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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

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Background Cardiogenic shock (CS) complicating acute myocardial infarction (AMI) still reaches excessively high mortality rates. This analysis is aimed to develop a new easily applicable biomarker-based risk score.

Methods and results A biomarker-based risk score for 30-day mortality was developed from 458 patients with CS complicating AMI included in the randomized CULPRIT-SHOCK trial. The selection of relevant predictors and the coefficient estimation for the prognostic model were performed by a penalized multivariate logistic regression analysis. Validation was performed internally, internally externally as well as externally in 163 patients with CS included in the randomized IABP-SHOCK II trial. Blood samples were obtained at randomization. The two trials are registered with ClinicalTrials.gov (NCT01927549 and NCT00491036), are closed to new participants, and follow-up is completed. Out of 58 candidate variables, the four strongest predictors for 30-day mortality were included in the CLIP score (cystatin C, lactate, interleukin-6, and N-terminal pro-B-type natriuretic peptide). The score was well calibrated and yielded high c-statistics of 0.82 [95% confidence interval (CI) 0.78–0.86] in internal validation, 0.82 (95% CI 0.75–0.89) in internal-external (temporal) validation, and 0.73 (95% CI 0.65–0.81) in external validation. Notably, it outperformed the Simplified Acute Physiology Score II and IABP-SHOCK II risk score in prognostication (0.83 vs 0.62; $P < 0.001$ and 0.83 vs. 0.76; $P = 0.03$, respectively).

Conclusions A biomarker-only score for 30-day mortality risk stratification in infarct-related CS was developed, extensively validated and calibrated in a prospective cohort of contemporary patients with CS after AMI. The CLIP score outperformed other clinical scores and may be useful as an early decision tool in CS.

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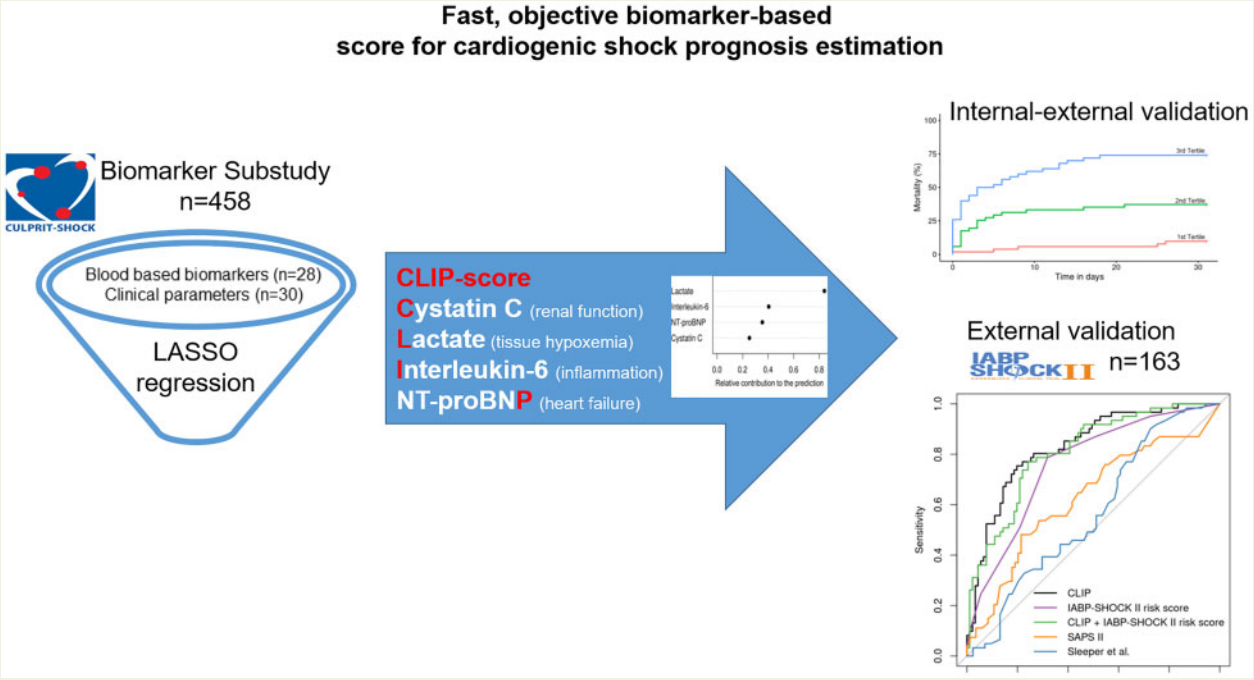
Graphical Abstract



Keywords Cardiogenic shock • Prognosis • Score • Biomarker • Myocardial infarction

Introduction

Cardiogenic shock (CS) is the leading cause of in-hospital death in acute myocardial infarction (AMI).[1] Although early revascularization by percutaneous coronary intervention (PCI) is considered standard of care and mechanical circulatory support (MCS) has been used more frequently in the last years, mortality rates still reach up to 50%.[1] Due to the large heterogeneity of the CS population, the individual risk of mortality is highly variable. Currently, decisions around management of patients presenting with CS involve mostly clinical acumen, linked to clinical experience of multidisciplinary CS teams—an approach which is supported to some degree by registry studies showing improved outcomes.[2] Estimation of the individual patient's prognosis is crucial for further treatment decisions such as more aggressive interventions including MCS or also de-escalation because of futility. In addition, better risk stratification of populations is required to conduct clinical studies in CS to tailor more precisely targeted treatment and to increase comparability of different studies.

Multiple risk scores exist to predict mortality in patients with CS. However, there is need for multiple input variables including clinical, angiographic, and biomarker parameters, which reduces their clinical applicability.[3–5] Although these scores can provide mortality risk stratification, they failed so far to provide meaningful characterization of CS severity in a way that can be easily communicated between providers and inform treatment decisions. In addition, no trial exists to determine the effects that overall illness severity may have on the risk-benefit profile of available therapeutic interventions.

Based on these considerations, the aim of this analysis was to improve early risk stratification in CS complicating AMI by developing and validating an easily applicable and objective risk score that includes the prognostically most important biomarkers. The project was performed in accordance with existing statistical frameworks.

Methods

Study population

The CULPRIT-SHOCK trial randomly assigned 706 patients with multivessel coronary artery disease, AMI and CS either to culprit-lesion-only PCI or immediate multivessel PCI. In brief, the trial showed a reduction in the composite primary endpoint of all-cause death or renal replacement therapy at 30 days in favour of the culprit-lesion-only PCI group which was mainly driven by a reduction in all-cause death.[6] The study was conducted according to the Declaration of Helsinki and written informed consent including blood sampling for laboratory analyses was obtained with the use of a pre-specified process. The predefined biomarker substudy incorporated all patients who underwent blood sampling for core laboratory analysis ($n = 458$). These patients from 54 centres in Europe served as the model development cohort. The baseline variables for the

CULPRIT-SHOCK biomarker substudy in comparison with patients without blood sampling for core laboratory analysis are shown in Supplementary material online, *Table S1*. For external validation of the prediction model, 163 patients from the randomized IABP-SHOCK II trial with baseline blood samples were available. In this randomized trial, intra-aortic balloon pump (IABP) support was compared with no IABP support in patients with AMI-related CS. There were no significant differences between the two treatment groups with respect to short- and long-term outcomes.[7,8] In both trials, 30-day mortality was among the primary or secondary outcomes.[6,8]

Biomarker analysis

Ethylenediaminetetraacetic acid (EDTA) and heparinized blood as well as serum were drawn in the catheterization laboratory according to a predefined standardized pre-analytical protocol for processing and storage during the initial PCI and on the three following days. Samples were centrifuged at 2200 *g* within 60 min, aliquoted, stored, and shipped at -80°C to the core laboratory at the University of Leipzig. For a detailed description of the biochemical methods, see Supplementary material online, *Table S2*.

Blood sampling in the IABP-SHOCK II population has been reported previously.[9,10] Lactate values were centre-derived and obtained from the case report form. Cystatin C, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and interleukin-6 were analysed from serum and lithium-heparin plasma stored at –80°C in the core laboratory.

Statistical analyses, model development, and validation

Model development

A detailed description of the statistical methods can be found in the Supplemental material online. For model development, we considered 30 clinical characteristics as well as 28 blood biomarkers as candidate variables. Numeric variables were transformed by area sinus hyperbolicus to achieve normal distribution. Due to the high total number of candidate variables ($n = 58$), a penalized multivariable logistic regression technique, Least Absolute Shrinkage and Selection Operator (LASSO), was chosen. Compared with conventional stepwise multivariable regression modelling, this technique enables a more rigid variable selection and is less likely to overestimate the predictive value.[11] For the LASSO regression, the shrinkage parameter lambda has to be defined. Lambda regulates the strictness of the model: the higher the value of lambda, the less candidate variables are included in the model, because more variables are 'penalized' (i.e. excluded). For our final model, lambda was set to yield at least 97% of the predictive power of a model including all 58 candidate variables. Out of all clinical and laboratory candidate variables, the LASSO regression identified those for the most parsimonious risk prediction model with the highest prognostic performance. This resulted in a final model with four predictive variables which is a linear function with the following structure: linear predictor = n + coefficient 1 * variable 1 + coefficient 2 * variable 2 + coefficient 3 * variable 3 + coefficient 4 * variable 4. By applying inverse logit function to this linear predictor, the score count is obtained, which is the probability of 30-day mortality between 0 and 1 (multiplied by 100 as percentage). To calculate the relative contribution to the total predictive performance for each of the four final variables, the coefficients from the CLIP equation were divided by the respective standard deviation. Missing values were completed by multiple imputation.

Model validation, discrimination, and calibration

The model was internally validated using 200 bootstrap samples. For internal–external (temporal) validation the CULPRIT-SHOCK population was non-randomly split by randomization date.[12] The same model was developed in the earlier two-thirds ($n = 306$) and validated in the latter third of the population ($n = 152$). Finally, external validation was performed in 163 patients from the IABP-SHOCK II biomarker substudy.[7,8] A correction term was applied to adjust for the lower mortality of the subset available from the IABP-SHOCK II trial (32.5% vs. 40.2% in the whole IABP-SHOCK II biomarker substudy).[13] The process of development and validation of the predictive model is depicted in *Figure 1*.

Discrimination was assessed by the area under the curve (AUC) of receiver operating characteristic analysis (ROC, c-index or c-statistic). Calibration was evaluated using the intercept and slope of the calibration curve showing the relationship between the observed and predicted 30-day mortality. Clinical usefulness was assessed with decision curve analysis. Kaplan–Meier curves were used to additionally visualize the mortality of the patients stratified by tertiles of predicted mortality. The CLIP score was compared with the Simplified Acute Physiology Score II (SAPS II), the IABP-SHOCK II risk score,[4] and the SHOCK trial score[14] in terms of discrimination (AUC) by DeLong's method.

A multivariable logistic regression was used to study the association of 53 clinical and laboratory variables with 30-day mortality adjusted for age, renal function, diabetes, sex, body mass index, and revascularization strategy (Supplementary material online, *Table S3*).

Statistical analyses

Continuous variables were compared using the Mann–Whitney *U* test and categorical variables were compared using Pearson's χ^2 test. Baseline characteristics were analysed with SPSS® Statistics 20 (IBM, Armonk, NY, USA). All other calculations were performed using R, version 3.4.1. The general framework for development, validation, and reporting of risk prediction models by Steyerberg and Harrell and the TRIPOD Statement was applied.[11,12,15]

Results

Patients and cohorts

Of 706 patients enrolled in the CULRIT-SHOCK trial, data could be evaluated for 701 patients. Out of these, 458 patients could be included in the development of the risk prediction model (*Figure 1*).

Patients without biobanking samples ($n = 237$) were significantly older, had lower values of systolic and diastolic blood pressure, had a higher prevalence of arterial lactate >2 mmol/L and a lower prevalence of procedural success [Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 in the culprit lesion after PCI]. There was no significant difference in all-cause 30-day mortality [43.4% (199/458) vs. 51.1% (121/237), $P = 0.065$; Supplementary material online, *Table S1*].

Table 1 describes the baseline characteristics of the score development cohort (CULPRIT-SHOCK, $n = 458$) and the external validation cohort (IABP-SHOCK II, $n = 163$). Compared with the validation cohort, patients in the development cohort had higher systolic and diastolic blood pressure and less frequently cold, clammy skin and extremities, previous myocardial infarction, and known renal insufficiency. Resuscitation within 24 h before randomization occurred more frequently in the development cohort. Furthermore, lower levels of NT-proBNP and creatinine were present. Procedural success (TIMI flow grade 3 restoration in the culprit lesion) was observed more frequently in the development cohort. The baseline characteristics of the CULPRIT-SHOCK cohorts for the internal–external

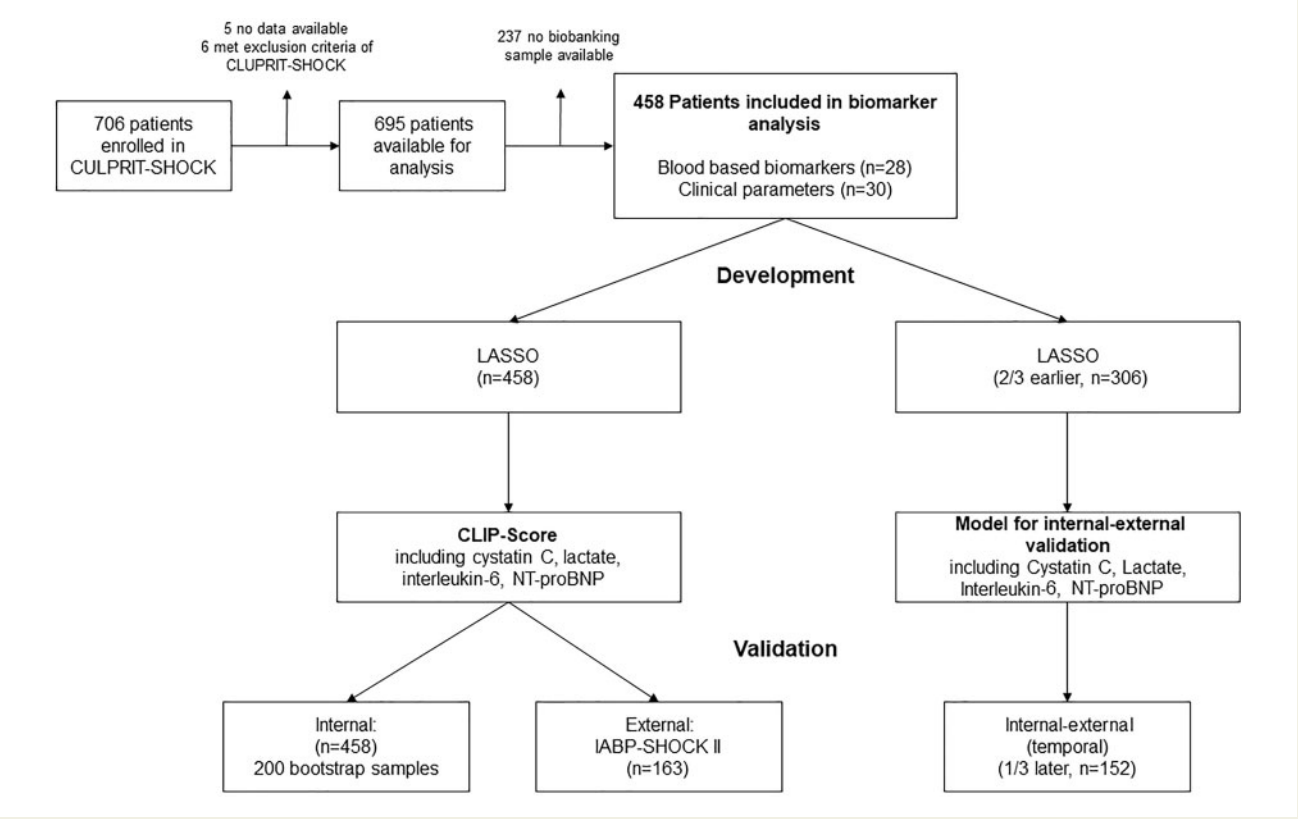


Figure 1 Flowchart of the process of development and validation of the CLIP score. LASSO, Least Absolute Shrinkage and Selection Operator; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(temporal) validation procedure are shown in Supplementary material online, *Table S4*.

Model development and internal validation

By applying the procedure specified before, the regularization parameter lambda was set to 0.12. Hence, the penalized multivariable logistic regression technique revealed four blood biomarkers, namely cystatin C, lactate, NT-proBNP, and interleukin-6 to predict 30-day mortality (*Figure 2A and B*). The 30-day mortality risk of patients in CS complicating AMI can be directly calculated from serum blood concentrations of these four biomarkers, with the equation of the CLIP score (*Figure 2C*). The relative contribution of each parameter to the prediction of mortality is depicted in *Figure 3*.

The internal validation with 200 bootstrap samples of the CULPRIT-SHOCK cohort ($n = 458$) revealed a c-index of 0.82 (95% CI 0.78–0.86). The calibration plot and the decision curve analysis in the whole CULPRIT-SHOCK population are presented in Supplementary material online, *Figures S1* and *S2*.

Internal–external (temporal) validation

The same predictive model based on the four blood-based parameters was developed for internal–external (temporal) validation in the earlier two-thirds of the CULPRIT-SHOCK population ($n = 306$). In the later third of the CULPRIT-SHOCK population, it yielded a c-statistics of 0.82 (95% CI 0.75–0.89). The Kaplan–Meier estimated cumulative event rate by tertiles of predicted risk is depicted in *Figure 4*. The calibration curve and the clinical usefulness assessment according to decision curve analysis in the internal–external (temporal) validation cohort can be found in the Supplementary material online. The model was well calibrated and showed large positive net benefit (Supplementary material online, *Figures S3* and *S4*).

External validation

The CLIP score was externally validated in 163 patients (53 non-survivors, 32.5%) of the IABP-SHOCK II trial. In terms of discrimination, it yielded a c-statistics of 0.73 (95% CI 0.65–0.81). The Kaplan–Meier estimated cumulative event rate, the calibration plot, and the decision curve analysis in the external validation cohort are displayed in Supplementary material online, *Figure S5*.

Comparison of the CLIP score with established risk prediction scores

In the later third of the CULPRIT-SHOCK population ($n = 152$), the discriminative ability (c-statistics) of the CLIP score was significantly higher compared with the SAPS II [0.83 (95% CI 0.77–0.90) vs. 0.62 (95% CI 0.53–0.72), $P < 0.001$], the IABP-SHOCK II score [0.83 (95% CI 0.77–0.90) vs. 0.76 (95% CI 0.68–0.84), $P = 0.03$], and the SHOCK score by Sleeper *et al.*[14] [0.83 (95% CI 0.77–0.90) vs. 0.57 (95% CI 0.47–0.66), $P < 0.001$]. Applying the CLIP score together with the

Table 1 Characteristics of the populations for development (CULPRIT-SHOCK) and external validation (IABP-SHOCK II) of the predictive model

Characteristic	CULPRIT-SHOCK (*N* = 458) Development	IABP-SHOCK II (*N* = 163) External validation	*P*-value
Culprit-lesion-only PCI strategy	52.4 (240)	—	—
Female gender	23.4 (107)	30.7 (50)	0.07
Age (years)	68 (60–77)	71 (59–79)	0.26
Body mass index (kg/m^2)	26.6 (24.6–29.4) [12]	27.3 (24.7–29.4)	0.53
Systolic blood pressure (mmHg)	105 (88–126) [59]	86 (79–106) [2]	<0.001
Diastolic blood pressure (mmHg)	62 (52–80) [62]	56 (48–66)	<0.001
Heart rate (b.p.m.)	90 (71–107) [6]	91 (75–110)	0.27
Resuscitation within 24 h before randomization	54.6 (249)	35.0 (57)	<0.001
Altered mental status	69.5 (317) [2]	71.8 (117)	0.62
Cold, clammy skin, and extremities	67.4 (306) [4]	81.6 (133)	<0.001
Oliguria (≤30 mL/h)	25.0 (113) [6]	31.9 (52)	0.10
pH <7.36	55.8 (252) [6]	60.1 (98)	0.36
Previous myocardial infarction	15.5 (71)	22.7 (37)	0.04
Previous PCI	19.4 (89)	19.6 (32)	>0.99
Previous CABG surgery	5.2 (24)	6.1 (10)	0.69
Previous congestive heart failure	8.1 (37)	—	—
Atrial fibrillation	10.7 (49)	15.3 (25)	0.12
Previous stroke	6.1 (28)	8.6 (14)	0.28
Known peripheral artery disease	10.5 (48)	12.9 (21)	0.39
Known renal insufficiency (eGFR <30 mL/min)	6.1 (28) [1]	28.8 (47)	<0.001
Current smoking	26.6 (121) [3]	29.4 (48)	0.48
Hypertension	61.7 (282) [1]	71.2 (116)	0.04
Dyslipidaemia	32.8 (150) [1]	32.5 (53)	>0.99
Diabetes mellitus	33.3 (152) [1]	35.6 (58)	0.63
Family history of coronary artery disease	12.4 (56) [6]	—	—
ST-segment elevation in ECG	59.6 (268) [8]	57.1 (93)	0.58
Triple vessel disease	64.0 (293)	52.2 (84) [2]	0.01
Procedural success (TIMI flow grade 3 in culprit lesion)	87.8 (389) [15]	75.5 (120) [4]	<0.001
Total amount of contrast dye index PCI (mL)	220 (157–300) [1]	—	—
Total fluoroscopy time index PCI (min)	15.2 (9.2–24.3) [4]	—	—
Haemoglobin (mmol/L)	8.4 (7.5–9.2) [10]	—	—
Haematocrit (%)	40.0 (35.8–44.0) [24]	—	—
White blood cells (Gpt/L)	14.7 (10.6–19.1) [17]	—	—
INR	1.19 (1.08–1.40) [44]	—	—
Lactate (mmol/L)	3.66 (1.99–7.20) [37]	3.70 (2.30–7.00) [2]	0.60
Creatine kinase (μkat/L)	7.02 (3.17–17.46) [25]	—	—
Creatine kinase MB isoform (μkat/L)	1.23 (0.67–2.45) [25]	—	—
Hs-cTnT (pg/mL)	635 (226–1993) [25]	—	—
NT-proBNP (pg/mL)	1380 (280–5275)	3784 (937–10 633)	<0.001
Myoglobin (μg/L)	928 (322–2063) [25]	—	—
Creatinine (μmol/L)	111 (90–141) [25]	118 (96–166) [4]	0.01
Cystatin C (mg/L)	1.26 (1.00–1.59) [25]	1.32 (1.01–1.98)	0.06
Glucose (mmol/L)	11.8 (8.2–16.2)	10.2 (7.7–15.1) [22]	0.07
Sodium (mmol/L)	137 (132–140) [25]	—	—
Potassium (mmol/L)	4.31 (3.79–5.02) [25]	—	—
ALAT (μkat/L)	1.35 (0.67–2.72) [25]	—	—
ASAT (μkat/L)	2.57 (1.18–5.08) [25]	—	—
hs-CRP (mg/L)	5.1 (2.0–21.9) [25]	—	—
Interleukin-6 (pg/mL)	90 (41–281)	78 (31–238)	0.35
Procalcitonin (ng/mL)	0.13 (0.08–0.36) [25]	—	—

Continued

Table I *Continued*

Characteristic	CULPRIT-SHOCK (*N* = 458) Development	IABP-SHOCK II (*N* = 163) External validation	*P*-value
Total cholesterol (mmol/L)	4.30 (3.36–5.06) [25]	—	—
LDL cholesterol (mmol/L)	3.00 (2.10–3.72) [25]	—	—
HDL cholesterol (mmol/L)	0.97 (0.78–1.20) [25]	—	—
Triglycerides (mmol/L)	1.30 (0.99–1.78) [25]	—	—
Copeptin (pmol/L)	216 (98–451) [25]	—	—
GDF-15 (µg/L)	7123 (3428–15 416) [26]	—	—
Angiopoietin-2 (ng/mL)	3.92 (2.53–6.77) [32]	—	—
Soluble ST2 (pg/mL)	45 649 (16 616–141 605)	—	—

Variables are given as median (interquartile range) or percentage (frequency). Numbers in square brackets represent the number of missing values. Where fields are empty, data were not available from the IABP-SHOCK II population.
ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CABG, coronary artery bypass grafting; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; INR, international normalized ratio; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

IABP-SHOCK II risk score did not improve the c-statistic compared with the CLIP score alone [0.81 (95% CI 0.74–0.88) vs. 0.83 (95% CI 0.76–0.90); $P = 0.32$]. The receiver operator characteristics are depicted in *Figure 5*.

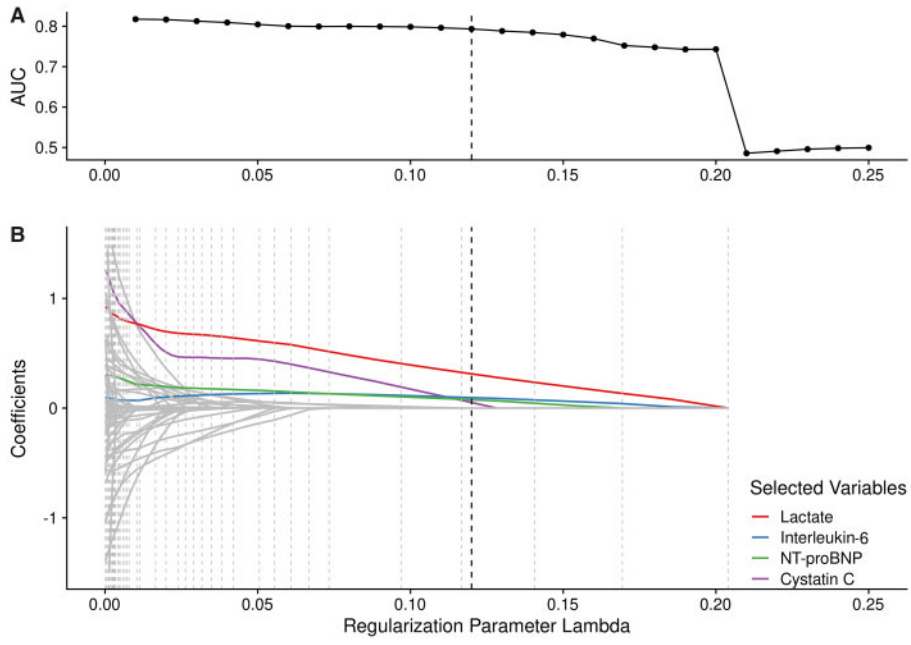
Discussion

The major findings of the current analysis are as follows: (i) a novel blood biomarker-based risk prediction model with the acronym CLIP score (Cystatin C, Lactate, Interleukin-6, NT-proBNP) was developed, predicting the probability of 30-day mortality of patients with CS complicating AMI; (ii) the score was extensively validated, and (iii) outperformed the SAPS II and the IABP-SHOCK II risk score in prognostication.

In CS, early risk prediction is crucial for the decision-making regarding further treatment strategies such as the initiation of MCS or withdrawal of treatment due to futility. Furthermore, correct risk stratification may be helpful for the design of future clinical studies to provide more individualized and tailored treatment and to increase comparability between different trial populations. The mortality risk scores for CS introduced earlier, share limitations such as small sample size, being developed in the pre-PCI era and/or a lack of strong validation.[14,16–18] In the recent past, two mortality prediction models developed from large clinical trials/studies have been published. Harjola *et al.*[3] derived a scoring system from the CardShock study, which is not specifically related to AMI as aetiology of CS. Our group introduced a mortality risk score in CS complicated by AMI from the IABP-SHOCK II trial.[4] The CardShock score has been validated in the IABP-SHOCK II cohort and vice versa. However, both scores include parameters concerning the patients' past medical history (IABP-SHOCK II risk score: history of stroke; CardShock risk score: previous AMI or coronary artery bypass graft surgery). Because of the emergency setting in which the patients are admitted and due to the fact that many patients with CS present with impaired mental status or mechanically ventilated, information on previous diseases is often lacking. Furthermore, the CardShock risk score includes the clinical finding of confusion as well as left ventricular ejection fraction; the IABP-SHOCK II score includes TIMI flow post-PCI. All of these are to a certain extent subjective variables, limiting the objectivity of these scores. More recently, the Society for Cardiovascular Angiography and Interventions (SCAI) classification of CS based on expert consensus has been introduced and validated in two CS cohorts.[5,19,20] However, validation depended on subjective clustering of groups as many variables in the SCAI classification are often not routinely assessed.[5,20] Taken together all previously introduced scores have multiple limitations and are also based in part on subjective parameters.

Studies assessing the prognostic value of different non-subjective biomarkers in CS have been conducted in a single-centre subset of patients from the IABP-SHOCK II trial[9,10,21] as well as in the CardShock population.[22] Rueda *et al.*[23] more recently presented a proteomic approach for mortality risk estimation in CS from the CardShock population. Although the study may provide pathophysiologic insights into CS, it has several limitations, such as small sample size and lack of internal–external and external validation. In addition, the score is not broadly clinically applicable due to the lack of availability of automated measurement of the four selected non-routine proteins.

To the best of our knowledge, the CLIP score is the first in CS to systematically evaluate objective, routinely available as well as novel biomarkers of mortality prediction in AMI (e.g. copeptin[24]) and in CS (e.g. angiopoietin-2,[10] growth differentiation factor-15,[21] and soluble ST2[22]). The major strength of the CLIP score is that it includes only four routinely available biomarkers, which outperformed clinical parameters as well as novel biomarkers. All of the four biomarkers are already established on commercial 24/7 laboratory analysers and should be accessible in dedicated shock centres within a short turnaround time. The availability of *in vitro* diagnostic-approved commercial test kits and external proficiency testing programmes for the four biomarkers makes a lab-independent, standardized measurement, and calculation of the CLIP score feasible. There is no need for considering clinical, PCI-related or anamnestic features and no manual



C

$$Linear\ Predictor = -15.8532036 + 0.6714669 \times \operatorname{asinh}(100 \times \boldsymbol{C}ystatin\ C\ in\ mg/L) + 1.0287073 \times \operatorname{asinh}(100 \times \boldsymbol{L}actate\ in\ mmol/L) + 0.2704829 \times \operatorname{asinh}(100 \times \boldsymbol{I}nterleukine\ 6\ in\ pg/mL) + 0.1923877 \times \operatorname{asinh}(100 \times NT\boldsymbol{p}roBNP\ in\ pg/mL)$$

$$\boldsymbol{CLIP - score} = \frac{e^{Linear\ Predictor}}{1 + e^{Linear\ Predictor}}$$

The count of the CLIP-score is the probability (between 0 and 1) to die of CS complicating AMI within 30 days. To obtain the probability in per cent multiply by 100.

Figure 2 Least absolute shrinkage and selection operator (LASSO) analysis and mathematical equation of the CLIP score. Dependent of the values of the regularization parameter lambda (*x*-axis) the resulting area under the curve (*A*) and the coefficients of the included variables (*B*) are shown. The dashed line marks the finally selected lambda value of 0.12, with the resulting area under the curve of 0.79, and the coefficients of the four selected parameters lactate, interleukin-6, N-terminal-pro B-type natriuretic peptide, and cystatin C. Including more variables by selecting a lower value of lambda (leading to a 'left shift' of the dashed black line) would not substantially improve the model performance (i.e. a relevant increase in area under the curve). (*C*) The CLIP score (i.e. the estimated mortality risk) is the inverse logit function of a linear predictor including the areasinus hyperbolicus (asinh)-transformed serum biomarker concentrations of lactate, interleukin-6, N-terminal pro-B-type natriuretic peptide, and cystatin C and their respective coefficients. AMI, acute myocardial infarction; CS, cardiogenic shock.

scoring must be conducted, leading to a high objectivity of the score (*Graphical abstract*).

The four biomarkers are all involved in the complex pathophysiology of CS. As previously reported, lactate as a determinant of global tissue hypoxaemia was the strongest predictor. The second relevant prognosticator, NT-proBNP, has been widely implemented as a marker of cardiac wall stress in congestive heart failure.[25] Its prognostic relevance in CS has been shown in smaller studies before.[22] In addition, it is pathophysiologically plausible that a stronger degree of heart failure is associated with higher mortality. Thirdly, the proinflammatory cytokine interleukin-6 was a significant determinant of prognosis. This is in line with previous findings showing that systemic inflammation plays a key role in the pathophysiology of CS.[26] The fourth contributing factor in the predictive model is cystatin C. Parameters of renal function have been previously described to have prognostic relevance in CS and are included in the IABP-SHOCK II and in the CardShock risk score.[3,4] Contrary to our results, creatinine was superior over cystatin C for mortality prediction in the IABP-SHOCK II biomarker population.[9] However, our results are in line with previous findings from large studies showing the prognostic superiority of cystatin C over creatinine in a general population meta-analysis and in patients presenting with acute coronary

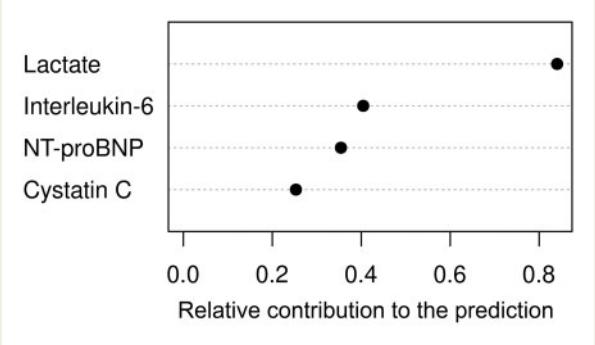


Figure 3 Relative contribution of the four biomarkers in the CLIP score to mortality prediction. The coefficients from the model equation are divided by the standard deviation of their respective biomarkers. Thus, the contribution of each biomarker can be comparatively evaluated independently of its variance. As an example, one standard deviation change in the blood level of lactate affects the prediction twice more than one standard deviation change in the interleukin-6 blood level. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

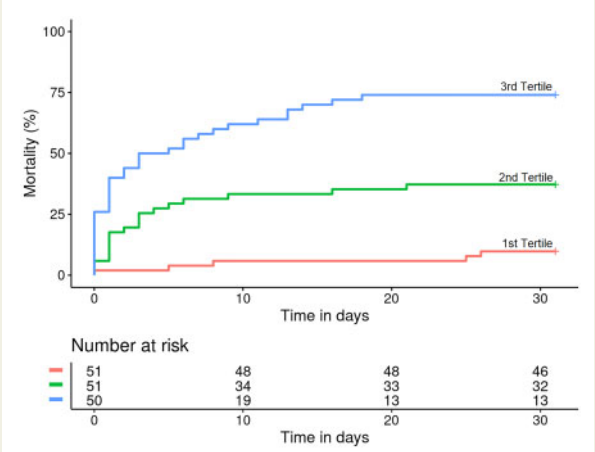


Figure 4 Kaplan–Meier cumulative event rates in the internal–external (temporal) validation cohort. Kaplan–Meier estimated cumulative event rate for 30-day mortality by tertiles of predicted probability.

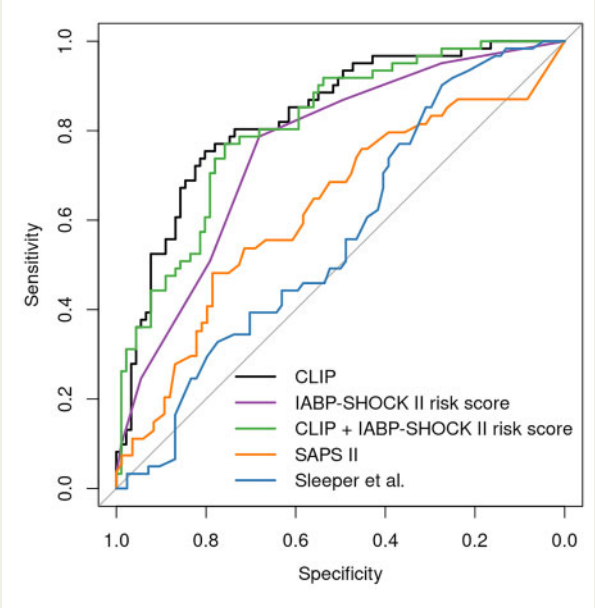


Figure 5 Receiver operating characteristics of the CLIP score, the IABP-SHOCK II score, the SHOCK score (Sleeper *et al.*[14]), and the Simplified Acute Physiology Score II (SAPS II) and the CLIP score together with the IABP-SHOCK II risk score. The receiver operating characteristics of each score were assessed in the internal–external (temporal) validation population (latter third of CULPRIT-SHOCK, $n = 152$).

syndromes.[27,28] Cystatin C may have a higher diagnostic accuracy than creatinine because it is less affected by muscle mass. Furthermore, cystatin C may be involved in inflammatory responses, e.g. by altering the response of macrophages to interferon-gamma.[29] This might partly explain its strong predictive power in the setting of CS.

The CLIP score might also be helpful for clinical decision-making regarding the selection of management strategies (e.g. whether or not to initiate MCS or to withdraw therapy due to futility). However, calculation of a score cannot be the only variable determining such far-reaching decisions, which must take into account many other individual aspects, such as the patient's wish, comorbidities, and the neurological situation. Nevertheless, the CLIP score might provide valuable assistance.

Limitations

One limitation of the present study might be that non-biomarker patients from the CULPRIT-SHOCK trial population showed some features of being more severely ill compared with biomarker patients. Therefore, a differential measurement bias cannot be excluded. However, there was no statistically different 30-day mortality in the non-biomarker population limiting a possible bias. Furthermore, the interpretability of the external validation cohort may be limited: the biomarker sampling was performed in only one centre, the blood samples were slightly older and had undergone repeated freeze-thaw cycles, hampering the pre-analytical conditions. Only 163 from the originally 190 patient blood samples were still available and the mortality rate of these patients was lower than in the whole reported IABP-SHOCK II biomarker population.[9] However, our predictive model still yielded an AUC equal to the one of the IABP-SHOCK II risk in the external validation. To overcome the limitations of the external validation population, we additionally performed internal–external (temporal) validation as proposed in statistical frameworks.[11,12,15] Another limitation with respect to the use of the score may be the turn-over time for laboratory assessment until the results are available.

Conclusion

The new CLIP predictive model in patients with CS complicating AMI, including only four well established blood-based biomarkers (cystatin C, lactate, interleukin-6, and NT-proBNP) can be rapidly and automatically calculated and is therefore easy to implement in clinical practice. It may serve as a tool for risk stratification of CS patients and may thus be helpful for clinical decision-making and for the design of future clinical trials.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability statement

All results presented in this article are in aggregate form, and no personally identifiable information was used for the CULPRIT-SHOCK trial. Individual participant data are not available for sharing.

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