Biomarker zur Mortalitätsprädiktion im infarktbezogenen kardiogenen Schock

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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Einführung

1. Akuter Myokardinfarkt

Der kardiogene Schock (CS) ist die führende Todesursache aufgrund eines akuten Myokardinfarkts (AMI) im Krankenhaus[1]. Gemäß der vierten universalen Definition des akuten Myokardinfarkts werden fünf Typen unterschieden[2] (siehe Abbildung 1).

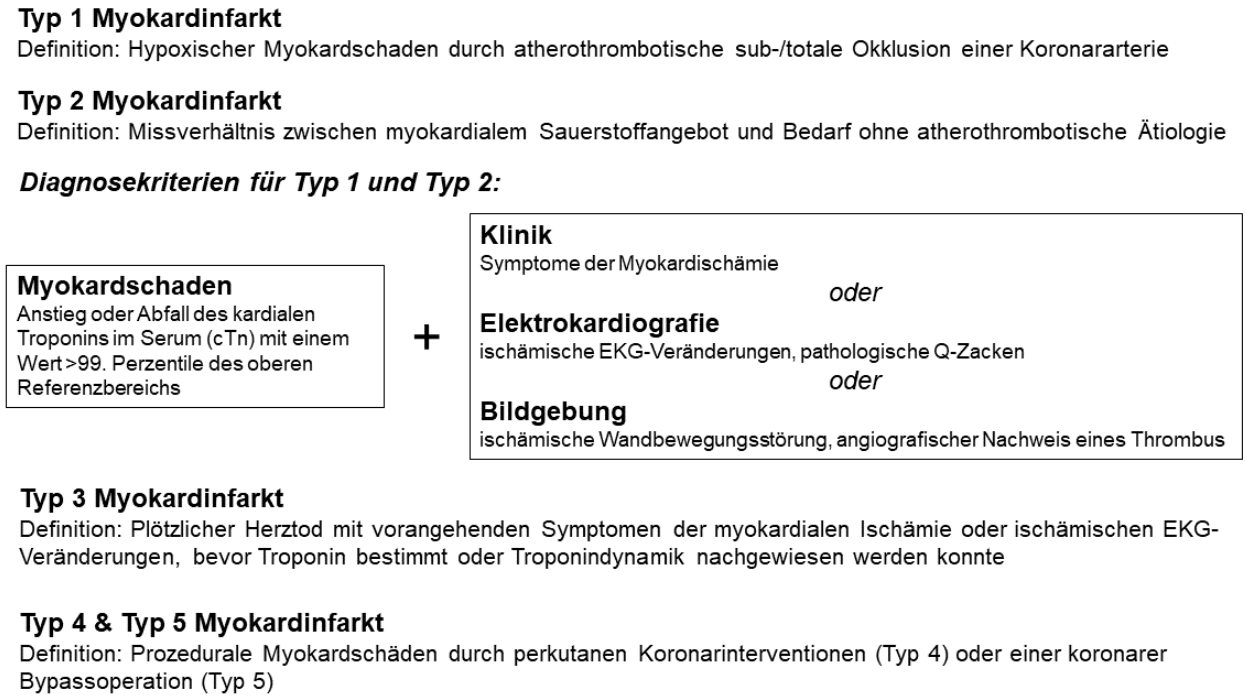

Abbildung 1: Fünf Typen gemäß der vierten universalen Definition des akuten Myokardinfarkts[2].

Typ 1 beschreibt den akuten Myokardinfarkt im klassischen Sinne. Er ist definiert als hypoxischer Myokardschaden ausgelöst durch eine thrombotische totale oder subtotale Okklusion einer Koronararterie aufgrund von Erosion oder Disruption eines Plaques bei atherosklerotischer koronarer Herzkrankheit. Die Diagnosekriterien bestehen einerseits aus dem Nachweis des Myokardschades durch eine Dynamik (Anstieg oder Abfallen) des kardialen Troponins (cTn) aus dem Serum mit einem Wert oberhalb der 99. Perzentile des oberen Referenzbereiches und andererseits einem klinischen (Symptomatik der myokardialen

Ischämie), oder elektrokardiografischen (ischämische EKG-Veränderungen, pathologische Q-Zacken) oder bildgebenden Kriterium (ischämische Wandbewegungsstörung, angiografischer Nachweis eines Thrombus). Typ 2 des akuten Myokardinfarkts ist definiert als Missverhältnis zwischen Sauerstoffangebot und Bedarf, mit den gleichen Diagnosekriterien wie Typ 1, nur, dass sich die myokardiale Ischämie nicht auf eine atherothrombotische Ätiologie zurückführen lässt. Der Typ 3 beschreibt den plötzlichen Herztod mit vorangehenden Symptomen der myokardialen Ischämie oder ischämischen EKG-Veränderungen, bevor eine Blutabnahme stattfinden konnte, oder eine Dynamik des kardialen Troponins nachgewiesen werden konnte. Die Typen 4 und 5 beziehen sich auf prozedurale Myokardschäden im Rahmen einer perkutanen Koronarinterventionen (PCI) oder einer koronarer Bypassoperation (CABG). Diese Arbeit bezieht sich auf den Akuten Myokardinfarkt Typ 1, wenn von einem AMI die Rede ist.

2. Infarktbezogener kardiogener Schock

2.1. Definiton, Ätiologie, Epidemiologie Pathophysiologie, und Klassifikation

Der kardiogene Schock ist definiert als Endorganhypoperfusion und –hypoxie mit kardialer Genese, in diesem Fall aufgrund eines akuten Myokardinfarkts[3]. Für die neueren Studien[4–6] wurde folgende Definition des kardiogenen Schocks verwendet: Hypotonie (systolischer Blutdruck <90mmHg für >30 Minuten oder Katecholaminbedarf, um mindestens 90mmHg aufrechtzuerhalten) und klinische Zeichen der pulmonalen Stauung und mindestens ein Zeichen der verminderten Organperfusion (Vigilanzminderung/Veränderter Geisteszustand, kalte, klamme Haut und Extremitäten, Oligurie mit einer Ausscheidung <30ml/h, oder arterielles Lactat >2,0 mmol/L).

Es gibt mehrere Ätiologien des kardiogenen Schocks (darunter chronische Herzinsuffizienz, Klappenvitien, Obstruktion), wobei die mit Abstand häufigste Ätiologie des kardiogenen Schocks mit circa 80% ein akutes Koronarsyndrom (ACS) ist, im Sinne eines ST-Hebungsmyokardinfarkts (STEMI) oder Nicht-ST-Hebungsmyokardinfarkts (NSTEMI)[7,8] als Ausdruck eines Akuten Myokardinfarkts des Typs I gemäß oben genannter Definition.

Die Inzidenzraten betragen circa 3-6% aller akuten Myokardinfarkte. Demnach werden 60 000 bis 70 000 Patient:innen pro Jahr in Europa mit infarktbezogenem kardiogenen Schock behandelt[8,9].

Die Pathophysiologie dieses Krankheitsbildes ist komplex und in den letzten zwei Jahrzehnten immer besser verstanden worden[3,8–11]. Zusammengefasst liegt eine starke Einschränkung der myokardialen Kontraktilität zu Grunde, die zur sog. „Schockspirale“ aus reduziertem kardialen Index (CI) und niedrigem Blutdruck mit konsekutiver Verstärkung der myokardialen Ischämie und somit weiter reduzierter myokardialer Kontraktilität führt. Es tritt eine initiale kompensatorische Vasokonstriktion hinzu, die nachfolgend durch eine pathologische Vasodilatation aufgrund einer systemischen Inflammationsreaktion möglicherweise konterkariert wird (Abbildung 2).

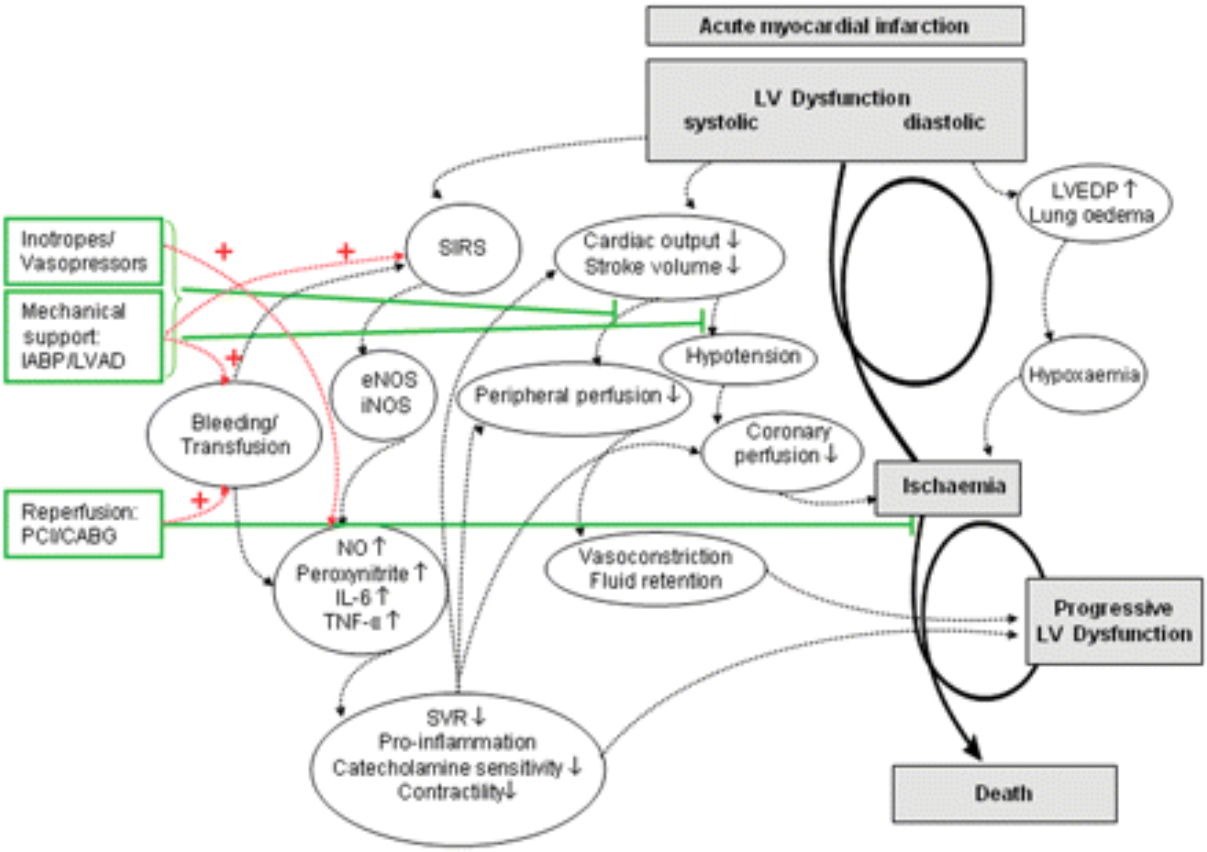

Abbildung 2: Aktuelles Konzept der Pathophysiologie des infarktbezogenen kardiogenen Schocks. Abbildung entnommen mit freundlicher Genehmigung des Erstautors aus Thiele et al Eur Heart J 2010.

2019 wurde durch die Society for Cardiovascular Angiography and Interventions (SCAI) mit Unterstützung durch US-amerikanische und europäische Fachgesellschaften eine Klassifikation des infarktbezogenen kardiogenen Schocks eingeführt[12]. Diese beinhaltet 5 Stufen (A – „at risk“ bis E „extremis“), welche sich durch die Kriterien Hypoperfusion, Notwendigkeit zur und Ausmaß an Kreislaufunterstützung unterscheiden (Abbildung 3). Es folgten mehrere retrospektive Validierungsstudien, um die prognostische Einordnung anhand dieser Klassifikation zu untersuchen. Dabei zeigte sich allerdings eine große Spannbreite der Mortalitätsraten in den einzelnen Klassen zwischen den verschiedenen Validierungsstudien[13–17], sodass eine weitere Objektivierung der Klassen angestrebt wird.

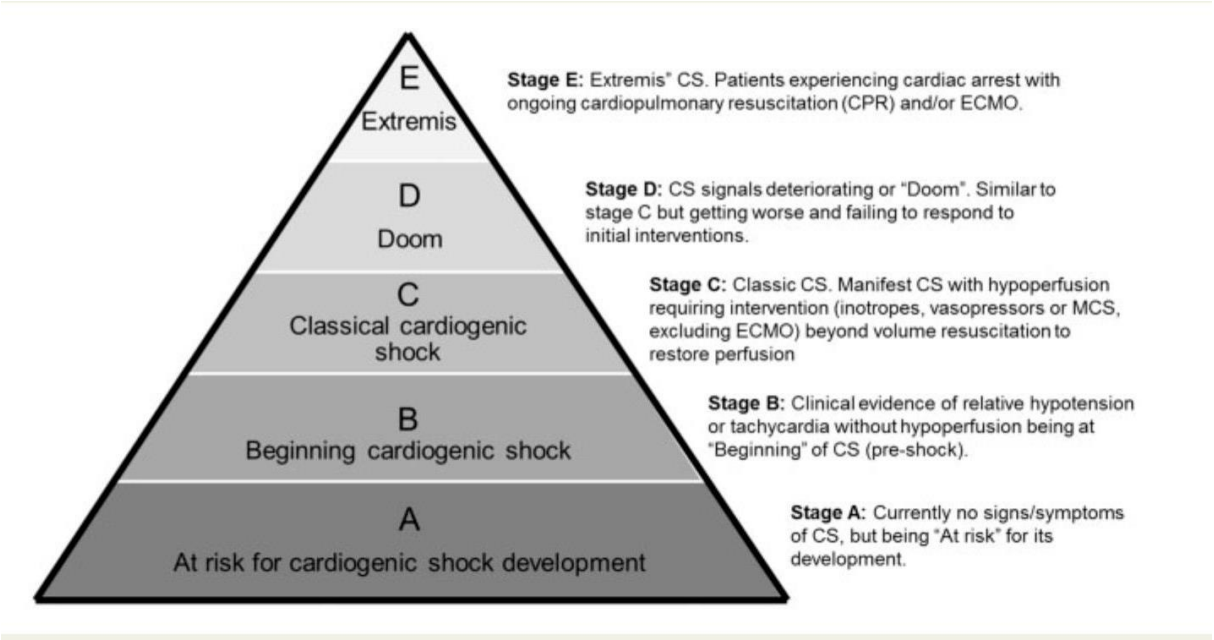

Abbildung 3: Pyramide der Klassifikation des infarktbezogenen kardiogenen Schocks gemäß dem SCAI Konsensuspapier[12]. Abbildung entnommen mit freundlicher Genehmigung des Erstautors aus Thiele et al Eur Heart J 2019[8],.

2.2. Therapieansätze

Vor der Anwendung der perkutanen Koronarintervention als Teil der klinischen Routine betrugen die Mortalitätsraten im infarktbezogener kardiogenen Schock mehr als 80%[3]. Ein erster Meilenstein in der Therapie des kardiogenen Schocks war die randomisierte SHOCK-Studie aus dem Jahr 1999[5]. In dieser Studie wurden untersucht, ob sich eine frühzeitige Revaskularisierung mittels PCI positiv auf das Überleben auswirkt. Obwohl sich kein Benefit für das Kurzzeitüberleben durch frühzeitige PCI zeigte, konnte im 6- und 12-Monate Follow-up eine Mortalitätsreduktion nachgewiesen werden[18]. Die nächste große Studie widmete sich Anfang der 2000er Jahre der inadäquaten systemischen Vasodilatation, welche zuvor als Teil der komplexen Pathophysiologie des AMI-bezogenen kardiogenen Schocks identifiziert worden war[10]. Alexander et al. untersuchten in der TRIUMPH- Studie, ob Tilargininacetat, ein Inhibitor der Nitiroxidsynthetase (NOS), über die Gegenregulation zur Vasodilatation einen wirksamen Therapieansatz darstellen könnte. Die Studie wurde allerdings vorzeitig gestoppt, da sich in den geplanten Zwischenanalysen kein signifikanter Nutzen des Tilargininacetats abzeichnete[19]. In der 2012 von Thiele et al veröffentlichten multizentrischen IABP-SHOCK II Studie wurde der Nutzen der bis dahin weit verbreiteten mechanischen Kreislaufunterstützung durch intraaortale Ballonkontrapulsation (IABP) randomisiert untersucht[4,20]. Hierbei konnte ebenfalls kein therapeutischer Benefit durch Einsatz von IABP gezeigt werden. In der Folge wurde ein deutlicher Rückgang des Einsatzes von IABP zur Kreislaufunterstützung beobachtet [21].

Nachfolgend etablierte sich zunehmend die venös-arterielle extrakorporale Membranoxygenierung (ECMO) als mechanisches Kreislaufunterstützungssystem[22]. Dabei wird das venös entnommene Blut über eine Membran oxygeniert und anschließend retrograd über die Aorta wieder dem Körperkreislauf zugeführt (rechtsventrikuläres „unloading“)[8]. Bisher liegen allerdings nur Hinweise aus kleineren Metaanalysen und einer kleinen randomisierten Studie (RCT) vor, die einen Überlebensvorteil durch den Einsatz der ECMO im kardiogenen

Schock zeigen[8,23,24]. Derzeit untersuchen zwei multizentrische randomisierte Studien diese Fragestellung[25,26].

An perkutanen linksventrikulären Kreislaufunterstützungssystemen (pLVAD) als weitere Therapieoption gibt es insbesondere deren prominenteste Vertreterin, die perkutan implantierbare linksventrikuläre Mikroaxialpumpe (IMPELLA®), wobei ein antegrader Fluss vom linken Ventrikel über die Aortenklappe in den Körperkreislauf hergestellt wird (linksventrikuläres „unloading“). Für dieses Verfahren gibt es bisher keine Evidenz hinsichtlich eines Mortalitätsbenefits durch RCTs[8]. Matched-Pair Analysen aus großen Registerstudien weisen bei diesem Verfahren auf keinen Überlebensvorteil, oder sogar auf eine erhöhte Mortalität bei erhöhter Komplikationsrate (z.B. Blutungen, Schlaganfälle, Niereninsuffizienz, Infektionen) hin[27–29].

Immer mehr Verwendung findet die Kombination von ECMO und pLVAD als sog. „venting“ oder „ECMELLA“, wobei sich ein Vorteil durch die Kombination der beiden Verfahren (rechts- und linksventrikuläres „unloading“) erhofft wird. Hierfür liegt bisher ebenfalls noch keine klare Evidenz aus RCTs vor, Registerdaten weisen hier allerdings auf einen gewissen Mortalitätsbenefit hin[30,31].

Hinsichtlich der Wahl der geeigneten medikamentösen Kreislaufunterstützung mittels Vasopressoren gibt es bisher nur sehr wenig Evidenz aus RCTs[3]. In einer kleineren multizentrischen prospektiven randomisierten Studie konnten zuletzt Hinweise auf einen Vorteil durch die Gabe von Noradrenalin gegenüber Adrenalin aufgezeigt werden[32].

2.3. CULPRIT-SHOCK Studie

Bei etwa 70-80% der Patient:innen im infarktbezogenen kardiogenen Schock findet sich eine koronare Mehrgefäßerkrankung („multivessel disease“) in der initialen Koronarangiografie, definiert als Stenose oder Okklusion in mindestens einem Koronargefäß zusätzlich zum aktuellen Infarktgefäß (sog. „culprit lesion“), diese Patient:innen weisen zudem eine erhöhte Mortalität auf[8,33]. In der europaweiten multizentrischen randomisierten CULPRIT-SHOCK Studie wurde der Fragestellung nachgegangen, ob eine sofortige Revaskularisierung aller stenosierter oder verschlossener Herzkranzgefäße (inklusive chronisch totaler Okklusionen, CTO) gegenüber der vorerst alleinigen Revaskularisierung der „culprit lesion“ überlegen ist[34]. Hierfür wurden 706 Patient:innen mit koronarer Mehrgefäßerkrankung und infarktbezogenem kardiogenen Schock 1:1 randomisiert in eine „multivessel“ versus „culprit-lesion-only“ PCI-Strategie. Als primärer Endpunkt wurde die 30-Tage-Mortalität oder Notwendigkeit zur Dialyse gewählt. Es zeigte sich ein signifikanter Vorteil für die „culprit-lesion-only“-Strategie, vor allem getrieben durch eine absolute 30-Tage-Mortalitätsreduktion von 8,3%[6]. Die Ergebnisse zeigten sich konsistent im 12-Monate Follow-up[35]. Teil der CULPRIT-SHOCK Studie war eine präspezifizierte Biomarkersubstudie, für die zum Baselinezeitpunkt (im Herzkatheterlabor) und an den folgenden drei Tagen Blut abgenommen, eingefroren und zum Biobanking eingeschickt wurde[34]. Die vorliegende Arbeit ist im Rahmen dieser Biomarkersubstudie entstanden.

2.4. Bisherige Biomarkeruntersuchungen

Seit Beginn der 2000er Jahre beschäftigten sich einige kleinere monozentrische Studien insbesondere mit pro-inflammatorischen Zytokinen im infarktbezogenen kardiogenen Schock[36–40]. Geppert et al konnten bereits früh die Möglichkeit einer Prognoseabschätzung durch die Bestimmung von Interleukin-6 zeigen[36,37,40]. In der Folge konnte dies auch für weitere pro-inflammatorische Zytokine nachgewiesen werden[38,39].

Die oben bereits erwähnte IABP-SHOCK II Studie schloss eine präspezifizierte monozentrische Biomarkersubstudie ein[4]. Mehrere etablierte, neuere wie auch experimentelle Biomarker wurden dabei in mehreren Einzelstudien untersucht. Als Mortalitätsprädiktoren wurden anhand dieser Population (N = 190) das stressinduzierte Zytokin Growth Differentiation Factor 15 (GDF-15)[41], der Player des Calcium-Phosphathaushaltes und Nierenfunktionsmarker Fibroblast Growth Factor (FGF-23)[42], sowie der Schlüsselmediator des Vaskularlecks Angiopoetin-2[43] identifiziert. Zusätzlich wurde ein Panel von pro-inflammatorischen Zytokinen analysiert[44]. Eine weitere Untersuchung aus dieser Kohorte widmete sich neueren und etablierten Nierenfunktionsparametern, wobei dem klassischen Marker Kreatinin eine bessere Performance im Vergleich zu neueren Markern wie Cystatin C, NGAL und KIM-1 attestiert wurde[45]. Zudem konnte eine prognostische Relevanz für das Vorliegen einer hypoxischen Hepatitis mittels Bestimmung der Aspartataminotransferase (ASAT) gezeigt werden. In einem größeren Subset der Patient:innen aus der IABP-SHOCK II-Studie gelang dies ebenso für die Bestimmung der Blutglucose zum Baselinezeitpunkt[46].

Im Rahmen der multizentrischen prospektiven „CardShock“-Beobachtungsstudie erfolgten ebenfalls Biomarkeruntersuchungen[7]. Die Arbeitsgruppe um Tolppanen et al konnten hieraus einerseits für die experimentellen Marker Adrenomedullin (Organdysfunktion, beeinträchtigte Hämodynamik) und sST2 (myokardiale Fibrose, adverses Remodelling), sowie andererseits für die Routinemarker NTproBNP und Glucose einen Stellenwert in der Risikostratifizierung demonstrieren[47–49].

2.5. Bisherige Prognosemodelle

Der Problemstellung der Prognoseabschätzung im infarktbezogenen kardiogenen Schock widmeten sich seit der Jahrtausendwende mehrere Arbeitsgruppen anhand verschiedener Kohorten. Als erste entwickelten Hasdai et al 1999 aus einer Subpopulation der GUSTO-I-Studie (n = 2968) einen Algorithmus zur Prognoseabschätzung[50]. Dieser besteht aus klinischen Charakteristika (Alter, vorheriger Myokardinfarkt, kalte Extremitäten, Oligurie),

zusätzlich können Messungen aus einer Rechtsherzkatheteruntersuchung einbezogen werden. Zeymer et al legten 2004 eine Untersuchung anhand von Registerdaten (n = 1333) der Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK) vor[51]. Es konnten vor allem angiografische Daten (Hauptstammbeteiligung, TIMI-Fluss, Mehrgefäßerkrankung, Zeit zwischen Symptombeginn und PCI, sowie Alter) als Prognosefaktoren identifiziert werden. 2005 wurde ebenfalls aus Registerdaten, diesmal aus den USA (n = 483, American College of Cardiology–National Cardiovascular Data Registry, ACC-NCDR), ein Risikoscore bezüglich der Krankenhausmortalität entwickeltt[52]. Es konnten Alter, Geschlecht, Niereninsuffizienz und vollständiger Verschluss des Ramus interventrikularis anterior (RIVA, LAD) als signifikante Prädiktoren nach multivariater Adjustierung in den Risikoscore aufgenommen werden. Eine retrospektive Studie an einer Kohorte von 113 Patient:innen mit versuchter PCI im kardiogenen Schock aus Großbritannien wurde ebenfalls 2005 veröffentlicht[53], in welcher Alter >70 Jahre, AMI in der Anamnese und Scheitern der thrombolytischen Therapie relevante Prognosefaktoren darstellten. Die Population (n = 396) der TRIUMPH Studie[19] diente einer 2009 erschienenen Arbeit zur Identifikation prognostischer Variablen[54]. Diese waren der systolische Blutdruck, die Kreatininclearance und die Anzahl an verabreichten Vasopressoren. Sleeper et al entwickelten 2010 einen Risikoscore auf der Basis der Studien- und Registerpopulation der SHOCK-Studie (n = 1217)[5,55], der die Variablen hypoxischer Hirnschaden, Schock bei Aufnahme, Nicht-inferiorer Infarkt, Alter, Hypoperfusion, anamnestische ACVB-OP, Kreatinin und systolischer Blutdruck eischließt.

Für diese älteren Arbeiten gelten eine Reihe von Limitationen: Zeymer et al, Sutton et al und Katz et al identifizierten zwar prognostisch relevante Variablen, entwickelten daraus jedoch keinen Risikoscore[51,53,54]; Die Arbeit von Hasdai et al ist anhand einer Population vor dem routinemäßigen Einsatz einer PCI im kardiogenen Schock enstanden[50]; Alle genannten Arbeiten bezogen entweder keine Biomarkerbestimmungen oder lediglich Creatinin oder die Creatininclearance mit ein. Die Risikoscores von Hasdai et al, Klein et al und Sleeper et al berichteten keine oder nur unzureichende Daten zur diskriminativen Aussagekraft („area

Under the Curve“, AUC, bzw „Receiver Operator Characteristics“, ROC, bzw. c-Statistik) oder zur internen oder externen Validierung der Prognosemodelle.

In den letzten Jahren sind drei neuere Mortalitätsprädiktionsscores für den kardiogenen Schock entstanden. Die eigens dafür angelegte prospektive „CardShock“-Beobachtungstudie (n = 219) ergab den 2015 von Harjola et al vorgelegten CardShock risk score mit den Variablen Alter, Vigilanzminderung, anamnestischer AMI oder ACVB, ACS als Ätiologie, linksventrikuläre Ejektionsfraktion (LVEF), Laktat und geschätzte glomeruläre Filtrationsrate (eGFR)[7]. In diese Studie wurden allerdings Patient:innen nicht nur im infarktbezogenen kardiogenen Schock, sondern auch im kardiogenen Schock anderer Ätiologie eingeschlossen. Die Kohorte der IABP-SHOCK II-Studie diente in diesem Fall zur externen Validierung, wobei eine AUC von 0.71 erreicht wurde. Den 2017 veröffentlichten IABP-SHOCK II risk score entwickelten Pöss et al aus dem Datensatz der gleichnamigen Studie[56]. Die Autor:innen identifizierten sowohl klinische/anamnestische, als auch laborchemische und angiografische Parameter als relevante Prädiktoren (Alter, Schlaganfallanamnese, Glucose, Kreatinin, Laktat, TIMI-Fluss nach PCI). Die externe Validierung erfolgte nun umgekehrt in der CardShock Population und erreichte eine AUC von 0.73. Zuletzt erschien von Rueda et al eine Untersuchung zum prognostischen Potential eines proteomischen Ansatzes[57]. Nach einem massenspektrometrischen Screeningverfahren wurden in einer Subopulation der CardShock Studie aus 51 Proteinen vier identifiziert, um einen Risikoklassifikator zu bilden (liver-type fatty acid-binding protein, beta-2-microglobulin, fructose-bisphosphate aldolase B und SerpinG1). Es erfolgte keine externe Validierung. Die Kandidatenproteine wurden nicht mit etablierten Biomarkern, klinischen oder angiografischen Parametern verglichen. Eine automatisierte Messung der vier Proteine für die klinische Routine ist bisher noch nicht verfügbar.

3. Rationale der vorliegenden Studie

Obwohl inzwischen eine Reihe elaborierter Therapieansätze im infarktbezogenen kardiogenen Schock vorhanden sind, werden nach wie vor Mortalitätsraten bis zu 50% beobachtet[8,12,58]. Aus diesem Grund ist es notwendig, die individuelle Prognose der Patient:innen abzuschätzen, um weitere Therapieentscheidungen hinsichtlich Einsatz oder Fortführung z.B. einer mechanischen Kreislaufunterstützung zu treffen. Zudem zeigt sich eine große Heterogenität der Patient:innenkollektive, sodass die Einteilung in unterschiedliche Risikopopulationen sehr erstrebenswert ist für die präzise Durchführung weiterer klinischer Studien[12]. In diesem akuten und zeitsensitiven Setting sollte demnach ein Tool zur Risikostratifizierung einfach handzuhaben sein, sowie schnell und zuverlässig zum Ergebnis führen.

Ziel der vorliegenden Arbeit war es, aus der großen Zahl der klinischen, angiographischen sowie neuen und etablierten laborchemischen Parameter, die bereits im Einzelnen oder in kleineren Gruppen untersucht worden sind, diejenigen mit dem besten Nutzen hinsichtlich einer Risikostratifizierung im infarktbezogenen kardiogenen Schock zu identifizieren. In der Folge sollte anhand der bisher größten internationalen multizentrischen Population aus einer randomisiert kontrollierten Studie zu diesem Krankheitsbild ein möglichst genaues aber einfaches Mortalitätsprädiktionsmodell entwickelt werden. Besondere Beachtung sollten dabei die aktuellen statistischen Leitlinien erfahren, die inzwischen als Standard für die Entwicklung derartiger Prädiktionsmodelle zu gelten haben[59,60].

Formatierte Publikation

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CLINICAL RESEARCH
Acute cardiovascular care

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

Uta Ceglarek[1]*†, Paul Schellong [1]†, Maciej Rosolowski [1], Markus Scholz [2], Anja Willenberg[1], Jürgen Kratzsch[1], Uwe Zeymer[3], Georg Fuernau [4], Suzanne de Waha-Thiele[4,5], Petra Büttner[6], Alexander Jobs[5,6], Anne Freund[6], Steffen Desch[5,6], Hans-Josef Feistritzer[6], Berend Isermann [1], Joachim Thiery [1], Janine Pöss[6]†, and Holger Thiele [6]*†

[1]Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital, P.-List-Str. 13, 04103 Leipzig, Germany; [2]Institute of Medical Informatics, Statistics and Epidemiology, University Leipzig, Germany; [3]Klinikum Ludwigshafen und Institut für Herzinfarktforschung, Ludwigshafen, Germany [4]University Heart Center Lübeck, Lübeck, Germany; [5]German Center for Cardiovascular Research (DZHK), Lübeck, Germany; and [6]Heart Center Leipzig at University of Leipzig, Department of Internal Medicine/Cardiology, Strümpellstr.. 39, 04289 Leipzig, and Leipzig Heart Institute, Leipzig, Germany

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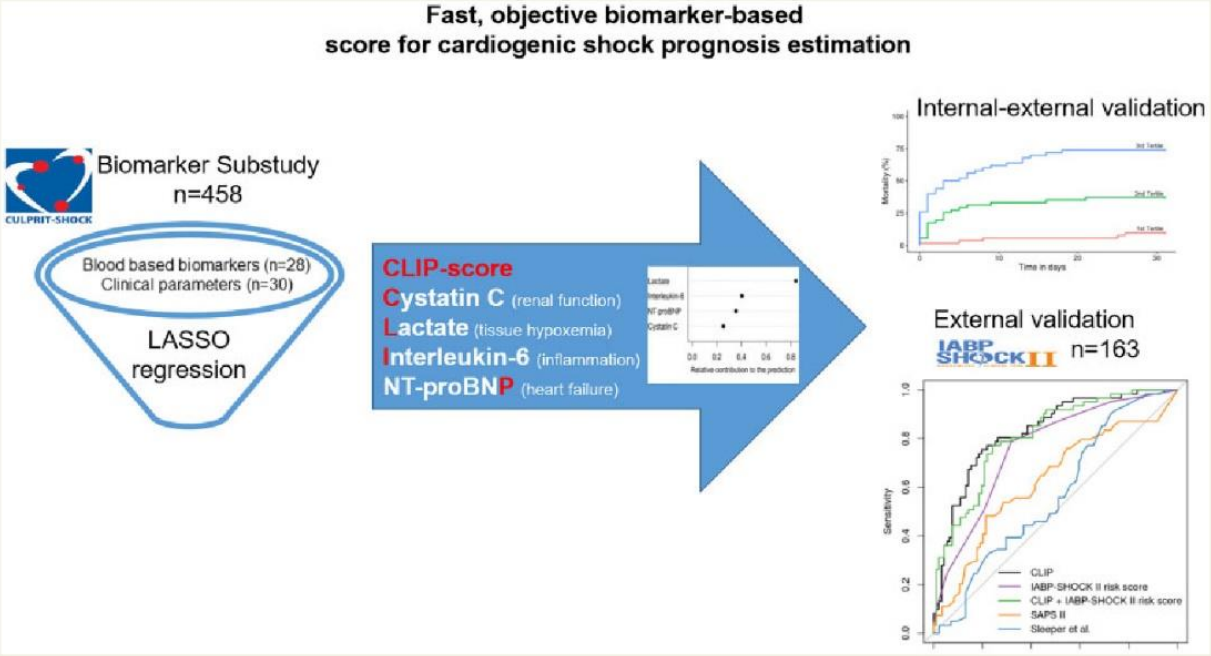
Background Cardiogenic shock (CS) complicating acute myocardial infarction (AMI) still reaches excessively high mortality rates. This analysis is aimed to develop a new easily applicable biomarker-based risk score.

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.

* Corresponding authors. Tel: +49 341 97 22460, Fax: +49 341 97 22209, Email: uta.ceglarek@medizin.uni-leipzig.de (U.C.); Tel: +49 341 865 1428, Fax: +49 341 865 1461, Email: holger.thiele@medizin.uni-leipzig.de (H.T.)
† These authors contributed equally to this study.

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

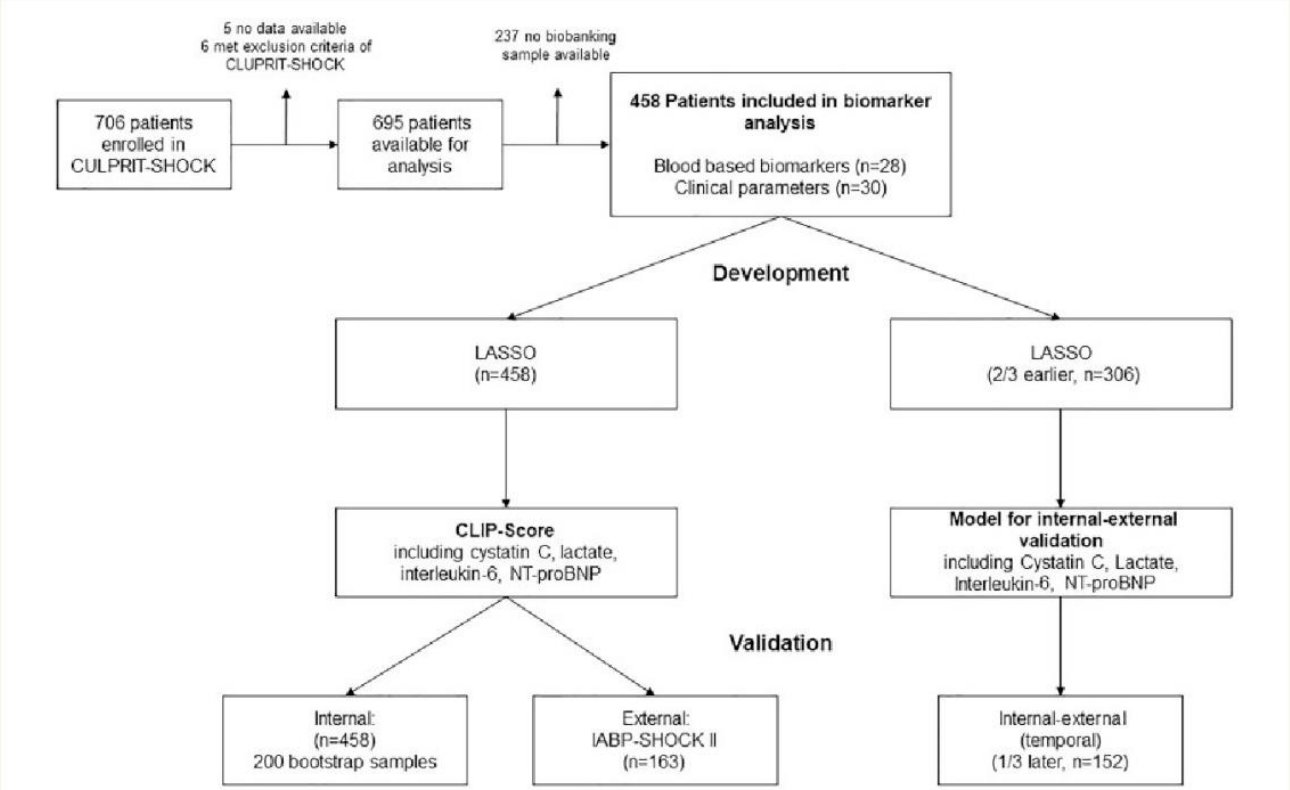


Figure 1 Flowchart of the process of development and validation of the CLIP score. LASSO, Least Absolute Shrinkage and Selection Operator; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(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*.

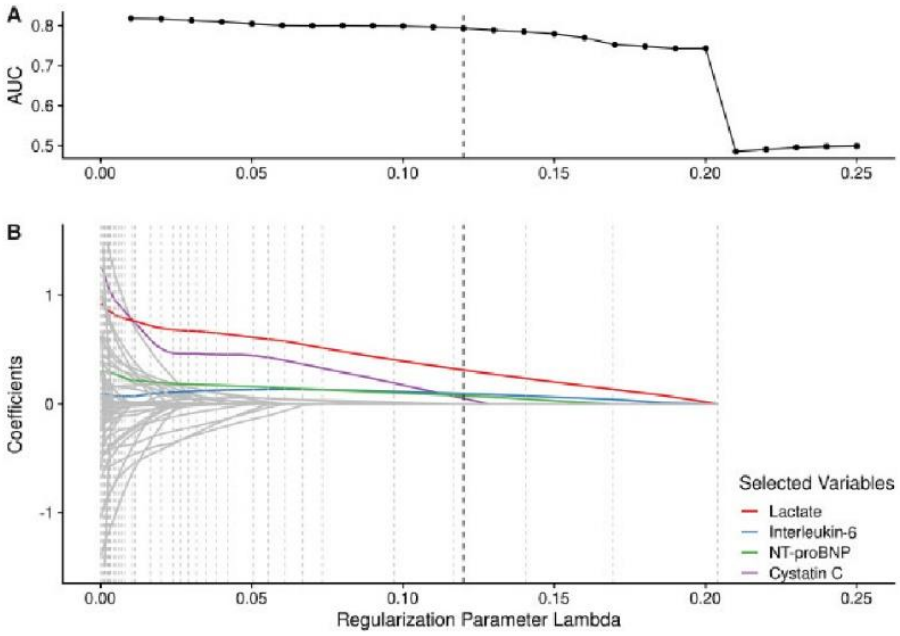
Discussion

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

$$Linear\ Predictor = -15.8532036 + 0.6714669 \times \operatorname{asinh}(100 \times Cystatin\ C\ in\ mg/L) + 1.0287073 \times \operatorname{asinh}(100 \times Lactate\ in\ mmol/L) + 0.2704829 \times \operatorname{asinh}(100 \times Interleukine\ 6\ in\ pg/mL) + 0.1923877 \times \operatorname{asinh}(100 \times NTproBNP\ in\ pg/mL)$$

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

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

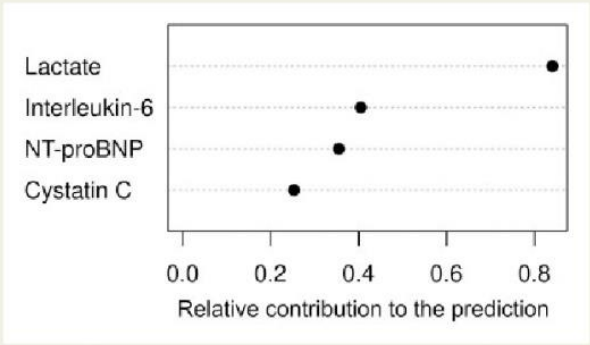


Figure 3 Relative contribution of the four biomarkers in the CLIP score to mortality prediction. The coefficients from the model equation are divided by the standard deviation of their respective biomarkers. Thus, the contribution of each biomarker can be comparatively evaluated independently of its 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.

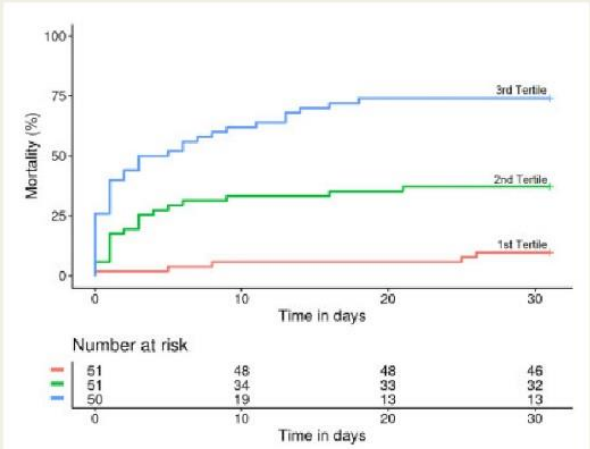


Figure 4 Kaplan–Meier cumulative event rates in the internal–external (temporal) validation cohort. Kaplan–Meier estimated cumulative event rate for 30-day mortality by tertiles of predicted probability.

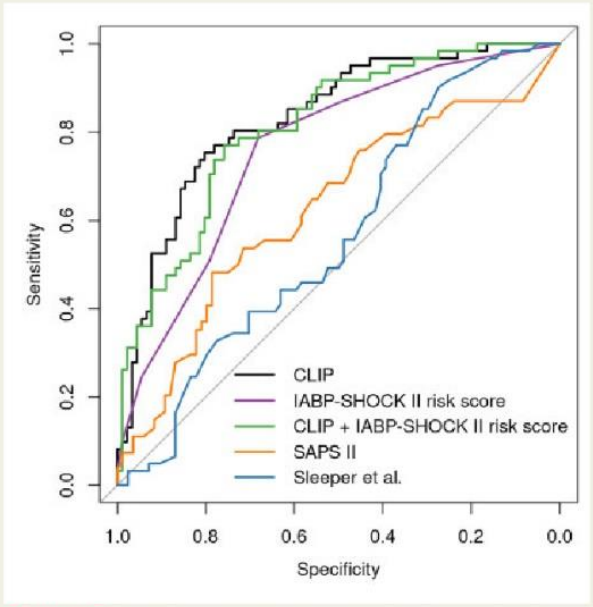


Figure 5 Receiver operating characteristics of the CLIP score, the IABP-SHOCK II score, the SHOCK score (Sleeper *et al.*[14]), and the Simplified Acute Physiology Score II (SAPS II) and the CLIP score together with the IABP-SHOCK II risk score. The receiver operating characteristics of each score were 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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Conflict of interest: none declared.

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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Zusammenfassung

Dissertation zur Erlangung des akademischen Grades

Dr. med.

Biomarker zur Mortalitätsprädiktion im Infarktbezogenen kardiogenen Schock

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

eingereicht von Paul Makiri Schellong

angefertigt am Institut für Labormedizin, Klinische Chemie und Molekulare Diagnostik
Medizinische Fakultät, Universität Leipzig

betreut von Prof. Dr. rer. nat. Uta Ceglarek

Juni 2021

Hintergrund:

Trotz der intensiven Behandlungsmöglichkeiten im infarktbezogenen kardiogenen Schock sind hohe Mortalitätsraten (ca 40-50%) weiterhin zu beobachten. Eine Reihe klinischer, angiografischer und laborchemischer Parameter sind hinsichtlich ihrer prognostischen Aussagekraft im Einzelnen oder in kleineren Gruppen untersucht worden. Bisherige Mortalitätsprädiktionsmodelle benötigen das Einholen klinischer/anamnestischer, angiografischer und biochemischer Variablen, was zu einer erschwerten Anwendbarkeit im klinischen Alltag führt. Eine frühe und valide Risikostratifizierung ist notwendig um weitere Therapieentscheidungen zu treffen und unterschiedliche Risikopopulationen für zukünftige klinische Studien zu identifizieren.

Ziele:

In der vorliegenden Arbeit sollte unter Einbezug einer großen Bandbreite von klinischen Parametern, sowie neuen und etablierten Biomarkern, ein Risikoscore entwickelt werden, der nur die relevantesten Prädiktoren der 30-Tage-Mortalität einschließt, um so ein einfach anzuwendendes Tool zur Risikostratifizierung zu erstellen.

Methoden

Der Risikoscore wurde anhand von 458 Patient:innen aus der multizentrischen randomisierten CULPRIT-SHOCK Studie mittels Least Absolute Shrinkage Selection Operator (LASSO), einem penalisierten multivariaten logistischen Regressionsmodell entwickelt. Als externe Validierungskohorte dienten 163 Patient:innen der IABP-SHOCK II Studie. Die prädiktive Aussagekraft wurde in interner, intern-extern (zeitlicher) und externer Validierung durch Diskrimination (AUC, c-Statistik), Kalibration, Klinischer Nutzen (decision curve analysis) und Kaplan-Meier-Kurven analysiert. Anschließend wurde der Risikoscore mit bisherigen Prognosemodellen hinsichtlich der diskriminativen Kraft (AUC, c-Statistik) verglichen.

Ergebnisse:

Aus 58 Kandidatenvariablen (30 klinische Parameter, 28 Biomarker) wurden nur vier als relevante Prädiktoren identifiziert. Aus Cystatin C, Laktat, Interleukin-6 und NTproBNP wurde somit der CLIP Score gebildet. In der internen Validierung wurde eine AUC von 0.82 (95% CI: 0.77-0.85) erreicht, in der intern-externen (zeitlichen) Validierung eine AUC von 0.83 (95% CI 0.76 – 0.90). Die externe Validierung ergab eine AUC von 0.73 (95% CI: 0.65 – 0.80). Es zeigte sich eine gute Kalibrierung und ein großer positiver Nettobenefit im klinischen Nutzen. Der CLIP Score überragte den SAPS II risk score (0.830 95% CI 0.765-0.896 vs 0.626 95% CI 0.528-0.725; P<0.001) und den IABP-SHOCK II risk score (0.830 95% CI 0.765-0.896 vs 0.761 95% CI 0.685-0.837; P=0.03) in der intern-externen (zeitlichen) Validierungskohorte.

Zusammenfassung/Schlussfolgerung:

Wir entwickelten und validierten einen reinen Biomarker Risikoscore zur Vorhersage der 30-Tage-Mortalität im infarktbezogenen kardiogenen Schock. Er stellt ein wertvolles Tool zur Unterstützung bei Entscheidungen für Therapieeskalation oder –deeskalation dar. Er kann automatisch aus vier rund um die Uhr verfügbaren Routinebiomarkern berechnet werden und übertrifft bisherige Risikoscores.

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Anlagen

Abkürzungsverzeichnis

ACS	Akutes Koronarsyndrom
ALKK	Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte
AMI	Akuter Myokardinfarkt
ASAT	Aspartataminotransferase
AUC	Area under the curve
CABG	Koronararterielle Bypassoperation
CI	Cardiac Index
CS	Kardiogener Schock
CTO	Chronisch totale Okklusion
ECMO	Extrakorporale Membranoxygenierung
eGFR	Geschätzte glomeruläre Filtrationsrate
EKG	Elektrokardiogramm
eNOS/iNOS	Endothelial/inducible nitric oxide synthase
GDF-15	Growth differentiation dactor 15
IABP	Intraaortale Ballonkontrapulsation
IL-6	Interleukin-6
LVEF	Linksventrikuläre Ejektionsfraktion
NOS	Nitirioxidsynthetase
NSTEMI	Nicht-ST-Hebungsmyokardinfarkt
NTproBNP	N-Terminales pro Brain-Typ natriuretisches Peptid
PCI	Perkutane Koronartintervention
pLVAD	Perkutanes linksventrikuläres Unterstützungssystem
RCT	Randomisiert kontrollierte Studie
RIVA/LAD	Ramus Interventricularis Anterior/Left anterior descending
ROC	Receiver Operator Characteristics
SCAI	Society for Cardiovascular Angiography and Interventions
STEMI	ST-Hebungsmyokardinfarkt
SVR	Systemic vascular resistance
TIMI	Thrombolysis In Myocardial Infarction
TNF-α	Tumour necrosis factor-α

SUPPLEMENTAL MATERIALS (Aus Ceglarek, Schellong, et al Eur HEart J 2021[61])

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Supplementary Table 1: **Baseline variables CULPRIT-SHOCK patients with blood sampling vs. patients without blood sampling**

Characteristic	Biomarker patients (N=458)	Non-biomarker patients (N=237)	P-value
Randomized to culprit lesion only PCI with potential staged revascularization	52.4 % (240/458)	45.6 % (108/237)	0.09
Death at 30 days	43.4 % (199/458)	51.1 % (121/237)	0.07
Age [year]	68 (60 - 77)	72 (61 - 79)	0.02
Male	76.6 % (351/458)	76.7 % (181/236 [1])	>0.99
BMI [kg/m^2]	26.6 (24.6 - 29.4) [12]	26.3 (24.2 - 29.3) [17]	0.17
Systolic blood pressure [mmHg]	105 (88 - 126) [59]	97 (80 - 124) [33]	0.02
Diastolic blood pressure [mmHg]	63 [52 - 80] [62]	60 (50 - 76) [41]	0.01
Heart rate [bpm]	90 (71 - 107) [6]	91 (73 - 109) [12]	0.72
ST-segment elevation	59.6 % (268/450) [8]	66.8 % (151/226) [11]	0.08
Resuscitation within 24 h before randomization	54.6 % (249/456) [2]	52.1 % (123/236) [1]	0.57
Triple vessel disease	64.0 % (293/458)	62.7 % (148/236) [1]	0.74
Cold, clammy skin and extremities	67.4 % (306/454) [4]	71.5 % (163/228) [9]	0.29
Altered mental status	69.5 % (317/456) [2]	63.0 % (148/235) [2]	0.09
Oliguria (≤30 ml/h)	25.0 % (113/452) [6]	27.2 % (59/217) [20]	0.57
pH <7.36	55.8 % (252/452) [6]	67.9 % (150/221) [16]	0.003
Arterial lactate >2 mmol/l	60.8 % (275/452) [6]	75.7 % (168/222)	<0.001
Current smoking	26.6 % (121/455) [3]	26.5 % (57/215) [22]	>0.99
Hypertension	61.7 % (282/457) [1]	56.1 % (128/228) [9]	0.19
Dyslipidaemia	32.8 % (150/457) [1]	34.5 % (78/226) [11]	0.67
Atrial fibrillation	10.7 % (49/458)	11.7 % (27/231) [6]	0.70
Diabetes mellitus	33.3 % (152/457) [1]	28.2 % (64/227) [10]	0.19
Known renal insufficiency (eGFR <30 mL/min)	6.1 % (28/457) [1]	6.5 % (15/231) [5]	0.87
Previous myocardial infarction	15.5 % (71/458)	18.4 % (42/228) [9]	0.33
Previous stroke	6.1 % (28/458)	9.1 % (21/231) [6]	0.16
Previous PCI	19.4 % (89/458)	16.7 % (38/228) [9]	0.41
Previous CABG surgery	5.2 % (24/458)	4.3 % (10/232) [5]	0.71
Previous congestive heart failure	8.1 % (37/458)	9.5 % (22/231) [6]	0.57
Known peripheral artery disease	10.5 % (48/458)	14.2 % (33/232) [5]	0.17
Family history of coronary artery disease	12.4 % (56/452) [6]	12.0 % (25/209)	>0.99

Procedural success (TIMI flow grade 3 in culprit lesion)	87.8 % (389/443) [15]	81.4 % (188/231) [6]	0.03
Total amount of contrast dye [mL]	220 (157 - 300) [1]	220 (150 - 300) [10]	0.45
Total fluoroscopy time [min]	15.2 (9.2 - 24.3) [4]	15.7 (9.2 - 25.9) [6]	0.99

Variables are represented as median (Interquartile range) or percentage (frequency). Numbers in parentheses represent the number of missing values.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index, eGFR, estimated glomerular filtration rate; TIMI, Thrombolysis In Myocardial Infarction.

Supplementary Table 2: **Biochemical methods of all candidate biomarkers**

Biomarker	Material	Biochemical method	Manufacturer
Alanine Aminotransferase (ALAT)	Lithium-heparin plasma	Recommendation of IFCC with activation by pyridoxalphosphate on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Aspartate Aminotransferase (ASAT)	Lithium-heparin plasma	Recommendation of IFCC with activation by pyridoxalphosphate on cobas® 8001	Roche Diagnostics, Mannheim, Germany
Creatine kinase (CK)	Lithium-heparin plasma	UV-assay on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Lactate	Fluoride-EDTA plasma	Enzymatic colorimetric assay on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Creatinine (Crea)	Lithium-heparin plasma	Enzymatic colorimetric assay on cobas® 8001	Roche Diagnostics, Mannheim, Germany
Cystatin C (CysC)	Lithium-heparin plasma	Particle-enhanced immunologic turbidimetric assay on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Potassium	Lithium-heparin plasma	ion-sensitive electrode on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Sodium	Lithium-heparin plasma	ion-sensitive electrode on cobas® 8001	Roche Diagnostics, Mannheim, Germany
high-sensitivity C-reactive protein (hsCRP)	Lithium-heparin plasma	Particle-enhaced immunologic turbidimetric assay on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Procalcitonin (PCT)	Serum	Immunoflourescence assay on Kryptor compact plus	BRAHMS/Thermo Fisher, Hennigsdorf, Germany
Interleukin-6 (IL-6)	Serum	ElectroChemiLuminescence ImmunoAssay (ECLIA) on cobas® 8000	Roche Diagnostics, Mannheim, Germany
high-sensitivity troponin T (hs-cTnT)	Lithium-heparin plasma	ElectroChemiLuminescence ImmunoAssay (ECLIA) on cobas® 8000	Roche Diagnostics, Mannheim, Germany
N-terminal B-type Natriuretic Peptide (NT-proBNP)	Lithium-heparin plasma	ElectroChemiLuminescence ImmunoAssay (ECLIA) on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Myoglobin (Mb)	Serum	ElectroChemiLuminescence ImmunoAssay (ECLIA) on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Creatine kinase MB isoform (CKMB)	Lithium-heparin plasma	Immunologic UV-assay on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Glucose	Fluoride-EDTA plasma	Enzymatic reference method with hexokinase on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Total cholesterol	Serum	Homogeneous enzymatic colorimetric assay on cobas®8000	Roche Diagnostics, Mannheim, Germany

High Density Lipoprotein Cholesterol (HDL)	Serum	Homogeneous enzymatic colorimetric assay on cobas®8000	Roche Diagnostics, Mannheim, Germany
Low Density Lipoprotein Cholesterol (LDL)	Serum	Homogeneous enzymatic colorimetric assay on cobas®8000	Roche Diagnostics, Mannheim, Germany
Triglycerides	Serum	Enzymatic colorimetric assay on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Copeptin	Serum	Immunoflourescence assay on Kryptor compact plus	BRAHMS/Thermo Fisher, Hennigsdorf, Germany
Angiopoietin-2 (Ang-2)	Serum	Enzyme-linked-immuno-absorbent-assay (ELISA)	R&D Systems, Minneapolis, USA
Growth-Differentiation-Factor 15 (GDF-15)	Lithium-heparin plasma	ElectroChemiLuminescence ImmunoAssay (ECLIA) on cobas® 8000	Roche Diagnostics, Mannheim, Germany
Soluble ST2	Serum	Enzyme-linked-immuno-absorbent-assay (ELISA)	R&D Systems, Minneapolis, USA

Supplementary Table 3: Demographics and baseline characteristics in the Development and internal-external validation cohorts of the alternative CLIP-formula

Characteristic	CULPRIT-SHOCK earlier 2/3 (n=306) Development	CULPRIT-SHOCK later 1/3 (n=152) Internal-external validation	p-Value
Culprit-lesion-only PCI strategy	52.3 % (160)	52.6 % (80)	>0.99
Gender: female	21.2% (65)	27.6% (42)	0.13
Age (years)	69 (59 - 77)	67 (61 - 77)	0.88
Body mass index (kg/m²)	26.3 (24.4 - 29.4) [8]	26.9 (24.7 - 29.6) [4]	0.30
Systolic blood pressure (mmHg)	102 (90 - 130) [31]	110 (86 - 125) [28]	0.91
Diastolic blood pressure (mmHg)	62 (53 - 80) [32]	66 (50 - 80) [30]	0.71
Heart rate (bpm)	91 (73 - 107) [3]	88 (68 - 107) [3]	0.39
Resuscitation within 24 h before randomization	56.2% (171)	51.3% (78)	0.32
Altered mental status	69.7% (212) [2]	69.1% (105)	0.91
Cold, clammy skin and extremities	70.0% (212) [3]	62.3% (94) [1]	0.11
Oliguria (≤30 ml/h)	26.6% (80) [5]	21.9% (33) [1]	0.30
Arterial pH <7.36	59.5% (179) [5]	48.3% (73) [1]	0.03
Previous myocardial infarction	16.3% (50)	13.8% (21)	0.58
Previous PCI	18.6% (57)	21.1% (32)	0.53
Previous CABG surgery	4.9% (15)	5.9% (9)	0.66
Previous congestive heart failure	9.8% (30)	4.6 % (7)	0.07
Atrial fibrillation	12.1% (37)	7.9% (12)	0.20
Previous stroke	6.1% (20)	5.3% (8)	0.68
Known peripheral artery disease	9.8% (30)	11.8% (18)	0.52
Known renal insufficiency (eGFR <30 ml/min)	5.2% (16) [1]	7.9% (12)	0.30
Current smoking	27.3% (83) [2]	25.2% (38) [1]	0.65
Hypertension	62.1% (190)	60.9% (92) [1]	0.84
Dyslipidaemia	34.0% (104)	30.5% (46) [1]	0.46
Diabetes mellitus	32.0% (98)	35.8% (54) [1]	0.46
Family history of coronary artery disease	14.9% (45) [3]	7.4% [11] [3]	0.02
ST-segment elevation in ECG	56.8% (172) [3]	65.3% (96) [5]	0.10
Triple vessel disease	65.4% (200)	61.2 (93)	0.41
Procedural success (TIMI flow grade 3 in culprit lesion)	88.9% (265) [8]	85.5% (124) [7]	0.35
Total amount of contrast dye index PCI (ml)	220 (152 - 300)	220 (167 - 300) [1]	0.97

Total fluoroscopy time index PCI (min)	15.2 (10 - 26.1) [3]	15.0 (8.5 - 22.2) [1]	0.18
Haemoglobin (mmol/L)	8.4 (7.5 - 9.2) [6]	8.6 (7.4 - 9.3) [4]	0.60
Haematocrit (%)	40 (36 - 44) [15]	40 (35 - 44) [9]	0.84
White blood cells (Gpt/L)	15.1 (10.7 - 19.1) [11]	14.1 (10.4 - 19.5) [6]	0.48
INR	1.19 (1.07 - 1.40) [28]	1.20 (1.08 - 1.43) [16]	0.77
Lactate (mmol/L)	3.57 (2.03 - 6.58) [27]	3.79 (1.87 - 7.89) [10]	0.58
Creatine kinase (µkat/L)	7.07 (3.16 - 18.87) [20]	6.70 (3.20 - 15.47) [5]	0.61
Creatine kinase MB isoform (µkat/L)	1.26 (0.67 - 2.60) [20]	1.18 (0.66 - 2.12) [5]	0.31
Hs-cTnT (pg/mL)	615 (227 - 2054) [20]	653 (212 - 1861) [5]	0.96
NT-proBNP (pg/mL)	1414 (311 - 4551) [20]	1188 (214 - 6108) [5]	0.65
Myoglobin (µg/L)	914 (314 - 2103) [20]	956 (377 - 1972) [5]	0.87
Creatinine (µmol/L)	111 (88 - 142) [20]	111 (91 - 136) [5]	0.92
Cystatin C (mg/L)	1.30 (1.01 - 1.63) [20]	1.22 (0.96 - 1.52) [5]	0.22
Glucose (mmol/L)	11.7 (8.2 - 15.6) [25]	12.0 (8.1 - 17.2) [10]	0.46
Sodium (mmol/L)	137 (132 - 141) [20]	136 (132 - 139) [5]	0.22
Potassium (mmol/L)	4.35 (3.82 - 5.03) [20]	4.28 (3.74 - 4.98) [5]	0.71
ALAT (µkat/L)	1.36 (0.67 - 2.71) [20]	1.23 (0.66 - 2.72) [5]	0.80
ASAT (µkat/L)	2.55 (1.17 - 5.04) [20]	2.67 (1.33 - 5.08) [5]	0.58
hs-CRP (mg/L)	5.6 (2.4 - 20.4) [20]	3.6 (1.6 - 24.2) [5]	0.41
Interleukine-6 (pg/mL)	90 (40 - 283) [20]	102 (42 - 279) [5]	0.59
Procalcitonin (ng/mL)	0.13 (0.08 - 0.31) [20]	0.13 (0.08 - 0.57) [5]	0.91
Total Cholesterol (mmol/L)	4.38 (3.39 - 5.13) [20]	4.14 (3.32 - 4.96) [5]	0.14
LDL Cholesterol (mmol/L)	3.07 (2.13 - 3.73) [20]	2.85 (2.07 - 3.67) [5]	0.23
HDL Cholesterol (mmol/L)	0.97 (0.81 - 1.19) [20]	0.97 (0.75 - 1.23) [5]	0.54
Triglycerides (mmol/L)	1.31 (0.99 - 1.77) [20]	1.28 (0.98 - 1.78) [5]	0.92
Copeptin (pmol/L)	217 (97 - 422) [20]	202 (99 - 474) [5]	0.87
GDF-15 (µg/L)	8060 (3633 - 15176) [21]	6326 (3285 - 15619) [5]	0.51
Angiopoietin-2 (ng/mL)	3.96 (2.57 - 7.26) [25]	3.92 (2.30 - 6.09) [7]	0.42
Soluble ST 2 (pg/mL)	53404 (18189 - 162040) [24]	32221 (15178 - 103494) [8]	0.06

Variables are represented as median (Interquartile range) or percentage (frequency). Numbers in parentheses represent the number of missing values.

For the development and validation of an alternative CLIP-formula, the CULPRIT-SHOCK dataset was split up by time. The earlier two thirds (N = 306) were used for development, the later third (N = 152) was used for internal-external validation of the alternative CLIP-formula.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ECG, electrocardiography; TIMI, thrombolysis in myocardial infarction; INR, international normalized ratio; hs-cTnT, high-sensitivity cardiac troponin T, NTproBNP, N-terminal pro

B-type brain natriuretic peptide; ALAT, Alanine aminotransferase; ASAT, Aspartate aminotransferase; hs-CRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein; HDL, high-density lipoprotein; GDF-15, growth differentiation factor 15.

Supplementary Table 4: Candidate predictors associated with 30-day mortality

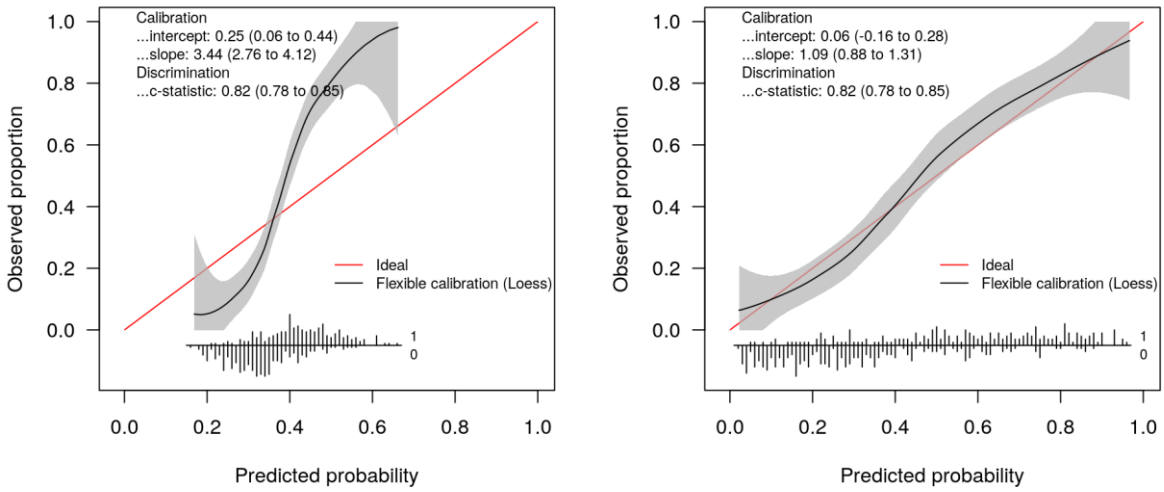
Biomarker	Odds ratio	95% Confidence interval		p-value FDR
Creatinine	7.38	3.91	14.63	<0.001
Cystatin C	6.52	3.45	12.88	<0.001
Lactate	3.18	2.30	4.47	<0.001
Glucose	2.56	1.56	4.28	0.001
Angiopoietin-2	2.42	1.71	3.48	<0.001
White blood cell count	2.37	1.39	4.11	0.01
Creatine kinase MB isoform	1.89	1.49	2.42	<0.001
Interleukine-6	1.79	1.49	2.17	<0.001
GDF-15	1.61	1.25	2.10	0.001
ASAT	1.61	1.31	2.01	<0.001
Copeptin	1.60	1.27	2.04	<0.001
Myoglobin	1.38	1.17	1.64	0.001
NT-proBNP	1.36	1.17	1.59	<0.001
hs-cTnT	1.30	1.13	1.50	0.001
Arterial hypertension	0.45	0.27	0.73	0.01
Dyslipidaemia	0.32	0.19	0.53	<0.001

Each parameter was put in a multivariable logistic regression model with the variables for adjustment BMI, renal function (by cystatin C and creatinine), age, sex, diabetes, PCI strategy. Creatinine and cystatin C were adjusted only for BMI, age, sex, diabetes, PCI strategy. Correction for multiple testing was performed by false discovery rate (FDR).

BMI; Body mass index; PCI, percutaneous coronary intervention; GDF-15, growth differentiation factor 15; ASAT, Aspartate aminotransferase; NT-proBNP, N-terminal pro B-type brain natriuretic peptide; hs-cTnT, high sensitivity cardiac troponin T.

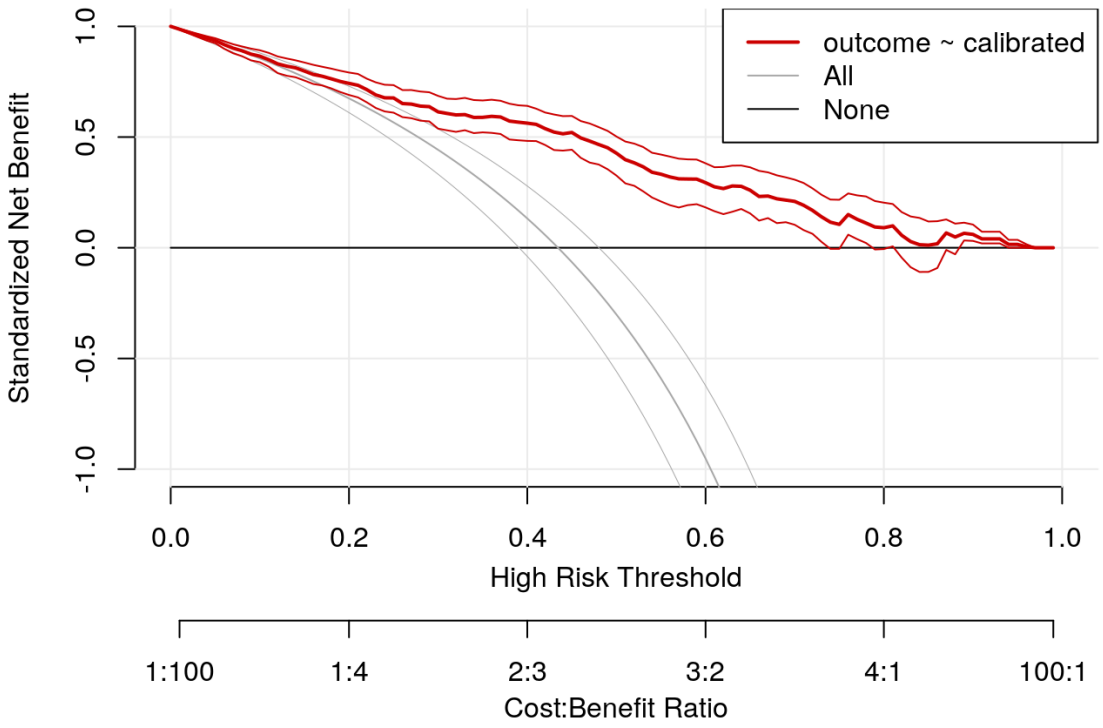
Supplementary Figure 1: Calibration plot in the whole CULPRIT-SHOCK population before and after recalibration

The predicted probabilities are plotted against the observed proportion of mortality.



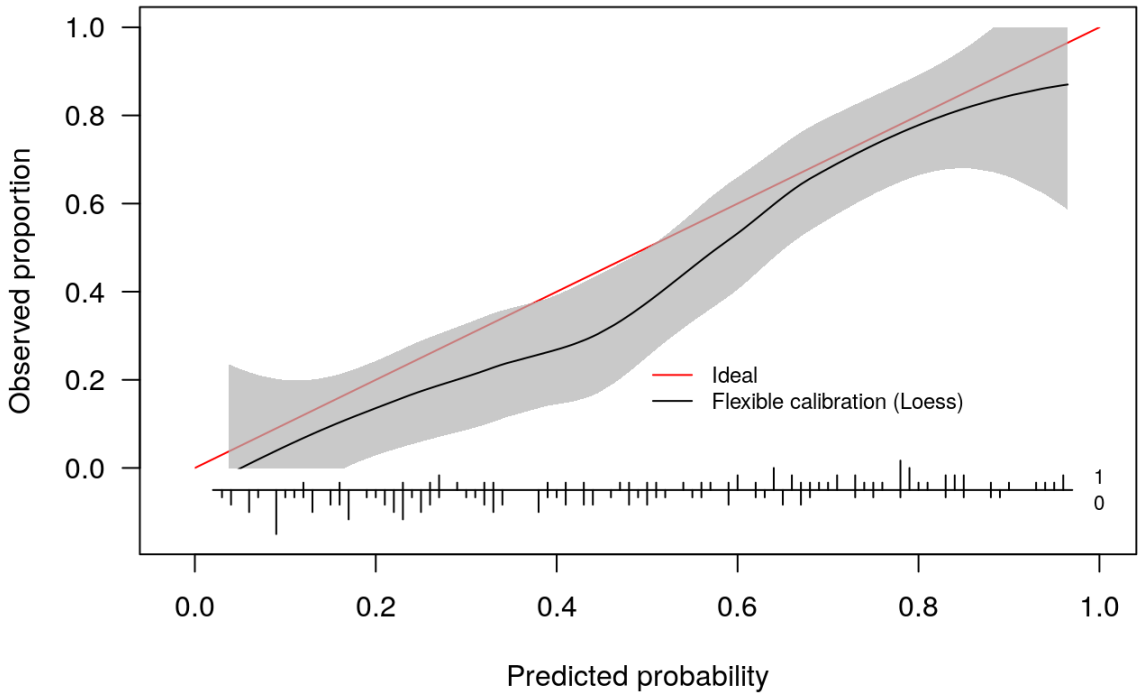
Supplementary Figure 2: **Decision curve analysis in the whole CULPRIT-SHOCK population**

Net benefit of using the CLIP-Formula/score/estimation to predict 30-day mortality compared to assuming high risk for all and for none of the patients.



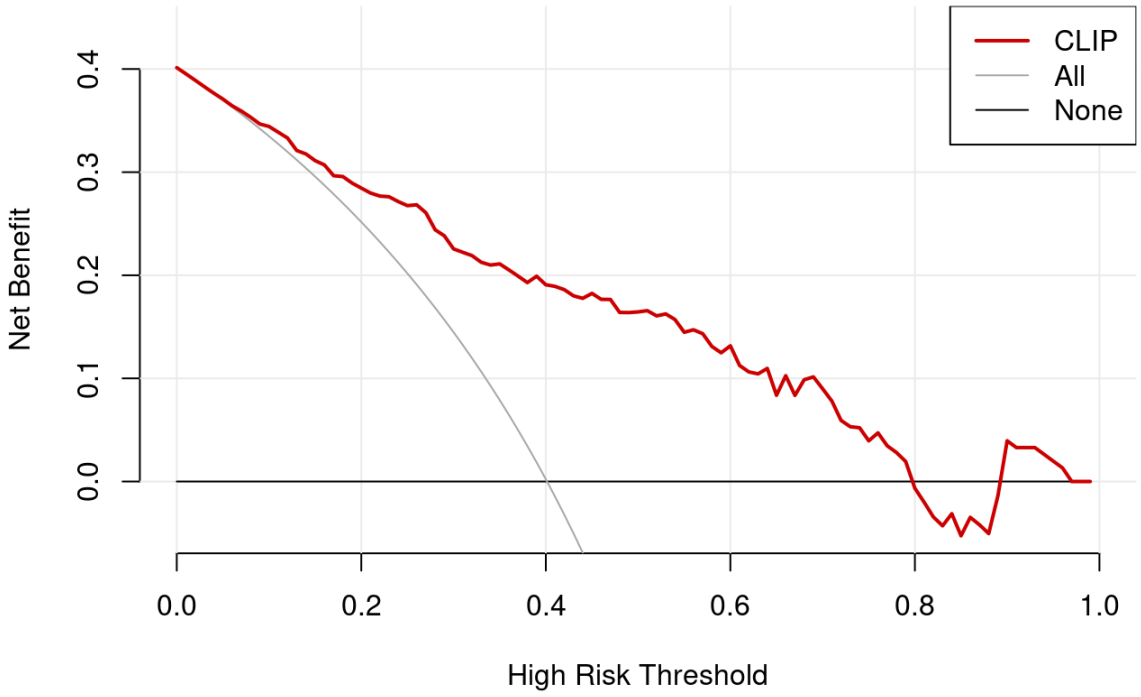
Supplementary Figure 3: Calibration plot in the development cohort for internal-external validation (earlier two thirds CULPRIT-SHOCK, N=306)

The predicted probabilities are plotted against the observed proportion of mortality



Supplementary Figure 4: Decision curve analysis in the internal-external (temporal) validation cohort (later third CULPRIT-SHOCK N = 152)

Decision curve analysis: Net benefit of using the CLIP score to predict 30-day mortality compared to assuming high risk for all and for none of the patients.



Supplementary Figure 5: C-statistics, Kaplan-Meier estimated cumulative event rate, the calibration plot and the decision curve analysis in the external validation cohort (IABP-SHOCK II, N=163)

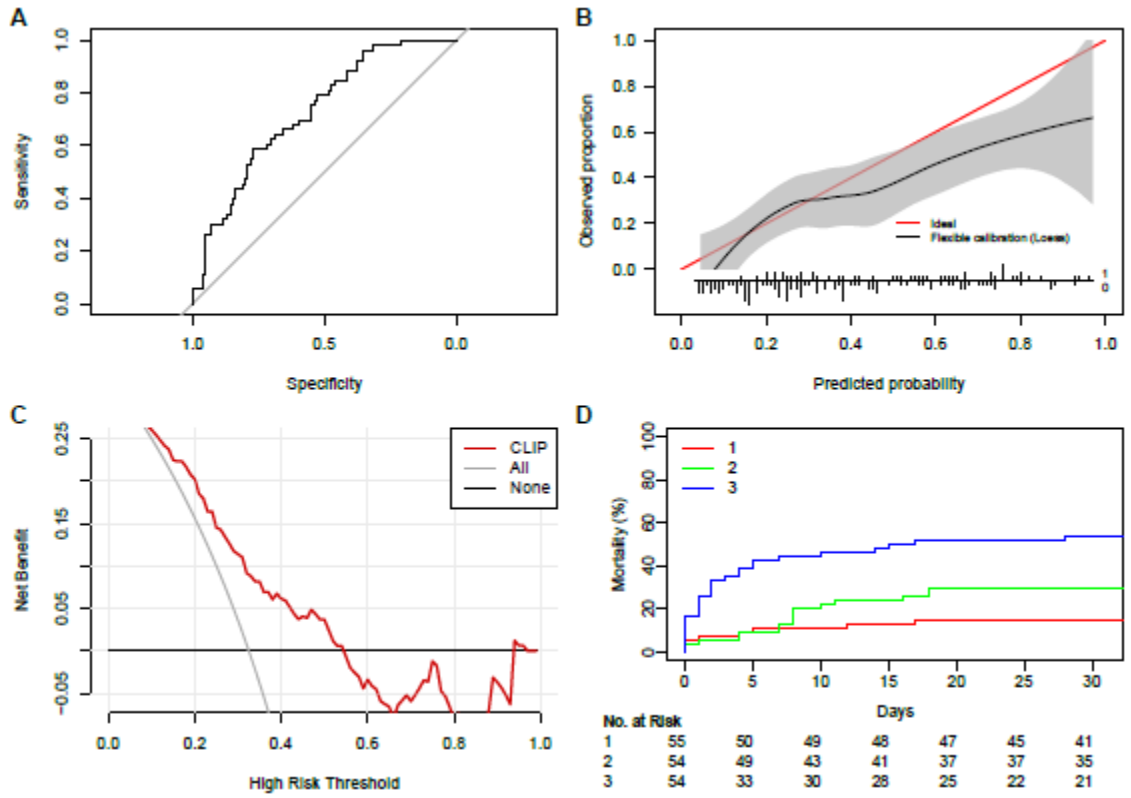
Results of the external validation in 163 patients from the IABP-SHOCK II trial.

A: discrimination by area under the curve from receiver operator characteristics.

B: Calibration curve. The predicted probabilities are plotted against the observed proportion of mortality.

C: Decision curve analysis. Net benefit of using the CLIP-Formula/score/estimation to predict 30-day mortality compared to assuming high risk for all and for none of the patients.

D: Kaplan-Meier estimated cumulative event rate by terciles of predicted probability of 30-day mortality.



eMethods: Detailed description of statistical analyses and model development

Analysis of baseline characteristics
Baseline characteristics were summarized as medians with interquartile ranges for continuous variables and counts with proportions for categorical variables. Biomarker levels were summarized as median concentrations with interquartile ranges. Continuous variables were compared using the Mann-Whitney-U test and categorical variables were compared using Pearson's chi-square test. No correction for multiple testing was performed.

Data preprocessing
Values of laboratory biomarkers, aPTT and BMI were transformed with area sinus hyperbolicus [asinh(100*x)] to make their distributions approximately symmetric. Values of the international normalized ratio (INR) were squared and inverted. Next, outliers, defined as values more than 4 interquartile ranges (IQR) above the 3rd quartile or more than 4 IQR below the 1st quartile of a variable were set to missing. Overall, nine outliers were found.
In the data set used for external validation (163 patients from the IABP-SHOCK II trial), measurements of the four parameters used in the predictive model were transformed using the same asinh(100*x) transformation as in the development cohort.

Treatment of missing values
Missing values were completed by multiple imputation using the Multivariate Imputation by Chained Equations (MICE)[1,2]. All candidate predictors and the outcome were included in the imputation model. Continuous and dichotomous variables were imputed using predictive mean matching and logistic regression, respectively. We constructed 10 imputed data sets. There were no missing values in the binary outcome variable (30-day mortality).

Candidate predictors
Initially, 60 candidate predictors were considered. 2 variables (PTT and body temperature) were excluded because they contained more than 20% missing values. 458 patients and 58 candidate predictors were used for further analysis. These predictors included baseline characteristics, such as 29 clinical features (demographic, anamnestic, vital parameters), 4 hematologic biomarkers reported on the case report form of the CULPRIT-SHOCK trial, and 25 laboratory biomarkers analyzed centrally at the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics at the University of Leipzig. The full list of the candidate variables is shown in baseline characteristics (Table 1).

Association of blood-based biomarkers with 30-day survival
In the 458 patients from the CULRPIT-SHOCK trial, 53 candidate predictors were tested for association with 30d survival adjusted for age, renal function (by creatinine and cystatin C), diabetes, sex, BMI and revascularization strategy by multivariate logistic regression as a first attempt. Therefore, each biomarker was put in a logistic regression model with these confounders. Cystatin C and Creatinine as biomarkers of renal function, but associated with mortality itself, were only adjusted for age, diabetes, sex, BMI and revascularization strategy. Correction for multiple testing was performed by false discovery rate[3].

Variable selection and fitting the predictive model
For developing the predictive model, the Least Absolute Shrinkage Selection Operator (LASSO)[4,5], a penalized multivariate logistic regression technique, was applied to each imputed data set. By incorporating shrinkage, this method provides rigid variable selection and coefficient estimation as well as it limits the overfitting of the model to the available dataset[6]. The shrinkage parameter lambda was selected from a grid of possible values as the highest value (i.e., leading to the most parsimonious model) such that the resulting area under the receiver operating characteristic (ROC) curve (AUC or c-index) was at least 97% of the maximal AUC attained over all possible values of lambda (see Supplementary Figure 2). The AUCs were estimated using the "optimism bootstrap"[7]. The selected shrinkage parameter lambda and the coefficients of the predictor variables were specific to each imputed data set.

Therefore, to obtain one model, the coefficients of the predictor variables that were non-zero in 9 of the 10 imputed data sets were averaged. To compute the AUC on a data set containing missing values, the model with the averaged coefficients was applied to each imputed data set and the resulting AUCs were averaged.

Validation of the predictive model

Internal validation

The model was internally validated using 200 bootstrap samples (using "optimism bootstrap"[7,8]), incorporating multiple imputation in each bootstrap iteration (see approach 4 in Musoro at al.[9]). First, the "apparent" AUC(orig, orig), i.e., the AUC resulting from a model trained on the whole CULPRIT-SHOCK data set and evaluated on the same data set was computed. Next, the optimism in the apparent AUC was estimated using bootstrap. Specifically, each bootstrap sample was drawn from the incomplete data set (i.e., data set containing missing values), missing values were imputed 10 times and a predictive model was developed as described above. Then, the predictive model was evaluated on: 1) the same bootstrap sample on which it was trained, resulting in AUC(boot, boot), and 2) on the original data, resulting in AUC(boot, orig). The optimism in the apparent AUC (optimism_AUC) was estimated as the mean of the differences AUC(Boot, BS) - AUC(Boot, Orig) over all bootstrap samples. The AUC corrected for optimism was equal to AUC(orig, orig) – optimism_AUC. To determine the 95% CI of the corrected AUC, quantiles of its bootstrap distribution were used.
To obtain a final predictive model to be evaluated on data set for external validation, the model coefficients were recalibrated[10,6,8] using "optimism bootstrap" estimates of the calibration intercept and slope computed in the internal validation step. Specifically, the calibration slope used to recalibrate the coefficients of the model was estimated as slope_corrected = slope(orig, orig) – optimism_slope, where

1. slope(orig, orig) is the slope calculated by regressing the original outcome on the linear predictor obtained by applying regression coefficients estimated using the *original* data on the *original* data.
2. optimism_slope = mean(slope(boot, boot) – slope(boot, orig)), where
    a. slope(boot, boot) is the slope calculated by regressing the bootstrap outcome on the linear predictor obtained by applying regression coefficients estimated using the *bootstrap* sample on the *bootstrap* sample.
    b. slope(boot, orig) is the slope calculated by regressing the original outcome on the linear predictor obtained by applying regression coefficients estimated using the *bootstrap* sample on the *original* sample.

The mean is taken over all bootstrap repetitions and imputations. Intercept_corrected was estimated in an analogous way. The recalibrated model was then Intercept_corrected + slope_corrected * linear_predictor, where linear_predictor was the linear predictor obtained by applying regression coefficients estimated using the original data on the original data. Using this formula, the recalibrated regression coefficients (the coefficients used to compute the linear predictor) were computed.

External validation

The predictive model trained on the whole data set of the Culprit study was externally validated on 163 patients from the IABP-SHOCK II biomarker substudy[11-14]. Regression coefficients of the final model determined using the training data only were applied to the measurements from the IABP study to compute a linear predictor, which was then transformed to probabilities using inverse logit function. As no values were missing in the IABP data set, the calculation of the performance measures and their 95% CIs was done in the standard way.

Discrimination was assessed by the area under the receiver operating characteristic (ROC) curve (AUC, c-index or c-statistic). Calibration was assessed 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[15]. Kaplan-Meier curves were used to additionally visualize survival of patients stratified by their predicted mortality.

The subset (n=163) of the IABP SHOCK II biomarker study[14,13] (n=190) which we used as an external validation set exhibits a 30d-day mortality rate of only 32.5% compared to 40.2% in the whole IABP-SHOCK II biomarker substudy. The latter value is closer to the mortality rate typically observed for patients with cardiogenic shock after acute myocardial infarction, e.g., mortality in the CULPRIT-SHOCK data set is 43.4%. Therefore, our predictor systematically overestimated mortality in the external validation set. To adjust for this, we added a correction term in the intercept of our linear predictor. The correction term was[16]

$$Correction\ term = \ln\left(\frac{\frac{mortality\ in\ the\ external\ validation\ cohort}{1 - mortality\ in\ the\ external\ validation\ cohort}}{\frac{mortality\ in\ the\ whole\ IABP\ cohort}{1 - mortality\ in\ the\ whole\ IABP\ cohort}}\right)$$

The purpose of the correction term was to be able to assess calibration of our predictive model, if the external validation cohort had mortality rate equal to that in the whole IABP cohort. Note that adding the correction term did not affect discrimination (AUC) of our predictor.

Internal-external validation of the predictive model

For internal-external validation the 458 patients of the CULPRIT-SHOCK data set were non-randomly split by their admission date[17,18] (see Supplementary Figure 1). A model was fitted to the 306 patients included in the trial before March 31st, 2016 (earlier two thirds of the patients). The whole procedure of imputing missing data, predictive model development and internal validation was conducted as specified above. The resulting predictive model was evaluated by internal-external validation on the 152 patients who were admitted to hospital after that date (later third of the population). Since this subset contained missing values, they were imputed 10 times (independently of the earlier two thirds subset). Performance estimates and their variances on the imputed data sets were combined using Rubin's rules[19], and the 95% CIs were computed using normal approximation. AUC estimates and variances were obtained from DeLong's test. The CLIP score was compared to the Simplified Acute Physiology Score (SAPS II) and IABP-SHOCK II risk score in terms of discrimination (AUC) by DeLong's method [20].

Software

Baseline characteristics were analyzed with IBM® SPSS® Statistics 20 (Armonk, NY, USA). All other calculations were performed using R, version 3.4.1[21]. For multiple imputation, the R-package mice[2] was used. LASSO models were fitted using the packages glmnet[5] and caret[22]. ROC curves and AUC were computed using the R package pROC[23]. Calibration plots were generated using the R package CalibrationCurves[24], decision curves using the R package rmda[25], and Kaplan-Meier curves using the R package survminer. Internal validation was performed using custom code. Parts of previously published code were adapted[9].

The analyses followed the general framework for development, validation and reporting of risk prediction models described by Steyerberg and Vergrouwe[6] and the TRIPOD Statement[17].

Mathematical equation of the CLIP-score

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, interleukine-6, NT-proBNP and CysC and their respective coefficients. The coefficients given here are already recalibrated as described in Methods.

CLIP-score = exp(Linear Predictor) / (1 + exp(Linear Predictor))
Linear Predictor = -15.8532036 + 1.0287073 * asinh(100 * lactate in mmol/L) + 0.2704829 * asinh(100 * interleukine-6 in pg/mL) + 0.1923877 * asinh(100 * NT-proBNP in pg/mL) + 0.6714669 * asinh(100 * cystatin C in mg/L)

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

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Darstellung des eigenen Beitrags

Der Promovend Paul Schellong, geboren am 09.09.1992, hat folgenden eigenen Beitrag zur Erstellung der vorliegenden Publikation (Ceglarek, Schellong et al., European Heart Journal (2021) 00, 1–9 doi:10.1093/eurheartj/ehab110) geleistet:

- Literaturrecherche
- Erstellung des zu Grunde liegenden Datensatzes durch Zusammenführung aus multiplen Quellen (klinische Variablen aus dem Case Report Form der CULPRIT-SHOCK Studie, Ergebnisse der Biomarkermessungen am Institut für Laboratoriumsmedizin)
- Konzeption der Publikation (gemeinsam mit Prof. Dr. Uta Ceglarek, Dr. Maciej Rosolowski und Prof. Dr Holger Thiele)
- Auswahl der Kandidatenvariablen für die Risikoscoreentwicklung
- Berechnung der Baseline Characteristics
- Planung, Festlegung und iterative Anpassung der statistischen Analysen zu Entwicklung und Validation des Risikoscores (gemeinsam mit Dr. Maciej Rosolowski)
- Erstellen aller Tabellen, Erstellen von Figure I und IIc,
- Erstellen des Manuskripts, wiederholte textliche Integration von Diskussionsergebnissen

Unterschriften der Koautor:innen:

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Dr. Maciej Rosolowski

Prof. Dr. Markus Scholz

Dr. Anja Willenberg

Prof. Dr. Jürgen Kratzsch

Prof. Dr. Berend Isermann

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