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Untersuchungen zur Risikostratifizierung und Prognoseabschätzung bei Patient:innen mit mechanischer Kreislaufunterstützung

Habilitationsschrift

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vorgelegt von

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Für Jonah und Leni

Präambel und Übersicht der zugrundeliegenden Originalarbeiten

Diese kumulative Habilitationsschrift basiert auf insgesamt sieben Originalarbeiten. Diese beschäftigen sich mit der Risikostratifizierung und Prognoseabschätzung bei Patient:innen mit mechanischer Kreislaufunterstützung. Konkret werden insbesondere die folgenden drei Teil-Aspekte aufgegriffen:

1) Prognoseabschätzung,

2) Ansätze zur Optimierung einer laufenden Therapie und

3) Endpunkte zur Evaluation des Therapieerfolgs.

Zunächst erfolgt eine Einleitung in die Thematik, in der die bestehenden Probleme sowie die Rationalen für die durchgeführten Untersuchungen dargestellt werden. Anschließend erfolgt eine Vorstellung der Methoden und Ergebnisse der jeweiligen Arbeiten. Schließlich werden die Ergebnisse im Kontext der aktuellen Literatur diskutiert und es wird ein Ausblick gegeben, welche Schritte - basierend auf den vorliegenden Untersuchungen - in Zukunft folgen könnten.

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2. **Roth S**, Jansen C, M'Pembele R, Stroda A, Boeken U, Akhyari P, Lichtenberg A, Hollmann MW, Huhn R, Lurati Buse G, Aubin H. Fibrinogen-Albumin-Ratio is an independent predictor of thromboembolic complications in patients undergoing VA-ECMO.
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platelet-lymphocyte-ratio and procalcitonin for early assessment of prognosis in patients undergoing VA-ECMO.
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5. M'Pembele R, **Roth S**, Metzger A, Nucaro A, Stroda A, Polzin A, Hollmann MW, Lurati Buse G, Huhn R. Evaluation of clinical outcomes in patients treated with Heparin or direct thrombin inhibitors during extracorporeal membrane oxygenation: A systematic review and meta-analysis.
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7. Tenge T, **Roth S**, M'Pembele R, Stroda A, Lurati Buse G, Westenfeld R, Tudorache I, Hollmann MW, Boeken U, Akhyari P, Lichtenberg A, Neukirchen M, Huhn R, Aubin H. Impact of Left Ventricular Assist Device Implantation on Outcome in Hemodynamically Stable Patients with End-Stage Heart Failure: A Propensity Score Matched Cohort Study.
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Abkürzungsverzeichnis

AUC	Area under the curve
BMI	Body Mass Index
BTT	Bridge to transplant
CKD	Chronische Nierenerkrankung
CVVHD	Continous venovenous hemodialysis
DAOH	Days alive and out of hospital
DTI	Direkte Thrombin-Inhibitoren
ELSO	Extracorporeal Life Support Organization
EUROMACS	European Registry for Patients with Mechanical Circulatory Support
FAR	Fibrinogen-Albumin-Ratio
HI	Herzindex
HR	Hazard ratio
HTX	Herztransplantation
HZV	Herzzeitvolumen
IDI	Integrierter Diskriminierungsindex
KDIGO	Kidney Disease: Improving Global Outcome
KI	Konfidenzintervall
KHK	Koronare Herzkrankheit
LOA	Limits of agreement
LVEF	Left ventricular ejection fraction
LVAD	Left ventricular assist device
NIPB	Non-invasive blood pressure
NIPKA	Nicht-invasive Pulskonturanalyse
NLR	Neutrophile-Lymphozyten-Ratio
NRI	Net reclassification index
NYHA	New York Heart Association
OR	Odds ratio

PCT	Procalcitonin
PE	Percentage error
PICS	Post-intensive care syndrome
PLR	Platelet-Lymphocyte-Ratio
pMCS	Preoperative mechanical circulatory support
PS	Propensity Score
ROC-Kurve	Receiver Operating Characteristic-Kurve
RVAD	Right ventricular assist device
SD	Standard deviation
SOFA-Score	Sequential Organ Failure Assessment Score
SV	Schlagvolumen
SVR	Systemisch-vaskulärer Widerstand
TD	Thermodilution
VA-ECMO	Veno-arterielle extrakorporale Membranoxygenierung

Inhaltsverzeichnis

1. Einleitung

Mit knapp 350.000 Todesfällen pro Jahr stellen kardiovaskuläre Erkrankungen die häufigste Todesursache in Deutschland dar. [1] Wenn medikamentöse Maßnahmen ausgeschöpft sind, besteht die Möglichkeit, eine Form der mechanischen Kreislaufunterstützung einzusetzen, um entweder temporär oder im Sinne einer definitiven Therapie eine adäquate Kreislauffunktion zur suffizienten Versorgung von wichtigen Endorganen wiederherzustellen. [2-4] Die Verfügbarkeit sowie die Verwendung von mechanischer Kreislaufunterstützung hat in den letzten Jahrzehnten stark zugenommen und in Industrieländern stellt sie mittlerweile ein etabliertes Verfahren im Rahmen der Behandlung einer terminalen Herzinsuffizienz dar. [5] Grundsätzlich muss unterschieden werden zwischen extrakorporalen Verfahren wie z.B. der veno-arteriellen extrakorporalen Membranoxygenierung (VA-ECMO) und intrakorporalen Verfahren wie z.B. Linksherzunterstützungssystemen („Left Ventricular Assist Device"; LVAD). Während die VA-ECMO immer ein temporäres Verfahren darstellt, das in den meisten Fällen notfallmäßig eingesetzt wird, stellen LVADs eine permanente Form der Kreislaufunterstützung dar, die vorrangig im Rahmen der chronischen terminalen Herzinsuffizienz zum Einsatz kommen. [6,7] Alle verfügbaren Formen der mechanischen Kreislaufunterstützung haben jedoch gemein, dass es sich um sehr invasive Verfahren handelt, die mit einer entsprechend hohen Rate an Komplikationen assoziiert sind und trotz zunehmender Erfahrung bleibt die Mortalität auch in spezialisierten Zentren hoch. [8] Für Patient:innen mit VA-ECMO liegt die Sterblichkeit innerhalb des Krankenhaus basierend auf dem Register der Extracorporeal Life Support Organization (ELSO) bei rund 50%. [9] Aktuelle Daten aus Deutschland zeigen sogar eine Sterblichkeit innerhalb des Krankenhauses von bis zu 80%. [10] Für Patient:innen mit LVADs liegt die 90-Tages Mortalität gemäß den Daten des European Registry of Mechanical Circulatory Support (EUROMACS) bei knapp 20%, was für einen elektiven Eingriff immer noch sehr hoch ist. [11] Allerdings sollte nicht nur die reine Sterblichkeit als Maß für den Therapieerfolg betrachtet werden, denn während eine VA-ECMO-Therapie oder die Implantation eines LVADs sicher in einigen Fällen dazu in der Lage sein kann, das Überleben zu verlängern, so kann darauf basierend noch keine Aussage zur Lebensqualität der Patient:innen getroffen werden. Aufgrund der hohen Komplikationsraten mit schweren Blutungen, Infektionen oder neurologischen Komplikationen sind außerdem häufig lange Aufenthalte auf der Intensivstation notwendig, um einen stabilen Zustand zu erreichen. [12-14] In der Folge kann es sowohl zu einer starken körperlichen Beeinträchtigung im Alltag, z.B. durch Abbau der Muskulatur oder bleibende somatische Folgeschäden, sowie zu einer psychischen Belastung durch ein sog. „Post Intensive Care Syndrome“ (PICS) bis hin zu einer schweren manifesten Depression kommen.[15,16] Diese Folgeerscheinungen werden durch die reine Erfassung der Sterblichkeit nicht berücksichtigt, spielen aber vermutlich bei Patient:innen mit mechanischer Kreislaufunterstützung eine besonders große Rolle. Neben den relevanten Auswirkungen auf das Behandlungsergebnis handelt es sich bei allen Formen der mechanischen Kreislaufunterstützung außerdem um sehr ressourcen-intensive Verfahren. [17] Dies betrifft sowohl den personellen Aufwand (z.B. hoher pflegerischer Aufwand und Einbindung der Kardiotechnik), als auch materielle Ressourcen, wie z.B. viele Transfusionen oder lange Aufenthalte auf der Intensivstation.[18]

Vor dem Hintergrund der hohen Sterblichkeitsraten und der häufigen Komplikationen sowie im Hinblick auf den Bedarf an teilweise knappen Ressourcen besteht die Notwendigkeit eines gezielten Einsatzes von mechanischer Kreislaufunterstützung. Eine adäquate Risikostratifizierung und Prognoseabschätzung spielen dafür eine entscheidende Rolle. In den vorliegenden Untersuchungen wurden folgende Aspekte aus diesem Themenkomplex näher beleuchtet: 1) Prognoseabschätzung, 2) Ansätze zur Optimierung einer laufenden Therapie und 3) Endpunkte zur Evaluation des Therapieerfolgs.

1.1 Prognoseabschätzung

Die frühzeitige Vorhersage, bei welchen Patient:innen ein günstiges (langfristiges) Nutzen-Risikoverhältnis durch die mechanische Kreislaufunterstützung besteht, hat eine enorm hohe

Bedeutung, denn wie oben beschrieben kann es im Rahmen der Therapie häufig zu schweren, langwierigen Komplikationen kommen, die mit einer dauerhaften Behinderung assoziiert sein können. Hierbei muss bedacht werden, dass einige Patient:innen auch ohne den Einsatz von mechanischer Kreislaufunterstützung noch eine Art von Lebensqualität haben können. Dies betrifft insbesondere die LVADs, die häufig zur Verbesserung der Symptomatik oder als Überbrückung bis zu einer Herztransplantation implantiert werden und somit nicht immer alternativlos sind. [19] Besonders im Rahmen der VA-ECMO-Therapie sind Risiko-Nutzen Betrachtungen schwierig, da die Entscheidung gegen eine Therapie in der Regel zum zeitnahen Versterben führt. [20] Es ist jedoch wichtig, keine Therapien zu initiieren, die aussichtslos sind, oder nicht im Einklang stehen mit dem Patient:innenwillen. [21] Dieses hier nur angedeutete Dilemma verdeutlicht die großen Herausforderungen, mit denen Kliniker konfrontiert sind sowie den Bedarf an Hilfsmitteln, die bei der Entscheidungsfindung herangezogen werden können. Objektive, einfach verfügbare, validierte Instrumente existieren allerdings bislang nicht, so dass in der klinischen Praxis in der Regel eine Vielzahl an unterschiedlichen Informationen nach persönlichem Ermessen berücksichtigt werden. Die finale Entscheidung ist dabei oft abhängig von den individuellen Überlegungen und Erfahrungen der handelnden Personen und folgt oftmals keinen objektivierbaren Kriterien (sog. „educated guess"). Es wurden in der Vergangenheit zwar mehrere Scores wie beispielsweise der SAVE-Score oder der RESP-Score entwickelt, [22,23] allerdings ist deren Anwendbarkeit in der Realität durch nicht vorliegende Informationen zu den inkludierten Variablen oder mangelnde Zeit in kritischen Notfallsituationen oftmals eingeschränkt.

Ein in vielen Bereichen der Medizin gängiges Hilfsmittel zur Risikostratifizierung und Prognoseabschätzung sind Biomarker. In den hier zusammengefassten Arbeiten wurden verschiedene Biomarker zur (Ergänzung) der Prognoseabschätzung bei mechanischer Kreislaufunterstützung untersucht, wobei der Fokus auf die VA-ECMO gelegt wurde. Die Auswahl der untersuchten Biomarker erfolgte literaturbasiert und es wurden insgesamt drei verschiedene Biomarker hinsichtlich ihres Mehrwerts im Rahmen der Risikostratifizierung und Prognoseabschätzung bei Initiierung der Therapie sowie während einer laufenden VA-ECMO

Therapie untersucht: Bilirubin, die Fibrinogen-Albumin-Ratio (FAR) und die Neutrophile-Lymphozyten-Ratio (NLR). Die Rationale für Bilirubin bestand in der Tatsache, dass in der Literatur Hinweise vorliegen, dass insbesondere ein beginnendes Leberversagen eine hohe prognostische Aussagekraft bei intensivpflichtigen Patient:innen hat. [24-27] Für Patient:innen mit mechanischer Kreislaufunterstützung liegen hierzu jedoch bisher nur wenig belastbare Daten vor. Bei der FAR handelt es sich ebenfalls um einen Marker, der in anderen Bereichen wie z.B. in der Onkologie vielversprechende Ergebnisse zeigt, vor allem bezüglich der Prädiktion von thromboembolischen Komplikationen. Diese gehören bei Patient:innen mit mechanischer Kreislaufunterstützung zu den häufigsten Komplikationen. [28-30] Die NLR hingegen ist ein inflammatorischer Marker, für den es im Rahmen der perioperativen Risikostratifizierung bereits vielversprechende Untersuchungsergebnisse gibt. [31-33] Auch hier existieren bei VA-ECMO- und LVAD-Patient:innen jedoch bislang kaum Daten. Da es im Rahmen der mechanischen Kreislaufunterstützung häufig zu einer ausgeprägten Inflammation kommt, [34,35] wurde die NLR unter diesen Bedingungen ebenfalls untersucht.

1.2 Ansätze zur Optimierung einer laufenden Therapie

Nicht nur die korrekte Indikationsstellung und Initiierung der mechanischen Kreislaufunterstützung sind für die adäquate Versorgung der Patient:innen relevant, sondern ebenso die Fortführung einer laufenden Therapie sowie die Vorbeugung von Komplikationen. So wurden folgende weitere Aspekte im Zusammenhang mit einer mechanischer Kreislaufunterstützung untersucht: 1) die Art der Evaluation der Hämodynamik und 2) die Form der Antikoagulation bei VA-ECMO.

Die Evaluation der Hämodynamik ist unter laufender mechanischer Kreislaufunterstützung von großer Bedeutung. [36] Neben dem Basismonitoring können abhängig von der Phase der Therapie verschiedene weitere Verfahren zum Einsatz kommen, wie z.B. der Swan-Ganz-Katheter als Gold-Standard zur Messung des Herzzeitvolumens (HZV), oder die transoesophageale oder transthorakale Echokardiographie zur Beurteilung der Kontraktilität bis hin zu nicht-invasiven Formen der HZV-Messung. [37-39] In dieser Arbeit wurde mit der nicht-invasiven Pulskonturanalyse (NIPKA) eine nicht-invasive Methode untersucht, die bisher nicht in der akuten Phase im intensivmedizinischen Umfeld bei Patient:innen mit mechanischer Kreislaufunterstützung zur Anwendung kommt, sondern eher in stabilen Situationen außerhalb der Intensivstation eine Einschätzung der Hämodynamik ermöglichen könnte. [40] Die Rationale bestand vor allem darin, dass Patient:innen mit mechanischer Kreislaufunterstützung (sowohl VA-ECMO-Patient:innen nach überstandener Therapie, als auch Patient:innen mit LVAD unter stabil laufender LVAD-Therapie) auch im Verlauf immer wieder hämodynamisch reevaluiert werden müssen. Die außerhalb der Intensivstation zur Verfügung stehenden Methoden wie die transthorakale Echokardiographie sind nur bedingt dazu in der Lage, das HZV adäquat zu messen. Gleichzeitig stellt das HZV jedoch eine wichtige Messgröße bei diesen Patient:innen dar. NIPKA könnte die Möglichkeiten zur Evaluation der Hämodynamik z.B. auch auf der Normalstation oder im ambulanten Umfeld erweitern und ggf. im Sinne eines Instrumentes zur Ersteinschätzung dabei unterstützen, die Notwendigkeit einer invasiven Evaluation zu eruieren.

Blutungskomplikationen sowie thromboembolische Komplikationen zählen zu den häufigsten Komplikationen unter mechanischer Kreislaufunterstützung und beeinflussen maßgeblich die Prognose. Verschiedene Antikoagulations-Regime (Heparin und direkte Thrombin-Inhibitoren (DTI)) kommen zur Anwendung [41,42] Es gibt bisher jedoch keine belastbare Evidenz bezüglich der Frage, welches Regime der Antikoagulation das günstigste Risiko/Nutzen-Profil bei VA-ECMO besitzt. Deshalb wurde die Literatur systematisch durchsucht und eine Meta-Analyse durchgeführt, um die Frage nach der geeigneten Antikoagulation bei VA ECMO beantworten zu können.

1.3 Endpunkte zur Evaluation des Therapieerfolgs

Die Sterblichkeit von Patient:innen mit mechanischer Kreislaufunterstützung ist wie eingangs erwähnt sehr hoch. Neben dem reinen Überleben spielt vor allem der funktionelle Status eine wichtige Rolle bezüglich der Evaluation des Therapieerfolgs. Dieses Problem besteht generell bei kritisch kranken Patient:innen, scheint jedoch bei Patient:innen mit mechanischer Kreislaufunterstützung aufgrund der Invasivität der Verfahren und den hohen Komplikationsraten besonders relevant zu sein. Somit besteht ein dringender Bedarf, weitere Endpunkte neben der Mortalität zur Verfügung zu haben, die im Rahmen der Risikostratifizierung und Prognoseabschätzung herangezogen werden können. Idealerweise müsste die Lebensqualität der Patient:innen vor sowie im Laufe der Therapie regelmäßig erfasst werden. Hierfür stehen zwar mehrere validierte Fragebögen zur Verfügung, allerdings ist deren Anwendung in der klinischen Praxis stark limitiert. [43,44] In den vorliegenden Untersuchungen wurde daher ein alternatives Maß untersucht, um den Einfluss auf das Leben der Patient:innen einfacher zu objektivieren: die „Days alive and out of Hospital" (DAOH). Die DAOH erfassen die Anzahl der Tage, die während eines definierten Zeitraums außerhalb des Krankenhauses bzw. außerhalb einer Versorgungseinrichtung verbracht wurden. [45,46] Die Vorteile der DAOH als patient:innenzentrierter Endpunkt bestehen vor allem in der einfachen Berechnung, der objektiven Erfassbarkeit sowie der breiten Verfügbarkeit.[47] In der Literatur liegen bislang vor allem Daten aus dem allgemeinen perioperativen Umfeld vor. [45,46] Bei Patient:innen mit mechanischer Kreislaufunterstützung gibt es bisher nur sehr wenige Daten. Dabei könnten es gerade diese Patient:innen sein, bei denen DAOH wichtige Informationen liefern, da lange komplikative Verläufe mit langen Krankenhausaufenthalten keine Seltenheit sind.

1.4 Hypothesen der vorliegenden Untersuchungen

Vor den genannten Hintergründen wurden in den vorliegenden Arbeiten die folgenden Hypothesen überprüft:

1) Prognoseabschätzung:

- Eine erhöhte Bilirubin-Konzentration ist bei Patient:innen mit VA-ECMO mit einer erhöhten Mortalität assoziiert.
- Eine erhöhte FAR ist bei Patient:innen mit VA-ECMO mit einer erhöhten Rate an thromboembolischen Komplikationen assoziiert.
- Eine erhöhte NLR ist bei Patient:innen mit VA-ECMO mit einer erhöhten Mortalität assoziiert.

2) Ansätze zur Optimierung einer laufenden Therapie:

- NIPKA ist bei Patient:innen nach Herztransplantation sowie nach LVAD-Implantation in stabilen Situationen außerhalb der Intensivstation dazu geeignet, eine erste Einschätzung der Hämodynamik zu ermöglichen.
- DTIs zur Antikoagulation sind bei Patient:innen mit VA-ECMO im Vergleich zu einer Antikoagulation mit Heparin mit weniger Komplikationen und mit einer niedrigeren Sterblichkeit assoziiert.

3) Endpunkte zur Evaluation des Therapieerfolgs:

- Bei Patient:innen mit LVAD besteht eine Diskrepanz zwischen den DAOH und der Mortalität ein Jahr nach der LVAD-Implantation, d.h. bestimmte Faktoren führen zwar nicht zum Versterben, sind jedoch mit einer signifikant längeren Hospitalisierung assoziiert.
- Bei Patient:innen mit terminaler Herzinsuffizienz, die auf eine Herztransplantation warten, ist eine LVAD-Implantation zur Überbrückung bis zur Transplantation mit signifikant niedrigeren DAOH assoziiert im Vergleich zu Patient:innen, die ohne LVAD auf ein Herzangebot warten.

2. Methoden

Diese kumulative Habilitationsschrift basiert auf sieben Originalarbeiten . Dabei handelt es sich um fünf retrospektive Kohortenstudien, eine prospektive Beobachtungsstudie sowie eine systematische Übersichtsarbeit mit Meta-Analyse. Alle durchgeführten Untersuchungen wurden vorab von der lokalen Ethik-Kommission genehmigt und im Einklang mit den Richtlinien für gute wissenschaftliche Praxis durchgeführt. Die Methoden der einzelnen Arbeiten werden im Folgenden beschrieben.

2.1 Bilirubin – ein möglicher prognostischer Mortalitätsmarker für Patient:innen mit ECLS

Bei dieser Studie handelte es sich um eine retrospektive Kohortenstudie. Patient:innen, die zwischen 2011 und 2018 in unserem Zentrum eine VA-ECMO-Therapie erhielten und älter als 18 Jahre waren, wurden in die Studie eingeschlossen.[48] Die primär untersuchte Variable war die Bilirubin-Konzentration. Der Bilirubin-Wert sowie die Transaminasen wurden bei Start der VA-ECMO-Therapie sowie am fünften Tag systematisch erhoben. Der primäre Endpunkt dieser Studie war die Gesamtmortalität während des Krankenhausaufenthaltes. Die Diskriminationsfähigkeit von Bilirubin bezüglich der Mortalität wurde unter Verwendung der Receiver Operating Characteristic Kurve (ROC) und der Fläche unter der Kurve (AUC) untersucht. Der Youden-Index wurde berechnet, um den Grenzwert mit der besten Sensitivität und Spezifität für den Endpunkt zu bestimmen. Um den unabhängigen Zusammenhang zwischen Bilirubin und Tod zu quantifizieren, wurde eine Cox-Regression mit vorab definierter multivariater Adjustierung für Geschlecht, Alter, linksventrikuläres/rechtsventrikuläres Unterstützungssystem (LVAD/RVAD) und kontinuierliche Nierenersatztherapie durchgeführt. In einer vorab definierten Sensitivitätsanalyse wurden Patient:innen mit Schockleber (definiert als GOT > 10 × Grenzwert (= 35 U/L)) ausgeschlossen.

2.2 Die Fibrinogen-Albumin-Ratio ist ein unabhängiger Prädiktor für thromboembolische Komplikationen bei Patient:innen mit VA-ECMO

Bei diesem Projekt handelte es sich ebenfalls um eine retrospektive Kohortenstudie. Die Studie umfasste alle Patient:innen, die zwischen 2011 und 2018 aufgrund eines refraktären kardiogenen Schocks am Universitätsklinikum Düsseldorf eine VA-ECMO-Therapie erhielten.[49] Die primär untersuchte Variable war die FAR am Tag des Beginns der VA-ECMO-Therapie. Die FAR wurde durch Division der Fibrinogenkonzentration durch die Albuminkonzentration berechnet. Darüber hinaus wurden die Fibrinogenkonzentration und die Albuminkonzentration unabhängig von der Ratio als Einzelwerte analysiert, um zu überprüfen, ob das Verhältnis beider Werte den Einzelwerten zur Prädiktion thromboembolischer Komplikationen überlegen ist. In einer zusätzlichen Analyse wurde die FAR am fünften Tag als Alternative zur FAR bei Therapiebeginn analysiert. Der primäre Endpunkt dieser Studie war die Inzidenz von im Krankenhaus auftretenden thromboembolischen Komplikationen. Thromboembolische Komplikationen wurden als eine Kombination aus nicht tödlichen arteriellen Thrombosen oder Embolien, nicht tödlichen venösen Thrombosen oder Embolien, nicht tödlichen ischämischen Schlaganfällen, nicht tödlichen Myokardinfarkten oder thromboembolischer vaskulärer Mortalität definiert. Auf der Grundlage der aktuellen Literatur erwarteten wir eine Inzidenz von etwa 30%. Bei einer geschätzten Studienstichprobe von 350 Patient:innen erwarteten wir demnach etwa 105 thromboembolische Ereignisse. Es durften somit bis zu 10 vorab definierte Kovariablen für die multivariate Analyse einbezogen werden. Die Unterscheidung der Ausgangs-FAR für die im Krankenhaus auftretenden thromboembolischen Komplikationen wurde mit Hilfe einer ROC-Analyse und der AUC analysiert. Ein Cut-off-Wert für die FAR wurde durch den Youden-Index bestimmt. Die multivariate logistische Regressionsanalyse wurde verwendet, um den unabhängigen Zusammenhang zwischen erhöhter FAR und im Krankenhaus aufgetretenen thromboembolischen Komplikationen zu bewerten. Es erfolgte eine Adjustierung für die folgenden Variablen: Alter, Geschlecht, koronare Herzerkrankung (KHK), ischämischer Schlaganfall in der Anamnese, Lungenembolie in der Anamnese, arterielle Hypertonie, Diabetes mellitus, Tage der VA-ECMO-Therapie, kontinuierliche veno-venöse Hämodialysebehandlung während des Krankenhausaufenthalts. Die Auswahl der Kovariablen basierte auf Literaturrecherchen und/oder klinischen Erfahrungen. Die Modellkalibrierung wurde mit dem Hosmer-Lemeshow-Test bewertet. Der Net Reclassification Index (NRI) und der integrierte Diskriminierungsindex (IDI) wurden berechnet.

2.3 Neutrophile-Lymphozyten-Ratio, Thrombozyten-Lymphozyten-Ratio und Procalcitonin zur frühzeitigen Beurteilung der Prognose bei Patient:innen mit VA-ECMO

In diese retrospektive Kohortenstudie wurden Patient:innen ≥ 18 Jahre, die zwischen 2011 und 2018 am Universitätsklinikum Düsseldorf aufgrund eines refraktären kardiogenen Schocks mit einer VA-ECMO behandelt wurden, eingeschlossen.[50] Die primär untersuchten Variablen dieser Studie waren die NLR, die Thrombozyten-Lymphozyten-Ratio (PLR) und Procalcitonin (PCT). Die Entscheidung für NLR und PLR basierte darauf, dass die prognostische Wertigkeit dieser Marker in anderen Population, wie z.B. perioperativ bei nicht-kardiochirurgischen Patient:innen, bereits gezeigt werden konnte. [31] . PCT wurde ausgewählt, um einen etablierten Marker für systemische Entzündungen vergleichend einzubeziehen. Alle Marker wurden innerhalb von 24 Stunden nach Beginn der VA-ECMO Therapie gemessen. Wenn mehrere Werte verfügbar waren, wurde die erste Messung nach Beginn der Behandlung ausgewählt. Die Anzahl der Leukozyten wurde mit automatisierten Laborgeräten gemessen. Die NLR wurde berechnet, indem die Anzahl der Neutrophilen durch die Anzahl der Lymphozyten dividiert wurden. Die PLR wurde auf die gleiche Art und Weise berechnet. Die PCT-Werte wurden durch das örtliche Labor gemessen.. Wir berechneten auch den SOFA-Score (Sequential Organ Failure Assessment Score) zum gleichen Zeitpunkt (= innerhalb von 24 Stunden nach Beginn der VA-ECMO) als zusätzliche Kovariable. Der primäre Endpunkt dieser Studie war die Gesamtmortalität im Krankenhaus. Da diese Studie eine retrospektive explorative Datenanalyse war, wurde keine formale Berechnung der Fallzahl durchgeführt. Auf der Grundlage der aktuellen Literatur erwarteten wir jedoch eine Gesamtmortalität im Krankenhaus für mit VA-ECMO behandelte Patient:innen von 50%. Es stand eine Stichprobe von 92 Patient:innen zur Verfügung, die die Ein- und Ausschlusskriterien erfüllten. Ausgeschlossen wurden Patient:innen, bei denen keine Werte für NLR, PLR und / oder PCT bzw. für den primären Endpunkt vorlagen. Daher erwarteten wir insgesamt etwa 45–50 Ereignisse, was eine multivariate Adjustierung mit bis zu fünf Kovariablen ermöglichte. Diese Kovariablen waren vordefiniert und umfassten das Alter, eine vorbestehende KHK, die Dauer der VA-ECMO-Therapie und die kontinuierliche venovenöse Hämodialyse. Die Diskrimination von NLR, PLR und PCT für die Sterblichkeit im Krankenhaus wurde anhand der ROC-Kurve mit der AUC analysiert. Ein Cut-off-Wert für NLR wurde durch den Youden-Index bestimmt. Cut-off-Werte für PLR und PCT wurden nicht berechnet, da es keine relevante Diskrimination bezüglich des primären Endpunktes gemäß der ROC-Kurve gab. Um die unabhängige Assoziation von NLR, PLR und PCT mit der Sterblichkeit im Krankenhaus zu quantifizieren, wurde eine multivariate binäre logistische Regression mit Einschluss der vordefinierten Kovariablen durchgeführt. Der NRI und der IDI wurden für alle drei Biomarker berechnet. Der De Long-Test wurde durchgeführt, um die AUCs der ROC-Kurven zu vergleichen. Wir führten dasselbe statistische Verfahren mit dem SOFA-Score durch (einschließlich ROC-Analyse und multivariater logistischer Regression) und bewerteten den prognostischen Wert der NLR, wenn sie zum SOFA-Score hinzugefügt wurde, indem wir die AUCs eines logistischen Regressionsmodells mit SOFA-Score mit und ohne NLR unter Verwendung des De Long-Tests verglichen.

2.4 Nichtinvasive Evaluation der Hämodynamik bei Patient:innen nach Herztransplantation oder Implantation eines linksventrikulären Unterstützungssystems

Bei dieser Studie handelte es sich um eine prospektive Beobachtungstudie von Patient:innen nach Herztransplantation (HTX) oder LVAD-Implantation.[51] Alle Patient:innen waren klinisch stabil und hatten zum Zeitpunkt der Untersuchung die Intensivstation verlassen. Ausschlusskriterien waren ein Alter < 18 Jahre, eine schwere Trikuspidalklappen-Dysfunktion und ein nichtinvasiver Blutdruckunterschied (NIBP) von > 20 mmHg zwischen linkem und rechtem Arm vor der Untersuchung. Patient:innen mit schwerer Trikuspidalklappen-Dysfunktion wurden ausgeschlossen, da dies zu einer Überschätzung bzw. Unterschätzung des Herzzeitvolumens (HZV) durch Thermodilution (TD) führen könnte (s. unten). Patient:innen mit Blutdruckdifferenz wurden ausgeschlossen, da dies zu einer falschen Blutdruckkalibrierung mit nachfolgenden falschen Berechnungen führen könnte. Die Patient:innen wurden einer Rechtsherzkatheteruntersuchung einschließlich TD unterzogen, die routinemäßig während des Krankenhausaufenthalts der Patient:innen in einer Ambulanz durchgeführt wurde. Es wurden mindestens drei TD-Messungen mit 10 ml-Boli kalter Kochsalzlösung (< 10 Grad Celsius) durchgeführt. Die kalte Kochsalzlösung wurde wie in der Literatur beschrieben zufällig während des gesamten Atemzyklus injiziert. Einzelmessungen wurden ausgeschlossen, wenn die Variabilität 10% im Vergleich zu den Durchschnittsergebnissen überstieg. Für die Datenanalyse wurde der Mittelwert von drei TD-Messungen innerhalb eines Bereichs von ± 10% verwendet. Herzindex (HI), Schlagvolumen (SV) und der sytemisch-vaskuläre Widerstand (SVR) wurden berechnet. Gleichzeitig wurde eine autokalibrierte NIPKA-Messung durchgeführt. Die Patient:innen wurden über zwei Fingermanschetten mit dem CNAP-Monitor (V.5.2.14; CNSystems Medizintechnik AG, Graz, Österreich) verbunden. Für die Kalibrierungsmessung wurde eine oszillometrische Blutdruckmanschette verwendet. Das HZV wurde kontinuierlich auf einer „Beat-to-Beat“-Basis aufgezeichnet. Die Dokumentation der NIPKA-Werte begann zum Zeitpunkt der kalten Kochsalzinjektion. Bei HTX-Patient:innen waren TD-Messungen nur zulässig, wenn das NIPKA-Signal visuell als ausreichend angesehen wurde. Kriterium hierfür war eine physiologische Form der arteriellen Druckkurve mit systolischem und diastolischem Anteil sowie Inzisur durch Schluss der Aortenklappe. Bei LVAD-Patient:innen konnte keine physiologische arterielle Druckkurve mit ausreichender Signalqualität erwartet werden. Daher wurden immer dann hämodynamische Messungen durchgeführt, wenn ein NIPKA-Signal mit der Möglichkeit zur Berechnung hämodynamischer Parameter verfügbar war. Kriterium war hier, dass eine Fläche unter der arteriellen Druckkurve als Surrogat für eigenen Auswurf visuell erkennbar war. Der Mittelwert der aufgezeichneten NIPKA-Messungen von Schlag zu Schlag wurde gemittelt und für die Datenanalyse verwendet. Zur Beschreibung der Übereinstimmung zwischen TD und NIPKA wurde eine Bland-Altman-Analyse durchgeführt. Diese statistische Methode bewertet die mittlere Differenz und berechnet die Grenzen der Übereinstimmung („Limits of Agreement" (LOA) = ± 1,96 x SD), um die Varianz der Werte zu ermitteln.

2.5 Evaluation des Outcomes bei Patient:innen, die während der extrakorporalen Membranoxygenierung mit Heparin oder direkten Thrombin-Inhibitoren behandelt wurden: Eine systematische Übersichtsarbeit und Meta-Analyse

Bei dieser Studie handelte es sich um eine systematische Übersichtsarbeit mit Meta-Analyse.[52] Die untersuchte Population bestand aus erwachsenen und pädiatrischen Patient:innen, die mit veno-arterieller oder veno-venöser extrakorporaler Membranoxygenierung ECMO behandelt wurden. Die Intervention bestand in DTI (Bivalirudin oder Argatroban) als primäre Antikoagulationsstrategie während der ECMO-Therapie. Die Antikoagulation mit Heparin während der ECMO war die Kontrollgruppe im Sinne eines „standard of care". Der primäre Endpunkt war die Sterblichkeit im Krankenhaus. Sekundäre Endpunkte waren die Anzahl der Patient:innen mit schweren und leichten Blutungsereignissen, patient:innen- und gerätebezogene thrombotische oder ischämische Ereignisse während der ECMO-Therapie, Anzahl der Stunden der ECMO-Unterstützung, Dauer des Krankenhausaufenthaltes in Tagen, Prozentsatz der aktivierten partiellen Thromboplastinzeit (aPTT) innerhalb des therapeutischen Fensters und Stunden bis zum Erreichen von therapeutischen aPTT-Werten. Eingeschlossen wurden veröffentlichte und unveröffentlichte randomisierte kontrollierte Studien (Anfrage der Daten bei den entsprechenden Autor:innen), prospektive oder retrospektive Kohortenstudien und Fall-Kontroll-Studien, die DTI im Vergleich zu Heparin bei ECMO-Patient:innen untersuchten. Die Studienauswahl war auf die englische Sprache beschränkt und es wurden nur vollständige wissenschaftliche Berichte berücksichtigt. Posterpräsentationen, Konferenzzusammenfassungen, systematische Übersichtsarbeiten und Meta-Analysen, Studien, in denen DTI nicht mit Heparin bei ECMO-Patient:innen verglichen wurde, Studien, in denen Patient:innen DTI nur als sekundäre Antikoagulationsstrategie erhielten, und Studien, die keinen der oben genannten Endpunkte berichteten, wurden ausgeschlossen. Die folgenden medizinischen Bibliotheken wurden nach geeigneten Studien durchsucht, die von der Gründung bis Januar 2022 veröffentlicht wurden: Pubmed/Medline, Cochrane Library, CINAHL, Embase. Medizinische Schlagwörter (MeSh), Feldbegriffe, Textwörter und Boolesche Operatoren wurden in einer blockbildenden Suche kombiniert. Die Suchbegriffe enthielten unter anderem „extrakorporale Membranoxygenierung", „Bivalirudin", „Argatroban", „direkter Thrombinhemmer", „Heparin", „Antikoagulation", „Embolie und Thrombose", „Blutung", „Überleben" und „unerwünschtes Arzneimittelereignis". Das erste Suchdatum war der 18. August 2021, das letzte Suchdatum war der 20. Januar 2022. Zusätzlich wurde die lokale medizinische Bibliothek der Universität Düsseldorf (ULB) durchsucht und die Autor:innen der in Frage kommenden Studien wurden bezüglich unveröffentlichter Daten kontaktiert. Zwei unabhängige Forscher:innen sichteten die Titel und Abstracts der Suchergebnisse aus jeder medizinischen Bibliothek und holten die in Frage kommenden Studien ein. Im zweiten Schritt wählten die beiden Forscher:innen unabhängig voneinander Studien aus, die die vordefinierten Eignungskriterien erfüllten und stützten sich dabei auf den vollständigen Text. Nach jedem Schritt wurden Meinungsverschiedenheiten zwischen den beiden Forscher:innen diskutiert. Bei diesem Prozess wurden keine automatischen Tools verwendet. Daten zu Studienmerkmalen und Endpunkten wurden von einem Prüfer aus dem vollständigen Text, aus Tabellen und aus Anhängen extrahiert. Die Einträge wurden von einem zweiten Prüfer unabhängig überprüft. Wenn Datenelemente (primäre oder sekundäre Endpunkte) nicht aus den Publikationen extrahiert werden konnten, wurden die Autor:innen per E-Mail kontaktiert und gebeten, die fehlenden Daten zu ergänzen. Darüber hinaus wurden die Autor:innen gebeten, die extrahierten Daten aus ihren Studien in der endgültigen Fassung dieses Manuskripts zu überprüfen. Das Bias-Risiko wurde von zwei unabhängigen Prüfer:innen getrennt anhand der Newcastle-Ottawa-Skala für nicht randomisierte Studien untersucht. Die Studienqualität wurde anhand der Skalenbewertungen als gut, mittelmäßig oder schlecht eingestuft. Für alle dichotomen Ergebnisse wurde die Odds Ratio als Effektmaß für die Datensynthese und die Darstellung der Ergebnisse verwendet. Für primäre und sekundäre Endpunkte wurde eine Meta-Analyse durchgeführt. Um die statistische Heterogenität zwischen den Studien zu bewerten, wurden I2-Tests und CochraneQ-Tests durchgeführt. Es wurden Subgruppenanalysen für erwachsene und pädiatrische Patient:innen durchgeführt.. Diese Subgruppen wurden a priori definiert. Für jedes Ergebnis wurden Funnel-Plots erstellt, um Verzerrungen bei der Berichterstattung zu berücksichtigen. Für die statistische Analyse wurde ein Review Manager (RevMan) verwendet und ein p-Wert von <0,05 als signifikant angesehen. Das Konfidenzniveau für jedes Ergebnis wurde nach dem GRADE-Ansatz bewertet und als Zusammenfassung der Ergebnisse in einer Tabelle dargestellt.

2.6 "Days alive and out of hospital" nach Implantation eines linksventrikulären Unterstützungssystems

Bei der vorliegenden Studie handelte es sich um eine retrospektive Kohortenstudie.[53] Es wurden konsekutive Patient:innen im Alter von ≥18 Jahren eingeschlossen, die zwischen 2010 und 2020 aufgrund einer ischämischen Herzerkrankung oder einer dilatativen Kardiomyopathie am Universitätsklinikum Düsseldorf eine LVAD-Implantation erhielten. Patient:innen mit fehlenden Daten oder unvollständigen medizinischen Unterlagen zum primären Endpunkt wurden ausgeschlossen. Patient:innen mit anderen Grunderkrankungen als ischämischer Herzkrankheit oder dilatativer Kardiomyopathie, die zu chronischer Herzinsuffizienz führen, wurden ebenfalls ausgeschlossen, um eine möglichst homogene Kohorte zu erhalten. Der primäre Endpunkt dieser Studie waren die DAOH während des ersten Jahres nach der LVAD-Implantation. DAOH wurden berechnet, indem die Tage aller

Krankenhausaufenthalte im ersten Jahr nach der LVAD-Operation addiert und von 365 Tagen abgezogen wurden. Falls der Patient innerhalb des ersten Jahres verstarb, wurde die Differenz zwischen den überlebten Tagen und 365 Tagen zu den Tagen der Krankenhausaufenthalte addiert, bevor sie von 365 Tagen abgezogen wurden. Diese Methode basiert auf der Validierungsstudie von DAOH bei Herzinsuffizienzpatient:innen. Da LVAD-Patient:innen sehr eng an unser Zentrum angebunden sind, ist es unwahrscheinlich, dass diese Patient:innen in einem externen Krankenhaus eingeliefert werden, sodass die retrospektive Berechnung von DAOH als zuverlässig angesehen werden kann. Der wichtigste sekundäre Endpunkt war die Mortalität 1 Jahr nach der LVAD-Implantation, um DAOH und Mortalität gegenüberzustellen. Die Auswahl der Variablen, die in die Analyse einbezogen wurden, basierte in erster Linie auf zwei großen Netzwerkstudien, die ein Bayes'sches Modell zur Vorhersage des Überlebens nach LVAD-Implantation verwendeten. Darüber hinaus wurde eine Literaturrecherche durchgeführt, um weitere perioperative Variablen zu finden, die nachweislich mit einer erhöhten Sterblichkeit nach LVAD-Implantation in Zusammenhang stehen. Dementsprechend haben wir die folgenden 10 Variablen vordefiniert: Alter (≥65 vs. <65 Jahre), Art der Grunderkrankung (ischämische Herzkrankheit vs. dilatative Kardiomyopathie), INTERMACS-Profil, intraoperative Implantation eines Rechtsherzunterstützungssystems (RVAD), chirurgische Technik (minimalinvasive Chirurgie vs. Sternotomie), vorbestehende chronische Nierenerkrankung (CKD) gemäß den Kriterien von Kidney Disease: Improving Global Outcomes (KDIGO) Kriterien, präoperative mechanische Kreislaufunterstützung (pMCS), präoperative Levosimendan-Therapie, postoperative Dialyse und postoperative Tracheotomie. Wir führten eine vollständige Fallanalyse durch. Zunächst führten wir eine univariate Analyse mit jeder der 10 vorab definierten Variablen durch. Anschließend nahmen wir alle Faktoren, die eine signifikante univariate Assoziation mit DAOH aufwiesen, in das multivariate Modell auf (Signifikanzniveau = $P \leq 0{,}05$). Darüber hinaus wurde der Einfluss jeder Variable auf die 1-Jahres-Mortalität untersucht, um DAOH und Mortalität zu vergleichen. DAOH wurden mit dem Mann-Whitney-U-Test verglichen, da davon ausgegangen wurde, dass diese Daten nicht normalverteilt sind. Es wurde eine multivariate quantile Regression durchgeführt. In dieser

Analyse wurde DAOH als abhängige Variable festgelegt. Die Überlebensanalyse wurde mit Kaplan-Meier Kurven sowie univariater und multivariater Cox-Regression durchgeführt. Für das INTERMACS-Profil wurden der Kruskal-Wallis-Test und der Jonckheere-Terpstra-Test durchgeführt. Um die Überlebensraten zu vergleichen, wurde ein Log-Rank-Test (Mantel-Cox) durchgeführt und die Ergebnisse werden als Prozentsatz des Überlebens (%) mit der Hazard Ratio (HR) und dem 95% Konfidenzintervall (KI) dargestellt. Da es sich um eine retrospektive und explorative Datenanalyse handelte, wurde keine formale Berechnung der Fallzahl durchgeführt.

2.7 Auswirkungen von linksventrikulären Herzunterstützungssystemen auf die "Days alive and out of hospital" bei hämodynamisch stabilen Patient:innen mit terminaler Herzinsuffizienz im Endstadium: Eine Propensity Score Matching-Kohortenstudie

Bei dieser Studie handelte es sich um eine retrospektive Kohortenstudie.[54] Alle Patient:innen im Alter von ≥18 Jahren, die zwischen September 2010 und Dezember 2020 am Universitätsklinikum Düsseldorf eine LVAD-Implantation oder HTX erhielten, wurden mit Hilfe der vorliegenden Datenbanken gescreent. Patient:innen, die für eine HTX gelistet waren, aber vor Erhalt einer HTX verstarben, wurden nicht in die Datenbank aufgenommen. Hämodynamisch stabile „bridge-to-transplant“ (BTT)-LVAD-Patient:innen (≥INTERMACS 4) und hämodynamisch stabile HTX-Patient:innen auf der regulären Warteliste, die zum Zeitpunkt der Aufnahme theoretisch für eine Therapie mit einem Herzunterstützungssystem in Frage kamen, wurden einbezogen. Hämodynamische Stabilität wurde definiert als die Unabhängigkeit von intravenöser inotroper oder vasoaktiver Unterstützung zum Zeitpunkt der LVAD-Implantation bzw. der alleinigen HTX-Aufnahme. Wenn der Zeitraum zwischen der Aufnahme in die Warteliste und der LVAD-Implantation mehr als einen Monat betrug, wurden die Patient:innen ausgeschlossen. Die Aufnahme in die HTX-Warteliste nach einer BTT-LVAD-Implantation war kein Ausschlusskriterium. Dadurch wollten wir eine Verzerrung durch

Patient:innen vermeiden, die aufgrund einer längeren HTX-Wartezeit eine LVAD-Implantation erhalten hatten. Patient:innen mit LVAD als „destination therapy“ (DT) aufgrund einer Kontraindikation für eine HTX und Patient:innen mit fehlenden Daten oder unvollständigen medizinischen Unterlagen zu den primären Endpunkten wurden ebenfalls ausgeschlossen. Da die Gruppen nicht randomisiert waren, führten wir eine Propensity-Score-(PS)-Analyse durch. Zur Schätzung des PS wurde ein logistisches Regressionsmodell mit sieben präoperativen Patient:innenmerkmalen verwendet. Das PS-Matching wurde mit einem Fall-Kontroll-Matching-Algorithmus mit einer Kaliberbreite von 0,2 Standardabweichungen des Logits durchgeführt. Die Ausgewogenheit der Patient:innenmerkmale vor und nach dem Matching wurde mithilfe von t-Tests für zwei Stichproben (kontinuierliche Variablen, nach Überprüfung auf Normalverteilung) oder Chi-Quadrat-Tests (kategoriale Variablen) bewertet. Es gibt nur wenige Literaturangaben zu Entscheidungskriterien für HTX oder BTT-LVAD bei hämodynamisch stabilen Patient:innen. Daher wurden die folgenden präoperativen Merkmale, die die Entscheidung für oder gegen jede Behandlungsoption beeinflussen könnten, zur Berechnung des PS ausgewählt: Alter, Geschlecht, Body-Mass-Index (BMI), Diagnose (ischämische Kardiomyopathie, dilatative Kardiomyopathie, andere), präoperatives Nierenversagen (definiert als Serumkreatinin ≥ 1,5 mg/dl), New York Heart Association (NYHA)-Status und die linksventrikuläre Auswurffraktion (LVEF, gemessen mittels transthorakaler Echokardiographie). Die LVEF wurde als erhalten (>50 %), leicht reduziert (40–49 %) und reduziert (<40 %) eingestuft. Der primäre Endpunkt dieser Studie waren die DAOH ein Jahr nach der Entscheidung für die HTX-Listung oder nach der BTT-LVAD-Implantation. Die DAOH wurden wie zuvor in der Literatur berichtet berechnet und als Summe der Krankenhaustage für jeden Patient:innen, subtrahiert von 365 Tagen, gemessen. Wenn ein Patient im ersten Jahr verstarb, wurde die Differenz zwischen den überlebten Tagen und 365 Tagen zur Summe der Tage im Krankenhaus vor dem Abzug von 365 Tagen addiert. Krankenhausaufenthalte wurden als geplante oder ungeplante Aufenthalte von mindestens einer Übernachtung im Krankenhaus definiert. Alle Patient:innen mit Herzinsuffizienz im Endstadium standen in enger Verbindung zu unserem Zentrum; daher erwarteten wir keine externen Krankenhausaufenthalte ohne einen Vermerk in der Krankenakte der Patient:innen. Zu den sekundären Endpunkten gehörten die Dauer bis zur HTX, eine HU-Listung, die Anzahl, Dauer und Gründe für Krankenhausaufenthalte sowie das Überleben. Da es sich um eine retrospektive und explorative Datenanalyse handelte, wurde keine formale Berechnung der Fallzahl durchgeführt. Aufgrund der geringen Stichprobengröße dieser Studie wurde der Shapiro-Wilks-Test verwendet, um die Normalverteilung zu testen und die geeignete statistische Methode auszuwählen. Basierend auf den Ergebnissen des Shapiro-Wilks-Tests wurde ein nichtparametrischer Mann-Whitney-U-Test verwendet, um DAOH in beiden Gruppen zu vergleichen. Der Test auf Signifikanz der Nullhypothese wurde unter Verwendung der Bayes'schen Analyse für die Mann-Whitney-U-Statistik durchgeführt. Um die sekundären Endpunkte zu vergleichen, wurden deskriptive Statistiken sowie eine Kaplan-Meier-Analyse für den Überlebenszeitvergleich durchgeführt.

3. Ergebnisse

Die Ergebnisse der inkludierten Studien werden in den folgenden Abschnitten zusammengefasst. Es werden ausschließlich Daten aus den zugrundeliegenden und publizierten Originalarbeiten vorgestellt.

3.1 Bilirubin – ein möglicher prognostischer Mortalitätsmarker für Patient:innen mit ECLS

Während des Beobachtungszeitraums unterzogen sich insgesamt 438 Patient:innen einer VA-ECMO-Therapie. Alle Patient:innen erhielten die Therapie aufgrund eines schweren kardiogenen Schocks oder Herzstillstands. Von ihnen überlebten 298 Patient:innen die ersten vier Tage und konnten in die finale Analyse eingeschlossen werden. Das mediane Alter betrug 59 ± 14 Jahre und 219 (74 %) Patient:innen waren männlich. Die mittlere VA-ECMO-Therapiedauer betrug 9 ± 7 Tage. Für die Sensitivitätsanalyse ohne Schockleber-Konstellation blieben 220 Patient:innen übrig. Die Krankenhaus-Mortalität betrug 42,6 % (n = 127). Der mittlere Bilirubinspiegel zu Beginn der VA-ECMO-Therapie lag bei 2,04 ± 2,73 mg/dL, und der mittlere Bilirubinspiegel am fünften Tag betrug 5,14 ± 12,01 mg/dL. Die AUC der ROC für Bilirubin am fünften Tag betrug 0,72 (95% KI: 0,66-0,78) (siehe Abbildung 1). Die AUC für den Trend (d. h. die absolute Differenz) zwischen Bilirubin zu Beginn und an Tag 5 betrug 0,70 (95% KI 0,64-0,77). Die ROC für Patient:innen ohne Schockleber ergab eine AUC von 0,67 (95% KI): 0,59-0,75). Der Youden-Index ergab einen Grenzwert für Bilirubin an Tag 5 von 2,23 mg/dl mit einer Sensitivität von 0,70. Die Cox-Regression mit multivariabler Anpassung ergab einen signifikanten Zusammenhang zwischen Bilirubin am Tag 5 und der Sterblichkeit mit einer Hazard Ratio (HR) von 2,24 (95% KI: 1,53-3,30). In der Sensitivitätsanalyse ohne Patient:innen mit Schockleber war dieser Zusammenhang immer noch signifikant (HR 2,08 (95% KI: 1,33-3,26).

3.2 Die Fibrinogen-Albumin-Ratio ist ein unabhängiger Prädiktor für thromboembolische Komplikationen bei Patient:innen mit VA-ECMO

Von den eingeschlossenen 344 Patient:innen erlitten insgesamt 117 Patient:innen (34 %) während ihres Krankenhausaufenthalts eine thromboembolische Komplikation. Die häufigsten thromboembolischen Komplikationen waren arterielle thromboembolische Ereignisse (63 Patient:innen = 18,3%) und ischämische Schlaganfälle (40 Patient:innen = 11,6%). Die Gesamtmortalität im Krankenhaus betrug 58,1 % (200/344). Patient:innen mit thromboembolischer Komplikation während des Krankenhausaufenthalts hatten eine signifikant höhere FAR (158±96) als Patient:innen ohne TeC (108±62). Die ROC-Analyse für die Baseline-FAR und thromboembolische Komplikationen im Krankenhaus ergab eine AUC von 0,67 [95% KI 0,61-0,74; p<0,0001] (siehe Abbildung 1). Am fünften Tag waren noch Daten für 212 Patient:innen verfügbar. Die ROC-Analyse für FAR am fünften Tag und thromboembolische Komplikationen im Krankenhaus ergab eine AUC von 0,66 [95% KI 0,57-0,76; p<0,0001]. Der basierend auf dem Youden-Index ermittelte Cut-off betrug 130 für die FAR zu Beginn der Untersuchung. Eine binäre logistische Regressionsanalyse mit multivariabler Adjustierung für zehn vorab definierte Ko-Variablen ergab einen signifikanten Zusammenhang zwischen der FAR zu Beginn der Behandlung und thromboembolischen Komplikationen während des Krankenhausaufenthaltes mit einer OR von 3,72 (95% KI 2,26-6,14). Die OR für den Zusammenhang zwischen der FAR an Tag 5 und thromboembolischen Komplikationen im Krankenhaus betrug 5,79 [95% KI 2,41-13,89].

3.3 Neutrophile-Lymphozyten-Ratio, Thrombozyten-Lymphozyten-Ratio und Procalcitonin zur frühzeitigen Beurteilung der Prognose bei Patient:innen mit VA-ECMO

Insgesamt wurden 344 Patient:innen für diese Studie untersucht. Da die Anzahl der weißen Blutkörperchen routinemäßig nur einmal wöchentlich gemessen wurde, mussten 252

Patient:innen aufgrund fehlender Werte ausgeschlossen werden. Somit blieben 92 Patient:innen mit vollständigen Daten für die statistische Analyse übrig. Die Sterblichkeitsrate während des Krankenhausaufenthaltes betrug 48,5%. Die ROC-Analyse der NLR ergab eine AUC von 0,65 [95% KI): 0,53-0,76; p=0.015] (siehe Abbildung 1). Die AUCs von PLR und PCT lagen bei 0,47 [95% KI 0,35-0,59; p=0,645] und 0,54 [95% KI 0,42-0,66; p=0,521]. Nach dem De Long-Test war die AUC der NLR nicht signifikant höher als die AUC von PLR und PCT. Die Berechnung des Youden-Index ergab einen Cut-off von 13 für die NLR. Für PLR und PCT wurde kein Cut-off Berechnung durchgeführt, da die Diskriminierung dieser Werte für die Mortalität auf der Grundlage der ROC-Analyse zu schwach war. Die multivariate binäre logistische Regression ergab eine adjustierte Odds Ratio (OR) von 3,32 [95% KI 1,13-9,76; p=0,029] für die NLR. Die adjustierten ORs für PLR und PCT waren 1,0 [95% KI 0,998-1,002; p=0,951] bzw. 1,02 [95% KI 0,99-1,05; p=0,093]. Neben der NLR war die CVVHD die einzige Kovariable, die in allen drei logistischen Regressionsmodellen einen unabhängigen Zusammenhang mit der Mortalität zeigte.

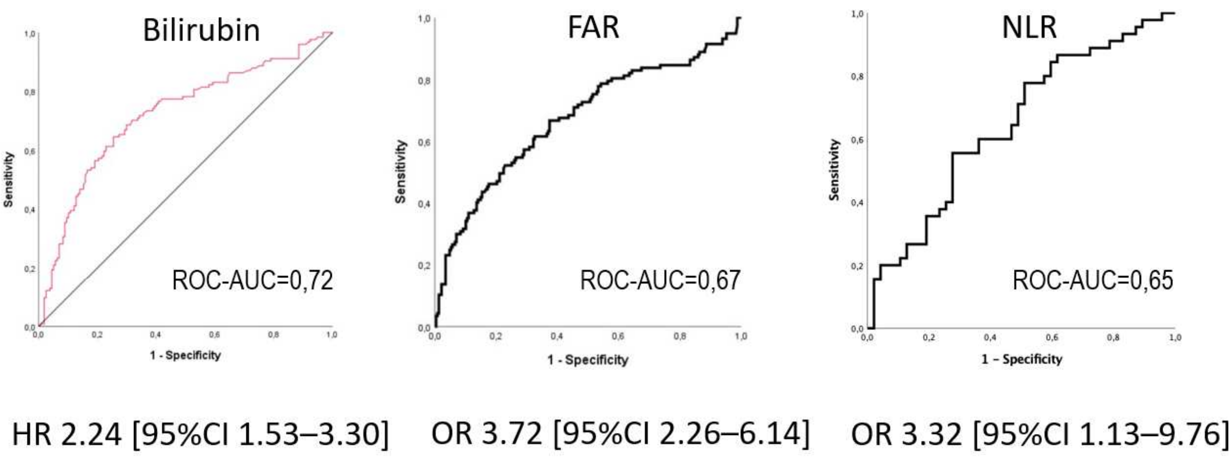

Abbildung 1: ROC Kurven für Bilirubin, FAR und NLR. X-Achse: 1-Spezifität. Y-Achse: Sensitivität. Die Abbildung wurde modifiziert nach Bunte et al.[48], Roth et al.[49] und Roth et al. [50] mit freundlicher Genehmigung der Verläge.

3.4 Nichtinvasive Evaluation der Hämodynamik bei Patient:innen nach Herztransplantation oder Implantation eines linksventrikulären Unterstützungssystems

Insgesamt 29 Patient:innen wurden prospektiv in diese Beobachtungsstudie eingeschlossen. Ein Patient musste aufgrund einer schweren Trikuspidalklappeninsuffizienz wieder ausgeschlossen werden, so dass 28 Patient:innen für die finale Analyse verblieben (10 HTX-Patient:innen (90 % männlich, Alter 47 ± 8 Jahre, LVEF 61 ± 7%) und 18 LVAD-Patient:innen (LVEF 24 ± 5%, 89% männlich, Alter 53 ± 10 Jahre, pulsatile Pumpe n = 4; continuous-flow Pumpe n = 14)). Bei HTX-Patient:innen zeigte die Messung der Hämodynamik mittels TD oder NIPKA unter Verwendung des CNAP-Monitors einen signifikanten Unterschied beim HZV (TD 6,06 ± 1,48 l/min, NIPKA 7,12 ± 1,08 l/min, p<0,001), Herzindex (TD 2,92 ± 0,86 l/min/m2, NIPKA 3,36 ± 0,42 l/min/m2 p<0,001), SV (TD 70 ± 22 ml, NIPKA 86 ± 17 ml, p<0,001), und beim SVR (TD 1397 ± 451 dyne*s*cm-5, NIPKA 1108 ± 189 dyne*s*cm-5, p<0,001). Die Bland-Altman-Analyse ergab eine mittlere Abweichung von +1,05 l/min (Grenzen der Übereinstimmung (LOA) ± 4,09 l/min, prozentualer Fehler (PE) 62,1 %) für das HZV, +0,45 l/min/m2 (LOA ± 1,92 l/min/m2, PE 61,1%) für den HI, +16 ml (LOA ± 49 ml, PE 63,1%) für das SV und -289 dyne*s*cm-5 (LOA ± 887 dyne*s*cm-5, PE 70,8%) für den SVR. Bei allen 18 LVAD-Patient:innen konnte mit dem CNAP-Monitor kein adäquates NIPKA-Signal ermittelt werden.

3.5 Evaluation des Outcomes bei Patient:innen, die während der extrakorporalen Membranoxygenierung mit Heparin oder direkten Thrombin-Inhibitoren behandelt wurden: Eine systematische Übersichtsarbeit und Meta-Analyse

Bei der systematischen Suche wurden insgesamt 4.385 Datensätze identifiziert, die in den Screeningprozess aufgenommen wurden. Nach Entfernung von 303 Duplikaten verblieben

4.082 Datensätze für das Screening der Titel und Abstracts. Von diesen Datensätzen wurden 4.031 Datensätze ausgeschlossen, da sie nicht den Einschlusskriterien für Titel und Abstracts entsprachen. Somit blieben 51 potenziell relevante Artikel. Unter diesen Artikeln identifizierten wir 25 reine Kongressbeiträge, 3 Studien, in denen die Patient:innen zwischen Interventions- und Kontrollgruppe gewechselt haben, und 5 Studien, die Nafamostatmesilat, nicht aber DTI im Vergleich zu Heparin untersuchten. Diese 33 Studien wurden daher ebenfalls ausgeschlossen, so dass schließlich 18 retrospektive Kohortenstudien in die finale Datenextraktion eingeschlossen wurden. Nach der Bewertung des „Risk of Bias" hatte die Mehrheit der Studien (10 Studien) ein hohes Bias-Risiko, 3 Studien hatten ein mittleres Bias-Risiko und 5 Studien hatten ein geringes Bias-Risiko. Das Hauptergebnis dieser Analyse ist, dass die Verwendung von DTI zur Antikoagulation in signifikantem Maße mit einer geringeren Sterblichkeit im Krankenhaus verbunden ist, sowohl bei pädiatrischen als auch bei erwachsenen ECMO-Patient:innen im Vergleich zu Heparin. Darüber hinaus sind DTI (insbesondere Bivalirudin) in Bezug auf schwerwiegende Blutungsereignisse sowie thrombotische Komplikationen im Vergleich zu Heparin gemäß unserer Analyse überlegen. Außerdem bieten DTI eine stabile Antikoagulation während der ECMO-Therapie, gemessen am prozentualen Anteil der Zeit im therapeutischen Bereich.

3.6 "Days alive and out of hospital" nach Implantation eines linksventrikulären Unterstützungssystems

Insgesamt lagen die Daten von 227 Patient:innen in der Datenbank vor. Sechs Patient:innen (2,6 %) mussten aufgrund unvollständiger Krankenakten oder anderer Grunderkrankungen als ischämische Herzkrankheit oder dilatative Kardiomyopathie ausgeschlossen werden. Somit blieben 221 Patient:innen für die statistische Analyse. Daten zum primären Endpunkt und allen anderen Ko-Variablen waren vollständig. Der Median der DAOH in der gesamten Kohorte betrug 273 (Interquartilsbereich 67-321). Die Gesamtmortalität nach einem Jahr betrug 24,9 %. In der univariaten Analyse zeigten sechs Variablen einen signifikanten Zusammenhang mit

DAOH. Als präoperative Faktoren waren CKD, pMCS und INTERMACS < 3 mit niedrigeren DAOH assoziiert [CKD: 280 (155-322) vs. 230 (0-219), P = 0,0286; pMCS: 294 (155-325) vs. 243 (0-293), P = 0,0004; INTERMACS 1: 218 (0-293) vs. INTERMACS 2: 264 (6-320) vs. INTERMACS 3: 299 (228-325) vs. INTERMACS 4: 313 (247-332), P ≤ 0.0001]. Die intraoperative zusätzliche Implantation eines RVAD war ebenfalls mit einer geringeren DAOH assoziiert [RVAD: 290 (160-325) vs. 174 (0-277), p ≤ 0,0001]. Postoperativ waren Dialyse und Tracheotomie assoziiert mit niedrigeren DAOH [Dialyse: 300 (252-326) vs. 186 (0-300), P ≤ 0,0001; Tracheotomie: 292 (139-325) vs. 168 (0-269), P ≤ 0,0001] (siehe Abbildung 2). Eine multivariate Analyse mit einem quantilen Regressionsmodell zeigte, dass alle univariat assoziierten Faktoren außer pMCS einen unabhängigen Zusammenhang mit der DAOH über verschiedene Quantile beibehielten (siehe Abbildung 3). Nach der Kaplan-Meier-Analyse war nur die postoperative Dialyse mit einer signifikant niedrigeren Überlebensrate 1 Jahr nach der Operation assoziiert (Überleben: keine Dialyse 89,4% vs. Dialyse 70,1%, HR: 0,56, 95% KI: 0,33-0,94; P = 0,031).

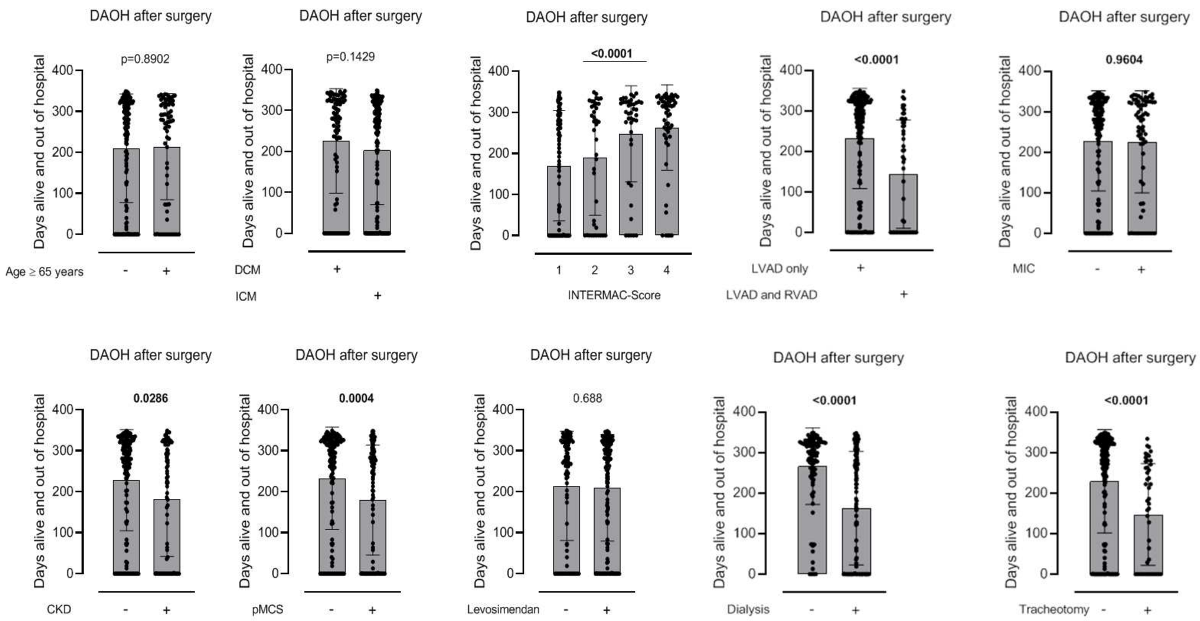

Abbildung 2: Univariate Analyse für die 10 vorab definierten Variablen und DAOH nach einem Jahr. Verwendung der Abbildung aus Roth et al. [53] mit freundlicher Genehmigung des Verlags.

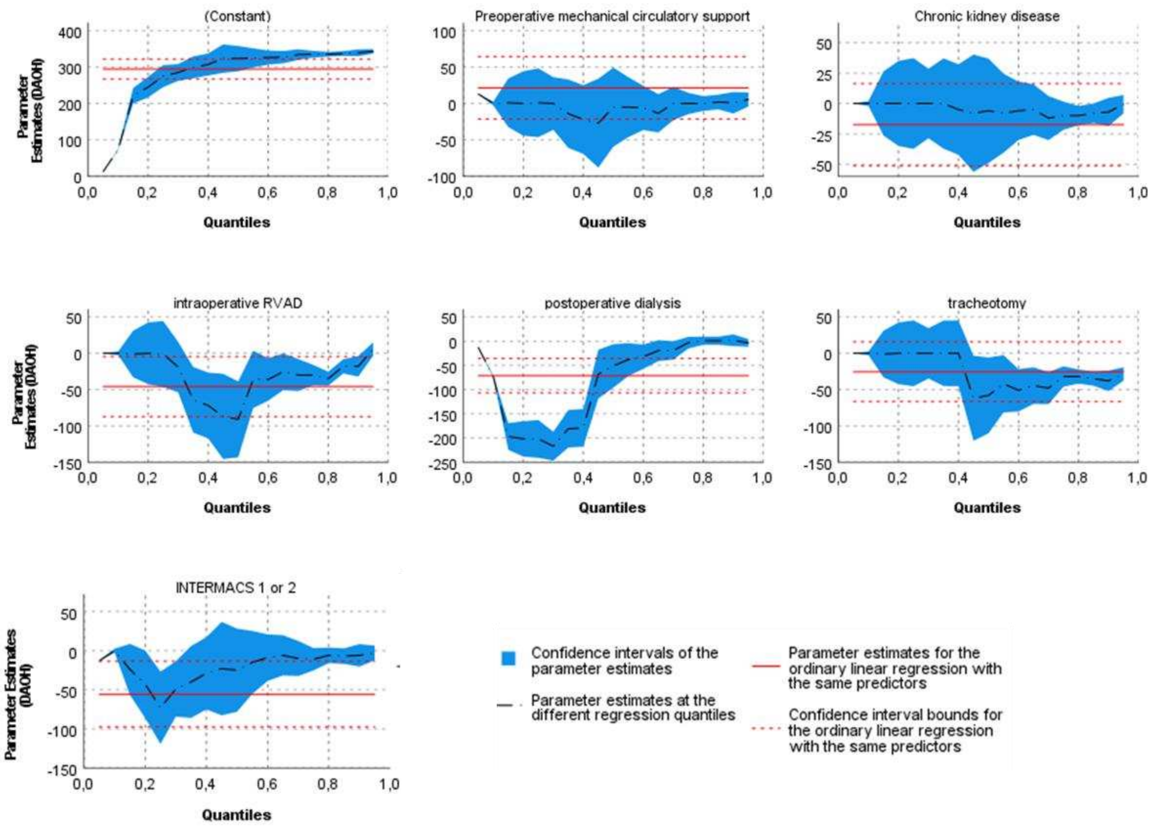

Abbildung 3: Quantile Regression für die sechs Variablen, die in der univariaten Analyse eine signifikante Assoziation zeigten. Verwendung der Abbildung aus Roth et al. [53] mit freundlicher Genehmigung des Verlags.

3.7 Auswirkungen von linksventrikulären Herzunterstützungssystemen auf die "Days alive and out of hospital" bei hämodynamisch stabilen Patient:innen mit terminaler Herzinsuffizienz im Endstadium: Eine Propensity Score Matching-Kohortenstudie

Insgesamt 187 Patient:innen mit einer HTx und 227 Patient:innen mit einer LVAD-Implantation standen für diese Studie in zwei lokalen Datenbanken zur Verfügung. Basierend auf den Ein- und Ausschlusskriterien wurden 21 BTT-LVAD-Patient:innen (HeartMate II™: 2; HeartMate 3™: 7; Medtronic HVAD™: 12) und 44 HTx-Patient:innen auf der Warteliste eingeschlossen. Propensity Score Matching führte zu 17 übereinstimmenden Paaren (= 34 Patient:innen). In beiden Gruppen waren die Patient:innen überwiegend männlich (BTT LVAD: n = 13 (76,5 %), HTx-waiting: n = 12 (70,6 %)), zwischen 50 und 60 Jahre alt, und etwa 30-40 % hatten eine vorbestehende Niereninsuffizienz. In den meisten Fällen war die Diagnose, die zur Herzinsuffizienz im Endstadium führte, eine ischämische Kardiomyopathie. Die Mehrheit der Patient:innen berichtete über Symptome einer Herzinsuffizienz (NYHA ≥ 3), und die mediane LVEF betrug 15 %. Insgesamt betrugen die medianen DAOH nach einem Jahr 313 Tage (IQR 88), wobei es keinen signifikanten Unterschied zwischen den Gruppen gab (BTT-LVAD-Gruppe: median 281, IQR 89; HTx-Wartegruppe: Median 329, IQR 74; p = 0,448; siehe Abbildung 4). In einer Subgruppenanalyse wurden alle Patient:innen verglichen, die im ersten Jahr nach der LVAD-Implantation oder nach der T-Listung keine HTx Implantation erhielten. Die DAOH waren bei Patient:innen, die auf eine HTx warteten, signifikant höher als bei LVAD-Patient:innen, die nicht transplantiert wurden (BTT-LVAD-Gruppe: n = 7, Median 334, IQR 39; HTx-Wartegruppe: Median 362, IQR 5; p = 0,025) (siehe Abbildung 5).

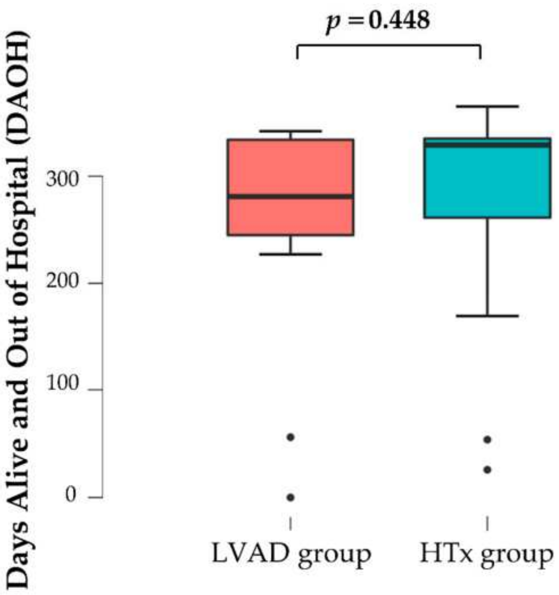

Abbildung 4: DAOH im Vergleich zwischen den beiden Gruppen. Verwendung der Abbildung aus Tenge et al. [54] mit freundlicher Genehmigung des Verlags.

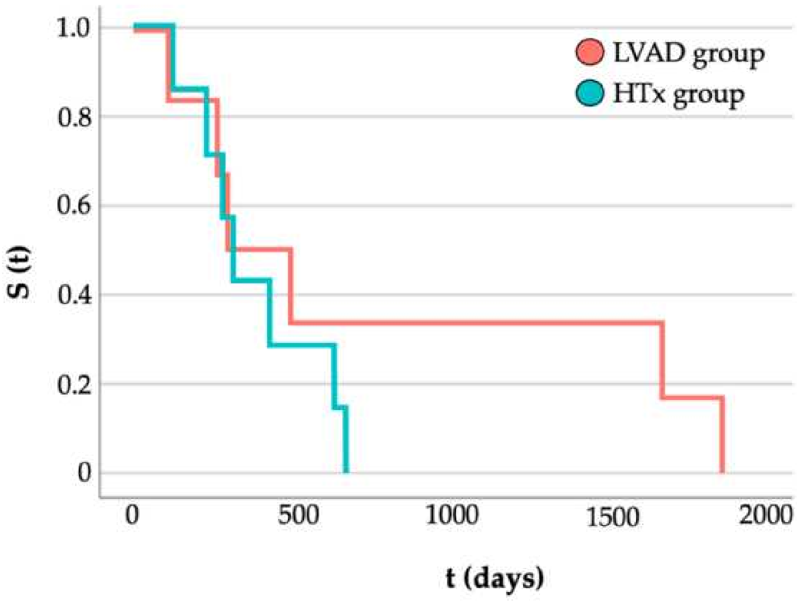

Abbildung 5: Kaplan-Meier Graph für die Mortalität. Verwendung der Abbildung aus Tenge et al. [54] mit freundlicher Genehmigung des Verlags.

4. Diskussion

Diese kumulative Habilitationsschrift fasst die Ergebnisse von insgesamt sieben Originalarbeiten zusammen. Basierend darauf ergeben sich die folgenden übergeordneten Erkenntnisse: 1) Es wurden drei Biomarker hinsichtlich Risikostratifizierung und Prognoseabschätzung untersucht, sowohl zu Beginn als auch unter laufender Therapie. Für alle drei Marker bestand eine unabhängige Assoziation mit der Mortalität (Bilirubin, NLR) bzw. mit thromboembolischen Komplikationen (FAR), so dass die initial aufgestellten Hypothesen formal bestätigt werden konnten. Allerdings war die Diskrimationsfähigkeit moderat (Bilirubin) bzw. schwach (FAR und NLR).

2) Es wurden mit der Evaluation eines potentiellen Instrumentes zur Ersteinschätzung vor invasiver Hämodynamikuntersuchung sowie mit der Wahl der Antikoagulation zwei Aspekte untersucht, die für die klinische Versorgung von Patient:innen mit mechanischer Kreislaufunterstützung im Alltag von großer Relevanz sind. Bezüglich der Evaluation der Hämodynamik zeigte sich, dass die nicht-invasive Pulskontur-Analyse nicht dazu geeignet ist, eine erste Einschätzung der Hämodynamik im Sinne eines sog. „Screening-Tools“ bei Patient:innen mit HTX oder LVAD unter stabilen Bedingungen zu ermöglichen. Die vorab aufgestellte Hypothese konnte somit nicht bestätigt werden. Insbesondere die Ergebnisse bei HTX-Patient:innen legen nahe, dass die NIPKA bei Patient:innen mit mutmaßlich schlechtem peripheren Gefäßstatus sehr ungenau ist, so dass hier Vorsicht bei der Nutzung bzw. Interpretation der gemessenen Werte geboten ist. Im Hinblick auf die Wahl der Antikoagulation zeigte sich ein Vorteil für direkte Thrombin-Inhibitoren, insbesondere für Bivalirudin im Vergleich mit Heparin. Die aufgestellte Hypothese, dass DTIs mit weniger Komplikationen sowie einer niedrigeren Sterblichkeit assoziiert sind, konnte also bestätigt werden. Die Datenlage muss jedoch aufgrund ausschließlich retrospektiver Studien als weiterhin sehr limitiert betrachtet werden.

3) Mit den DAOH konnte ein patient:innenzentrierter Endpunkt identifiziert werden, der eine sinnvolle Ergänzung der Mortalität bei der Bewertung des Therapieerfolgs darstellen könnte.

Bezüglich der zugrundeliegenden Hypothesen zeigte sich einerseits, dass wie angenommen mehrere Faktoren existieren, die zwar nicht mit einer erhöhten Sterblichkeit, allerdings mit einer signifikant längeren Hospitalisierung assoziiert sind. Andererseits konnte nicht bestätigt werden, dass die DAOH bei Patient:innen mit BTT-LVAD signifikant niedriger sind als bei Patient:innen auf der HTX-Warteliste, die ohne LVAD auf ein Herzangebot warten.

4.1 Biomarker zur Unterstützung der Prognoseabschätzung

Trotz einer unabhängigen Assoziation in den jeweiligen multivariaten Regressionsmodellen zeigen die drei untersuchten Biomarker Bilirubin, FAR und NLR eine eher moderate bis schwache Diskriminationsfähigkeit für die Mortalität (Bilirubin und NLR) bzw. für thromboembolische Komplikationen (FAR) in der ROC-Analyse. Somit kann ein routinemäßiger Einsatz zur Unterstützung der Prognoseabschätzung nicht empfohlen werden. Diese Erkenntnis steht im Einklang mit der Literatur. So bestand zwar in der retrospektiven Studie von Masha et al. in 223 ECMO-Patient:innen ebenfalls eine starke Assoziation zwischen Leberschaden definiert über Bilirubin und der Krankenhaussterblichkeit, allerdings war die Diskriminationskraft unzureichend, um für klinische Entscheidungen angewendet zu werden. [55] Ein interessanter Aspekt unserer Analyse besteht in der Tatsache, dass der Youden-Index-basierte Cut-off für Bilirubin an Tag 5 der Therapie bei 2,23 mg/dl lag, was einer lediglich leichten Erhöhung des Bilirubin-Wertes entspricht. Zu diesem Zeitpunkt betrug die ROC-AUC 0,72 (95% KI: 0,66-0,78) und es deutet sich somit an, dass ein Leberschaden möglicherweise bereits bei deutlich niedrigeren Werten relevant die Prognose beeinflusst als bisher angenommen. Freundt et al. untersuchten in einer retrospektiven Kohortenstudie den zeitlichen Verlauf der Bilirubin-Werte im Hinblick auf die Sterblichkeit bei 502 VA-ECMO Patient:innen.[25] Die Autor:innen stellten ebenfalls fest, dass Bilirubin-Werte unter laufender VA-ECMO besser zur Prognoseabschätzung geeignet sind als die Ausgangswerte. Bezüglich der Interpretation der Ergebnisse für die FAR verhält es sich sehr ähnlich. Während zwar eine starke unabhängige Assoziation in der multivariaten Analyse besteht (OR= 3,72 mit 95% KI

2,26-6,14), liegt die ROC-AUC zu Beginn der VA-ECMO-Therapie bei lediglich 0,67 (95% KI 0,61-0,74), so dass eine Risikostratifizierung mittels FAR in der klinischen Praxis nicht empfohlen werden kann. Diese Daten ergänzen die Daten einer retrospektiven Analyse von Acharya et al., die eine ähnliche Analyse bei 157 ECMO Patient:innen für die Assoziation der FAR mit einem ischämischen Schlaganfall durchgeführt haben und basierend auf ihren Ergebnisse die FAR zur frühen Risikostratifizierung empfehlen, ohne eine Angabe zur Diskriminationsfähigkeit zu machen. [56] Diese Empfehlung ist unter Berücksichtigung unserer Erkenntnisse kritisch zu bewerten.

Auch die NLR zeigte zwar eine unabhängige Assoziation mit der Mortalität, aber ebenfalls lediglich mit einer schwachen Diskriminationskraft. Eine kürzlich publizierte retrospektive Kohortenstudie von Nunez et al. mit 253 VA-ECMO-Patient:innen bestätigt zwar die in unserer Analyse beschriebene Assoziation mit der Krankenhausmortalität, macht jedoch keine Angabe zur Diskrimination und lässt somit keine Aussage zu, inwiefern die NLR die Entscheidungsfindung unterstützen kann. [57] Die hier exemplarisch vorgestellten Studien verdeutlichen somit vor allem die Dichotomie zwischen Assoziation und prädiktivem Wert, was in den zitierten früheren Arbeiten zu Biomarkern bei VA-ECMO Patient:innen unzureichend beachtet wurde. Dieser Aspekt ist wichtig, denn während die in unseren Analysen konsistent nachgewiesene unabhängige Assoziation zwischen untersuchtem Biomarker und primärem Endpunkt auf den ersten Blick eine klinische Relevanz nahelegt, so zeigt die ebenfalls konsistent schwache bis moderate Diskriminationsfähigkeit in den ROC-Analysen, dass der Nutzen für den klinischen Alltag als marginal eingeschätzt werden muss.

4.2 Evaluation der Hämodynamik und Wahl der Antikoagulation

Die Ergebnisse der prospektiven Beobachtungsstudie zur Evaluation der Hämodynamik zeigen, dass eine Anwendung von NIPKA bei den untersuchten Kohorten (HTX- bzw. LVAD-Patient:innen) nicht empfohlen werden kann. Patient:innen, die nach einer Herztransplantation in ihr häusliches Umfeld zurückkehren konnten, stellen eine Population dar, die zwar aufgrund des neuen Herzens in den meisten Fällen formal nicht mehr herzinsuffizient ist, allerdings kann nach wie vor ein schlechter peripherer Gefäßstatus vorliegen, nicht zuletzt bedingt durch vielfache Katheterisierungen in der Vergangenheit. Da die NIPKA auf einer Analyse der Pulskontur beruht, konnte bereits vor der Untersuchung angenommen werden, dass die Messgenauigkeit möglicherweise beeinträchtigt sein könnte. Unsere Daten bei HTX-Patient:innen bestätigen dies. Insbesondere zeigt die starke Streuung der Werte mit teilweise ganz erheblichen Abweichungen zur Swan-Ganz-Messung (Goldstandard), dass die Validität der mittels NIPKA erhobenen Werte gering ist. Unsere Daten sind konsistent mit Ergebnissen einer prospektiven Studie bei 84 Patient:innen mit terminaler Herzinsuffizienz mit reduzierter linksventrikulärer Ejektionsfraktion.[58] Die genannte Analyse konnte darüber hinaus zeigen, dass NIPKA die HZV-Werte im Vergleich zur Thermodilution systematisch überschätzt, was in der klinischen Praxis zu falschen Therapieentscheidungen führen könnte. Gleichzeitig kann in der Literatur eine deutliche Zunahme der Veröffentlichungen zu NIPKA verzeichnet werden. Häufig werden dabei eher gesunde Populationen untersucht, in denen NIPKA gute Ergebnisse erzielt.[59] Die Ergebnisse der hier durchgeführten Analyse können exemplarisch dafür gesehen werden, dass die Messgenauigkeit vor allem bei kritisch kranken Patient:innen mit schlechtem Gefäßstatus mutmaßlich nicht akzeptabel ist.

In der durchgeführten Meta-Analyse zur Antikoagulation besteht die wichtigste Erkenntnis zunächst einmal darin, dass mit den direkten Thrombin-Inhibitoren Bivalirudin und Argatroban zwei Alternativen zu Heparin existieren, die möglicherweise vorteilhaft bezüglich Blutungskomplikationen sein könnten. Bei der Interpretation bezüglich eines potentiellen Überlebensvorteils durch Bivalirudin ist jedoch Vorsicht geboten, da es sich bei den eingeschlossenen Studien ausschließlich um retrospektive Studien handelt, die allesamt ein relevantes Bias-Risiko aufweisen. Vor dem Hintergrund der aktuellen Literatur bestätigt unsere Meta-Analyse die Ergebnisse in mehreren fast zeitgleich publizierten Meta-Analysen, die alle zu demselben Schluss kommen. [60-62] Relevante Ergänzungen zur existierenden Literatur sind die Untersuchung von zwei DTI (Bivalirudin + Argatroban) statt nur einer einzelnen Substanz sowie die bis dato höchste Anzahl an eingeschlossenen Patient:innen. Prospektive oder gar randomisierte Studien zu dieser Fragestellung sind weiterhin nicht vorhanden, so dass die Literatur weiterhin als sehr limitiert angesehen werden muss.

4.3 DAOH als ergänzender Endpunkt zur Mortalität

Beide Untersuchungen zu DAOH verdeutlichen, dass eine relevante Diskrepanz zur Mortalität besteht. So haben beispielsweise terminal herzinsuffiziente Patient:innen mit vorbestehender chronischer Niereninsuffizienz, die ein LVAD erhalten, signifikant niedrigere DAOH innerhalb des ersten Jahres als Patient:innen mit LVAD, die vor der Implantation eine erhaltene Nierenfunktion hatten, während sich bei der 1-Jahres Mortalität kein signifikanter Unterschied zeigt. Auch eine Tracheotomie oder der Einsatz eines temporären Rechtsherzunterstützungssystems zeigen einen signifikanten Einfluss auf die DAOH bei gleichzeitig nicht-signifikant unterschiedlicher Mortalität. Solche Informationen sind nicht nur für die reine Einschätzung der Prognose, sondern vor allem auch für die Information der Patient:innen relevant. Darüber hinaus stellen die Ergebnisse unserer Analysen eine erste Grundlage dar, um DAOH als Endpunkt für klinische Studien bei Patient:innen mit LVAD zu nutzen. Dieser Endpunkt verbindet mehrere Vorteile: Patient:innen-Zentriertheit und einfache Erfassung (z.B. auch im Rahmen von „Big-Data“-Projekten) sowie eine einfache statistische Handhabung durch die Erfassung der DAOH als absolute Zahl. Eine kürzlich publizierte Arbeit von Noly et al. bei 3387 retrospektiven Patient:innen mit LVAD zeigte, dass ein unabhängiger Zusammenhang zwischen DAOH und Komplikationen besteht, wodurch die Konstruktvalidität von DAOH für diesen Endpunkt belegt wird. Die Studie von Noly et al. bestätigt außerdem, dass eine hohe Varianz bei den DAOH während des ersten Jahres nach LVAD Implantation besteht und dass diverse präoperative Risikofaktoren die DAOH beeinflussen können. [63] Für LVAD-Patient:innen existieren abgesehen von unseren Analysen dagegen bislang keine publizierten Studien, die sich mit der potentiellen Diskrepanz zwischen der Sterblichkeit und DAOH beschäftigt haben. Unsere Ergebnisse unterstreichen somit die Wertigkeit von DAOH als Ergänzung zur Mortalität für die Evaluation des Therapieerfolges.

4.4. Ausblick

Bezüglich der Prognoseabschätzung bei Patient:innen mit mechanischer Kreislaufunterstützung bestehen für die Zukunft noch große Herausforderungen. Während einzelne Biomarker basierend auf den erworbenen Erkenntnissen eher einen geringen Stellenwert haben werden, so wird es dennoch notwendig sein, Faktoren zu identifizieren, die im Rahmen der Entscheidungsfindung hilfreich bzw. wegweisend sein können. Dabei wird auch die Entwicklung von Scores eine Rolle spielen, die dann aber im Gegensatz zu den vorhandenen Scores einfacher verfügbar und schneller zu erheben sein sollten, um auch in zeitkritischen Notfallsituationen einen Mehrwert zu haben. Dabei sollten nicht nur biomedizinische Faktoren (z.B. Biomarker, Komorbiditäten usw.), sondern auch ethische Aspekte bei der Entscheidungsfindung berücksichtigt werden. Auch die Erwartungen und Einstellungen der Behandelnden spielen eine relevante Rolle bei Entscheidungen bezüglich Etablierung bzw. Fortführung einer VA-ECMO-Therapie. Allerdings gibt es bislang keine Daten dazu, wie gut die Prognose-Einschätzung der Behandelnden mit dem tatsächlichen Patient:innen-Outcome übereinstimmt. Es ist zudem unklar, wie patient:innen-unabhängige Faktoren, wie z.B. Stress, die Prognoseschätzung beeinflussen. Um dieser Fragestellung weiter nachzugehen, führen wir derzeit eine multizentrische prospektive Beobachtungsstudie bei VA-ECMO-Patient:innen durch, die die Übereinstimmung des vom Personal geschätzten Outcomes mit dem tatsächlichen Outcome vergleicht. Hierfür wird an Tag 1 sowie an Tag 4-7 der VA-ECMO-Therapie ein Fragebogen an das Personal verteilt, auf dem das Outcome der Patient:innen nach 6 und 12 Monaten abgefragt wird inkl. Angaben zur Funktionalität im Alltag und DAOH. Basierend auf telefonischen bzw. postalischen Follow-Ups nach 6 und 12 Monaten wird dann die Einschätzung mit dem tatsächlichen Ergebnis verglichen. Eine wichtige Hypothese dieser Studie ist, dass das Outcome von Patient:innen mit VA-ECMO häufig durch das Personal überschätzt wird. Des Weiteren werden nicht nur Ärzt:innen, sondern auch Pflegekräfte befragt, die bei der Entscheidungsfindung eine geringe Rolle spielen. Schließlich wird auch der Einfluss der Berufserfahrung untersucht und es ist geplant, mit Hilfe der finalen

Ergebnisse einen Risikoscore zu entwickeln, der den oben genannten Ansprüchen (objektivierbar, jederzeit verfügbar, schnell zu erheben) besser gerecht wird. Auch die DAOH werden in diesem Projekt aufgegriffen und es soll eine Validierung des Endpunktes mit Hilfe dieser großen multizentrischen Kohorte mit geplant 1000 prospektiven Patient:innen erfolgen. In einer geplanten Sub-Studie wird darüber hinaus der moralische Stress des Personals anhand einer validierten Skala erfasst. Dies ist ein weiterer wichtiger Aspekt für die Zukunft, denn die Behandlung von Patient:innen mit mechanischer Kreislaufunterstützung kann für das zuständige Personal nicht nur körperlich, sondern auch psychisch sehr belastend sein, insbesondere dann, wenn die Sinnhaftigkeit der Therapie in Frage gestellt wird und gleichzeitig ein hohes Maß an Ressourcen, wie z.B. Blutprodukte zum Einsatz kommt. In einer weiteren Sub-Studie dieses großen multizentrischen Projektes wird das Antikoagulations-Regime prospektiv erfasst. Diese Datenerhebung basiert auf den Erkenntnissen der durchgeführten Meta-Analyse und soll zusätzliche Daten zu diesem Thema liefern. Im nächsten Schritt soll dann eine erste randomisiert-kontrollierte Machbarkeitsstudie durchgeführt werden, die eine Antikoagulation mit Heparin versus Argatroban bei VA-ECMO-Therapie vergleicht. Diese Machbarkeitsstudie soll dann die Grundlage für eine multizentrische Studie zu diesem Thema bilden.

Das Thema patient:innenzentrierte Endpunkte wird bei Patient:innen mit mechanischer Kreislaufunterstützung in Zukunft ganz grundsätzlich eine immer größere Rolle spielen. So sollten kommende große Studien als primären Endpunkt nicht nur die Mortalität, sondern ergänzend (oder ggf. auch primär) ein Maß für Lebensqualität wählen. Um die Frage nach den am besten geeigneten Endpunkten besser beantworten zu können, führen wir derzeit eine systematische Suche zu patient:innenzentrierten Endpunkten bei Patient:innen mit VA-ECMO durch und versprechen uns von den Ergebnissen, diesbezüglich erste Empfehlungen geben zu können.

Schließlich betrifft ein wichtiger Aspekt für die Zukunft der Forschung bei Patient:innen mit mechanischer Kreislaufunterstützung die bessere Integration der Palliativmedizin. Während die Onkologie bereits seit vielen Jahren selbstverständlich mit der Palliativmedizin eng zusammenarbeitet, so besteht in der Intensivmedizin noch viel unausgeschöpftes Potential. Viele Patient:innen mit mechanischer Kreislaufunterstützung erfüllen durchaus die Kriterien einer palliativen Situation, allerdings herrscht häufig noch zu sehr der Eindruck vor, dass Palliativmedizin gleichzusetzen sei mit einer Beendigung der Therapie. Dabei wären Patient:innen mit mechanischer Kreislaufunterstützung ganz im Gegenteil eine exzellent geeignete Gruppe, die von einer frühzeitigen Einbindung profitieren könnte. Dies könnte einerseits in der frühen Phase nach der Implantation der Fall sein, andererseits aber auch im Langzeitverlauf unter laufender Therapie zu einer patient:innengerechteren Versorgung führen. Um diesen Aspekten weiter nachzugehen, wird derzeit eine weitere multizentrische prospektive Studie durchgeführt, die die Integration der Palliativmedizin in die Intensivmedizin generell bei Intensivpatient:innen zunächst beobachtend und dann interventionell untersucht und die auch Patient:innen mit mechanischer Kreislaufunterstützung einschließen wird. Im Rahmen dieser europäischen Studie etablieren wir derzeit eine Sub-Studie zur Integration der Palliativmedizin in die intensivmedizinische Versorgung von Patient:innen mit VA-ECMO.

5. Zusammenfassung

Die Anwendung von Verfahren der mechanischen Kreislaufunterstützung nimmt stetig zu. Gleichzeitig bleibt die Mortalität konstant hoch und viele Patient:innen erleiden Komplikationen. Eine große Herausforderung besteht somit in einem gezielten Einsatz dieser Verfahren. Hierfür sind geeignete Instrumente zur Risikostratifizierung und Prognoseabschätzung notwendig. Außerdem werden neue Ansätze benötigt, um die hohen Komplikationsraten unter einer laufenden Therapie zu reduzieren. Bei der Bewertung des Therapieerfolgs ist es wichtig, nicht nur die reine Mortalität als Endpunkt heranzuziehen, sondern auch Endpunkte in die Bewertung miteinzubeziehen, die den Einfluss auf das Leben der Patient:innen mitberücksichtigen.

In dieser kumulativen Habilitationsschrift wurden die drei genannten Aspekte (1 Prognoseabschätzung, 2) Ansätze zur Optimierung einer laufenden Therapie und 3) Endpunkte zur Evaluation des Therapieerfolgs aufgegriffen. Insgesamt liegen dieser Arbeit sieben Originalarbeiten zugrunde, davon fünf retrospektive Kohortenstudien, eine prospektive Beobachtungsstudie und eine systematische Übersichtsarbeit mit Meta-Analyse. Bezüglich der Prognoseabschätzung wurden drei Biomarker untersucht (Bilirubin, FAR, NLR) und es wurden jeweils Hypothesen aufgestellt, dass diese mit einer erhöhten Mortalität (Bilirubin, NLR) bzw. mit einer erhöhten Rate an thromboembolischen Komplikationen (FAR) assoziiert sind. Im Hinblick auf neue Ansätze zur Optimierung einer laufenden Therapie wurde die Hypothese untersucht, dass DTIs die Rate an Komplikationen sowie die Sterblichkeit im Vergleich mit Heparin reduzieren. Außerdem wurde mit der NIPKA ein potentielles Instrument zur Ersteinschätzung der Hämodynamik in einem stabilen Umfeld außerhalb der Intensivstation untersucht. Hinsichtlich neuerer Endpunkte zur Evaluation des Therapieerfolgs wurden die DAOH in zwei Analysen untersucht. Einerseits wurde versucht, Faktoren zu identifizieren, die mit reduzierten DAOH, aber gleichzeitig nicht mit einer erhöhten Sterblichkeit assoziiert sind. Andererseits wurde die Hypothese geprüft, dass Patient:innen mit BTT-LVAD niedrigere DAOH haben als Patient:innen, die ohne LVAD auf ein Herzangebot warten.

Die Ergebnisse der durchgeführten Analysen zeigen, dass die drei untersuchten Biomarker zwar alle gemäß multivariater Regressionsanalyse mit einer erhöhten Mortalität (Bilirubin, NLR) bzw. mit einer erhöhten Rate an thromboembolischen Komplikationen assoziiert sind, allerdings jeweils eine nur schwache Diskriminationsfähigkeit für die jeweiligen Endpunkte zeigen. Somit kann eine Anwendung zur Risikostratifizierung und Prognoseabschätzung in der klinischen Praxis eher nicht empfohlen werden. Die Meta-Analyse zu DTIs konnte zeigen, dass DTIs mit weniger Komplikationen sowie einer niedrigeren Sterblichkeit im Vergleich mit Heparin assoziiert sind und somit eine geeignete Alternative im klinischen Alltag darstellen könnten. Die NIPKA hingegen ist zur Evaluation der Hämodynamik nicht geeignet. Bezüglich der DAOH konnten mehrere Faktoren identifiziert werden, die mit signifikant weniger DAOH bei gleichzeitig nicht beeinflusster Sterblichkeit assoziiert sind. Dieser Endpunkt könnte somit eine sinnvolle Ergänzung zur Mortalität darstellen. Die Hypothese, dass BTT-LVAD Patient:innen niedrigere DAOH haben als Patient:innen, die ohne LVAD auf ein Herzangebot warten, konnte nicht bestätigt werden.

Zusammenfassend tragen die Ergebnisse dieser kumulativen Habilitationsschrift bzw. die zugrundeliegenden Originalarbeiten Aspekte bei, die in Zukunft in der Versorgung von Patient:innen mit mechanischer Kreislaufunterstützung zur Anwendung kommen könnten. Basierend auf den gewonnen Erkenntnissen befinden sich außerdem derzeit mehrere prospektive Studien in der Rekrutierungsphase und werden hoffentlich zeitnah weitere Beiträge zu einer Verbesserung der Versorgung von Patient:innen mit mechanischer Kreislaufunterstützung leisten können.

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8. Originalarbeiten

Die Genehmigungen zur Verwendung der Originalarbeiten im Anhang sowie die Verwendung und Änderung aller inkludierten Abbildungen wurden vorab bei den jeweiligen Verlägen eingeholt.

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Bilirubin—A Possible Prognostic Mortality Marker for Patients with ECLS

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Abstract: Extracorporeal life support (ECLS) is a promising therapeutic option for patients with refractory cardiogenic shock. However, as the mortality rate still remains high, there is a need for early outcome parameters reflecting therapy success or futility. Therefore, we investigated whether liver enzyme levels could serve as prognostic mortality markers for patients with ECLS. The present study is a retrospective single-center cohort study. Adult patients >18 years of age who received ECLS therapy between 2011 and 2018 were included. Bilirubin, glutamic-oxaloacetic transaminase (GOT), and glutamic-pyruvic-transaminase (GPT) serum levels were analyzed at day 5 after the start of the ECLS therapy. The primary endpoint of this study was all-cause in-hospital mortality. A total of 438 patients received ECLS during the observation period. Based on the inclusion criteria, 298 patients were selected for the statistical analysis. The overall mortality rate was 42.6% (n = 127). The area under the curve (AUC) in the receiver operating characteristic curve (ROC) for bilirubin on day 5 was 0.72 (95% confidence interval (CI): 0.66–0.78). Cox regression with multivariable adjustment revealed a significant association between bilirubin on day 5 and mortality, with a hazard ratio (HR) of 2.24 (95% CI: 1.53–3.30). Based on the results of this study, an increase in serum bilirubin on day 5 of ECLS therapy correlates independently with mortality.

Keywords: bilirubin; ECLS; prognosis; liver function; mortality

1. Introduction

Coronary heart disease remains the number one cause of death in the US. Depending on its severity, it can lead to life-threatening complications such as malignant arrhythmias, cardiogenic shock, or sudden cardiac arrest. According to current data from the American Heart Association (AHA), one out of eight Americans (13.8%) dies from sudden cardiac arrest [1]. Although immediate cardiopulmonary resuscitation (CPR) with immediate defibrillation is crucial to patient survival, the outcome after sudden cardiac arrest is poor and decreases dramatically with the increasing duration of CPR [2,3]. In case of prolonged cardiopulmonary resuscitation, extracorporeal life support (ECLS) can be a therapeutic option for restoring the blood circulation [4–6].

Since its first description over 40 years ago, ECLS has become an important tool for managing critically ill patients. Cardiogenic shock in adults has become the most common indication for ECLS therapy, with a reported survival until hospital discharge of up to 42% [7]. Most recent data indicate that ECLS can lead to survival benefits compared to classic CPR in patients with cardiogenic shock or cardiac arrest [8]. However, though promising, the mortality rate when using ECLS is still high. Known complications of ECLS are lethal bleeding in up to 40% of the patients, systemic infections, sepsis, septic shock, as well as acute kidney injuries requiring renal replacement therapy [9,10]. In addition to these complications, liver function plays a crucial role for the outcome of patients treated with ECLS [11]. Acute liver dysfunction and hypoxic liver injury are life-threatening events associated with a mortality rate of up to 80% [12,13]. Some authors tried to identify pre-ECLS factors with prognostic value, e.g., the "Survival after Veno-Arterial Extracorporeal Membrane Oxygenation" (SAVE) score, which may be a tool to predict the survival of patients receiving ECLS for refractory cardiogenic shock [7]. In a retrospective analysis, Freundt et al. showed that bilirubin levels may be related to mortality in patients under ECLS therapy [14]. The authors demonstrated that patients who died under ECLS therapy had significantly higher bilirubin levels than those who survived. Obviously, the initial trauma that leads to initiation of ECLS substantially influences patients' outcome and may even lead to early therapy futility [10,15–17]. With regard to this aspect, it seems even more interesting to evaluate the prognostic value of liver function when this initial damage is excluded as far as possible. In the present study, we therefore investigated whether liver enzyme levels could serve as prognostic markers in patients who survived the first four days of ECLS therapy.

2. Materials and Methods

2.1. Study Design and Patients

The present study is a retrospective, single-center cohort study, approved by the ethical committee of the Heinrich-Heine-University, Duesseldorf, (reference number 5141R), Germany. Data of all patients older than 18 years of age undergoing ECLS therapy between 2011 and 2018 in our hospital were collected from the institutional database. ECLS therapy and ancillary therapy were performed as previously described [18,19]. All ECLS systems were temporary devices. Only patients who survived the first four days were included into the study, hence excluding patients for whom the initial trauma led to therapy futility and limiting the impact of the index event on liver function and subsequent changes in bilirubin levels. Day 5 was chosen based on local experiences suggesting that this might be the time point of a "steady state" where clinicians often have to decide about prognosis and whether therapy should be continued or not. In a sensitivity analysis, patients presenting without shock liver (defined as a tenfold increase in glutamic-oxaloacetic transaminase (GOT) values compared to the local upper cutoff value (35 U/L)) were excluded. This subgroup analysis was performed to further exclude the influence of the initial damage.

2.2. Data Collection

Data including sex, age, duration of ECLS therapy, and blood levels of total bilirubin, GOT and glutamic-pyruvic-transaminase (GPT) were collected at pre-defined time points: day 0 (start of ECLS therapy) and day 5 (after five days of ECLS therapy). If no blood values were available on the corresponding days, results from the adjacent days (cut-off date ± 2 days) were used.

2.3. Statistical Analysis

The primary endpoint of this trial was all-cause in-hospital mortality. Categorical data are presented as absolute numbers (percent). Continuous data are presented as mean ± standard deviation (SD) or median (quartile 1, quartile 3, as applicable). Differences between baseline characteristics were calculated by Pearson χ^2 test, Fisher exact test, Student t test, or Mann–Whitney U test, as appropriate. The discrimination of bilirubin for mortality was examined employing receiver operating characteristic curve (ROC) and the area under the curve (AUC). The Youden index was calculated to determine the cutoff value for bilirubin. To quantify the independent association between bilirubin and death, Cox regression was performed with pre-defined multivariable adjustment for sex, age, left ventricular assist device/right ventricular assist device (LVAD/RVAD), and continuous renal replacement therapy (CRRT). Cox regression was also performed for GOT and GPT. In a predefined sensitivity analysis, patients with shock liver (defined as GOT >10 × cutoff (= 35 U/L)) were excluded.

3. Results

3.1. Baseline Characteristics

A total of 438 patients underwent ECLS therapy during the observation period. All patients received ECLS due to severe cardiogenic shock or cardiac arrest. Of these, 298 patients survived the first four days, and their data were available for statistical analysis (see Table 1). To allow generalizability, all indications for ECLS therapy were included. The median age was 59 ± 14 years, 219 (74%) patients were male, 79 (26%) were female. The mean ECLS therapy duration was 9 ± 7 days. With regard to the baseline characteristics, the only significant difference was sex ($p < 0.05$). For the sensitivity analysis without shock liver constellation, 220 patients remained.

Table 1. Patient characteristics.

	All Patients	Non-Survival	Survival	*p*-Value
Number of Patients (*n*) (%)	298	133 (45%)	165 (55%)	ns
Age (Years)	59 ± 14	61 ± 14	56 ± 14	ns
Male (*n*) (%)	219	100 (46%)	119 (54%)	ns
Female (*n*) (%)	79	33 (42%)	46 (58%)	ns
Days of ECLS	9 ± 7	11 ± 7	8 ± 7	ns

Data are presented as mean ± SD or as absolute numbers (percent). ECLS = extracorporeal life support.

3.2. Laboratory Values and Outcome

Laboratory values were followed over a period of five days from the start of the ECLS therapy. In-hospital mortality rate was 42.6% ($n = 127$). The mean bilirubin level at the beginning of ECLS was 2.04 ± 2.73 mg/dL, and the mean bilirubin level on day five was 5.14 ± 12.01 mg/dL. The AUC from the ROC for bilirubin on day five was 0.72 (95% confidence interval (CI): 0.66–0.78) (see Figure 1). The AUC for the trend (i.e., the absolute difference) between bilirubin at the start and on day 5 was 0.70 (95% CI 0.64–0.77). ROC for patients without shock liver demonstrated an AUC of 0.67 (95% confidence interval (CI): 0.59–0.75) (see Figure 2).

The Youden index showed a cutoff for bilirubin on day 5 of 2.23 mg/dl, with a sensitivity of 0.70. Cox regression with multivariable adjustment revealed a significant association between bilirubin on day 5 and mortality, with a hazard ratio (HR) of 2.24 (95% CI: 1.53–3.30) (see Table 2 and Figure 3). In the sensitivity analysis without shock liver patients, this association was still significant (HR 2.08 (95% CI: 1.33–3.26) (see Table 2 and Figure 4). Cox regression for GOT and GPT showed a significant association between GOT on day 5 and mortality, but not between GPT on day 5 and mortality, with HR of 1.87 (95% CI: 1.23–2.83) for GOT and 1.41 (95% CI: 0.94–2.10) for GPT (see Table 3).

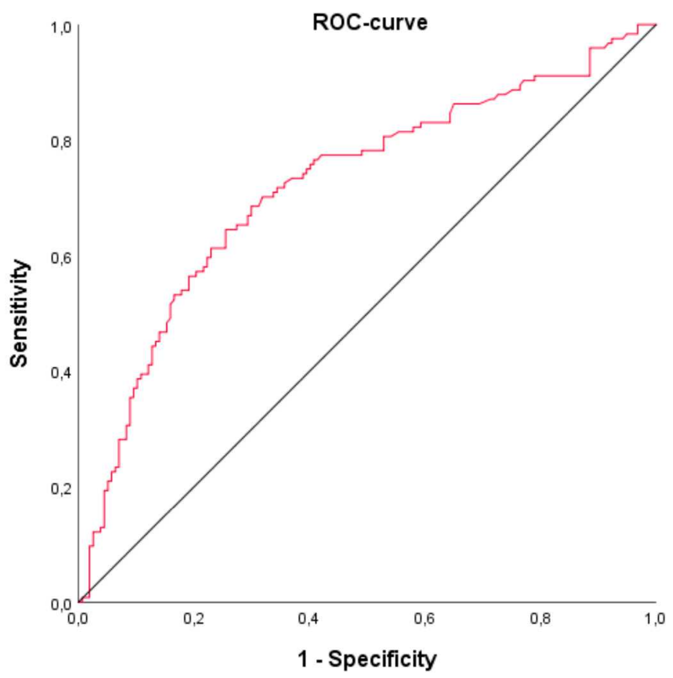

Figure 1. Receiver operating characteristic curve (ROC) and area under the curve (AUC) for bilirubin on day 5 of ECLS therapy as a discriminator for mortality (n = 298). AUC = 0.72 (95% confidence interval (CI): 0.66–0.78).

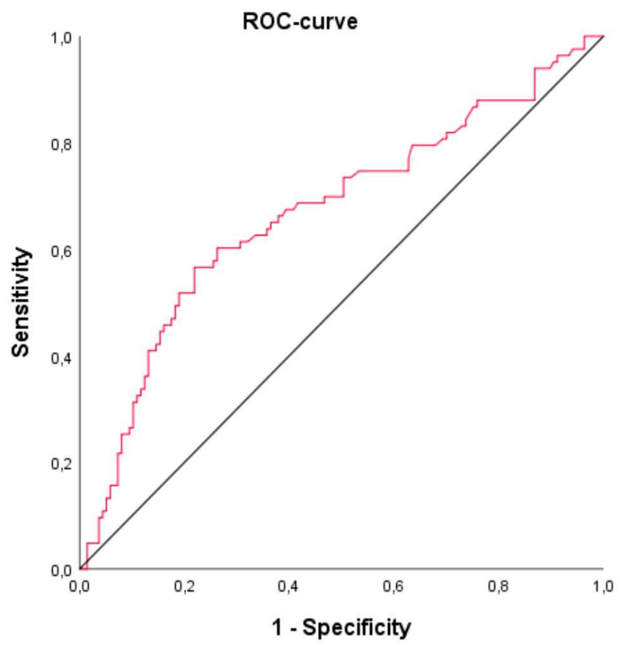

Figure 2. ROC and AUC for bilirubin on day 5 of ECLS therapy as a discriminator for mortality, excluding shock liver patients (n = 220). AUC = 0.67 (95% confidence interval (CI): 0.59–0.75).

Table 2. Multivariate analysis for bilirubin with and without shock liver patients.

	Hazard Ratio	Lower 95% CI	Upper 95% CI	*p*-Value
Bilirubin on day 5 including shock liver patients (n = 298)				
Bilirubin	2.243	1.525	3.297	<0.0001
Age	1.010	0.996	1.024	0.153
Sex	1.119	0.743	1.684	0.590
LVAD	0.433	0.235	0.795	0.007
RVAD	1.268	0.630	2.551	0.506
CRRT	1.758	1.142	2.707	0.010
Bilirubin on day 5 excluding shock liver patients (n = 220)				
Bilirubin	2.080	1.328	3.256	0.001
Age	1.013	0.996	1.031	0.136
Sex	1.243	0.753	2.051	0.395
LVAD	0.334	0.154	0.721	0.005
RVAD	2.000	0.822	4.865	0.127
CRRT	1.640	1.005	2.677	0.048

LVAD = left ventricular assist device; RVAD = right ventricular assist device; CRRT = continuous renal replacement therapy.

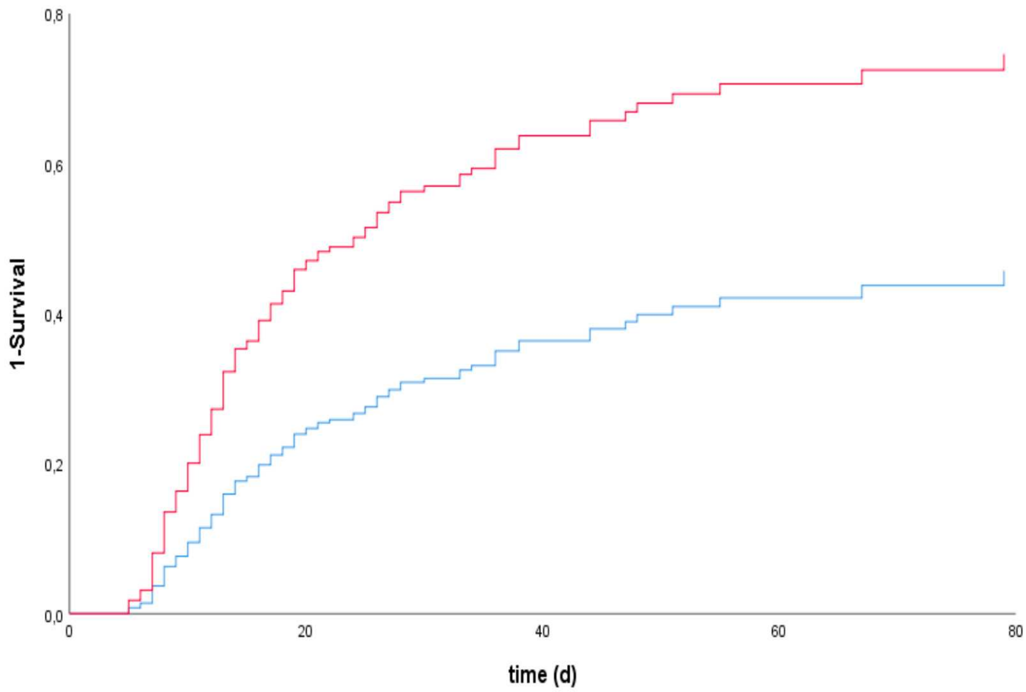

Figure 3. Cox proportional hazards model for investigating the association between the survival time of patients undergoing ECLS therapy and bilirubin levels on day 5 if bilirubin was >2.23 mg/dL (red line) or <2.23 mg/dL (blue line) (cutoff value as determined by the Youden index), including a predefined multivariable adjustment.

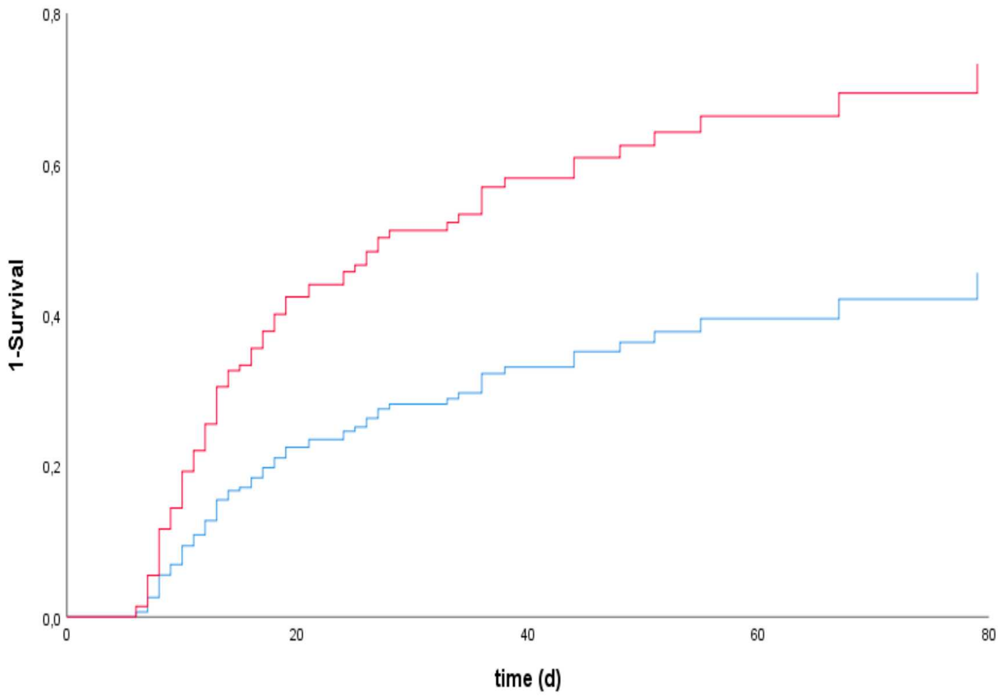

Figure 4. Cox proportional hazards model for investigating the association between the survival time of patients undergoing ECLS therapy with the exclusion of shock liver patients and bilirubin levels on day 5 if bilirubin was >2.23 mg/dL (red line) or <2.23 mg/dL (blue line) (cutoff- alue as determined by the Youden index), including a predefined multivariable adjustment.

Table 3. Multivariate analysis for glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic -transaminase (GPT).

	Hazard Ratio	Lower 95% CI	Upper 95% CI	*p*-Value
		GOT on day 5		
GOT	1.868	1.233	2.830	0.003
Age	1.011	0.998	1.025	0.088
Sex	1.223	0.816	1.835	0.330
LVAD	0.460	0.249	0.848	0.013
RVAD	1.387	0.688	2.793	0.360
CRRT	1.667	1.070	2.599	0.024
		GPT on day 5		
GPT	1.406	0.941	2.100	0.097
Age	1.017	1.002	1.031	0.021
Sex	1.222	0.805	1.854	0.346
LVAD	0.518	0.270	0.993	0.047
RVAD	1.411	0.686	2.901	0.350
CRRT	1.933	1.209	3.093	0.006

4. Discussion

ECLS therapy is a promising treatment for life support of cardiogenic shock patients. However, the method itself also involves many potential lethal complications such as acute bleeding, futile intracerebral stroke, or kidney failure [9,10]. In addition to these factors, acute liver failure is a serious complication of ECLS therapy, with potential survival implications [14–17]. In recent years, some studies tried to identify pre-ECLS factors that may predict survival in these patients. In 2015, Schmidt and co-workers created the SAVE score and concluded that this score may be a tool to predict survival in patients receiving ECLS for refractory cardiogenic shock [20]. In everyday clinical practice, however, there is no reliable prognostic marker of mortality for patients that survived the first few days of therapy. This time point may be even more important, for example, to decide whether therapy should be limited or not. The results of our current study suggest that bilirubin measured on day 5 of ECLS might serve as a prognostic marker in this context and thus could help guide therapy.

In general, liver function is important for the survival of patients undergoing ECLS, and an elevated baseline bilirubin inversely correlates with long-term survival [11]. In 2016, Roth et al. confirmed the latter results and suggested that bilirubin and alkaline phosphatase are predictors of 30-day and long-term mortality following ECLS. Strikingly, the relevance of the bilirubin values during the course of ECLS remained unclear. Obviously, the initial trauma that leads to the initiation of ECLS therapy influences patients' outcome and may even lead to early therapy futility. Therefore, it seems even more interesting to evaluate the prognostic value of bilirubin when this initial damage is excluded as far as possible. Hence, this is the first study to investigate the potential of bilirubin as a prognostic marker in patients who survived the first few days of ECLS therapy.

Freundt et al. were the first to look at the time course of bilirubin values with regard to mortality [14]. Patients that survived after explantation of the device had a regression of their bilirubin levels within two days, whereas patients that died showed a further bilirubin increase. The authors concluded that a decrease in bilirubin levels over time might be a predictor of successful weaning from ECLS in hemodynamically stable patients [14].

Those data support the idea that bilirubin values during ECLS therapy may be more relevant with regard to prognostic information than baseline values and may support an early recognition of problems as well as the optimization of the therapy. Worth mentioning, the study protocol in the latter study differed significantly from ours. Freundt et al. included all patients that received ECLS therapy and followed them over a period of six days and at least two days after explantation. The authors stated that the mean ECLS duration was three days [14]. In our current study, patients who died within the first four days of ECLS therapy were excluded from the study, and the mean ECLS duration was nine days. The admission of initially deceased patients as well as the short ECLS duration make it very difficult to distinguish whether the initial trauma or the ECLS therapy was the cause of the measured effects. Roedl et al. showed that the original trauma has a major effect on the liver function of patients [16]. The authors demonstrated that a trauma such as cardiac arrest can trigger an impairment of the liver function such as hypoxic liver injury (HLI) [16]. Out of 1068 patients with cardiac arrest after CPR, 21% developed HLI [16]. Iesu et al. investigated the occurrence of acute liver failure (ALF) after cardiac arrest. In their study, 56% of patients with return of spontaneous circulation (ROSC) developed acute liver failure that significantly affected mortality. Iseu et al. also showed that ALF occurred within the first three days after the initial event due to the elevation of bilirubin [15].

Based on the results of Roedl et al. and Iseu et al., we did our best to avoid a possible influence of the initial event (e.g., cardiogenic shock) on liver function. Therefore, all patients that did not survive at least four days after ECLS implantation in our study were excluded. When comparing our data with those of Freundt et al., it is noteworthy that in our study no significant difference in the initial bilirubin values between the groups existed. However, during ECLS therapy, a significant increase in bilirubin was detected. Even more, as determined by the Youden index, our data show that bilirubin levels with a cutoff of 2.23 mg/dL and a sensitivity of 0.7 on day 5 of ECLS therapy correlated with increased mortality (see Figure 3). Although this cutoff represents the point with the highest sensitivity and specificity according to the ROC analysis, it has to be taken into account that bilirubin levels were higher in most patients (mean on day five, 5.14 ± 12.01) and not every level of bilirubin slightly higher than normal is correlated with high mortality. However, this cutoff may serve as a "warning signal" for clinicians treating ECLS patients.

To further minimize the involvement of the initial trauma in liver function for our results, we performed a subgroup analysis in which we excluded all patients with an initial shock liver, defined as a tenfold increase in GOT values compared to the upper cutoff value (35 U/L). The association of bilirubin and mortality, which was seen before, was significant also in this case (see Table 2 and Figure 4).

However, given the fact that we did a retrospective analysis, we cannot rule out an influence of the initial event on bilirubin levels. In order to be able to make a definite statement, a prospective, randomized study should be carried out. It also has to be mentioned that we showed no significant difference between GPT and mortality (see Table 3), indicating that other underlying mechanisms than liver injury may have led to increased bilirubin values, e.g., hemolysis. Nonetheless, combined with previously published work, our results suggest that bilirubin levels might be a prognostic marker for mortality in patients with ongoing ECLS therapy, useful to prevent or recognize therapy-related problems and to optimize treatment.

Limitations

Our study has the following limitations. First, an important limitation is the retrospective design. Second, this study is a single-center study, and the therapy of ECLS patients may be totally different in other centers so that we cannot generalize our findings. Third, we only looked at bilirubin measurements at baseline and on day 5 of ECLS therapy. We did this to exclude the initial trauma as far as possible and to define a time point that might be clinically relevant with regard to prognostication and optimization of therapy. However, more bilirubin values would be useful to evaluate the importance of its changes over time. These values were not included in the analysis because of a relevant amount of missing data which is related to the retrospective data collection. Fourth, there was a significant difference depending on sex in the baseline characteristics of our cohort which may also influence generalization. Fifth, our decision to focus on day 5 was based on local experience, and there is no scientific reference supporting this choice. Sixth, our database did not include more variables to be considered in the multivariate analysis.

5. Conclusions

In summary, our results suggest that serum bilirubin may act as a prognostic marker for mortality in patients undergoing ECLS therapy who survived the first few days of therapy. In those patients, bilirubin may be used for an early recognition of problems and thus could be seen as a useful indicator for early optimization of ECLS therapy or to guide decision-making.

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Fibrinogen–Albumin-Ratio is an independent predictor of thromboembolic complications in patients undergoing VA-ECMO

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Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) supports patients suffering from refractory cardiogenic shock. Thromboembolic complications (TeC) are common in VA-ECMO patients and are associated with increased morbidity and mortality. Valid markers to predict TeC in VA-ECMO patients are lacking. The present study investigated the predictive value of baseline Fibrinogen–Albumin-Ratio (FAR) for in-hospital TeC in patients undergoing VA-ECMO. This retrospective cohort study included patients who underwent VA-ECMO therapy due to cardiogenic shock at the University Hospital Duesseldorf, Germany between 2011 and 2018. Main exposure was baseline FAR measured at initiation of VA-ECMO therapy. The primary endpoint was the in-hospital incidence of TeC. In total, 344 patients were included into analysis (74.7% male, mean age 59 ± 14 years). The in-hospital incidence of TeC was 34%. Receiver operating characteristics (ROC) curve of FAR for in-hospital TeC revealed an area under the curve of 0.67 [95% confidence interval (CI) 0.61–0.74]. Youden index determined a cutoff of 130 for baseline FAR. Multivariate logistic regression revealed an adjusted odds-ratio of 3.72 [95% CI 2.26–6.14] for the association between FAR and TeC. Baseline FAR is independently associated with in-hospital TeC in patients undergoing VA-ECMO. Thus, FAR might contribute to the prediction of TeC in this cohort.

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is used to temporarily support the cardiac cycle and gas exchange in patients with acute cardiorespiratory failure[1–3]. Despite of continuous improvements in oxygenators and pump technologies, VA-ECMO therapy is still associated with a high rate of complications[4–6]. Previous studies state a mortality rate between 40 and 60%[7,8]. The incidence of thromboembolic complications (TeC) such as ischemic stroke, cannula-associated deep vein thrombosis or arterial thromboembolism is estimated at 33%, 41% and 14% respectively[9]. These data show clearly that further improvement of VA-ECMO therapy is warranted. One approach is to identify prognostic biomarkers, for example to predict thromboembolic events in advance[10]. This could possibly improve the outcome due to early identification of therapeutic measures and potential treatment targets. In addition, the use of valid biomarkers could help to understand which patients could really benefit from VA-ECMO.

The Fibrinogen–Albumin-Ratio (FAR) has been suggested as an indicator for disease severity during prothrombotic conditions[11–13]. Fibrinogen and Albumin both have effects on blood clotting. While Fibrinogen is a clotting factor that elevates the aggregation of thrombocytes[14], Albumin plays a role in inhibiting the function of thrombocytes and thrombus formation[15,16]. So far, data on the prognostic value of FAR for patients with VA-ECMO are scarce. A retrospective cohort study revealed that an elevated FAR within the first 24 h after initializing VA-ECMO therapy was associated with a higher risk of ischemic stroke[17]. To our best knowledge, the association

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between FAR and TeC in general has not been investigated yet. Therefore, we aimed to determine whether early FAR is associated with in-hospital TeC in patients undergoing VA-ECMO therapy.

Methods

This retrospective, single-center cohort study was conducted according to the guidelines for good clinical practice (GCP) and the declaration of Helsinki. The study was approved by the ethical committee of the Heinrich-Heine-University, Duesseldorf, Germany (reference number 5141R). All patients gave written informed consent to be registered in a dedicated database. This manuscript follows the STROBE reporting guidelines for retrospective cohort studies.

Participants. The present study included all patients who underwent extracorporeal life support (ECLS) at the University Hospital Duesseldorf, Germany between 2011 and 2018 due to refractory cardiogenic shock. Exclusion criteria were missing data regarding the primary endpoint, incomplete medical records so that documentation of TeC was not possible, age < 18 years and the use of veno-venous ECMO. Anticoagulation was performed with unfractionated heparin according to the local standard or with argatroban, if appropriate. Anticoagulation monitoring was based on activated partial thromboplastin time (aPTT) or anti-factor Xa-activity.

Definition and assessment of main exposure. Main exposure was FAR on the day of initiation of VA-ECMO therapy. Measurements of Fibrinogen and Albumin values were performed in the central laboratory of the University Hospital Duesseldorf. The FAR was calculated by dividing Fibrinogen to Albumin[12,17]. Furthermore, baseline Fibrinogen and baseline Albumin were investigated alone to see if the ratio of both values is superior to the single values. In an additional analysis, FAR on day five was analysed as alternative exposure. The decision to choose these two time points for analysis was based on the rationale that VA-ECMO initiation itself might be associated with TeC, for example due to cannula associated thrombosis. Hence, the predictive value of FAR before or after start of VA-ECMO therapy might be different. Day five was chosen based on local experiences suggesting that this might be a typical point of time where clinicians often have to decide about prognosis and whether therapy should be continued or not.

Outcome assessment. The primary endpoint of this study was the incidence of in-hospital TeC. TeC were defined as a composite of non-fatal arterial thrombosis or embolism, non-fatal venous thrombosis or embolism, non-fatal ischemic stroke, non-fatal myocardial infarction, or thromboembolic vascular mortality[18]. Arterial and venous thromboembolisms were defined as any new and symptomatic non-cardiac and non-cerebral arterial or venous thrombosis or embolism not causing death. Non-fatal myocardial infarction was defined according to the fourth universal definition of myocardial infarction[19]. Non-fatal ischemic stroke was defined according to the guidelines by the American Stroke Association[20]. Thromboembolic vascular mortality was defined as any TeC causing death. Data on TeC were extracted from electronic medical charts by personnel trained in the study definitions. TeC was confirmed when there was a clearly documented diagnosis that was approved by a physician specialized in intensive care medicine. Plausibility checks were done whenever further source documents were available.

Sample size. Due to the nature of this retrospective exploratory data analysis, we did not conduct formal sample size calculation. However, based on the current literature, we expected TeC in approximately 30% of patients[8]. With an estimated study sample of 350 patients, we expected approximately 105 thromboembolic events. This allowed to include up to 10 predefined co-variables for multivariable adjustment (see "Statistical analysis"). As 117 events could be observed in this study, we were able to add two further covariates (= 12 covariates in total) to a separate analysis that was conducted post factum during review process.

Statistical analysis. Patient characteristics are presented as absolute values with corresponding percentages for categorical data or as mean ± standard deviation for continuous data, as appropriate. Shapiro–Wilks test was used to test for normal distribution of data. Fisher exact test and t-tests were used to test for differences between categorical and dichotomous data. Discrimination of baseline FAR for in-hospital TeC was analyzed by receiver operating characteristics (ROC) curve and the "area under the curve" (AUC). ROC analysis was also done for Fibrinogen and Albumin alone. De Long-Test was performed to compare ROC curves. A cutoff value for FAR was determined by Youden Index. Multivariable logistic regression analysis was used to assess the independent association (Odds ratio (OR); 95% confidence interval (CI)) between elevated FAR and in-hospital TeC after adjustment by the following predefined covariables (forced entry): age, sex, chronic coronary syndrome, history of ischemic stroke, history of pulmonary embolism, arterial hypertension, diabetes mellitus, days of VA-ECMO therapy, continuous veno-venous hemodialysis treatment during hospitalization. The choice of covariates was based on literature research[2,3,21–23] and/or clinical experiences so that covariates were included if an association with TeC seemed possible. Baseline quick and baseline activated partial thromboplastin time (aPTT) could be added to an additional post factum logistic regression model. Model calibration was assessed using Hosmer–Lemeshow-Test. Net reclassification index (NRI) and integrated discrimination index (IDI) were calculated for FAR and for Fibrinogen and Albumin alone. For all statistical tests, $p < 0.05$ was considered significant. Analyses were performed with IBM SPSS Statistics version 26 (IBM, Armonk, New York, United States) and GraphPad-Prism© statistical software version 6 (GraphPad software Inc, San Diego, California, United States).

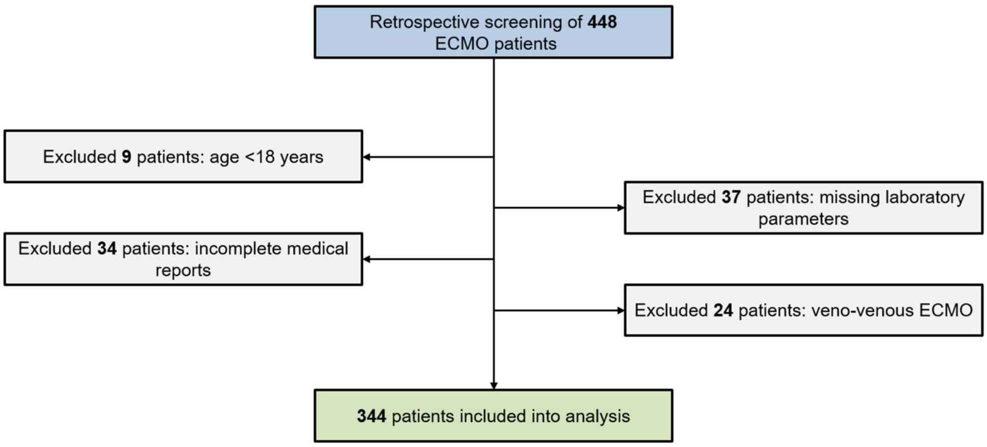

Figure 1. Study flow chart.

Ethics approval and consent to participate. The study was approved by the ethical committee of the Heinrich-Heine-University, Duesseldorf, Germany (reference number 5141R). All patients gave written informed consent to be registered in a dedicated database.

Results

Study cohort and baseline characteristics. The study flow chart is shown in Fig. 1. Of the included 344 patients, 257 (74.7%) were male, the mean age was 59 ± 14. Table 1 reports detailed patients characteristics of the whole cohort and by primary outcome. In total, 117 patients (34%) had a TeC during their hospital stay. The most common TeCs were arterial thromboembolic events (63 patients = 18.3%) and ischemic stroke (40 patients = 11.6%). Overall in-hospital mortality was 58.1% (200/344). Patients with TeC during hospitalization had a significantly higher FAR (158 ± 96) than patients without TeC (108 ± 62) (see Fig. 2). Table 2 summarizes characteristics by FAR above and below the cut-off established by Youden Index. Patients with FAR < 130 had significantly more major bleedings (122 (52.8%) versus 44 (38.9%)) and a higher rate of acute kidney injury requiring renal replacement therapy (132 (57.1%) versus 78 (69.0%)). In addition, patients with FAR below the calculated cutoff had significantly fewer non-fatal myocardial infarctions (3 (1.3%) versus 8 (7.1%)) and other non-fatal arterial thromboembolisms (29 (12.6%) versus 34 (30.1%)). Furthermore, patients with FAR < 130 had a significantly lower baseline quick value (45 ± 20% versus 52 ± 20%).

ROC analysis and determination of cutoff. ROC analysis for baseline FAR and in-hospital TeC revealed an AUC of 0.67 [95% CI 0.61–0.74; p < 0.0001] (see Fig. 3). On day five, data for 212 patients were still available. ROC analysis for FAR on day five and in-hospital TeC revealed an AUC of 0.66 [95% CI 0.57–0.76; p < 0.0001]. Youden index determined a cutoff of 130 for baseline FAR. ROC analysis for baseline Fibrinogen alone and baseline Albumin alone revealed an AUC of 0.61 [95% CI 0.54–0.67; p = 0.001] and 0.61 [95% CI 0.54–0.67; p = 0.001], respectively (see Supplementary Fig. 1). Comparison of ROC curves revealed that AUC-FAR was significantly higher than AUC-Fibrinogen (difference between areas = 0.064 [95% CI 0.018–0.111), p = 0.0066]. Difference between area of AUC-FAR and AUC-Albumin was 0.064 [95% CI − 0.002 to 0.13), p = 0.056].

Multivariate binary logistic regression. Binary logistic regression analysis with multivariable adjustment for ten predefined co-variables revealed a significant association between baseline FAR and in-hospital TeC with an OR of 3.72 (95% CI 2.26–6.14) (see Table 3). The OR for the association between FAR on day 5 and in-hospital TeC was 5.79 [95% CI 2.41–13.89]. A post factum logistic regression model including aPTT and quick as further covariables (= 12 covariables in total) revealed no new significant or relevant findings (see Supplementary Table 1).

Net reclassification index and integrated discrimination index. The overall NRI of FAR was 40.9%. FAR-NRI for events was 26.4% [95% CI 20.8–32.7%; p < 0.0001] and FAR-NRI for non-events was 14.5% [95% CI 8.7–22.2%; p < 0.0001]. Calculation for Fibrinogen alone revealed an overall NRI of 30.1% with an Fibrinogen-NRI of 9.4% [95% CI 4.8–16.2%; p = 0.0013] for events and 20.7% [95% CI 15.6–26.6%; p < 0.0001] for non-events. Calculation for Albumin alone revealed an overall NRI of 22.1% with an Albumin-NRI of 11.1% [95% CI 6.1–18.3%; p = 0.0004] for events and 11% [95% CI 7.3–15.8%; p < 0.0001] for non-events. The IDI for FAR was 0.074 [95% CI 0.041–0.107; p < 0.0001] and IDI for Fibrinogen and Albumin alone was 0.053 [95% CI 0.025–0.081; p = 0.0002] and 0.033 [95% CI 0.012–0.056; p = 0.003], respectively.

	All VA-ECMO patients (N = 344)	Patients without TEC (N = 227)	Patients with TEC (N = 117)	p-value[a]
Baseline characteristics				
Male sex no. (%)	257 (74.7)	167 (73.6)	90 (76.9)	0.516
Age (years)	59 ± 14	58.7 ± 14.9	58.8 ± 13.7	0.930
Duration of ECMO (days)	7.6 ± 5.9	6.7 ± 5.2	9.3 ± 6.9	< 0.0001
Comorbidities no. (%)				
Arterial hypertension	111 (32.3)	73 (32.2)	38 (32.5)	0.999
Diabetes	72 (20.9)	46 (20.3)	26 (22.2)	0.677
Chronic coronary syndrome	176 (51.2)	123 (54.2)	53 (45.3)	0.139
Peripheral artery disease	37 (10.8)	20 (8.8)	17 (14.5)	0.141
Prior MI	162 (47.1)	99 (43.6)	63 (53.8)	0.087
Prior stroke	22 (6.4)	14 (6.2)	8 (6.8)	0.819
Prior pulmonary embolism	14 (4.1)	7 (3.1)	7 (6.0)	0.250
Clinical endpoints no. (%)				
In hospital death	200 (58.1)	133 (58.6)	67 (57.3)	0.819
Major bleeding	166 (48.3)	115 (50.7)	51 (43.6)	0.255
AKI with CVVHD	210 (61.0)	127 (55.9)	83 (70.9)	0.007
Thromboembolic complications no. (%)	117 (34.0)			
MI	11 (3.2)	0 (0)	11 (9.4)	< 0.0001
Stroke	40 (11.6)	0 (0)	40 (34.2)	< 0.0001
Art. thromboembolism	63 (18.3)	0 (0)	63 (53.8)	< 0.0001
Ven. thromboembolism	11 (3.2)	0 (0)	11 (9.4)	< 0.0001
Vascular death	3 (0.9)	0 (0)	3 (2.6)	0.039
Laboratory parameters at baseline				
Creatinine (mg/dl)	1.9 ± 1.6	1.9 ± 1.5	1.9 ± 1.6	0.944
Leukocytes (× 1000/µl)	14.5 ± 7.5	14.7 ± 7.6	14.1 ± 7.3	0.492
Hemoglobin (g/dl)	10.7 ± 2.3	10.6 ± 2.3	10.8 ± 2.4	0.377
Hematocrite (%)	33 ± 17	33.3 ± 20.6	32.5 ± 7.5	0.688
Thrombocytes (× 1000/µl)	174 ± 97	171 ± 90	179 ± 110	0.477
aPTT (s)	76 ± 47	77 ± 48	73 ± 46	0.510
Quick (%)	48 ± 21	47 ± 21	50 ± 20	0.151
Antithrombin III (%)	55 ± 32	58 ± 36	52 ± 20	0.184
D-Dimer	16.2 ± 21.8	15 ± 20	19 ± 25	0.221
Fibrinogen (mg/dl)	288 ± 149	269 ± 139	326 ± 162	0.001
Albumin (g/l)	2.5 ± 0.8	2.6 ± 0.8	2.3 ± 0.8	0.001
FAR	125 ± 79	108 ± 62	158 ± 96	< 0.0001

Table 1. Baseline characteristics of the whole cohort and in patients without and with TeC. Data are presented as mean ± standard deviation or as absolute values with percentages, as appropriate. *TEC* thromboembolic complication, *AKI* acute kidney injury, *aPTT* activated partial thromboplastin time, *CVVHD* continuous Veno-venous hemodialysis, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *FAR* Fibrinogen–Albumin ratio, *MI* myocardial infarction. [a]*p* value of Chi-square test or two-tailed unpaired t-test after Levene's test for equality of variances.

Discussion

The main finding of the present study is that baseline FAR is independently associated with in-hospital TeC in patients requiring VA-ECMO due to refractory cardiogenic shock. Furthermore, this study identified a cutoff of 130 for baseline FAR, which was related to a higher likelihood of TeC. The independent association between FAR and TeC was also present when FAR was measured on day 5 of VA-ECMO therapy.

Prediction and prevention of TeC in VA-ECMO patients. One of the most important issues in terms of treating VA-ECMO patients is to understand which patients could really benefit from VA-ECMO. This decision has to be faced prior to the initiation of VA-ECMO. Once initiated, another important question in terms of prognosis and risk stratification is to decide whether VA-ECMO therapy should be continued or limited, for example if patients suffer from severe complications.

In the last decade, several scores such as the Survival after Veno-Arterial ECMO (SAVE) score[21] have been suggested to help clinicians with these issues, but data focused on the prediction of TeC are rare. In a small retrospective cohort study with 62 patients, Trudzinski and colleagues tried to find predictors for TeC in patients

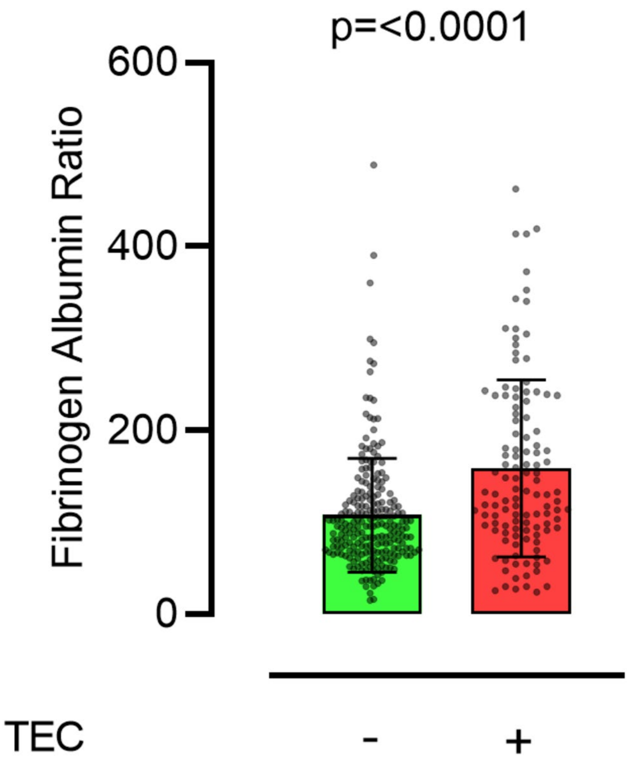

Figure 2. Box plot shows that Fibrinogen–Albumin-Ratio levels in patients with or without thromboembolic complication (TEC) are significantly different.

undergoing veno-venous ECMO due to respiratory failure. This study found that the quality of anticoagulation and ECMO runtime predicted thromboembolic events[22]. Most other studies in this field also focused on the role of anticoagulation and the monitoring of coagulation parameters such as activated clotting time (ACT), aPTT or anti-factor Xa-activity[24,25]. Pieri et al. performed a small case–control study with a total of 20 patients to compare bivalirudin-based anticoagulation with heparin-based protocols in a population of patients treated with VV-ECMO or VA-ECMO with a target aPTT of 45–60 s[26]. The authors concluded that Bivalirudin-based anticoagulation may represent a new method of anticoagulation for reducing thromboembolic complications. A recently published study by Fisser and colleagues investigated Argatroban versus heparin in patients without heparin-induced thrombocytopenia during VV-ECMO[27]. This prospective cohort study included 465 patients and found out that Argatroban was non-inferior to Heaprin regarding bleeding and thrombosis. In summary, data regarding anticoagulation and monitoring of coagulation parameters are still inconclusive.

FAR to predict TeC in VA-ECMO patients. Regarding pathophysiologic mechanisms behind the association of FAR and TeC, Albumin is an essential plasma protein that has been proposed to be related to inflammatory and hemostatic processes[11]. Moreover, Albumin plays a role in the inhibition of platelet activation[15]. Fibrinogen on the other hand is an indicator of a procoagulatory status and contributes to inflammation at diverse levels[12,14]. The combination of these characteristics served as a basis to hypothesize that the ratio of Fibrinogen and Albumin may predict TeC in VA-ECMO patients as this cohort is at high risk for TeC. To date—to our best knowledge—there is only one study by Acharya and colleagues that investigated the predictive value of FAR in patients undergoing VA-ECMO[17]. In a retrospective single-center cohort study, this study analysed 157 patients regarding FAR measured within the first 24 h of VA-ECMO therapy and determined its prognostic value for the incidence of in-hospital ischemic stroke[17]. This study showed a significant association between an elevated FAR (>125) and in-hospital ischemic stroke. Our results add to these data by not only investigating the association between FAR and ischemic stroke, but with TeC in general. In addition, our data reveal a very similar cutoff for FAR (=130) so that this cutoff seems to be suitable. Finally, our study had a larger sample size (344 vs. 157).

Referring to patient characteristics of our study, overall in-hospital mortality rate was 58.1%. This is in line with previously published data[2]. Interestingly, mortality was not influenced by TeC (see Table 1). However, it is important to mention that similar mortality rates do not automatically mean that there was no life impact. Unfortunately, we cannot provide data on more patient-centered outcomes such as "days alive and out of hospital"[28]. Another remarkable finding was that duration of VA-ECMO was significantly different between patients with or without TeC (9.3 ± 6.9 vs. 6.7 ± 5.2). This aspect is underlined by the results of multivariate analysis, which also showed that the length of VA-ECMO therapy was independently associated with TeC (OR 1.08 [95% CI 1.04–1.13]. Thus, taken together, days of VA-ECMO seem to be a relevant risk factor to develop TeC.

	Patients with FAR < 130 (N = 231)	Patients with FAR ≥ 130 (N = 113)	p-value[a]
Baseline characteristics			
Male sex no. (%)	169 (73.2)	88 (77.9)	0.359
Age (years)	58 ± 15	59 ± 14	0.788
Duration of ECMO (days)	7.5 ± 5.9	7.7 ± 6.0	0.777
Comorbidities no. (%)			
Arterial hypertension	76 (32.9)	35 (31.0)	0.806
Diabetes	49 (21.2)	23 (20.4)	0.889
Chronic coronary syndrome	121 (52.4)	55 (48.7)	0.566
Peripheral artery disease	26 (11.3)	11 (9.7)	0.715
Prior MI	109 (47.2)	53 (46.9)	0.999
Prior stroke	16 (6.9)	6 (5.3)	0.646
Prior pulmonary embolism	9 (3.9)	5 (4.4)	0.779
Clinical endpoints no. (%)			
In hospital death	135 (58.4)	65 (57.5)	0.908
Major bleeding	122 (52.8)	44 (38.9)	0.016
AKI with CVVHD	132 (57.1)	78 (69.0)	0.035
Thromboembolic complications no. (%)	56 (24.2)	61 (54.0)	< 0.0001
MI	3 (1.3)	8 (7.1)	0.007
Stroke	23 (10.0)	17 (15.0)	0.209
Art. thromboembolism	29 (12.6)	34 (30.1)	< 0.0001
Ven. thromboembolism	8 (3.5)	3 (2.7)	0.999
Vascular death	1 (0.4)	2 (1.8)	0.252
Laboratory parameters at baseline			
Creatinine (mg/dl)	1.9 ± 1.5	1.6 ± 1.5	0.439
Leukocytes (× 1000/µl)	14.5 ± 7.6	14.5 ± 7.3	0.965
Hemoglobin (g/dl)	10.8 ± 2.4	10.4 ± 2.0	0.122
Hematocrite (%)	33 ± 8	34 ± 28	0.424
Thrombocytes (× 1000/µl)	171 ± 93	180 ± 106	0.451
aPTT (s)	79 ± 48	69 ± 44	0.087
Quick (%)	45 ± 20	52 ± 20	0.003
Antithrombin III (%)	56 ± 36	54 ± 20	0.624
D-Dimer	17.2 ± 22.0	14.5 ± 21.2	0.299
Fibrinogen (mg/dl)	222 ± 87	423 ± 161	< 0.0001
Albumin (g/l)	2.7 ± 0.8	2.1 ± 0.6	< 0.0001
FAR	82.5 ± 26.7	212.2 ± 78.9	< 0.0001

Table 2. Baseline characteristics in patients with FAR < 130 and ≥ 130. Data are presented as mean ± standard deviation or as absolute values with percentages, as appropriate. *AKI* acute kidney injury, *aPTT* activated partial thromboplastin time, *CVVHD* continuous Veno-venous hemodialysis, *ECMO* extracorporeal membrane oxygenation, *FAR* Fibrinogen–Albumin ratio, *MI* myocardial infarction. [a]*p* value of Chi-square test or two-tailed unpaired t-test after Levene's test for equality of variances.

Strengths and limitations

This study has several strengths. One strength of this study is that there was a high number of events (TeC: 117/344 = 34%) so that we could adjust for ten covariables in our multivariate logistic regression model (12 covariables post factum). Another strength is that all included patients were registered in a dedicated database, which ensured higher quality of our data.

This study also has limitations: first, this is a retrospective, single-center cohort study. However, baseline characteristics and in-hospital mortality rate (58.1%) were in line with previously published data[2], suggesting that both VA-ECMO indication and outcome in our centre might be representative for larger practice. Importantly, before drawing final conclusions, the predictive value of FAR for TeC should be investigated in prospective multicenter studies. Second, no cox regression could be performed as the exact time point of TeCs was not always documented in patients' medical records. Third, our database did not include reasons for initiation of VA-ECMO therapy. Although we know that all patients had refractory cardiogenic shock, we do not have information regarding the reason that led to cardiogenic shock.

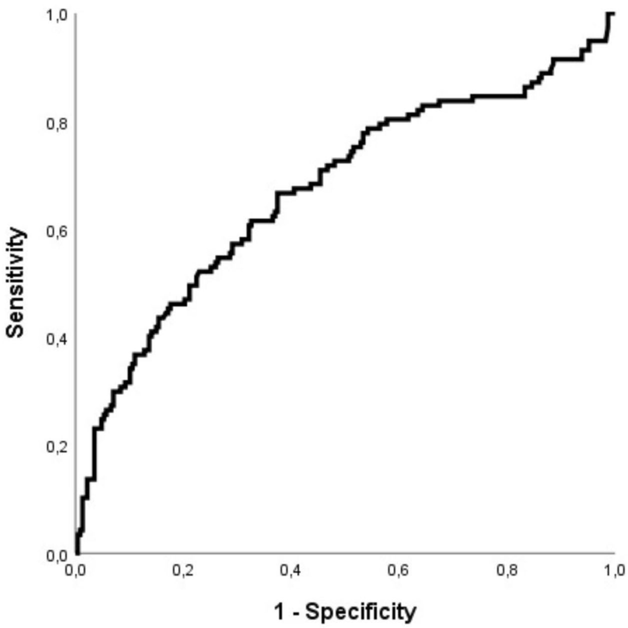

Figure 3. ROC curve shows moderate discrimination of baseline Fibrinogen–Albumin-Ratio for in-hospital thromboembolic complications (AUC = 0.67 [95% CI 0.61–0.74]).

Covariables	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
FAR	3.722	2.258	6.135	< 0.001
Sex	0.814	0.464	1.428	0.472
Age	1.004	0.986	1.022	0.667
CCS	0.661	0.393	1.114	0.120
Prior Stroke	1.066	0.392	2.895	0.900
Prior PE	2.127	0.643	7.033	0.216
Diabetes mellitus	1.255	0.669	2.354	0.479
Arterial hypertension	0.886	0.504	1.558	0.674
CVVHD	1.383	0.819	2.336	0.226
Days of VA-ECMO	1.083	1.037	1.130	< 0.001

Table 3. Multivariate logistic regression for the association between baseline Fibrinogen–Albumin-Ratio and thromboembolic complications. *CCS* Chronic coronary syndrome, *CI* Confidence Interval, *CVVHD* Continous Veno-Venous Hemodialysis, *FAR* Fibrinogen–Albumin-Ratio, *PE* Pulmonary Embolism, *VA-ECMO* Veno-Arterial Extracorporeal Membrane Oxygenation.

Conclusions

In conclusion, this study shows that baseline FAR is independently associated with in-hospital TeC in patients undergoing VA-ECMO. Therefore, FAR might be used to support the prediction of TeC in this cohort. Future studies should validate these findings with a prospective design.

Data availability

The datasets generated during and/or analysed during the current study are available from the first author on reasonable request.

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Author contributions

S.R.: concept/design, data analysis/interpretation, statistics, writing of article. C.J.: data collection, data analysis/interpretation, statistics, writing of article. R.M. and A.S.: data analysis/interpretation, statistics, critical revision of article. U.B., P.A., M.W.H. and R.H.: critical revision of article. A.L.: drafting article, critical revision of article. G.L.B and H.A.: concept/design, data analysis/interpretation, critical revision of article.

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Neutrophil-lymphoycyte-ratio, platelet-lymphocyte-ratio and procalcitonin for early assessment of prognosis in patients undergoing VA-ECMO

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The use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasing, but mortality remains high. Early assessment of prognosis is challenging and valid markers are lacking. This study aimed to investigate Neutrophil–Lymphocyte Ratio (NLR), Platelet-Lymphocyte-Ratio (PLR) and Procalcitonin (PCT) for early assessment of prognosis in patients undergoing VA-ECMO. This retrospective single-center cohort study included 344 consecutive patients ≥ 18 years who underwent VA-ECMO due to cardiogenic shock. Main exposures were NLR, PLR and PCT measured within 24 h after VA-ECMO initiation. The primary endpoint was all-cause in-hospital mortality. In total, 92 patients were included into final analysis (71.7% male, age 57 ± 14 years). In-hospital mortality rate was 48.9%. Receiver operating characteristics (ROC) curve revealed an area under the curve (AUC) of 0.65 [95% confidence interval (CI) 0.53–0.76] for NLR. The AUCs of PLR and PCT were 0.47 [95%CI 0.35–0.59] and 0.54 [95%CI 0.42–0.66], respectively. Binary logistic regression showed an adjusted odds ratio of 3.32 [95%CI 1.13–9.76] for NLR, 1.0 [95%CI 0.998–1.002] for PLR and 1.02 [95%CI 0.99–1.05] for PCT. NLR is independently associated with in-hospital mortality in patients undergoing VA-ECMO. However, discriminative ability is weak. PLR and PCT seem not to be suitable for this purpose.

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is supposed to support patients suffering from refractory cardiogenic shock[1–3]. The use of VA-ECMO has increased in recent years[3,4]. However, mortality of these patients is still high with mortality rates of approximately 50%[4,5]. One of the most important issues in terms of treating VA-ECMO patients is to understand which patients really benefit from VA-ECMO. The initiation of VA-ECMO is often done in emergency situations so that treating physicians do not have a lot of time to select suitable patients. Therefore, once initiated, the assessment of prognosis and the decision about therapy futility is even more crucial. Several scores such as the SAVE-score have been suggested in this context[6], but to date, valid markers are lacking.

Typical complications of patients undergoing VA-ECMO include bleeding, major adverse cardiovascular events (MACE), thromboembolic complications, acute kidney injury or acute liver failure[2,7,8]. Another factor that has been shown to be associated with mortality in patients with VA-ECMO is systemic inflammation[9]. To quantify systemic inflammation, several inflammation markers are available. Calculated from white blood cell count, the Neutrophil–Lymphocyte Ratio (NLR) and the Platelet-Lymphocyte-Ratio (PLR) are two new markers of systemic inflammation which are easily available[10–12]. Previous studies revealed that elevated NLR and PLR are

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independently associated with all-cause mortality and cardiovascular disease in diverse cohorts[11–13]. In patients with VA-ECMO, data on the prognostic value of NLR and PLR are scarce. Another marker of systemic inflammation is Procalcitonin (PCT) which is regularly used in intensive care medicine, e.g. as a marker of sepsis[14]. However, the value of PCT in terms of early prognosis of VA-ECMO patients is also still underexplored. Against this background, we aimed to investigate NLR, PLR and PCT to predict in-hospital mortality and compared discriminative ability and independent association of these markers.

Methods

We conducted a retrospective, single-center cohort study in accordance with the guidelines for good clinical practice (GCP) and the declaration of Helsinki. The study was approved by the ethical committee of the Heinrich-Heine-University, Duesseldorf, Germany (reference number 5141R). All included patients are registered in the local VA-ECMO database and gave written informed consent for registration in advance. This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for retrospective cohort studies.

Participants. 344 patients ≥ 18 years of age treated with VA-ECMO due to refractory cardiogenic shock between 2011 and 2018 at the University hospital Duesseldorf, Germany were included. All VA-ECMO systems were temporary devices. Exclusion criteria were missing values for NLR, PLR or PCT or inconclusive medical records regarding the primary endpoint.

Main exposures. The main exposures of this study were NLR, PLR and PCT. The rationale to choose NLR and PLR was based on the promising results in other settings[11,12]. PCT was chosen to include one established marker of systemic inflammation as comparison that may also be useful in patients with cardiac disease[15]. All markers were measured within 24 h after VA-ECMO initiation. If multiple values were available, first measurement after initiation was chosen. White blood cell count was measured via automated laboratory devices. NLR was calculated by dividing absolute neutrophils to absolute lymphocytes as calculated from automated white blood cell count. PLR was calculated in the same manner using absolute platelets and absolute lymphocytes. PCT values were extracted as determined by the local laboratory. As white blood cell count is routinely measured only once a week in our center, a relevant number of missing NLR and PLR values could be expected, but was considered acceptable as no selection bias could be identified. We also calculated Sequential Organ Failure Assessment (SOFA) score at the same time point (= within 24 h after VA-ECMO initiation) as additional exposure.

Outcome assessment and data collection. The primary endpoint of this study was all-cause in-hospital mortality. Data for this endpoint and all further patient characteristics were extracted from patients medical records by trained personnel of the study team.

Sample size and choice of covariables. As we conducted a retrospective exploratory data analysis, formal sample size calculation was not implemented. However, based on the current literature, we expected an all cause in-hospital mortality for patients treated with VA-ECMO of 50%[4,6]. A sample size of 92 patients meeting the inclusion and exclusion criteria was available. Thus, we expected approximately 45–50 events in total which allowed multivariable adjustment including up to five co-variables[16]. These co-variables were predefined and included age[17], pre-existing coronary artery disease[18], duration of VA-ECMO therapy[19] and continous veno-venous hemodialysis (CVVHD)[20]. The choice of these covariables was driven by the fact that all variables have been shown to be associated with mortality in VA-ECMO patients in the literature as referenced next to each variable. Post-factum, we observed 45 events so that the inclusion of all predefined variables was acceptable.

Statistical analysis. Complete case analysis was performed. Categorical data are presented as absolute counts (percent). Continuous data are presented as mean ± standard deviation. Discrimination of NLR, PLR and PCT for in-hospital mortality was analyzed by receiver operating characteristics (ROC) curve and the resulting area under the curve (AUC). A cutoff value for NLR was determined by Youden Index. Cutoff-values for PLR and PCT were not calculated as there was no discrimination according to ROC curve. To quantify the independent association of NLR, PLR and PCT with in-hospital mortality, multivariate binary logistic regression with forced entry of the predefined covariables was conducted. For NLR, data-driven cutoff was used. Net reclassification index (NRI) and integrated discrimination index (IDI) were calculated for all three biomarkers. De Long-test was performed to compare AUCs of ROC-curves. A p-level < 0.05 was considered significant. We performed the same statistical procedure with SOFA score (including ROC analysis and multivariate logistic regression) and evaluated the prognostic value of NLR when added to SOFA score by comparing the AUCs of a logistic regression model including SOFA score with and without NLR using De Long test.

Ethics approval and consent to participate. This retrospective cohort study was approved by the ethical committee of the Heinrich-Heine-University, Duesseldorf, Germany (reference number 5141R).

Results

In total, 344 patients were screened for this study. As white blood cell count was routinely measured only once a week, 252 patients had to be excluded due to missing values. Consequently, 92 patients with complete data remained for statistical analysis (see Fig. 1). 71.7% patients were male and mean age 57 ± 14 years. In-hospital mortality rate was 48.5%. Detailed patient characteristics are presented in Table 1.

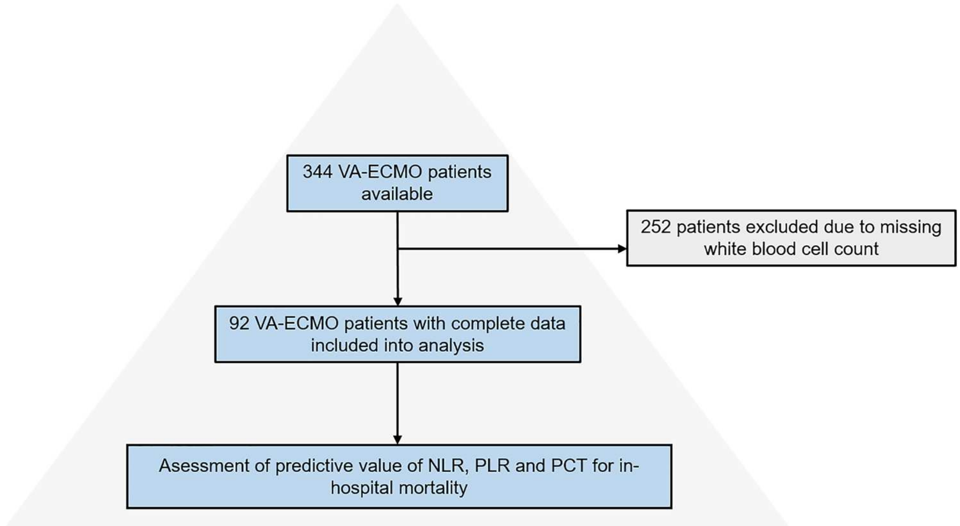

Figure 1. Study flow chart showing selection process of the study cohort. *VA-ECMO* veno-arterial membrane oxygenation, *NLR* neutrophil–lymphocyte-ratio, *PLR* platelet-lymphocyte-ratio, *PCT* procalcitonin.

ROC analysis. ROC analysis of NLR revealed an AUC of 0.65 [95% confidence interval (CI): 0.53–0.76; p = 0.015]. The AUCs of PLR and PCT were 0.47 [95%CI 0.35–0.59; p = 0.645] and 0.54 [95%CI 0.42–0.66; p = 0.521], respectively (see Fig. 2). According to De Long test, AUC of NLR was not significantly higher than AUC of PLR and PCT.

Youden index. Calculation of Youden index showed a cutoff of 13 for NLR. For PLR and PCT, no cutoff calculation was performed as the discrimination of these values for in-hospital mortality was poor based on ROC analysis.

Multivariate binary logistic regression. Multivariate binary logistic regression revealed an adjusted odds ratio (OR) of 3.32 [95%CI 1.13–9.76; p = 0.029] for NLR (see Table 2). Adjusted ORs for PLR and PCT were 1.0 [95%CI 0.998–1.002; p = 0.951] and 1.02 [95%CI 0.99–1.05; p = 0.093], respectively (see Tables 3 and 4). Next to NLR, CVVHD was the only covariable that showed an independent association with in-hospital-mortality in all three logistic regression models (p < 0.0001).

Net reclassification index and integrated discrimination index. Overall NRI of NLR was 19.6%. NRI of NLR for events was 6.8% [95%CI 1.4–18.7%] and NRI of NLR for non-events was 12.8% [95%CI 4.8–25.7%]. Overall NRI of PLR was – 7% (NRI events = – 7% [95%CI – 19 to 1.5%]; NRI non-events = 0%) and overall NRI of PCT was 8.8% (NRI events = 2.4% [95%CI 0.1–12.6%]; NRI non-events = 6.4% [95%CI 1.3–17.5%]. IDI of NLR, PLR and PCT was 3.6%, 0% and 1.5%, respectively.

ROC analysis and multivariate logistic regression for SOFA score. Mean SOFA score measured within 24 h after initiation of VA-ECMO therapy was 11.4 ± 2.4. ROC analysis for SOFA score and in-hospital mortality revealed an AUC of 0.58 [95%CI 0.46–0.70; p = 0.182] (see Supplementary Fig. 1). According to multivariate binary logistic regression, there was no significant association between SOFA score and in-hospital mortality (adjusted OR: 1.01 [95%CI 0.81–1.25; p = 0.967] (see Supplementary Table 1). The AUC of the whole model was 0.8 [95%CI 0.71–0.89; p < 0.0001]. The AUC improved to 0.83 [95%CI 0.74–0.91; p < 0.0001] when NLR was added to this model. This improvement was not significantly different based on De Long test (p = 0.365).

Discussion

In this study, we found out that NLR is independently associated with in-hospital mortality in patients undergoing VA-ECMO. In addition, we could show that there was no association for PLR and PCT. The discriminative ability of NLR, PLR and PCT was weak.

According to the current literature, systemic inflammation plays a key role in the complex pathophysiology of critical illness and there is good evidence that systemic inflammation is associated with worse outcome in patients undergoing VA-ECMO[9]. In the following, we will discuss existing knowledge regarding the predictive value of NLR, PLR and PCT in VA-ECMO patients. In addition, we will state what our results do add to the literature.

To date – to our best knowledge—there is only one study by Yost and colleagues that investigated the predictive value of NLR in adult patients supported by VA-ECMO[21]. This study included 107 retrospective patients who underwent VA-ECMO implantation for cardiogenic shock and reported that NLR is suitable as a prognostic marker for survival in this cohort. Unfortunately, the authors only performed a comparison of mean NLR values

	N (%)	Mean (± SD)
Baseline characteristics	66 (71.7%)	
Male sex no. (%)		
Age (years)		57 ± 14
Indications for VA-ECMO		
Post-cardiotomy	36 (39.1%)	
Acute myocardial infarction	21 (22.8%)	
Cardiopulmonary resuscitation	11 (12%)	
Other reasons of cardiogenic shock	24 (26.1%)	
Comorbidities		
Coronary artery disease	57 (62%)	
History of myocardial infarction	45 (48.9%)	
Peripheral artery disease	10 (10.9%)	
History of stroke	9 (9.8%)	
Diabetes mellitus	26 (28.3%)	
Arterial hypertension	36 (39.1%)	
Inflammatory markers and SOFA score		
C-reactive protein (mg/dl)		7 ± 12.5
Procalcitonin (ng/ml)		10.7 ± 22
Neutrophil–lymphocyte-ratio (× 1000/ul)		12.2 ± 7.7
Platelet-Lymphocyte-Ratio (× 1000/ul)		244 ± 205
SOFA score		11.4 ± 2.4
Hospital stay		
Death in hospital	45 (48.9%)	
Duration of VA-ECMO therapy		9 ± 7
Duration of hospital stay		28 ± 31
Thromboembolic complication	31 (33.7%)	
Major bleeding complication	35 (38%)	
AKI requiring CVVHD	53 (57.6%)	
Coagulation parameters		
Fibrinogen (mg/dl)		316 ± 139
Quick (%)		47 ± 20
aPTT (sec)		69 ± 46
D-Dimer (mg/l)		15 ± 24
Other laboratory parameters		
Bilirubin (mg/dl)		1.7 ± 1.7
Creatinine (mg/dl)		1.9 ± 1.5
High-sensitive troponin T (ng/l)		5527 ± 12,069
Creatinine kinase (U/l)		1531 ± 2481
Creatinine kinase – MB (U/l)		141 ± 152
Lactate dehydrogenase (U/l)		1090 ± 1329

Table 1. Patient characteristics. Data are presented as mean ± standard deviation (SD) or as absolute numbers with percentages. *SOFA* sequential organ failure assessment, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *AKI* acute kidyney injury, *CVVHD* continous veno-venous hemodialysis, *aPTT* activated partial thromboplastin time.

and neither ROC analysis nor multivariate analysis was done. The results of our study add to these limited data by showing that after multivariable adjustment, NLR is still associated with an increased in-hospital mortality (OR = 3.32 [95%CI 1.13–9.76; p = 0.029]). In addition, we defined the first potential cutoff value for NLR in VA-ECMO patients which was 13 according to Youden Index. This cutoff is higher than the existings cutoffs of NLR in the noncardiac surgery setting (e.g. NLR cutoff = 4)[11], but with regard to the extent of systemic inflammation that is caused by cardiogenic shock and VA-ECMO itself, higher cutoff seems plausible in this setting. Furthermore, we could show that the AUC of a logistic regression model including SOFA score (and our 4 predefined variables) could be improved when NLR was added to this model. Although this improvement was not significantly different, our findings clarify that NLR should be considered as early prognostic marker.

While literature on NLR and VA-ECMO is scarce, there are some studies that analyzed the relevance and prognosis of other leukocyte profiles. For example, Siegel et al. prospectively investigated 22 VA-ECMO patients

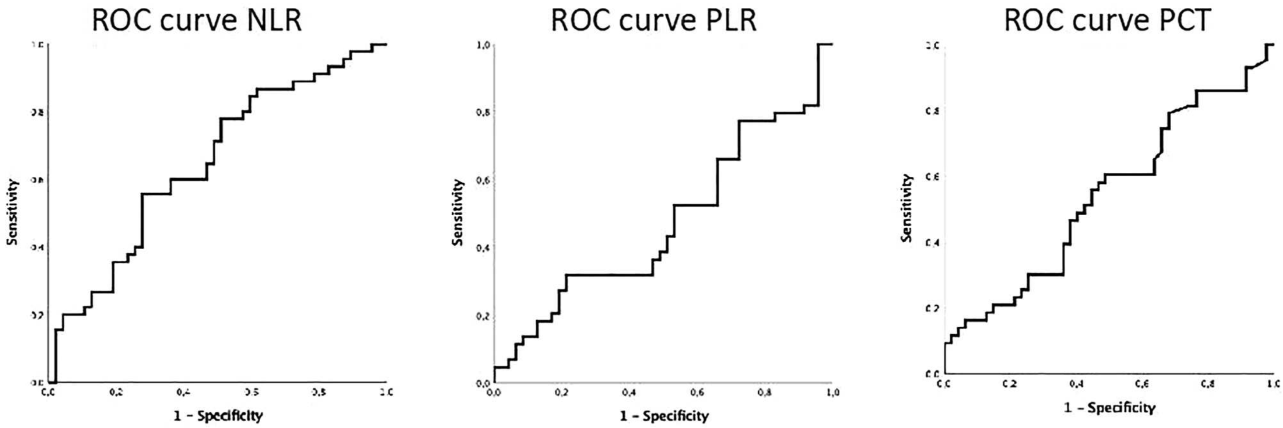

Figure 2. Receiver operating characteristics (ROC) curves showing the discrimination of Neutrophile-Lymphocyte Ratio (NLR), Platelet-Lymphocyte-Ratio (PLR) and Procalcitonin (PCT) for all-cause in-hospital mortality. ROC analysis of NLR revealed an AUC of 0.65 [95% confidence interval (CI) 0.53–0.76; p = 0.015] for NLR. The AUCs of PLR and PCT were 0.47 [95%CI 0.35–0.59; p = 0.645] and 0.54 [95%CI 0.42–0.66; p = 0.521].

Variable	Regression coefficient	Odds ratio	95% Confidence interval	p-value
NLR cutoff	1.2	3.32	1.13–9.76	**0.029**
Age	0.01	1.01	0.97–1.05	0.74
Coronary artery disease	0.57	1.78	0.55–5.69	0.334
Days of VA-ECMO therapy	0.04	1.04	0.96–1.12	0.346
CVVHD	2.2	8.99	3.01–26.28	**< 0.0001**

Table 2. Multivariate binary logistic regression—neutrophil–lymphocyte-ratio. Significant values are in bold. *NLR* neutrophile lymphocyte ratio, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *CVVHD* continous veno-venous hemodialysis.

Variable	Regression coefficient	Odds ratio	95% Confidence interval	p-value
PLR	0.0	1.0	0.998–1.002	0.951
Age	0.02	1.02	0.98–1.06	0.31
Coronary artery disease	0.23	1.26	0.42–3.84	0.681
Days of VA-ECMO therapy	0.04	1.04	0.96–1.12	0.336
CVVHD	2.15	8.59	3.05–24.25	**< 0.0001**

Table 3. Multivariate binary logistic regression—platelet-lymphocyte-ratio. Significant values are in bold. *PLR* platelet-lymphocyte-ratio, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *CVVHD* continous veno-venous hemodialysis.

Variable	Regression coefficient	Odds ratio	95% Confidence interval	p-value
Procalcitonin	0.02	1.02	0.996–1.053	0.093
Age	0.03	1.03	0.99–1.07	0.188
Coronary artery disease	0.23	1.25	0.4–3.89	0.696
Days of VA-ECMO therapy	0.03	1.03	0.94–1.12	0.542
CVVHD	2.25	9.53	3.22–28.18	**< 0.0001**

Table 4. Multivariate binary logistic regression—procalcitonin. Significant values are in bold. *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *CVVHD* continous veno-venous hemodialysis.

and 15 control subjects in terms of monocyte dysfunction and found out that this pathology could be suitable to predict mortality in patients undergoing VA-ECMO[22].

Referring to PLR, this is the first study that investigated this marker in adult VA-ECMO patients. There is only one study by Arslanoglu and colleagues that assessed the prognostic value of PLR in 67 pediatric cardiac surgery patients with VA-ECMO[23]. This study found out that there was no significant relationship between PLR and various postoperative blood parameters and blood gas values. Our results add to these data and show that PLR seems not to be suitable to predict in-hospital mortality as discrimination in ROC analysis was poor. As the sample size in our study was rather small, these results are not sufficient to draw final conclusions. However, based on our data we can say that NLR seems to be superior to PLR in this context so that physicians might rather have a look on NLR than PLR if both values are available.

In terms of PCT, several studies are available that investigated the predictive value of this marker in cardiac surgery and most of these studies came to the conclusion that PCT is a valuable prognostic marker in this setting[24]. In patients undergoing VA-ECMO, literature is very limited. Do Wan Kim and co-authors found out in 38 adult cardiogenic shock patients that a PCT level > 10 ng/mL during VA-ECMO treatment was significantly associated with increased in-hospital mortality ($p < 0.01$)[25]. Although multivariate analysis was performed, the authors could only adjust for age and nosocomial infections. Most other studies concentrated on the association between PCT and infections, but did not assess the predictive value in terms of mortality. Our study therefore adds new knowledge by showing that the discrimination of PCT for in-hospital-mortality in VA-ECMO patients seems to be poor.

This study has several limitations. The main limitation is the huge amount of missing data. As explained above, this is mainly due to the fact that white blood cell count is routinely measured only once a week in our center. This measurement is mostly performed on a specific week day and does not depend on patient- or procedure-related factors so that we concluded that no or only low selection bias should be present. Another limitation is the retrospective design. However, mortality rate in this study corresponds to the current literature so that we assume that our study cohort can be regarded as representative. Finally, this study did only analyze three inflammatory markers, although other markers (e.g. Interleukin-6) are available that might also be investigated in this context.

Conclusions

In conclusion, this study showed that NLR is independently associated with in-hospital mortality in patients with VA-ECMO. However, the discriminative ability of NLR is weak and the sample size of our cohort was small so that further studies with a prospective design and larger cohorts are needed to reevaluate our findings. According to our limited data, PLR and PCT seem not to be suitable for assessment of prognosis in patients with VA-ECMO.

Data availability

The datasets generated during and/or analysed during the current study are available from the first author on reasonable request.

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Author contributions

S.R.: Concept/design, Data analysis/interpretation, Statistics, Writing of article. R.M., A.S. and C.J.: Data analysis/interpretation, Statistics, Critical revision of article. U.B., P.A., M.W.H. and G.L.B.: Critical revision of article. A.L.: Drafting article, Critical revision of article. R.H. and H.A.: Concept/design, Data analysis/interpretation, Critical revision of article.

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RESEARCH ARTICLE

Noninvasive evaluation of the hemodynamic status in patients after heart transplantation or left ventricular assist device implantation

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Abstract

Introduction

Hemodynamic assessment is crucial after heart transplantation (HTX) or left ventricular assist device (LVAD) implantation. Gold-standard is invasive assessment via thermodilution (TD). Noninvasive pulse contour analysis (NPCA) is a new technology that is supposed to determine hemodynamics completely noninvasive. We aimed to validate this technology in HTX and LVAD patients and conducted a prospective single-center cohort study.

Methods

Patients after HTX or LVAD implantation underwent right heart catheterization including TD. NPCA using the CNAP Monitor (V.5.2.14; CNSystems Medizintechnik AG, Graz, Austria) was performed simultaneously. Three TD measurements were compared with simultaneous NPCA measurements for hemodynamic assessment. To describe the agreement between TD and NPCA, Bland–Altman analysis was done.

Results

In total, 28 patients were prospectively enrolled (HTX: n = 10, LVAD: n = 18). Bland-Altman analysis revealed a mean bias of +1.05 l/min (limits of agreement ± 4.09 l/min, percentage error 62.1%) for cardiac output (CO). In LVAD patients, no adequate NPCA signal could be obtained. In 5 patients (27.8%), any NPCA signal could be detected, but was considered as low signal quality.

point of contact who is able to field data access queries.

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Conclusion

In conclusion, according to our limited data in a small cohort of HTX and LVAD patients, NPCA using the CNAP Monitor seems not to be suitable for noninvasive evaluation of the hemodynamic status.

Introduction

After heart transplantation (HTX) or left ventricular assist device (LVAD) implantation, hemodynamic assessment plays a crucial role [1]. Hemodynamic assessment is not only important in the acute postoperative phase, but also in follow-up visits to evaluate graft function or LVAD functionality [2,3]. Current gold-standard is invasive assessment via thermodilution (TD) using a Swan-Ganz-catheter [4]. However, this method is invasive and may be associated with certain risks such as injuries to the nerves and vessels, cardiac arrhythmias or infections [5–7]. Noninvasive pulse contour analysis (NPCA) is a promising new technology that is supposed to determine hemodynamics completely noninvasive via two simple finger cuffs [8]. These inflatable cuffs keep the capillary blood flow constant. The pressure needed is recorded by a pressure transducer and corresponds to the true arterial pressure waveform (= vascular unloading technique or so-called Penaz principle) [9]. Based on the arterial pressure waveform (= pulse contour), it is then possible to determine cardiac output as the area under the arterial curve correlates with cardiac stroke volume. Further hemodynamic parameters such as cardiac index (CI) and systemic vascular resistance (SVR) can be calculated on this basis.

Several studies investigated the accuracy and precision of hemodynamic assessment using NPCA in diverse cohorts and revealed conflicting results [10–13]. In patients post HTX or LVAD implantation, no data are available yet. However, NPCA may be a promising technology in these cohorts as all of these patients regularly need an evaluation of their hemodynamic status and NPCA may provide an estimation of cardiac output (CO) without risks. In the following, this may help to avoid invasive assessment, especially when patients are clinically stable. E.g., patients might receive noninvasive assessment in advance to get an idea if invasive assessment is necessary or not. Therefore, we aimed to investigate if NPCA is a suitable method for noninvasive hemodynamic assessment in patients after HTX or LVAD implantation.

Methods

Study design

A prospective single-center cohort study was conducted. The study was approved by the Ethical Review Board of the Ruhr University Bochum (Registration number: 47/2016) and all patients gave written informed consent. The study was performed in compliance with the declaration of Helsinki and according to the guidelines for good clinical practice (GCP). This report follows the STARD guidelines.

Participants

Patients after HTX or LVAD implantation were prospectively enrolled. All patients were clinically stable and had left the intensive care unit at the time of investigation. Exclusion criteria were age < 18 years, severe tricuspid valve dysfunction and a noninvasive blood pressure

(NIBP) difference $\geq$ 20 mmHg between left and right arm before investigation. Patients with severe tricuspid valve dysfunction were excluded as this might lead to an overestimation of CO by TD. Patients with blood pressure difference were excluded as this might result in wrong blood pressure calibration with consecutive wrong measurements. All participating patients have been recruited parallelly to another clinical trial that investigated NPCA in patients with chronic heart failure and has been published previously [11].

Test methods

Patients underwent right heart catheterization including TD which was routinely performed during patients' hospitalization in an outpatient department. At least three TD-CO measurements were performed using 10 ml boluses of cold saline (< 10 degree Celsius). Cold saline was randomly injected throughout the respiratory cycle as performed previously [4,11]. Single measurements were excluded if variability exceeded 10% compared with mean results. For data analysis, the mean value of three TD-CO measurements within a range of $\leq$ 10% was used. CI, SV and SVR were calculated. Auto calibrated NPCA was performed simultaneously. Patients were connected with the CNAP Monitor (V.5.2.14; CNSystems Medizintechnik AG, Graz, Austria) via two finger cuffs. An oscillometric blood pressure cuff was used for calibration measurement. CO was recorded continuously on a beat-to-beat basis. Documentation of NPCA values was started at the time of cold saline injection. In HTX patients, TD measurements were only allowed if the NPCA signal was visually considered adequate. In LVAD patients, no physiological arterial pressure waveform with adequate signal quality could be expected. Therefore, hemodynamic measurements were also performed if any NPCA signal with the possibility to calculate hemodynamic parameters was available. The mean value of recorded beat-to-beat NPCA measurements was averaged and used for data analysis.

Analysis

All statistical analyses were performed using IBM SPSS version 26. Continuous variables are presented as means with standard deviation or as median with interquartile range, as appropriate. Categorical variables are presented as counts and percentages. To describe the agreement between TD and NPCA, Bland–Altman analysis was done. This statistical method assesses the mean difference (bias) and calculates the limits of agreement (LOA = ± 1.96 x SD of bias of the methods) to find out the variance of the values and is recommended as the gold standard to compare two methods for CO measurement [8].

Results

Participants

In total, 107 patients were screened for this trial. 29 patients met the inclusion criteria for the enrollment of HTX and LVAD patients. One patient had to be excluded due to severe tricuspid valve dysfunction. Finally, 28 prospectively enrolled patients (10 HTX patients (90% male, age 47 ± 8 years, LVEF 61 ± 7%) and 18 LVAD patients (LVEF 24 ± 5%, 89% male, age 53 ± 10 years, pulsatile pump n = 4; continuous-flow pump n = 14)) could be included into the study (Fig 1). Detailed patient characteristics can be found in Table 1.

Test results

HTX patients. In HTX patients, hemodynamic assessment using TD or NPCA using the CNAP Monitor demonstrated a significant difference for mean CO (TD 6.06 ± 1.48 l/min, NPCA 7.12 ± 1.08 l/min, $p<0.001$), CI (TD 2.92 ± 0.86 l/min/m^2, NPCA 3.36 ± 0.42 l/min/m^2,

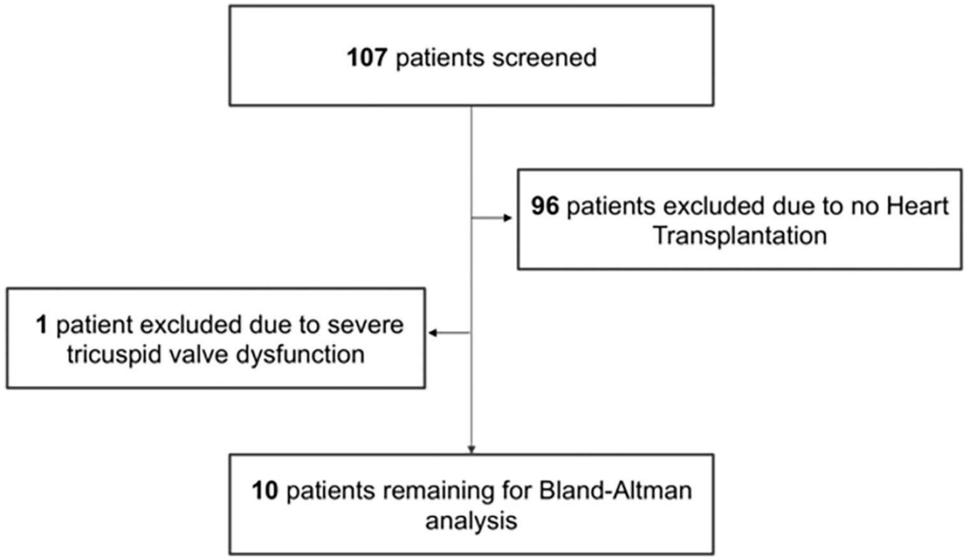

Fig 1. Flow chart.

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p<0.001), SV (TD 70 ± 22 ml, NPCA 86 ± 17 ml, p<0.001), and SVR (TD 1397 ± 451 dyne*s*cm^{-5}, NPCA 1108 ± 189 dyne*s*cm^{-5}, p<0.001). Bland-Altman analysis revealed a mean bias of +1.05 l/min (limits of agreement (LOA) ± 4.09 l/min, percentage error (PE) 62.1%) for CO, +0.45 l/min/m^2 (LOA ± 1.92 l/min/m^2, PE 61.1%) for CI, +16 ml (LOA ± 49 ml, PE 63.1%) for SV, and -289 dyne*s*cm^{-5} (LOA ± 887 dyne*s*cm^{-5}, PE 70.8%) for SVR (Table 2 and Fig 2).

LVAD patients

In all 18 LVAD patients, no adequate NPCA signal by the CNAP Monitor could be obtained. In patients with pulsatile pumps (n = 4), NPCA signal with any arterial pressure curve could be detected so that noninvasive measurement of hemodynamics could be performed as values for analysis. In patients with continuous-flow pumps, only 1 patient had any NPCA signal that revealed hemodynamic parameters to be included into analysis. In the remaining 13 LVAD patients with continuous flow pumps, no NPCA signal with the possibility to calculate hemodynamic parameters could be detected. Accordingly, hemodynamic data of only 5 LVAD patients have been analysed. In these 5 patients, hemodynamic assessment using TD or NPCA demonstrated a significant difference for mean CO (TD 4.74 ± 0.74 l/min, NPCA 5.58 ± 1.61 l/min, p<0.001), CI (TD 2.34 ± 0.41 l/min/m^2, NPCA 2.69 ± 0.62 l/min/m^2, p<0.001), SV (TD 69 ± 9 ml, NPCA 77 ± 20 ml, p<0.001), and SVR (TD 1303 ± 216 dyne*s*cm^{-5}, NPCA 1126 ± 692 dyne*s*cm^{-5}, p<0.001). Due to the inacceptable signal quality and the limited number of only 5 patients, Bland-Altman analysis was not done in this sub-group to avoid overinterpretation of these data.

Discussion

With regard to our results, we have to conclude that NPCA using the CNAP Monitor is not suitable to evaluate the hemodynamic status in patients after HTX or LVAD implantation. While in HTX patients the percentage error (= 62.1%; Fig 2) did not meet the statistical criterion standard by Critchley and Critchley (≤ 30%) [14], in LVAD patients, signal quality of NPCA by the CNAP Monitor was low and any NPCA signal could be detected in only 27.8%

Table 1. Patient characteristics HTX and LVAD patients.

HTX patients	n	%	mean	SD
Baseline data				
Age			47	±8
Male sex	9	90		
BMI			27.3	±3.5
LVEF (%)			61	±7
LVEDD (mm)			47	±5
LAD (mm)			43	±6
Severe heart valve regurgitation / stenosis	0	0		
Sinus Rhythm	10	100		
BNP (pg/ml)			297	±319
Troponin I (pg/ml)			44	±66
Hemoglobin (g/dl)			11.9	±2.5
Creatinine (mg/dl)			1.86	±1.22
Glomerular filtration rate (ml)			49	±21
History of chronic kidney disease	7	70		
History of diabetes mellitus	0	0		
Medication				
ACE inhibitors	4	40		
Angiotensin receptor blocker	2	20		
Diuretics	8	80		
Beta-blocker	4	40		
Digitalis	0	0		
Amiodarone	0	0		
Hemodynamic data				
Heart rate (bpm)			90	±15
Mean arterial pressure (mmHg)			108	±11
Central venous pressure (mmHg)			10	±5
Mean pulmonary arterial pressure (mmHg)			23	±7
Cardiac output (l/min)			6.1	±1.5
Cardiac index (l/min/m2)			2.9	±0.9
Stroke volume (ml)			70	±22
Systemic vascular resistance (dynsec/cm5)			1397	±451
LVAD patients	**n**	**%**	**mean**	**SD**
Baseline data				
Age			53	±10
Male sex	16	89		
BMI			28.5	±6.5
LVEF (%)			24	±5
LVEDD (mm)			62	±17
LAD (mm)			47	±9
Severe heart valve regurgitation / stenosis	3	16.7		
Ischemic heart disease	11	61.1		
Dilative cardiomyopathy	7	38.9		
Diabetes mellitus	4	22.2		
BNP (pg/ml)			935	±1112
Hemoglobin (g/dl)			11.6	±2.8
Creatinine (mg/dl)			1.94	±1.13

(*Continued*)

Table 1. (Continued)

HTX patients	n	%	mean	SD
Glomerular filtration rate (ml)			47	±23
History of chronic kidney disease	12	66.7		
History of diabetes mellitus	4	22.2		
Medication				
ACE inhibitors	7	38.9		
Angiotensin receptor blocker	2	11.1		
Diuretics	15	83.3		
Beta-blocker	17	94.4		
Digitalis	3	16.7		
Amiodarone	8	44.4		
LVAD with pulsatile pump	4	22.2		
LVAD with continous flow pump	14	77.8		
Estimated pump speed (rpm)			7670	±1360
Hemodynamic data				
Heart rate (bpm)			75	±15
Mean arterial pressure (mmHg)			80	±18
Central venous pressure (mmHg)			11	±8
Mean pulmonary arterial pressure (mmHg)			24	±10
Cardiac output (l/min)			4.5	±0.8
Cardiac index (l/min/m2)			2.2	±0.5
Stroke volume (ml)			69	±11
Systemic vascular resistance (dynsec/cm5)			1249	472

Data are presented as absolute values with corresponding percentages or as mean values ± standard deviation. SD = Standard Deviation; BMI = Body Mass Index; LVEF = Left Ventricular Ejection Fraction; LVEDD = Left Ventricular Enddiastolic Diameter; LAD = Left Atrial Diameter; BNP = Brain Natriuretic Peptide; ACE = Angiotensin-Converting Enzyme; LVAD = Left Ventricular Assist Device.

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of patients. In the following, we want to discuss some possible reasons for the limited measurement performance of NPCA in these cohorts.

In HTX patients, two factors may have influenced the insufficient measurement performance of NPCA: 1) the patients' characteristics and 2) the calibration mode [15]. Referring to HTX patients' characteristics, one possible etiology might relate to the phenomenon of vasoplegia which can be observed regularly after HTX. With regard to Table 2, we can see that CO was overestimated and SVR was underestimated by NPCA. However, in our study, it is not very likely that relevant vasoplegia was still present at the time of investigation as all patients had left the intensive care unit and were clinically stable.

Table 2. Hemodynamic assessment HTX patients–Thermodilution versus NPCA.

	TD	NPCA	Bias	LOA	PE (%)
CO (l/min)	6.06±1.48	7.12±1.08	1.05±2.09	±4.09	62.1
CI ($l/min/m^2$)	2.92±0.86	3.36±0.42	0.45	±1.92	61.1
SV (ml)	70±22	86±17	16	±49	63.1
SVR ($dyn^*s^*cm^{-5}$)	1397±451	1108±189	-289	±887	70.8

Data are presented as mean values ± standard deviation. TD = Thermodilution; NPCA = Noninvasive Pulse Contour Analysis; LOA = Limit of Agreement; PE = Percentage error; CO = Cardiac Output; CI = Cardiac Index; SV = Stroke Volume; SVR = Systemic Vascular Resistance.

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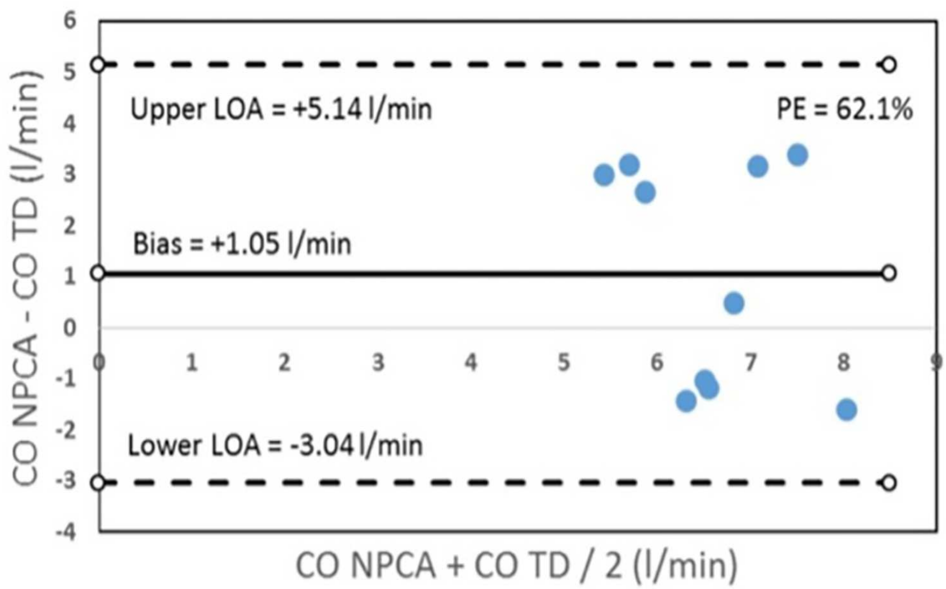

Fig 2. Bland-Altman plot for cardiac output (CO); Bias, limits of agreement (LOA) and percentage error (PE) were calculated.

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A further factor that might complicate the use of NPCA after HTX consists in the possibility of denervation. Transplantation of a new heart surgically interrupts the parasympathetic vagal neurons and the intrinsic postganglionic sympathetic nerves which causes extrinsic cardiac denervation [16]. In the following, this may lead to discrepancies between cardiac hemodynamics and the control of peripheral vasoconstriction / vasodilation.

Another aspect in terms of patients characteristics refers to the vascular status of HTX patients. One can assume that the accuracy of a completely noninvasive pulse contour analysis device suffers from poor vascular status which might be present after HTX, e.g. due to numerous arterial catheterizations for invasive blood pressure measurement or because of severe arteriosclerosis. Although this assumption seems plausible from a clinical perspective, evidence is also lacking.

The second main factor next to patient characteristics that may have influenced the results of NPCA refers to the calibration mode. It is important to mention that NPCA calculated CO on the basis of biometric patient data in this study. A recent study by our working group revealed that, in comparison to the current gold standard TD, auto-calibrated NPCA using the CNAP Monitor systematically overestimates CO with decrease in cardiac function in patients with severe chronic heart failure (NYHA-class III-IV) [11]. Moreover, with decreasing CI as determined by TD, there was an increasing gap between CO values obtained by TD and NPCA ($r = -0.75$, $p < 0.001$). These data suggest that NPCA may not be able to detect low CO values at all. In the present study, left ventricular function according to echocardiopraphy was good (mean LVEF = 61%±7) and CI was also in the normal range. Nevertheless, this aspect should be considered when interpreting absolute NPCA values in patients after HTX. Against this background, one of the main messages of this manuscript is that although NPCA seems to perform well in healthy subjects, this technology might have problems in patients who really need evaluation of hemodynamic status such as patients after HTX or LVAD implantation or patients with severe chronic heart failure.

On the other hand, there are also studies that could reveal more promising results: Wagner et al. have not only assessed the agreement between absolute CNAP Monitor-based CO values, but also performed a trend analysis. They could show in 51 intensive care unit patients after cardiothoracic surgery that NPCA is able to track changes of CO due to passive leg raising maneuvers with an accordance rate of 100% in four-quadrant plots (exclusion zone 0.5 l/min) [10]. Unfortunately, we have not performed any trend analysis to measure CO changes over time, which is a major limitation of this study (see limitations section). Future studies should address this aspect in more detail.

In LVAD patients, our results show clearly that this population seems not to be suitable for noninvasive hemodynamic assessment via NPCA as in only 27.8% of patients, any NPCA signal could be obtained by the CNAP Monitor. In this sub-group, hemodynamic assessment also revealed significantly different values in comparison with the gold standard TD. Most patients (4/5, 80%) with any NPCA signal had LVADs with pulsatile pumps. In this context, it is important to mention that pulsatile pumps are no longer utilized today. Unfortunately, we cannot say how many of the continuous-flow LVAD patients had aortic valve opening (and therefore some degree of arterial pulsatility) at the time of NPCA evaluation. This information would be helpful to denote if the NPCA signal was unable to be obtained as there was no pulsatility or because the degree of pulsatility was so low that the signal was inadequate. In contrast, patients exhibiting myocardial recovery while on LVAD who exhibit aortic valve opening with every beat and significant pulsatility on arterial waveform might prove to be a subpopulation of LVAD patients in whom NPCA might prove helpful.

An additional aspect specifically for LVAD patients refers to the interference between LVAD pumps and NPCA technologies. Possibly, technological factors such as speed or magnetic levitation of the LVAD pump may lead to different measurement results by NPCA. We cannot provide evidence on this assumption, but we think that this point should also be considered when evaluating NPCA in LVAD patients.

Regarding the current literature, studies investigating NPCA in LVAD patients are missing. However, some studies investigated invasive pulse contour analysis, for example the study by Scoletta et al. [17] In this study, a good correlation was found between TD-CO and invasive pulse contour analysis so that the authors concluded that this method may be a complementary tool in the hemodynamic assessment of patients supported with LVAD. The discrepancies between this study and our results might be explained by the fact that invasive assessment performs more accurate than noninvasive assessment. Referring to studies that investigated noninvasive pulse wave analysis devices in general, there is a meta-analysis by Saugel et al. which concluded that study heterogeneity in the literatur12e is high and the pooled results revealed that CO measurements were not interchangeable in surgical or critically ill patients [18].

Limitations

This study has several limitations: First, the sample size of 28 patients is small so that it is not possible to draw final conclusions. It is definitely necessary to perform further prospective studies in HTX and LVAD patients in larger cohorts. Also, as the nature of this study was exploratory, no formal sample size calculation has been performed. Second, a major limitation of this study is that we did not perform any trend analysis. Even if measurement of absolute values is inaccurate, measurement of trends might help to evaluate hemodynamic status in the course of time, e.g. to see if a new therapeutic approach has been successful or not. Third, we cannot provide any information on the presence of aortic valve opening in LVAD patients as these data were not included into our database. It would definitely be interesting to investigate if this factor correlates with the quality of NPCA signal. Fourth, no patient had invasive blood pressure monitoring at the time of investigation so that we cannot provide information if blood pressure measurement using NPCA was accurate in this study. For LVAD patients, blood pressure measurement via doppler was also not available. Fifth, in HTX patients, we cannot report data on the transplanted organs which may also be a factor influencing hemodynamics. Sixth, some baseline characteristics in this study are not representative (e.g. history of diabetes mellitus in 0/10 HTX patients). This may also be related to the very limited sample size. Seventh, and finally, the direct Fick method might be more suitable to measure CO in LVAD patients compared to TD. However, necessary values for mixed venous oxygen saturation and oxygen consumption were not available so that Fick method-based CO could not be calculated.

Conclusions

In conclusion, according to our data, NPCA using the CNAP Monitor seems not to be suitable to evaluate hemodynamic status in patients after HTX or LVAD implantation. Therefore, NPCA by the CNAP Monitor cannot be recommended for this purpose so far. As the sample size in this study was small, it is not possible to draw final conclusions. Nevertheless, our data add to the limited literature in this field and might be helpful for clinicians to correctly interpret hemodynamic parameters by NPCA in HTX and LVAD patients. This is important as clinical decisions might be based on these values. Further studies are needed to clarify if correction factors may improve accuracy of NCPA or if this technology might not be able at all to evaluate hemodynamics noninvasively in patients who really need it, such as patients with HTX or LVAD.

Author Contributions

Conceptualization: Sebastian Roth, Thomas Bitter.

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Project administration: Ragnar Huhn.

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Writing – review & editing: Henrik Fox, René M'Pembele, Michiel Morshuis, Giovanna Lurati Buse, Markus W. Hollmann, Ragnar Huhn, Thomas Bitter.

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Thrombosis Journal

RESEARCH **Open Access**

Evaluation of clinical outcomes in patients treated with heparin or direct thrombin inhibitors during extracorporeal membrane oxygenation: a systematic review and meta-analysis

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Abstract

Background: The number of patients treated with extracorporeal membrane oxygenation (ECMO) devices is increasing. Anticoagulation therapy is crucial to prevent thrombosis during ECMO therapy. Predominantly, heparin has been used as primary anticoagulant but direct thrombin inhibitors (DTI) have been established as alternatives. The aim of this systematic review and meta-analysis was to evaluate clinical outcomes in patients treated with heparin compared to different DTI during ECMO.

Methods: A systematic search was conducted. Full scientific articles were sought for inclusion if heparin anticoagulation was compared to DTI (argatroban/bivalirudin) in ECMO patients. Risk of bias was assessed by Newcastle Ottawa scale. Primary endpoint was in-hospital mortality. Bleeding events, thrombotic events, hours of ECMO support, days of hospital stay, percentage of time within therapeutic range and time to therapeutic range were extracted from full texts as secondary endpoints. Results were presented as Forrest-plots. GRADE was used for confidence assessment in outcomes.

Results: Systematic search identified 4.385 records, thereof 18 retrospective studies for a total of 1942 patients, complied with the predefined eligibility criteria:15 studies investigated bivalirudin and 3 studies investigated argatroban versus heparin. Risk of bias was high for most studies. In-hospital mortality, major bleeding events and pump-related thrombosis were less frequent in DTI group as compared to heparin [mortality—OR 0.69, 95% CI 0.54–0.86; major bleeding—OR 0.48, 95% CI 0.29–0.81; pump thrombosis—OR 0.55, 95% CI 0.40–0.76]. Additionally, percentage of time within therapeutic range was higher for DTI [SMD 0.54, 95% CI 0.14–0.94]. GRADE approach revealed a very low level of certainty for each outcome.

Conclusion: In this meta-analysis, DTI and especially bivalirudin showed beneficial effects on clinical outcomes in ECMO patients as compared to heparin**.** However, due to the lack of randomized trials, certainty of evidence is low.

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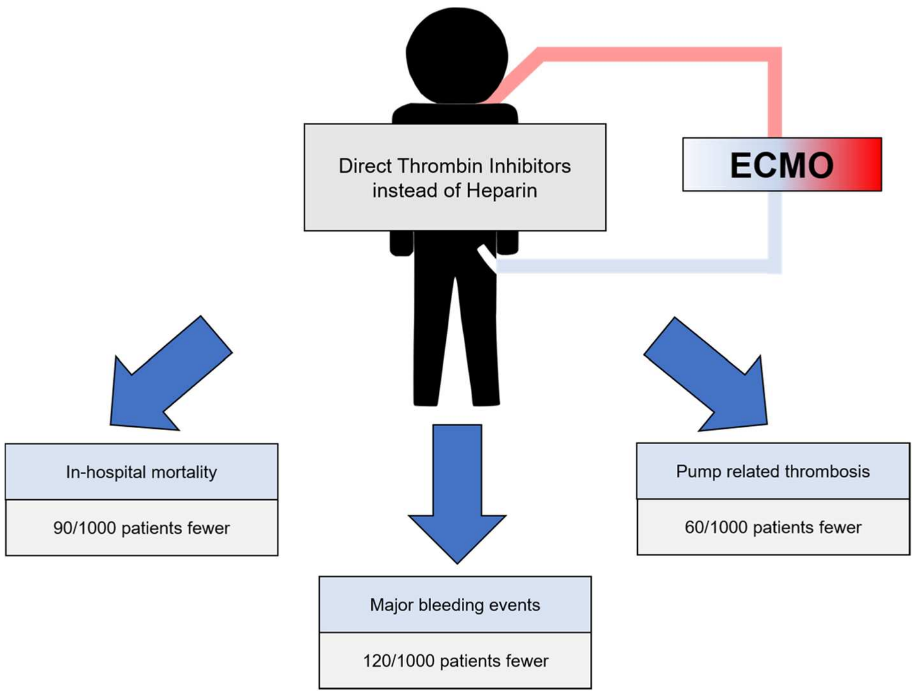
Trial Registration: This systematic review and meta-analysis was prospectively registered at PROSPERO data base (reference number CRD42021237252).

Keywords: Bivalirudin, Argatroban, Anticoagulation, Bleeding, Thrombosis, Mechanical circulatory support

Graphical Abstract



Introduction

Numbers of patients treated with extracorporeal membrane oxygenation (ECMO) devices have been constantly increasing during the past decade [1]. Frequent indications for ECMO therapy are cardiogenic shock (CS), respiratory failure, severe sepsis, or failure to wean from cardiopulmonary bypass after cardiac surgery [2, 3]. During extracorporeal circulation the exposure to exogenous surfaces leads to activation of blood coagulation [4]. Therefore, anticoagulation therapy is mandatory to prevent thrombosis during ECMO therapy. Heparin is used in most centers for anticoagulation in ECMO patients [5, 6]. However, heparin induced thrombocytopenia and heparin resistance are conditions frequently requiring the use of alternative anticoagulants [7, 8]. In this context direct thrombin inhibitors (DTI) like bivalirudin and argatroban have been established as alternatives [8]. Previous research indicate that titration of anticoagulation within therapeutic range might be more feasible with DTI as compared to heparin [9, 10]. Maintenance of therapeutic anticoagulation is crucial, as subtherapeutic doses may results in thrombotic and supratherapeutic doses in bleeding complications with deleterious impact on outcome of ECMO patients. Therefore, some centers primarily use DTI for anticoagulation during ECMO as they might have beneficial influence on outcome [11]. A meta-analysis recently indicated a survival benefit and a reduced incidence of thrombosis in adults treated with bivalirudin as compared to heparin during ECMO therapy [12, 13]. For argatroban, while systematic reviews were conducted, meta-analyses are lacking [14]. Especially comparison of evidence between different DTIs versus heparin has not been demonstrated. The aim of this systematic review and meta-analysis was to evaluate clinical outcomes (in hospital mortality, bleeding complications, thrombotic complications, length of hospital stay, and ECMO duration) in patients treated with Heparin compared to DTI during ECMO and to compare evidence for different DTI by subgroup analysis.

Methods

The report of this systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The protocol and predefined analysis plan is attached as Supplementary material (Supplement 1). The review was registered at PROSPERO on 22th March 2021 (CRD42021237252).

PICO-statement

Population of interest were adult and pediatric patients treated with venoarterial or venovenous ECMO. Intervention was DTI (bivalirudin or argatroban) as primary anticoagulation strategy during ECMO. Anticoagulation using heparin during ECMO was the control strategy. Primary endpoint was in-hospital mortality. Secondary outcomes were number of patients with major and minor bleeding events, patient- and device-related thrombotic or ischemic events during ECMO run, hours of ECMO support, length of hospital stay in days, percentage of activated partial thromboplastin time (aPTT) within therapeutic window and hours to therapeutic aPTT levels.

Eligibility criteria

Published and unpublished randomized controlled trials, prospective or retrospective cohort studies and case–control studies investigating DTI versus heparin in ECMO patients were eligible. Study selection was restricted to English language and only full scientific reports were included. Poster presentations, conference abstracts, systematic reviews and meta-analysis, studies not comparing DTI to heparin in ECMO patients, studies in which patients received DTI only as secondary anticoagulation strategy and studies not reporting on any of the endpoints mentioned above were excluded.

Information sources & search strategy

The following medical libraries were searched for eligible studies published from inception to January 2022: Pubmed/Medline, Cochrane library, CINAHL, Embase. Medical subject headings (MeSh), field terms, text words and Boolean operators were combined in a block building search. Search term contained "extracorporeal membrane oxygenation", "bivalirudin", "argatroban", "direct thrombin inhibitor", "heparin", "anticoagulation", "embolism and thrombosis", "hemorrhage", "survival" and "adverse drug event" amongst others. First date of search was 18th August 2021, last date of search was 20th January 2022. Detailed search strategies are listed in supplement 2. Additionally, the local medical library of the University of Duesseldorf (ULB) was searched and authors of eligible studies were contacted for unpublished data.

Selection process

Two independent researchers screened titles and abstracts of search results from each medical library and retrieved eligible studies. In the second step, the two researchers independently selected studies fulfilling the predefined eligibility criteria based on the full text. After each step, disagreements between both researchers were discussed. No automation tools were used in this process.

Data collection & data items

Data regarding study characteristics and endpoints was extracted from full text, tables and supplements by one reviewer. Entries were independently checked by a second investigator.

If data items (primary or secondary outcomes) were not extractable from publications, authors were contacted via email and requested to complement missing data. Additionally, authors were asked to check the extracted data from their studies in the final version of this manuscript. In case outcomes were available before and after adjustment (for example propensity score matching), we included adjusted data into analysis. If data was not available in desired measurement unit authors were contacted to provide this data. Apart from primary and secondary outcomes, other variables were sought as study characteristics: Study design, number of patients, type of anticoagulation, sex, mean age, type of ECMO, indication for ECMO, aPTT-aim and regime for dosage of anticoagulation. Again, authors were contacted for missing information.

Study risk of bias assessment

Risk of bias was examined separately by two independent investigators using the Newcastle–Ottawa-Scale for non-randomized trials [15]. Study quality was determined as good, fair or poor quality according to scale ratings. Good quality was defined as 3–4 points within selection section and 1–2 points within comparability section and 2–3 points within outcome section. Fair quality was defined as 2 points within selection section and 1–2 points within comparability section and 2–3 points within outcome section. Poor quality was defined as 0–1 points within selection section or 0 points within comparability section or 0–1 point within outcome section.

Effect measures for outcomes

For all dichotomous outcomes Odds ratio (OR) was used as effect measure for data synthesis and presentation of results. Results for continuous outcomes were presented as standardized mean difference (SMD).

Methods of data synthesis and statistical analysis

Meta-analysis was performed for primary and secondary outcomes. Study data were included into analysis if the study reported separately outcomes for heparin and DTI patients. No data conversion was conducted. Study results were presented as tables. Additionally, Forrest plots with pooled estimates of effect were generated for each outcome. Assuming that effects differed across studies a random-effects model was used to account for within and between study variance. To assess for statistical heterogeneity between studies, I^2 tests and Cochrane-Q tests were conducted. Subgroup analysis for adult versus pediatric patients, risk of bias and argatroban versus bivalirudin were conducted to explore possible reasons for heterogeneity. These subgroups were defined a priori. Planned sensitivity analysis was performed for analysis methods by using fixed effects models instead of random effects models and using risk ratio (RR) and risk difference instead of OR for dichotomous outcomes. For continuous variables, MD for individual scale measures were explored and compared to SMD.

Funnel plots were created for each outcome to address for reporting bias. For statistical analysis Review Manager (RevMan) [Computer program]. Version 5.4. (The Cochrane Collaboration, 2020) was used and a *p*-value of < 0.05 was considered as significant, refuting the null hypothesis. Level of confidence for each outcome was assessed by GRADE approach and presented as summary of findings table.

Results

Study selection

The systematic search identified a total of 4.385 records. After removing of 303 duplicates 4.082 records remained for screening of titles and abstracts. Of these records 4.031 records were excluded for not meeting inclusion criteria for titles and abstracts, leaving 51 potentially relevant articles. Among these articles we identified 25 conference abstracts [16–40], 3 studies in which patients were switched between intervention and control group [41–43] and 5 studies that investigated nafamostat mesilate but not DTI versus heparin [44–48]. These 33 studies were excluded, leaving 18 studies for inclusion into data synthesis. Of note, one of these studies was provided by an author and contained unpublished data. A summary of study selection process is presented in Fig. 1.

Study characteristics

In total 17 studies published from years 2011 to 2022 and one unpublished study were included in this meta-analysis [9–11, 49–63]. All studies had a retrospective study design and only one study was multi-center. These studies included 1.942 ECMO patients of which 1.097 patients received heparin, 703 patients received bivalirudin and 89 patients received argatroban. Of note, 55 patients received bivalirudin as secondary anticoagulation strategy, therefore their data were excluded from meta-analysis. Detailed study characteristics and

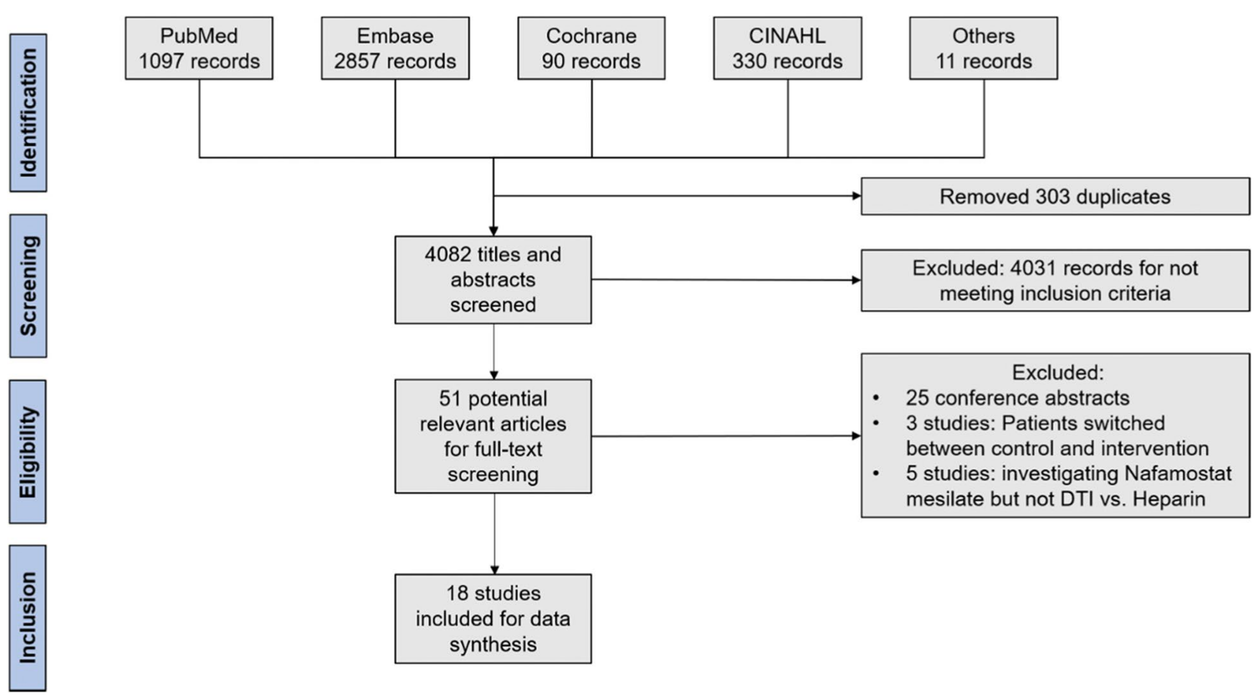


Fig. 1 Flow-chart of study selection process

definitions of outcomes are presented as (supplementary) tables. (Table 1, Table S1, Table S2).

Risk of bias assessment

After assessment of risk of bias, the majority of studies (10 studies) presented a high risk of bias, 3 studies had intermediate risk and only 5 studies had low risk of bias (Fig. 2).

Results of individual studies and data syntheses for primary and secondary outcomes

In-hospital mortality

Seventeen studies reported on mortality and were included into analysis. In 14 studies, bivalirudin was compared to heparin, the remaining 3 studies compared argatroban to heparin. Four studies had a low risk of bias and contributed to analysis with a weight of 55.9%, 3 studies had intermediate risk of bias with a weight of 10.2% and 10 studies had high risk of bias with a weight of 34%. In-hospital mortality was significantly lower for DTI as compared to heparin [pooled estimate OR 0.69, 95% CI 0.54–0.86; Z = 3.20; $p = 0.001$]. Overall heterogeneity was low with $I^2 = 10\%$ [$Chi^2 = 17.85$, df = 16; $p = 0.33$]. Subgroup analysis for bivalirudin and argatroban showed significant reduction of in-hospital mortality for bivalirudin but not for argatroban as compared to heparin [bivalirudin—pooled estimate OR 0.71, 95% CI 0.54–0.94; Z = 2.42; p = 0.02; argatroban—pooled estimate OR 0.61, 95% CI 0.34–1.12; Z = 1.59; p = 0.11]. Heterogeneity measured by I^2 within subgroups was 21% for bivalirudin and 0% for argatroban [bivalirudin—$Chi^2 = 16.42$, df = 13; p = 0.23; argatroban—$Chi^2 = 1.34$, df = 2; $p = 0.51$]. However, no statistical difference between subgroups was detected [$Chi^2 = 0.20$, df = 1; $p = 0.66$; $I^2 = 0\%$]. Adult and pediatric patients both showed lower incidence of mortality with DTI as compared to heparin [pediatric—pooled estimate OR 0.65, 95% CI 0.43–0.99; Z = 2.02; $p = 0.04$; adult—pooled estimate OR 0.67, 95% CI 0.53 -0.85; Z = 3.31; $p = 0.0009$]. No heterogeneity within subgroups or subgroup differences were detected. Additionally, we explored risk of bias of studies as potential source for heterogeneity. We identified studies with high risk of bias as source for heterogeneity with $I^2 = 24\%$ as compared to studies with low and intermediate risk of bias with $I^2 = 0\%$ respectively. Sensitivity analysis using RR and fixed effects model did not affect these results. Estimates for each study and the subgroups are presented within the Forrest-plots (Figs. 3, S1, S2) (Table 2).

Major bleeding events

Fifteen studies reported on major bleeding events of which 12 studies compared bivalirudin and 3 studies compared argatroban to heparin. Three studies had low risk of bias and contributed to analysis with a weight of 32%, another 3 studies had intermediate risk of bias with a weight of 17.4% and 10 studies presented high risk of bias with a weight of 50,6%. Major bleeding was lower in DTI group as compared to heparin group [pooled estimate OR 0.48, 95% CI 0.29–0.81; Z = 2.75; $p = 0.006$] however, overall heterogeneity was high [$I^2 = 57\%$, $Chi^2 = 35.1$, df = 15, $p = 0.002$]. Subgroup analysis revealed that major bleeding was significantly reduced for bivalirudin but not for argatroban, and in pediatric patients but not in adult patients with DTI [bivalirudin—pooled estimate OR 0.44, 95% CI 0.23–0.83; Z = 2.54; $p = 0.01$; argatroban—pooled estimate OR 0.66, 95% CI 0.35–1.24; Z = 1.29; p = 0.20; pediatric—pooled estimate OR 0.22, 95% CI 0.13–0.38; Z = 5.43; $p = <0.0001$; adult—pooled estimate OR 0.74, 95% CI 0.38–1.41; Z = 0.92; $p = 0.36$]. We used subgroup analysis to explore potential sources of heterogeneity and identified that heterogeneity was high between studies that investigated bivalirudin versus heparin and studies which investigated anticoagulation regime in adult patients [Bivalirudin subgroup—$I^2 = 62\%$, $Chi^2 = 32$, df = 12, $p = 0.001$; adult subgroup—$I^2 = 63\%$, $Chi^2 = 24$, df = 9, $p = 0.004$]. Sensitivity analysis using RR and fixed effects model did not change the overall results but use of fixed effect model additionally lead to a significant reduction in major bleeding for subgroup of adult patients with DTI by narrowing the CI [adult—pooled estimate OR 0.54, 95% CI 0.39–0.74; Z = 3.75; $p = 0.0002$]. Estimates for each study and the subgroups are presented within the Forrest-plots (Figs. 4, S3).

Minor bleeding events

A total of 8 studies reported on minor bleeding events of which 5 studies compared bivalirudin and 3 studies compared argatroban to heparin during ECMO therapy. Overall no significant differences in minor bleeding events was detected between DTI and Heparin [pooled estimate OR 0.74, 95% CI 0.47–1.17; Z = 1.27; $p = 0.20$], Use of argatroban showed no effect on minor bleeding events as compared to heparin [pooled estimate OR 1.02, 95% CI 0.49–2.15; Z = 0.05; $p = 0.96$]. Overall heterogeneity and heterogeneity within subgroups were low [overall—$I^2 = 3\%$, $Chi^2 = 7.19$, df = 7, $p = 0.41$; bivalirudin subgroup—$I^2 = 0\%$, $Chi^2 = 3.22$, df = 4, $p = 0.52$; argatroban subgroup—$I^2 = 15\%$, $Chi^2 = 2.35$, df = 2, $p = 0.31$]. Sensitivity analysis using RR and fixed effects model did not change the overall results but use of RR changed non-significant trend to a significant reduction in minor bleeding in bivalirudin patients by narrowing the CI [adult—pooled estimate RR 0.68, 95% CI 0.48–0.97; Z = 2.11; $p = 0.04$] Estimates for each study and the subgroups are presented within the Forrest-plots. (Fig. 5).

Table 1 Characteristics of included studies

Author	Year of publication	Study design	Type of Comparison	Number of participants per group	Adult / pediatric patients	Type of ECMO	Indication for ECMO	Male sex	Mean age ± SD (years)	aPTT aim (s)
Hamzah [63]	2022 (under review)	Multi center, retrospective	Heparin vs. Bivalirudin	Total: 225 Hep.: 150 Biv.: 75	pediatric	VV-ECMO: 36 VA-ECMO: 141 eCPR: 48	eCPR: 48 CPB weaning: 115 Not reported: 62	Hep.: 74 Biv.: 38	Hep.: 8 (1, 36) Biv.: 7 (2, 37) (months, median, IQR)	Not reported
Pieri [58]	2021	Single center, retrospective	Heparin vs. Bivalirudin	Total: 125 Hep.: 26 Biv.: 99	All adult patients	VV-ECMO only	ARDS only	Total: 93	Not reported	Hep.: 55–60 Biv.:55–60
Sheridan [9]	2021	Single center, retrospective	Heparin vs. Bivalirudin	Total: 150 Hep.: 50 Biv.: 100	All adult patients	VV-ECMO: 52 VA-ECMO: 88	CS: 58 Resp. fail.: 59 PE: 10 CPB weaning: 11 Others:12	Total: 106 Hep.: 32 Biv.: 74	Total: 53 ± 14.5 Hep.: 53 ± 14 Biv.: 54 ± 15	Hep.: < 95 and anti-FXa 0.3–0.7 IU/mL Biv.:45–75
Machado [54]	2021	Single center, retrospective	Heparin vs. Bivalirudin	Total: 32 Hep.: 14 Biv.: 18	All pediatric patients	VA-ECMO: 30 VV-ECMO: 1 Hybrid: 1	Not reported	Total: 12 Hep.: 9 Biv.: 7	Hep.: 39.8 ± 76.1 Biv.: 36 ± 58.8 (months)	Not reported (individual goals)
Seelhammer [62]	2021	Single center, retrospective	Heparin vs. Bivalirudin	Total: 422 Hep.: 288 Biv.: 134	Adult: 333 Pediatric: 89	VA-ECMO: 358 VV-ECMO: 64	Post cardiotomy: 162 CS: 100 Resp. fail.: 86 eCPR: 69 Transplant: 5	Total: 265 Hep.: 183 Biv.: 82	Not reported	Hep.: 60–90 Biv.: 60–80
Schill [63]	2021	Single center, retrospective	Heparin vs. Bivalirudin vs. switched	Total: 54 Hep.: 34 Biv.: 14 Switched: 8	All pediatric patients	VA-ECMO: 38 VV-ECMO: 18	Post cardiotomy: 20 Resp. fail.: 19 CS: 17	Not reported	Hep.: 16.3 (4.8, 143.7) Biv.: 5.5 (3.7, 79.6) (months, median,IQR)	Hep.: anti-FXa 0.3–0.7 IU/mL Biv.: 60–95
Kaushik [52]	2021	Single center, retrospective	Heparin vs. Bivalirudin vs. switched	Total: 39 Hep.: 27 Biv.: 8 Switched: 4	All pediatric patients	VA-ECMO:34 VV-ECMO: 4 Hybrid: 1	Resp. Fail.: 12 CS: 11 eCPR: 6	Total: 20 Hep.: 15 Biv.: 3	Hep.: 4.0 (0.5, 92.0) Biv.: 0.6 (0.0, 80.0) (months, median, IQR)	Hep.: 60–90 Biv.: 60–90
Rivosecchi [60]	2021	Single center, retrospective	Heparin vs. Bivalirudin	Total: 295 Hep.: 162 Biv.: 133	All adult patients	VV-ECMO only	Resp. fail.: 145 Pre/post-transplant: 108 Post cardiotomy: 20 Others: 22	Total: 146 Hep.: 95 Biv.: 81	Hep.: 49 (36,61) Biv.: 49 (36,61) (median, IQR)	Hep.: anti-FXa 0.25–0.35 IU/mL Biv.: 60–75
Fisser [10]	2021	Single center, retrospective	Heparin vs. Argatroban	Total: 117 Hep.: 78 Arg.: 39	All adult patients	VV-ECMO only	ARDS only	Total: 80 Hep.: 51 Arg.: 29	Hep.: 56 (48,63) Arg.: 55 (46,61) (median, IQR)	Hep.: 45–55 Arg.:45–55
Cho [50]	2021	Single center, retrospective	Heparin vs. Argatroban	Total: 35 Hep.: 24 Arg.: 11	All adult patients	VA-ECMO: 10 VV-ECMO: 21 Hybrid: 4	Not reported	Total: 22 Hep.: 15 Arg.: 7	Total: 46 ± 17 Hep.: 45 ± 16 Arg.: 49 ± 20	Hep.: 40–60 or 60–80 (high dose) Arg.:43–85

Table 1 (continued)

Author	Year of publication	Study design	Type of Comparison	Number of participants per group	Adult / pediatric patients	Type of ECMO	Indication for ECMO	Male sex	Mean age ± SD (years)	aPTT aim (s)
Hamzah [11]	2020	Single center, retrospective	Heparin vs. Bivalirudin	Total: 32 Hep.: 16 Biv.: 16	All pediatric patients	VA-ECMO: 29 VV-ECMO: 3	Post cardiotomy:13 Others: not reported	Total: 14 Hep.: 8 Biv.: 6	Total: 12 (0–212) Hep.: 59 (0, 212) Biv.: 31 (0–99) (months, median, IQR)	Hep.: 60–80 Biv.: 58–78 or 50–70 (open chest)
Kaseer [51]	2020	Single center, retrospective	Heparin vs. Bivalirudin	Total: 52 Hep.: 33 Biv.: 19	All adult patients	VA-ECMO: 28 VV-ECMO: 24	CS:15 ARDS:24 Transplant: 17 Others:1	Total: 37 Hep.: 25 Biv.: 12	Total: 55 (18, 83) Hep.: 53 (21, 83) Biv.: 56 (18, 71) (median, IQR)	Hep.: 50–70 or 40–60 Biv.: 60–90 or 50–70
Macielak [55]	2019	Single center, retrospective	Heparin vs. Bivalirudin vs. switched	Total: 153 Hep.: 100 Biv.: 10 Switched: 43	All adult patients	VA-ECMO: 134 Other types not reported	Salvage: 61% CS: 46% ARDS:29% Resp. fail.: 29% CPB weaning: 23% Others: 12%	Total: 127	Total: 52.8 ± 14.2 Hep.: 51.4 ± 14.0 Biv.: 57.9 ± 13.8	Hep.: 72–95 Biv.: 60–80
Berei [49]	2018	Single center, retrospective	Heparin vs. Bivalirudin	Total: 72 Hep.: 28 Biv.: 44	All adult patients	VA-ECMO: 66 VV-ECMO: 6	CS: 51 Sepsis: 11 Resp. fail.: 4 Others: 6	Total: 47 Hep.: 18 Biv.: 29	Hep.: 55.9 ± 13.1 Biv.: 55.2 ± 15.2	Hep.: 45–65 or 65–90 Biv.: 45–65 or 65–90
Menk [56]	2017	Single center, retrospective	Heparin vs. Argatroban	Total: 78 Hep.: 39 Arg.: 39	All adult patients	VV-ECMO: 43 pECLA: 24 Hybrid: 11	ARDS only	Total: 54 Hep.: 27 Arg.: 27	Hep.: 48 (35,64) Arg.: 47 (36,60) (median, IQR)	Hep.: 50–75 Arg.:50–75
Ljajikj [53]	2017	Single center, retrospective	Heparin vs. Bivalirudin	Total: 20 Hep.: 10 Biv.: 10 (after PS-Matching)	All adult patients	VA-ECMO only	support pre, during and after LVAD implantation only	Total: 17 Hep.: 9 Biv.: 8	Hep.: 52.5 ± 9.7 Biv.: 48.2 ± 14.1	Not reported
Pieri [57]	2013	Single center, retrospective	Heparin vs. Bivalirudin	Total: 20 Hep.: 10 Biv.: 10	All adult patients	VA-ECMO: 10 VV-ECMO: 10	Not reported	Total: 16 Hep.: 9 Biv.: 7	Hep.: 54 ± 12.7 Biv.: 59.5 ± 14.4	Hep.: 45–60 Biv.: 45–60
Ranucci [59]	2011	Single center, retrospective	Heparin vs. Bivalirudin	Total: 21 Hep.: 8 Biv.: 13	Adult: 12 Pediatric: 9	VVA-ECMO: 21	Post cardiotomy only	Not reported	Hep.: 13.9 ± 19 Biv.: 36.5 ± 29	Hep.: 50–80 Biv.: 50–80

ARDS acute respiratory distress syndrome, *Arg* Argatroban, *Biv* Bivalirudin, *CPB* cardiopulmonary bypass, *CS* cardiogenic shock, *eCPR* extracorporeal cardio pulmonary resuscitation, *Hep* Heparin, *IQR* interquartile range, *PE* pulmonary embolism, *Resp. Fail.* respiratory failure, *VA-ECMO* venoarterial extracorporeal membrane oxygenation, *VV-ECMO* venovenous extracorporeal membrane oxygenation

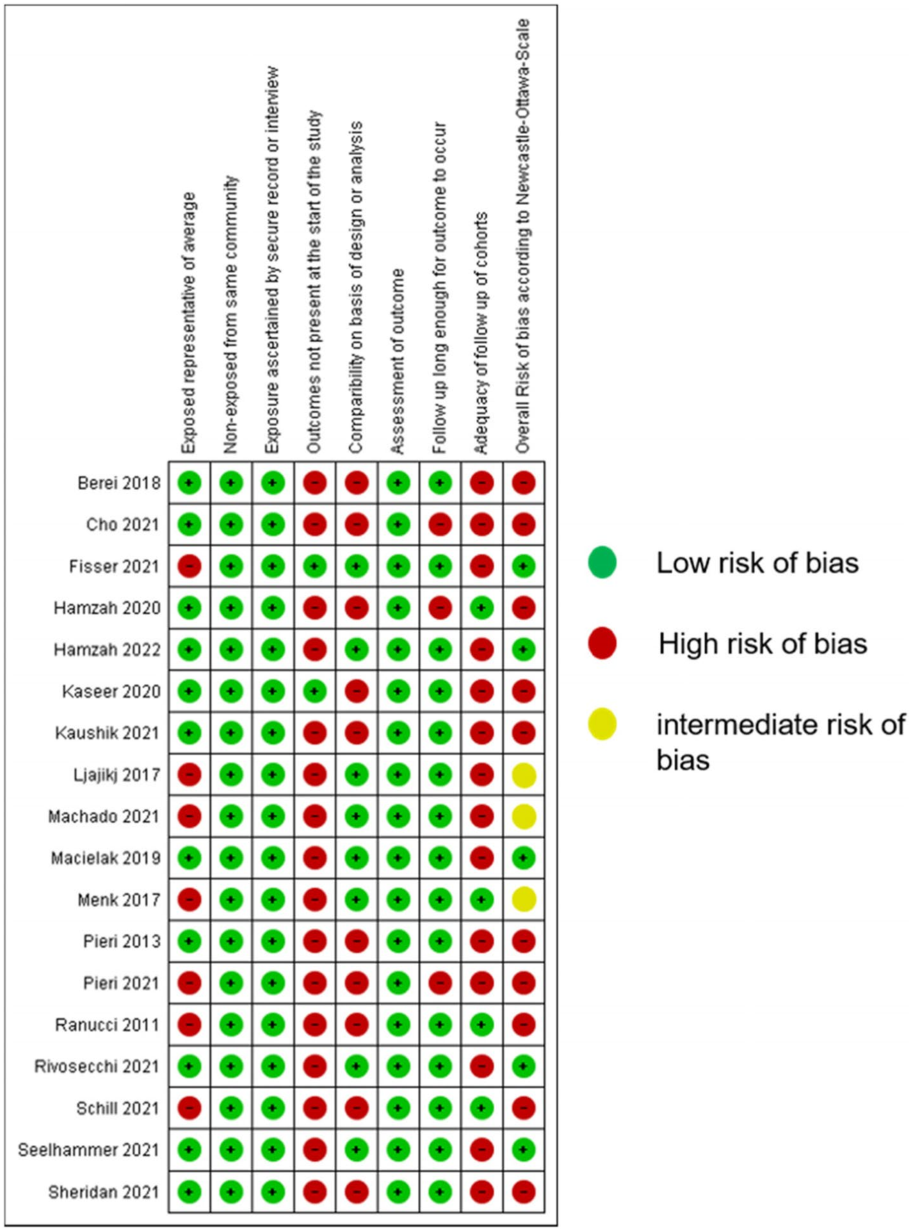


Fig. 2 Risk of bias assessment. Legend: The figure shows risk of bias for included studies using the Newcastle Ottawa scale. Overall risk of bias is presented as low (green), intermediate (yellow) or high (red)

Patient-related thrombosis

Fifteen studies reported on patient-related thrombosis including 12 studies comparing bivalirudin and all 3 studies comparing argatroban to heparin. Overall pooled estimates indicated that use of DTI might be beneficial however, the finding was not statistically significant [pooled estimate OR 0.73, 95% CI 0.53–1.02; Z = 1.87; p = 0.06]. Subgroup analysis for anticoagulants revealed that use of bivalirudin reduces patient-related thrombosis while use of argatroban might be not beneficial as trend favored heparin [bivalirudin- pooled estimate OR 0.55, 95% CI 0.38–0.81; Z = 3.09; p = 0.002; argatroban—pooled estimate OR 1.79, 95% CI 0.92–3.50; Z = 1.70; p = 0.09]. This resulted in significant difference between subgroups [test for subgroup differences—$I^2 = 88.8\%$, $Chi^2 = 8.94$, df = 1, $p = 0.003$]. Overall heterogeneity and heterogeneity within subgroups was not detected [overall—$I^2=0\%$, $Chi^2=13.89$, df = 14, p = 0.46; bivalirudin subgroup—$I^2=0\%$, $Chi^2=3.94$, df = 11, p = 0.97; argatroban subgroup—$I^2=0\%$, $Chi^2=1.0$, df = 2, $p=0.61$]. Use of RR did not change the results. Sensitivity analysis with fixed effects model changed the non-significant trend to significant benefit of DTI for patient-related thrombosis by narrowing the CI [pooled estimate OR 0.71, 95% CI 0.52–0.98; Z = 2.10; $p=0.04$]. Estimates for each study and the subgroups are presented within the Forrest-plots. (Fig. 6).

Pump-related thrombosis

Thirteen studies reported on pump-related thrombosis. Ten of these studies compared bivalirudin to heparin, 3 studies used argatroban as DTI. Three of these studies presented low risk of bias, 2 studies had intermediate risk of bias, and 8 studies had high risk of bias. Pump-related thrombosis occurred less frequent in DTI group as compared to heparin group [pooled estimate OR 0.55, 95% CI 0.40–0.76; Z = 3.62; $p=0.0003$]. This finding was mainly driven by patients who received bivalirudin compared to heparin [subgroup bivalirudin—pooled estimate OR 0.47, 95% CI 0.33–0.67; Z = 4.19; $p=<0.0001$]. Argatroban showed no beneficial influence on occurrence of pump-related thrombosis as compared to heparin [subgroup argatroban—pooled estimate OR 1.09, 95% CI 0.52–2.30; Z = 0.23; $p=0.82$]. Thus, significant difference between subgroups was detected [test for subgroup differences—$I^2=75.1\%$, $Chi^2=4.02$, df = 1, p = 0.04]. However, this did not lead to overall heterogeneity [$I^2=1\%$, $Chi^2=12.07$, df = 12, p = 0.44]. Estimates for each study and the subgroups are presented within the Forrest-plots. (Fig. 7).

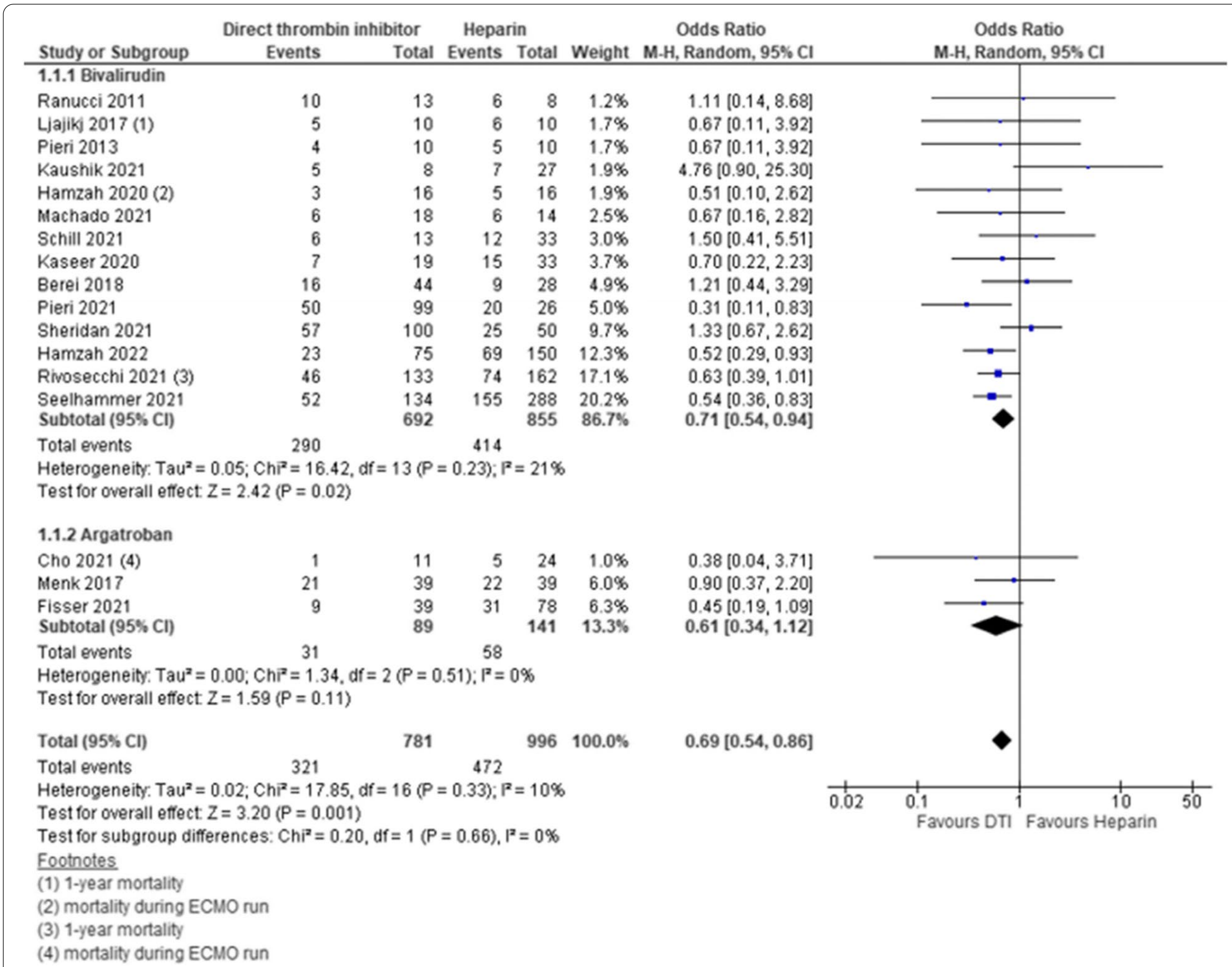


Fig. 3 Mortality. Legend: The figure shows results of data synthesis for mortality. Pooled estimates are presented as Odds ratios for direct thrombin inhibitors versus heparin as well as for bivalirudin and argatroban subgroups

Table 2 Summary of findings table

Research topic: Direct thrombin inhibitors compared with heparin for extracorporeal membrane oxygenation therapy						
Patients: Adult and pediatric patients **Setting: In-hospital extracorporeal membrane oxygenation therapy** **Intervention: Direct thrombin inhibitors** **Comparison: Unfractionated heparin**						
Outcomes	**Illustrative comparative risks[b] (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk[a]	**Corresponding risk**				
	unfractionated heparin	**Direct thrombin inhibitors**				
Mortality	**474 per 1000**	**393 per 1000** (346 to 450)	**RR 0.83** (0.73 to 0.95)	1777 (17)	⊕⊖⊖⊖ **very low** due to lack of RCTs, risk of bias, publication bias	
Major bleeding events	**501 per 1000**	**336 per 1000** (251 to 456)	**RR 0.67** (0.5 to 0.91)	1355 (16)	⊕⊖⊖⊖ **very low** due to lack of RCTs, risk of bias, publication bias	
Minor bleeding events	**287 per 1000**	**247 per 1000** (195 to 316)	**RR 0.86** (0.68 to 1.10)	632 (8)	⊕⊖⊖⊖ **very low** due to lack of RCTs, risk of bias, imprecision	
Pump-related thrombosis	**233 per 1000**	**163 per 1000** (121 to 217)	**RR 0.7** (0.52 to 0.93)	1361 (13)	⊕⊖⊖⊖ **very low** due to lack of RCTs, risk of bias, imprecision, publication bias	
Patient-related thrombosis	**200 per 1000**	**162 per 1000** (118 to 220)	**RR 0.81** (0.59 to 1.10)	1447 (15)	⊕⊖⊖⊖ **very low** due to lack of RCTs, risk of bias, inconsistency, publication bias	
length of ECMO therapy (hours and days)	See comment	The SMD in length of ECMO therapy in the intervention groups was 0.12 higher (-0.03 lower to 0.27 higher)		1274 (12)	⊕⊖⊖⊖ **very low** due to lack of RCTs, risk of bias, imprecision, publication bias	Mean for control group not estimable as different measures were used for outcome assessment

Table 2 (continued)

Research topic: Direct thrombin inhibitors compared with heparin for extracorporeal membrane oxygenation therapy

Patients: Adult and pediatric patients
Setting: In-hospital extracorporeal membrane oxygenation therapy
Intervention: Direct thrombin inhibitors
Comparison: Unfractionated heparin

Outcomes	Illustrative comparative risks[b] (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[a]	Corresponding risk				
	unfractionated heparin	Direct thrombin inhibitors				
length of hospital stay (days)	The mean time to anticoagulation goal ranged across control groups from 5 to 47 days	The SMD in length of hospital stay in the intervention groups was 0.19 higher (-0.30 lower to 0.69 higher)		467 (4)	⊕⊝⊝⊝ **very low** due to lack of RCTs, risk of bias, imprecision, publication bias	
time to anticoagulation goal (hours)	The mean time to anticoagulation goal ranged across control groups from 9 to 32 h	The SMD in time to anticoagulation goal in the intervention groups was 0.2 lower (-0.73 lower to 0.34 higher)		324 (4)	⊕⊝⊝⊝ **very low** due to lack of RCTs, risk of bias, imprecision, publication bias	
Percentage of time within therapeutic range (percentage)	The mean percentage of time within therapeutic range ranged across control groups from 11 to 31 percent	The SMD of percentage of time within therapeutic range in the intervention groups was 0.54 higher (0.14 to 0.94 higher)		491 (5)	⊕⊝⊝⊝ **very low** due to lack of RCTs, risk of bias, publication bias	

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

CI Confidence interval, *RR* Risk Ratio, *SMD* Standardized mean difference, *RCTs* randomized controlled trials

[a] Control group risk estimates come from pooled estimates of control groups

[b] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

Length of ECMO therapy

We analyzed length of ECMO therapy between DTI and heparin patients. In total 12 studies reported on length of ECMO therapy. Ten studies compared bivalirudin to heparin and 2 studies used argatroban. Of these studies 4 studies had low risk of bias, 1 study had intermediate risk of bias and 7 studies had high risk of bias. Overall length of ECMO therapy showed no difference between DTI and Heparin [pooled estimate SMD 0.12, 95% CI -0.03–0.27; Z = 1.60; $p = 0.11$] with a moderate overall heterogeneity [$I^2 = 16\%$, $Chi^2 = 13.17$, df = 11, $p = 0.28$]. Bivalirudin subgroup was detected as possible source for heterogeneity [$I^2 = 21\%$, $Chi^2 = 11.42$, df = 9, $p = 0.25$]. Use of fixed effects model and Mean difference did not change the results in sensitivity analysis. Estimates for each study and the subgroups are presented within the Forrest-plots. (Fig. 8).

Percentage of time within therapeutic range

Only 5 studies reported on percentage of time within therapeutic range during ECMO therapy. All studies compared bivalirudin to heparin for ECMO therapy. Among these studies 2 had low risk of bias, 1 study had intermediate risk of bias and 2 studies had high risk of bias. Overall pooled estimate indicated that patients with DTI during ECMO had higher percentage of time within therapeutic range [pooled estimate SMD 0.54, 95% CI 0.14–0.94; Z = 2.65; p = 0.008]. However, heterogeneity was high between studies [$I^2 = 67\%$, $Chi^2 = 12.12$, df = 4, $p = 0.02$]. Subgroup analysis for risk of bias revealed that studies with low risk of bias showed no heterogeneity [$I^2 = 0\%$, $Chi^2 = 0.07$, df = 1, $p = 0.79$] but heterogeneity was present in studies with intermediate and high risk of bias [$I^2 = 57\%$, $Chi^2 = 4.63$, df = 2, $p = 0.1$]. Sensitivity analysis changed results for adult patients by using fixed effects model, overall result was not affected [adult—pooled estimate SMD 0.74, 95% CI 0.47–1.01; Z = 5.42; $p = < 0.0001$] (Fig. S4).

Length of hospital stay and time to anticoagulation goal

Only 4 studies reported for length of hospital stay and time to anticoagulation goal respectively. No difference

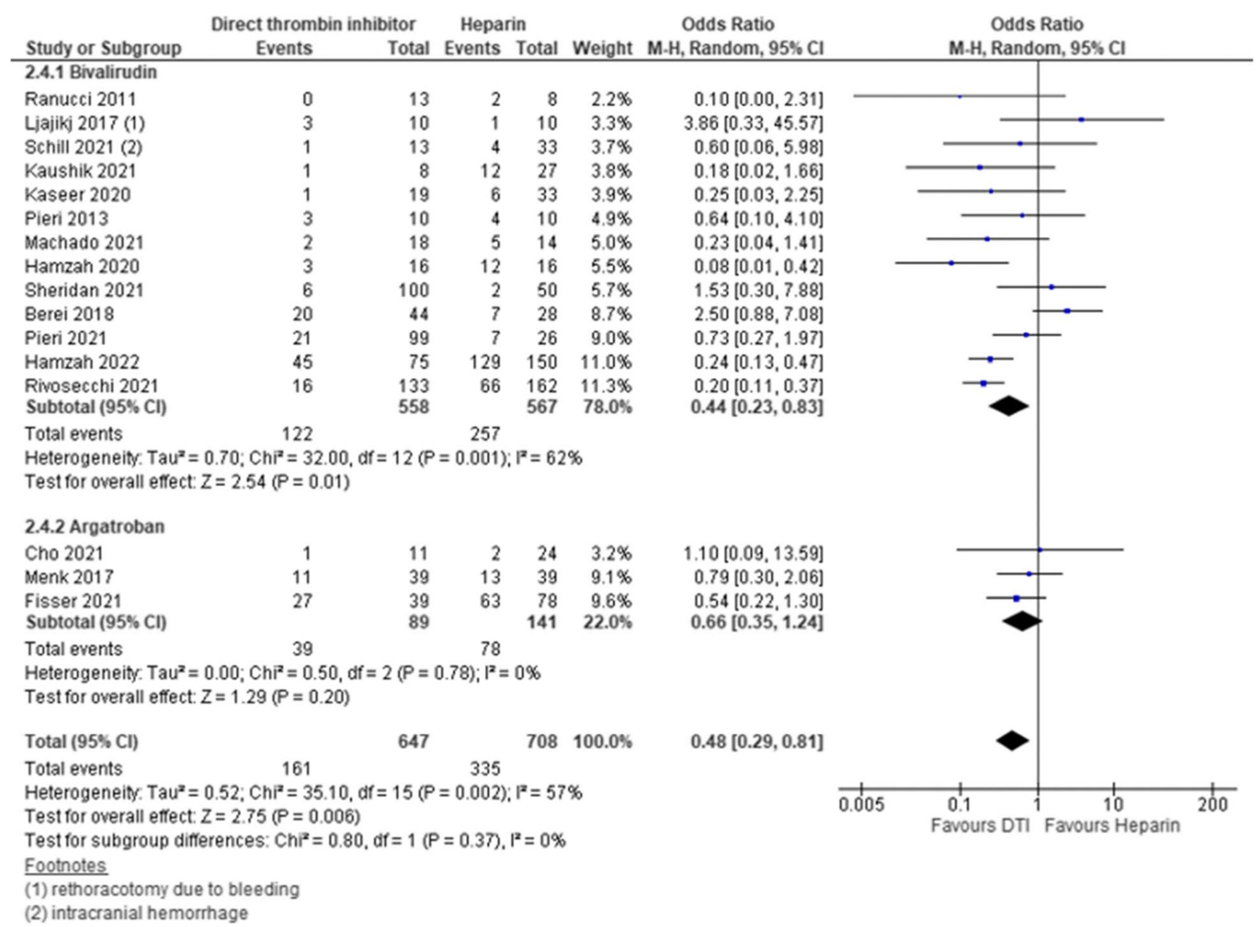


Fig. 4 Major bleeding events. Legend: The figure shows results of data synthesis for major bleeding events. Pooled estimates are presented as Odds ratios for direct thrombin inhibitors versus heparin as well as for bivalirudin and argatroban subgroups

could be detected between DTI and heparin patients. Additional information and Forrest-plots are attached as supplementary figures (Figs. S5, S6).

Evaluation of reporting biases

We evaluated publication bias by creating funnel plots for each outcome. By visual inspection we detected relevant asymmetry of funnel plots for all outcomes beside of minor bleeding events. To reduce reporting bias, we contacted authors to contribute additional information as not all studies reported for all outcomes. However, only 4 authors responded to our request and added additional data for analysis (Fig. S7).

Certainty of evidence

We assessed the certainty of evidence for each outcome using the GRADE approach. For every outcome certainty of evidence was judged as very low, mainly resulting from lack of randomized controlled trials and high risk of bias as well as high risk for reporting bias. (Table 1).

Discussion

This systematic review and meta-analysis investigated the effects of DTI versus heparin on clinical outcomes in patients undergoing ECMO. The main finding of this analysis is that the use of DTI for anticoagulation is significantly associated with reduced in-hospital mortality in both pediatric and adult ECMO patients compared to heparin. In addition, DTI (especially bivalirudin) are superior to heparin in terms of major bleeding events as well as patient and pump-related thrombotic complications in our analysis. Furthermore, DTI provide a stable anticoagulation during ECMO as measured by percentage of time within therapeutic range.

Existing literature in this field

To date, three meta-analyses are available that compared bivalirudin and heparin in patients undergoing ECMO while no meta-analysis is available for argatroban [12–14, 64]. All of the bivalirudin analyses were published in 2022 which clarifies the high relevance of this topic. We will discuss the results in the following to put our own findings in context.

Di-Huan Li and colleagues selected ten articles for their meta-analysis including 997 ECMO patients. For the primary endpoint in-hospital mortality, seven studies including 670 patients (bivalirudin group = 242 patients) remained. Based on a heterogeneity of I2 = 15%, the authors report that there was no significant difference between bivalirudin treated patients and patients receiving heparin regarding in-hospital mortality (OR = 0.81, 95%CI [0.54, 1.22], P = 0.32). However, subgroup analyses based on patient characteristics revealed potential survival benefit for adults (OR = 0.65, 95%CI [0.44, 0.95], P = 0.03). In pediatric ECMO patients, there was no significant difference in terms of survival (OR = 1.30,

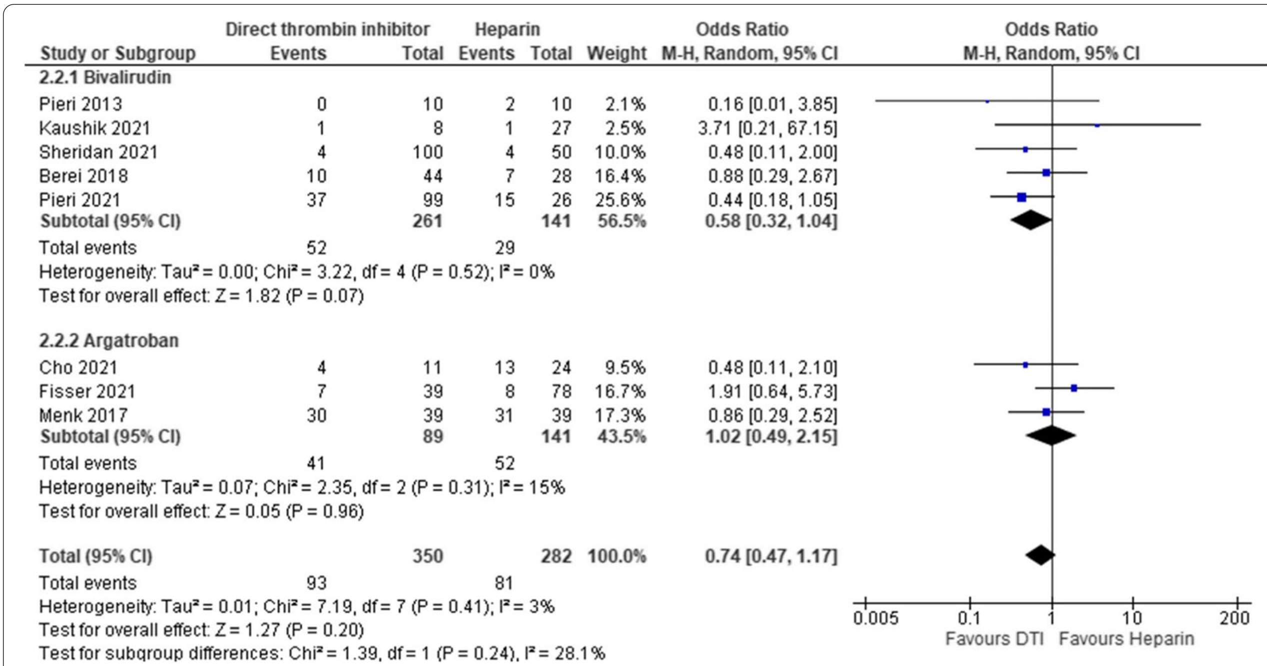


Fig. 5 Minor bleeding events. Legend: The figure shows results of data synthesis for minor bleeding events. Pooled estimates are presented as Odds ratios for direct thrombin inhibitors versus heparin as well as for bivalirudin and argatroban subgroups

95%CI [0.47, 3.56], $P = 0.61$). Regarding secondary outcomes, the analysis by Li et al. revealed that there was a significantly lower incidence of thrombosis in the bivalirudin group (OR = 0.53, 95%CI [0.36, 0.79], $P = 0.002$). Major bleeding events and ECMO duration showed no significant difference. The differences to our findings might be explained by the limited number of included studies (in total 9 studies versus 15 bivalirudin studies in our analysis). As all studies had a retrospective design and investigated rather small cohorts, even small differences regarding design, study population, intervention or endpoint definitions may account for relevant changes regarding the results. This underlines the urgent need for prospective trials. The authors also performed an analysis of cost-effectiveness which showed that the use of bivalirudin did not result in higher costs [64]. Unfortunately, only three studies comparing the cost difference between bivalirudin and heparin were available. As all data were presented as median (minimum–maximum or 25–75 percentile), a pooled meta-analysis could not be performed. This aspect remains to be investigated in future studies.

The second available meta-analysis by Mei-Juan Li and colleagues included 9 studies (= 994 patients). The authors also found a survival benefit for the bivalirudin group in adult ECMO patients (risk ratio: 0.82, 95% CI 0.69–0.99). Additionally, the use of bivalirudin was associated with reduced major bleeding events (risk ratio: 0.32, 95% confidence interval [CI] 0.22–0.49), reduced incidences of ECMO in-circuit thrombosis (risk ratio: 0.57, 95% CI 0.43–0.74) and stroke (RR: 0.52, 95% CI 0.29–0.95) and higher survival rates until weaning from ECMO (RR: 1.18, 95% CI 1.03–1.34). Of note, the authors performed a „leave-one-out " sensitivity analysis which showed that the results for in-hospital-mortality, stroke and survival until ECMO weaning should be interpreted carefully and more prospective / good-quality studies are needed [13].

Finally, there is a third meta-analysis by Liyao Liu and colleagues which is the largest of these three as 14 studies with a total of 1501 adult and pediatric patients

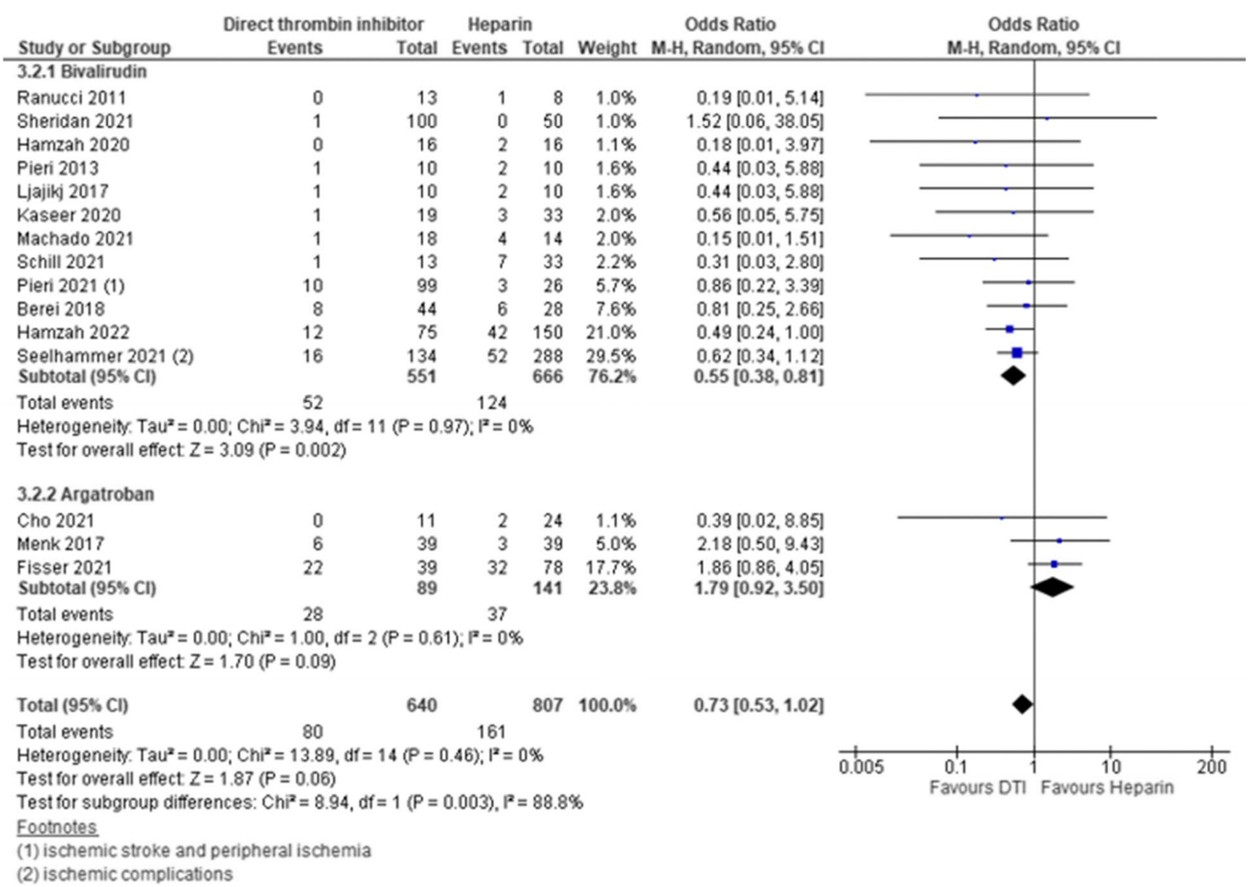


Fig. 6 Patient-related thrombosis. Legend: The figure shows results of data synthesis for patient-related thrombotic events. Pooled estimates are presented as Odds ratios for direct thrombin inhibitors versus heparin as well as for bivalirudin and argatroban subgroups

were included into analysis. The endpoints of interest in this study were in-hospital mortality, ECMO survival, thrombotic events, major bleeding and in-circuit thrombosis. Similar to the other meta-analyses, in-hospital-mortality was significantly lower in the bivalirudin group (OR = 0.78, 95% CI [0.61–0.99], $p = 0.04$). Furthermore, patients receiving bivalirudin for anticoagulation had significantly improved results for all other clinical outcomes (ECMO survival rate: OR = 1.50, 95% CI [1.04–2.16], $p = 0.032$; thrombotic events: OR = 0.61, 95% CI [0.45–0.83], $p = 0.002$; major bleeding: OR = 0.36, 95% CI [0.14–0.91], $p = 0.031$; in-circuit thrombosis: OR = 0.44, 95% CI [0.31–0.61], $p = 0.000$) [12].

Referring to argatroban, no meta-analysis comparing argatroban with heparin in ECMO patients is currently available. However, there is one systematic review by Geli and colleagues dealing with this topic. A total of 13 studies could be identified that investigated the use of argatroban for anticoagulation in ECMO patients. Notably, 9 out of these 13 studies were only case series which were not included into the present meta-analysis. Based on their literature review, the authors conclude that major bleeding events as well as thrombotic complications seem to be comparable between argatroban-treated patients and heparin-treated patients. However, no formal analysis was conducted [14].

What does our analysis add to the existing literature?

Based on the existing evidence, the present analysis adds multiple new aspects to the field of anticoagulation strategies in patients undergoing ECMO. First and most importantly, we did not only focus on one specific drug (bivalirudin or argatroban), but performed an anaylsis for DTI versus heparin in general. Of course, we were also able to perform separate analyses for both drugs alone, but from a clinical perspective, the comparison seems to be suitable as both substances are following the same pharmacological target. Second, our analysis has the largest number of included studies (18 studies, 1942 patients) so far. With regard to the increasing number of ECMO-treated patients worldwide, the topic is of high relevance so that updated data are urgently needed.

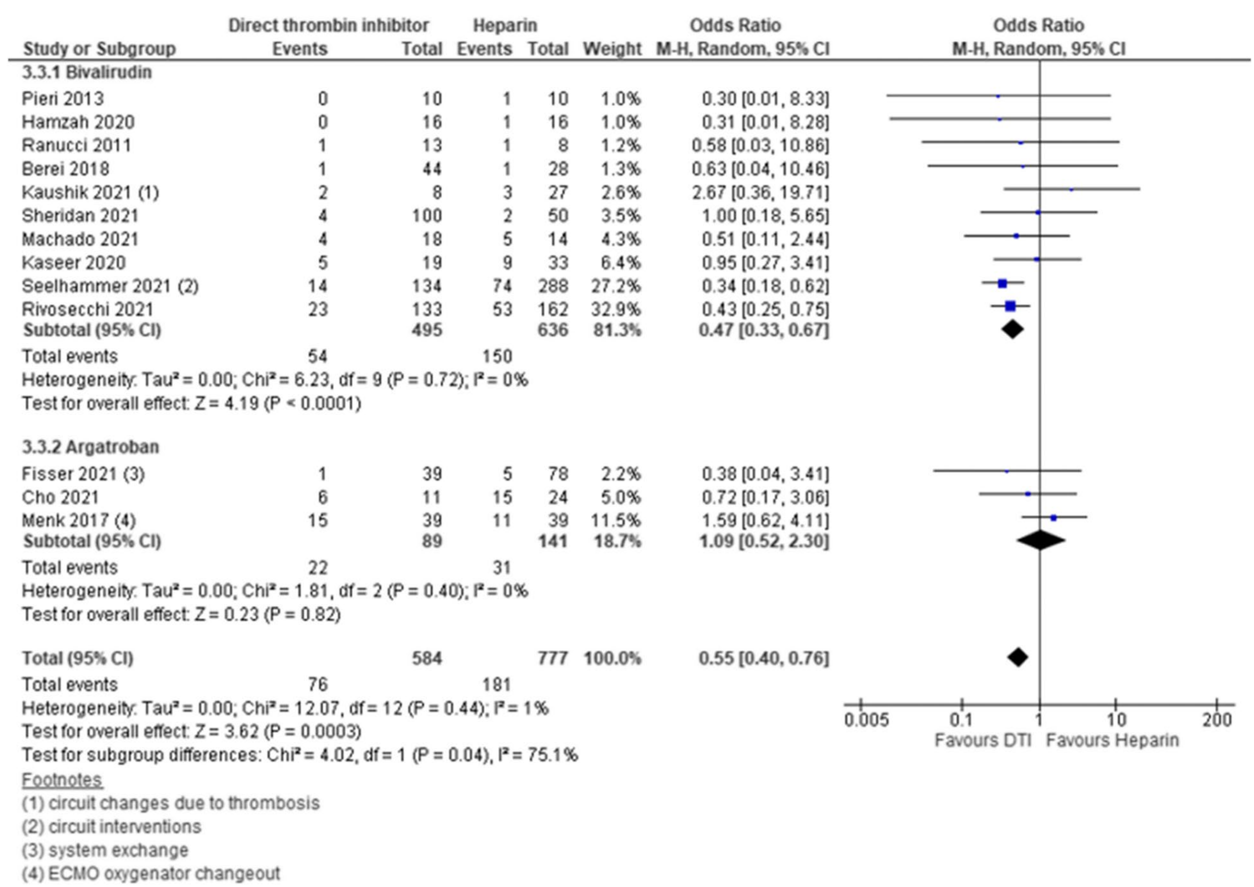


Fig. 7 Pump-related thrombosis. Legend: The figure shows results of data synthesis for pump-related thrombotic events. Pooled estimates are presented as Odds ratios for direct thrombin inhibitors versus heparin as well as for bivalirudin and argatroban subgroups

Study or Subgroup	Direct thrombin inhibitor Mean	SD	Total	heparin Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.1.1 Bivalirudin								
Ranucci 2011	143	73	13	80	52	8	2.4%	0.92 [-0.02, 1.85]
Pieri 2013	11	12	10	5.7	5.49	10	2.6%	0.54 [-0.35, 1.44]
Machado 2021	166.6	65.1	18	154.8	107.7	14	4.1%	0.13 [-0.57, 0.83]
Hamzah 2020	137.7	87.01	16	136.3	96.4	16	4.2%	0.01 [-0.68, 0.71]
Macielak 2019	6.4	2.8	10	7.1	4.8	100	4.7%	-0.15 [-0.80, 0.50]
Kaseer 2020	443	404	19	258	173	33	5.8%	0.65 [0.07, 1.23]
Berei 2018	156.9	112.3	44	162.1	125.5	28	8.2%	-0.04 [-0.52, 0.43]
Pieri 2021	16	16	99	10	8	26	9.5%	0.40 [-0.03, 0.84]
Hamzah 2022	183.1	257	75	155.4	160.2	150	18.5%	0.14 [-0.14, 0.42]
Rivosecchi 2021	229.2	284.7	133	238.8	333	162	23.3%	-0.03 [-0.26, 0.20]
Subtotal (95% CI)			**437**			**547**	**83.2%**	**0.16 [-0.01, 0.33]**
Heterogeneity: Tau² = 0.01; Chi² = 11.42, df = 9 (P = 0.25); I² = 21%								
Test for overall effect: Z = 1.83 (P = 0.07)								
4.1.2 Argatroban								
Cho 2021	136	57	11	180	153	162	5.3%	-0.29 [-0.91, 0.32]
Fisser 2021	14.74	13.29	39	13.65	11.95	78	11.5%	0.09 [-0.30, 0.47]
Subtotal (95% CI)			**50**			**240**	**16.8%**	**-0.03 [-0.37, 0.32]**
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 1 (P = 0.30); I² = 6%								
Test for overall effect: Z = 0.15 (P = 0.88)								
Total (95% CI)			**487**			**787**	**100.0%**	**0.12 [-0.03, 0.27]**
Heterogeneity: Tau² = 0.01; Chi² = 13.17, df = 11 (P = 0.28); I² = 16%								
Test for overall effect: Z = 1.60 (P = 0.11)								
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² = 0%								

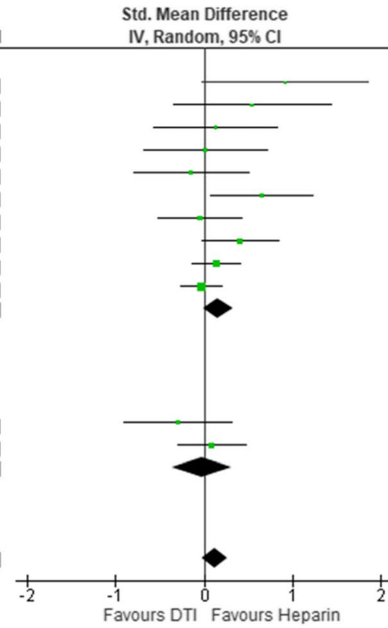


Fig. 8 Length of extracorporeal membrane oxygenation therapy. Legend: The figure shows results of data synthesis for length of extracorporeal membrane oxygenation therapy. Pooled estimates are presented as standardized mean difference for direct thrombin inhibitors versus heparin as well as for bivalirudin and argatroban subgroups

This aspect is even more important referring to the fact that the quality of the existing studies is low as only retrospective data are available. Thus, the addition of only one or two (good-quality) studies might be enough to change the results completely. Against this background, it is a strength of our analysis that we could include a first multicenter study that was not included into the existing meta analyses. Third, our study analyzed new endpoints that have not been investigated yet. Importantly, clinicians probably will not base their decision on the anticoagulation regimen solely on mortality data and it is essential to focus on further endpoints. Therefore, next to the established endpoints of interest (mortality, bleeding, thrombosis etc.), we also included length of ECMO support, length of hospital stay, percentage of activated partial thromboplastin time (aPTT) within therapeutic window and hours to therapeutic aPTT levels as secondary outcomes. E.g. it is a new finding that patients receiving bivalirudin were significantly longer within the therapeutic range for anticoagulation (SMD = 0.54, 95% CI [0.14–0.94], $p = 0.008$) which might be an explanation why bleeding complications and thrombotic complications were significantly reduced in these patients. However, only five studies were available for this analysis so that these findings should be interpreted with caution. The time until the therapeutic window was reached was also lower in the bivalirudin group, although these results (based on four studies) were not statistically significant. Length of hospital stay and length of ECMO therapy showed no significant differences between the two groups. Though, there was a non-significant trend for longer ECMO therapy in the bivalirudin group. This observation might be related to the fact that mortality during ECMO therapy was lower in these patients. Fourth, our analysis differentiated between minor and major bleeding events as well as between patient-related and pump-related thrombotic complications. Interestingly, the use of bivalirudin was more protective in terms of major bleeding events (OR: 0.5, 95% CI [0.30–0.85]. This finding suggests that bivalirudin might be a suitable and safe alternative even in high-risk patients for bleeding complications. Fifth, and finally, this is the first analysis comparing heparin and argatroban. While the use of bivalirudin was clearly associated with improved clinical outcomes, argatroban alone was not superior, but rather comparable to the standard therapy heparin for most endpoints. Importantly, only three studies comparing heparin and argatroban could be included. Therefore, our results might serve as a first insight, but transferability of these data must be regarded as very limited.

Strengths and limitations

This was a preplanned, protocol-based analysis, of four large electronic medical libraries. In total we detected 18 relevant articles. We enrolled a large number of ECMO patients in this meta-analysis and added new information to the existing literature. Despite promising results this meta-analysis has some limitations. Due to the lack of randomized controlled trials which introduces high risk of bias, certainty in our findings must be regarded as very limited. We tried to address reporting bias by contacting authors and requesting additional data for analysis as not all studies reported for every outcome. However, only four authors responded to our request and therefore a majority of data could not be included into our analysis. Of note we were able to include unpublished data of a multicenter retrospective study which complements the existing data in this field. Another limitation of this study is that the definitions of secondary outcomes (e.g. minor / major bleeding or patient and pump related thrombosis) may be different in the included studies. To ensure more transparency, the exact definitions of relevant secondary outcomes are presented in table S2. Furthermore, there might be several other important factors clinicians might consider when deciding about the choice of anticoagulation. As mentioned in the discussion, mortality data alone probably will not be sufficient and although several secondary endpoints have been investigated, multiple other factors are still lacking. In particular, there are no data on more patient-centered outcomes such as life impact or quality of life which becomes more and more important in the setting of mechanical circulatory support. Additionally, center effects, publication bias or reporting bias have to be considered when interpreting the results. Finally, although comparing two DTI is a strength of this study, this may also be regarded as a limitation as the information gathered is only through comparing them via heparin as an intermediary which limits this comparison.

Conclusions

In conclusion, the present meta-analysis revealed that the use of DTI for anticoagulation in patients undergoing ECMO is associated with reduced in-hospital mortality as well as a reduced incidence of major bleeding and thrombotic events. Especially the use of bivalirudin showed positive effects on these outcomes in comparison with the standard therapy heparin. Before drawing final conclusions if DTI are really superior to the standard therapy heparin, well designed prospective (randomized) studies are urgently needed. Until these data are available, DTI may at least be regarded as a safe, effective and potentially beneficial strategy for anticoagulation in this cohort.

Abbreviations

aPTT: Activated partial thromboplastin time; CS: Cardiogenic shock; DTI: Direct thrombin inhibitors; ECMO: Extracorporeal membrane oxygenation; OR: Odds ratio; RR: Risk ratio; SMD: Standardized mean difference.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12959-022-00401-2.

Additional file 1: Figure S1. Mortality analysisfor adult and pediatric patients. **FigureS2.** Mortality analysis for risk of bias. **Figure S3.** Major bleeding events for adult and pediatric patients. **Figure S4.** Percentage of time withintherapeutic range. **Figure S5.** lengthof hospital stays. **Figure S6.** Timeto reach anticoagulation goal. **Figure S7.**Funnel plots.

Additional file 2. Supplementary materials 1 protocol.

Additional file 3. Supplementary materials 2 search strategies.

Additional file 4: Table S1. Detailedcharacteristics of included studies.

Additional file 5: Table S2. Definitions of outcomes.

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Authors' contributions

R.M.: Concept/design, Methodology, Data collection (search), data extraction, Data analysis / interpretation, Risk of bias assessment, Statistics, Writing of article. S.R.: Writing of article, data extraction, Critical revision of article. A.M.: Data collection (search), data extraction, Data analysis, Risk of bias assessment, Critical revision of article. A.N.: Contacting authors, Data collection (search), data extraction Critical revision of article. A.S.: Data extraction, Critical revision of article. G.L.B.: Concept/Design, Methodology, Critical revision of article. A.P., M.W.H: Data interpretation, Critical revision of article. R.H.: Concept/design, Drafting article, Critical revision of article. The author(s) read and approved the final manuscript.

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Availability of data and materials

All data used for analysis is available in supplementary table S1. Further data is available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interest

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ORIGINAL ARTICLE

Days alive and out of hospital after left ventricular assist device implantation

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Abstract

Aims Implantation of left ventricular assist devices (LVADs) as a bridge to transplant or as destination therapy is increasing. The selection of suitable patients and outcome assessment belong to the key challenges. Mortality has traditionally been a focus of research in this field, but literature on quality of life is very limited. This study aimed to identify perioperative factors influencing patients' life as measured by days alive and out of hospital (DAOH) in the first year after LVAD implantation.
Methods and results This retrospective single-centre cohort study screened 227 patients who underwent LVAD implantation at the University Hospital Duesseldorf, Germany, between 2010 and 2020. First, the influence of 10 prespecified variables on DAOH was investigated by univariate analysis. Second, multivariate quantile regression was conducted including all factors with significant influence on DAOH in the univariate model. Additionally, the impact of all variables on 1 year mortality was investigated using Kaplan–Meier curves to oppose DAOH and mortality. In total, 221 patients were included into analysis. As pre-operative factors, chronic kidney disease (CKD), pre-operative mechanical circulatory support (pMCS), and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) stadium < 3 were associated with lower DAOH at 1 year [CKD: 280 (155–322) vs. 230 (0–219), $P = 0.0286$; pMCS: 294 (155–325) vs. 243 (0–293), $P = 0.0004$; INTERMACS 1: 218 (0–293) vs. INTERMACS 2: 264 (6–320) vs. INTERMACS 3: 299 (228–325) vs. INTERMACS 4: 313 (247–332), $P \leq 0.0001$]. Intra-operative additional implantation of a right ventricular assist device (RVAD) was also associated with lower DAOH [RVAD: 290 (160–325) vs. 174 (0–277), $P \leq 0.0001$]. As post-operative values that were associated with lower DAOH, dialysis and tracheotomy could be identified [dialysis: 300 (252–326) vs. 186 (0–300), $P \leq 0.0001$; tracheotomy: 292 (139–325) vs. 168 (0–269), $P \leq 0.0001$]. Multivariate analysis revealed that all of these factors besides pMCS were independently associated with DAOH. According to Kaplan–Meier analysis, only post-operative dialysis was significantly associated with increased mortality at 1 year (survival: no dialysis 89.4% vs. dialysis 70.1%, hazard ratio: 0.56, 95% confidence interval: 0.33–0.94; $P = 0.031$).
Conclusions The results of this study indicate that there can be a clear discrepancy between hard endpoints such as mortality and more patient-centred outcomes reflecting life impact. DAOH may relevantly contribute to a more comprehensive selection process and outcome assessment in LVAD patients.

Keywords Heart failure; Cardiac surgery; Quality of life; Mechanical circulatory support; Patient-centred outcomes

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Introduction

Implantable left ventricular assist devices (LVADs) are increasingly used as a bridge to heart transplantation strategy or as destination therapy for patients with end-stage heart failure.[1–3] Although outcomes have continuously improved in recent years, the selection of patients who really profit from LVAD implantation remains one of todays' key challenges and there is good evidence that appropriate selection is critical for improved outcomes.[4–7] Numerous studies tried to identify perioperative factors influencing patient outcome; for example, an Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis in 2019 revealed that age is a significant predictor of mortality.[8] Further factors such as post-operative acute kidney injury requiring dialysis or intra-operative right ventricular failure have also been shown to be associated with reduced survival rates.[9–13] While mortality has been traditionally in the focus of research in this field, literature on factors influencing patients' life is very limited, although this knowledge might be of utmost importance to decide whether a patient could really profit from LVAD implantation or not. Days alive and out of hospital (DAOH) is a potentially useful quality measure in this context that has been suggested to quantify life impact.[14–16] It combines several clinically important outcomes including death, length of hospital stay, hospital readmissions, and (indirectly) health care costs. Further advantages of DAOH include its patient-centredness, its easy collection (including dispensability of adjudication), and statistical efficiency.[16]

Against this background, the aim of this study was to identify perioperative factors with impact on patients' life as measured by DAOH within the first year after surgery. Our primary hypothesis was that there is a discrepancy between mortality and DAOH for several variables.

Methods

Study design

The present study is a retrospective, single-centre cohort study that was conducted in accordance with the guidelines for good clinical practice (GCP) and the Declaration of Helsinki. The study was approved by the ethical review board of the Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany (reference number 2020-1058). All patients gave written informed consent in the past to be registered in a dedicated prospective local database. This manuscript follows the STROBE reporting guidelines for retrospective cohort studies.

Participants

Consecutive patients aged ≥18 years who received LVAD implantation due to ischaemic heart disease or dilated cardiomyopathy at the University Hospital Duesseldorf, Germany, between 2010 and 2020 were included. Patients with missing data or incomplete medical records regarding the primary endpoint were excluded. Patients with other underlying diseases than ischaemic heart disease or dilated cardiomyopathy leading to chronic heart failure were also excluded to ensure a more homogenous cohort.

Outcome assessment

The primary endpoint of this study was DAOH 1 year after LVAD implantation. As performed previously,[15] DAOH were calculated by summing up the days of all hospitalizations in the first year after LVAD surgery and subtracting them from 365 days. In case the patient died within the first year, the difference between survived days and 365 days was added to days of hospitalizations before subtracting them from 365 days. This method is based on the validation study of DAOH in heart failure patients.[15] As LVAD patients are very closely connected to our centre, it is unlikely that these patients are hospitalized elsewhere so that retrospective calculation of DAOH can be regarded as reliable. The main secondary endpoint was mortality 1 year after LVAD implantation to oppose DAOH and mortality.

Data collection

Patient characteristics, comorbidities, comedication, and survived days at 1 year were extracted from electronic medical records and the local electronic LVAD database. This prospective database is continuously updated and consists of patients' perioperative values, which were directly extracted from patients' charts at the intensive care unit and electronic medical records.

Identification of candidate variables

The choice of variables that were included in the analysis was primarily based on two large network studies using a Bayesian model to predict survival after LVAD implantation.[17,18] In addition, literature research was performed to find further perioperative variables that have been shown to be associated with increased mortality after LVAD implantation. Accordingly, we predefined the following 10 variables: age (≥65 vs. <65 years), type of underlying disease (ischaemic heart disease vs. dilated cardiomyopathy), INTERMACS profile, intra-operative right ventricular assist device (RVAD) implantation, surgical approach (minimally invasive surgery vs. sternotomy), pre-existing chronic kidney disease (CKD) according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria, pre-operative mechanical circulatory support (pMCS), pre-operative levosimendan therapy,

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post-operative dialysis, and post-operative tracheotomy. As the nature of this study was only exploratory, the choice of these variables does not claim to be complete and there are obviously numerous other variables that may influence DAOH and mortality after LVAD implantation.

Statistical approach and analysis

We conducted a complete case analysis. We first performed univariate analysis using each of the 10 candidate variables. We then included all factors showing significant univariate association with DAOH using step-wise forced entry into the multivariate model (level of significance = $P \leq 0.05$). Additionally, the influence of each variable on 1 year mortality was investigated to oppose DAOH and mortality.

For statistical analysis, GraphPad Prism© Version 8.02 (La Jolla, California, USA) and IBM SPSS© software Version 25.0 (Armonk, NY, USA) were used. Continuous data are presented as mean ± standard deviation (SD) or as median and interquartile ranges (25–75%), as appropriate. Categorical data are presented as counts (*n*) with corresponding percentages (%). DAOH were compared by Mann–Whitney *U*-test given that these data were supposed to be skewed. Multivariate quantile regression was conducted. In this analysis, DAOH was set as a dependent variable. Survival analysis was performed using Kaplan–Meier diagrams as well as univariate and multivariate Cox regression. For INTERMACS profile, Kruskal–Wallis test and Jonckheere–Terpstra test were performed. To compare survival rates, log-rank (Mantel–Cox) test was performed and results are presented as a percentage of survival (%) with hazard ratio (HR) and 95% confidence interval (CI). As this was a retrospective and exploratory data analysis, a formal sample size calculation was not implemented.

Results

In total, 227 patients were included in the institutional database. Six patients (2.6%) had to be excluded due to incomplete medical records or other underlying diseases than ischaemic heart disease or dilated cardiomyopathy. Thus, 221 patients remained for statistical analysis (*Figure 1*). Data on the primary endpoint and all other co-variables were complete. Median DAOH in the whole cohort was 273 (interquartile range 67–321). Overall 1 year mortality was 24.9%. Detailed patient characteristics are presented in *Table 1*.

Univariate analysis of days alive and out of hospital

After univariate analysis of the prespecified variables, six variables showed significant association with DAOH. As pre-operative factors, CKD, pMCS, and INTERMACS < 3 were associated with lower DAOH [CKD: 280 (155–322) vs. 230 (0–219), $P = 0.0286$; pMCS: 294 (155–325) vs. 243 (0–293), $P = 0.0004$; INTERMACS 1: 218 (0–293) vs. INTERMACS 2: 264 (6–320) vs. INTERMACS 3: 299 (228–325) vs. INTERMACS 4: 313 (247–332), $P \leq 0.0001$]. Intra-operative additional implantation of RVAD was also associated with lower DAOH [RVAD: 290 (160–325) vs. 174 (0–277), $P \leq 0.0001$]. As post-operative values that were associated with lower DAOH, dialysis and tracheotomy could be identified [dialysis: 300

Figure 1 Study flow chart. DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; LVAD, left ventricular assist device.

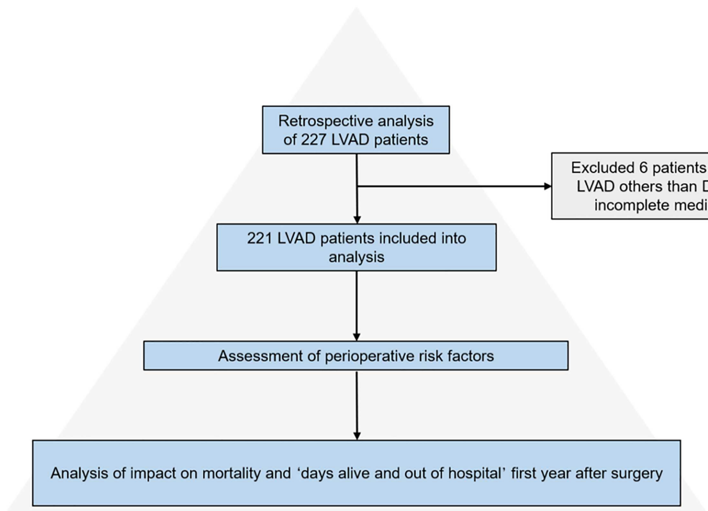


Table 1 Baseline patient characteristics

	LVAD patients (N = 221)	Survivors (N = 166)	Non-survivors (N = 55)	DAOH ≥ 273 days (N = 111)	DAOH < 273 days (N = 110)
Baseline characteristics, mean ± SD or no. (%)					
Male sex, no. (%)	191 (86.4)	144 (86.7)	47 (85.5)	100 (90.1)	91 (82.7)
Age (years)	58 ± 11	57 ± 11	59 ± 12	57 ± 12	58 ± 11
BMI (kg/m^2)	27 ± 5	27 ± 5	27 ± 6	27 ± 5	28 ± 6
LVEF (%)	18 ± 7	18 ± 7	18 ± 8	18 ± 7	17 ± 7
INTERMACS 1	84 (38)	60 (36.1)	24 (43.6)	28 (25.2)	56 (50.9)
INTERMACS 2	40 (18.1)	30 (18.1)	10 (18.2)	19 (17.1)	21 (19.1)
INTERMACS 3	41 (18.6)	32 (19.3)	9 (16.4)	29 (26.1)	12 (10.9)
INTERMACS 4	56 (25.3)	44 (26.5)	12 (21.8)	35 (31.5)	21 (19.1)
Pre-operative conditions, no. (%)					
Pre-operative mechanical circulatory support	89 (40.3)	65 (39.2)	24 (43.6)	34 (30.6)	55 (50.0)
Ischaemic heart disease	137 (62)	101 (60.8)	36 (65.5)	66 (59.5)	71 (64.5)
Dilated cardiomyopathy	84 (38)	65 (39.2)	19 (34.5)	45 (40.5)	39 (35.5)
CKD	80 (36.2)	59 (35.5)	21 (38.2)	33 (29.7)	47 (42.7)
CKD requiring dialysis	44 (19.9)	30 (18.1)	14 (25.5)	11 (9.9)	33 (30)
Levosimendan	134 (60.6)	103 (62.0)	31 (56.4)	67 (60.4)	67 (60.9)
Laboratory parameters before surgery, mean ± SD					
Creatinine (mg/dL)	1.4 ± 0.7	1.4 ± 0.8	1.5 ± 0.6	1.4 ± 0.8	1.5 ± 0.7
Bilirubin (mg/dL)	1.8 ± 2	1.7 ± 2	3.7 ± 13	1.3 ± 1	3.3 ± 9
Intra-operative conditions, no. (%)					
Minimally invasive cardiac surgery	70 (31.7)	53 (31.9)	17 (30.9)	37 (33.3)	33 (30.0)
Sternotomy	151 (68.3)	113 (68.1)	38 (69.1)	74 (66.7)	77 (70.0)
Additional RVAD implantation	51 (23.1)	39 (23.5)	12 (21.8)	13 (11.7)	38 (34.5)
Post-operative conditions, no. (%)					
Dialysis	117 (52.9)	82 (49.4)	35 (63.6)	39 (35.1)	78 (70.9)
Sepsis	37 (16.7)	28 (16.9)	9 (16.4)	10 (9.0)	27 (24.5)
Stroke	25 (11.3)	16 (9.6)	9 (16.4)	3 (2.7)	22 (20.0)
ARDS	24 (10.9)	17 (10.2)	7 (12.7)	5 (4.5)	19 (17.3)
Tracheotomy	48 (21.7)	34 (20.5)	14 (25.5)	11 (9.9)	37 (33.6)
Outcomes, median days (IQR) or no. (%)					
Days on ICU	18 (8–35)	17 (7–32)	25 (9–48)	12 (6–24)	29 (13–56)
DAOH	273 (67–321)	284 (172–321)	158 (1–293)	321 (298–333)	67 (0–232)
1 year mortality, no. (%)	55 (24.9)	0 (0)	55 (100)	18 (16.2)	37 (33.6)

ARDS, acute respiratory distress syndrome; BMI, body mass index; CKD, chronic kidney disease; DAOH, days alive and out of hospital; ICU, intensive care unit; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IQR, interquartile range; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; RVAD, right ventricular assist device; SD, standard deviation.
Data are presented as mean ± standard deviation or as absolute values with percentages, as appropriate.

(252–326) vs. 186 (0–300), $P \leq 0.0001$; tracheotomy: 292 (139–325) vs. 168 (0–269), $P \leq 0.0001$] (*Figure 2*).

Multivariate analysis of days alive and out of hospital

Multivariate analysis using quantile regression model was performed using DAOH as dependent variable and CKD, pMCS, INTERMACS profile, intra-operative RVAD implantation, post-operative dialysis, and post-operative tracheotomy as independent variables. In this model, all factors besides pMCS showed an independent association with DAOH over different quantiles (*Figure 3*).

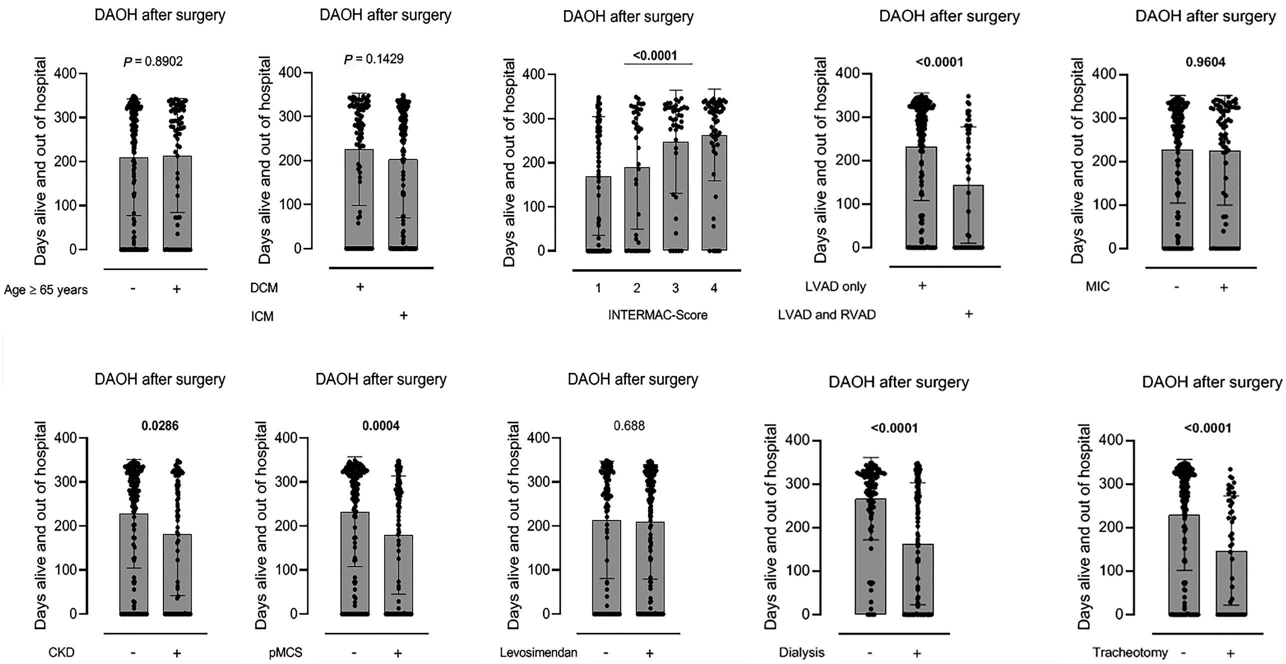
Survival analysis

According to Kaplan–Meier analysis, only post-operative dialysis was associated with significantly lower survival rates at 1 year after surgery (survival: no dialysis 89.4% vs. dialysis 70.1%, HR: 0.56, 95% CI: 0.33–0.94; P = 0.031). Univariate Cox regression confirmed these results (see Supporting Information, *Table S1*). Multivariate Cox regression revealed that none of the prespecified variables had a significant influence on 1 year mortality in this patient cohort (see Supporting Information, *Table S2*). Detailed results from Kaplan–Meier analysis are presented in *Table 2*. Kaplan–Meier curves for all 10 variables are presented in Supporting Information, *Figure S1*.

Discussion

This study investigated DAOH after LVAD implantation. The INTERMACS stadium, pre-existing CKD, RVAD, post-operative dialysis, and post-operative tracheotomy could be identified as independent factors associated with reduced DAOH. Pre-operative MCS showed a significant association

Figure 2 Univariate analysis: impact of 10 predefined variables on days alive and out of hospital after LVAD implantation. CKD, chronic kidney disease; DAOH, days alive and out of hospital; DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; MIC, minimally invasive chest surgery; pMCS, pre-operative mechanical circulatory support; RVAD, right ventricular assist device.



with reduced DAOH only in the univariate model. Age ≥ 65 years, underlying disease, surgical approach, and pre-operative levosimendan therapy seem to have no significant impact on DAOH according to our data. Only post-operative dialysis was significantly associated with increased mortality according to Kaplan–Meier and Cox regression analysis. These results indicate discrepancies between DAOH and mortality, which is supposed to be discussed in the following (*Figure 4*).

Existing literature

To begin with a short review, there is extensive literature investigating outcomes after LVAD implantation. A huge amount of the existing studies focused on survival. A large number of patient-related and procedure-related factors associated with reduced survival could already be identified. Regarding the impact on quality of life of LVAD itself, the literature is clear: LVADs significantly improve quality of life in patients living with end-stage heart failure. But which factors do have an impact on that? As explicit data on DAOH after LVAD are scarce, we will also discuss data on other quality of life measures such as questionnaires or functional capacity.

Pavol and co-authors found out in a recently published retrospective cohort study including 59 patients that pre-operative cognitive status is suitable to predict DAOH after LVAD implantation.[19] The authors conclude that information about pre-LVAD cognition may be useful to optimize the selection of LVAD patients. Unfortunately, this study did not investigate other perioperative factors next to cognition. In a prospective comparison study, Kiernan and co-authors also tried to identify characteristics that are associated with quality of life and functional capacity response after LVAD implantation. This study included patients that were enrolled in the Heartmate II clinical trials[20] that were still alive at 6 months after LVAD implantation. Quality of life was quantified based on the Minnesota Living With Heart Failure Questionnaire or the Kansas City Cardiomyopathy Questionnaire (KCCQ). The authors concluded that several pre-operative comorbidities such as diabetes mellitus, right heart failure, and increased pulmonary artery pressure may limit quality of life. Therefore, these factors should be considered during the shared decision-making process pre-LVAD.[21] In another study by Cowger and co-authors, the European Quality of Life (EQ-5D-5L) and the KCCQ were obtained at baseline and 6 months after HeartMate 3 (*n* = 151) or HeartMate II (*n* = 138) implant as part of the MOMENTUM 3 randomized clinical trial.[22,23] This study revealed that younger age, higher pre-operative

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Figure 3 Multivariate analysis: quantile regression graphs. Due to the highly skewed nature of the primary endpoint 'days alive and out of hospital' (DAOH), a quantile regression model was performed. In contrast to linear regression, quantile regression modelling estimates how specified quantiles of the distribution of the primary outcome variable (= DAOH) vary dependent on patient-related or procedure-related characteristics. On the *x*-axis, the five quantiles are displayed. The *y*-axis displays the change of DAOH in days. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; RVAD, right ventricular assist device.

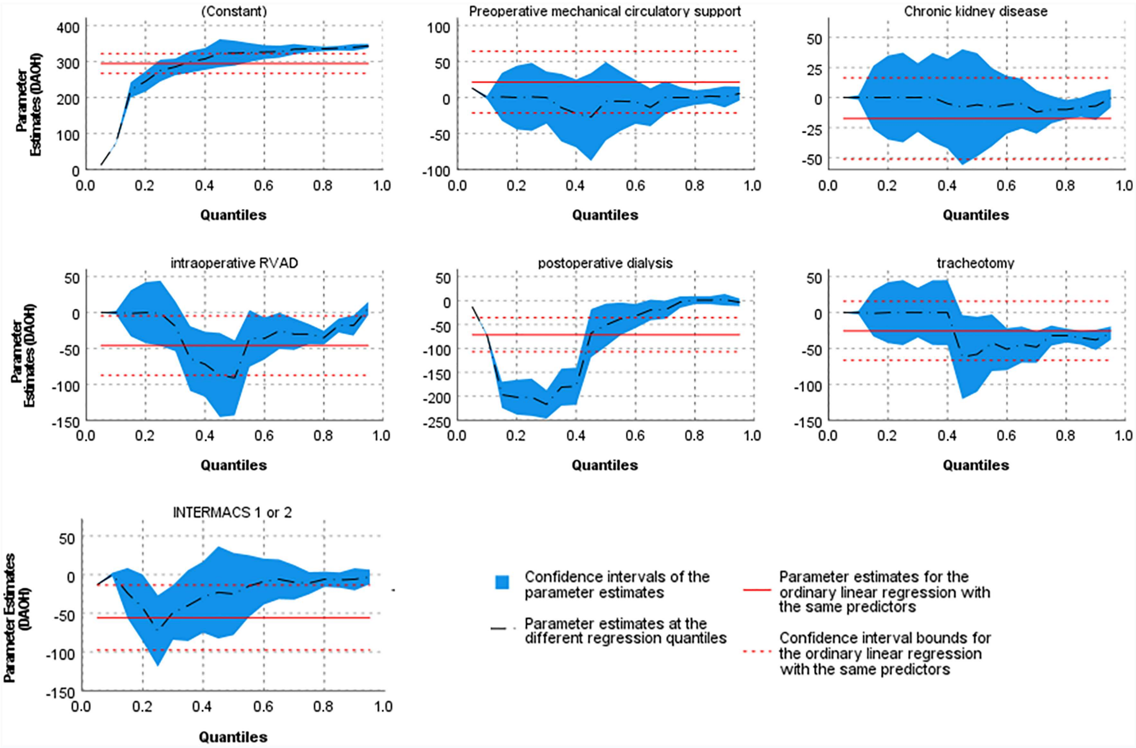

Table 2 Survival analysis

Variable	Classification	1 year survival (%)	HR	95% CI	*P* value
Age	≥65 years	74.7	1.02	0.57–1.80	0.936
	<65 years	75.3			
Underlying disease	ICM	73.7	0.93	0.54–1.61	0.813
	DCM	76.2			
INTERMACS	1	71.4	n/a	n/a	0.647
	2	75.0			
	3	78.6			
	4	78.0			
RVAD	Yes	76.5	1.05	0.59–1.97	0.886
	No	74.7			
Surgical approach	MIC	75.7	1.16	0.66–2.02	0.609
	Sternotomy	74.8			
Chronic kidney disease	Yes	73.8	0.95	0.55–1.63	0.886
	No	75.8			
Pre-op MCS	Yes	73.0	0.79	0.46–1.35	0.374
	No	76.5			
Pre-op levosimendan	Yes	76.9	1.29	0.75–2.23	0.341
	No	72.4			
Post-op dialysis	Yes	70.1	0.56	0.33–0.94	**0.031**
	No	89.4			
Post-op tracheotomy	Yes	70.8	0.77	0.40–1.46	0.385
	No	76.3			

CI, confidence interval; DCM, dilated cardiomyopathy; HR, hazard ratio; ICM, ischaemic cardiomyopathy; MCS, mechanical circulatory support; MIC, minimally invasive chest surgery; Post-op, Post-operative; Pre-op, Pre-operative; RVAD, right ventricular assist device.
Significant *P* values are presented in bold.

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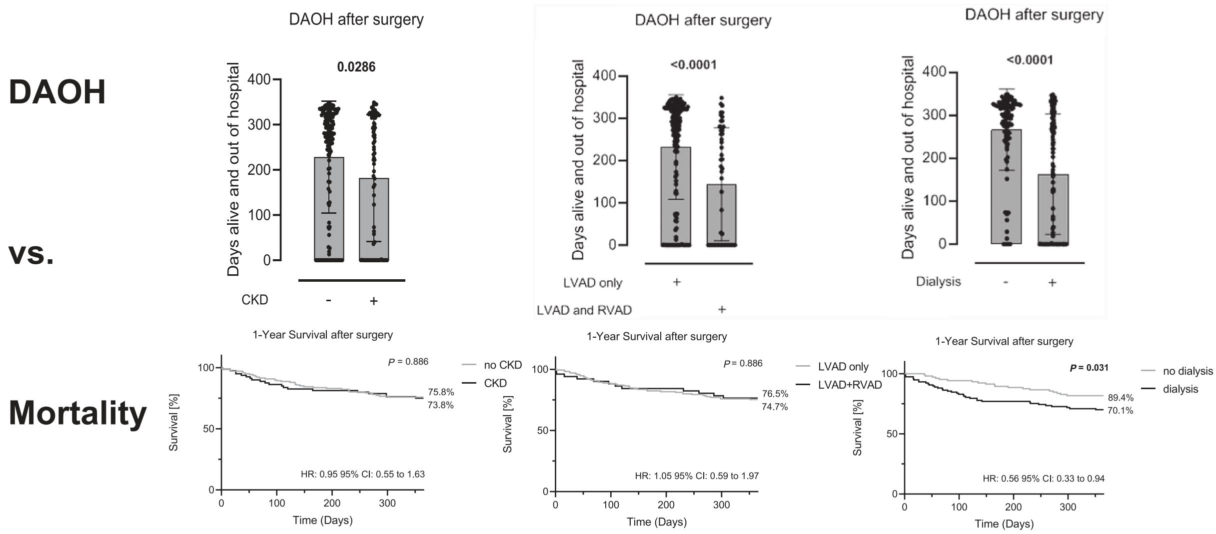
Figure 4 Three examples to illustrate the discrepancies between days alive and out of hospital and mortality. CI, confidence interval; CKD, chronic kidney disease; DAOH, days alive and out of hospital; HR, hazard ratio; LVAD, left ventricular assist device; RVAD, right ventricular assist device.



haemoglobin, higher baseline quality of life score, and the ability to complete the 6 min walk test pre-operatively were pre-implantation predictors for higher quality of life.

Factors influencing days alive and out of hospital and mortality after left ventricular assist device implantation

Regarding the results of the present analysis, some relevant points need to be discussed. First, this study identified not only pre-operative but also perioperative factors that seem to have an impact on DAOH. While intra-operative and post-operative factors (RVAD, dialysis, and tracheotomy) might not be modifiable, pre-operative factors (e.g. INTERMACS and CKD) might be used to optimize the selection process pre-LVAD. Our data show clearly that despite similar survival rates, lower INTERMACS profiles and pre-existing CKD are independently associated with reduced DAOH at 1 year. In addition, the information on perioperative factors without life impact might be of equal importance. For example, it is an interesting finding that age $\geq$ 65 years is not associated with reduced DAOH according to univariate analysis with age as dichotomized variable and by quartiles (*Figure 2* and Supporting Information, *Figure S2*). This might underline that higher age is not a contraindication for LVAD implantation and is strengthened by further analyses including linear regression that revealed the same results.

Second, this study shows clearly that survival rates may not always be an adequate endpoint from a patient-centred perspective. Our data reveal some interesting findings in this context: for example, temporary RVAD implantation is not associated with increased mortality but leads to a relevant reduction of DAOH. The same phenomenon could be found for INTERMACS profile, CKD, and post-operative tracheotomy. This is important knowledge from an epidemiologic perspective, but also to streamline patients and families' expectation management. From a patient point of view, it seems to be of utmost importance to know that an LVAD may be able to keep patients alive although the quality of life may be very limited under certain circumstances. DAOH is very easy to explain and to understand. This may help to improve shared decision-making.

Third, the choice of candidate variables in this study was based on two large network analyses. Both studies had a much larger sample size and analysis contained up to 10 000 LVAD patients with follow-up periods reaching from 30 days up to 2 years.[17,18] Against this background, the sample size and the follow-up period of the present study seem rather limited. While DAOH is statistically very efficient, the results of Kaplan–Meier analysis may have been influenced by that. Possibly, at least some of the included variables might get significant when increasing the sample size or length of follow-up. Nevertheless, our data should be sufficient to clarify the key message that only 'surviving the procedure' may not always be enough and to present DAOH as a sensitive marker for patients' outcome. Thus, this study might serve as 'hypothesis-generating'. In addition, we provide first epidemiologic data on DAOH after LVAD implantation in the so far largest cohort of LVAD patients. These data might be used for sample size calculations in further trials using DAOH as a primary endpoint.

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Strengths and limitations

A strength of this study includes its 365 day follow-up period to calculate DAOH, which represents a more patient-centred outcome compared with mortality. Unfortunately, we cannot provide follow-up data exceeding 1 year. Further notable limitations of the study include its single-centre, retrospective nature and the limited sample size. Another relevant limitation is that only a limited number of perioperative factors influencing DAOH after LVAD implantation could be investigated. The reason for that mainly consists of the fact that other variables were not included in our database. To ensure an adequate choice of candidate variables, we based our decision on large registry data and performed a separate literature research. However, there might be additional relevant confounders that could not be included and should be investigated in future studies. Finally, a limitation is that we cannot guarantee that every hospitalization in the first year after surgery was reported as patients may have entered another hospital without our knowledge. In those cases, DAOH calculation might be incorrect. However, LVAD patients represent a cohort that is very closely connected to our centre and it is unlikely that these patients are hospitalized elsewhere without our knowledge.

Conclusions

The present study could identify a number of perioperative variables that are associated with reduced DAOH 1 year after LVAD implantation. Furthermore, this study found discrepancies between DAOH und mortality as most variables associated with reduced DAOH had no significant association with reduced survival rates. These findings indicate that only 'surviving the procedure' may not be enough and emphasize the relevance of more patient-centred outcomes reflecting life impact like DAOH. Although this is a retrospective cohort study, the results of this study may immediately be used by clinicians that are integrated into the challenging selection process of patients suitable for LVAD implantation. In addition, our data might contribute to a more comprehensive assessment of outcome in this cohort. In the future, further studies are warranted to replicate the results in a variety of larger cohorts and other settings.

Acknowledgements

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Conflict of interest

The authors have no conflict of interest to declare.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier graphs.
Figure S2. Univariate analysis for the association between age and „Days alive and out of hospital" (DAOH) presented by quartiles.
Table S1. Univariate Cox regression model.
Table S2. Multivariate Cox regression model.

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Impact of Left Ventricular Assist Devices on Days Alive and Out of Hospital in Hemodynamically Stable Patients with End-Stage Heart Failure: A Propensity Score Matched Study

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Abstract: The two main surgical options to treat end-stage heart failure are heart transplantation (HTx) or left ventricular assist device (LVAD) implantation. In hemodynamically stable patients, the decision for HTx listing with or without LVADs is challenging. We analyzed the impact of both options on days alive and out of hospital (DAOH) and survival. This retrospective study screened all patients with HTx or LVAD implantation between 2010 and 2020. The main inclusion criterion was hemodynamic stability defined as independence of intravenous inotropic/vasoactive support at decision. Propensity score matching (PSM) was performed. The primary endpoint was DAOH within one year after the decision. Secondary endpoints included survival, duration until HTx, and hospitalizations. In total, 187 patients received HTx and 227 patients underwent LVAD implantation. There were 21 bridge-to-transplant (BTT)-LVAD patients (implantation less than a month after HTx listing or listing after implantation) and 44 HTx-waiting patients included. PSM identified 17 matched pairs. Median DAOH at one year was not significantly different between the groups (BTT-LVAD: median 281, IQR 89; HTx waiting: median 329, IQR 74; $p = 0.448$). Secondary endpoints did not differ significantly. Our data suggest that BTT-LVAD implantation may not be favorable in terms of DAOH within one year for hemodynamically stable patients compared to waiting for HTx. Further investigations on quality of life and long-term outcomes are warranted.

Keywords: heart failure; cardiac surgery; heart transplantation; left ventricular assist devices; patient-centered outcomes

1. Introduction

In end-stage heart failure, heart transplantation (HTx) remains the gold-standard therapy according to American and European guidelines [1,2]. However, left ventricular assist devices (LVADs) have not only shown improved survival and quality of life compared to optimized pharmacological treatment [3,4], but also show comparable survival to HTx [5,6]. From a patient point of view, the decision to solely wait for the gold-standard HTx or to undergo LVAD implantation with its possible risks and complications as a bridge to transplant (BTT) is absolutely crucial. Especially in hemodynamically stable patients, clinicians are often confronted with the decision of listing their patients for HTx with or without BTT-LVAD implantation [7].

Within the Eurotransplant region, patients in an acute life-threatening status can be "high-urgency (HU) listed" on the HTx waiting list, while stable patients being "t-listed" on the regular waiting list often have to wait for elective HTx for a much longer period. Patients receiving a LVAD implantation can be further classified using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile. INTERMACS 1 to 3 typically indicate a patient who is dependent on vasoactive or inotropic therapies and represent the majority of patients receiving LVAD implantation [8]. Studies focusing on patients with an INTERMACS 4 who are not inotropic-dependent, only on oral medication and therefore stable in their end-stage heart failure, are rare. A re-evaluation of the ROADMAP study compared INTERMACS 4–7 patients to optimal medical management and favored LVAD therapy, especially in INTERMACS 4 regarding survival and health-related quality of life [9]. However, adverse events are still more frequent in LVAD compared to medical therapy only [6,7,9–11]. Despite this, it is important to note that the recent developments in the pumps with a centrifugal continuous flow significantly improved survival free of a debilitating stroke or reoperation [12,13]. A comparison of hemodynamically stable end-stage heart failure patients awaiting HTx on the regular waiting list and INTERMACS 4 patients receiving a BTT-LVAD has not yet been performed. In addition, data on the life impact and quality of life of LVAD implantation in these patients are scarce. Days alive out of hospital (DAOH) has been proposed as a more patient-centered outcome in this context, which is easy to measure, readily available, statistically efficient, and cost-effective [14,15].

The primary aim of this study was to compare DAOH in hemodynamically stable patients awaiting HTx on the regular waiting list vs. patients undergoing BTT-LVAD implantation. We hypothesized that BTT-LVAD patients have more DAOH than patients solely waiting for HTx. We also aimed to characterize the different trajectories of these patients after the decision.

2. Materials and Methods

2.1. Study Design

This study was a retrospective single-center study conducted at University Hospital Duesseldorf, Germany. Ethical approval was obtained for studying both, the LVAD and HTx databases, by the local ethics committee (reference numbers: 2020-1058 and 4567). Written informed consent for this analysis could be waived due to the retrospective nature of the study, but all patients gave written informed consent in advance to be registered in a dedicated prospective local database. This article was written to strengthen the reporting of the observational studies in epidemiology (STROBE) checklist for retrospective cohort studies.

2.2. Patients

All patients aged ≥18 years who received LVAD implantation or HTx at University Hospital Duesseldorf between September 2010 and December 2020 were screened from the databases. Patients that were listed for a HTx but died before receiving a HTx were not included in the database. Hemodynamically stable BTT-LVAD patients (≥INTERMACS 4) and hemodynamically stable HTx patients on the regular waiting list theoretically eligible for ventricular assist device therapy at the time of listing were included. Hemodynamic stability was defined as the independence of intravenous inotropic or vasoactive support at the time of LVAD implantation or sole HTx listing, respectively. If the time difference between t-listing and LVAD implantation was more than one month, patients were excluded. HTx listing after BTT-LVAD implantation was no exclusion criterion. Thus, we aimed to avoid bias from patients who have had LVAD implantation due to a prolonged HTx waiting time. Patients with LVAD as destination therapy (DT) due to a common contraindication for HTx and patients with missing data or incomplete medical records regarding the endpoints of interest were also excluded. Data on patient characteristics, medical history, and hospitalizations within one year were extracted from electronic medical charts and entered in the local and continuously updated database. Information on the study selection process can be found in Figure 1.

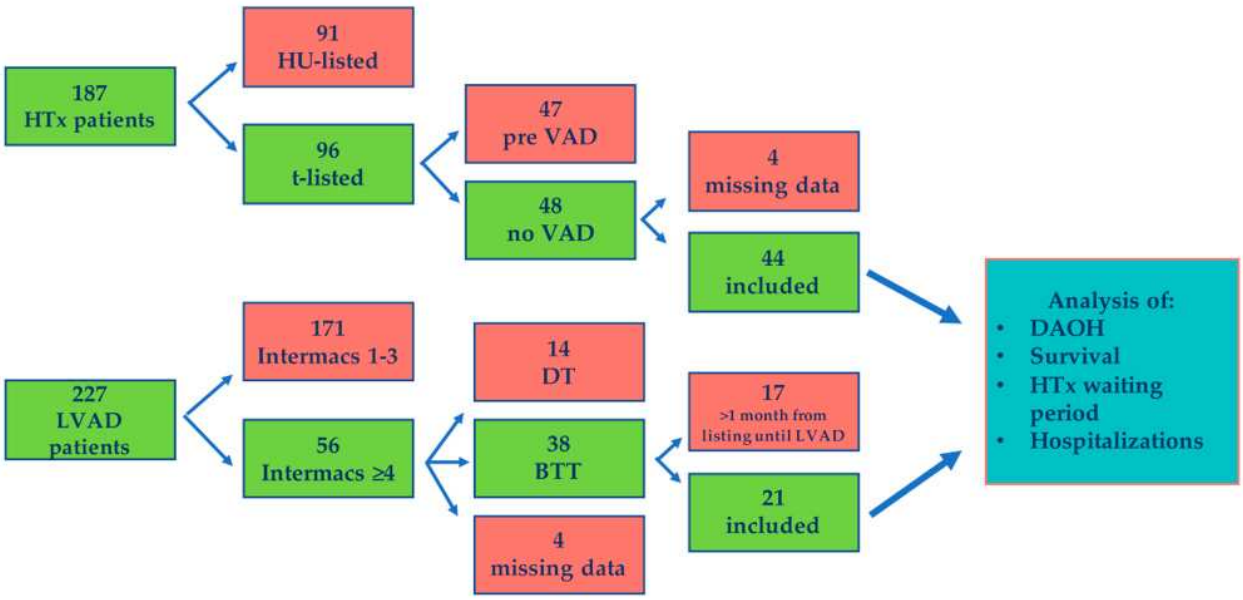

Figure 1. Study flowchart. Process of data search in the two databases, HTx and LVAD. Patients who followed up and were finally included are marked in green. Marked in red are the patients who were excluded in the respective databases. HTx = heart transplantation; HU = high-urgency status; (L)VAD = (Left) ventricular assist device; Intermacs = Interagency Registry for Mechanically Assisted Circulatory Support; DT = destination therapy; BTT = bridge to transplant; DAOH = days alive and out of hospital.

2.3. Propensity Score Matching

As the groups were non-randomized, we performed a matched propensity score (PS) analysis. A logistic regression model including seven preoperative patient characteristics was used to estimate the PS. The PS matching was performed using a case–control matching algorithm with a caliper width of 0.2 standard deviations of the logit. Balance between patient characteristics before and after matching was assessed using 2-sample t-tests (continuous variables, after checking for normality) or chi-square tests (categorial variables). There is a lack of literature on decision criteria for HTx or BTT-LVAD in hemodynamically stable patients. Therefore, the following preoperative characteristics which might influence the decision for or against each treatment option were chosen to calculate the PS [15]: age, sex, body mass index (BMI), diagnosis (ischemic cardiomyopathy, dilatative cardiomyopathy, others), preoperative renal failure (defined as serum creatinine $\geq$1.5 mg/dL), New York Heart Association (NYHA) status, and the left ventricular ejection fraction (LVEF, measured via transthoracic echocardiogram). The LVEF was classified as preserved (>50%), mildly reduced (40–49%), and reduced (<40%).

2.4. Outcomes

The primary endpoint of this study was DAOH at one year after decision for HTx listing or after BTT-LVAD implantation. DAOH was calculated as previously reported [15] and measured as the sum of days in hospital for each patient subtracted from 365 days. If a patient died during the first year, the difference between days survived and 365 days was added to the sum of days in hospital before subtraction from 365. Hospitalizations were defined as planned or unplanned stays of at least one overnight stay in hospital. All end-stage heart failure patients were closely connected to our center; thus, we did not expect external hospitalizations without a note in the patient's medical record. Secondary endpoints included the duration until HTx; reasons for delisting or HU listing; the amount, durations, and reasons for hospitalizations; as well as survival analysis.

2.5. Statistical Analysis

Statistical analysis was performed using IBM SPSS© software version 28.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2020 (version 16.42, Microsoft Corp., Redmond, WA, USA). As this was a retrospective and exploratory data analysis, a formal sample size calculation was not implemented. Categorical data are presented as counts (*n*) with corresponding percentages (%). Continuous variables are reported as mean ± standard deviation (SD) or as median with interquartile ranges (IQR). $p < 0.05$ was considered as statistically significant. Due to the small sample size of this study, the Shapiro–Wilks test was used to test for normality and for choosing the appropriate statistical method. Based on the results of the Shapiro–Wilks test, a non-parametric Mann–Whitney U-test was used to compare DAOH in both groups. Null-hypothesis significant testing was conducted using Bayesian analysis for the Mann–Whitney-U statistics (JASP Team (2020). JASP (Version 0.14.1, Amsterdam, The Netherlands) [Computer software]). To compare the secondary endpoints, descriptive statistics as well as Kaplan–Meier analysis for survival comparison were performed.

3. Results

3.1. Propensity Score Matching

Between September 2010 and December 2020, a total of 187 patients underwent HTx and 227 patients underwent LVAD implantation at our center, respectively. Based on the in- and exclusion criteria, 21 BTT-LVAD patients (HeartMate II™: 2; HeartMate 3™: 7; Medtronic HVAD™: 12) and 44 HTx-waiting patients were included. Propensity score matching resulted in 17 matched pairs. In the matched BTT-LVAD group, two patients had a HeartMate II™, five had a HeartMate 3™, and ten patients were implanted with a Medtronic HVAD™ device. Table 1 summarizes the preoperative patient characteristics before and after matching. In both groups, patients were mostly male (BTT-LVAD: $n = 13$ (76.5%), HTx-waiting: $n = 12$ (70.6%)), between 50 and 60 years old, and around 30–40% had pre-existing renal failure. In most cases, the diagnosis leading to end-stage heart failure was ischemic cardiomyopathy. The majority of patients reported heart failure symptoms (NYHA $\geq$ 3) and median LVEF was 15%.

Table 1. Patient characteristics before and after PSM. PSM = propensity score matching; LVAD = left ventricular assist device; HTx = heart transplantation; BMI = body mass index; ICM = ischemic cardiomyopathy; DCM = dilatative cardiomyopathy; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction.

	Before PSM			**After PSM**		
	LVAD Group (*n* = 21)	**HTx Group (*n* = 44)**	***p*-Value**	**LVAD Group (*n* = 17)**	**HTx Group (*n* = 17)**	***p*-Value**
Age, mean (SD)	59.97 (6.2)	55.69 (11.2)	0.108	59.92 (6.7)	57.70 (7.0)	0.352
Male sex, *n* (%)	17 (80.9)	26 (59.1))	0.08	13 (76.5)	12 (70.6)	0.697
BMI, mean (SD)	28.75 (4.9)	25.96 (4.2)	0.021	27.30 (3.8)	27.49 (3.4)	0.882
Renal failure, *n* (%)	6 (28.6)	19 (43.2)	0.258	5 (29.4)	7 (41.2)	0.473
diagnosis						
ICM, *n* (%)	16 (76.2)	17 (38.6)	0.07	12 (70.6)	8 (47.1)	0.163
DCM, *n* (%)	5 (23.8)	22 (50.0)		5 (29.4)	9 (52.9)	
others, *n* (%)	0 (0)	5 (11.4)		0 (0)	0 (0)	

Table 1. *Cont.*

	Before PSM			After PSM		
	LVAD Group (n = 21)	HTx Group (n = 44)	p-Value	LVAD Group (n = 17)	HTx Group (n = 17)	p-Value
NYHA						
NYHA I, n (%)	1 (4.8)	1 (2.3)	0.608	0 (0)	1 (5.9)	0.415
NYHA II, n (%)	0 (0)	0 (0)		0 (0)	0 (0)	
NYHA III, n (%)	14 (66.7)	24 (54.5)		11 (64.7)	8 (47.1)	
NYHA IV, n (%)	6 (28.5)	19 (43.2)		6 (35.3)	8 (47.1)	
LVEF						
Preserved (>50%), n (%)	0 (0)	1 (2.3)	0.472	0 (0)	0 (0)	
Mild reduced (40–49%), n (%)	0 (0)	2 (4.5)		0 (0)	0 (0)	
Reduced (<40%), n (%)	21 (100)	41 (93.2)		17 (100)	17 (100)	

3.2. Primary Endpoint

Overall, median DAOH at one year was 313 (IQR 88) days, with no significant difference between the groups (BTT-LVAD group: median 281, IQR 89; HTx waiting group: median 329, IQR 74; p = 0.448, see Figure 2). The Bayes factor 1:2.246 indicates that an alternative hypothesis is 2.246 times less likely than a null hypothesis. In a sub analysis, we further compared all patients that did not receive a HTx in the first year after LVAD implantation or after t-listing on the waiting list. We excluded patients that were delisted in the first year. The DAOH was significantly higher in HTx-waiting patients compared to LVAD patients (BTT-LVAD group: n = 7, median 334, IQR 39; HTx waiting group: median 362, IQR 5; p = 0.025).

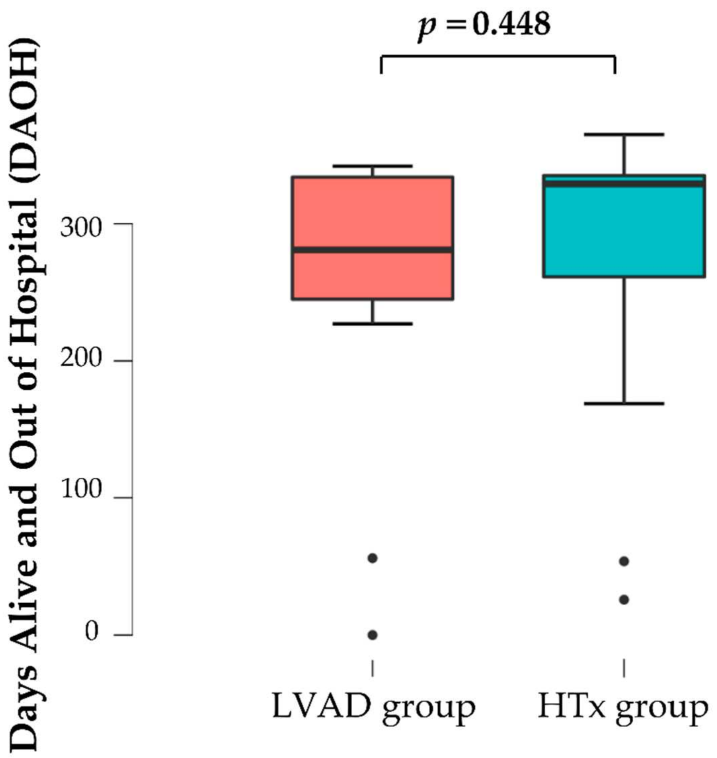

Figure 2. Days alive and out of hospital (DAOH) within one year in non-inotropic-dependent end-stage heart failure patients awaiting heart transplantation (HTx) on the regular waiting list and after bridge-to-transplant left ventricular assist device (LVAD) implantation.

3.3. Secondary Endpoints

In the first year after the decision for BTT-LVAD implantation or to wait on the regular waiting list, three LVAD patients and four patients on the HTx waiting list died. Survival analysis by the Kaplan–Meier method showed no significant difference between the groups at one year (BTT-LVAD group = 82% vs. HTx-waiting group = 76%; log rank: $p = 0.673$; Table 2). Figure 3 shows the survival rate of all deceased patients.

Table 2. Secondary endpoints. HTx = heart transplantation; LVAD = left ventricular assist device; HU = high-urgency status.

	LVAD Group (*n* = 17)	HTx Waiting (*n* = 17)
Survival		
1 y survival, *n* (%)	14 (82.4)	13 (76.5)
3 y survival, *n* (%)	13 (76.5)	10 (58.8)
Duration until death in days, median (IQR)	401 (1122)	314 (279)
HTx waiting period		
Duration until HTx in days, median (IQR)	256 (275)	179 (308)
HU-listed, *n* (%)	4 (23.5)	2 (11.8)
Delisted, *n* (%)	5 (29.4)	0 (0)
Hospitalizations within one year		
Number of stays, mean (SD)	3 (1.97)	2.53 (2.12)
Duration in days, mean (SD)	32.24 (28.39)	25.77 (25.17)

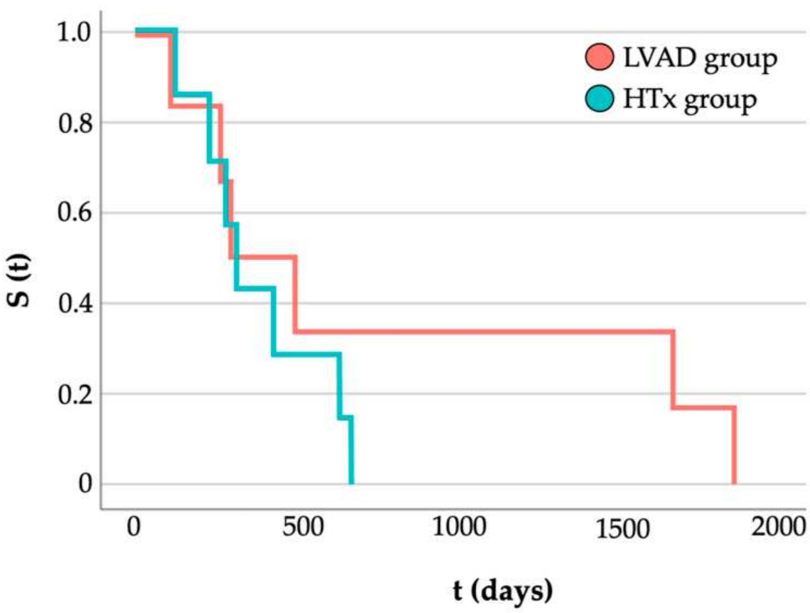

Figure 3. Survival rate (S) over time (t) of the deceased after left ventricular assist device (LVAD, $n = 6$, red) implantation or listing for heart transplantation (HTx, $n = 7$, green) on the regular waiting list in days as estimated according to the Kaplan–Meier method (log-rank test: $p = 0.673$).

The median waiting time for HTx for patients without LVAD on the list was 179 (IQR 308) days with two patients being HU-listed in the process. In the first year after listing, 12/17 (70.6%) patients received a HTx. In the BTT-LVAD population, nine patients (52.9%) received a HTx after waiting for a median time of 256 (IQR 275) days after implantation (no statistical significance between the groups from t-decision until HTx: $p = 0.651$). In the first year, five patients (29.4%) were transplanted. Five patients were delisted and changed from BTT-LVAD to a DT concept due to increased incompliance and multimorbidity, and one patient due to intracerebral bleeding. Of the 17 included LVAD patients, 4 became HU-listed due to LVAD pump thrombosis, cerebral ischemia, or driveline infection. Because we needed to include not only matched patients in the analysis of LVAD-associated complications leading to a HU status, we also examined all 21 BTT-LVAD patients (unmatched). The additional four patients did not have any further HU listing due to LVAD complications.

Analyzing the amounts, durations and reasons of hospitalization within the first year revealed the following: the mean number of hospital stays in initially hemodynamically stable patients awaiting HTx in the first year after listing on the regular waiting list was 2.53 (SD 2.12) with a mean duration of 25.77 (SD 25.17) days. Other than the HTx in 12 patients, right or left heart catheterization, cardiac decompensations before HTx, and myocardial biopsies after HTx also led to the hospitalization of patients on the waiting list. In the first year after LVAD implantation, the patients' mean number of hospital admissions was 3 (SD 1.97) with a duration of 32.24 (SD 28.39) days. Besides the five patients (29.4%) that received HTx in the first year and were therefore admitted longer, analyzing the LVAD patients revealed the following interesting result: five (29.4%) patients were only admitted for LVAD implantation and had no further hospitalizations in the following year. One patient died during the index LVAD-implantation admission due to right heart failure.

4. Discussion

This is the first study to compare the life impact between hemodynamically stable patients with end-stage heart failure that were either eligible for sole HTx listing or BTT-LVAD implantation. Supporting the decision-making process between both options through valid data is of great and immediate relevance for clinical practice. Therefore, we aim to help patients to evaluate and compare both options with relevant endpoints from their point of view. We used the available retrospective data to assess and compare DAOH at one year in both groups. Additionally, we analyzed survival, the HTx waiting period, and hospitalizations. Our findings show that BTT-LVAD implantation (maximum one month after HTx listing) as an end-stage heart failure patient who is still hemodynamically stable does not lead to a significant difference over sole HTx listing in terms of hospitalized days in the year after the decision and 1-year mortality. Nevertheless, further investigation on quality-of-life parameters and with larger cohorts should follow.

The systematic reviews and meta-analyses by Theochari and colleagues and Zhang and colleagues synthesized the published evidence on mortality and adverse events in HTx and BTT-LVAD patients and did not find any statistically significant difference (Theochari et al.—seven studies, no difference in 1-year mortality, pooled odd's ratio (OR): 0.91, 95% confidence interval (CI): 0.62–1.32; Zhang et al.—twelve studies in total, two studies on five-year mortality with no significant differences, pooled OR: 1.02, 95% CI: 0.93–1.11, and no difference in stroke, bleeding, and infection adverse events) [5,16]. Additionally, ten-year survival does not show statistical significance in a recently published study (9420 patients with LVAD; 23,877 with direct HTx; 76% overall survival at ten years; $p = 0.380$) [17]. However, one included article in both reviews found the in-hospital mortality to be significantly higher for HTx waiting list patients compared to BTT-LVAD patients (42.3% versus 4.3%, $p = 0.002$) [18]. This last-mentioned study published by Attisani and colleagues compared patients on the waiting list for HTx with urgent conditions and LVAD patients with an INTERMACS 1 or 2 status and is therefore not comparable to our present study [18]. A study that included INTERMACS 4 patients and compared these to optimal medical treatment showed improved 1-year survival and health-related quality of life in the device group [9]. In our data, survival also did not differ between the HTx-waiting and BTT-LVAD patients. However, further studies with larger sample sizes and longer periods need to validate the effect on survival.

The life impact parameter DAOH itself was investigated in both HTx and LVAD patients separately [15,19]. In LVAD patients, the INTERMACS performance status and other parameters such as chronic kidney failure significantly influence DAOH [15]. The authors agreed to use these factors to optimize patient selection in LVAD treatment, therefore, we used these for PSM [15]. Our study did not find any statistical significance in DAOH at one year between the groups of stable HTx-waiting patients and INTERMACS ≥4 BTT-LVAD patients. One could draw the conclusion that HTx waiting might be superior to avoid LVAD-associated burdens and complications. However, LVAD implantation improves heart failure symptoms and the patient's overall condition with increased blood flow of organs. We could see in our study that no hospitalizations occurred due to cardiac decompensations in the LVAD group. However, patients might suffer from LVAD-related complications and the waiting period for HTx is longer (not statistically significant). As the Bayes factor of the analysis is BF01: 2.246, the evidence for the null hypothesis is only anecdotal. Therefore, it is important to interpret the results of this study as a first approach to analyze therapeutic options for hemodynamically stable end-stage heart failure patients. Prospective studies to evaluate the impact of each invasive and the medical treatment on quality-of-life parameters should be performed. A sub-analysis of our data that compared DAOH in HTx patients and BTT-LVAD patients waiting for more than one year and not being delisted in that time showed DAOH in the group without LVAD to be higher. This was expected, as the LVAD group undergoes an operation with a postoperative intensive care unit stay.

Our data suggest that BTT-LVAD implantation might not be favorable over sole HTx listing in hemodynamically stable heart failure patients as the DAOH and survival do not differ from HTx waiting. Additional information on improved quality of life, hospitalizations, and adverse events should be investigated in this patient cohort and might also contribute to the decision-making process in practical use. Another aspect besides the patient-centered outcomes concerns healthcare system effects due to hospitalizations and operations. Fewer days in hospital in terms of a lower DAOH means less financial burden. As we could see in this present study, the number of hospitalizations did not differ between the groups. In the country of this study site, Germany, there is no prioritization for HTx in BTT-LVAD patients as there is in the United States. Therefore, the waiting period is longer, as our data revealed in accordance with previous literature [20]. Almost 30% of our included patients did not have any further hospitalization in the year after LVAD implantation. Moreover, almost 30% of our patients received a HTx in the first year; two of them had an HU status due to LVAD-associated complications. It would be beneficial to find predictors for patients that will have a long-time benefit from the LVAD implantation and for those who will need a HTx shortly after implantation, therefore having two high-risk surgeries.

Study Limitations

This study has several limitations. First, as our study is retrospective, the usual limitation for this study design appears. However, our database was constantly and prospectively updated. We reviewed all HTx and LVAD patients in our database and included HTx patients with a regular waiting list status. If a patient was transferred to HU status later in the process, they were also included for the LVAD patients. However, patients that died while waiting for HTx were not included, as we used the database containing all HTx patients that received a HTx. This aspect is a crucial limitation and must also be regarded for our survival analysis. In the LVAD database, we included all INTERMACS ≥4 patients and excluded patients with a DT intention at the time of implantation. Additionally, patients that were listed for transplantation more than one month before LVAD implantation were excluded, as we aimed to exclude LVAD implantation as a second-choice option. For better comparability, we performed propensity score matching. Through this process, the second limitation is the modest sample size. As this study was performed in a single center, following studies with greater sample sizes are necessary. Thirdly, for the assessment of our parameter DAOH, we cannot exclude external hospitalizations of the included patients. However, all LVAD and HTx-waiting patients were very closely connected to our center, so it is unlikely that these patients were hospitalized elsewhere. Lastly, we reviewed only a one-year follow-up after the decision for regular HTx waiting list or after LVAD implantation. Studies with long-time follow ups are crucial for generalizability and translation of the results into clinical practice.

5. Conclusions

In the present study, we showed that both decisions, to wait for a HTx or to undergo a LVAD implantation as a BTT (maximum one month after HTx listing), do not differ in terms of DAOH and survival in the first year after the decision. These data suggest that early LVAD implantation in patients eligible for HTx and still being hemodynamically stable might have no advantage over sole HTx listing. Investigations on quality of life after both decisions should follow. We cannot draw conclusions to enhance patient selection for each decision with this present study, especially with regard to the very low number of included patients and the long study duration of ten years with different devices and probably different pharmacologic treatments. It is crucial to verify and reproduce the results of this study in larger cohorts with a longer follow-up period or even with a prospective (randomized) design to gather further evidence in this important field.

Author Contributions: Conceptualization, T.T., S.R. and H.A.; methodology, T.T., S.R., H.A. and G.L.B.; formal analysis, T.T., S.R. and R.M.; investigation, F.B., C.B., I.T., M.N., U.B. and R.H.; data curation, T.T., S.R. and R.M.; writing—original draft preparation, T.T. and S.R.; writing—review and editing, R.M., G.L.B., H.A., F.B., C.B., I.T., M.N. and U.B.; supervision, H.A., A.L. and R.H.; project administration, H.A., U.B. and A.L. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Heinrich Heine University Duesseldorf (reference numbers: 2020-1058 (LVAD, approval date: 20 August 2020) and 4567 (HTx, approval date: 25 January 2021)).

Informed Consent Statement: All patients gave their written informed consent to be included in the prospective databases of the University Hospital Duesseldorf. Therefore, the need for additional written informed consent for this retrospective analysis could be waived.

Data Availability Statement: All relevant data for the understanding and interpretation of this study are included in the present manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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