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ORIGINAL ARTICLE

Validation of a biomarker-based mortality score for cardiogenic shock patients: Comparison with a clinical risk score

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Abstract

Aims Cardiogenic shock (CS) is the deadliest manifestation of acute heart failure, with persistently high mortality rates and a lack of recent therapeutic breakthroughs. Accurate risk prediction is crucial in clinical decision-making and the design of future clinical trials. We aimed to validate the CLIP score, a biomarker-based risk score comprising cystatin C, lactate, interleukin-6 and NT-proBNP, for predicting mortality in acute coronary syndrome (ACS) related CS, and to compare its predictive value with the previously published CardShock risk score.

Methods and results The study is a post hoc analysis of the CardShock Study, a prospective, observational European multicentre study on CS. The CLIP score was calculated 12 h after hospital admission, and its ability to predict 90-day mortality was assessed using are under the curve (AUC) of the receiver-operating characteristics (ROC) curve analysis. The discriminative ability of the CLIP score was compared with the CardShock risk score by comparing the AUC's. The cohort was dichotomized into low and high risk groups by the optimal cut-off value derived from the ROC analysis of the CLIP score. Kaplan–Meier curves were constructed to evaluate risk stratification when combining the CLIP and CardShock risk scores. The cohort (n = 121) comprised 77% (n = 93) men and the median age was 67 years (IQR 61–76). A total of 21% (n = 25) of the patients had non-ACS related CS. The CLIP score demonstrated appropriate predictive accuracy for 90-day mortality (AUC 0.84, 95% CI 0.77–0.91), comparable with the CardShock risk score (AUC 0.77 [95% CI 0.69–0.85]; P = 0.064 for comparison). A CLIP score cut-off of 0.28 stratified patients into high risk (65% mortality) and low risk (16% mortality) groups. In addition, incorporating the CLIP score enhanced risk stratification in all CardShock risk score categories.

Conclusions The CLIP score, calculated within 12 h of hospital admission, accurately predicted 90-day mortality in CS and complemented the CardShock risk score. The biomarker-based score has potential utility in dynamic mortality risk assessment and could inform clinical management and trial design.

Keywords Cardiogenic shock; Biomarkers; Mortality prediction; Risk score

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Introduction

Cardiogenic shock (CS) is the deadliest manifestation of acute heart failure, with in-hospital mortality rates remaining high, ranging from 30% to 50% depending on the aetiology of CS.[1–5] CS is characterized by inadequate cardiac output resulting in hypoperfusion and further multiorgan dysfunction syndrome.[1,5,6] The severity of the symptoms ranges from

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mild hypoperfusion to refractory shock, multiorgan injury, and death.[7]

Accurate risk stratification tools are needed in timely therapy selection[8] and are crucial for therapeutic strategy selection.[9] A few risk scores have been established for predicting mortality risk among CS patients, for example the CardShock risk score,[10] the IABP-SHOCK II score[11] and the Cardiogenic Shock score.[12] These scores' variables consist of clinical variables, angiography findings and biomarker data. The CLIP score, a completely biomarker-based risk score for short-term mortality prediction in ACS related CS, was recently developed in the CULPRIT-SHOCK randomized trial population. Out of multiple candidate biomarkers, the four strongest predictors for short-term mortality were selected: cystatin C, lactate, interleukin-6 (IL-6) and NT-proBNP. The count of the score is the probability between 0 and 1 to die of ACS related CS within the first 30 days following shock.[13]

The aim of our study was to externally validate the CLIP score in a cohort of patients with various aetiologies of cardiogenic shock and to compare its predictive ability in 90-day mortality and clinical usefulness with the CardShock risk score, which is a validated risk score primarily based on clinical variables at admission.

Methods

Study population and outcome

The study is a post hoc analysis of The CardShock Study (NCT01374867), a prospective, observational European multicentre study on CS. The study included patients over the age of 18 years within 6 h after CS establishment. The criteria for CS in addition of an acute cardiac cause were (i) systolic blood pressure $<$90 mmHg for 30 min (despite adequate fluid challenge) or a need for vasoactive therapy to keep systolic blood pressure $>$90 mmHg and (ii) one or more signs of inadequate organ perfusion (confusion or an altered mental status, cool extremities, oliguria $<$0.5 mL/kg/h for the previous 6 h or blood lactate $>$2 mmol/L). The patients with ongoing haemodynamically significant arrhythmias or CS following surgery were excluded. Shock aetiology was determined by local investigators and patients were treated according to local guidelines. Written informed consent was obtained from patients or the next of kin. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki.

A total of 219 patients were recruited from nine centres in eight countries between October 2010 and December 2012. Harjola and Lassus et al.[10] have previously reported the study population in more detail. Demographic data and previous medical history were collected. Clinical and haemodynamic parameters were recorded until 96 h after detection of CS, echocardiography was performed at baseline.

The primary outcome was 90-day mortality. Vital status in the 90-day follow-up was obtained through direct contact with the patient or next of kin, or hospital records and population registries.

Biomarker analysis

Blood was drawn for biochemical analyses at 12–24 h time intervals from baseline up until 96 h after detection of CS. In this analysis, all four biomarkers used in CLIP score calculation were available at 12 h timepoint.[13] Cystatin C and NT-proBNP (Roche Diagnostics, Basel, Switzerland), IL-6 (R&D Systems, Minneapolis, MN, USA) and creatinine (routine automated analyses at ISLAB, Kuopio University Hospital, Finland) were analysed centrally from blood samples stored at −80°C. Arterial blood gas with lactate and glucose were analysed locally. Estimated glomerular filtration rate (eGFR) was calculated from baseline creatinine values using the CKD-EPI equation.[14]

Calculation of the scores

We calculated the CLIP score with the linear predictor equation as published by Ceglarek et al.[13] based on the value of cystatin C, arterial lactate, IL-6 and NT-proBNP at 12 h after study admission. Ninety-eight patients were excluded from calculations due to missing biomarker data, therefore the calculation was done both as complete cases only (n = 121) and by using multiple imputations by chained equations for missing biomarker values (n = 219). The CardShock risk score was calculated from variables at baseline (age, confusion at presentation, previous MI or CABG, ACS aetiology, LVEF, blood lactate and eGFR) as published by Harjola and Lassus et al.[10] and patients were categorized in low-intermediate and high-risk groups accordingly (see also https://cardshock.org).

Statistical analysis

Categorical variables are reported as frequencies and percentages, and statistical differences were analysed using the Pearson's χ^2 test. Continuous variables are reported as the mean and standard deviation (SD), or the median and interquartile range (IQR) and statistical differences were analysed by using the Mann–Whitney U test or Student's t-test, as appropriate.

The area under the curve (AUC) of receiver-operating characteristic analysis (ROC) was calculated to assess the discriminative ability of the scores for 90-day mortality prediction. DeLong's method was used to compare CLIP score with the CardShock risk score. The optimal cut-off value for the CLIP

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score was determined in the ROC analysis by using the Youden's J statistic,[15] categorizing patients in two groups (high/low CLIP score). CardShock risk score low/intermediate/high risk groups were used as previously reported.[10] Kaplan–Meier curves were constructed to visualize the survival of the patients classified by the scores and the log-rank test was used to compare the survival distributions. Goodness-of-fit for the CLIP score alone and in combination with the CardShock risk score was assessed with the Hosmer–Lemeshow's goodness-of-fit test. Likelihood test for nested models was used to determine the added benefit of the combination of the scores.

A *P*-value <0.05 was considered statistically significant. Statistical analyses were conducted by using the IBM SPSS Statistics Version 27 (baseline characteristics, logistic regression, ROC analysis and Kaplan–Meier curves) and Stata/MP 17.0 (comparison of the AUC's).

Results

In the CardShock study cohort, CLIP score could be calculated for 126 patients. Out of these, 121 patients had the data available to calculate both the CLIP score and the CardShock risk score. *Figure 1* illustrates a flowchart of the study cohort and *Table 1* illustrates the baseline characteristics of the patients included in the study. The overall 90-day mortality was 44% (*Figure 2*).

The CLIP score appeared to be an appropriate model for predicting 90-day mortality. In logistic regression, the score has good goodness-of-fit in the population (Hosmer–Lemeshow test $\chi^2(8) = 7.3$, $P = 0.50$). In terms of discrimination, the CLIP score had an AUC of 0.84 (95% CI 0.77–0.91), which was numerically, although not statistically ($P = 0.064$), higher than that of the CardShock risk score (AUC 0.77 [95% CI 0.69–0.85]) (*Figure 3*).

Due to the proportion of excluded patients, we also conducted the ROC analysis for the CLIP score by imputing the missing biomarker data for the excluded patients using multiple imputation by chained equations. This method yielded an AUC of 0.81 (95% CI 0.73–0.89) for the CLIP score ($n = 219$), a result similar to the complete cases only analysis ($n = 121$). When only patients who did not have an ACS aetiology to their CS were included, the CLIP score ($n = 27$) had an AUC of 0.78 (95% CI 0.56–0.99) and the CardShock risk score ($n = 25$) an AUC of 0.85 (95% CI 0.67–1.00).

Based on Youden's J statistic on the patients who had the data available for the calculation of the CLIP score ($n = 126$), the optimal cut-off was identified as a CLIP score of 0.2839

Figure 1 A flowchart of the patient exclusion in this study.

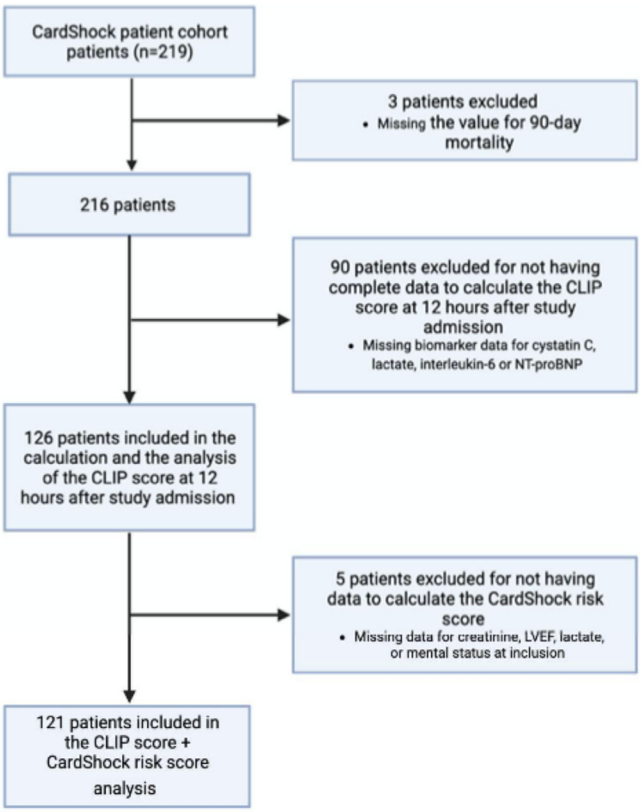

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Table 1 Clinical characteristics, medical history, biochemistry, and outcome of patients with available data for score calculation.

Characteristics	All (n = 121)
Age (years)	67 (61–76)
Female	23% (28)
Patient history of	
Cerebrovascular disease	8% (10)
Myocardial infarction	27% (33)
PCI	15% (18)
CABG	9% (11)
Diabetes mellitus	25% (30)
Congestive heart failure	16% (19)
Atrial fibrillation	15% (18)
Stroke or TIA	7% (9)
ACS aetiology	
ACS	79% (96)
Vitals, clinical findings and laboratory values at inclusion	
Systolic BP inclusion, mmHg	78 (70–85) [1]
MAP inclusion, mmHg	56 (10) [7]
Heart rate, b.p.m.	88 (28) [3]
LVEF inclusion, %	32 (13)
Confusion at inclusion	65% (78)
Oliguria at inclusion	56% (67) [1]
Glucose inclusion, mmol/L	12.3 (6.0) [3]
Cystatin C 12 h, mg/L	1.42 (0.724)
Lactate 0 h, mmol/L	2.6 (1.6–5.2)
Lactate 12 h, mmol/L	1.6 (1.1–2.8)
IL-6 12 h, ng/L	148.1 (75.3–354.9)
NT-proBNP 12 h, ng/L	4505 (1632–11 050)
Treatment	
Resuscitation	31% (38)
Intubation or invasive mechanical ventilation	66% (78) [3]
Angiography	83% (100)
PCI	67% (81)
CABG	2% (2) [1]
LVAD or ECMO	4% (5)
IABP	57% (69)
Outcome	
Death by 90 days	44% (53)
Days alive by 90 days	58 (40)

Baseline characteristics of the patients with data to calculate both the CLIP score and the CardShock risk score (n = 121). Results are given as numbers (percentage), median (IQR) or mean (SD) as appropriate. The number of patients missing the data for a given variable is presented in square brackets.
ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IL-6, interleukin 6; LVAD, left ventricular assist device; LVEF, left ventricle ejection fraction; MAP, mean arterial pressure; PCI, percutaneous coronary intervention, TIA, transient ischaemic attack.

categorizing 55% (n = 69) of patients at high mortality risk, with a 90-day mortality of 65%. Patients with low risk (CLIP score ≤0.2839; 45% (n = 57) of the CardShock population) had a mortality of 16%. Clinical differences between groups are shown in *Table 2*.

The CardShock risk score divides patients into three risk categories (low, intermediate and high mortality risk).[11] Combining the CLIP score (high/low) with the CardShock risk score groups improved risk stratification provided by the CardShock risk score alone. The stratification into subgroups is illustrated in detail in *Figure 3*. In the CardShock low/CLIP low group (n = 37) mortality was 11% whereas the CardShock low/CLIP high group (n = 11) had a mortality of 36%. In the CardShock intermediate group, the CLIP score divided the group into two subgroups with very distinctive mortality profiles: the CardShock intermediate/CLIP low group (n = 13) having 90-day mortality of 31% compared with the CardShock intermediate/CLIP high group (n = 29) having 90-day mortality of 69%. In the CardShock high/CLIP low classification the number of patients was naturally small (n = 5), and their 90-day mortality was low (20%). The patients with a classification of both CardShock high/CLIP high risk (n = 26) had a desolate 90-day mortality rate of 77%. The Kaplan–Meier survival curves for the CLIP score and the CardShock risk score individually and together are shown in the *Figure 4*.

Discussion

This study validates the performance of the CLIP score in an unselected cohort of patients with CS and compares its discriminative ability with the previously validated CardShock risk score. The major findings of this analysis are, that the CLIP score (i) possesses appropriate discriminative ability in other CS aetiologies in addition to ACS, (ii) provides accurate risk prediction in terms of 90-day mortality, with biomarkers measured at 12 h from baseline, and (iii) supplements risk stratification provided by the CardShock risk score.

Mortality risk assessment in CS is a cardinal step in developing better guidelines for treating patients in CS. Previously established risk scores, for example, the CardShock risk score and the IABP-SHOCK II risk score have proven to be good predictors for short-term mortality after CS. The aforementioned scores include variables regarding patients' medical history in addition to subjective clinical variables, and biomarkers such as lactate, renal function markers and glucose measured at baseline. Though the scores perform well, some variables (e.g., the confusion at inclusion in the CardShock risk score and the angiography dependent TIMI flow grade post percutaneous coronary intervention (PCI) in the IABP-SHOCK II score) affect their reproducibility and objectivity.[11,16] Entirely, biomarker-based scores, such as the CLIP score, are promising contestants in the CS mortality risk assessment field, and we took great interest in its validation.

This external validation in the CardShock patient cohort revealed the CLIP score to have good discrimination in predicting 90-day mortality. The CLIP score was able to predict mortality well and seemed to have better discriminatory properties than the CardShock risk score. Our findings further build on the results attained by Ceglarek et al. Their validation analysis found the CLIP score to have superior discrimination in 30-day mortality prediction, when compared with the previously established IABP-SHOCK II score, SAPS II score

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Figure 2 Comparison of ROC-analysis curves for 90-day mortality of the CardShock risk score and the CLIP score (n = 121). The CLIP score yielded an AUC of 0.84 (95% CI 0.77–0.91) and the CardShock risk score an AUC of 0.77 (95% CI 0.69–0.85), P = 0.064 for comparison between models.

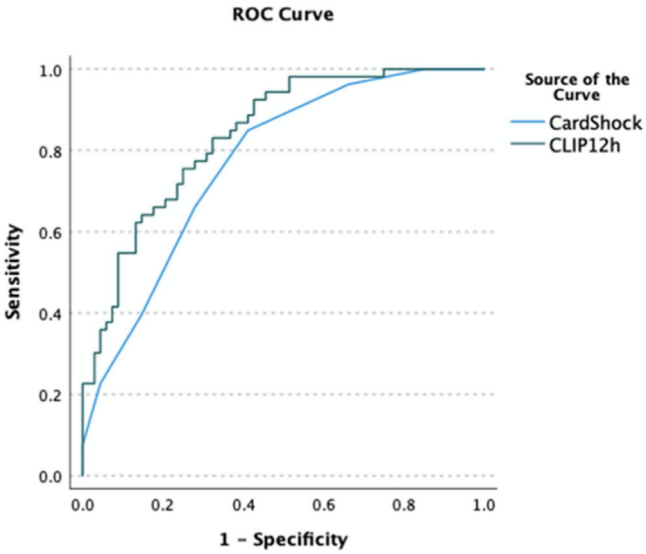
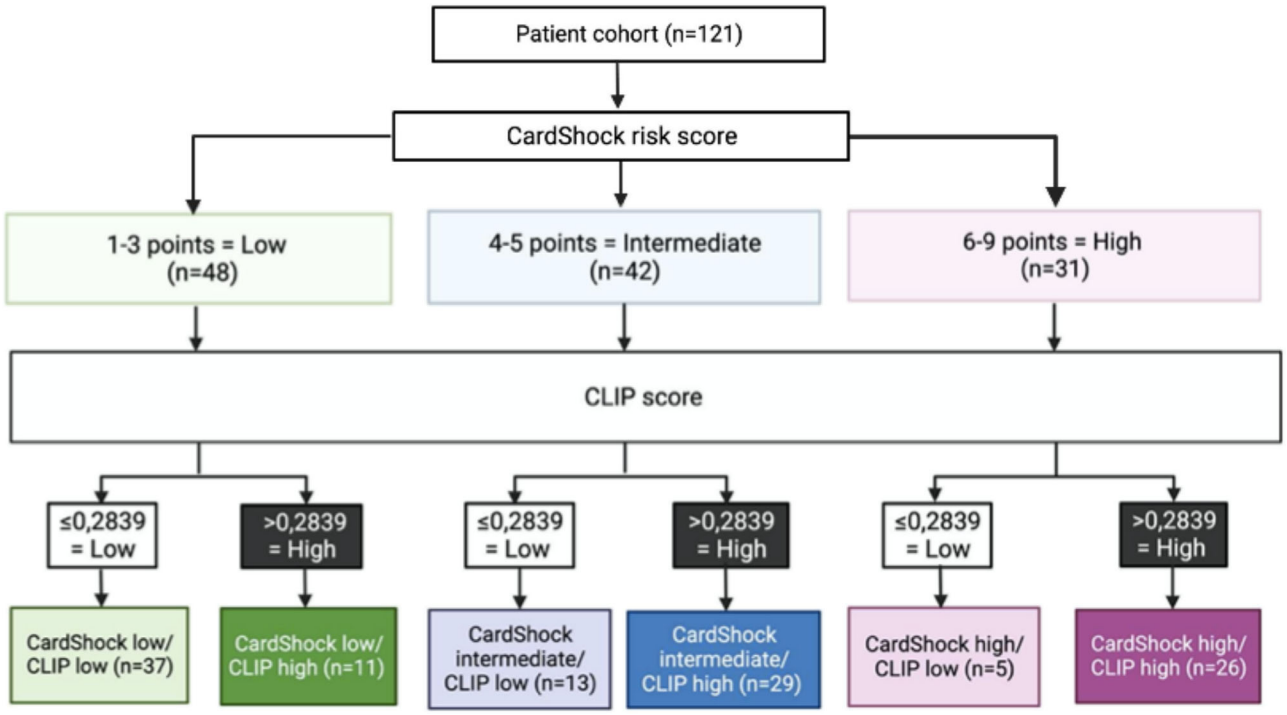


Figure 3 Flowchart of how the patients were classified to six groups according to the CardShock risk score and the CLIP score together.



and the Sleeper score.[13] These results suggest, as of now, that the CLIP score has superior ability of predicting mortality after CS.

As stated by Ceglarek et al., the CLIP score was originally designed to predict the probability of one patient dying of ACS related CS within 30 days. In this substudy, 21% of the patients did not have ACS as their underlying condition for CS. The results of our study suggest good performance in a CS population with mixed aetiology and for predicting mortality at 90 days. Furthermore, recent data suggest that the

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Table 2 Clinical characteristics, medical history, biochemistry, treatment, and outcome stratified by CLIP score value.

Variable	CLIP low (n = 57)	CLIP high (n = 69)	P-value
Age, years	63 (56–72)	70 (63–79)	<0.001
Female	25% (14)	23% (16)	0.9
Patient history of			
Cerebrovascular disease	9% (5)	7% (5)	0.8
Myocardial infarction	21% (12)	30% (21)	0.2
PCI	16% (9)	13% (9)	0.6
CABG	4% (2)	13% (9)	0.06
Diabetes mellitus	14% (8)	35% (24)	0.008
Congestive heart failure	11% (6)	19% (13)	0.19
Atrial fibrillation	9% (5)	19% (13)	0.11
Stroke or TIA	7% (4)	7% (5)	1.0
ACS aetiology	79% (45)	78% (54)	1.0
Vitals, clinical findings and laboratory values at inclusion			
Systolic blood pressure inclusion, mmHg	76 (70–85)	80 (70–85)	0.8
MAP inclusion, mmHg	57 (11) [4]	57 (10) [3]	0.9
Hear rate, b.p.m.	81 (26)	93 (27) [3]	0.01
LVEF inclusion, %	35 (13)	30 (12) [3]	0.02
Confusion at inclusion	53% (29) [2]	73% (50)	0.02
Oliguria at inclusion	36% (20) [1]	72% (49) [1]	<0.001
Glucose at inclusion, mmol/L	10.6 (4.8)	13.3 (6.6) [3]	0.01
Cystatin C 12 h, mg/L	1.0 (0.3)	1.8 (0.8)	<0.001
Lactate 0 h, mmol/L	1.5 (1.1–2.4)	4.0 (2.6–6.9)	<0.001
Lactate 12 h, mmol/L	1.0 (0.8–1.2)	2.7 (1.7–4.1)	<0.001
IL-6 12 h, ng/L	94.4 (52.5–155.0)	258.5 (118.5–444.2)	<0.001
NT-proBNP 12 h, ng/L	1924 (1003–4419)	7338 (3565–21 529)	<0.001
Treatment			
Resuscitation	25% (14)	35% (24)	0.2
Intubation or invasive mechanical ventilation	53% (29)	75% (51) [1]	0.01
Angiography	88% (50)	78% (54)	0.16
PCI	75% (43)	58% (40)	0.04
CABG	4% (2)	3% (2)	0.8
LVAD or ECMO	4% (2)	4% (3)	0.8
IABP	49% (28)	62% (43)	0.14
Outcome			
Death by 90 days	16% (9)	65% (45)	0.01
Days alive by 90 days	80 (26)	40 (40)	<0.001

Baseline characteristics of the patients with data to calculate the CLIP score (n = 126). Patients are classified into low risk (CLIP low, n = 57) and high risk (CLIP high, n = 69) groups. Results are given as numbers (percentage), median (IQR) or mean (SD) as appropriate. The number of patients missing the data for a given variable is presented in square brackets.
ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IL-6, interleukin 6; LVAD, left ventricular assist device; LVEF, left ventricle ejection fraction; MAP, mean arterial pressure; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

CLIP score might have good mortality prediction ability in other conditions in addition to CS.[13] An external validation analysis of the CLIP score by Deniau et al. in the French FROG-ICU cohort revealed that the CLIP score had excellent discrimination for predicting 30-day mortality in all intensive care unit patients, regardless of their cause of admission.[17] This interesting finding suggests that the CLIP score might be an overall good tool for mortality prediction in the critically ill. The association of cystatin C, lactate, IL-6 and NT-proBNP to cardiovascular mortality has been previously extensively reported.[18–25] As they represent the different neurohormonal responses occurring in the body during critical illness, it is therefore rather foreseeable, that this assembly of biomarkers might describe the body's state of distress.

The complete premise of biomarker-based risk scoring relies on the kinetics of the biomarkers following cardiac injury. Due to dynamic nature of biomarker levels, biomarker-based risk scores are sensitive to performance variance, if biomarkers are measured at different timepoints. Both the CLIP score and the CardShock risk score were originally designed to aid in mortality risk assessment immediately upon hospital admission. We have previously demonstrated that while biomarker levels may be rather low at baseline, a considerable rise occurs 12–24 h after baseline assessment.[18,26,27] In the critical care setting, we propose that a more clinically useful application of biomarker-based risk scoring would be after the first-line critical life-saving measures and treatment have taken place. Thus, we assessed and validated the CLIP score for biomarker levels at measured 12 h. Our results suggest that both the CardShock and the CLIP score perform well also after presentation and extend the utility of these scores beyond baseline assessment. More importantly, combining the entirely biomarker-based CLIP score with the CardShock risk score comprising some baseline patient characteristics refines risk stratification within the low, intermediate and high risk strata.

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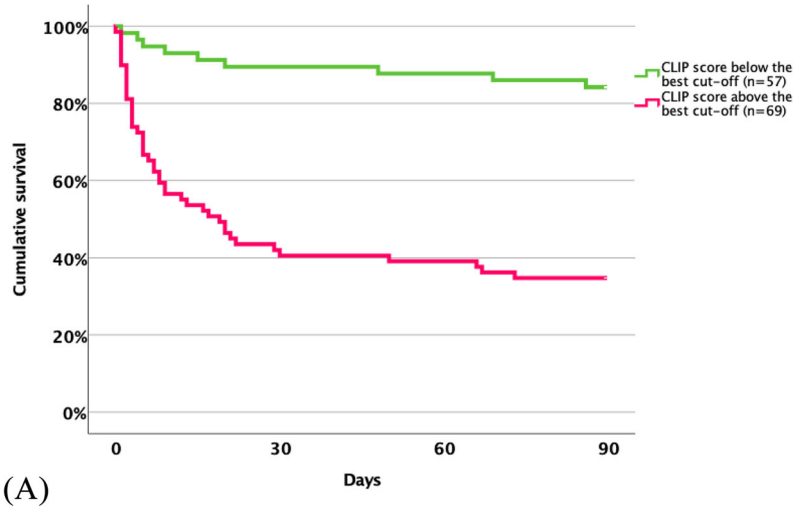
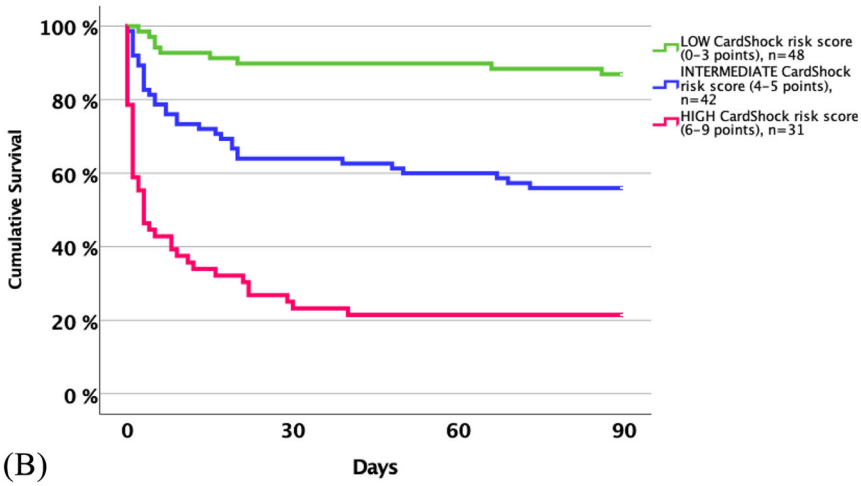
Figure 4 Kaplan–Meier survival curves for 90-day-survival: (A) the CLIP score divided by the best cut-off value in the ROC analysis (0.2839) determined by the Youden's J statistic (n = 126), (B) the CardShock risk score risk groups in this subpopulation and (n = 121), (C) the CLIP score and CardShock risk score together, as illustrated in *Figure 3* (n = 121).



(A)



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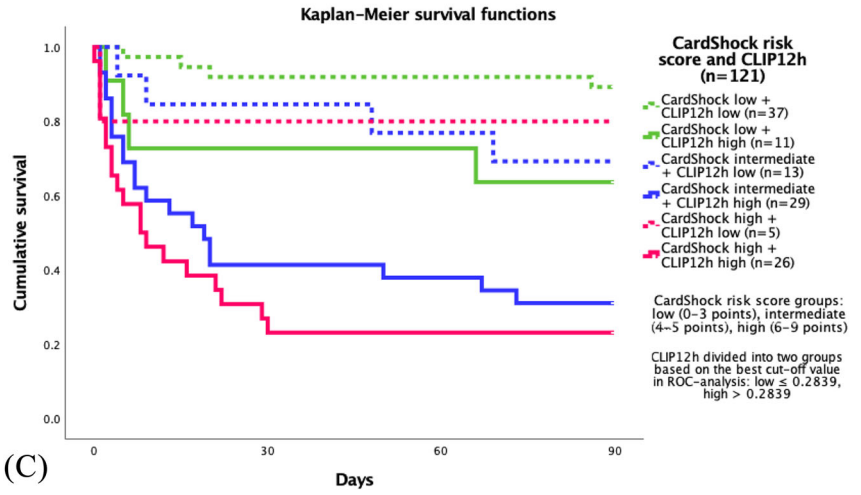

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Risk prediction at a later time-point will inevitably lead to a selection bias due to early deaths in the course of CS, and the performance of both the CLIP and CardShock risk scores will be affected. Still, we see much promise in biomarker-based risk scoring in CS and hypothesize that the maximal benefit lies in dynamically recalculating the risk by repeated biomarker sampling. In addition to offering the ability to re-assess the risk as the clinical situation progresses, dynamic risk scoring also aids with illustrating trends, which might be of even greater prognostic importance compared with a single value calculated upon admission.[28]

The repeatability and objectivity of the biomarker-based scores make them good candidates for dynamic risk scoring, which might give a more realistic picture of the patient's state given the nature of CS as a syndrome with complex pathophysiologic pathways. Further research is needed to establish the most suitable markers for risk stratification and to guide therapeutic decisions.

The CLIP score itself has some drawbacks limiting clinical utility. The equation to calculate the CLIP score requires mathematical software seldom available at the bedside and interpreting the CLIP score is far from easy. As of now, IL-6 is most often not performed around the clock in most hospitals, which hampers the scores clinical applicability in acute settings. As stated previously, the numerical value of the CLIP score is the probability for a patient to die of ACS related CS. Yet there is not any established threshold value as to when a patient is to be interpreted at high or low risk. In this study, we determined the threshold by using the Youden's J statistic in the ROC analysis in our cohort. To make the CLIP score more applicable for interpretation and clinical use, threshold values and/or categories should be established to make the validation and interpretation process more uniform.

Conclusions

In the CardShock cohort, where 21% had non-ACS aetiology of CS, the biomarker-based CLIP score performed well in mortality risk stratification. The results of our validation study extend the utility of the CLIP score to biomarkers measured at 12 hours after detection of CS and for prediction of 90-day mortality. The CLIP score further refines risk stratification provided by the previously established CardShock risk score.

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Conflict of interest statement

None declared.

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