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International Journal of Cardiology 443 (2026) 133961

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Insulin-like growth factor binding protein 2 (IGFBP-2) as prognostic parameter in infarct-related cardiogenic shock

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ARTICLE INFO

Keywords:
IGFBP-2
Cardiogenic shock
Acute myocardial infarction
Biomarker

ABSTRACT

Background: Cardiogenic shock (CS) caused by acute myocardial infarction (AMI) is a critical condition with high mortality rate. Insulin-like growth factor binding protein 2 (IGFBP-2) is dysregulated in cardiovascular diseases. The purpose of the present study was to investigate the prognostic value of IGFBP-2 in patients with AMI-CS.
Methods: This study is a post-hoc analysis of the randomized multicentre CULPRIT-SHOCK trial. IGFBP-2 levels were measured in serum samples from 423 patients using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Associations of IGFBP-2 with 30-day and one-year mortality were investigated.
Results: Median IGFBP-2 concentration was 415 ng/ml (IQR 274–699 ng/ml). Patients with IGFBP-2 ≥ median demonstrated higher 30-day (54 % vs. 37 %; $p < 0.001$) and one-year mortality (60 % vs. 42 %; $p < 0.001$) compared to the < median group. Higher IGFBP-2 concentrations were associated with increased 30-day and one-year mortality, irrespective of it being analysed as continuous or categorical variable (per 100 ng/ml IGFBP-2, hazard ratio (HR) 1.06; 95 % confidence interval (CI) 1.04–1.09; $p < 0.001$, respectively; IGFBP-2 ≥ vs. < median, HR 1.70, 95 % CI 1.23–2.35, $p = 0.001$ and HR 1.72, 95 %CI 1.27–2.33, $p < 0.001$). Furthermore, IGFBP-2 ≥ median was associated with increased 30-day (HR 1.70; 95 %CI 1.23–2.35; $p = 0.001$) and one-year mortality (HR 1.72; 95 %CI 1.27–2.33; $p < 0.001$), even after adjustment for established prognostic factors.
Conclusions: In AMI-CS, elevated levels of IGFBP-2 were associated with higher mortality at 30 days and one year after admission. IGFBP-2 represents a promising prognostic biomarker and could add value to risk stratification in this high-risk patient cohort, potentially informing early clinical decision-making.

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https://doi.org/10.1016/j.ijcard.2025.133961
Received 27 August 2025; Received in revised form 3 October 2025; Accepted 6 October 2025
Available online 9 October 2025

1. Introduction

Cardiogenic shock (CS) is a critical condition defined by hemodynamic impairment and/or systemic hypoperfusion resulting from cardiac dysfunction of various causes [1,2]. One of the most common aetiologies of CS is acute myocardial infarction (AMI) [3,4]. CS occurs in around 10 % of hospitalized AMI patients, representing the leading cause of death in this patient cohort [5,6]. Despite advances in cardiovascular care, particularly immediate revascularization of the culprit lesion, mortality rates of CS complicating AMI remain high, ranging around 40–50 % within 30 days [5]. Clinicians in advanced healthcare systems often face the dilemma of choosing between advanced treatment options, such as mechanical circulatory support devices, and implementing reasonable therapy limitations. Thus, fast and precise risk stratification is crucial for decision making in acute clinical settings. To date several risk scores containing clinical or hemodynamic features or laboratory parameters, have been proposed. Whereas, some of them, such as Simplified Acute Physiology Score (SAPS II), were developed for an unselected cohort of critically ill patients, also scores for mixed CS populations, such as the CardShock or the Cardiogenic Shock scores, have been previously described [3,7,8]. In AMI-related CS populations, the IABP-SHOCK II score as well as the biomarker-based Cystatin C, Lactate, Interleukin 6, NT-proBNP (CLIP) score have been shown to predict prognosis [9–11]. In addition to these scores, requiring implementation of several parameters, which can be challenging in case of scarce resources at the intensive care unit (ICU), we have previously reported delta-lactate, defined as the change in serum lactate levels within 24 h after ICU admission, as an easy and handy tool for outcome prediction in an unselected ICU population [12]. In the present study, we sought to identify a single biomarker that can be used as a simple risk stratification parameter, in patients with AMI-related CS, as add-on to the general assessment by the treating physician, without the need for additional calculations.

Insulin-like growth factors (IGFs) are peptide hormones, involved in several metabolic signaling pathways, evolutionary mostly controlling growth in relation to nutritional environment and thus regulating glucose up-take, glycogen storage, lipogenesis, and suppression of protein degradation [13,14]. Insulin-like growth factor binding proteins (IGFBP) act as decoy receptor for IGF ligands, thereby modulating their half-life in the bloodstream, the tissue distribution, and interaction with cell receptors [15]. IGFBP-2 is a member of the IGFBP superfamily and is involved in several physiological and pathological processes; inter alia, protective effects in diabetes development or involvement in development of diabetic kidney disease have been shown [16,17]. The potential role of IGFBP-2 as a biomarker in cardiovascular disease is of particular interest due to its involvement in metabolic pathways that may influence cardiac function and recovery. Regarding the cardiovascular system, only few studies have investigated the role of IGFBP-2. In patients with peripheral artery disease elevated IGFBP-2 levels were associated with increased long-term mortality [18]. Our group has previously demonstrated that preprocedural elevated IGFBP-2 in patients receiving transcatheter aortic valve implantation (TAVI) were not only associated with increased 30-day and one-year mortality but also a worse functional outcome [19].

The purpose of the present study was to evaluate the prognostic value of IGFBP-2 in patients with AMI-related CS enrolled in one of the largest randomized CS trials, with the aim of identifying a clinically applicable biomarker for early risk stratification that could potentially guide therapeutic decisions.

2. Methods

2.1. Study population

The present analysis is a post-hoc substudy of the multicentre randomized CULPRIT-SHOCK trial. In this trial, patients with AMI-related CS and multivessel disease were randomized to either percutaneous coronary intervention (PCI) of the culprit lesion only with the option of staged revascularization of non-culprit lesions or immediate multivessel PCI. Overall, 706 patients were enrolled in the trial. CS was defined as a sustained low systolic blood pressure of less than 90 mmHg for >30 min, need for catecholamine support, clinical signs of pulmonary congestion, and signs of poor organ perfusion such as altered mental status, cold and clammy skin or limbs, urine output of <30 ml/h or arterial lactate levels >2 mmol/l. Exclusion criteria included prolonged resuscitation >30 min, absence of heart activity, single-vessel disease, urgent need for bypass surgery, severe cerebral impairment, defined as coma with fixed dilated pupils, non-cardiac causes of shock, shock onset >12 h before randomization, very advanced age, severe renal insufficiency, and other life-limiting conditions (life-expectancy <6 months). Written informed consent was obtained from all participants. The local ethics committee of each site approved the study protocol, which conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Non-randomizable patients with CS were included in the CULPRIT-SHOCK registry. The detailed trial design has been published previously [20]. Blood was collected from the patients at hospital admission before angiography and PCI. EDTA-anticoagulated serum samples were isolated and stored at −80 °C until further analysis. Biobanking samples were available from 423 patients from both randomization groups. IGFBP-2 values in these patients were analysed in the present study.

2.2. IGFBP-2 measurements

IGFBP-2 measurements in patients with available biobanking samples at admission were performed retrospectively. Serum levels of IGFBP-2 were determined using a commercially available enzyme-linked sandwich immunosorbent assay (ELISA) kit (Mediagnost, Reutlingen, Germany) according to the manufacturer's protocol. In short, a 5-point calibration (2–80 ng/ml) and two control levels were applied for quantification of IGFBP-2. Samples (15 μl serum) were diluted (1:21) with dilution reagent and added to a microtiter plate pre-coated with specific antibodies for IGFBP-2. After 1 h the plate was washed and a second antibody, conjugated with streptavidin peroxidase enzyme, was added. After an additional incubation for 30 min at 25 °C and a second washing step the substrate for the enzyme reaction was added. Absorbance were measured at 450 nm. The intensity of the resulting colour was proportional to the IGFBP-2 content of the samples.

2.3. Statistical analysis

Statistical analyses were performed using STATA statistic software (StataNow/BE 18.5). Patients were divided in two groups based on IGFBP-2 values below or above the median level (415 ng/ml). Differences in IGFBP-2 levels between 30-day survivors and non-survivors were compared using Mann-Whitney *U* test. Categorical variables are expressed as numbers (percentage). Chi-Square test was applied to assess differences between groups. For continuous variables, data are presented as median with interquartile-range (IQR) and compared using Kruskal-Wallis test. Univariable and multivariable Cox regression analyses were used to analyse associations of IGFBP-2 with 30-day and one-year mortality and to adjust for potential confounding factors. Due to missing values, only 343 (30-days) and 368 (one-year) patients were analysed in the multivariable regression model. Associations between IGFBP-2 and cardiac biomarkers were assessed using Spearman rank correlation coefficients due to non-normal distribution of biomarker data. Pearson correlations yielded similar results. A *p*-value of <0.05 was considered statistically significant.

3. Results

IGFBP-2 levels were measured and analysed in 423 patients. Median serum concentration of IGFBP-2 in these patients was 415 ng/ml (IQR

274–699 ng/ml). Patients' baseline characteristics are presented in the Table 1. Patients in the IGFBP-2 ≥ median group ($n = 211$) were older ($p < 0.001$) and more often male ($p < 0.001$) than patients in the IGFBP-2 < median group ($n = 212$). The prevalence of arterial hypertension ($p = 0.008$), atrial fibrillation ($p = 0.019$) or a history of heart failure ($p = 0.023$) was higher in the IGFBP-2 ≥ median group, whereas other comorbidities, such as diabetes mellitus, previous myocardial infarction or dyslipidemia did not differ between groups. Patients in both groups had a similar severity of CS, as reflected by similar SAPS II score and initial lactate levels. However, patients in the IGFBP-2 ≥ median group had lower hemoglobin ($p < 0.001$) and higher creatinine ($p < 0.001$) levels (Table 1). Survivors after 30 days displayed significantly lower IGFBP-2 levels than non-survivors ($p < 0.001$; Fig. 1). IGFBP-2 levels showed a moderate correlation with NT-proBNP (Spearman rho = 0.51, $p < 0.001$) and weak correlations with troponin T (rho = 0.17, $p < 0.001$) and left ventricular ejection fraction (rho = −0.15, $p = 0.055$). Results were similar using Pearson correlations.

We analysed 30-day as well as longer-term one-year survival depending on IGFBP-2. As continuous variable, higher IGFBP-2 was associated with increased 30-day as well as one-year mortality (both associations with hazard ratio (HR) 1.06, 95 % confidence interval (CI) 1.04–1.09; $p < 0.001$, per 100 ng/ml IGFBP-2). When analyzing IGFBP-2 as dichotomous variable, patients with IGFBP-2 above the median showed higher 30-day (54 % vs. 37 %; $p < 0.001$) and long-term mortality (60 % vs. 42 %; $p < 0.001$) rates compared to the below median group. In a Cox regression analysis, IGFBP-2 ≥ median was associated with higher mortality after 30 days (HR 1.70; 95 %CI 1.23–2.35; $p = 0.001$) and one year (HR 1.72; 95 %CI 1.27–2.33; log-rank $p < 0.001$; Fig. 2). This association of IGFBP-2 ≥ median and one-year mortality was confirmed in multivariable regression models correcting for SAPS II and lactate (HR 2.10; 95 %CI 1.50–2.93; $p < 0.001$; Table 2) and other possible confounders like age, sex or randomization to culprit-lesion-only vs. multivessel PCI group (HR 1.77; 95 %CI 1.26–2.48; $p = 0.001$; Table 2). There were no significant interaction effects between IGFBP-2 levels and other prognostic factors including serum lactate concentrations, creatinine, SAPS II score, left ventricular ejection fraction, age, sex, previous congestive heart failure, ST-elevation myocardial infarction or randomization group with regard to one-year mortality (Supplementary Table 1). Additional adjustment for the IABP-SHOCK II score did not attenuate the association between IGFBP-2 and one-year mortality (HR 1.062 per 100 ng/ml, 95 %CI 1.036–1.090, $p < 0.001$).

Table 1
Laboratory and clinical patient characteristics according to IGFBP-2 levels.

Parameter	IGFBP-2 < 415 ng/ml	IGFBP-2 ≥ 415 ng/ml	Overall cohort	*p*-value
	Median (IQR)	Median (IQR)	Median (IQR)	
Age	64.0 (56.0–74.0)	73.0 (64.0–79.0)	69.0 (60.0–77.0)	<0.001
Male gender (%)	84 %	68 %	76 %	<0.001
Systolic BP (mmHg)	102 (88–126)	105 (85–125)	103 (87–125)	0.74
Heart rate (bpm)	87 (72–102)	90 (70–112)	89 (70–108)	0.24
SAPS II (pts)	47 (27–69)	53 (37–69)	51 (31–69)	0.11
Afib at admission (%)	8 %	15 %	11 %	0.019
Arterial hypertension (%)	56 %	68 %	62 %	0.008
Diabetes mellitus (%)	30 %	36 %	33 %	0.17
Smoker (%)	28 %	25 %	27 %	0.44
Dyslipidemia (%)	34 %	32 %	33 %	0.56
Previous MI (%)	15 %	15 %	15 %	0.89
Previous heart failure (%)	4 %	10 %	7 %	0.023
Lactate (mmol/l)	3.6 (2.0–7.5)	3.7 (2.0–7.1)	3.7 (2.0–7.4)	0.75
Hemoglobin (g/dl)	8.8 (7.9–9.4)	8.0 (6.8–8.8)	8.4 (7.4–9.2)	<0.001
Creatinine (μmol/l)	104.0 (85.5–128.0)	120.0 (94.0–159.0)	111.0 (91.0–141.0)	<0.001
STEMI (%)	64 %	56 %	60 %	0.089
Use of mechanical support (%)	27 %	28 %	28 %	0.89
CPR during procedure (%)	17 %	16 %	17 %	0.81
Bleeding events (%)	22 %	20 %	21 %	0.72

BP = blood pressure, SAPS = simplified acute physiology score, Afib = atrial fibrillation, MI = myocardial infarction, STEMI = ST elevation myocardial infarction, CPR = cardiopulmonary resuscitation.

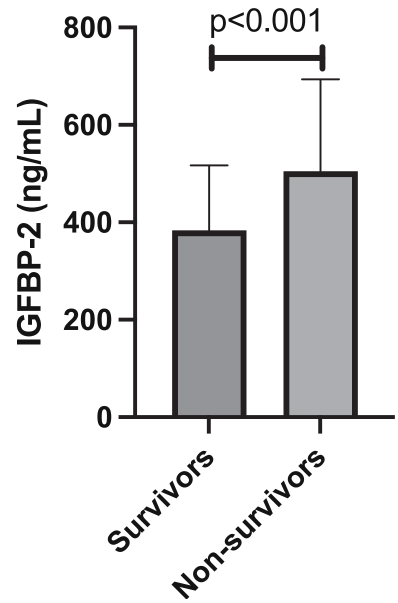

Fig. 1. Box plots showing serum IGFBP-2 concentrations (ng/ml) in patients with acute myocardial infarction-related cardiogenic shock stratified by 30-day survival status. Survivors ($n = 230$) had significantly lower IGFBP-2 levels compared to non-survivors ($n = 193$) with median values of 383.7 ng/ml (IQR 250.5–555.4) versus 505.3 ng/ml (IQR 316.9–774.9), respectively ($p < 0.001$).

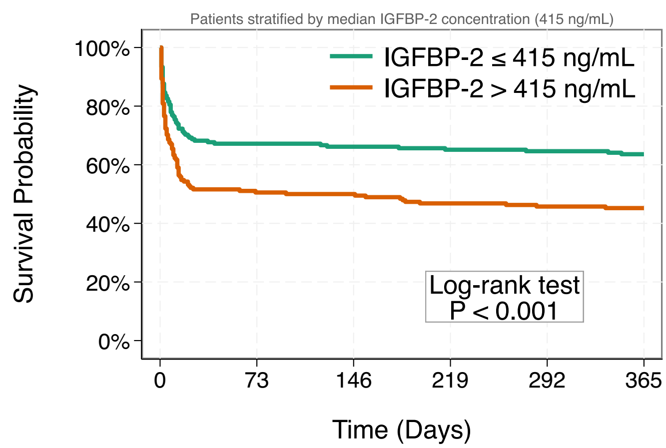

Fig. 2. High IGFBP-2 levels were associated with mortality in patients with AMI-CS. Kaplan-Meier curve showing a significantly lower survival rate in patients with IGFBP-2 serum concentrations above median of 415 ng/ml (HR 1.72; 95 %CI 1.27–2.33; $p < 0.001$).

4. Discussion

In patients with AMI-CS, higher IGFBP-2 levels at admission were

Table 2
IGFBP-2 above median of 415 ng/ml is associated with one-year-mortality after correction for confounders in a multivariable analysis.

Model 1			
Variable	HR	95 %CI	*p*-value
IGFBP-2 ≥ median	2.10	1.50–2.93	<0.001
SAPS II	1.01	1.00–1.01	<0.001
Lactate	1.16	1.11–1.20	<0.001
Model 2			
Variable	HR	95 %CI	p-value
IGFBP-2 ≥ median	1.77	1.26–2.48	0.001
Age	1.03	1.01–1.04	0.002
Male gender	1.40	0.95–2.08	0.095
CHF	0.92	0.54–1.58	0.779
STEMI	0.76	0.55–1.05	0.092
Rand grp (culprit-only)	0.97	0.71–1.32	0.847
Lactate	1.16	1.12–1.21	<0.001

HR = hazard ratio, CI = confidence interval, SAPS = simplified acute physiology score, CHF = chronic heart failure, STEMI = ST elevation myocardial infarction, Rand grp = randomization group.

associated with an increased 30-day and one-year mortality. This association was independent of age, sex or established parameters reflecting the severity of disease such as lactate levels or SAPS II score.

4.1. Risk stratification in infarction-related cardiogenic shock

CS is characterized by high mortality rates despite enormous advances in cardiovascular care in the last decades. Due to heterogeneity of patients and variability of mortality rates in AMI-CS, accurate risk assessment is a crucial task in clinical CS management [9]. Despite several conventional scores proposed for outcome prediction in mixed CS cohorts, novel risk stratification tools are machine learning models, developed from datasets from large studies, possibly allowing a very fast and precise prognosis prediction in different patient cohorts in the future [21,22]. Another approach is the identification of biomarkers predicting the course of disease which may allow targeted drug therapies. For instance, circulating dipeptidyl peptidase 3 (cDPP-3) has been shown to be a prognostic marker in AMI-CS and a specific drug against cDPP-3 is currently under investigation [23,24]. In the present study, we propose a new serum biomarker robustly associated with 30-day and one-year mortality.

4.2. IGFBP-2 as prognostic marker in cardiovascular diseases

IGFBP-2, a component of the somatotropic axis, is the second most abundant circulating IGFBP and influenced by several physiological and pathological conditions [25,26]. Previous studies have demonstrated a correlation between IGFBP-2 levels and insulin sensitivity, proposing it as a marker for the metabolic syndrome [13,27,28]. Furthermore, it plays a crucial role in signaling pathways during critical illness [29]. In the context of cardiovascular system, only few studies have investigated the role of IGFBP-2. In patients with peripheral artery disease (PAD) elevated IGFBP-2 levels were associated with increased long-term mortality [18]. Our group has previously demonstrated that preprocedural elevated IGFBP-2 in patients receiving transcatheter aortic valve implantation (TAVI) were not only associated with increased 30-day and one-year mortality but also a worse functional outcome [19]. In our patient cohort, the median IGFBP-2 concentration of 415 ng/ml was higher than in the mentioned studies with PAD patients (313 ng/ml) or TAVI patients (227 ng/ml) [18,19]. This might be the reflection of the acute state of the AMI-CS patients in our study, whereas patients with PAD had a chronic condition and TAVI procedures were most likely performed in an elective setting. In another single-centre study, including a hemodynamically stable cohort of AMI patients, median IGFBP-2 levels were still lower than in our cohort (e.g. 364 ng/ml in patients with ST-elevation myocardial infarction), suggesting, that not only the acute setting but also hemodynamic deterioration contributes to higher IGFBP-2 concentrations [30]. This is also in line with observations in heart failure (HF) patients: In a study investigating three different cohorts of HF patients, Barutaut and colleagues have found more than double median IGFBP-2 levels in acutely decompensated HF patients than in two chronic stable cohorts (393 ng/ml vs. 165 and 172 ng/ml). Baseline IGFBP-2 levels in healthy individuals vary throughout the literature (e.g. 137,9 ng/ml or 199 ng/ml), but are always considerably lower than in our AMI-CS cohort [30,31].

As IGFBP-2 is involved in multiple molecular pathways, there are several potential mechanisms leading to elevated IGFBP-2 levels in AMI-related cardiogenic shock to consider. Thus, IGFBP-2 has been shown to be increased in critical illness due to cytokine activity [26]. Moreover, it is involved in the PI3K/Akt signaling pathway, which has been shown to play a critical role in the regulation of cardiomyocyte function, growth and survival in myocardial infarction and ischemia/reperfusion injury [32,33]. Finally, IGFBP2 has been shown to increase VEGF expression under oxidative stress, which is known to be involved in several physiological and pathological processes, such as angiogenesis or endothelial function [34,35]. Although further studies are needed to understand the underlying mechanisms of IGFBP-2 elevation in cardiogenic shock, our results suggest it as a possible marker of disease severity and an independent prognostic parameter.

In our cohort, IGFBP-2 levels showed a moderate correlation with NT-proBNP (Spearman rho = 0.51, $p < 0.001$) but only weak correlations with troponin T (rho = 0.17, p < 0.001) and left ventricular ejection fraction (rho = −0.15, $p = 0.055$), suggesting that IGFBP-2 reflects pathophysiological dimensions beyond myocardial necrosis and contractile dysfunction alone. Notably, in multivariable Cox regression models adjusting for age, sex, previous heart failure, STEMI, randomization group, and lactate, IGFBP-2 remained independently associated with one-year mortality after additional adjustment for NT-proBNP (HR 1.057 per 100 ng/ml, 95 %CI 1.021–1.093, $p = 0.001$, $n = 368$) or troponin (HR 1.060, 95 %CI 1.028–1.093, p < 0.001, n = 368). In these models, neither NT-proBNP nor troponin retained independent prognostic significance. Similarly, IGFBP-2 remained predictive after adjustment for the IABP-SHOCK II score (HR 1.062, 95 %CI 1.036–1.090, p < 0.001, $n = 383$). This underscores the unique prognostic value of IGFBP-2, potentially reflecting systemic metabolic derangement, inflammatory response, or other pathophysiological processes characteristic of cardiogenic shock that extend beyond the degree of cardiac injury or hemodynamic impairment captured by conventional parameters.

4.3. Clinical implications and future perspective

In the present study, we showed for the first time the prognostic relevance of IGFBP-2 in AMI-CS. We could clearly demonstrate an additional benefit of IGFBP-2 as outcome predictor to established parameters such as serum lactate, thus, proposing a novel and valuable risk stratification parameter in this cohort. Of note, in the present study we have focused on survival analyses, explicitly showing an add-on effect of IGFBP-2 as predictor of mortality. In the future, risk stratification based on integration of individually assessed biomarkers such as IGFBP-2 in machine learning models, could be a helpful comprehensive approach.

Interestingly, patients in the IGFBP-2 above median group had significantly higher creatinine levels. In previous studies, IGFBP-2 has been found to be increased in patients with chronic kidney disease [36,37]. Ravassa et al. analysed IGFBP-2 levels in patients with heart failure and chronic kidney disease (CKD) and reported increased IGFBP-2 levels in patients with decreased estimated glomerular filtration rate (eGFR) while also demonstrating an association between IGFBP-2 levels and cardiovascular mortality [38]. This is in line with our findings in our AMI-CS patient cohort. However, in the stated work, there was a stronger association between IGFBP-2 levels and cardiovascular death in patients with impaired eGFR [38], whereas in our cohort there was no interaction between IGFBP-2 concentrations and creatinine levels. Furthermore, patients with IGFBP-2 levels above median were significantly older, which is consistent with published literature describing an increase of IGFBP-2 levels with age [39]. Nevertheless, the association of IGFBP-2 with mortality in our cohort remained robust after correction for age.

4.4. Strengths and limitations

One of the main strengths of our study is the relatively large patient number and the multicentre design derived from a large randomized controlled trial (RCT), delivering a high-quality dataset. Nevertheless, the rationale behind an early risk stratification in this vulnerable patient collective is to support clinical decision-making and treatment guiding, and unfortunately, to date, no model or laboratory parameter has shown value for therapeutic selection [11]. Therefore, there is still no consensus on implementing the established scores or parameters into decision-making regarding initiation of mechanical circulators support [11,40]. Furthermore, the two large RCTs on mechanical circulatory support (MCS) use in AMI-CS patients, the DanGer-Shock and ECLS-SHOCK trials have reported differing results, underlining the importance of proper patient selection for this treatment strategy [41,42]. This constitutes one of the main limitations of our and other studies concentrating on risk stratification in CS patients, as it remains unclear how this prognostic information should influence therapeutic decisions. There is a general ethical limitation in relying on biomarker-based prognoses in bedside decision making, possibly running the risk of retraining treatment to certain patient groups. However, we suggest here a reliable marker, which can be combined with further clinical parameters. Implementation of novel biomarkers in CS characterization could be crucial for a better patient selection for prospective trials regarding therapeutic strategies such as MCS. Another limitation is the post-hoc analysis of this originally prospective study, resulting in missing parameters, affecting the analysed sample size. Unfortunately, not all participating sites of this multicentre trial collected biosampling material, which leads to a decreased patient cohort size ($n = 423$) as compared to the original study ($n = 706$) and potential selection bias. Another possible selection bias is the inclusion of only patients with multi-vessel-disease due to the design of the original trial. Furthermore, we do not have any information on the time course of symptom development and hemodynamic worsening prior to presentation at the hospital and therefore cannot provide a correlation of the temporal evolvement of cardiogenic shock with single-point IGFBP-2 measurements.

5. Conclusions

IGFBP-2 was robustly associated with mortality after 30 days and 1 year in patients with AMI-CS. Accordingly, we propose IGFBP-2 as a reliable prognostic biomarker with additional value to other clinical and laboratory parameters. Nevertheless, future prospective studies including IGFBP-2 in prognosis estimation and treatment decision are warranted in order to further evaluate its clinical value.

CRediT authorship contribution statement

Maryna Masyuk: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Bernhard Wernly:** Writing – review & editing, Visualization, Investigation, Formal analysis, Conceptualization. **Malte Kelm:** Writing – review & editing, Supervision. **Anne Freund:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Data curation. **Janine Pöss:** Investigation, Data curation. **Steffen Desch:** Writing – review & editing, Project administration, Investigation, Funding acquisition. **Steffen Schneider:** Writing – review & editing, Investigation. **Ibrahim Akin:** Writing – review & editing, Investigation. **Georg Fürnau:** Investigation. **Uta Ceglarek:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Mara Schemmelmann:** Writing – review & editing, Validation. **Berend Isermann:** Writing – review & editing, Methodology, Investigation. **Norbert Gerdes:** Writing – review & editing, Formal analysis, Conceptualization. **Benedikt Schrage:** Writing – review & editing, Investigation. **Uwe Zeymer:** Writing – review & editing, Investigation. **Petra Büttner:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition, Data curation. **Holger Thiele:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Christian Jung:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Funding

The CULPRIT-SHOCK randomized trial was supported by a grant (FP7/2007–2013) from the European Union 7th Framework Program and by the German Heart Research Foundation and the German Cardiac Society.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.133961.

References

[1] R. Waksman, M. Pahuja, S. van Diepen, W.T. Abraham, et al., Standardized definitions for cardiogenic shock research and mechanical circulatory support devices: scientific expert panel from the Shock academic research consortium (SHARC), Circulation 148 (2023) 1113–1126.
[2] S.S. Naidu, D.A. Baran, J.C. Jentzer, , et al.T.D. Henry, SCAI SHOCK Stage Classification Expert Consensus Update: a review and incorporation of validation studies: this statement was endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) in December 2021, J. Soc. Cardiovasc. Angiogr. Interv. 1 (2022) 100008.
[3] V.P. Harjola, J. Lassus, A. Sionis, G. network., et al., Clinical picture and risk prediction of short-term mortality in cardiogenic shock, Eur. J. Heart Fail. 17 (2015) 501–509.
[4] M.D. Samsky, D.A. Morrow, A.G. Proudfoot, J.S. Hochman, H. Thiele, S.V. Rao, Cardiogenic shock after acute myocardial infarction: a review, JAMA 326 (2021) 1840–1850.
[5] H. Thiele, E.M. Ohman, S. de Waha-Thiele, U. Zeymer, S. Desch, Management of cardiogenic shock complicating myocardial infarction: an update 2019, Eur. Heart J. 40 (2019) 2671–2683.
[6] R.A. Byrne, X. Rossello, J.J. Coughlan, E.S.C.S.D. Group, et al., 2023 ESC guidelines for the management of acute coronary syndromes, Eur. Heart J. 44 (2023) 3720–3826.
[7] A. Granholm, M.H. Moller, M. Krag, A. Perner, P.B. Hjortrup, Predictive performance of the simplified acute physiology score (SAPS) II and the initial sequential organ failure assessment (SOFA) score in acutely ill intensive care patients: post-hoc analyses of the SUP-ICU inception cohort study, PLoS One 11 (2016) e0168948.
[8] B.N. Beer, J.C. Jentzer, J. Weimann, D. Westermann, et al., Early risk stratification in patients with cardiogenic shock irrespective of the underlying cause - the cardiogenic shock score, Eur. J. Heart Fail. 24 (2022) 657–667.
[9] J. Poss, J. Koster, G. Fuernau, S. Desch, et al., Risk stratification for patients in cardiogenic shock after acute myocardial infarction, J. Am. Coll. Cardiol. 69 (2017) 1913–1920.
[10] U. Ceglarek, P. Schellong, M. Rosolowski, H. Thiele, et al., The novel cystatin C, lactate, interleukin-6, and N-terminal pro-B-type natriuretic peptide (CLIP)-based mortality risk score in cardiogenic shock after acute myocardial infarction, Eur. Heart J. 42 (2021) 2344–2352.
[11] E. Lusebrink, L. Binzenhofer, M. Adamo, , et al.H. Thiele, Cardiogenic shock, Lancet 404 (2024) 2006–2020.
[12] M. Masyuk, B. Wernly, C. Jung, Prognostic relevance of serum lactate kinetics: a powerful predictor but not chuck Norris in intensive care medicine, Intensive Care Med. 45 (2019) 1174–1175.
[13] A. Heald, R. Stephens, J.M. Gibson, The insulin-like growth factor system and diabetes–an overview, Diabet. Med. 23 (Suppl. 1) (2006) 19–24.
[14] M. Shin, H.S. Kang, J.H. Park, J.H. Bae, D.K. Song, S.S. Im, Recent insights into insulin-like growth factor binding protein 2 transcriptional regulation, Endocrinol. Metab. (Seoul) 32 (2017) 11–17.

[15] R.C. Baxter, IGF binding proteins in cancer: mechanistic and clinical insights, Nat. Rev. Cancer 14 (2014) 329–341.
[16] S.B. Wheatcroft, M.T. Kearney, A.M. Shah, , et al.P.A. Crossey, IGF-binding protein-2 protects against the development of obesity and insulin resistance, Diabetes 56 (2007) 285–294.
[17] J. Liang, Y. Huang, D. Peng, J. Xu, et al., IGFBP2 and IGFBP4 interact to activate complement pathway in diabetic kidney disease, Ren. Fail. 47 (2025) 2440528.
[18] G. Urbonaviciene, J. Frystyk, S. Urbonavicius, J.S. Lindholt, IGF-I and IGFBP2 in peripheral artery disease: results of a prospective study, Scand. Cardiovasc. J. 48 (2014) 99–105.
[19] J.M. Muessig, M. Lichtenauer, B. Wernly, C. Jung, et al., Insulin like growth factor binding protein 2 (IGFBP-2) for risk prediction in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI), Int. J. Cardiol. 277 (2019) 54–59.
[20] H. Thiele, S. Desch, J.J. Piek, C.-S. Investigators, et al., Multivessel versus culprit lesion only percutaneous revascularization plus potential staged revascularization in patients with acute myocardial infarction complicated by cardiogenic shock: design and rationale of CULPRIT-SHOCK trial, Am. Heart J. 172 (2016) 160–169.
[21] Z. Bai, S. Hu, Y. Wang, , et al.B. Shi, Development of a machine learning model to predict the risk of late cardiogenic shock in patients with ST-segment elevation myocardial infarction, Ann. Transl. Med. 9 (2021) 1162.
[22] E. Zweck, M. Kanwar, S. Li, N.K. Kapur, et al., Clinical course of patients in cardiogenic shock stratified by phenotype, JACC Heart Fail. 11 (2023) 1304–1315.
[23] F.A. Wenzl, F. Bruno, S. Kraler, T.F. Luscher, et al., Dipeptidyl peptidase 3 plasma levels predict cardiogenic shock and mortality in acute coronary syndromes, Eur. Heart J. 44 (2023) 3859–3871.
[24] K. Takagi, A. Blet, B. Levy, A. Kimmoun, et al., Circulating dipeptidyl peptidase 3 and alteration in haemodynamics in cardiogenic shock: results from the OptimaCC trial, Eur. J. Heart Fail. 22 (2020) 279–286.
[25] D.R. Clemmons, D.K. Snyder, W.H. Busby Jr., Variables controlling the secretion of insulin-like growth factor binding protein-2 in normal human subjects, J. Clin. Endocrinol. Metab. 73 (1991) 727–733.
[26] C. Savvidis, E. Kouroglou, E. Kallistrou, I. Ilias, et al., IGFBP-2 in critical illness: a prognostic marker in the growth hormone/insulin-like growth factor axis, Pathophysiology 31 (2024) 621–630.
[27] J. Frystyk, C. Skjaerbaek, E. Vestbo, S. Fisker, H. Orskov, Circulating levels of free insulin-like growth factors in obese subjects: the impact of type 2 diabetes, Diabetes Metab. Res. Rev. 15 (1999) 314–322.
[28] K. Hedbacker, K. Birsoy, R.W. Wysocki, J.M. Friedman, et al., Antidiabetic effects of IGFBP2, a leptin-regulated gene, Cell Metab. 11 (2010) 11–22.
[29] R.C. Baxter, The insulin-like growth factor (IGF)-IGF-binding protein axis in critical illness, Growth Hormon. IGF Res. 9 (Suppl A) (1999) 67–69.
[30] W. Wang, K. Yu, S.Y. Zhao, , et al.H.C. Yao, The impact of circulating IGF-1 and IGFBP-2 on cardiovascular prognosis in patients with acute coronary syndrome, Front. Cardiovasc. Med. 10 (2023) 1126093.
[31] S. Carter, Z. Li, I. Lemieux, , et al.F. Picard, Circulating IGFBP-2 levels are incrementally linked to correlates of the metabolic syndrome and independently associated with VLDL triglycerides, Atherosclerosis 237 (2014) 645–651.
[32] S. Ghafouri-Fard, A. Khanbabapour Sasi, B.M. Hussen, S.A. Ayatollahi, et al., Interplay between PI3K/AKT pathway and heart disorders, Mol. Biol. Rep. 49 (2022) 9767–9781.
[33] R. Mehrian-Shai, C.D. Chen, T. Shi, , et al.C.L. Sawyers, Insulin growth factor-binding protein 2 is a candidate biomarker for PTEN status and PI3K/Akt pathway activation in glioblastoma and prostate cancer, Proc. Natl. Acad. Sci. USA 104 (2007) 5563–5568.
[34] P.I. Imoukhuede, A.O. Dokun, B.H. Annex, A.S. Popel, Endothelial cell-by-cell profiling reveals the temporal dynamics of VEGFR1 and VEGFR2 membrane localization after murine hindlimb ischemia, Am. J. Physiol. Heart Circ. Physiol. 304 (2013) H1085–H1093.
[35] C.S. Facemire, A.B. Nixon, R. Griffiths, H. Hurwitz, T.M. Coffman, Vascular endothelial growth factor receptor 2 controls blood pressure by regulating nitric oxide synthase expression, Hypertension 54 (2009) 652–658.
[36] S. Mahesh, F. Kaskel, Growth hormone axis in chronic kidney disease, Pediatr. Nephrol. 23 (2008) 41–48.
[37] S.M. Feld, R. Hirschberg, Insulin-like growth factor-I and insulin-like growth factor-binding proteins in the nephrotic syndrome, Pediatr. Nephrol. 10 (1996) 355–358.
[38] S. Ravassa, J. Beaumont, G. Cediel, , et al.A. Gonzalez, Cardiorenal interaction and heart failure outcomes. A role for insulin-like growth factor binding protein 2? Rev. Esp. Cardiol. (Engl Ed) 73 (2020) 835–843.
[39] A.W. van den Beld, O.D. Carlson, M.E. Doyle, J.M. Egan, et al., IGFBP-2 and aging: a 20-year longitudinal study on IGFBP-2, IGF-I, BMI, insulin sensitivity and mortality in an aging population, Eur. J. Endocrinol. 180 (2019) 109–116.
[40] T.A. McDonagh, M. Metra, M. Adamo, E.S.C.S.D. Group, et al., 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur. Heart J. 42 (2021) 3599–3726.
[41] H. Thiele, U. Zeymer, I. Akin, E.-S. Investigators, et al., Extracorporeal life support in infarct-related cardiogenic shock, N. Engl. J. Med. 389 (2023) 1286–1297.
[42] J.E. Moller, T. Engstrom, L.O. Jensen, I. DanGer Shock, et al., Microaxial flow pump or standard care in infarct-related cardiogenic shock, N. Engl. J. Med. 390 (2024) 1382–1393.