Clin Res Cardiol (2017) 106:341–349
DOI 10.1007/s00392-016-1060-3

ORIGINAL PAPER

Incidence, laboratory detection and prognostic relevance of hypoxic hepatitis in cardiogenic shock

Christian Jung[1] · Georg Fuernau[2,3] · Ingo Eitel[2,3] · Steffen Desch[2,3] · Gerhard Schuler[4] · Malte Kelm[1] · Volker Adams[4] · Holger Thiele[2,3]

Received: 13 September 2016 / Accepted: 1 December 2016 / Published online: 8 December 2016

Abstract

Background Despite the improvement of therapeutic options for patients in acute myocardial infarction (AMI), cardiogenic shock (CS) remains a complication with high mortality rates. Organ failure centrally determines the prognosis of these high-risk patients. Aim of the current study was to assess the incidence of hypoxic hepatitis (HH) in CS, its laboratory detection evaluating novel and established biomarkers and to estimate the prognostic relevance of HH in current clinical practice.

Methods In 172 patients with CS complicating AMI, blood samples were collected at admission and after 1 day as prespecified subanalysis of the intra-aortic balloon pumping IABP-SHOCK II trial. Classic parameters of HH were measured in addition to argininosuccinate synthase 1 and sulfotransferase isoform SULT2A1 was determined as new biomarker using standard enzyme-linked immunosorbent assay kits. All-cause mortality at 30 days was used for outcome assessment.

Results The overall mortality rate was 40%. The incidence of HH with an increase of aminotransferase levels to be 20 times above the upper normal level was 18%. Patients with HH had a distinctly higher 30-day mortality rate compared to patients without HH (68 vs. 34%; $p < 0.001$). After multivariable adjustment aspartate-aminotransferase (ASAT) remained an independent predictor of 30-day mortality together with serum lactate and serum creatinine, while the new biomarkers failed to predict outcome. Comparing different liver markers using receiver operating characteristic analysis, ASAT showed the highest area under the curve for the prediction of outcome.

Conclusions HH occurs frequently in CS and is associated with particular poor outcome. As conventional biomarker, ASAT is the strongest laboratory predictor of outcome.
ClinicalTrials.gov Identifier: NCT00491036.

C. Jung and G. Fuernau contributed equally and sharing the first authorship to this work.

✉ Christian Jung
christian.jung@med.uni-duesseldorf.de

Georg Fuernau
georg.fuernau@uksh.de

Ingo Eitel
ingo.eitel@uksh.de

Steffen Desch
steffen.desch@uksh.de

Gerhard Schuler
gerhard.schuler@medizin.uni-leipzig.de

Malte Kelm
malte.kelm@med.uni-duesseldorf.de

Volker Adams
volker.adams@medizin.uni-leipzig.de

Holger Thiele
holger.thiele@uksh.de

[1] Medical Faculty, Division of Cardiology, Pulmonology and Vascular Medicine, University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

[2] Medical Clinic II, Cardiology/Angiology/Intensive Care Medicine, University Heart Center Lübeck, Lübeck, Germany

[3] German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Lübeck, Germany

[4] Department of Internal Medicine/Cardiology, University of Leipzig-Heart Center, Leipzig, Germany

Keywords Cardiogenic shock · Liver failure · Hypoxic hepatitis · Organ failure · Critical care

Abbreviations

ALAT	Alanine-aminotransferase
ASAT	Aspartate-aminotransferase
AMI	Acute myocardial infarction
ASS1	Argininosuccinate synthase 1
BMI	Body mass index
CS	Cardiogenic shock
GLDH	Glutamate-dehydrogenase
HH	Hypoxic Hepatitis
IABP	Intra-aortic balloon pump
MODS	Multiorgan dysfunction syndrome
PCI	Percutaneous coronary intervention
SUL	Sulfotransferase isoform SULT2A1

Introduction

Despite huge efforts in the treatment of cardiogenic shock (CS), it remains the most life-threatening complication of acute myocardial infarction (AMI) [1, 2]. Key features of CS are hypotension and global tissue hypoxia leading to an impaired microcirculation [3], vascular leakage, increased platelet and leucocyte adhesion to endothelial cells as well as endothelial dysfunction [4], and an activation of the sympathoadrenal system [5]. All these changes ultimately lead to multiorgan dysfunction syndrome (MODS), centrally determining the patients' prognosis. Therefore, current treatment in CS patients aims at optimal prevention and therapy of MODS [6].

Different organ systems can be affected including the liver. Hepatic dysfunction is associated with poor outcome in critically ill patients [7, 8]. This disease state is referred to as hypoxic hepatitis (HH), ischemic hepatitis or shock liver [9]. It is characterized by centrilobular liver cell necrosis and distinctly elevated serum aminotransferase levels and occurs in the clinical setting of cardiac, circulatory or respiratory failure [10]. To date, HH is the most frequent cause of acute liver injury and has been reported with a prevalence of up to 10% of critically ill patients [11]. Although there is no specific treatment available aiming at improving hepatic function in HH, it is still of clinical relevance due to complications caused by HH. This includes alterations of glucose metabolism including spontaneous hypoglycemia, respiratory insufficiency caused by hepatopulmonary syndrome and hyperammonemia [12].

To date, the most frequent used diagnostic method is the determination of serum aminotransferase levels. Although other diagnostic modalities are available, such as determination of hepatic blood flow, liver biopsy, the invasive assessment of hepatic hemodynamics and the use of imaging techniques such as computed tomography [10], in the majority of patients the evaluation of the typical time pattern of transaminases during the course of HH is used. However, also new laboratory markers have been proposed. This includes argininosuccinate synthase 1 (ASS1) and the sulfotransferase isoform SULT2A1 (SUL), which is a major catalyst of the sulfation of dehydroepiandrosterone. Both are hepatic proteins that are degraded in the liver and rapidly released into circulation during liver ischemia [13]. Prima and coworkers were able to show in different animal models of liver injury that both new markers had higher sensitivity and specificity regarding liver injury determination compared to standard laboratory values and suggested them for clinical evaluation [14]. Therefore, the aims of the study were to assess the incidence of HH in CS complicating AMI, its prognostic implication and to evaluate the diagnostic value of new liver parameters in this clinical scenario.

Methods

The present study is a predefined substudy of the Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial (ClinicalTrials.gov Identifier: NCT00491036) that investigated the use of Intra-aortic Balloon Pump (IABP) counterpulsation vs. control in patients with CS complicating AMI and showed no significant difference between the two treatment groups regarding the primary outcome 30-day mortality. The detailed design and main results of the trial have been published previously [15–18]. In summary, 600 patients were enrolled in 37 centers in Germany and underwent randomization to IABP support or to control in a 1:1 fashion. CS was defined as systemic hypotension, pulmonary congestion, and signs of impaired end-organ perfusion. Exclusion criteria were: duration of CS >12 h, cardiopulmonary resuscitation >30 min, severe cerebral deficit, mechanical causes of cardiogenic shock, age >90 years, contraindications against IABP insertion, shock of other cause, or severe concomitant disease with limited life expectancy. Of the total 600-patient study population, 218 were enrolled at the University of Leipzig-Heart Center with planned prospective blood sampling in the catheterization laboratory during the initial invasive procedure. Most importantly, cardiac catheterization was performed as soon as possible in all patients after hospital admission. In resuscitated patients, cooling was initiated after percutaneous coronary intervention (PCI) and blood sample drawing. The study was approved by an institutional review committee and the subjects gave informed consent. The study protocol conforms to the ethical

guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Assessment of biomarker serum levels

For the evaluation of different serum markers blood samples were drawn at the end of PCI from the catheterization sheath (day 1) and on the next day (day 2) on intensive care unit. The EDTA-plasma was immediately separated by centrifugation (2400×g for 10 min) and aliquots were stored at −80 °C until assayed. Aspartate-aminotransferase (ASAT) and alanine-aminotransferase (ALAT) and glutamate-dehydrogenase (GLDH) were measured using techniques established in clinical routine. Therefore, a fully automated system (Architect ci16200, Abbott, IL, USA) has been used allowing standardized and validated measurements using established immunoassays. Regarding the definition of HH, several authors proposed that ALAT or ASAT should be at least 20 times the upper normal level [10] which is 14.8 µmol/l*s (normal range <0.74 µmol/l*s) for ALAT and 11.6 µmol/l*s (normal range <0.58 µmol/l*s) for ASAT. In the current study, the diagnosis of HH was met if at least one measurement of ALAT or ASAT was above these thresholds. The reference value of GLDH is <120 nmol/l*s.

ASS1 and SUL levels were measured with standard enzyme-linked immunosorbent assay kits (ASS1: Hoelzel Diagnostika, Germany; SUL: Acris Antibodies, Germany). Samples were assayed in duplicate. Serum lactate probes were taken at the same time point and analyzed by conventional blood gas analysis. Serum creatinine, troponin T and serum creatine kinase, with blood also drawn simultaneously, were determined via standard institutional laboratory measurements.

Statistical analysis

Categorical data are presented as counts or proportions with the corresponding percentages. Most continuous variables had non-normal distribution. For reasons of uniformity, summary statistics for all continuous variables are, therefore, presented as medians with interquartile range (IQR). For primary outcome analysis, all-cause mortality at 30-day was used. Patients were stratified according to the 30-day outcome. Logistic regression modeling was used to identify predictors of death at 30 days. All admission variables with an association (p value <0.1) to 30-day mortality in univariable analysis entered a multivariable stepwise logistic regression model consisting of forward inclusion and subsequent backward removal of parameters not needed within the model. This results in a robust model with high statistic power. Statistical analysis was performed using commercially available software (MedCalc for Windows, version 16.4.3; MedCalc Software, Ostend, Belgium). A two-tailed p value <0.05 was considered statistically significant.

Results

In total, 172 patients with blood available for the present analysis (79% of 218 patients randomized in Leipzig) were included in this predefined substudy. Table 1 shows the admission characteristics of the study population. The overall mortality rate after 30 days was 40%. Following the common definition of HH with an increase of ALAT or ASAT to be 20 times above the upper normal level on day 1 or day 2, the incidence of HH was 18%. Important differences between patients having HH or not were increased creatinine levels, increased serum lactate levels, increased creatine kinase levels, increased troponin levels, prior myocardial infarction and impaired flow following revascularization in patients with HH. Since only patients with available frozen plasma samples were included in the substudy, it is important to note that there were no important differences regarding baseline characteristics between patients within the substudy and the general study population [19]. To determine factors associated with the occurrence of HH, uni- and multivariable analyses were performed revealing serum lactate and impaired flow following revascularization as independent predictors of HH (Table 2).

Values regarding the different laboratory markers of liver injury are given in Table 3. All classical markers including ALAT, ASAT and GLDH were higher in non-survivors compared to survivors, whereas no differences could be observed for ASS1 and SUL. ALAT, ASAT, GLDH served as diagnostic parameters and were, therefore, by definition increased in HH. ASAT correlated strongly with ALAT ($r = 0.939$, $p < 0.001$) but showed only a weak correlation to serum lactate ($r = 0.276$, $p < 0.001$) and creatinine ($r = 0.325$, $p < 0.001$). Furthermore, on day 1, SUL was increased in patients with HH. In addition, an increase could be observed for ASAT between day 1 and 2 ($p < 0.001$), whereas a decrease for ASS1 was observed ($p < 0.001$). Patients with HH had a mortality rate of 68%, which was substantially higher compared to patients without HH (Fig. 1). There was no significant difference in the incidence of HH between patients randomized to IABP and the control group (21 vs. 15%, $p = 0.36$).

To determine predictors of outcome, uni- and multivariate Cox regression analyses were performed including the different laboratory liver values. Univariable logistic regression analysis identified baseline ASAT and baseline ALAT among others to be of relevance for prediction of

Table 1 Characteristics of the study population

	Overall $n = 172$	No hypoxic hepatitis $n = 141$	Hypoxic hepatitis $n = 31$	p value
Age (years)	70 (58; 79)	70 (59; 78)	69 (55; 80)	0.76
Male sex, *n* (%)	119 (69)	74 (72)	45 (65)	0.36
BMI (kg/m^2)	27.2 (24.6; 29.4)	27.2 (24.5; 29.4)	27.5 (25.4; 30.2)	0.59
Admission serum creatinine (μmol/L)	116 (93; 165)	112 (92; 147)	163 (95; 224)	0.01
Admission serum lactate (mmol/L)	3.7 (2.4; 7.3)	3.4 (2.3; 5.8)	7.5 (3.6; 12.7)	<0.001
Admission serum creatine kinase (mmol/L)	9.8 (3.5; 26.2)	9.3 (3.4; 20.3)	19.2 (5.5; 65.0)	0.01
Admission serum troponin T (ng/L)	0.88 (0.30; 3.20)	0.78 (0.27; 1.94)	3.26 (0.62; 7.86)	0.01
Heart rate at admission (n/min)	91 (75; 110)	90 (75; 110)	100 (81; 115)	0.30
Systolic blood pressure at admission (mmHg)	85 (78; 102)	85 (79; 100)	85 (74; 110)	0.88
History of hypertension, *n* (%)	122 (71)	104 (74)	18 (58)	0.08
Hypercholesterolemia, *n* (%)	55 (32)	44 (31)	11 (36)	0.64
Diabetes mellitus, *n* (%)	62 (36)	54 (38)	8 (26)	0.19
Known peripheral artery disease, *n* (%)	21 (12)	19 (14)	2 (7)	0.28
Prior myocardial infarction, *n* (%)	37 (22)	35 (25)	2 (7)	0.02
Prior PCI, *n* (%)	32 (19)	30 (21)	2 (7)	0.06
Prior CABG, *n* (%)	10 (6)	9 (6)	1 (3)	0.50
Prior stroke, *n* (%)	14 (8)	11 (8)	3 (10)	0.73
TIMI-flow <3 after PCI, *n* (%)	44 (26)	31 (22)	13 (45)	0.01
Randomized to IABP, *n* (%)	87 (51)	69 (49)	18 (58)	0.36
Coronary 3-vessel disease, *n* (%)	89 (52)	75 (53)	14 (45)	0.42
Cardiopulmonary resuscitation, *n* (%)	64 (37)	51 (36)	13 (42)	0.55
Mechanical ventilation, *n* (%)	89 (52)	73 (52)	16 (52)	0.99

BMI body mass index, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *TIMI* thrombolysis in myocardial infarction, *IABP* intra-aortic balloon pump

Table 2 Logistic regression analysis for prediction of the occurrence of hypoxic hepatitis in cardiogenic shock

	Univariable			Multivariable stepwise			
	OR	95% CI	p value	Wald	OR	95% CI	p value
Age per 10 years	0.92	0.68–1.24	0.57				
Admission serum creatinine per 100 mmol/l	1.73	1.11–2.70	0.02	–	–	–	–
Admission serum lactate per 5 mmol/l	2.67	1.66–4.28	<0.001	12.4	2.44	1.48–4.01	<0.001
Admission creatine kinase per 1 mmol/l	1.01	1.00–1.02	0.07	–	–	–	–
History of arterial hypertension	0.49	0.22–10.52	0.001	–	–	–	–
Prior AMI	0.21	0.05–0.92	<0.001	–	–	–	–
TIMI <3 following PCI	2.86	1.24–6.57	0.01	4.5	2.63	1.07–6.44	0.03
Admission troponin T per 10 ng/L	1.38	0.94–2.05	0.10				
Randomization to IABP	1.44	0.66–3.17	0.36				
Prior resuscitation	1.27	0.58–2.81	0.55				
Mechanical ventilation at admission	0.99	0.46–2.16	0.99				

AMI acute myocardial infarction, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction, *IABP* intra-aortic balloon pump, *OR* odds ratio, *CI* confidence interval

30-day mortality. After multivariable adjustment baseline ASAT remained an independent predictor of 30-day mortality together with serum lactate and serum creatinine (Table 4).

Then, the different laboratory values were compared using ROC analysis and the area under the curves (Fig. 2; Table 5). Using this model, classical liver function tests were confirmed to be superior to the new laboratory values.

Table 3 Liver serum markers of comparing survivors and non-survivors on day 1 and day 2 of the treatment as well as serum markers comparing patients with and without hypoxic hepatitis

	N	Overall cohort	30-day survivors	30-day non-survivors	*p* value	Hypoxic hepatitis	No hypoxic hepatitis	*p* value
ALAT (µmol/l*s)								
Day 1	172	0.82 (0.43; 1.65)	0.71 (0.37; 1.36)	0.95 (0.60; 2.56)	0.007	4.03 (1.11; 19.5)	0.71 (0.39; 1.24)	<0.001
Day 2	145	0.87 (0.54; 1.53)	0.74 (0.47; 1.35)	1.24 (0.66; 2.05)	0.008	3.75 (1.75; 11.2)	0.72 (0.45; 1.21)	<0.001
ASAT (µmol/l*s)								
Day 1	172	2.7 (1.1; 5.8)	2.0 (1.0; 4.1)	3.9 (1.6; 9.1)	<0.001	12.7 (6.1; 34.9)	2.1 (1.0; 3.9)	<0.001
Day 2	145	4.4 (2.0; 8.3)	4.0 (1.8; 7.0)	5.3 (3.7; 14.0)	0.003	15.3 (12.9; 30.8)	3.9 (1.8; 6.2)	<0.001
GLDH (µmol/l*s)								
Day 1	172	193 (72; 591)	148 (65; 486)	242 (91; 850)	0.03	872 (286; 3668)	139 (66; 384)	<0.001
Day 2	145	157 (65; 454)	120 (52; 378)	238 (117; 622)	0.002	638 (310; 8301)	120 (55; 258)	<0.001
ASS1 (pg/ml)								
Day 1	169	113 (53; 256)	112 (54; 267)	119 (53; 254)	0.61	158 (53; 302)	110 (56; 235)	0.28
Day 2	146	18 (5; 56)	17 (6; 51)	18 (3; 63)	0.75	14 (5; 50)	20 (5; 58)	0.79
SUL (µg/ml)								
Day 1	169	0.70 (0.35; 1.34)	0.68 (0.35; 1.32)	0.74 (0.35; 1.43)	0.99	1.12 (0.50; 1.98)	0.65 (0.34; 1.22)	0.01
Day 2	146	0.69 (0.32; 1.32)	0.69 (0.34; 1.34)	0.67 (0.31; 1.18)	0.69	1.01 (0.47; 1.73)	0.62 (0.31; 1.28)	0.11

ALAT alanine-aminotransferase, *ASAT* aspartate-aminotransferase, *GLDH* glutamate-dehydrogenase, *ASS1* Argininosuccinate synthase 1, *SUL* sulfotransferase isoform SULT2A1

Comparing ALAT, ASAT and GLDH to each other, there was no statistical difference regarding the prediction of mortality. However, the highest area under the curve was calculated for ASAT.

Discussion

The major findings of our study can be summarized as follows: (1) HH occurs in approximately every fifth patient in CS and is associated with particularly poor outcome, (2) as conventional biomarker, ASAT is the strongest laboratory predictor of outcome while newer proposed biomarkers failed to predict outcome. Of note, after multivariable adjustment ASAT, serum lactate and serum creatinine revealed to be independent predictors of 30-day mortality.

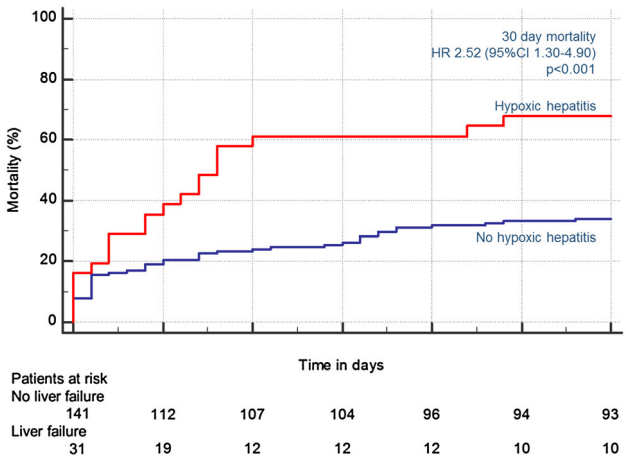

Fig. 1 Kaplan–Meier curves indicating the prognostic relevance of the incidence of hypoxic hepatitis in cardiogenic shock as defined by an increase of aminotransferase levels ($p < 0.001$)

The central dilemma of CS is the fact that it is not simply a decrease in cardiac contractile function, but also a MODS as consequence of peripheral hypoperfusion with microcirculatory dysfunction [20, 21], often complicated by a systemic inflammatory response syndrome (SIRS). Dysfunctional organs contribute to a further impairment of renal function, a dysfunctional intestinal barrier or respiratory failure [22]. Therefore, the central treatment aim of pharmacological therapy as well as mechanical support is to maintain adequate perfusion and to prevent irreversible end-organ failure [23, 24].

An organ which is also prone to fail in CS is the liver, resulting in HH. This organ failure may be induced by hemodynamic instability or arterial hypoxemia in critically ill patients. In recent registries, the incidence of HH has been estimated to be at 1–11% of all patients admitted to intensive care units [11, 25, 26]. The most common cause of HH is cardiogenic or septic shock and most frequently these patients are characterized by other organ failures. Most importantly, HH represents an independent predictor of poor outcome as indicator of markedly compromised patients, but also by mediating several complications such as hepatopulmonary syndrome and hypoglycemia [27]. Of note, the current literature lacks a comprehensive description of acute heart failure and CS effects on the liver. Van

Table 4 Logistic regression analysis for prediction of the primary endpoint (30-day mortality)

	Univariable			Multivariable stepwise			
	OR	95% CI	*p* value	Wald	OR	95% CI	*p* value
Baseline ALAT*	2.38	1.29–4.42	0.006	–	–	–	–
Baseline ASAT*	3.26	1.69–6.28	<0.001	8.1	3.10	1.42–6.75	0.004
Baseline GLDH*	1.63	0.98–2.72	0.06	–	–	–	–
Baseline ASS-1*	1.17	0.67–2.02	0.59				
Baseline SUL*	0.96	0.51–1.80	0.90				
Age per 10 years	1.29	1.01–1.66	0.04	–	–	–	–
Heart rate per 10/min	1.10	0.97–1.25	0.98				
Systolic blood pressure per 10 mmHg	0.95	0.81–1.10	0.47				
Diabetes mellitus	1.13	0.60–2.12	0.71				
Body mass index per kg/m^2	1.03	0.96–1.10	0.42				
Admission serum lactate*	8.02	2.76–23.33	<0.001	4.7	3.64	1.13–11.75	0.03
Admission serum creatinine*	17.78	3.22–98.21	0.001	5.0	8.68	1.32–57.31	0.02
Randomized to IABP	0.83	0.45–1.53	0.55				
Prior stroke	2.94	0.94–9.19	0.06	–	–	–	–
Male sex	0.73	0.38–1.42	0.36				
Coronary three-vessel disease	1.52	0.82–2.81	0.18				
TIMI-flow <3 after PCI	2.02	1.01–4.04	0.048	–	–	–	–
Prior resuscitation	1.41	0.75–2.64	0.29				
Mechanical ventilation at admission	1.85	1.00–3.44	0.051	–	–	–	–

ALAT alanine-aminotransferase, *ASAT* aspartate-aminotransferase, *GLDH* glutamate-dehydrogenase, *ASS1* Argininosuccinate synthase 1, *SUL* sulfotransferase isoform SULT2A1, *IABP* intra-aortic balloon pump, *IABP* intra-aortic balloon pump, *TIMI* thrombolysis in myocardial infarction. *OR* odds ratio, *CI* confidence interval

* Per 10LOG

Deursen was able to show that elevated liver function tests mainly indicate higher central venous pressure. However, ASAT showed also the strongest association with low cardiac index [28]. In a review, Samsky and coworkers summarized the pathophysiological liver changes in HF: venous congestion may increase the susceptibility of the liver leading in acute settings such as acute decompensated HF and CS to HH as second hit. The main reasons for hepatic dysfunction are increased hepatic venous pressure, decreased hepatic blood flow and decreased arterial oxygen saturation, all exaggerated in CS [29]. However, abdominal congestion might lead to increased abdominal pressure subsequently leading to impaired liver perfusion as well as dysregulated splanchnic vessel regulation [30].

The overall mortality in a mixed cohort of critically ill patients with HH has been estimated at 50–60% within 1 month, but no recent data are available in current practice in CS.

Our new data now comprehensively show that in a large contemporary study, the incidence of HH was high, namely 18%. These patients were characterized by a distinctly elevated mortality rate (68%). Considering the above-mentioned high mortality rates, this finding is consistent with the current literature on critically ill patients. Contemporary data on patients with liver failure in CS are lacking, older, smaller registries estimate the short-term mortality in acute decompensated heart failure and CS to be around 50% [31]. In addition, it has been shown that an increase in transaminases is associated with poor outcome in these patients [32].

The central diagnostic modality in HH is the determination of aminotransferase levels. In the present analysis, baseline ASAT levels had the highest diagnostic accuracy and remained an independent predictor of outcome even after multivariable adjustment. Therefore, baseline ASAT levels might serve to identify patients characterized by an excessively increased mortality risk. Of note, the proposed new parameters ASS1 and SUL failed to distinguish survivors and non-survivors yielding no prognostic information, although SUL was also increased in patients with HH on day 1. While SUL did not change between 1 and 2, there was a marked decline of ASS1 between 1 and 2. This might indicate a parameter with rapid increase and clearance following hepatic ischemia. Since baseline ASS1 was of no prognostic relevance this does not warrant further investigation in this clinical setting. Preclinical data also indicate rapid dynamics of ASS1 levels [13]; however, this might be of interest in other clinical scenarios. In the current

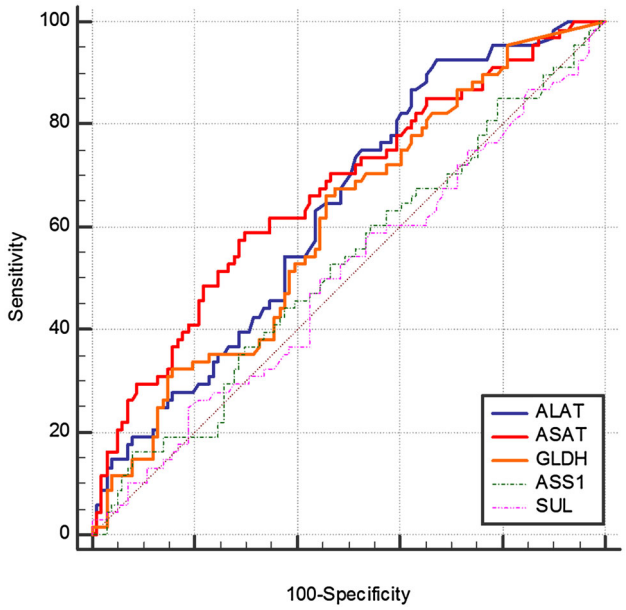

Fig. 2 Receiver operator characteristic curves comparing classical and new parameters regarding the prediction of the 30-day mortality endpoint at baseline. *ALAT* alanine-aminotransferase, *ASAT* aspartate-aminotransferase, *GLDH* glutamate-dehydrogenase, *ASS1* argininosuccinate synthase 1, *SUL* sulfotransferase isoform SULT2A1

Table 5 Comparison of the area under the curve (AUC) using ROC analysis to predict 30-day mortality regarding different liver laboratory values. Conventional biomarkers yield non-significant findings

	AUC	*p* value against AUC	
		ASS-1	SUL
ALAT	0.632	0.06	0.02
ASAT	0.667	0.02	0.003
GLDH	0.604	0.17	0.007
ASS-1	0.523	–	0.70
SUL	0.500		–

ALAT alanine-aminotransferase, *ASAT* aspartate-aminotransferase, *GLDH* glutamate-dehydrogenase, *ASS1* argininosuccinate synthase 1, *SUL* sulfotransferase isoform SULT2A1

study, ASS1 and SUL provided no additional information, although the AUC are rather low also for the conventional liver markers. Although HH might be one important contributor to excess mortality, patients' prognosis is dependent on a number of different pathophysiological processes in CS.

A major problem in HH is that no specific treatment is available. The overall aim in these patients is to restore cardiac output and hemodynamic stability although this is the case also for patients with CS without HH. Still HH, should be taken into consideration while planning fluid balancing since too aggressive diuretic therapy might further decrease hepatic perfusion. An interesting observation has been described by Drolz and coworkers in patients on statin treatment prior to the index admission. Critically ill patients with HH and statin pretreatment had improved 28-day survival compared to patients without statin treatment. However, long-term survival was not positively influenced. This study might suggest that statins mediate protective effects [33], although this needs to be confirmed in additional studies. Another treatment option in case of severe HH is the use of a Molecular Adsorbent Recirculating System (MARS) as extracorporeal liver support device. However, again no larger trials are available and only case reports exist [27]. Nevertheless, this device might help to temporarily bridge the hepatic detoxification function in HH complicated CS. The detoxification process might also help to reduce rates of hepatopulmonary syndrome. Although the exact mechanisms in hepatopulmonary syndrome remain elusive, pulmonary vasodilatation is present due to reduced liver detoxification processes [34]. Another complication in critically ill patients has been brought into connection by Warkentin and Pai. A small minority of critically ill patients with CS, multiorgan failure, and disseminated intravascular coagulation develop symmetrical acral limb loss due to microvascular thrombosis. This has recently been linked with HH [35]. It has been speculated that the profoundly disturbed procoagulant–anticoagulant balance results in uncontrolled generation of thrombin due to the failure of the liver in protein C and antithrombin synthesis as natural anticoagulants. However, as HH precedes the onset of limb ischemia by several days, early therapeutic intervention may be possible [35]. In addition, it is tempting to speculate that also liver function is of prognostic relevance in another context. PCI is a central feature in the treatment of patients with CS and the patency of the revascularized vessel is warranted by dual antiplatelet therapy. Two of the three frequently used substances (clopidogrel and prasugrel) need hepatic activation which is possibly limited due to HH. The use of ticagrelor or the bridging of critical episodes with cangrelor might be useful to bypass liver activity-dependent processes [36].

There are certain limitations of our study that need to be discussed. First, only blood samples on day 1 and day 2 are available in our cohort and the onset of shock until hospital arrival differs as well as pre-hospital treatment. Although it can be expected that the increase in aminotransferase levels occurs until day 2 we cannot exclude that these levels might have peaked later and led to an underestimation of HH rates. However, baseline levels are available in all patients and indicate the prognostic relevance of liver function tests and help the clinician to identify patients at risk. Second, we did not collect data on baseline statin treatment which might have prognostic relevance in this cardiovascular patient cohort. Third, the investigated

parameters mainly reflect hepatocellular injury and other parameters reflecting liver synthesis function and excretory function have not been investigated but might provide additional information [37]. In addition, no data on bilirubin, alkaline phosphatase, cholinesterase and antithrombin were recorded but might also provide additional information. Fourth, no biopsy has been taken as gold standard to diagnose HH. This should be taken into account in the evaluation of new biomarkers. Fifth, ASAT is also released by cardiac tissue and this might influence the potential to predict outcome in the setting of AMI.

In summary, HH occurs frequently in CS and is associated with particularly poor outcome. As conventional liver biomarker, ASAT is the strongest laboratory predictor of outcome while newer proposed parameters failed in the clinical scenario. Baseline liver function tests might serve as important parameters to identify patients at high risk. Future studies need to investigate the role of HH for several complications including the hepatopulmonary syndrome and the potential therapeutic role of liver detoxification.

Compliance with ethical standards

Funding Supported by Grants from the German Research Foundation, the German Heart Research Foundation, the German Cardiac Society, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte, and the University of Leipzig–Heart Center and by unrestricted grants from Maquet Cardiopulmonary and Teleflex Medical.

Conflict of interest All authors have no conflicts to declare regarding the content of the present study and approved the final version of the manuscript.

References

1. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J (2009) Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. Circulation 119(9):1211–1219. doi:10.1161/CIRCULATIONAHA.108.814947
2. Fengler K, Fuernau G, Desch S, Eitel I, Neumann FJ, Olbrich HG, de Waha A, de Waha S, Richardt G, Hennersdorf M, Empen K, Hambrecht R, Fuhrmann J, Bohm M, Poess J, Strasser R, Schneider S, Schuler G, Werdan K, Zeymer U, Thiele H (2015) Gender differences in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial. Clin Res Cardiol 104(1):71–78. doi:10.1007/s00392-014-0767-2
3. Jung C, Ferrari M, Roediger C, Fritzenwanger M, Goebel B, Lauten A, Pfeifer R, Figulla HR (2009) Evaluation of the sublingual microcirculation in cardiogenic shock. Clin Hemorheol Microcirc 42(2):141–148
4. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM (2002) Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 106(5):562–568
5. Richardt G, Munch G, Neumann FJ, Rauch B, Kurz T (1997) Systemic and cardiac catecholamines during elective PTCA and during immediate PTCA for acute myocardial infarction. Basic Res Cardiol 92(1):52–60
6. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S (2015) Management of cardiogenic shock. Eur Heart J 36(20):1223–1230. doi:10.1093/eurheartj/ehv051
7. Kramer L, Jordan B, Druml Wv, Bauer P, Metnitz PG, Austrian Epidemiologic Study on Intensive Care ASG (2007) Incidence and prognosis of early hepatic dysfunction in critically ill patients—a prospective multicenter study. Crit Care Med 35(4):1099–1104. doi:10.1097/01.CCM.0000259462.97164.A0
8. Jung C, Kelm M, Westenfeld R (2016) Liver function during mechanical circulatory support: from witness to prognostic determinant. Crit Care 20(1):134. doi:10.1186/s13054-016-1312-7
9. Chavez-Tapia NC, Balderas-Garces BV, Meza-Meneses P, Herrera-Gomar M, Garcia-Lopez S, Gonzalez-Chon O, Uribe M (2014) Hypoxic hepatitis in cardiac intensive care unit: a study of cardiovascular risk factors, clinical course, and outcomes. Ther Clin Risk Manag 10:139–145. doi:10.2147/TCRM.S59312
10. Fuhrmann V, Jager B, Zubkova A, Drolz A (2010) Hypoxic hepatitis - epidemiology, pathophysiology and clinical management. Wien Klin Wochenschr 122(5–6):129–139. doi:10.1007/s00508-010-1357-6
11. Fuhrmann V, Kneidinger N, Herkner H, Heinz G, Nikfardjam M, Bojic A, Schellongowski P, Angermayr B, Schoniger-Hekele M, Madl C, Schenk P (2011) Impact of hypoxic hepatitis on mortality in the intensive care unit. Intensive Care Med 37(8):1302–1310. doi:10.1007/s00134-011-2248-7
12. Stravitz RT, Kramer AH, Davern T, Shaikh AO, Caldwell SH, Mehta RL, Blei AT, Fontana RJ, McGuire BM, Rossaro L, Smith AD, Acute Liver Failure Study G, Lee WM (2007) Intensive care of patients with acute liver failure: recommendations of the US Acute Liver Failure Study Group. Crit Care Med 35(11):2498–2508. doi:10.1097/01.CCM.0000287592.94554.5F
13. Svetlov SI, Xiang Y, Oli MW, Foley DP, Huang G, Hayes RL, Ottens AK, Wang KK (2006) Identification and preliminary validation of novel biomarkers of acute hepatic ischaemia/reperfusion injury using dual-platform proteomic/degradomic approaches. Biomarkers 11(4):355–369. doi:10.1080/13547500600775110
14. Prima V, Cao M, Svetlov SI (2013) ASS and SULT2A1 are novel and sensitive biomarkers of acute hepatic injury-A comparative study in animal models. J Liver 2(1)
15. Thiele H, Schuler G, Neumann FJ, Hausleiter J, Olbrich HG, Schwarz B, Hennersdorf M, Empen K, Fuernau G, Desch S, de Waha S, Eitel I, Hambrecht R, Bohm M, Kurowski V, Lauer B, Minden HH, Figulla HR, Braun-Dullaeus RC, Strasser RH, Rochor K, Maier SK, Mollmann H, Schneider S, Ebelt H, Werdan K, Zeymer U (2012) Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock: design and rationale of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial. Am Heart J 163(6):938–945. doi:10.1016/j.ahj.2012.03.012
16. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Bohm M, Ebelt H, Schneider S, Werdan K, Schuler G, Intraaortic Balloon Pump in cardiogenic shock IIti (2013) Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. Lancet 382(9905):1638–1645. doi:10.1016/S0140-6736(13)61783-3
17. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G,

Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebelt H, Schneider S, Schuler G, Werdan K, Investigators I-SIT (2012) Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 367(14):1287–1296. doi:10.1056/NEJMoa1208410

18. Fuernau G, Fengler K, Desch S, Eitel I, Neumann FJ, Olbrich HG, de Waha A, de Waha S, Richardt G, Hennersdorf M, Empen K, Hambrecht R, Jung C, Bohm M, Poss J, Strasser RH, Schneider S, Ouarrak T, Schuler G, Werdan K, Zeymer U, Thiele H (2016) Culprit lesion location and outcome in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial. Clin Res Cardiol. doi:10.1007/s00392-016-1017-6
19. Fuernau G, Poenisch C, Eitel I, de Waha S, Desch S, Schuler G, Adams V, Werdan K, Zeymer U, Thiele H (2014) Growth-differentiation factor 15 and osteoprotegerin in acute myocardial infarction complicated by cardiogenic shock: a biomarker substudy of the IABP-SHOCK II-trial. Eur J Heart Fail 16(8):880–887. doi:10.1002/ejhf.117
20. Jung C, Fuernau G, de Waha S, Eitel I, Desch S, Schuler G, Figulla HR, Thiele H (2015) Intraaortic balloon counterpulsation and microcirculation in cardiogenic shock complicating myocardial infarction: an IABP-SHOCK II substudy. Clin Res Cardiol 104(8):679–687. doi:10.1007/s00392-015-0833-4
21. Jung C, Kelm M (2015) Evaluation of the microcirculation in critically ill patients. Clin Hemorheol Microcirc 61(2):213–224. doi:10.3233/CH-151994
22. Buerke M, Russ M, Prondzinsky R, Werdan K (2009) Infarct-related cardiogenic shock—diagnosis, monitoring and therapy. Intensivmed 46:132–146
23. Jung C, Janssen K, Kaluza M, Fuernau G, Poerner TC, Fritzenwanger M, Pfeifer R, Thiele H, Figulla HR (2016) Outcome predictors in cardiopulmonary resuscitation facilitated by extracorporeal membrane oxygenation. Clin Res Cardiol 105(3):196–205. doi:10.1007/s00392-015-0906-4
24. Jung C, Schlosser M, Figulla HR, Ferrari M (2008) Providing macro- and microcirculatory support with the lifebridge system during high-risk PCI in cardiogenic shock. Heart Lung Circ 18(4):296–298
25. Birrer R, Takuda Y, Takara T (2007) Hypoxic hepatopathy: pathophysiology and prognosis. Intern Med 46(14):1063–1070
26. Raurich JM, Llompart-Pou JA, Ferreruela M, Colomar A, Molina M, Royo C, Ayestaran I, Ibanez J (2011) Hypoxic hepatitis in critically ill patients: incidence, etiology and risk factors for mortality. J Anesth 25(1):50–56. doi:10.1007/s00540-010-1058-3
27. Drolz A, Saxa R, Scherzer T, Fuhrmann V (2011) Extracorporeal artificial liver support in hypoxic liver injury. Liver Int 31(Suppl 3):19–23. doi:10.1111/j.1478-3231.2011.02583.x
28. van Deursen VM, Damman K, Hillege HL, van Beek AP, van Veldhuisen DJ, Voors AA (2010) Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Card Fail 16(1):84–90. doi:10.1016/j.cardfail.2009.08.002
29. Samsky MD, Patel CB, DeWald TA, Smith AD, Felker GM, Rogers JG, Hernandez AF (2013) Cardiohepatic interactions in heart failure: an overview and clinical implications. J Am Coll Cardiol 61(24):2397–2405. doi:10.1016/j.jacc.2013.03.042
30. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, Mullens W (2013) Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol 62(6):485–495. doi:10.1016/j.jacc.2013.04.070
31. Denis C, De Kerguennec C, Bernuau J, Beauvais F, Cohen Solal A (2004) Acute hypoxic hepatitis ('liver shock'): still a frequently overlooked cardiological diagnosis. Eur J Heart Fail 6(5):561–565. doi:10.1016/j.ejheart.2003.12.008
32. Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF Jr, Dorobantu MI, Grinfeld L, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Prescott MF, Edwards C, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin T, Teerlink JR, Investigators R-A (2013) Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. J Am Coll Cardiol 61(2):196–206. doi:10.1016/j.jacc.2012.11.005
33. Drolz A, Horvatits T, Michl B, Roedl K, Schellongowski P, Holzinger U, Zauner C, Heinz G, Madl C, Trauner M, Fuhrmann V (2014) Statin therapy is associated with reduced incidence of hypoxic hepatitis in critically ill patients. J Hepatol 60(6):1187–1193. doi:10.1016/j.jhep.2014.01.019
34. Porres-Aguilar M, Gallegos-Orozco JF (2014) Hepatopulmonary syndrome: Is it time to redefine the MELD exception score for better organ allocation and outcomes? Ann Hepatol 13(4):468–470
35. Warkentin TE, Pai M (2016) Shock, acute disseminated intravascular coagulation, and microvascular thrombosis: is 'shock liver' the unrecognized provocateur of ischemic limb necrosis? J Thromb Haemost 14(2):231–235. doi:10.1111/jth.13219
36. Teng R (2015) Ticagrelor: pharmacokinetic, pharmacodynamic and pharmacogenetic profile: an update. Clin Pharmacokinet 54(11):1125–1138. doi:10.1007/s40262-015-0290-2
37. Kortgen A, Paxian M, Werth M, Recknagel P, Rauchfuss F, Lupp A, Krenn CG, Muller D, Claus RA, Reinhart K, Settmacher U, Bauer M (2009) Prospective assessment of hepatic function and mechanisms of dysfunction in the critically ill. Shock 32(4):358–365. doi:10.1097/SHK.0b013e31819d8204