Interdisciplinary CardioVascular and Thoracic Surgery 2023, 36(2), ivad024
https://doi.org/10.1093/icvts/ivad024 Advance Access publication 27 January 2023

ORIGINAL ARTICLE

Cite this article as: Doldi PM, Stolz L, Buech J, Saha S, Weckbach L, Gmeiner J *et al.* Indocyanine green clearance predicts outcome in patients undergoing transcatheter valve intervention for severe atrio-ventricular valve regurgitation. Interdiscip CardioVasc Thorac Surg 2023; doi:10.1093/icvts/ivad024.

Indocyanine green clearance predicts outcome in patients undergoing transcatheter valve intervention for severe atrio-ventricular valve regurgitation

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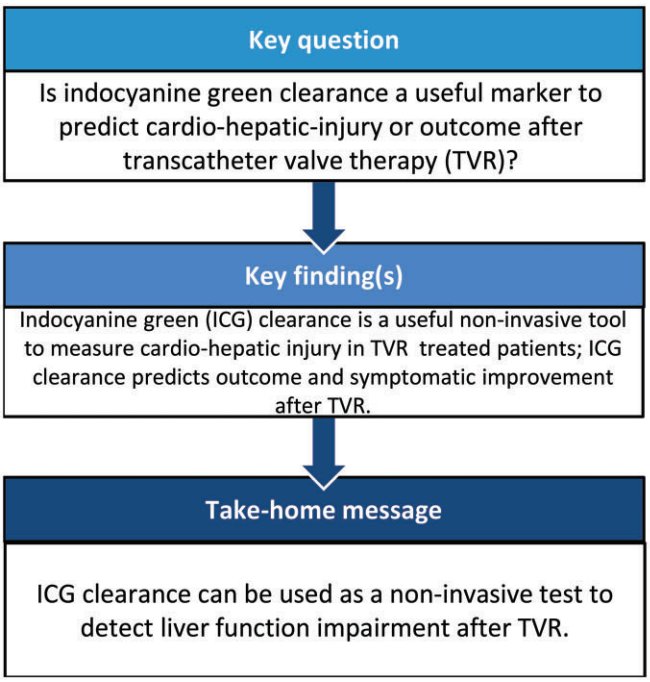
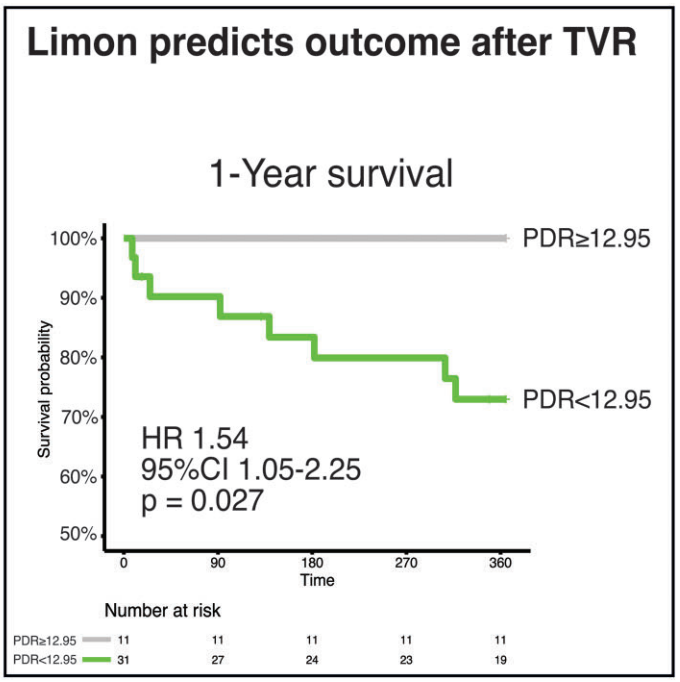
Received 26 September 2022; received in revised form 23 January 2023; accepted 25 January 2023





Abstract

OBJECTIVES: Severe mitral regurgitation (MR) and tricuspid regurgitation (TR) aggravate haemodynamic stress leading to congestive heart failure with impaired hepatic function, also known as cardiohepatic syndrome (CHS). Current perioperative risk calculators do not sufficiently consider CHS and serum liver function parameters lack sensitivity to diagnose CHS. Indocyanine green and its elimination (measured by the LIMON® test) represent a dynamic and non-invasive test which correlates with the hepatic function. Nevertheless, its utility in the setting of transcatheter valve repair/replacement (TVR) to predict CHS and outcome remains unknown.

METHODS: We analysed liver function and outcomes of patients undergoing TVR for MR or TR between August 2020 and May 2021 at the Munich University Hospital.

RESULTS: Out of a total of 44 patients treated at the University Hospital of Munich, 21 (48%) were treated for severe MR, 20 (46%) for severe TR and 3 (7%) for both diseases. Procedural success defined as MR/TR ≤2+ was 94% among MR patients and 92% among TR patients. While classical serum liver function parameters did not change after TVR, there was a significant improvement in liver function as assessed by the LIMON® test ($P \leq 0.001$). Patients with baseline indocyanine green plasma disappearance rate <12.95%/min showed significantly increased 1-year mortality (hazard ratio: 1.54, 95% confidence interval: 1.05–2.25, $P = 0.027$) and lower New York Hear Association class improvement ($P = 0.05$).

CONCLUSIONS: Especially in the context of the recently stressed importance of a careful patient selection prior to the interdisciplinary treatment of valvular heart disease, the LIMON® test may provide further real-time information on the patients' cardiohepatic injury and prognosis.

Keywords: Transcatheter valve repair • Indocyanine green • LIMON • Cardiohepatic syndrome

ABBREVIATIONS

AP	Alkaline phosphatase
CE	Cholinesterase
CHS	Cardiohepatic syndrome
CI	Confidence interval
EuroSCORE	European System for Cardiac Operative Risk Evaluation
ICG	Indocyanine green
IQRs	Interquartile ranges
LA	Left atrial
MELD-XI	Model for End-Stage Liver Disease Excluding INR
MR	Mitral regurgitation
NYHA	New York Heart Association
PDR	Plasma disappearance rate
RA	Right atrial
ROC	Receiver operating characteristic
RV	Right ventricular
STS	Society of Thoracic Surgeons
TMVR	Transcatheter mitral valve replacement
TR	Tricuspid regurgitation
T-TEER	Tricuspid valve transcatheter edge-to-edge repair
TVR	Transcatheter valve repair/replacement

INTRODUCTION

For cardiac surgeons and cardiologists, transcatheter technologies have evolved to a core element for the treatment of atrioventricular valvular heart disease, especially in patients with increased surgical risk [1–4]. When left untreated, progressive mitral regurgitation (MR) and tricuspid regurgitation (TR) aggravate haemodynamic stress on pulmonary and systemic circulation leading to congestive heart failure (HF) [5] with impaired hepatic function, also known as cardiohepatic syndrome (CHS) [6–8]. Transcatheter valve repair/replacement (TVR) has shown to effectively reduce MR and TR burden, which improves HF symptoms and quality of life. However, a growing body of literature stresses the critical importance of a careful patient selection prior to TVR to further optimize treatment outcomes [9, 10].

Recently, the CHS has been identified as a key prognostic parameter in patients treated for severe MR or TR [8, 11, 12]. CHS is a known contributor to increased mortality after tricuspid valve transcatheter edge-to-edge repair (T-TEER) and mitral valve transcatheter edge-to-edge repair [8, 11]. Increased congestive haemodynamic stress promotes liver cell necrosis and leads to the elevation of serum liver parameters [7, 13]. Especially in the presence of heart failure with reduced ejection fraction, liver damage is promoted by reduced forward stroke volume. Nevertheless, current risk calculators [European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, Society of Thoracic Surgeons (STS) Predicted Risk of Mortality and TRI-SCORE] fail to adequately consider CHS in their calculation. In addition, all known serum liver parameters are static (non-dynamic) tests with variable sensitivity and therefore cannot be used for a rapid detection of changes within the cardiohepatic interplay [14, 15]. Moreover, their half-lives vary between days and weeks, which complicates their interpretation in the setting of acute HF and postinterventional evaluation of treatment success [7, 16]. Thus, dynamic tests assessing liver function by determining the livers' ability to eliminate metabolites over time might be beneficial. Indocyanine green (ICG) is a fluorescent dye selectively taken up and eliminated by the hepatocytes [17, 18]. Due to its unique features, the ICG elimination represents a dynamic and non-invasive test, which correlates with the hepatic function [15]. The ICG plasma disappearance rate (PDR) is a validated and widely used dynamic liver function test in patients undergoing hepatectomy, liver transplantation, coronary bypass surgery or critically ill patients requiring intensive care [19–21].

Nevertheless, its utility to assess liver function impairment and to predict outcome in the setting of TVR remains unknown. Therefore, we aimed to invasively and non-invasively assess the liver function and outcomes of patients undergoing TVR at a high-volume centre.

METHODS

Study population

Patients undergoing TVR for moderate-to-severe or severe MR or TR between August 2020 and May 2021 at the Munich University Hospital (Munich, Germany) were included in this analysis. For all patients undergoing TVR, non-invasive dynamic liver function test was optional and only patients with informed written consent received ICG PDR measurement and were included in this analysis. Patients were symptomatic despite optimal medical therapy, defined as maximally tolerated guideline-directed medical therapy, complemented by cardiac resynchronization therapy

implemented when indicated. Prior to TVR, a multidisciplinary heart team consensus by cardiac surgeons, interventional cardiologists as well as imaging specialists was obligatory to evaluate the best treatment option in each individual patient. Among indication criteria, the heart team evaluated the age, comorbidities, prior surgeries, frailty, valve anatomy and the patients' wish.

Data collection and procedural techniques

Collected data included demographic data (age, sex and body mass index), medical history, echocardiographic and clinical parameters. Patient data were collected and stored in a database according to the local requirements for quality control. Ethical approval was obtained from the institutional ethics board (LMU, EVERY-Valve-Registry, ethical code number 19-840; date: 20 December 2019). Data collection at follow-up was performed according to the study protocol. The study was conducted according to international rules for scientific studies as well as the Declaration of Helsinki. Patients needed to be legal of age and capable of giving informed consent.

Invasive serum liver function parameters were collected at admission and before discharge corresponding to non-invasive liver function parameters. On the same day, serum total bilirubin (mg/dl), aspartate aminotransaminase (U/l), alanine aminotransferase (U/l), gamma-GT (U/l), alkaline phosphatase (AP) (U/l) and cholinesterase (CE) (kU/l) were recorded. Echocardiograms were performed and analysed at admission prior to TVR and before discharge by experienced physicians at the study site according to current echocardiographic guidelines. Baseline MR or TR severity was assessed according to current recommendations of the European Association of Echocardiography [22]. Right ventricular (RV) parameters were assessed through an apical four-chamber view [23]. RV-to-pulmonary artery coupling was assessed using the tricuspid annular plane systolic excursion–systolic pulmonary artery pressure ratio, as previously described [2, 10, 24–26]. The TVR procedures were performed under general anaesthesia with two- and three-dimensional transoesophageal echocardiography as well as fluoroscopic guidance as previously described. Included patients received mitral valve transcatheter edge-to-edge repair, T-TEER, transcatheter mitral valve replacement (TMVR) or transcatheter tricuspid valve replacement accordingly.

Indocyanine green measurements

Due to its features, ICG elimination is considered to correlate with hepatic function and thereby useful as a dynamic liver function test. ICG PDR and ICG retention ratio after 15 min (ICG R15) are the most widely used parameters to express the elimination, and thereby hepatic function. In this study, we used the LIMON® (Pulsion Medical Systems, Munich, Germany) method of measuring ICG elimination by pulse spectrophotometry. ICG PDR (PDR%/min) and ICG-R15 (R15%/min) were measured in all patients non-invasively by pulse spectrophotometry after injection of an intravenous bolus of 0.25 mg/kg of ICG-PULSION® dye dissolved in 5 ml of normal saline at admission and before discharge. Measurements were performed during stable cardiovascular circulation. Low ICG PDR was defined by an ICG PDR value of <12.95%/min calculated by receiver operating characteristic (ROC) analysis with a sensitivity of 100% and a specificity of 31%.

Follow-up

Follow-up was completed on the last medical interview date, the last examination date or the date when an end point event was observed, whichever came first. Clinical follow-up was part of standard clinical care and included survival status through either outpatient visit or telephone interviews with the patient, the patient's relatives or local physicians. Among these follow-up examinations, we also assessed the New York Hear Association (NYHA) functional class.

Statistical analysis

For descriptive statistics, continuous data were presented as means with standard deviation and medians with interquartile ranges (IQRs), respectively. Categorical data were presented as proportions. Normality of data distribution was assessed graphically and using the Shapiro–Wilk test. Comparisons between groups were performed using the Pearson's chi-square test for categorical variables, Student's *t*-test or Mann–Whitney *U*-test for unpaired continuous variables, and Wilcoxon rank-sum test for paired variables, according to the data distribution. ROC analysis with Youden (*J*) index method was performed to define the optimal cut-off value for dichotomizing ICG PDR according to its discriminatory value for 1-year mortality. Cumulative survival after 2 years was estimated and graphically displayed using Kaplan–Meier curves. The risk of mortality was assessed using Cox regression analysis and expressed as hazard ratio, 95% confidence interval (CI) and *P*-value. The statistical tests applied yielded a two-sided *P*-values with a level of significance (alpha) of <0.05 to determine statistical significance. The statistical software used for data analysis and visualization was R studio version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Out of 44 patients (age, 81 [76, 84] years; female, 45.5%), 21 (48%) were treated for severe MR, 20 (46%) for severe TR and 3 (7%) for both diseases. Thirty-three patients (75%) received TEER, 3 patients (7%) underwent TMVR, 6 patients (13.6%) were treated by transcatheter tricuspid valve replacement and 2 patients (4.6%) received TMVR as a valve-in-valve (or ring) procedure in mitral position. Within patients treated for MR, 60.9% showed secondary aetiology and 39.1% showed primary aetiology of MR. In patients treated for TR, secondary aetiology was present in 95.3%. Preprocedural risk for mortality was elevated with a EuroSCORE II of 4.9% [IQR: 2.9%, 8.0%] and an STS score of 5.3% [IQR: 3.3%, 8.7%]. The mean liver Model for End-Stage Liver Disease Excluding INR (MELD-XI) score was 12.5 ± 6.1. Hypertension was reported by 91% and the prevalence of atrial fibrillation was 73%. NYHA class III was present in 36 patients (82%) and NYHA IV in 8 patients (18%). Ninety-one percentage of patients received diuretics prior to the intervention. Fifty-two percentage received an angiotensin receptor blocker or ACE inhibitor at baseline and 89% received a ß-blocker. Baseline characteristics are demonstrated in Table 1. A study flow chart is shown in Supplementary Material, Fig. S1.

Echocardiographic imaging showed that the rate of preprocedural MR grade ≥3+ was 96% in patients treated for severe

Table 1: Clinical characteristics

Characteristic	Overall	PDR ≥12.95	PDR <12.95	*P*-Value
n	44	11	31	
Age (years), median [IQR]	81.0 [75.5, 84.0]	80.0 [72.0, 81.0]	81.0 [77.0, 84.0]	0.20
Gender (male), *n* (%)	24 (54.5)	6 (54.5)	16 (51.6)	1.00
Height (cm), *n* (%)	168.3 (9.4)	168.7 (10.6)	167.3 (8.8)	0.67
Weight (kg), *n* (%)	70.8 (11.9)	72.5 (11.6)	69.1 (11.4)	0.41
BMI (kg/m^2), *n* (%)	24.9 (3.2)	25.4 (2.7)	24.7 (3.5)	0.55
EuroSCORE II (%)	4.9 [2.9, 8.0]	1.8 [1.4, 5.1]	5.4 [3.8, 8.5]	0.01
STS score (%)	5.3 [3.3, 8.7]	3.4 [1.4, 6.3]	5.4 [3.8, 9.8]	0.08
MELD-XI score, *n* (%)	12.5 (6.1)	10 (4.9)	13.9 (6.1)	0.09
Type of procedure, *n* (%)				0.15
M-TEER	16 (36.4)	5 (45.5)	10 (32.3)	
T-TEER	14 (31.8)	5 (45.5)	9 (29.0)	
M-TEER + T-TEER	3 (6.8)	0 (0.0)	3 (9.7)	
TTVR	6 (13.6)	0 (0.0)	6 (19.4)	
TMVR	3 (6.8)	0 (0.0)	3 (9.7)	
TAVR in MV	2 (4.5)	1 (9.1)	0 (0.0)	
NYHA functional class (%), *n* (%)				0.96
II	0 (0.0)	0 (0.0)	0 (0.0)	
III	36 (81.8)	9 (81.8)	25 (80.6)	
IV	8 (18.2)	2 (18.2)	6 (19.4)	
Ischaemic aetiology (%), *n* (%)	24 (54.5)	4 (36.4)	18 (58.1)	0.38
Diabetes (%), *n* (%)	9 (20.5)	1 (9.1)	7 (22.6)	0.59
Hypertension (%), *n* (%)	40 (90.9)	10 (90.9)	28 (90.3)	1.00
Hyperlipidaemia (%), *n* (%)	23 (52.3)	7 (63.6)	15 (48.4)	0.60
Previous myocardial infarction (%), *n* (%)	11 (25.0)	3 (27.3)	8 (25.8)	1.00
Previous PCI (%), *n* (%)	18 (40.9)	3 (27.3)	15 (48.4)	0.39
Previous CABG (%), *n* (%)	5 (11.4)	0 (0.0)	5 (16.1)	0.38
Previous stroke (%), *n* (%)	7 (15.9)	2 (18.2)	4 (12.9)	1.00
Chronic obstructive lung disease (%), *n* (%)	9 (20.5)	2 (18.2)	7 (22.6)	1.00
History of atrial fibrillation or flutter (%), *n* (%)	32 (72.7)	5 (45.5)	26 (83.9)	0.04
Previous ICD (%), *n* (%)	4 (9.1)	0 (0.0)	3 (9.7)	0.70
Previous CRT (%), *n* (%)	2 (4.5)	0 (0.0)	2 (6.5)	0.97
ACE inhibitors/AT1 antagonists (%), *n* (%)	23 (52.3)	7 (63.6)	14 (45.2)	1.00
ß-Blockers (%), *n* (%)	39 (88.6)	7 (63.6)	30 (96.8)	0.02
Aldosterone antagonists (%), *n* (%)	19 (43.2)	5 (45.5)	13 (41.9)	1.00
Diuretics (%), *n* (%)	40 (90.9)	8 (72.7)	30 (96.8)	0.08
Neprilysin inhibitor (%), *n* (%)	3 (6.8)	0 (0.0)	3 (9.7)	0.70
NTproBNP level (pg/ml), median [IQR]	2918 [1449, 7156]	1550 [1105, 4174]	3580 [1611, 9176]	0.08

BMI: body mass index; CABG: coronary artery bypass graft; EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; IQR: interquartile range; MELD-XI: Model for End-Stage Liver Disease Excluding INR; M-TEER: mitral valve transcatheter edge-to-edge repair; NYHA: New York Hear Association; PCI: percutaneous coronary intervention; PDR: plasma disappearance rate; STS: Society of Thoracic Surgeons; MV: Mitral valve; ICD: Internal cardioverter defibrillator; CRT: Cardiac resynchronization therapy; TMVR: transcatheter mitral valve replacement; T-TEER: tricuspid valve transcatheter edge-to-edge repair; TTVR: transcatheter tricuspid valve replacement; TAVR: Transcatheter aortic valve replacement-Prothesis; ACE: Angiotensin Converting Enzyme; NTproBNP: N-terminal prohormone of brain natriuretic peptide

MR and that of TR grade ≥3+ was 91% among those treated for severe TR (Fig. 1). TVR-treated patients had normal left ventricular volumes indexed to their body surface area. Baseline indexed left atrial (LA) volume and right atrial (RA) area were increased (LA volume$_{index}$: 64.4 ± 29.7 ml/m^2, RA area: 28.4 ± 10.8 cm^2). The mean left ventricular ejection fraction and RV fractional area change were preserved (left ventricular ejection fraction: 51 ± 12%; RV fractional area change: 40 ± 10%). The mean RV dimensions were increased (RV end-diastolic area$_{index}$: 13 ± 5.2 cm^2/m^2; RV end-systolic area$_{index}$: 8.5 ± 3.6 cm^2/m^2). All echocardiographic baseline parameters are shown in Table 2. MR and TR severity were significantly reduced after TVR (both, $P < 0.001$, Fig. 1A and B). Procedural success among MR patients defined as MR ≤2+ at the end of the procedure was 94% and 89% showed MR ≤1+. Procedural success defined as TR ≤2+ among TR patients was 92% and 85% showed TR ≤1+ (Fig. 1B).

Liver function tests and impact of transcatheter valve repair/replacement on liver function

Patients received both static and dynamic liver function tests at admission and before discharge. Static liver function analysis included serum liver parameters (bilirubin, aspartate aminotransaminase, alanine aminotransferase, gamma-GT, AP and CE). For dynamic liver function assessment, the ICG PDR (%/min) and R15 (%/min) were assessed. In addition, the MELD-XI score was calculated. The dynamically measured liver function at admission was impaired with a mean PDR of 10.4 ± 5.3%/min and a mean R15 of 27.5 ± 18.8%/min. Overall, serum liver function parameters were within normal ranges (Table 3). Baseline ICG clearance and serum liver function parameters did not differ between patients with isolated mitral valve intervention, isolated tricuspid valve intervention or combined mitral and tricuspid interventions. Lower PDR and higher R15 values correlated with serum liver function

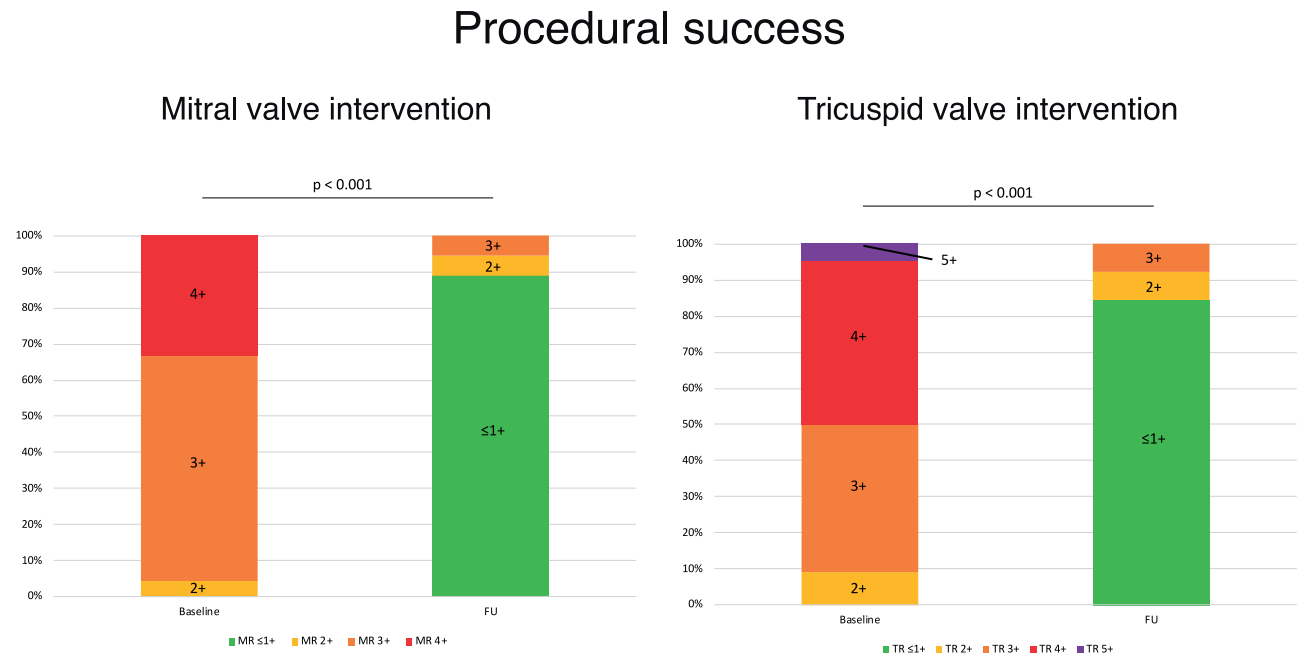


Figure 1: Procedural success. This figure demonstrates the procedural success stratified by mitral- and tricuspid valve intervention.

Table 2: Echocardiographic characteristics

Characteristic	Overall	PDR ≥12.95	PDR <12.95	*P*-Value
n	44	11	31	
MR severity, *n* (%)				0.19
1+	13 (29.5)	1 (9.1)	12 (38.7)	
2+	6 (13.6)	3 (27.3)	3 (9.7)	
3+	17 (38.6)	4 (36.4)	11 (35.5)	
4+	8 (18.2)	3 (27.3)	5 (16.1)	
Biplanar vena contracta (mm), *n* (%)	0.4 (0.3)	0.5 (0.3)	0.4 (0.2)	0.42
ERO (cm^2), *n* (%)	0.3 (0.2)	0.3 (0.3)	0.3 (0.2)	0.85
LVEDV index (ml/m^2), *n* (%)	64.4 (29.7)	61.7 (21.5)	64.8 (32.5)	0.78
LVESV index (ml/m^2), *n* (%)	31.7 (21.5)	23.9 (14.6)	33.4 (22.3)	0.22
LA $volume_{index}$ (ml/m^2), *n* (%)	57.5 (27.9)	42.4 (11.3)	63.2 (30.5)	0.04
LV-EF (%), *n* (%)	51.5 (12.1)	57.2 (9.0)	50.0 (11.6)	0.09
TR severity, *n* (%)	2.5 (1.2)	2.0 (1.0)	2.8 (1.3)	0.07
1+	11 (25.0)	4 (36.4)	6 (19.4)	
2+	8 (18.2)	4 (36.4)	3 (9.7)	
3+	13 (29.5)	2 (18.2)	11 (35.5)	
4+	10 (22.7)	1 (9.1)	9 (29.0)	
5+	1 (2.3)	0 (0.0)	1 (3.2)	
TV annulus (ed) (mm), *n* (%)	43.0 (9.8)	38.6 (6.0)	44.6 (10.6)	0.10
RV EDA_{index} (cm^2/m^2), *n* (%)	13.2 (5.2)	10.2 (3.2)	14.2 (5.6)	0.04
RV ESA_{index} (cm^2/m^2), *n* (%)	8.5 (3.6)	6.7 (2.4)	9.2 (3.8)	0.06
RV FAC, *n* (%)	0.4 (0.1)	0.3 (0.1)	0.4 (0.1)	0.79
RA area (cm^2), *n* (%)	28.4 (10.8)	21.8 (7.8)	30.6 (10.9)	0.02
TR VC (mm), *n* (%)	0.7 (0.5)	0.5 (0.3)	0.8 (0.5)	0.06
TR ERO (cm^2), *n* (%)	0.6 (0.5)	0.3 (0.2)	0.7 (0.5)	0.19
TAPSE (mm), *n* (%)	15.1 (6.6)	16.7 (8.1)	14.8 (6.3)	0.44
VCI diameter (mm), *n* (%)	8.2 (10.2)	6.7 (8.0)	7.2 (9.5)	0.86
TrmaxPG (mmHg), *n* (%)	32.8 (15.7)	36.1 (10.0)	31.1 (17.2)	0.41

EDA: end-diastolic area; ERO: effective regurgitant orifice; ESA: end-systolic area; FAC: fractional area change; LA: left atrial; LVEDV: left ventricular end-diastolic volume; LV-EF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; PDR: plasma disappearance rate; RA: right atrial; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; TrmaxPG: max. tricuspid valve gradient; TV: tricuspid valve; VC: Vena contracta; VCI: inferior vena cava.

impairment parameters. There were a negative correlation of PDR with AP and gamma-GT (AP: r = -0.40, P = 0.017; gamma-GT: r = -0.37, P = 0.016) and a positive correlation with CE (r = 0.50, P = 0.005, Fig. 2A). Correspondingly, there were a positive correlation of R15 with AP and gamma-GT (AP: r = 0.40, P = 0.016; gamma-GT: r = 0.34, P = 0.030) and a negative correlation with CE (r = -0.50, P = 0.004, Fig. 2B). After TVR procedure, there were no changes in static serum liver function parameters

Table 3: Laboratory parameters

Characteristic	Overall	PDR ≥12.95	PDR <12.95	*P*-Value
n	44	11	33	
LIMON® parameters, *n* (%)				
PDR (%/min)	10.4 (5.3)	17.7 (3.2)	7.9 (3.0)	<0.01
R15 (%)	27.5 (18.8)	7.8 (3.3)	34.5 (16.9)	<0.01
Serum liver function parameters, *n* (%)				
eGFR (ml/min)	44.2 (22.2)	53.7 (23.3)	40.5 (21.7)	0.10
Bilirubin (mg/dl)	1.2 (1.5)	0.7 (0.5)	1.3 (1.7)	0.32
AST (U/l)	31.1 (14.1)	30.6 (11.5)	31.0 (15.4)	0.94
ALT (U/l)	23.1 (13.3)	23.5 (17.2)	22.3 (12.1)	0.81
Gamma-GT (U/l)	100.6 (86.2)	71.1 (72.3)	105.7 (83.0)	0.23
AP (U/l)	106.9 (48.4)	91.0 (46.8)	114.4 (48.7)	0.20
Cholinesterase (kU/l)	5.2 (2.1)	6.0 (0.9)	4.8 (2.3)	0.15

ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransaminase; eGFR: estimated glomerular filtration rate; PDR: plasma disappearance rate.

(Supplementary Material, Fig. S2). However, TVR lead to a significant improvement in liver function (PDR and R15) measured non-invasively with the LIMON® assay (both, $P \leq 0.001$, Fig. 3).

Survival and long New York Hear Association functional class

The median follow-up time was 15.5 (IQR 11.6–19.4) months. The estimated overall 1-year survival rate was 81.2% (95% CI: 70–94%). Survival rates did not differ between either mitral valve or tricuspid valve intervention ($P = 0.34$ by log-rank test, Supplementary Material, Fig. S3A) or TEER and valve replacement ($P = 0.95$ by log-rank test, Supplementary Material, Fig. S3B).

Patients showed significant reduction in NYHA functional class at follow-up. The mean time to last NYHA functional class assessment was 107 ± 86 days. The rate of NYHA class III/IV decreased from 100% at baseline to 56.6% at follow-up ($P < 0.001$, Fig. 4).

Liver dysfunction and its impact on outcome

ROC analysis showed that a cut-off of 12.95%/min of the ICG PDR parameter at admission had the best discriminatory value for 1-year survival. Baseline clinical and echocardiographic characteristics of both groups are presented in Tables 1 and 2. Patients with ICG PDR <12.95%/min at admission presented with a higher surgical risk estimate (EuroSCORE II: 1.8% [IQR: 1.4%, 5.1%] vs 5.4% [IQR: 3.8%, 8.5%], $P = 0.01$) and higher left and right atrial dimensions [LA $volume_{index}$: 42.4 (±11.3) vs 63.2 (±30.5) cm^2/m^2, $P = 0.04$; RA area: 21.8 cm^2 (±7.8 cm^2) vs 30.6 cm^2 (±10.9 cm^2), $P = 0.02$]. In addition, RV dimensions were significantly larger in patients with lower ICG PDR [RV end-diastolic $area_{index}$: 10.2 (±3.2) cm^2/m^2 vs 14.2 (±5.6) cm^2/m^2, $P = 0.04$]. MELD-XI score did not differ significantly between groups. All other clinical and echocardiographic characteristics were comparable. Serum liver function parameters were also comparable in both groups (Table 3). Patients with PDR <12.95%/min at admission showed significantly higher mortality compared to those with PDR ≥12.95%/min (adjusted hazard ratio for mortality: 1.54, 95% CI: 1.05, 2.25, $P = 0.027$, Fig. 5A). A low ICG PDR remained an independent predictor for 1-year mortality in a multivariate regression analysis. In addition, the rate of patients with an NYHA functional class improvement of ≥1 grade was significantly lower in patients with low ICG PDR (86% vs 44%, $P = 0.05$, Fig. 5B).

DISCUSSION

In this study, we analysed for the first time procedural and long-term outcome of TVR patients according to their dynamic and non-invasively quantified liver function measured by ICG clearance. Our main findings can be summarized as follows: (i) procedural success rates were high in each group, regardless of the liver function; (ii) LIMON® parameters correlated with serum liver function parameters and LIMON® parameters identified liver function impairment as an indicator of CHS while serum parameters were still within normal ranges; (iii) in addition, the liver function measured dynamically by ICG clearance improved significantly after TVR, while serum parameters did not change; and (iv) impaired liver function at admission measured by ICG clearance was associated with higher mortality and less symptomatic improvement after TVR.

Hypoperfusion and congestion causing secondary organ dysfunction are known complications in patients with severe valvular heart disease (VHD). While several organs can be damaged by this condition, due to its anatomy and the additive haemodynamic stress of both arterial hypoperfusion and congestion, the liver is strongly affected [27, 28]. Without causal treatment of the underlying valvular heart disease, this condition promotes progressive liver cell necrosis leading to cardiac cirrhosis, worsening of HF and death [27]. In addition, cardiogenic liver injury often remains asymptomatic making an early detection of this life-threatening condition challenging [29]. Therefore, an early detection of liver function impairment as a sign for a CHS is crucial to determine therapeutic options and improve prognosis in patients with valvular heart disease. In patients treated for severe TR, T-TEER is known to not only reduce right atrial pressure, leading to hepatic decongestion, but also increase cardiac output with improved organ perfusion and function [8, 30]. However, the authors emphasize the necessity of evaluating preprocedural hepatic function when evaluating patients for T-TEER, enabling the heart team to provide the best therapeutic recommendation. Similar studies or recommendations for patients with severe MR and CHS are yet absent.

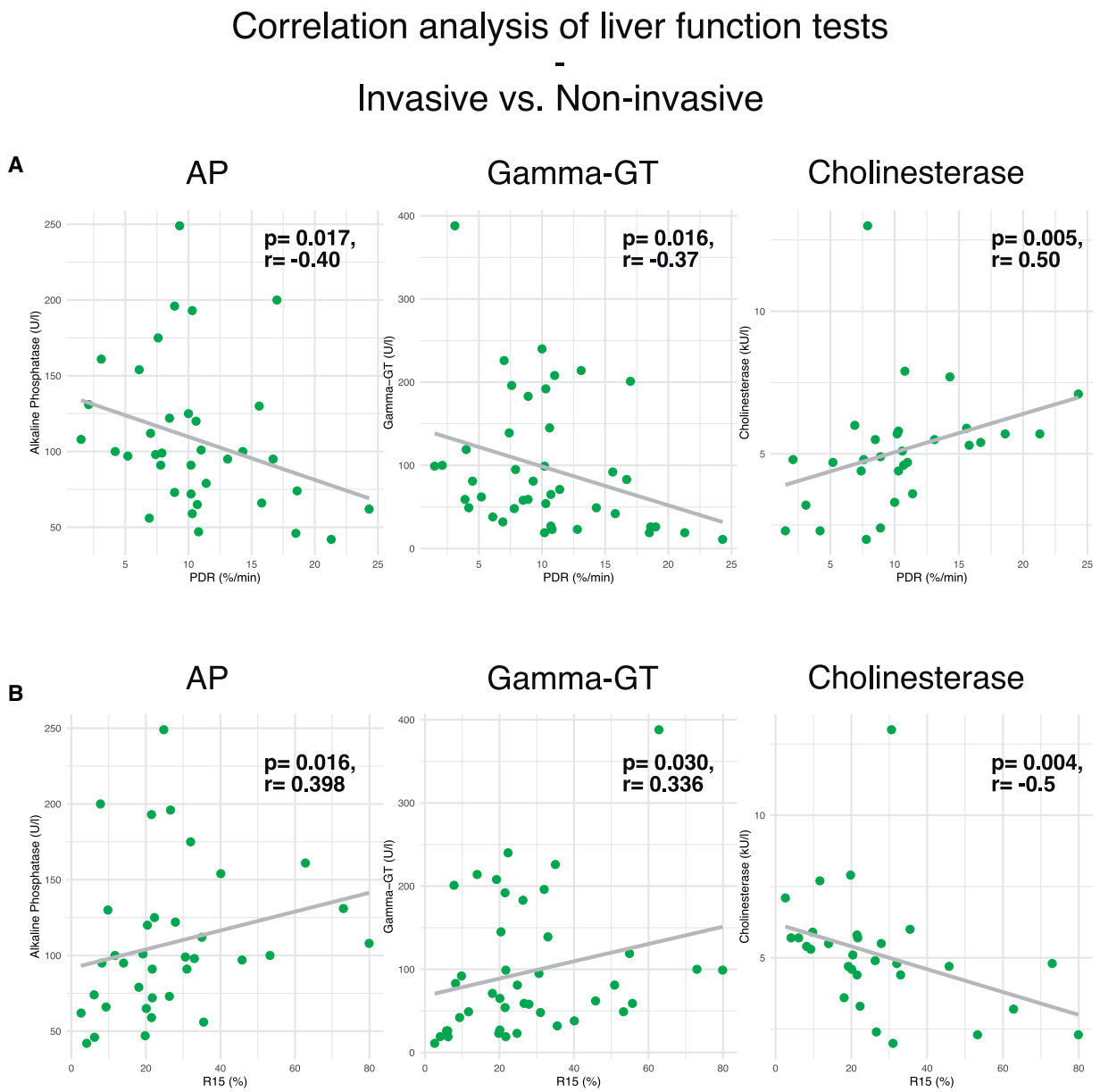


Figure 2: Correlation analysis of liver function tests—invasive versus non-invasive. (**A**) The correlation between AP, gamma-GT and Cholinesterasis and PDR. (**B**) The correlation between AP, gamma-GT and Cholinesterasis and R15. AP: alkaline phosphatase; PDR: plasma disappearance rate.

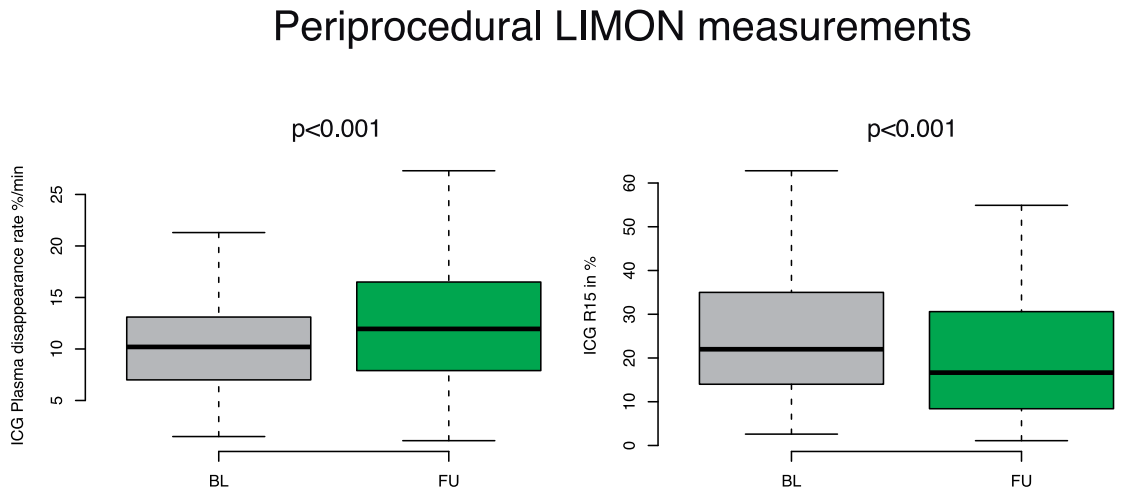


Figure 3: Periprocedural LIMON® measurements. This figure illustrates the changes in plasma disappearance rate and R15 between baseline and discharge.

An elevation of serum liver function parameters can be a sign for a CHS [29]; however, these parameters have a variable sensitivity and long half-lives. Recently, a CHS has been defined as a sex-specific elevation of 2 out of 3 cholestasis parameters (gamma-GT, AP and bilirubin) [8]. However, the authors also outline the necessity of a better characterization and understanding of CHS, most importantly due to its predominantly absent consideration in all current risk calculators (EuroSCORE I, EuroSCORE II, TRI-SCORE, STS score) and the lack of sensitivity of the serum liver function parameters. In contrast to commonly used static tests, the ICG clearance is a dynamic, real-time and non-invasive liver function test. Here, we demonstrate that the ICG clearance can detect a liver function impairment in patients with valvular heart disease while serum parameters are still within normal ranges. In addition, it is noteworthy that 31 patients (71%) showed a liver function impairment according the established ICG PDR cut-off and 37 patients (84%) had an ICG PDR <18%/min which is generally considered a liver function impairment. Given the fact that serum liver parameters were still within normal ranges, the LIMON® test seems to highlight a degree of liver function impairment which is occult to serum tests. Besides, our established ICG PDR cut-off was able to identify 90% of patients who fulfil the above-mentioned CHS criteria deriving from static tests. Moreover, it is noteworthy, that also the MELD-XI score as a validated and accurate metric of the degree of liver disease did not differ significantly between both ICG PDR cut-off groups and was out ruled as a predictor for mortality in this selective patient cohort.

However, values for ICG clearance were associated with increased mortality and less symptomatic improvement after TVR, making the LIMON® test a valuable diagnostic tool in patients with VHD. Especially in the context of the recently stressed importance of a careful patient selection prior to the interdisciplinary treatment of VHD, the fast and non-invasive ICG PDR may provide further real-time information on the patients' haemodynamic situation and prognosis.

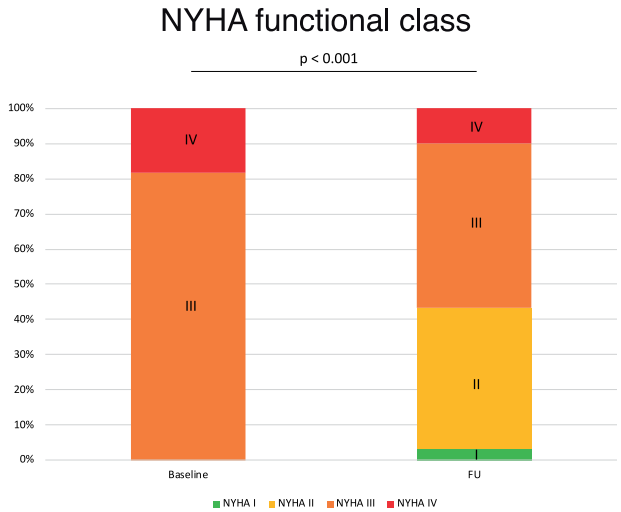


Figure 4: NYHA functional class improvement. This figure depicts the overall NYHA functional class improvement after transcatheter valve repair/replacement. NYHA: New York Hear Association.

Limitations

This was a prospective observational study without core laboratory evaluation of echocardiographic imaging. In addition, the small number of patients with a short NYHA class follow-up period in this study which was treated for both severe MR and TR needs to be acknowledged. In addition, a detailed comparison with the recently proposed definition of CHS cannot be made due to the sample size. Due to the size and heterogeneity of the study cohort, generalizability can be questioned and larger studies will be needed to approve these results. However, this is the first prospective study analysing the impact of liver function impairment measured by ICG clearance on outcome in patients treated with TVR for VHD.

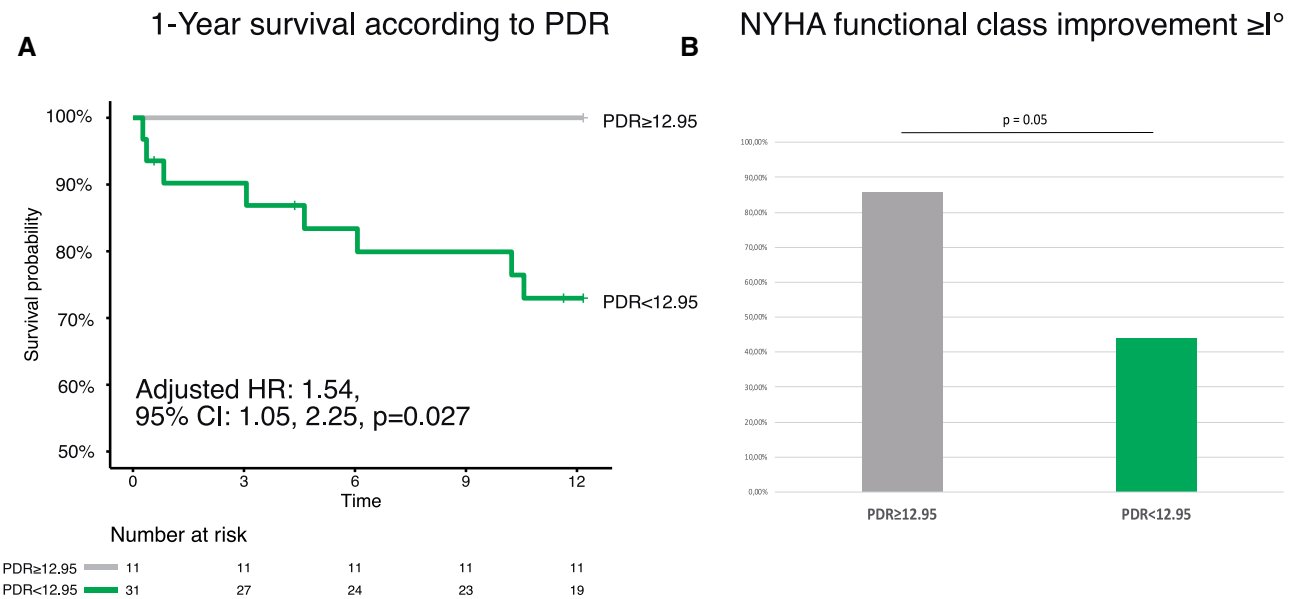


Figure 5: Impact of liver dysfunction on outcome. (**A**) A Kaplan–Meier curve comparing the survival of patients with a PDR of <12.95 to those with a PDR of ≥12.95. (**B**) The NYHA class improvement of ≥1° according to the established PDR cut-off. NYHA: New York Hear Association; PDR: plasma disappearance rate.

CONCLUSION

The CHS in patients with VHD represents an underdiagnosed condition with a high prognostic impact. However, it is not sufficiently considered in currently used perioperative risk scores. The detection of a liver function impairment can be challenging due to the utilization of mostly static serum tests with variable sensitivity and long half-lives. The LIMON® test measuring the ICG clearance is a dynamic and non-invasive liver function test, which can be used to determine the degree of liver function impairment and prognosis in patients treated with TVR for VHD.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: Martin Orban receives speaker honoraria from Abbott Medical, AstraZeneca, Abiomed, Bayer Vital, BIOTRONIK, Bristol-Myers Squibb, CytoSorbents, Daiichi Sankyo Deutschland, Edwards Lifesciences Services and Sedana Medical. Daniel Braun receives speaker honoraria from Abbott Vascular. Christian M. Lange receives speaker honoraria or advisory fees from AbbVie, Astra Zeneca, Boston Scientific, CSL-Behring, Eisai, Gilead, Falk, Norgine, Roche, Shionogi and Sobi. Jörg Hausleiter receives speaker honoraria from and serves as consultant for Abbott Vascular and Edwards Lifesciences. The other authors report no conflict of interest.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Philipp Maximilian Doldi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Visualization; Writing—original draft. **Lukas Stolz:** Data curation; Writing—review & editing. **Joscha Buech:** Data curation; Writing—review & editing. **Shekar Saha:** Data curation; Writing—review & editing. **Ludwig Weckbach:** Data curation; Writing—review & editing. **Jonas Gmeiner:** Writing—review & editing. **Martin Orban:** Writing—review & editing. **Daniel Braun:** Writing—review & editing. **Thomas J. Stocker:** Writing—review & editing. **Michael Nabauer:** Writing—review & editing. **Christian M. Lange:** Validation; Writing—review & editing. **Steffen Massberg:** Supervision; Writing—review & editing. **Christian Hagl:** Conceptualization; Supervision; Writing—review & editing. **Jörg Hausleiter:** Project administration; Supervision; Writing—review & editing.

Reviewer information

Interdisciplinary CardioVascular and Thoracic Surgery thanks Thomas M. Beaver, Ko Bando and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

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