, cm²	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**
Echo-sPAP, mmHg	46.6 ± 15.6	49.1 ± 17.1	45.7 ± 15.4	0.062
2E. Severity of MR, TR and NYHA functional class				
MR Severity				
2+	10 (0.9)	2 (0.9)	8 (1.1)	
3+	437 (40.7)	92 (41.4)	297 (40.5)	0.946
4+	627 (58.4)	128 (57.7)	428 (58.4)	
TR Severity				
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)	**0.005**
3+	196 (19.4)	59 (27.6)	122 (18.0)	
4+	37 (3.7)	6 (2.8)	27 (4.0)	
NYHA functional class				
II	68 (6.4)	7 (3.2)	53 (7.3)	
III	739 (69.5)	131 (59.8)	522 (71.8)	**<0.001**
IV	256 (24.1)	81 (37.0)	152 (20.9)	

Data are presented as mean ± standard deviation, median [Interquartile range (IQR)] or number (%)

* CHS vs no CHS

ACE = Angiotensin converting enzyme; 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; NYHA = New York Heart Association functional class; PG = Pressure gradient; PISA = Proximal isovelocity surface area; RV = Right ventricle; sPAP = Systolic pulmonary artery pressure; TAPSE = Tricuspid annular plane systolic excursion; TIA = Transient ischemic attack; TR = Tricuspid regurgitation

Table 3 – Predictors of two-year all-cause mortality

3A. Overall study cohort (PMR and SMR)

	univariate			multivariate		
	hazard ratio	confidence interval	p-value	hazard ratio	confidence interval	p-value
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

3B. PMR

	univariate			multivariate		
	hazard ratio	confidence interval	p-value	hazard ratio	confidence interval	p-value
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

3C. SMR

	univariate			multivariate		
	hazard ratio	confidence interval	p-value	hazard ratio	confidence interval	p-value
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
Ischemic type I CHS	1.542	1.146-2.074	0.004	2.732	1.477-5.056	0.001

Cox regression model; CHS = Cardio-hepatic syndrome; CRT = Cardiac resynchronization therapy; eGFR = Estimated glomerular filtration rate; ICD = Implantable cardioverter-defibrillator; LVEDV = Left ventricular end diastolic volume; LVEF = Left ventricular ejection fraction; MR = Mitral regurgitation; MV = Mitral valve; NYHA = New York Heart Association functional class; PMR = Primary mitral regurgitation; SMR = Secondary mitral regurgitation; TAPSE = Tricuspid annular plane systolic excursion; TIA = Transient ischemic attack; TR = Tricuspid regurgitation