Aus der Klinik für Anästhesiologie

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Untersuchungen zur perioperativen Risikostratifizierung und Prognoseabschätzung bei Patient*innen mit orthotoper Herztransplantation

Habilitationsschrift

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Widmung

Für meine Eltern

Präambel und Übersicht der zugrundeliegenden Originalarbeiten

Der Inhalt dieser kumulativen Habilitationsschrift diskutiert die Ergebnisse der folgenden Originalarbeiten. Diese beschäftigten sich mit der Identifikation von perioperativ prognoserelevanten Faktoren nach orthotoper Herztransplantation. Zusätzlich wurden Methoden zur Risikostratifizierung bei diesen Patient*innen untersucht und die Rolle der postoperativen Organdysfunktion beleuchtet.

Es folgen zunächst eine Einleitung in die Thematik, sowie die Darstellung der Methodik und die Zusammenfassung der Ergebnisse aus den oben genannten Originalarbeiten. Diese Ergebnisse werden abschließend im Kontext der Erkenntnisse aus aktueller Literatur diskutiert.

1. **M'Pembele R**, Roth S, Stroda A, Lurati Buse G, Sixt SU, Westenfeld R, Polzin A, Rellecke P, Tudorache I, Hollmann MW, Aubin H, Akhyari P, Lichtenberg A, Huhn R, Boeken U. Life impact of VA-ECMO due to primary graft dysfunction in patients after orthotopic heart transplantation.

   ESC Heart Fail. 2022 9:695-703. doi: 10.1002/ehf2.13686

2. **M'Pembele R**, Roth S, Stroda A, Lurati Buse G, Sixt SU, Westenfeld R, Polzin A, Rellecke P, Tudorache I, Hollmann MW, Aubin H, Akhyari P, Lichtenberg A, Huhn R, Boeken U. Risk Factors for Acute Kidney Injury Requiring Renal Replacement Therapy after Orthotopic Heart Transplantation in Patients with Preserved Renal Function.

   J Clin Med. 2021 Sep 12;10(18):4117. doi: 10.3390/jcm10184117.

3. **M'Pembele R,** Roth S, Stroda A, Reier T, Lurati Buse G, Sixt SU, Westenfeld R, Rellecke P, Tudorache I, Hollmann MW, Aubin H, Akhyari P, Lichtenberg A, Huhn R, Boeken U. Validation of days alive and out of hospital as a new patient-centered outcome to quantify life impact after heart transplantation.

   Sci Rep. 2022 Nov 1;12(1):18352. doi: 10.1038/s41598-022-21936-4.

4. Roth S, **M'Pembele R**, Nucaro A, Stroda A, Tenge T, Lurati Buse G, Sixt SU, Westenfeld R, Rellecke P, Tudorache I, Hollmann MW, Aubin H, Akhyari P, Lichtenberg A, Huhn R, Boeken

U..Impact of cardiopulmonary resuscitation of donors on days alive and out of hospital after orthotopic heart transplantation.

J Clin Med. 2022 Jul 3;11(13):3853. doi: 10.3390/jcm11133853.

5. **M'Pembele R,** Roth S, Nucaro A, Stroda A, Tenge T, Lurati Buse G, Bönner F, Scheiber D, Ballázs C, Tudorache I, Aubin H, Lichtenberg A, Huhn R, Boeken U.Postoperative high-sensitive troponin t predicts one-year mortality and days alive and out of hospital after orthotopic heart transplantation.

   Eur J Med Res. 2023 Jan 9;28(1):16. doi: 10.1186/s40001-022-00978-4.

6. **M'Pembele R**, Roth S, Jenkins F, Hettlich V, Nucaro A, Stroda A, Tenge T, Polzin A, Ramadani B, Buse GL, Aubin H, Lichtenberg A, Huhn R, Boeken U. Association between early postoperative hypoalbuminemia and outcome after orthotopic heart transplantation.

   Interdiscip Cardiovasc Thorac Surg. 2024 doi: 10.1093/icvts/ivae012.

Abkürzungsverzeichnis

AKI	Acute Kidney Injury = Akute Nierenschädigung
AUC	Area under the curve = Fläche unter der Kurve
BMI	Body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	Cytomegalie-Virus
CPR	Kardiopulmonale Reanimation
DAOH	Days alive and out of hospital
GFR	Glomeruläre Filtrationsrate
HTX	Herztransplantation
IMPACT	Index for Mortality Prediction After Cardiac Transplantation
ISHLT	International Society for Heart and Lung Transplantation
MELD	Model for end-stage liver disease
NARI	Netto-Reklassifizierungsindex
NRI	Netto-Reklassifizierungsverbesserung
OR	Odds Ratio
PGD	Primary Graft Dysfunction = Primäres Transplantatversagen
RIPC	Remote ischemic preconditioning
ROC Kurve	Receiver Operating Characteristic Kurve = Grenzwertoptimierungskurve
StEP	Standardisierte Endpunkte in der perioperativen Medizin
VA-ECMO	Veno-arterielle extrakorporale Membranoxygenierung
VV-ECMO	Veno-venöse extrakorporale Membranoxygenierung
WHODAS 2.0	World Health Organization Disability Assessment Schedule 2.0

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1 Einleitung

In der europäischen Bevölkerung nimmt die Inzidenz kardialer Erkrankungen stetig zu. Neben der koronaren Herzerkrankung nimmt auch die Prävalenz der Herzinsuffizienz zu, von der ungefähr 17 von 1000 Erwachsenen in Europa betroffen sind [1]. Trotz positiver Entwicklungen in der medikamentösen Therapie dieser Patient*innen, bietet nur die orthotope Herztransplantation (HTX) eine kurative Therapieoption. Daher stellt diese weiterhin den Goldstandard zur Therapie der terminalen Herzinsuffizienz dar [2]. So wurden im Jahre 2023 in der Eurotransplant Region 645 Herzen transplantiert, davon 330 in Deutschland. Demgegenüber steht die hohe Zahl von 1044 Patient*innen, die am Ende des Jahres 2023 auf der aktiven Warteliste für ein Spenderorgan verblieben. Diese Zahlen verdeutlichen das Missverhältnis zwischen Angebot und Nachfrage an Spenderorganen in der Eurotransplant Region und somit auch in Deutschland. Bei steigender Zahl von potenziell betroffenen Patient*innen, bedarf es in Zukunft einer optimierten Strategie zur Patientenauswahl, um das limitierte Angebot an Spenderorganen effizient nutzen zu können. Die Identifikation von prognoserelevanten Faktoren in der präoperativen Phase spielt hierbei eine zentrale Rolle. Für die Risikorestratifizierung nach HTX können zusätzlich intra- und postoperative Faktoren von Bedeutung sein. Während perioperative Faktoren, die mit erhöhter Mortalität nach HTX assoziiert sind bereits teilweise identifiziert wurden, sind patientenzentrierte Endpunkte und deren Einflussfaktoren in dieser Population kaum untersucht.

Die frühe postoperative Dysfunktion von Organsystemen nach HTX ist eine häufige Komplikation, die zu einer erhöhten Morbidität und Mortalität bei diesen Patient*innen führen kann. Neben der primären Transplantatdysfunktion spielt hier das Auftreten einer akuten Nierenschädigung (AKI) eine führende Rolle. Strategien zur Früherkennung und Prävention der schweren AKI wurden zwar für kardiochirurgische Patient*innen bereits beschrieben, bei Herztransplantationspatient*innen sind diese Strategien jedoch bislang nur unzureichend untersucht worden.

Das übergeordnete Ziel der hier zusammengefassten Arbeiten, war es somit prognoserelevante Faktoren nach Herztransplantation zu identifizieren und deren Assoziation zur Mortalität und einem patientenzentrierten Endpunkt zu untersuchen. Zusätzlich wurde der Einfluss der frühen postoperativen Dysfunktion von Organsystemen und die Rolle von postoperativen Biomarkern zur Risikorestratifizierung in dieser Patientengruppe beleuchtet.

1.1 Unterschiede zwischen den Endpunkten Mortalität und „Days alive and out of hospital" nach Herztransplantation

1.1.1 Mortalität als Endpunkt nach Herztransplantation

Die HTX ist ein maximal invasiver chirurgischer Eingriff, der häufig bei multimorbiden Patient*innen durchgeführt wird. Die Kombination aus eingriffsassoziierten Faktoren und patientenseitigen Komorbiditäten beeinflusst maßgeblich die Komplikationsrate nach HTX. Häufig wird der Erfolg der HTX mit dem Überleben der Patient*innen assoziiert, da die Mortalität einen gut messbaren und patientenrelevanten Endpunkt darstellt. Die Mortalitätsdaten werden durch die Transplantationszentren erfasst und in Registerdatenbanken wie beispielsweise dem Internationalen Organtransplantationsbericht der Internationalen Gesellschaft für Herz- und Lungentransplantation (ISHLT) regelmäßig berichtet. So zeigte eine große Fall-Kontrollstudie mit Daten von 31.883 HTX Patient*innen und 159.415 Kontrollpatient*innen aus den Jahren 1990 bis 2007, dass HTX Patient*innen im Vergleich zur Normalbevölkerung ein insgesamt 3-fach höheres Risiko haben innerhalb von 10 Jahren nach HTX zu versterben. Jedoch zeigte sich auch, dass sich das Langzeitüberleben über die Jahre deutlich verbessert hat [3]. So liegt die durch den ISHLT-Report aktuell berichtete 1-Jahres Mortalität nach HTX im Jahr 2021 in Europa bei 15-20 % [4]. Es wird beschrieben, dass in den darauffolgenden Jahren die Mortalität bei 4 % pro Jahr liegt, sodass nach 10 Jahren noch die Hälfte der transplantierten Patient*innen lebt [5,6]. Durch die flächendeckende Erfassung konnten in bisherigen Untersuchungen bereits perioperative Risikofaktoren identifiziert werden, die mit einer erhöhten Mortalität nach HTX assoziiert sind [6]. Hierbei ist es jedoch wichtig, Risikofaktoren in der frühen Phase nach HTX (im ersten Jahr nach HTX) von Risikofaktoren für Mortalität in der späten Phase nach HTX zu unterscheiden. Eine

Registeranalyse von über 30.000 HTX Patient*innen zeigte, dass in der frühen Phase nach HTX vor allem Risikofaktoren wie höheres Alter der Empfänger*innen, Übergewicht, Bilirubinerhöhung, kardiale Voroperationen, präoperative mechanische Kreislaufunterstützung, präoperative Beatmung, lange Ischämiezeit des Spenderorgans, präoperative Nierenfunktionsstörung und ein höheres Alter der Spender*innen mit einer erhöhten Mortalität nach HTX assoziiert sind [6]. Es wird in dieser Arbeit geschlussfolgert, dass die Mortalität nach HTX vor allem von der präoperativen Dysfunktion von Organsystemen (Lungen-, Leber- sowie Nierenfunktion) abhängt. In einer Metaanalyse bestätigten Foroutan et al. diese Ergebnisse und konnten zusätzlich eine Geschlechtsinkongruenz von Organempfänger*innen und Organspender*innen (weibliche Spenderin und männlicher Empfänger) als unabhängigen Risikofaktor für die 1-Jahres-Mortalität identifizieren [7]. Der 2021 veröffentliche HTX Bericht der ISHLT fokussierte sich ebenfalls auf Empfängercharakteristika [4]. In diesem Bericht wird hervorgehoben, dass die 1-Jahres-Mortalität nach HTX in Europa höher ist als in Nordamerika. Hier scheint die zunehmende Verwendung von Organen älterer und kränkerer Organspender*innen eine führende Rolle zu spielen. Zusätzlich werden in dem Bericht das Empfängeralter, die präoperative Nierenfunktionsstörung, eine ischämische oder kongenitale Kardiomyopathie als Grunderkrankung, kardiale Voroperationen, die mechanische Kreislaufunterstützung sowie der präoperative Krankenhausaufenthalt und invasive Beatmung als Risikofaktoren für 1-Jahres Mortalität identifiziert. Außerdem scheint hier auch das Übergewicht der Empfänger*innen, das Alter der Spender*innen, eine pulmonale Hypertonie, eine Leberfunktionsstörung sowie die Erfahrung des transplantierenden Zentrums gemessen an der Anzahl an HTX-Operationen pro Jahr eine Rolle für die 1-Jahres-Mortalität zu spielen [4]. Obwohl die 1-Jahres Mortalität ein einfach zu erhebender Parameter zur Qualitätskontrolle darstellt, können nicht alle für Patient*innen relevante Komplikationen und Verläufe durch diesen Endpunkt abgebildet werden. Unter diesem Aspekt gewinnen patientenzentrierte Endpunkte immer mehr an Bedeutung [8].

1.1.2 „Days alive and out of hospital" als patientenzentrierter Endpunkt nach Herztransplantation

Patientenzentrierte Endpunkte gewinnen in der perioperativen Medizin immer mehr an Relevanz und umfassen mehrere verschiedene Endpunkte, die neben dem alleinigen Überleben einer Operation andere für Patient*innen wichtige Faktoren mit Einfluss auf das alltägliche Leben untersuchen. Hierbei stehen vor allem auch Aspekte der Lebensqualität und der Einschränkungen im täglichen Alltag im Vordergrund, die durch die Analyse der Mortalität nur unzureichend oder überhaupt nicht abgebildet werden können. Die wichtigsten patientenzentrierten Endpunkte für die perioperative Medizin wurden von der Initiative für standardisierte Endpunkte in der perioperativen Medizin (StEP) zusammengefasst und nach ihrem Nutzen bewertet [8]. Einer der durch die Initiative vorgeschlagenen Endpunkte ist „days alive and out of hospital" (DAOH) der zur Einschätzung des Einflusses einer Intervention auf das alltägliche Leben genutzt wird. DAOH beschreibt hierbei die innerhalb eines bestimmten Zeitraums (z.B. 30 Tage, 180 Tage, 1 Jahr) überlebten Tage außerhalb einer Versorgungseinrichtung (Krankenhäuser oder Rehabilitationseinrichtungen) und dient somit als Surrogat Parameter für die Lebensqualität. Der Vorteil dieses Endpunktes liegt darin, dass er relativ einfach zu erheben ist, statistische Effizienz bietet und die mit einer Operation verbundenen Kurzzeit- und Langzeitkomplikationen (z.B. Mortalität, Krankenhausaufenthaltsdauer und Krankenhauswiederaufnahmen) gut abbilden kann [9]. In der perioperativen Medizin sowie im Bereich der Herzinsuffizienz wurde die Validität von DAOH bereits erfolgreich untersucht. Diesbezüglich analysierten Jerath et al. DAOH in über 540,000 Patient*innen die sich einem großen nicht-kardiochirurgischen Eingriff unterzogen [10]. Die Autor*innen identifizierten das männliche Geschlecht, mehrere Komorbiditäten und eine lange Operationsdauer als führende Einflussfaktoren für eine geringere Anzahl an DAOH nach 30 Tagen. Auch scheint eine Assoziation von niedrigen DAOH nach 30 Tagen mit postoperativen Komplikationen wie Myokardinfarkt, Schlaganfall, Herzinsuffizienz, Lungenembolie, Atmungsversagen, Infektion, akutes Nierenversagen und Wundheilungsstörungen zu bestehen. In der Gruppe von Patient*innen mit niedrigen DAOH erlitten 24 % in der Studie von

Jerath et al. eine postoperative Komplikation, während nur 2 % der Patient*innen mit hohen DAOH eine Komplikation im Verlauf erfuhren [10]. Neben dieser großen Studie wurde der Endpunkt DAOH noch in weiteren Studien im perioperativen Bereich validiert, jedoch variiert die Art der Anwendung des Endpunkts zwischen verschiedenen Studien [11,12]. Im Bereich der konservativen Herzinsuffizienztherapie wurden DAOH ebenfalls untersucht. In einer Sekundäranalyse der „Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity" (CHARM) Studie konnten Ariti et al. den Endpunkt erfolgreich anwenden [13]. Im Vergleich zu den Studien von Jerath oder Myles et al. erfolgte die Berechnung der DAOH jedoch anders. Patient*innen die innerhalb des Beobachtungszeitraum verstarben haben unabhängig von den bereits verbrachten Tagen außerhalb des Krankenhauses nicht automatisch einen DAOH Wert von „0" [13]. Für den Bereich der HTX sind die Daten zu DAOH sehr begrenzt. Eine kleinere Studie, die 235 HTX Patient*innen umfasst, hat Unterschiede in DAOH innerhalb des ersten Jahrs nach HTX zwischen Patient*innen mit und ohne präoperative mechanische Kreislaufunterstützung untersucht. Es wurde kein signifikanter Unterschied zwischen den Gruppen detektiert [14]. Dagegen wurden das Transplantationsjahr, die pulmonale Hypertonie und eine erhöhte Ischämiezeit des Spenderorgans als unabhängig assoziierte Risikofaktoren für niedrige DAOH identifiziert [14]. Aktuell fehlt für den HTX-Bereich eine dezidierte Analyse des Einflusses von präoperativen Risikofaktoren und postoperativen Komplikationen auf DAOH. Die zusätzliche Wertigkeit des Endpunkts für die Prognoseabschätzung nach HTX ist somit unklar.

Zusätzlich ist unter dem Gesichtspunkt der Organknappheit der Einfluss von kardiopulmonaler Reanimation des Organspenders auf DAOH zu beleuchten, auch wenn sich bezüglich der Mortalität hier keine Unterschiede zu zeigen scheinen [15,16]. In dieser Arbeit wurden diese Einflussfaktoren näher evaluiert [17].

1.2 Einfluss der Organdysfunktion auf den Krankheitsverlauf nach Herztransplantation und Identifikation assoziierter Risikofaktoren

1.2.1 Primäre Transplantatdysfunktion

Die primäre Transplantatdysfunktion oder „primary graft dysfunction“ (PGD) ist definiert als ein Versagen des transplantierten Herzens innerhalb der ersten 24 Stunden nach HTX und tritt mit einer Inzidenz von 20-25 % auf [18]. Man unterscheidet je nach betroffener Herzkammer zwischen linksventrikulärem, rechtsventrikulärem und biventrikulärem PGD [19]. Da es erst seit 2014 eine einheitliche Definition von PDG gibt, ist die Inzidenz der einzelnen Unterformen nicht flächendeckend beschrieben und variiert stark [20-23]. PGD ist mit einer schlechteren Prognose nach HTX vergesellschaftet, so scheint das Auftreten von PGD mit einer erhöhten 1-Jahres Mortalität einherzugehen und mit 66 % die führende Ursache für die frühe Mortalität nach 30 Tagen zu sein [19,24-26]. Risikofaktoren für PGD oder Mortalität scheinen unter anderem das Spenderalter, eine Geschlechtsinkongruenz, die präoperative mechanische Kreislaufunterstützung, die Diabeteserkrankung, das Empfängeralter, eine kardiale Voroperationen, eine linksventrikuläre Hypertrophie, die Ischämiezeit des Organs und die Zeit an der Herzlungenmaschinen zu sein [19,25]. Patient*innen die ein schweres PDG erleiden müssen in der Regel mittels mechanischer Kreislaufunterstützung (meistens ECMO) therapiert werden. Als maximalinvasives Verfahren ist die ECMO-Therapie jedoch auch mit periprozeduralen Risiken assoziiert, die den Krankheitsverlauf zusätzlich negativ beeinflussen können [18]. Interessanterweise zeigten mehreren frühere Arbeiten, dass Patient*innen die erfolgreich von der ECMO entwöhnt werden konnten ein ähnliches Langzeitüberleben aufweisen wie Patient*innen ohne PGD [27-29]. Daten für DAOH sind in diesem Kontext nicht vorhanden, es ist jedoch durchaus denkbar, dass sich durch die Invasivität der ECMO-Behandlung die Krankenhausaufenthaltsdauer verlängern könnte. Auch assoziierte Komplikationen wie beispielsweise neurologische Komplikationen und Therapie von Wundheilungsstörungen könnten Einfluss auf DAOH haben. In dieser Arbeit sollte der Einfluss der schweren PGD mit ECMO-Therapie auf DAOH und Mortalität von HTX Patient*innen untersucht werden.

1.2.2 Postoperative Nierenfunktionsstörung

Die akute Nierenschädigung (AKI) ist eine häufige und relevante Komplikation nach HTX [30,31]. So wird in einer aktuellen Übersichtsarbeit und Metaanalyse von Thongprayoon et al. die Inzidenz von AKI auf 62,8 % geschätzt. Zusätzlich zeigt diese Arbeit, dass die Notwendigkeit eines Nierenersatzverfahrens bei 11,8 % liegt [32]. Wie bei anderen chirurgischen Populationen bereits demonstriert, ist AKI auch nach HTX mit einem reduzierten Langzeitüberleben assoziiert [32,33]. Vor allem Patient*innen mit postoperativer Dialysepflichtigkeit wiesen im Vergleich zu Patient*innen ohne Dialysepflichtigkeit hier ein bis zu 5-fach erhöhtes Risiko auf im ersten Jahr nach HTX zu versterben [33]. Zusätzlich scheint AKI mit postoperativer Dialysepflichtigkeit bei kardiochirurgischen Patient*innen auch mit einer niedrigeren Lebensqualität über das erste postoperative Jahr hinaus einherzugehen [34]. In der Metaanalyse von Thongprayoon et al. wurden diverse Risikofaktoren dargestellt, die eine Assoziation mit dem Auftreten eines postoperativen AKI zeigten. Vornehmlich wurden in mehreren der analysierten Studien eine vorbestehende Einschränkung der Nierenfunktion, eine Diabeteserkrankung, ein höheres Empfängeralter, eine verlängerte Herzlungenmaschinenzeit, ein hoher Transfusionsbedarf, die Verwendung von Calcineurininhibitoren sowie das Rechtsherzversagen als assoziierte Risikofaktoren identifiziert. Vor allem die eingeschränkte präoperative Nierenfunktion wurde in 5 von 13 Studien, die Risikofaktoren berichtet haben angeführt, was die Relevanz dieses Patienten-assoziierten Risikofaktors unterstreicht [32]. Aber auch bei Patient*innen mit präoperativ erhaltener Nierenfunktion scheint eine postoperative Dialysepflichtigkeit vorzukommen. Risikofaktoren für das Auftreten eines schweren AKI nach HTX bei Patient*innen mit initial erhaltener Nierenfunktion sind jedoch nur unzureichend untersucht worden und wurden in dieser Arbeit analysiert und diskutiert.

1.3 Assoziation von postoperativen Biomarkern mit der 1-Jahres Mortalität und „Days alive and out of Hospital“ und deren Nutzen zur frühen postoperativen Risikostratifizierung

Aufgrund des Missverhältnisses zwischen Angebot und Bedarf an Spenderorganen ist eine effektive Strategie zur Patientenauswahl notwendig. Hier spielt die Optimierung der

perioperativen Risikostratifizierung und die Identifikation von Risikofaktoren eine große Rolle [35-37]. Es wurden in den letzten Jahren einige Risikoprädiktionsmodelle vorgestellt die Kliniker*innen bei der Entscheidungsfindung unterstützen sollen. Ihr klinischer Nutzen ist aufgrund von unzureichender Diskriminationsfähigkeit in externen Kohorten jedoch fraglich [36]. In diesem Kontext wurde der „Index for Mortality Prediction After Cardiac Transplantation“ (IMPACT) Score entwickelt [38,39]. Auch dieser zeigte in einigen Kohorten unzureichende prädiktive Leistungen [40-42] . Biomarker könnten die prädiktive Leistung dieser Modelle und somit auch die Risikostratifizierung verbessern.

1.3.1 Postoperatives kardiales Troponin

Kardiales Troponin ist ein Biomarker der bei myokardialem Zelluntergang freigesetzt wird. Die perioperative Freisetzung von kardialem Troponin ist in ihrer Ätiologie multifaktoriell und noch nicht gänzlich verstanden [43,44]. Bei kardiochirurgischen Patient*innen ist die Höhe der Freisetzung von kardialem Troponin unabhängig mit einem erhöhten Risiko für Mortalität assoziiert, wie eine aktuelle Studie von Devereaux et al. zeigte [46]. Die Datenlage zur Assoziation einer postoperativen Freisetzung von kardialem Troponin nach HTX mit der 1-Jahres-Mortalität und DAOH ist noch unzureichend, wie in einer Metaanalyse von Liu et al. dargestellt [47]. So zeigte sich zwar ein Zusammenhang zwischen postoperativer Troponinerhöhung und PGD, die 3 eingeschlossenen Studien, die die Mortalität als Endpunkt untersuchten, variierten jedoch stark im Studiendesign, in den Zeitpunkten der Troponinbestimmung und in der Dauer der Nachverfolgungsperiode [47]. Daten zu DAOH und anderen patientenzentrierten Endpunkten wurden nicht untersucht. Die vorliegende Arbeit hat den Nutzen von Troponin als frühen Biomarker zur Risikostratifizierung evaluiert.

1.3.2 Postoperatives Serumalbumin

Das Auftreten einer postoperativen Hypoalbuminämie ist nach kardiochirurgischen Operationen unter Verwendung der Herzlungenmaschine häufig und wird durch intraoperativen Blutverlust, Hämodilution, inflammatorische Antwort und Kapillarleck beeinflusst [48]. Vorherige Studien bei kardiochirurgischen Patient*innen zeigten eine

Assoziation von postoperativer Hypoalbuminämie und verringertem Kurz- und Langzeitüberleben [48,49]. So zeigten Berbel-Franco et al. in einer Kohorte von 2.818 Patient*innen, die sich einem kardiochirurgischen Eingriff mit Verwendung der Herzlungenmaschine unterzogen haben, dass normale postoperative Albuminwerte mit einem höheren 5-Jahres Überleben einhergingen. Reduzierte Albuminwerte waren hingegen je nach Schwere der Hypoalbuminämie mit einem erhöhten Mortalitätsrisiko assoziiert. Die Analyse wies nach, dass je niedriger der Albuminwert, desto höher das Mortalitätsrisiko, wobei das Risiko ab postoperativen Albuminwerten unter 2,5 g/dl markant anstieg [48]. Bei HTX Patient*innen ist zusätzlich die präoperative Einschränkung der Leberfunktion mit dem postoperativen Mortalitätsrisiko assoziiert. Aus diesem Grund enthalten viele Risiko-Scores (z.B. der IMPACT Score) auch Parameter der Leberfunktion [38,39]. Der „Model for endstage liver disease“ (MELD) Score wurde unter diesem Aspekt auch schon zur Risikoprädiktion nach HTX verwendet [50]. Albumin ist ein Biomarker, der bei eingeschränkter Leberfunktion ebenfalls erniedrigt vorliegen kann. Frühere Untersuchungen bei HTX und Patient*innen mit Herzinsuffizienz deuten darauf hin, dass präoperativ niedrige Albuminwerte allein oder in Kombination mit dem MELD Score prädiktiv für ein schlechtes Langzeitergebnis sein können [51,5253,54]. Die Rolle einer früh-postoperativen Albuminmessung für die Risikostratifizierung nach HTX wurde jedoch bisher nur unzureichend untersucht. Diese Arbeit hat die Assoziation einer postoperativen Hypoalbuminämie mit DAOH und der 1-Jahres Mortalität untersucht. Zusätzlich wurde der prädiktive Nutzen einer kombinierten Betrachtung von Albumin und MELD Score bzw. IMPACT Score evaluiert.

1.4 Ziele und Fragestellungen der Arbeit

In der vorliegenden kumulativen Habilitationsschrift sollen folgende Fragestellungen beantwortet werden:

1. Welche prä-, intra- und postoperativen Faktoren haben signifikanten Einfluss auf den patientenzentrierten Endpunkt DAOH nach HTX?

2. Hat der CPR-Status des Spenderorgans Einfluss auf die Mortalität oder DAOH nach HTX?
3. Welchen Einfluss hat die PGD mit VA-ECMO Therapie auf die Mortalität und DAOH nach HTX?
4. Wie hoch ist die Inzidenz einer postoperativen Dialysepflichtigkeit nach HTX bei Patient*innen mit präoperativ erhaltener Nierenfunktion und was sind assoziierte Risikofaktoren?
5. Ist postoperativ gemessenes Troponin mit der Mortalität oder DAOH nach HTX assoziiert und kann ein etabliertes Risikoprädiktionsmodell (IMPACT-Score) durch die Ergänzung von Troponin verbessert werden?
6. Ist postoperativ gemessenes Albumin mit der Mortalität oder DAOH nach HTX assoziiert und kann ein etabliertes Risikoprädiktionsmodell (MELD-Score) durch die Ergänzung von Albumin verbessert werden?

2 Methoden:

Dieses Kapitel fasst die Untersuchungsmethoden, die in den Originalpublikationen zur Anwendung gekommen sind zusammen.

2.1 Studiendesigns

Alle hier beschriebenen Originalarbeiten sind retrospektive Kohortenstudien.

2.2 Patientenkohorte

Für alle in den Originalarbeiten beschriebenen Untersuchungen wurden Patient*innen eingeschlossen, die älter als 18 Jahre waren und sich am Universitätsklinikum Düsseldorf einer HTX-Operation zwischen den Jahren 2010 und 2023 unterzogen haben, wobei je nach Untersuchung nicht die Gesamtkohorte von 2010 bis 2023 zur Anwendung kam. Diesbezügliche Details werden im Folgenden beschrieben.

2.3 Datenkollektion und Datenextraktion

Die Klinik für Herzchirurgie des Universitätsklinikum Düsseldorf führt seit dem Jahr 2010 eine prospektive Datenbank über alle Patient*innen die sich am Standort Düsseldorf einer Herztransplantation unterzogen haben. Die Datenbank umfasst über 200 Variablen und dient der Nachverfolgung und der postoperativen Verlaufsdokumentation der Patient*innen. Alle in der Datenbank erfassten Patient*innen gaben im Voraus Ihr Einverständnis zur prospektiven Erfassung ihrer Daten in pseudonymisierter Form. Es wurde im Vorfeld ein Ethikvotum bei der Ethikkommission Düsseldorf (Referenznummer 4567) eingeholt. Die Datenspeicherung auf einem lokalen Klinikrechner entspricht den aktuellen Datenschutzrichtlinien. Die in den Originalpublikationen analysierten Daten wurden aus der oben beschriebenen Datenbank extrahiert. Die Datenbank wurde für diese Analysen um einige Variablen erweitert. Die in der Datenbank enthaltenen Daten wurden aus der Patientenverlaufsdokumentation entnommen und durch Mitarbeiter*innen der Klinik für Herzchirurgie fortlaufend aktualisiert. Die Werte der zusätzlichen Variablen wurden aus der digitalen Patientenakte (Medico-System) des Universitätsklinikums Düsseldorf extrahiert.

2.4 Studienprotokolle

2.4.1 Validierung von „Days alive and out of hospital" als patientenzentrierten Endpunkt nach Herztransplantation.

In der ersten Arbeit planten wir den Endpunkt „days alive and out of hospital" (DAOH) nach HTX zu charakterisieren und assoziierte Faktoren zu identifizieren. Wir schlossen hierzu HTX Patient*innen im Zeitraum von 2010 bis 2020 ein. Patient*innen mit fehlenden Daten für die Endpunkte wurden von der Analyse ausgeschlossen. Der primäre Endpunkt waren die DAOH innerhalb des ersten Jahres nach HTX. Die Erhebung der DAOH erfolgte wie bereits zuvor beschrieben. Die unabhängigen Variablen wurden literaturbasiert ausgewählt. Hierfür wurde eine Metaanalyse von Foroutan et al. verwendet, die Risikofaktoren für die 1-Jahres Mortalität charakterisiert hatte [7]. Es resultierten folgende, in unserer Datenbank verfügbaren prä- und postoperative Faktoren, die in die Analyse mit einbezogen werden konnten: Alter, Geschlecht, kardiale Grunderkrankung, Diabeteserkrankung, geschätzte glomeruläre Filtrationsrate

(eGFR), arterielle Hypertonie, Body-Mass-Index (BMI), pulmonale Hypertonie, Zytomegalie-Virus (CMV)-Status, und eine frühere Herz-Thorax-Operationen und das Vorhandensein eines linksventrikuläres Unterstützungssystem bei Empfänger*innen, sowie Alter, Geschlecht, und Diabeteserkrankung der Spender*innen. Zusätzlich wurden die Variablen Geschlechtsinkongruenz zwischen Spender*innen und Empfänger*innen, gesamte Ischämie, postoperative Nierenersatztherapie, Dauer der postoperativen mechanischen Beatmung und die postoperative Verwendung der veno-arteriellen extrakorporalen Membranoxygenierung (VA-ECMO) einbezogen. Die Zusammenhänge dieser Variablen mit den DAOH wurden zunächst univariat untersucht. Variablen mit signifikanter Assoziation wurden dann in ein multivariates quantiles Regressionsmodell eingespeist und die unabhängige Assoziation wurde für jedes Quantil einzeln dargestellt. Der Fokus lag dabei auf der Assoziation von Variablen im zehnten und zwanzigsten DAOH-Quantil, da diese Gruppe besonders stark in ihrem Alltag betroffen ist. Als Sensitivitätsanalyse wurden die univariaten Zusammenhänge zwischen den unabhängigen Variablen und den DAOH nochmals unter Ausschluss der verstorbenen Patient*innen untersucht. [17]

2.4.2 Einfluss der kardiopulmonalen Reanimation von Spendern auf „Days alive and out of hospital“ nach Herztransplantation.

Die zweite Arbeit beschäftigte sich mit dem Einfluss der vorherigen kardiopulmonalen Reanimation (CPR) von Organspender*innen auf die DAOH nach HTX als potenziellen Faktor der die Organqualität beeinflussen könnte. Diese Analyse stellte damit eine komplementäre Analyse zur Validierung von DAOH nach HTX dar. Wir schlossen hierzu wieder HTX Patient*innen im Zeitraum von 2010 bis 2020 ein. Der primäre Endpunkt der Arbeit war wiederum DAOH innerhalb des ersten Jahres nach HTX. Die Kohorte wurde basierend auf dem CPR-Status der Organspender*innen in zwei Gruppen unterteilt. Als sekundäre Variable wurde zusätzlich die Reanimationsdauer in der CPR-Gruppe in einer Subgruppenanalyse untersucht. Univariate Unterschiede der DAOH wurden zwischen den beiden Gruppen mittels Mann-Whitney U Test exploriert. In der CPR-Gruppe wurden die Patient*innen auf Basis der CPR Dauer in Quartile unterteilt (<9 Minuten, 9-14 Minuten, 15-21 Minuten und >21 Minuten).

Die Unterschiede der DAOH in den Subgruppen wurden mittels Kruskal Wallis Test untersucht. Zusätzlich wurde ein multivariates lineares Regressionsmodell verwendet, um den Einfluss der CPR-Dauer auf die DAOH darzustellen, indem für die Kovariablen Spenderalter, Beatmungsdauer und Nierenersatzverfahren adjustiert wurde. Eine Überlebensanalyse wurde zwischen der CPR- und nicht CPR-Gruppe mittels Kaplan-Meier Kurve durchgeführt. [55]

2.4.3 Einfluss einer VA-ECMO Therapie auf den Krankheitsverlauf von Patient*innen mit primärem Transplantatversagen.

In dieser Arbeit untersuchten wir den Einfluss einer VA-ECMO Therapie auf den Krankheitsverlauf von Patient*innen mit primärem Transplantatversagen in Bezug auf die Mortalität und Tage der Hospitalisierung innerhalb des ersten Jahres nach Herztransplantation. Der Beobachtungszeitraum belief sich auf die Jahre 2010 bis 2020. Eine VA-ECMO Therapie aufgrund von frühem Transplantatversagen wurde definiert als VA-ECMO Therapiebeginn <24 Stunden nach HTX. Das Patientenkollektiv wurde demnach in eine VA-ECMO Gruppe und eine Kontrollgruppe aufgeteilt. In die VA-ECMO Gruppe wurde zusätzlich noch eine Subgruppe der erfolgreich entwöhnten Patient*innen eingeführt. Eine erfolgreiche Entwöhnung wurde definiert als erfolgreicher Ausbau der VA-ECMO während des initialen Krankenhausaufenthaltes. Patient*innen mit fehlenden Daten bezüglich der Endpunkte, Patient*innen mit initialer VV-ECMO Therapie sowie Patient*innen die während der HTX-Operation verstorben sind wurden von der Analyse ausgeschlossen. Der primäre Endpunkt dieser Studie waren die DAOH innerhalb des ersten Jahres nach HTX. Diese wurden berechnet, indem die Krankenhausaufenthaltstage addiert und von 365 Tagen subtrahiert wurden. Falls das Individuum im ersten Jahr nach HTX verstorben ist wurde die Differenz der überlebten Tage zu 365 Tagen vor der Subtraktion zu den im Krankenhaus verbrachten Tagen addiert. Die sekundären Endpunkte der Studie waren 1-Jahres Mortalität, Dauer der Hospitalisierung innerhalb des ersten Jahres und die Gründe der Hospitalisierungen. Hospitalisierung wurde definiert als geplanter oder ungeplanter Krankenhausaufenthalt von mindestens 24 h innerhalb des ersten Jahres nach HTX. Hospitalisierungsgründe wurden in die folgenden 10 Kategorien unterteilt: Gastrointestinale Störungen, Pneumonie /

Atemwegsinfektionen, Wundinfektionen, Nierenfunktionsstörungen, Transplantatabstoßung, Blutungskomplikationen, nicht-kardiochirurgische Operationen, andere Infektionen, geplante Endomyokardbiopsie sowie primärer Krankenhausaufenthalt bei HTX. Primäre und sekundäre Endpunkte wurden zwischen Patient*innen mit und ohne primärem Transplantatversagen verglichen. [56]

2.4.4 Risikofaktoren für eine akute Nierenschädigung mit Dialysepflichtigkeit nach Herztransplantation bei Patient*innen mit präoperativ erhaltener Nierenfunktion

In der vierten Arbeit untersuchten wir Risikofaktoren für eine schwere akute Nierenschädigung bei Patient*innen mit präoperativ erhaltener Nierenfunktion. Wir schlossen Patient*innen im Zeitraum von 2010 bis 2021 ein, die eine erhaltene Nierenfunktion vor der Operation aufwiesen. Diese war definiert als glomeruläre Filtrationsrate (GFR) ≥ 60 ml/min und wurde mit Hilfe der „Chronic Kidney Disease Epidemiology Collaboration" (CKD-EPI) Formel aus der Kreatinin-Clearance am Operationstag berechnet. Alle Patient*innen mit GFR ≤ 60 ml/min oder mit vorbestehender Dialysepflichtigkeit oder vorbestehender akuter Nierenschädigung, sowie Patient*innen mit fehlenden Werten zur GFR oder den Endpunkten wurden von der Analyse ausgeschlossen. Der primäre Endpunkt der Studie war das Auftreten einer akuten Nierenschädigung mit Dialysepflichtigkeit innerhalb der ersten 72 Stunden postoperativ. Die Assoziation von Variablen aus der Datenbank zum primären Endpunkt wurden mittels univariater logistischer Regression untersucht. Univariat signifikante Variablen mit plausiblem pathophysiologischem Bezug zur akuten Nierenschädigung wurden dann in ein multivariates logistisches Regressionsmodell eingefügt. [57]

2.4.5 Prädiktiver Wert von hochsensitivem Troponin T für Mortalität und „Days alive and out of hospital" nach Herztransplantation.

Die fünfte Arbeit beschäftigte sich mit der Frage, ob die postoperative Freisetzung von hochsensitivem Troponin T zur frühen Risikostratifizierung nach HTX verwendet werden kann. Hierzu wurden Patient*innen aus der HTX Datenbank im Zeitraum von 2010 und 2021 eingeschlossen. Der primäre Endpunkt der Arbeit war die 1-Jahres Mortalität. Der sekundäre

Endpunkt der Studie war DAOH im ersten Jahr nach HTX. Die Troponinwerte wurden postoperativ zu vier verschiedenen Zeitpunkten erfasst: 12 Stunden, 24 Stunden, 48 Stunden und 72 Stunden. Als präoperatives klinisches Risikomodell, welches für die 1-Jahres Mortalität validiert ist, wurde der "index for mortality prediction after cardiac transplantation“ (IMPACT-Score) für alle Patient*innen berechnet. Dieser enthält folgende Variablen: Alter, Bilirubin, glomeruläre Filtrationsrate (GFR), Dialysepflichtigkeit, Geschlecht, Genese der Herzinsuffizienz, präoperative Infektion, Ethnie, mechanische Kreislaufunterstützung und Modell des Linksherzunterstützungssystems. Die Troponinwerte zu den einzelnen Zeitpunkten wurden zwischen Überlebenden und Verstorbenen Patient*innen mittels t-Tests verglichen. Die Diskriminationsfähigkeit der Troponinwerte für die 1-Jahres Mortalität wurde mittels Fläche unter der Grenzwertoptimierungskurve (ROC-AUC) untersucht. Der Grenzwert der ROC-AUC mit der besten Diskriminationsfähigkeit wurde mittels Youden-Index festgelegt. Dieser Grenzwert wurde dann in einem logistischen Regressionsmodell für den IMPACT-Score adjustiert. Die Verbesserung der Risikostratifizierung des IMPACT-Scores durch das Hinzufügen des Troponinwertes wurde mittels Netto-Reklassifizierungsverbesserung (NRI) und absolutem Netto-Reklassifizierungsindex (NARI) untersucht. Die ROC-AUCs der beiden Modelle wurden mittels Delong-Tests verglichen. Um den Vorteil des neuen Modells in der Risikoprädiktion darzustellen wurde eine Entscheidungskurvenanalyse durchgeführt. DAOH wurden für Patient*innen mit Troponinwerten über und unter dem errechneten Grenzwert dargestellt und verglichen. Um die unabhängige Assoziation des Troponin Grenzwertes mit den DAOH zu untersuchen, wurde eine multivariate lineare Regression mit Adjustierung für den IMPACT-Score verwendet. [58]

2.4.6 Assoziation der frühen postoperativen Hypoalbuminämie mit dem Krankheitsverlauf nach Herztransplantation.

In der letzten Arbeit untersuchten wir, ob niedrige Albuminwerte mit einem schwereren Krankheitsverlauf nach Herztransplantation assoziiert sind. Hierzu wurden Patient*innen aus der HTX Datenbank im Zeitraum von 2010 bis 2022 eingeschlossen. Es wurden die Albuminwerte der Patient*innen innerhalb der ersten 12 h nach HTX erfasst. Als klinische

Risikomodelle wurden der präoperative IMPACT-Score sowie der postoperative „Model for endstage liver disease“ (MELD) Score berechnet. Der primäre Endpunkt der Untersuchung war die 1-Jahres Mortalität. Als sekundärer Endpunkt wurden die DAOH untersucht. Um den prognostischen Wert von postoperativem Albumin für die 1-Jahres Mortalität zu untersuchen, wurde die ROC-AUC verwendet und ein Grenzwert mittels Youden-Index berechnet. Kaplan-Meier Kurven wurden erstellt für Patient*innen mit Albuminwerten über und unter dem errechneten Grenzwert. Ein multivariates logistisches Regressionsmodell wurde erstellt in dem die Assoziation von postoperativem Albumin mit der 1-Jahres Mortalität für vorher identifizierte Risikofaktoren adjustiert wurde. Um zu untersuchen, ob die Erhebung von postoperativen Albuminwerten die Risikostratifizierung durch den IMPACT-Score und den MELD-Score für die 1-Jahres Mortalität verbessern kann, wurden NRI und NARI berechnet. Die Diskrimination der Modelle mit und ohne Albumin wurde durch ROC-AUC dargestellt und mittels Delong-Test verglichen. Die DAOH von Patient*innen mit Albuminwerten über und unter dem errechneten Grenzwert wurden mittels Mann-Whitney U Test verglichen. In einem quantilen Regressionsmodell wurde die Assoziation von postoperativem Albumin mit DAOH, unter Adjustierung von klinischen Risikofaktoren multivariat untersucht. Hier wurde dann der Einfluss in den 10 % der Patient*innen mit den niedrigsten DAOH dargestellt. [59]

3 Ergebnisse:

3.1 Charakterisierung von „days alive and out of hospital” nach Herztransplantation und assoziierte Risikofaktoren

3.1.1 Validierung von „Days alive and out of hospital” als patientenzentrierten Endpunkt nach Herztransplantation.

In dieser Untersuchung wurden gemäß der Einschlusskriterien 175 HTX Patient*innen eingeschlossen. Das Durchschnittsalter der Kohorte war 54 ± 11 Jahre darunter 134 männliche Patienten (76,6 %). Im Median hatten die Patient*innen im ersten Jahr nach HTX 295 [223-322, (25 % bis 75 % Quartil)] DAOH. Die 1-Jahres Mortalität betrug 18,3 % (32 Patient*innen). Von diesen Patient*innen verstarben 11 außerhalb des Krankenhauses, daher konnte die

Todesursache retrospektiv nicht eruiert werden. Im Krankenhaus verstarben 21 Patien*innen, darunter 8 an schwerer Sepsis, 3 an intrakranieller Blutung, 3 an Mesenterialischämie, 2 an Transplantatversagen, 3 an zerebraler Hypoxie, 1 an Blutungskomplikationen, und 1 Patient verstarb im Multiorganversagen.

Zunächst wurde die univariate Assoziation zwischen 13 dichotomen Variablen mit DAOH untersucht. Als präoperative dichotome Variablen zeigte eine Diabeteserkrankung sowohl der Spender*innen als auch der Empfänger*innen einen signifikanten Zusammenhang mit reduzierten DAOH [Diabeteserkrankung Empfänger*innen: 303 (247–323) Tage vs. 272 (97–293) Tage p-Wert = 0,0314; Diabeteserkrankung Spender*innen: 308 (229–323) Tage vs. 211 (65–303) Tage p-Wert = 0,0329]. Als postoperative Variablen zeigten die Nierenersatztherapie und die VA-ECMO Therapie einen negativen Einfluss auf DAOH [Nierenersatztherapie: 316 (295–329) Tage vs. 267 (75–305) Tage p-Wert < 0,0001; VA-ECMO: 309 (273–327) Tage vs. 243 (0–290) Tage p-Wert < 0,0001].

Zusätzlich wurde die univariate Assoziation von 6 kontinuierlichen Variablen mit DAOH untersucht. Von diesen Variablen zeigten die GFR der Empfänger*innen, der BMI der Empfänger*innen und die postoperative Beatmungsdauer eine signifikante Assoziation mit DAOH [GFR: < 45 ml/min = 260 (90–303) Tage vs. 45-62 ml/min = 289 (226–317) Tage vs. 63-80 ml/min = 310 (255–329) Tage vs. > 80 ml/min = 311 (210–329) Tage; p-Wert = 0,01; BMI: < 19 kg/m2 = 282 (159–332) Tage vs. 19–25 kg/m2 = 308 (253–327) Tage vs. 25–29 kg/m2 = 290 (228–317) Tage vs. > 30 kg/m2 = 250 (23–295) Tage; p-Wert = 0,011 Beatmungsdauer: < 28 Stunden = 318 (299–334) Tage vs. 28–78 Stunden = 311 (285–326) Tage vs. 78–182 Stunden = 289 (229–311) Tage vs. > 182 Stunden = 199 (0–277) Tage; p-Wert < 0,0001]. Interessanterweise zeigte sich kein signifikanter Einfluss des Patientenalters von Organspender*innen oder -empfänger*innen auf DAOH trotz visuell erkennbarem Trend im Balkendiagramm.

Eine Sensitivitätsanalyse der univariaten Assoziationen unter Ausschluss der Verstorbenen Patient*innen wurde durchgeführt um zu prüfen, ob die Assoziationen nicht primär durch die

1-Jahres Mortalität beeinflusst wurden. Die meisten Assoziationen zeigten sich unverändert, nur die Diabeteserkrankung der Organspender*innen war nicht mehr signifikant mit DAOH assoziiert. Zusätzlich zeigte sich nun auch kein visueller Trend mehr für die Assoziation von Spender- und Empfängeralter mit DAOH.

Alle univariat assoziierten Variablen wurden schließlich in einem multivariaten quantilen Regressionsmodell untersucht. Hierbei wurden unabhängige Assoziationen zu DAOH in der zehnten und der zwanzigsten Perzentile untersucht. Die Werte für das pseudo-R^2 des finalen Modells waren 0,39 und 0,41 für die selektierten Quantile. In diesem Modell zeigten die Diabeteserkrankung der Empfänger*innen, die präoperative GFR, die Beatmungsdauer und die postoperative Nierenersatztherapie eine unabhängige Assoziation mit niedrigen DAOH.

3.1.2 Einfluss der kardiopulmonalen Reanimation der Organspender*innen auf die „days alive and out of hospital“ der Organempfänger*innen

In diese Analyse konnten 171 HTX Patient*innen mit vollständigen DAOH- und CPR-Daten eingeschlossen werden. Von diesen Patient*innen erhielten 42 (24,6 %) Organe von reanimierten Organspender*innen. Das Durchschnittsalter der Kohorte betrug 54 ± 11 Jahre und 43 % waren Frauen. Im Median betrugen die DAOH im ersten Jahr 295 (206–322) Tage und die 1-Jahresmortalität betrug 18,7 %. Die mediane CPR-Dauer von Organspender*innen der CPR-Gruppe betrug 15 (9–21) Minuten. Es gab keinen signifikanten Unterschied bezüglich der DAOH zwischen der Kontrollgruppe und der CPR-Gruppe [Kontrollgruppe: 295 (215–324) Tage vs. CPR-Gruppe: 291 (211–318) Tage; p-Wert = 0,619]. In der Subgruppenanalyse der Patient*innen, die ein Herz von einem reanimierten Spender*innen erhielten, zeigte sich ebenfalls kein Einfluss der Reanimationsdauer auf die Anzahl an DAOH. Auch in der multivariaten linearen Regressionsanalyse zeigte sich kein signifikanter Zusammenhang zwischen CPR-Dauer und DAOH (Regressionskoeffizient: −0,06, Standard Fehler : 0,81, 95 % Konfidenzintervall −1,65 bis 1,53, p-Wert = 0,943), während andere Risikofaktoren eine unabhängige signifikante Assoziation mit DAOH aufwiesen (Alter der Spender*innen: Regressionskoeffizient: −2,26, Standard Fehler : 0,61, 95 % Konfidenzintervall −3,47 bis -

1,05, p-Wert <0,0001; Beatmungsdauer: Regressionskoeffizient: −0,23, Standard Fehler : 0,04, 95 % Konfidenzintervall −0,32 bis -0,14, p-Wert <0,0001; Nierenersatztherapie: Regressionskoeffizient: −50,84, Standard Fehler : 17,18, 95 % Konfidenzintervall −84,76 bis -16,91, p-Wert = 0,004). Die Analyse der 1-Jahres Mortalität ergab keinen Unterschied zwischen der Kontrollgruppe und der CPR-Gruppe [CPR Gruppe = 79,9 % versus Kontrollgruppe = 85,8 %; HR = 1,39 (95 % Konfidenzintervall 0,62 bis 3,10, p-Wert = 0,41].

3.2 Inzidenz einer postoperativen Organdysfunktion bei Patient*innen nach Herztransplantation und ihr Einfluss auf den postoperativen Verlauf

3.2.1 Einfluss der VA-ECMO Therapie aufgrund von primärem Transplantatversagen auf den postoperativen Verlauf

Insgesamt wurden die Daten von 144 HTX Patient*innen analysiert. Das mittlere Alter dieser Kohorte war 54 ± 12 Jahre und 114 Patienten (79,2 %) waren männlichen Geschlechts. Insgesamt erlitten 46 Patient*innen ein primäres Transplantatversagen, das eine VA-ECMO Therapie notwendig machte. Von diesen Patient*innen wiesen 30 (65,2 %) ein biventrikuläres Pumpversagen auf, während 16 Patient*innen (34,8 %) ein isoliertes rechtsventrikuläres Pumpversagen hatten. Aus der VA-ECMO Gruppe konnten 34 von 46 Patient*innen (80,4 %) erfolgreich von der VA-ECMO entwöhnt werden. Die mittlere Dauer der VA-ECMO Therapie betrug 8 ± 7 Tage. Die Patient*innen der VA-ECMO Gruppe waren signifikant älter, wiesen eine höhere Prävalenz von Diabetes mellitus, längere Zeiten an der Herzlungenmaschine (HLM), höhere postoperative Dialyseraten, eine höhere Anzahl an neurologischen Komplikationen, höhere Revisionsoperationsraten und eine längere primäre Krankenhausverweildauer auf.

Die Gesamtmortalitätsrate der Kohorte betrug 20,8 % im ersten Jahr nach HTX, wobei Patient*innen mit VA-ECMO Therapie eine signifikant höhere Mortalitätsrate zeigten [Kontrollgruppe 14,3 % (14/98) vs. VA-ECMO Gruppe 34,8 % (16/46), HR: 0,32, 95 % Konfidenzintervall: 0,15–0,74; p-Wert = 0,002]. Jedoch konnte kein signifikanter Unterschied zwischen Patient*innen ohne VA-ECMO Therapie und erfolgreich entwöhnten VA-ECMO

Patient*innen im ersten Jahr nach HTX beobachtet werden [Kontrollgruppe 14,3 % (14/98) vs. VA-ECMO Gruppe (entwöhnt) 18,9 % (7/37), HR: 0,72, 95 % Konfidenzintervall: 0,27–1,90; p-Wert = 0,48].

Im Median betrugen die DAOH im Gesamtkollektiv 293 (224–321) Tage. Patient*innen ohne VA-ECMO Therapie hatten signifikant höhere DAOH im ersten Jahr nach HTX im Vergleich zur VA-ECMO Gruppe [Kontrollgruppe vs. VA-ECMO Gruppe: 310 (277–327) Tage vs. 243 (0–288) Tage; p-Wert < 0,0001]. Im Vergleich zu erfolgreich entwöhnten VA-ECMO Patient*innen zeigte die Kontrollgruppe ebenfalls höhere DAOH [Kontrollgruppe vs. VA-ECMO Gruppe (entwöhnt): 310 (277–327) Tage vs. 253 (208–299) Tage; p-Wert < 0,0001]. In einer Sensitivitätsanalyse für eine alternative Definition von DAOH waren die Ergebnisse vergleichbar.

In einem linearen Regressionsmodell adjustierten wir den Effekt von VA-ECMO Therapie auf DAOH für die Kovariablen Alter, Operationsdauer, postoperative Dialyse und neurologische Komplikationen. In diesem Modell zeigten die VA-ECMO Therapie sowie neurologische Komplikationen einen unabhängigen signifikanten Zusammenhang mit DAOH (VA-ECMO Therapie - Regressionskoeffizient: −54,10, Standard Fehler: 22,19, 95 % Konfidenzintervall -97,99 bis -10,22, p-Wert = 0,016; Neurologische Komplikationen - Regressionskoeffizient: −91,14, Standard Fehler: 24,78, 95 % Konfidenzintervall −140,15 bis −42,13, p-Wert = 0,0003).

3.2.2 Risikofaktoren für eine schwere Nierenfunktionsstörung nach Herztransplantation bei Patient*innen mit präoperativ erhaltener Nierenfunktion

Von 206 HTX Patient*innen wiesen 107 eine präoperativ erhaltene Nierenfunktion gemäß Einschlusskriterien auf und konnten in die Analyse eingeschlossen werden. Das Durchschnittsalter der Kohorte betrug 52 ± 12 Jahre und 84 Patienten (78,5 %) waren männlich. Postoperativ erlitten 49 Patient*innen (45,8 %) eine schwere Nierenfunktionsstörung, die eine postoperative Dialyse innerhalb der ersten 72 Stunden nach HTX notwendig machte.

In einer univariaten Analyse untersuchten wir den Zusammenhang von 41 Variablen aus der HTX-Datenbank mit einer schweren postoperativen Nierenfunktionsstörung. Die folgenden 9 Variablen waren signifikant univariat mit dem primären Endpunkt assoziiert: Eine postoperative VA-ECMO Therapie (OR 5,12, 95 % Konfidenzintervall: 2,07–12,67, p-Wert = 0,0004), eine postoperative Infektion (OR 3,60, 95 % Konfidenzintervall: 1,27–10,22, p-Wert = 0,016), eine postoperative Levosimendan Therapie (OR 6,27, 95 % Konfidenzintervall: 2,09–18,79, p-Wert = 0,001), die postoperative Dauer der Noradrenalin Therapie in Stunden (OR 1,01, 95 % Konfidenzintervall: 1,00–1,02, p-Wert = 0,002), die Anzahl der postoperativ verabreichten Blutprodukte (OR 1,00, 95 % Konfidenzintervall: 1,00–1,00, p-Wert = 0,0004), die Dauer des Intensivaufenthalts (OR 1,04, 95 % Konfidenzintervall: 1,01–1,08, p-Wert = 0,008), die postoperative Beatmungsdauer in Stunden (OR 1,02, 95 % Konfidenzintervall: 1,01–1,02, p-Wert < 0,0001), der Tacrolimus Spitzenspiegel im Plasma innerhalb der ersten 72 Stunden (OR 1,15, 95 % Konfidenzintervall: 1,03–1,27, p-Wert = 0,011) und der maximale tägliche Anstieg des Tacrolimus Plasmaspiegels innerhalb der ersten 72 Stunden nach HTX (OR 1,14, 95 % Konfidenzintervall: 1,01–1,29, p-Wert = 0,041).

Basierend auf einer Literaturrecherche wurden folgende dieser univariat signifikanten Variablen in einem multivariaten logistischen Regressionsmodell weiter analysiert: Die VA-ECMO, die postoperative Infektion, die Levosimendan Therapie, die Dauer der Noradrenalin Therapie und der Anstieg des Tacrolimus Plasmaspiegels. Die Anzahl der eingeschlossenen Variablen musste aufgrund der Stichprobengröße eingeschränkt werden. In diesem Modell zeigten die Dauer der Noradrenalin Therapie (OR 1,01, 95 % Konfidenzintervall: 1,00–1,02, p-Wert = 0,005), sowie der maximale Anstieg des Tacrolimus Plasmaspiegels (OR 1,18, 95 % Konfidenzintervall: 1,01–1,37, p-Wert = 0,036) eine unabhängige signifikante Assoziation mit dem Auftreten einer postoperativ dialysepflichtigen Nierenfunktionsstörung, während die anderen Variablen trotz starker univariater Assoziation nach Adjustierung nicht mehr signifikant mit einer Dialysepflichtigkeit assoziiert waren.

3.3 Der prognostische Wert von Biomarkern nach Herztransplantation

3.3.1 Prognostischer Wert von hochsensitivem postoperativen Troponin-T nach Herztransplantation.

Insgesamt wurden 212 HTX Patient*innen in die finale Analyse eingeschlossen. Das durchschnittliche Alter betrug 55 ± 11 Jahre. Die 1-Jahres Mortalität in der Kohorte betrug 19 % (40 Patient*innen). Im Median betrugen die DAOH in der Kohorte 298 Tage (229–322). Die präoperativen Troponin-Werte unterschieden sich nicht signifikant zwischen den überlebenden und verstorbenen Patient*innen [165 ± 687 ng/L vs. 228 ± 906 ng/L, p-Wert = 0,638]. Im Gegensatz dazu waren die Troponin-Werte bei verstorbenen Patient*innen nach 12, 24, 48 und 72 Stunden signifikant höher als bei Patient*innen, die im ersten Jahr nach HTX überlebten [12 Stunden: 5089 ± 5305 ng/L vs. 7972 ± 7419 ng/L, p-Wert = 0,005; 24 Stunden: 3309 ± 2934 ng/L vs. 7266 ± 7942 ng/L, p-Wert ≤ 0,0001; 48 Stunden 1911 ± 1598 ng/L vs. 5115 ± 5196 ng/L, p-Wert ≤ 0,0001; 72 Stunden: 1363 ± 1565 ng/L vs. 3651 ± 4126 ng/L, p-Wert ≤ 0,0001]. Zu allen postoperativen Messzeitpunkten zeigte Troponin eine signifikante Diskriminationsfähigkeit für die 1-Jahres Mortalität nach HTX in der ROC-AUC Analyse, wobei die Messung 48 h nach HTX die beste Diskrimination aufwies [12 Stunden ROC-AUC = 0,66, 95 % Konfidenzintervall 0,56–0,75; 24 Stunden ROC-AUC = 0,74, 95 % Konfidenzintervall 0,66–0,82; 48h ROC-AUC = 0,79, 95 % Konfidenzintervall 0,71–0,87; 72 Stunden ROC-AUC = 0,77, 95 % Konfidenzintervall 0,68–0,86]. Der berechnete Troponin Grenzwert für die beste Sensitivität und Spezifität lag bei 1640 ng/L.

In einem binären logistischen Regressionsmodell zeigte sich nach Adjustierung für den IMPACT-Score eine unabhängige Assoziation des Troponin Grenzwertes nach 48h mit der 1-Jahres Mortalität [Troponin 48 Stunden—OR 8,10 95 % Konfidenzintervall 2,99–21,89, p-Wert ≤ 0,0001; IMPACT-Score—OR 1,09 95 % Konfidenzintervall 1,01–1,18, p-Wert = 0,025]. Wir untersuchten dann inwiefern sich die Risikoprädiktion des IMPACT-Scores durch das hinzufügen des Troponin Grenzwerts verbessert. Der NRI für das Model mit Troponin betrug 7,6 % (95 % Konfidenzintervall: 4,1–12,6) für Patient*innen ohne Ereignis und 27,5 % (95 % Konfidenzintervall 14,6–43,9) für Patient*innen mit Ereignis. Mittels NARI konnte gezeigt

werden, dass der um den Biomarker erweiterte Score 114 von 1000 Patient*innen mehr identifizieren konnte, die ein erhöhtes Risiko für 1-Jahres Mortalität aufwiesen. Die ROC-AUC des Modells mit Troponin war signifikant höher als die ROC-AUC des IMPACT-Scores [IMPACT-Score ROC-AUC = 0,65 95 % Konfidenzintervall: 0,56–0,74; IMPACT-Score mit Troponin 48 h ROC-AUC = 0,77 95 % Konfidenzintervall: 0,70–0,84; Unterschied zwischen den ROC-AUC: 0,12, 95 % Konfidenzintervall 0,04–0,19, p-Wert = 0,0016]. Die Ergebnisse der Entscheidungskurvenanalyse bestätigten den höheren Nutzen des kombinierten Modells.

In einer univariaten Analyse für DAOH zeigten Patient*innen mit Troponin-Werten über dem vorher festgelegten Grenzwert 48 Stunden nach HTX signifikant niedrigere DAOH [Troponin unter dem Grenzwert 317 (283–328) Tage vs. Troponin über dem Grenzwert 278 (14–308) Tage, p-Wert ≤ 0,0001]. Nach Adjustierung für den IMPACT Score zeigte sich ein unabhängiger Zusammenhang zwischen Troponin 48 Stunden nach HTX und DAOH [pro 100ng/L Troponin-Erhöhung—Regressionskoeffizient: -1,54, 95 % Konfidenzintervall −2,02 bis −1,06, p-Wert ≤ 0,0001; pro Punkt auf dem IMPACT-Score - Regressionskoeffizient: −4,79, 95 % Konfidenzintervall −7,83 bis −1,76, p-Wert = 0,002].

3.3.2 Prognostischer Wert der Albumin-Messung in der frühen postoperativen Phase nach Herztransplantation

In die letzte Analyse konnten 229 Patient*innen eingeschlossen werden. Die 1-Jahres-Mortalität betrug 17,4 % (40 Patient*innen) und die medianen DAOH dieser Kohorte betrug 299 (230–322) im ersten Jahr nach HTX. Die präoperativen Albumin-Werte unterschieden sich nicht signifikant zwischen überlebenden und verstorbenen Patient*innen (Überlebende: 3,9 ± 0,7 g/dl vs. Verstorbene: 3,7 ± 0,7 g/dl, p-Wert = 0,084). Die postoperativen Albumin-Werte waren signifikant niedriger bei Patient*innen, die im ersten Jahr nach HTX verstarben (Überlebende: 3,3 ± 0,6 g/dl vs. Verstorbene: 2,8 ± 0,6 g/dl, P < 0,001). Die ROC-Analyse zeigte eine moderat gute Diskriminationsfähigkeit von postoperativem Albumin (bei Ankunft auf der Intensivstation) für die 1-Jahres Mortalität (ROC-AUC 0,75; 95 % Konfidenzintervall 0,66–0,83). Der berechnete Grenzwert für die beste Diskrimination lag bei 2,95 g/dl Albumin.

Die univariate logistische Regression zeigte eine signifikante Assoziation zwischen Albumin unterhalb des Grenzwertes von 2,95 g/dl und der 1-Jahres Mortalität (OR: 4,54, 95 % Konfidenzintervall: 2,34–8,78, p-Wert ≤0,001). Auch die Überlebensanalyse mittels Kaplan-Meier-Kurve zeigte eine erhöhte Mortalität bei Patient*innen mit postoperativen Albumin-Werten unter dem errechneten Grenzwert (Hazard Ratio 7,95, 95 % Konfidenzintervall: 3,7–17,1, p-Wert < 0,001). Nach Adjustierung für 13 Kovariablen zeigte sich weiterhin ein unabhängiger Zusammenhang von postoperativem Albumin-Wert und der 1-Jahres Mortalität in der logistischen Regression (OR: 4,76, 95 % Konfidenzintervall: 1,94–11,67, p-Wert = 0,001). Zusätzlich bestand ein signifikanter Einfluss des Alters der Organspender*innen (OR: 1,11, 95 % Konfidenzintervall: 1,05–1,17, p-Wert ≤0,001).

Wir untersuchten, ob sich die Prädiktionen für die 1-Jahres Mortalität durch den IMPACT-Score oder MELD-Score durch das Hinzufügen des postoperativen Albumin-Wertes verbessern lassen. Der NRI für das IMPACT-Score Modell mit Albumin war 15,87 % (95 % Konfidenzintervall: 9,43–23,53) für Patient*innen ohne Ereignis und 5 % (95 % Konfidenzintervall: 1,64–11,28) für Patient*innen mit Ereignis. Der NRI für das MELD-Score Modell mit Albumin war 4,23 % (95 % Konfidenzintervall: 1,64–9,93) für Patient*innen ohne Ereignis und 5 % (95 % Konfidenzintervall: 16,88–34,66) für Patient*innen mit Ereignis. Die Analyse des NARI zeigte, dass die um den Biomarker erweiterten Scores 139 von 1000 und 78 von 1000 Patient*innen mit Risiko für 1-Jahres Mortalität mehr identifizieren konnten als die ursprünglichen Modelle. Die ROC-AUCs der erweiterten Modelle war signifikant höher als die der herkömmlichen Scores (IMPACT Score ROC-AUC = 0,65, 95 % Konfidenzintervall: 0,57–0,74; IMPACT-Score mit Albumin ROC-AUC = 0,77, 95 % Konfidenzintervall: 0,70–0,84; Unterschied der ROC-AUC: 0,12, 95 % Konfidenzintervall: 0,02–0,21, p-Wert = 0,016 und MELD-Score ROC-AUC = 0,60, 95 % Konfidenzintervall: 0,50–0,70; MELD-Score mit Albumin ROC-AUC = 0,78, 95 % Konfidenzintervall: 0,70–0,85; Unterschied der ROC-AUC: 0,17, 95 % Konfidenzintervall: 0,06–0,29, p-Wert = 0,002).

Die univariate Analyse ergab, dass Patient*innen mit Serumalbuminspiegel über dem errechneten Grenzwert eine höhere Anzahl an DAOH aufwiesen [Albumin über dem Grenzwert 308 (271–325) Tage vs. Albumin unter dem Grenzwert 253 (0–305) Tage, p-Wert ≤ 0,001]. Auch unter Ausschluss der verstorbenen Patient*innen blieb diese univariate Assoziation erhalten. Nach Adjustierung für 13 Kovariablen im Regressionsmodell zeigte sich eine unabhängige Assoziation von niedrigen Albumin-Werten und niedrigen DAOH (Postoperatives Albumin - Regressionskoeffizient: −46,97, 95 % Konfidenzintervall: −83,81 bis −10,13, p-Wert = 0,013).

4 Diskussion:

Die Herztransplantation ist eine invasive, kurative Therapieoption für Patient*innen mit terminaler Herzinsuffizienz. Prognoserelevante Faktoren, die mit einer erhöhten Mortalität nach HTX assoziiert sind konnten bereits in früheren wissenschaftlichen Arbeiten identifiziert werden. Daten zu patientenzentrierten Endpunkten, die die Lebensqualität der Patient*innen besser beleuchten, wurden in diesem Kontext nur unzureichend untersucht. Auch bezüglich dieser Endpunkte ist es notwendig prognoserelevante Faktoren zu identifizieren um die aktuellen Methoden zur Risikostratifizierung zu ergänzen.

Die dieser kumulativen Habilitationsschrift zugrundeliegenden Arbeiten hatten das primäre Ziel DAOH als patientenzentrierten Endpunkt nach HTX zu charakterisieren, und Einflussgrößen auf diesen Endpunkt zu identifizieren. Eine Diabeteserkrankung der Empfänger*innen, eine präoperative Nierenfunktionsstörung, eine längere postoperative Beatmungsdauer und eine postoperative, dialysepflichtige AKI konnten als unabhängige Einflussgrößen für niedrige DAOH identifiziert werden. Interessanterweise scheint eine CPR der Organspender*innen keinen Einfluss auf DAOH zu haben. Bezüglich der Rolle einer postoperativen Organdysfunktion zeigte sich, dass eine schwere PGD bei erfolgreich von der mechanischen Kreislaufunterstützung entwöhnten HTX Patient*innen zwar keinen Einfluss auf die Mortalität

zu haben scheint, jedoch zu signifikant längeren Krankenhausaufenthalten im ersten Jahr nach HTX führt. Ein wichtiger unabhängiger Einflussfaktor auf DAOH ist die postoperative, dialysepflichtige AKI. Es konnte gezeigt werden, dass diese mit ungefähr 46 % auch häufig bei Patient*innen mit erhaltener präoperativer Nierenfunktion auftritt. Als Risikofaktoren scheinen die Katecholamintherapie und die Dosierung der Immunsuppressiva eine Rolle zu spielen. Darüber hinaus deuten unsere Analysen darauf hin, dass postoperative Biomarker wie Troponin und Albumin einen unabhängigen prognostischen Wert bezüglich Mortalität und DAOH nach HTX haben, und die Risikostratifizierung etablierter Scores verbessern können.

4.1 Bedeutung des Endpunktes „Days alive and out of Hospital" nach Herztransplantation

DAOH ist ein patientenzentrierter Endpunkt, der als Surrogat Parameter Informationen über Lebensqualität von Patient*innen nach einer Operation geben kann. Dieser Endpunkt wurde bereits in einigen perioperativen Kohorten erfasst. Bei Patient*innen die sich einer HTX unterziehen sind DAOH und die mit dem Endpunkt assoziierten perioperativen Faktoren jedoch weniger gut charakterisiert.

In der vorliegenden Arbeit wiesen die Diabeteserkrankung der Empfänger*innen, eine präoperative Nierenfunktionsstörung, eine längere postoperative Beatmungsdauer und eine postoperative, dialysepflichtige AKI als unabhängige Risikofaktoren einen relevanten Einfluss auf die Lebensqualität der Patient*innen gemessen an DAOH auf. Für diese Risikofaktoren konnte in früheren Untersuchungen auch eine Assoziation mit der Mortalität nach HTX beobachtet werden [7]. Die in vorherigen Studien bereits beschriebene Risikofaktoren wie beispielsweise die kongenitale Kardiomyopathie konnten in der vorliegenden Arbeit nicht als Risikofaktoren für niedrige DAOH bestätigt werden. Dies könnte an der niedrigen Inzidenz dieser Risikofaktoren in unserer analysierten Kohorte gelegen haben, in der vornehmlich Patient*innen mit dilatativer und ischämischer Kardiomyopathie als Grunderkrankung eingeschlossen wurden. Auch andere Variablen wie die Geschlechtsinkongruenz zwischen Spender*innen und Empfänger*innen, und das erhöhte Spenderalter zeigten zwar keine

statistische Signifikanz für niedrige DAOH aber einen deutlichen visuellen Trend. Es ist anzunehmen, dass die limitierte Fallzahl einen Einfluss auf die Ergebnisse hatte. Eine Sensitivitätsanalyse zeigte, dass einige Variablen (Nierenfunktion, ECMO Therapie, Dialyse, Beatmungsdauer, Diabeteserkrankung der Spender*innen) unabhängig von der Mortalität einen signifikanten Einfluss auf DAOH zeigten. Dies unterstreicht die Tatsache, dass dieser Endpunkt die Darstellung des Verlaufes nach HTX ergänzen kann. Aktuell gibt es zwei weitere Studien, die DAOH bei HTX Patient*innen untersucht haben [14,60]. In einer großen multizentrischen retrospektiven Analyse, die nach unserer Studie publiziert wurde, untersuchten Pegues et al. DAOH bei 5.104 HTX Patient*innen in Nordamerika vor und nach HTX [60]. Die Angabe der DAOH erfolgte in Prozent und die Kohorte wurde in Terzile aufgeteilt. Patient*innen im untersten DAOH Terzil hatten im Vergleich zu Patient*innen im obersten Terzil längere präoperative Krankenhausaufenthalte und eine höhere Rate an postoperativen Komplikationen [60]. Als Komplikationen wurden PGD, neurologische Komplikationen und Wundinfektionen berichtet. Es wurden im Gegensatz zu unserer Arbeit darüber hinaus keine dezidierten Einflüsse von prä-, intra- oder postoperativen Variablen auf DAOH untersucht. Unsere Daten waren bezüglich des Einflusses von postoperativen Komplikationen auf DAOH mit denen von Pegues et al. kongruent. [60]. Es ist jedoch wichtig festzuhalten, dass sich Ergebnisse aus nordamerikanischen Kohorten nicht unbedingt auf den Eurotransplantraum übertragen lassen. Hier spielen Unterschiede in der Patientenauswahl, sowie in der Organisation des Gesundheitswesens eine Rolle. Dies spiegelt sich in einer niedrigeren Mortalität nach HTX in Nordamerika wider [4]. In einer zweiten Arbeit untersuchten Bruce et al. DAOH bei 235 HTX Patient*innen mit dem Fokus des Einflusses von präoperativer mechanischer Kreislaufunterstützung [14]. Sie identifizierten die pulmonale Hypertonie, und eine lange Ischämiezeit als unabhängige Risikofaktoren für niedrige DAOH. Die präoperative mechanische Kreislaufunterstützung zeigte hier keine Assoziation zu DAOH. In unserer Arbeit dagegen, bestand kein Einfluss dieser beiden Größen auf DAOH. Neben strukturellen und geographischen Unterschieden könnte auch hier eine limitierte Fallzahl in unserer Kohorte eine Rolle gespielt haben [14].

4.2 Bedeutung der Transplantation von Organen von reanimierten Organspendern für den Krankheitsverlauf nach Herztransplantation

Es besteht ein großes Missverhältnis zwischen Angebot und Nachfrage von Spenderorganen. Auch Organe von Organspender*innen, die im Therapieverlauf eine CPR erhielten werden häufiger als Spenderorgane in Betracht gezogen. In früheren Arbeiten konnte gezeigt werden, dass eine CPR der Organspender*innen keinen relevanten Einfluss auf die Mortalität von HTX Patient*innen hat. Der Einfluss von CPR der Organspender*innen auf DAOH als patientenzentrierten Endpunkt ist jedoch unklar.

In dieser Arbeit konnten wir keinen Einfluss von CPR der Organspender*innen auf die DAOH und die Mortalität nach HTX zeigen. Auch die Dauer der CPR war nicht mit niedrigeren DAOH oder höherer 1-Jahres Mortalität assoziiert [55]. Dieses Ergebnis ist von Interesse, da neben der Mortalität auch die Rehospitalisierungsrate und die Dauer der Krankenhausaufenthalte im ersten Jahr nach HTX nicht unterschiedlich zu sein scheinen. Diese Arbeit unterstützt vorherige Daten für die Mortalität von Mehdiani et al. die zeigten, dass die postoperative Mortalität und Morbidität von Organempfänger*innen durch CPR der Spender*innen unbeeinflusst bleibt [61]. Auch Cheng et. al wiesen keinen signifikanten Zusammenhang zwischen Dauer der CPR und postoperativer Mortalität von Organempfänger*innen nach[15]. Darüber hinaus zeigte eine weitere Analyse aus über 29.000 HTX Patient*innen ähnliche Ergebnisse. Die Ergebnisse wurden so gedeutet, dass die reanimierten CPR Patient*innen jünger waren und weniger Vorerkrankungen aufwiesen als nicht reanimierte Organspender*innen [62]. In unserer Kohorte konnte kein Altersunterschied zwischen den beiden Kollektiven nachgewiesen werden, jedoch hatten reanimierte Organspender*innen weniger häufig eine Diabeteserkrankung [55]. Diese Arbeit konnte zusätzlich die bereits vorhandene Literatur um die Daten zum Endpunkt DAOH ergänzen. Unter dem Aspekt der Organknappheit bestätigen unsere Daten, dass CPR per se kein alleiniges Ausschlusskriterium für eine Organakzeptanz darstellt, nicht nur bezogen auf die Mortalität, sondern auch auf DAOH als Maß für die Lebensqualität nach HTX.

4.3 Bedeutung der primären Transplantatdysfunktion nach Herztransplantation

Die PGD ist eine der Haupttodesursachen nach HTX. Häufig wird im Rahmen der Behandlung der PGD eine VA-ECMO Therapie initiiert. Der Einfluss der PGD mit VA-ECMO Therapie auf DAOH als patientenzentrierten Endpunkt ist jedoch unklar und sollte in dieser Arbeit untersucht werden.

Diese Arbeit bestätigte zunächst die höhere Mortalität bei Patient*innen mit PGD und VA-ECMO Therapie nach HTX [18]. Jedoch hatten Patient*innen die erfolgreich von der VA-ECMO entwöhnt werden konnten eine ähnliche Mortalität im Vergleich zu Patient*innen ohne PGD. Patient*innen ohne PGD wiesen jedoch signifikant höhere DAOH auf [56]. In vorherigen, retrospektiven Analysen von D'Alessandro et al. und Marasco et al. zeigte sich wie in unserer Analyse kein Unterschied in der Mortalität von erfolgreich von der VA-ECMO entwöhnten HTX Patient*innen im Vergleich zu Patient*innen ohne PGD [63,64]. Zusätzlich zeigte eine Analyse von Loforte et al., dass kein Unterschied zwischen diesen Patientengruppen im Langzeitüberleben bis 5 Jahre nach HTX besteht [27]. Keine dieser Analysen berichtet DAOH als Endpunkt für die Beobachtungszeiträume. Es ist zu erwähnen, dass DAOH auf zwei unterschiedliche Arten berechnet werden können. Nach der Definition von Ariti et al. werden alle Tage außerhalb des Krankenhauses erfasst, während nach einer Definition von Myles et al. das Versterben im Beobachtungszeitraum mit dem DAOH Wert von „0" gewertet wird [12,13]. Wir haben uns in dieser Analyse dazu entschieden, die Definition von Ariti et al. zu übernehmen, zum einen da diese im Bereich Herzinsuffizienz validiert wurde und zum anderen durch die hohe Mortalität von ungefähr 20 % nach HTX, DAOH mit der Definition nach Myles unterschätzt werden könnte. In einer Sensitivitätsanalyse ergab die Verwendung der anderen Definition nach Myles et al. (Tod im Beobachtungszeitraum = 0 DAOH) jedoch keinen Einfluss auf die Ergebnisse. Unsere Ergebnisse legten eine klare Diskrepanz zwischen den Endpunkten Mortalität und DAOH dar. DAOH scheint somit die Erfassung des Verlaufs nach HTX um Informationen zur postoperativen Ressourcennutzung (z.B. Anzahl und Dauer der Krankenhausaufenthalte) zu ergänzen[60].

4.4. Bedeutung der postoperativen akuten Nierenschädigung auf den Krankheitsverlauf nach Herztransplantation

Die postoperative AKI ist eine häufige Komplikation nach HTX. Eine präoperativ bereits eingeschränkte Nierenfunktion scheint ein Hauptrisikofaktor für die Entwicklung einer postoperativen AKI zu sein. Aber auch Patient*innen mit erhaltener Nierenfunktion scheinen nach HTX häufig betroffen zu sein. Diese Arbeit sollte Risikofaktoren für eine postoperative Dialysepflichtigkeit nach HTX in dieser selektierten Patientengruppe untersuchen.

In der Analyse zur Rolle von AKI nach HTX konnten wir zeigen, dass AKI auch bei präoperativ erhaltener Nierenfunktion eine häufige Komplikation nach HTX darstellt und mit prolongierter Noradrenalintherapie und einem schnellen Anstieg der Tacrolimusplasmakonzentration assoziiert ist [57]. Während Risikofaktoren für AKI nach HTX relativ gut charakterisiert sind [32], ist die Charakterisierung für Risikofaktoren bei Patient*innen mit erhaltener Nierenfunktion nur unzureichend beschrieben. Nur bei einigen der bereits publizierten Risikofaktoren bestand in unserer Population mit präoperativ erhaltener Nierenfunktion eine univariate Assoziation mit einer schweren AKI. Unsere Daten deuten darauf hin, dass für die Dauer der Noradrenalintherapie und für den schnellen Anstieg der Tacrolimusplasmakonzentration unabhängige Assoziationen bestehen[32]. Tacrolimus ist ein nephrotoxisches Immunsuppressivum, welches nach HTX zur Unterdrückung einer Abstoßungsreaktion verwendet wird [65,66]. In einer retrospektiven Analyse zeigten Sikma et al., dass supratherapeutische Tacrolimusplasmaspiegel mit AKI nach HTX vergesellschaftet sind [67]. Auch im Bereich der Lungentransplantation wurde eine frühe postoperative Tacrolimus Exposition mit AKI in Zusammenhang gebracht [68]. Unsere Daten bestätigen, dass sowohl hohe Plasmaspitzenkonzentration als auch ein schneller Anstieg der Plasmakonzentration von Tacrolimus AKI begünstigen. In diesem Kontext konnten Immunsuppressionsregime ohne Calcineurininhibitoren, beispielsweise mittels Basiliximab oder Anti-Thymbozyten-Globulin (ATG) eine reduzierte Inzidenz von AKI aufweisen und stellen eine vielversprechende Alternative dar [69]. Eine hohe Dosis von vasoaktiven Substanzen wie Noradrenalin ist mit einem erhöhten Risiko von AKI vergesellschaftet [70]. Unsere Analyse bestätigt die Ergebnisse einer

retrospektiven Analyse von Jocher et al., dass eine höhere Dosis von vasoaktiven Substanzen unabhängig vom mittleren arteriellen Blutdruck das Risiko für AKI erhöht [70]. Es muss hierbei bedacht werden, dass der Blutdruck nur ein unzureichendes Maß der regionalen Organperfusion darstellt. Eine prolongierte Noradrenalintherapie spiegelt am ehesten die Effekte von zugrundliegenden, schwerwiegenderen Krankheitszuständen, wie Hypovolämie, Vasoplegie oder niedrigem Herzzeitvolumen wider, die neben einer durch Noradrenalin bewirkten Vasokonstriktion der Nierengefäße selbst zu einer renalen Minderperfusion führen und AKI zusätzlich begünstigen können [71,72]. Da hier nur retrospektive Daten betrachtet wurden, war es nicht möglich neben der Assoziation der Noradrenalintherapie mit einer postoperativen Dialysepflichtigkeit auch eine klare Kausalität darzustellen, was eine wichtige Limitation der Analyse darstellt.

4.5 Der Nutzen von Troponin als Biomarker nach Herztransplantation

Troponin ist ein kardialer Biomarker dessen Erhöhung bei nicht-kardiochirurgischen und kardiochirurgischen Eingriffen mit einer erhöhten Mortalität einher geht. Diese Arbeit untersuchte ob eine Assoziation von Troponin mit der 1-Jahres Mortalität und DAOH nach HTX besteht.

Diese Analyse zeigte eine unabhängige Assoziation von Troponin 48 Stunden nach HTX mit der 1-Jahres Mortalität und DAOH. Zusätzlich konnten wir eine verbesserte Risikoprädiktion des IMPACT Scores nachweisen, wenn dieser um Troponin ergänzt wurde. In der aktuellen Literatur ist der prognostische Wert von Troponin nach HTX kaum untersucht. Eine systematische Übersichtsarbeit identifizierte 3 Studien, die sich mit der Assoziation von Troponin und der Mortalität nach HTX beschäftigten [47]. In einer Studie untersuchten Labarrere et al. die Assoziation von persistent erhöhten Troponin Werten nach HTX in 110 Patient*innen. Die Autoren berichten einen Zusammenhang zwischen der Troponinerhöhung und spätem Transplantatversagen. Es wurden nur überlebende Patient*innen eingeschlossen und die Troponinmessungen wurden nicht direkt postoperativ durchgeführt [73]. Eine weitere Studie mit 141 HTX Patient*innen untersuchte den prognostischen Wert von Troponin 6 Wochen nach

HTX für die 1-Jahres Mortalität. Es wurde ein signifikanter Zusammenhang festgestellt, jedoch fehlt auch hier die Troponin Messung zu einem früheren Zeitpunkt [74]. Eine Studie von Franeková et al. (n = 121 Patient*innen) untersuchte Troponin 10 Tage nach HTX und zeigte einen signifikanten Zusammenhang zur 1-Jahres Mortalität [75]. Zur frühen Risikostratifizierung sind jedoch direkt postoperativ durchgeführte Messungen von höherer klinischer Relevanz. Bei kardiochirurgischen Patient*innen wurde Troponin bereits als früher postoperativer Marker mit prognostischem Wert untersucht [46]. Unsere Daten stellen eine relevante Ergänzung für die HTX-Population dar, sodass Troponin auch hier zukünftig als prognostischer Marker für die Mortalität verwendet werden könnte [58].

4.6 Der Nutzen von Albumin als prognostischer Biomarker nach Herztransplantation

Niedrige Serumalbuminspiegel sind bei kardiochirurgischen Patient*innen mit einer erhöhten Mortalität assoziiert. Diese Arbeit untersuchte ob direkt postoperativ erhobene Albuminmessungen zur Risikostratifizierung bezüglich der 1-Jahres Mortalität nach HTX genutzt werden können.

In dieser Arbeit konnte eine unabhängige Assoziation von frühem postoperativen Albumin nach HTX mit der 1-Jahres Mortalität und DAOH nachgewiesen werden. Zusätzlich konnten wir eine verbesserte Risikoprädiktion des postoperativen MELD Score und des präoperativen IMPACT Scores unter Mitberücksichtigung des Albuminwertes zeigen. In der bisher verfügbaren Literatur wurde bei HTX Patient*innen vor allem die Assoziation von **prä**operativen Albuminwerten mit der 1-Jahres Mortalität untersucht. So wiesen Kato et al. in zwei Studien, darunter eine Analyse mit 13.671 HTX Patient*innen nach, dass ein präoperativer Albuminwert <3.5 g/dl mit einer erhöhten 1-Jahres Mortalität assoziiert ist [53,76]. In weiteren Kohorten führte die Berücksichtigung von präoperativen Albuminwerten in Ergänzung zu Risiko-Scores, unter anderem dem MELD Score, zu einer Prädiktionsverbesserung [52,77]. Die Bedeutung von **post**operativen Albuminwerten früh nach HTX wurde dagegen bislang nicht untersucht, wenn auch Studien in anderen kardiochirurgischen Patientenkollektiven ebenfalls eine starke Assoziation von niedrigen

postoperativen Albuminwerten und der Mortalität nachwiesen[48,49]. Unsere Daten zeigen einen Zusammenhang von niedrigen Albuminwerten unter 3 g/dl und der 1-Jahres Mortalität, der mit den bereits früher beschriebenen Ergebnissen übereinstimmt. Zusätzlich zeigten HTX Patient*innen mit längerer Zeit an der Herzlungenmaschine und höherem Transfusionsbedarf niedrigere Albuminwerte, was die Fähigkeit des Biomarkers unterstreicht, komplexe intraoperative Verläufe abzubilden. Der zusätzliche Nutzen dieses Biomarkers spiegelt sich insbesondere in der Verbesserung der Prädiktion etablierter Risikomodelle wider, wenn der postoperative Albuminwert zusätzlich mit einbezogen wird.

4.7 Ausblick:

In der vorliegenden Arbeit wurde die Validität des neuen patientenzentrierten Endpunktes DAOH bei Patient*innen mit HTX monozentrisch untersucht. Es konnten einige klinische Faktoren identifiziert werden die mit einer Einschränkung von DAOH einhergingen. Die Diabeteserkrankung der Empfänger*innen, die präoperative Nierenfunktionsstörung, eine längere postoperative Beatmungsdauer und die postoperative, dialysepflichtige AKI zeigten hier eine unabhängige Assoziation mit niedrigen DAOH. Die vorliegende Arbeit unterliegt jedoch einigen Limitationen: Zum einen handelt es sich um retrospektiv erhobene Daten, sodass das Risiko besteht, dass nicht alle relevanten Einflussgrößen erfasst wurden. Zum anderen besteht die Möglichkeit, dass nicht alle Krankenhausaufenthalte im ersten Jahr nach HTX dokumentiert wurden. Darüber hinaus ist die Fallzahl limitiert und durch das monozentrische Design könnten zentrumsspezifische Störgrößen die Ergebnisse beeinflusst haben. Es konnten zusätzlich auch keine Daten zur tatsächlichen Lebensqualität der Patient*innen erhoben werden. Daher sollten sich zukünftige Untersuchungen darauf konzentrieren, diesen Endpunkt in einer größeren multizentrischen Kohorte zu untersuchen. Zusätzlich sollte untersucht werden, ob dieser Endpunkt mit anderen patientenzentrierten und patienten-berichteten Endpunkten, wie z.B. der Lebensqualität, korreliert. Die Identifikation von Risikofaktoren für eine eingeschränkte Lebensqualität könnte die Patientenauswahl für die HTX verbessern und zu einer effizienteren Nutzung des bereits knappen Angebots an Spenderorganen führen, auch wenn dies mit dem individuellen Nutzen für die einzelnen

Patient*innen abgewogen werden muss. Diese ethischen Abwägungen sind sicherlich auch eine zentrale Kompetenz ärztlichen Handelns. Die Patientenauswahl sollte aufgrund der ethischen Komplexität nicht alleine auf Basis der bekannten Risikofaktoren getroffen werden. Vielmehr können diese zusätzlichen Informationen jedoch die ärztliche Entscheidungsfindung unterstützen. Darüber hinaus können gewonnene Informationen genutzt werden, um Patient*innen über ihr individuelles Risiko einer postoperativ eingeschränkten Lebensqualität zu informieren und den Ressourcenbedarf nach der Initialhospitalisierung abzuschätzen. Des Weiteren konnte in der vorliegenden Arbeit die Bedeutung von postoperativen Komplikationen wie der PGD und der akuten Nierenschädigung für den Langzeiterfolg einer HTX dargestellt werden. In zukünftigen Untersuchungen sollten Strategien erarbeitet werden, die das Auftreten dieser Komplikationen reduzieren. Diese Strategien könnten dann zukünftig angewendet werden, um die perioperative Versorgung und den Krankheitsverlauf von HTX Patient*innen zu verbessern.

4.7.1 Untersuchung patientenzentrierter Endpunkte zur Lebensqualität nach Herztransplantation

DAOH ist ein patientenzentrierter Endpunkt, der dazu genutzt werden kann, den Einfluss einer Intervention oder Operation auf das Leben von Patient*innen zu quantifizieren. Dieser Endpunkt wird häufig als Surrogatparameter für die Lebensqualität verwendet unter der Annahme, dass die Lebensqualität von Patient*innen mit langer oder häufiger Hospitalisierung niedriger ist als bei Patient*innen, die den Großteil ihrer Zeit nach einer Operation zuhause verbringen. Ein entscheidender Schwachpunkt dieses Endpunktes ist jedoch, dass die Lebensqualität selbst nicht erfasst wird. Es gibt in der Literatur einige Hinweise, dass DAOH mit anderen patientenzentrierten Endpunkten korreliert, die die Lebensqualität abbilden können. Beispielsweise wies eine aktuelle Arbeit von Delaney et al. eine schwache Korrelation von DAOH mit dem EQ-5D Fragebogen bei Patient*innen mit Sepsis nach. Bei Patient*innen mit Kunstherz konnte ebenfalls eine Korrelation zwischen DAOH und EQ-5D gezeigt werden [78]. Jedoch gibt es andere Arbeiten, die keine Korrelation zwischen den beiden Metriken beweisen konnten [79]. Aktuell gibt es keine Arbeiten, die die Korrelation zwischen DAOH und

Messinstrumenten der Lebensqualität untersucht, sodass diese weiterhin unklar bleibt. Der „World Health Organization Disability Assessment Schedule“ (WHODAS 2.0) ist ein weiteres patientenzentriertes Messinstrument zur Erhebung von Einschränkungen der funktionalen Gesundheit und Behinderungen. Dieser Endpunkt wurde bereits in der perioperativen Medizin validiert [80,81]. Aus einer bislang nicht veröffentlichten Sekundäranalyse der PRACTICE Studie (NCT04877795) unserer Arbeitsgruppe geht hervor, dass ungefähr 20% der Patient*innen nach einem elektiven kardiochirurgischen Eingriff eine neuaufgetretene Behinderung erfährt. In der abgeschlossenen aber bislang unveröffentlichten multizentrischen PACORUS-D Studie (NCT04675905) unserer Arbeitsgruppe bei nicht-kardiochirurgischen Patient*innen konnte gezeigt werden, dass DAOH mit WHODAS 2.0 korreliert. Im Bereich HTX gibt es aktuell keine Daten zu WHODAS 2.0 und einschränkungsfreiem Überleben. Die weitere Untersuchung dieses Endpunktes ist wünschenswert, um die bereits verfügbaren Daten zur Mortalität zu ergänzen und eine Korrelation mit DAOH bei Patient*innen nach HTX nachzuweisen. Die Ergebnisse von zukünftigen Untersuchungen könnten verwendet werden, um weitere perioperative Risikofaktoren zu identifizieren.

4.7.2 Strategien zur Vermeidung der primären Transplantatdysfunktion

PGD ist ein Hauptrisikofaktor für die frühe Mortalität innerhalb der ersten 30 Tage nach HTX. Ein führender aktuell bekannter Hauptrisikofaktor für PGD ist eine lange Ischämiezeit des Spenderorgans [22,82,83]. Die verlängerte Ischämiezeit kann konsequenterweise zu einer erhöhten Gewebeschädigung im Sinne des Ischämie-Reperfusionsschaden führen [84]. Diese Gewebeschädigung kann durch erhöhte Troponinfreisetzung quantifiziert werden und ist, wie in der vorliegenden Arbeit beschrieben, mit einer erhöhten Mortalität assoziiert. Strategien zur Reduktion der Ischämiezeit und Strategien zur besseren Organprotektion könnten somit zukünftig einen vielversprechenden Ansatzpunkt zur Vermeidung von PGD darstellen. In diesem Kontext konnten Rega et al. in einer randomisiert kontrollierten Studie zeigen, dass eine ex-vivo hypotherme Perfusion des Spenderorgans im Vergleich zur konventionellen gekühlten Lagerung die Inzidenz von PGD und Komplikationen klinisch relevant reduzieren kann [85]. Diese neue Technologie könnte zu einer Verbesserung von Mortalität und

patientenzentrierten Endpunkten nach HTX beitragen. Zusätzlich könnte eine bessere geographische Allokation der Spenderorgane zu einer Reduktion der Ischämiezeit und damit einer Reduktion der Inzidenz von PGD beitragen. Unter Berücksichtigung der Knappheit an Spenderorganen ist dieser Ansatz aktuell jedoch nur schwer realisierbar.

4.7.3 Strategien zur Vermeidung der akuten Nierenschädigung

AKI nach HTX ist eine häufige Komplikation, die sowohl mit einem geringeren Überleben, als auch mit niedrigen DAOH assoziiert ist [17]. Selbst bei Patient*innen ohne höhergradige präoperative Nierenfunktionseinschränkung tritt diese Komplikation häufig auf. Pathophysiologisch kommen während einer HTX gleich mehrere Risikofaktoren zum Tragen, die eine AKI begünstigen: Hoher Volumenumsatz, lange Zeit an der Herzlungenmaschine, hämodynamische Behinderung des renalen Blutflusses, sowie die Verwendung von nephrotoxischen Substanzen zur Immunsuppression. Die meisten dieser Faktoren sind während der HTX nur schlecht vermeidbar, sodass andere protektive Strategien gefunden werden müssen. Die Ischämische Fern-Präkonditionierung (RIPC) ist eine nicht-invasive Methode, die zur renalen Protektion verwendet werden könnte. Eine Metaanalyse aus randomisiert kontrollierten Studien gibt Hinweise darauf, dass das Auftreten einer schweren AKI durch RIPC bei kardiochirurgischen Patient*innen reduziert werden könnte [86]. Zwei größere publizierte Studien bestätigten diese positiven Effekte bei kardiochirurgischen Patient*innen [87,88]. Für Patient*innen mit HTX liegt dagegen nur eine Studie vor, die die Effekte von RIPC auf die myokardiale Funktion untersucht hat [89]. Diese Studie hat renale Endpunkte jedoch nur unzureichend betrachtet. Als Vorbereitung für eine größere randomisiert kontrollierte Studie, die Effekte von RIPC auf renale Endpunkte prüfen soll, hat unsere Arbeitsgruppe in den Jahren 2022-2024 eine Machbarkeitsstudie durchgeführt, bei der 40 HTX Patient*innen eingeschlossen wurden (NCT05364333). Das Protokoll erwies sich als durchführbar. Bei der niedrigen Fallzahl sind jedoch keine Effekte auf renale Endpunkte zu erwarten. Es sind größere Studien notwendig, um die Rolle dieser vielversprechenden Methode für die Prävention von AKI bei HTX Patient*innen zukünftig weitgehender zu untersuchen. Zusätzlich könnte ein verzögertes oder alternatives Regime der

immunsuppressiven Therapie unter Einsparung von Calcineurininhibitoren die nephrotoxischen Effekte minimieren und somit als ein zusätzlicher Ansatz für künftige Untersuchungen dienen.

5 Zusammenfassung:

Die HTX stellt trotz Fortschritten in der medikamentösen Therapie weiterhin die einzige kurative Therapie der terminalen Herzinsuffizienz dar. Angesichts des Mangels an Spenderorganen ist eine präzise Prognoseabschätzung und Risikostratifizierung von entscheidender Bedeutung. Traditionell wurde der Erfolg einer HTX überwiegend anhand der Mortalität bewertet. Zunehmend gewinnen jedoch patientenzentrierte Endpunkte, die zusätzlich zur Mortalität auch die Lebensqualität der Patienten abbilden können, an Bedeutung. Einer dieser patientenzentrierten Endpunkte ist DAOH. In dieser kumulativen Habilitationsschrift wurden zentrale Risikofaktoren identifiziert, die einen Einfluss auf DAOH bei Patient*innen nach HTX haben. Ein zusätzlicher Fokus lag dabei auf der Rolle postoperativer Organdysfunktionen und der prognostischen Bedeutung postoperativ gemessener Biomarker.

Diese Arbeit basiert auf sechs retrospektiven Kohortenstudien, die Patient*innen einschlossen, die sich zwischen 2010 und 2023 am Universitätsklinikum Düsseldorf einer HTX Operation unterzogen haben. Die Datenerhebung erfolgte aus einer prospektiven HTX-Datenbank der Klinik für Herzchirurgie. Diese Datenbank wurde durch gezielte Variablenextraktion aus der digitalen Patientenakte ergänzt. Eine zentrale Rolle spielte die Validierung von DAOH als patientenzentrierter Endpunkt nach HTX. Weitere Untersuchungen analysierten den Einfluss einer Reanimation der Organspender*innen auf die Mortalität und DAOH nach HTX, die Auswirkungen einer VA-ECMO-Therapie bei PGD auf DAOH und Mortalität nach HTX, Risikofaktoren für eine dialysepflichtige AKI nach HTX bei präoperativ erhaltener Nierenfunktion, sowie die prädiktive Rolle von postoperativem Troponin T und postoperativem

Albumin für die Mortalität und DAOH nach HTX. Für diese Analysen wurden multivariate Regressionsmodelle und ROC-Analysen verwendet um assoziierte Risikofaktoren zu identifizieren und die prognostischen Wertigkeiten zu untersuchen.

Der Endpunkt DAOH wurde in einer retrospektiven Kohorte von HTX Patient*innen validiert. Eine Diabeteserkrankung, eine präoperativ eingeschränkte Nierenfunktion, eine längerer Beatmungsdauer und eine postoperative Dialysepflichtigkeit zeigten in diesem Kontext eine unabhängige Assoziation mit niedrigen DAOH nach HTX. Eine vorherige Reanimation der Organspender*innen zeigte hingegen keinen signifikanten Einfluss auf DAOH oder Mortalität. In der Untersuchung zum Einfluss von VA-ECMO Therapie bei PGD zeigte sich bei HTX Patient*innen, die erfolgreich von der VA-ECMO entwöhnt werden konnten, eine vergleichbare Mortalität zur Kontrollgruppe. Dennoch war die VA-ECMO Therapie mit signifikant niedrigeren DAOH Werten assoziiert. Die Untersuchung zur postoperativen Dialysepflichtigkeit von HTX Patient*innen mit initial erhaltener Nierenfunktion ergab eine Inzidenz von fast 45,6 %. Wesentliche assoziierte Risikofaktoren waren die postoperative Dauer der Noradrenalin-Therapie, sowie ein starker postoperativer Anstieg der Tacrolimus-Plasmakonzentration. Bezüglich der Untersuchungen zu den postoperativ gemessenen Biomarkern zeigte Troponin T, insbesondere 48 Stunden postoperativ, eine starke prognostische und prädiktive Wertigkeit für die 1-Jahres-Mortalität, sowie eine signifikante Assoziation mit niedrigeren DAOH. Ebenso wies postoperatives Serumalbumin unter 2,95 g/dl eine starke Assoziation mit erhöhter Mortalität und reduzierten DAOH auf. Die Erweiterung herkömmlicher Risikomodelle (z. B. IMPACT-Score und den MELD-Score) um Biomarker wie Troponin oder Albumin verbesserte die Vorhersagequalität der etablierten Risikomodelle signifikant.

Zusammenfassend identifizierten die vorliegenden Arbeiten DAOH als validen Endpunkt nach HTX, der zum einen von präoperativen Variablen als auch maßgeblich durch postoperative Komplikationen nach HTX beeinflusst wird. DAOH scheint als patientenzentrierter Endpunkt herkömmliche Endpunkte wie die Mortalität gut zu ergänzen, um den Einfluss einer HTX auf das Leben von Patient*innen abzubilden. Weitere Studien werden benötigt, um den

Zusammenhang von DAOH und weiteren patientenzentrierten Endpunkten, die die Lebensqualität nach HTX erfassen vollständig zu charakterisieren. Eine perioperative Organdysfunktion wie die PGD und die schwere AKI wurden als relevante Komplikationen identifiziert, die zum einen das Überleben aber auch patientenzentrierte Endpunkte negativ beeinflussen. Folgende Studien sollten sich auf die Entwicklung von Strategien konzentrieren, um das Auftreten dieser Komplikationen zu verhindern. Zusätzlich konnte demonstriert werden, dass postoperative Biomarker wie Troponin und Albumin zur Prognoseabschätzung für die 1-Jahres Mortalität und DAOH beitragen. Diese aus den vorliegenden Arbeiten gewonnenen Erkenntnisse, könnten in Zukunft die Erstellung neuer Risikoprädiktionsmodelle unterstützen und somit die Versorgung von HTX Patient*innen in Deutschland verbessern.

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8 Originalarbeiten

Die Genehmigung zur Verwendung der Originalarbeiten im Anhang sind beim jeweiligen Verlag im Vorfeld eingeholt worden.

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ORIGINAL ARTICLE

Life impact of VA-ECMO due to primary graft dysfunction in patients after orthotopic heart transplantation

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Abstract

Aims Primary graft dysfunction (PGD) is a feared complication after heart transplantation (HTX). HTX patients frequently receive veno-arterial extracorporeal membrane oxygenation (VA-ECMO) until graft recovery. Long-term mortality of patients weaned from VA-ECMO after HTX is comparable with non-ECMO patients. However, impact on quality of life is unknown. This study investigated days alive and out of hospital (DAOH) as patient-centred outcome in HTX patients at 1 year after surgery.

Methods and results This retrospective single-centre cohort study included patients who underwent HTX at the University Hospital Düsseldorf, Germany, from 2010 to 2020. Main exposure was VA-ECMO due to PGD. VA-ECMO and non-VA-ECMO patients were compared regarding the primary endpoint DAOH at 1 year after HTX. Subgroup analysis for patients weaned from VA-ECMO was performed. In total, 144 patients were included into analysis; 1 year mortality was significantly lower in non-ECMO patients [non-ECMO 14.3% (14/98) vs. VA-ECMO 34.8% (16/46), adjusted hazard ratio: 0.32, 95% confidence interval: 0.15–0.74; $P = 0.002$]. Mortality did not differ significantly between patients weaned from VA-ECMO and non-ECMO patients [non-ECMO 14.3% (14/98) vs. VA-ECMO (weaned) 18.9% (7/37), adjusted hazard ratio: 0.72, 95% confidence interval: 0.27–1.90; $P = 0.48$]. DAOH were significantly higher in non-ECMO patients compared with VA-ECMO patients and patients weaned from VA-ECMO [non-ECMO vs. VA-ECMO: median 310 (inter-quartile range 277–327) days vs. 243 (0–288) days; $P < 0.0001$; non-ECMO vs. VA-ECMO (weaned): 310 (277–327) days vs. 253 (208–299) days; $P < 0.0001$]. These results were still significant after multivariable adjustment with forced entry of predefined covariables.

Conclusions Despite similar survival rates, VA-ECMO due to PGD has a relevant life impact as defined by DAOH in the first year after HTX. As a more patient-centred endpoint, DAOH may contribute to a more comprehensive assessment of outcome in HTX patients.

Keywords VA-ECMO; ECLS; Quality of life; Days alive and out of hospital; Patient-centred outcomes; Cardiac surgery

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Introduction

Orthotopic heart transplantation (HTX) is the causal therapy for patients with end-stage heart failure.[1,2] After HTX, primary graft dysfunction (PGD) is a feared complication occurring in up to 30% and strongly affecting survival chances of patients.[3] Therefore, these patients frequently receive extracorporeal mechanical support by veno-arterial extracorpo-

real membrane oxygenation (VA-ECMO) devices.[4,5] VA-ECMO is the first-line therapy for severe PGD and helps to maintain circulation as well as to overcome cardiac failure until graft recovery.[6–9] Previous studies indicated that long-term survival of patients weaned from VA-ECMO after HTX was comparable with patients who did not experience PGD.[10–12] However, data on functionality in daily life and rehospitalization rates remain limited in these patients. Days alive and out of hospital (DAOH) has been recently introduced and evaluated as patient-centred outcome in different clinical settings.[13–15] It combines clinically important outcomes such as death, hospital length of stay, and rehospitalization rate. To date, impact of VA-ECMO on DAOH in patients after HTX is underexplored. Therefore, we aimed to investigate this topic and hypothesized that use of VA-ECMO due to PGD is associated with lower DAOH at 1 year after HTX.

Methods

The present study is a retrospective single-centre cohort study that has been conducted in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. The study was approved by the ethical review board of the Heinrich Heine University Düsseldorf, Germany (reference number: 4567). All patients gave written informed consent. This report follows the STROBE guidelines.

Study design and study population

This study included patients >18 years who underwent HTX between 2010 and 2020 at the University Hospital Düsseldorf, Germany. The main explanatory variable of this study was the early use of VA-ECMO therapy due to PGD (= initiation within the first 24 h after surgery according to consensus conference on PGD).[16] Patients were assigned to VA-ECMO group, if they had early VA-ECMO therapy due to PGD. Patients without PGD were assigned to non-VA-ECMO group. Afterwards, a subgroup of weaned VA-ECMO patients was set out of the VA-ECMO group. This group was defined as patients who had PGD and VA-ECMO therapy but were successfully weaned from VA-ECMO during the index hospital stay. Weaning was performed from peripheral and central cannulated ECMO while ventilated, according to local standards. Exclusion criteria were incomplete medical records, death during HTX, and the use of veno-venous ECMO. Central and peripheral VA-ECMO cannulation was included. Average caseload of VA-ECMO therapy in our centre is 60–80 patients per year, which was deemed appropriate in terms of experience and expertise in this field.

Outcome assessment

The primary endpoint was DAOH at 1 year after HTX. DAOH for the first year after HTX were calculated by individually summing up the days of all hospital stays per patient and subtracting them from 365 days. If the patient did not survive 365 days, the difference between survived days and 365 days was added to days of hospital stays before subtraction from 365 days. This method refers to the validation study of DAOH in heart failure patients.[15] According to the validation study of DAOH in major surgery, DAOH can also be calculated in another way: in a previously published approach, patients who died during the study period were assigned DAOH of 0 days. To test if the way to calculate DAOH influences our results, a sensitivity analysis using this additional definition of DAOH was performed. Secondary endpoints included mortality, duration of hospitalization, and reasons for hospitalization during the first year after HTX. Hospitalization was defined as every planned or unplanned readmission to the hospital of at least 1 day occurring within 1 year after HTX. Hospitalizations were divided into 10 categories: gastrointestinal disorders, pneumonia/respiratory infection, wound infection, kidney disorders including acute kidney injury, graft rejection reaction, bleeding complications, non-cardiac surgery, other infections than respiratory infections, endomyocardial biopsy, and HTX index hospitalization. All observed hospitalizations of our study cohort are included into these categories. HTX patients are very closely connected to our centre so that all information on hospitalizations could be assessed by screening local medical records.

Data collection

All data of patients were collected by screening electronic medical charts and the local electronic HTX database. Patient characteristics, co-morbidities, comedication, and survived days at 1 year were extracted from these sources.

Statistical analysis

Statistical analysis was conducted in GraphPad Prism© Version 8.02 (La Jolla, CA, USA) and IBM SPSS© software Version 22.0 (Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation or as median with inter-quartile ranges, as appropriate. Categorical variables are presented as absolute numbers (*n*) and percentage (%) in brackets. χ^2 test and Fisher's exact test were used for statistical comparison. Kaplan–Meier diagrams were used for graphical presentation of survival 1 year after HTX. Comparison of survival rates was performed using the log-rank (Mantel–Cox) test, and results are presented as percentage of survival (%) with hazard ratio (HR) and confidence interval

(CI) with confidence level of 95%. DAOH were compared by using Mann–Whitney *U* test given that these data were likely to be skewed. Normality testing was carried out by using Shapiro–Wilk test. Multivariate linear regression including ANOVA analysis was conducted as previously performed,[15] setting DAOH as dependent variable and VA-ECMO therapy, age, continuous veno-venous haemodialysis, duration of surgery, and neurological complications as predefined independent variables. Neurological complications were defined as a composite of ischaemic stroke or any intracranial bleeding with new onset of any documented neurological impairment. Transient ischaemic attack or neurological symptoms with duration $<$24 h were not included. No power analysis was conducted because of the retrospective nature of this study.

Results

Study population and patient characteristics

We investigated data of 154 HTX patients registered in the local HTX database of the University Hospital Düsseldorf, Germany; 10 patients (6.5%) were excluded from analysis due to incomplete medical records and impossibility to calculate DAOH [6 patients (3.9%)], death during surgery [3 patients (1.9%)], and veno-venous ECMO [1 patient (0.7%)]. Thus, we included 144 HTX patients into analysis (*Figure 1*). Overall mean age was 54 ± 12 years, and 114 patients (79.2%) were male. Mean age of donor hearts was 43 ± 13 years; 98 patients (68.1%) did not have VA-ECMO after surgery, and 46 patients (31.9%) had VA-ECMO due to PGD. Out of the VA-ECMO group, 30 (65.2%) patients suffered from biventricular failure while 16 (34.8%) patients had isolated right ventricular failure according to the International Society for Heart and Lung Transplantation PGD classification; 37/46 patients (80.4%) could be weaned successfully. There was no difference in successful weaning between biventricular and right ventricular failure group [biventricular 24 (80%) patients vs. right ventricular 13 patients (81.2%)]. Mean duration of VA-ECMO support was 8 ± 7 days. VA-ECMO patients were significantly older, and diabetes was more frequent than in patients without VA-ECMO (*Table 1*). Regarding laboratory parameters, VA-ECMO patients had higher levels of albumin compared with non-VA-ECMO patients. Intraoperative duration of surgery, cardiopulmonary bypass, and total ischaemia time were significantly longer in VA-ECMO group (*Table 1*). The use of continuous veno-venous haemodialysis, neurological complications, and resternotomy rates were higher in these patients compared with non-VA-ECMO patients (*Table 1*). In addition, reasons for hospital admissions and durations of hospital stays within the first year after HTX did not

Figure 1 Flow chart. HTX, heart transplantation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VV-ECMO, veno-venous extracorporeal membrane oxygenation.

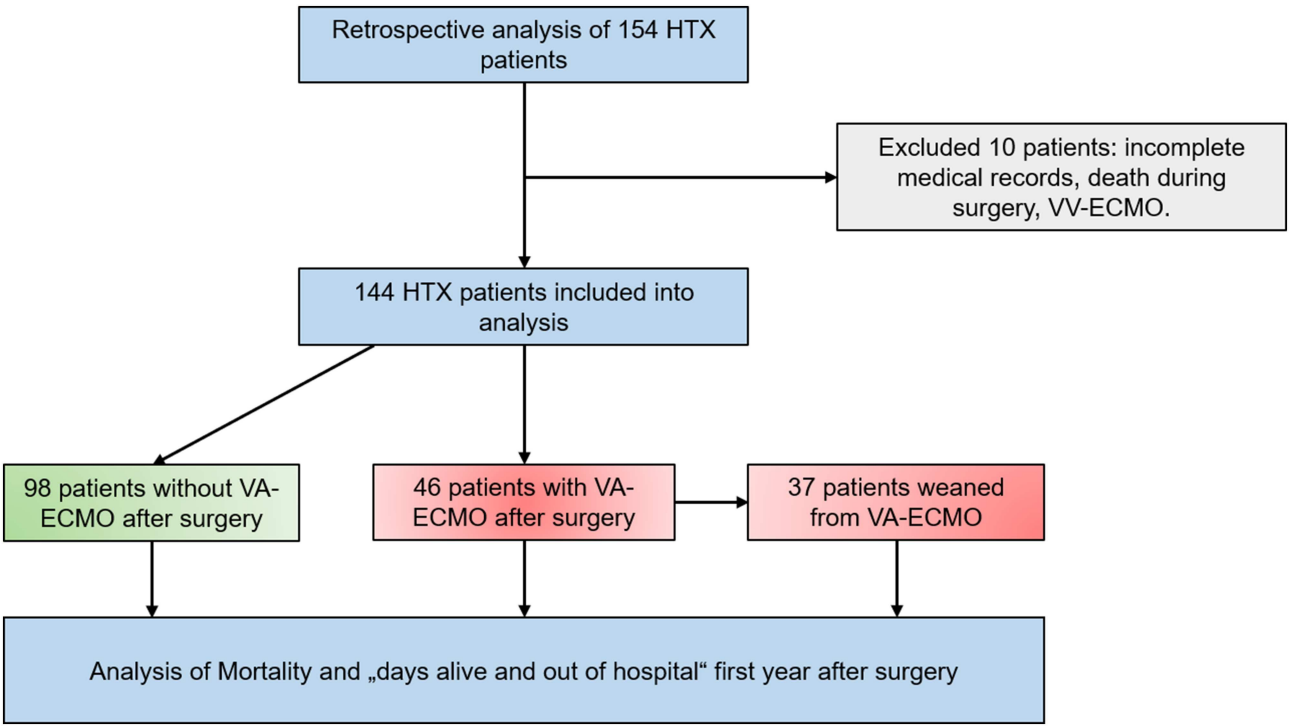

Table 1 Baseline characteristics, co-morbidities, laboratory parameters, and intraoperative and post-operative parameters

	Non-ECMO patients (N = 98)	ECMO patients (N = 46)	P-value[a]
Baseline characteristics			
Male sex, no. (%)	77 (78.7%)	37 (80.4%)	0.999
Age (years)	54 ± 12	58 ± 9	**0.031**
BMI (kg/m^2)	25.3 ± 4.3	26.1 ± 5	0.360
MELD score	14.2 ± 6.6	14.8 ± 7.6	0.658
Co-morbidities, no. (%)			
Smokers	21 (21.4%)	11 (23.9%)	0.830
Diabetes	15 (15.3%)	14 (30.4%)	**0.045**
Hyperlipidaemia	32 (32.7%)	15 (32.6%)	0.999
Arterial hypertension	48 (49.0%)	30 (65.2%)	0.076
Pulmonary hypertension	9 (9.2%)	7 (15.2%)	0.393
COPD	10 (10.2%)	3 (6.5%)	0.551
CKD requiring dialysis	3 (3.1%)	4 (8.7%)	0.210
VAD	53 (54.1%)	29 (63.0%)	0.368
Laboratory parameters before surgery			
Creatinine (mg/dL)	1.40 ± 1.10	1.49 ± 0.64	0.580
GFR (mL/min)	62 ± 23	62 ± 29	0.983
Haemoglobin (g/dL)	11.8 ± 2.1	11.5 ± 3.2	0.538
Haematocrit (%)	36.4 ± 5.6	35.6 ± 9.6	0.610
aPTT (s)	37 ± 13	34 ± 9	0.110
Quick (%)	46 ± 29	46 ± 26	0.970
Bilirubin (mg/dL)	0.64 ± 0.75	0.69 ± 1.12	0.732
Albumin (g/L)	1.52 ± 1.98	2.36 ± 2.07	**0.020**
LDH (mg/dL)	290 ± 388	370 ± 343	0.232
Intraoperative parameters			
Duration of surgery (min)	417 ± 98	528 ± 100	<**0.0001**
Duration of CPB (min)	249 ± 64	317 ± 73	<**0.0001**
Total ischaemia time (min)	214 ± 43	239 ± 68	**0.011**
Post-operative parameters, no. (%)			
CVVHD	47 (48.0%)	36 (78.3%)	**0.001**
Neurological complications	11 (11.2%)	13 (28.3%)	**0.016**
Resternotomy	11 (11.2%)	31 (67.4%)	<**0.0001**

aPTT, activated partial thromboplastin time; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVVHD, continuous veno-venous haemodialysis; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; LDH, lactate dehydrogenase; MELD, model for end-stage liver disease; VAD, ventricular assist device.
Data are presented as mean ± standard deviation or as absolute values with percentages, as appropriate. Bolded values indicate significant differences between both groups.
[a]P value of χ^2 test or two-tailed unpaired t-test after Levene's test for equality of variances.

Table 2 Reasons for hospital admissions and durations of hospital stays within the first year after heart transplantation

Reason for hospital admission	Days of hospital stay Non-ECMO patients (N = 98)	Days of hospital stay ECMO patients (N = 46)	P-value[a]
HTX	40 ± 28	55 ± 41	**0.029**
Endomyocardial biopsy	7 ± 4	6 ± 3	0.162
Gastrointestinal disorders	19 ± 14	9 ± 3	0.173
Pneumonia/respiratory infections	16 ± 7	30 ± 17	0.071
Wound infection/impaired wound healing	18 ± 22	29 ± 35	0.512
AKI	11 ± 7	10 ± 2	0.875
Graft rejection reaction	17 ± 21	13 ± 9	0.717
Bleeding complications	21 ± 9	21 ± 16	0.953
Non-cardiac surgery	7 ± 2	19 ± 16	0.083
Other infections	24 ± 29	27 ± 18	0.839

AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; HTX, orthotopic heart transplantation.
Data are presented as mean ± standard deviation. Bolded values indicate significant differences between both groups.
[a]P value of two-tailed unpaired t-test after Levene's test for equality of variances.

differ between groups. Patients with VA-ECMO had significantly longer initial hospital stay compared with non-VA-ECMO patients (non-VA-ECMO 40 ± 28 days vs. VA-ECMO 55 ± 41 days; P = 0.029; *Tables 1* and *2*).

Survival analysis

Overall mortality of the whole cohort was 20.8%. Patients without VA-ECMO therapy had significant lower rates of 1 year

mortality after HTX compared with patients who had VA-ECMO [non-ECMO 14.3% (14/98) vs. VA-ECMO 34.8% (16/46), HR: 0.32, 95% CI: 0.15–0.74; P = 0.002]. However, mortality did not differ significantly between weaned VA-ECMO patients and non-ECMO patients at 1 year after HTX [non-VA-ECMO 14.3% (14/98) vs. VA-ECMO (weaned) 18.9% (7/37), HR: 0.72, 95% CI: 0.27–1.90; P = 0.48] (*Figure 2*).

Days alive and out of hospital

Overall, median DAOH of the whole cohort were 293 (interquartile range 224–321). Data did not pass normality testing. DAOH were significantly higher in non-VA-ECMO patients compared with VA-ECMO patients [non-ECMO vs. VA-ECMO: 310 (277–327) days vs. 243 (0–288) days; $P < 0.0001$]. Non-VA-ECMO patients also had significantly higher rates of DAOH compared with patients weaned from VA-ECMO [non-ECMO vs. VA-ECMO (weaned): 310 (277–327) days vs. 253 (208–299) days; $P < 0.0001$] (*Figure 3*). In a sensitivity analysis using the alternative definition of DAOH from the non-cardiac surgery setting, results were comparable (Supporting Information, *Figure S1*).

Prediction of days alive and out of hospital in a linear regression model

We determined the influence of VA-ECMO and other covariates on DAOH in a multivariate linear regression model with DAOH as dependent variable. In addition to VA-ECMO therapy, we included age, duration of surgery, continuous veno-venous haemodialysis, and neurological complications as independent variables. The R^2 for the overall model was 0.258 (adjusted R^2 = 0.231) and therefore indicates a moderate goodness of fit. ANOVA analysis revealed that the included parameters could significantly predict DAOH with a significance level of <0.0001. In this multivariate linear regression model, VA-ECMO and neurological complications showed a significant impact on DAOH (VA-ECMO—unstandardized coefficients B: −54.10, standard error: 22.19, 95% CI −97.99 to −10.22, P = 0.016; neurological complications—unstandardized coefficients B: −91.14, standard error: 24.78, 95% CI −140.15 to −42.13, P = 0.0003) (*Table 3*). Of note, multivariable logistic and linear regression models showed no influence of continuous veno-venous haemodialysis, neurological complications, resternotomy, and ECMO cannulation type on DAOH, mortality, and successful weaning in a subgroup analysis of 46 VA-ECMO patients (Supporting Information, *Tables S1–S3*).

Post factum analysis

Based on review process, a *post factum* analysis of the yearly incidence of PGD and VA-ECMO after HTX revealed that there was a change over time. While in the first 5 years (2010–2014), PGD with VA-ECMO was present in 7/45 patients (= 15.6%), there were 39/99 (= 39.4%) HTX patients with PGD and VA-ECMO between 2015 and 2019. To address a potential centre bias, we performed a sensitivity analysis and compared the two observation periods, which did not change the results.

Discussion

The present study reveals two main findings: first, mortality at 1 year after HTX did not differ between weaned VA-ECMO

Figure 2 (A) Survival in non-extracorporeal membrane oxygenation (non-ECMO) patients is higher as compared with extracorporeal membrane oxygenation (ECMO) patients 1 year after heart transplantation (HTX). (B) Survival does not differ between non-ECMO patients and patients weaned from ECMO 1 year after HTX. CI, confidence interval; HR, hazard ratio.

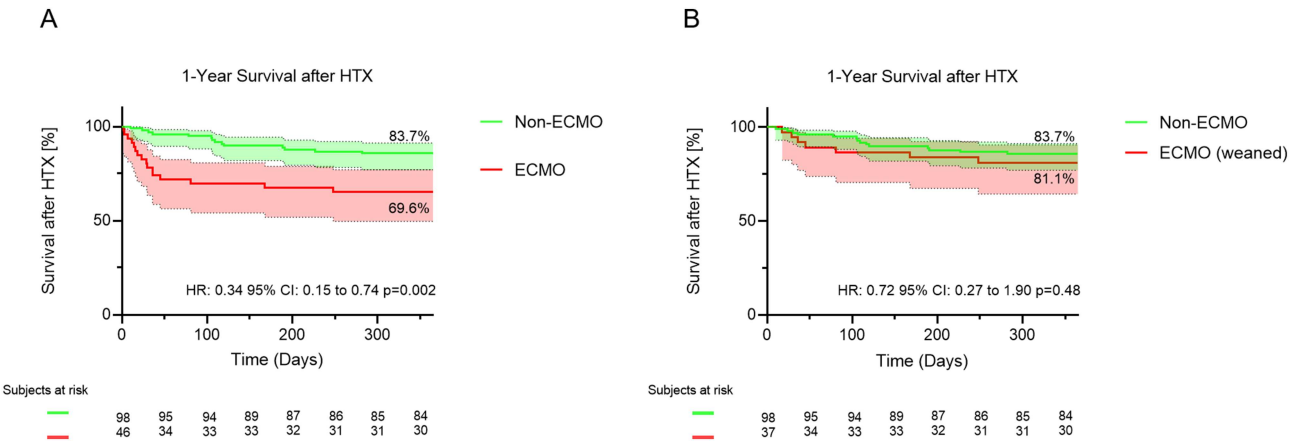

Figure 3 (A) Non-extracorporeal membrane oxygenation (non-ECMO) patients had significantly higher rates of 'days alive and out of hospital' (DAOH) as compared with extracorporeal membrane oxygenation (ECMO) patients 1 year after heart transplantation (HTX). (B) Non-ECMO patients had significantly higher rates of DAOH as compared with patients weaned from ECMO 1 year after HTX.

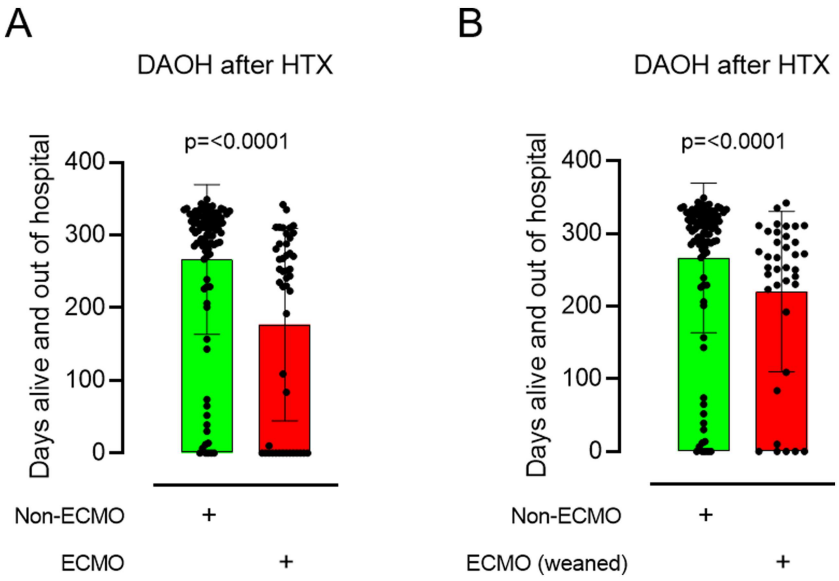

Table 3 Prediction of days alive out of hospital in a multivariate linear regression model

Model with DAOH as dependent variable	Unstandardized coefficients (*B*/standard error)	Standardized coefficients	95% CI of *B*	*P*-value[a]
Constant	376.83/59.26		259.65 to 494.01	<**0.0001**
VA-ECMO therapy	−54.10/22.19	−0.211	−97.99 to −10.22	**0.016**
Age	−1.29/0.81	−0.119	−2.85 to 0.15	0.112
Neurological complications	−91.14/24.78	−0.284	−140.15 to −42.13	**0.0003**
CVVHD	−37.10/19.15	−0.153	−74.97 to 0.77	0.055
Duration of surgery	−0.031/0.091	−0.029	−0.21 to 0.15	0.731

CI, confidence interval; CVVHD, continuous veno-venous haemodialysis; DAOH, days alive out of hospital; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.
Bolded values indicate significant differences between both groups.
[a]*P* value of multivariate linear regression.

patients receiving VA-ECMO therapy due to PGD and patients not receiving VA-ECMO therapy. This is remarkable as PGD is a relevant complication and VA-ECMO is a really invasive therapy. Second, weaned VA-ECMO patients had significantly lower DAOH compared with non-VA-ECMO patients at 1 year after HTX. Therefore, although survival is the same, VA-ECMO therapy due to PGD seems to have a relevant life impact in patients after HTX as these patients stay significantly longer in hospital during the first year after surgery.

Impact of veno-arterial extracorporeal membrane oxygenation on mortality

To date, there is limited evidence regarding the impact of VA-ECMO due to PGD in patients after HTX on outcome. According to our literature research, all existing studies had a retrospective design and no randomized trials exist so far. Focusing on short-term outcome, 45–80% of patients receiving VA-ECMO due to PGD survived until hospital discharge and the duration of VA-ECMO varied from 4 to 8 days.[3] Considering long-term outcome, current literature reports similar survival rates between patients weaned from VA-ECMO and non-VA-ECMO patients. D'Alessandro *et al*. retrospectively investigated the impact of temporary VA-ECMO due to early graft failure on mortality and 1 year survival in 394 HTX patients of whom 54 patients were treated with VA-ECMO. This study reported that VA-ECMO patients have the same survival rate compared with patients without PGD.[6] Another retrospective study by Marasco *et al*. also investigated 239 HTX patients with similar results: There was no difference in overall survival between non-VA-ECMO patients and weaned VA-ECMO patients with PGD.[17] Notably, this study defined weaned VA-ECMO patients as surviving the first 30 days and not only surviving VA-ECMO therapy as defined in the present study. In addition, there are also studies that

investigated VA-ECMO impact on survival at >1 year. Loforte *et al*. not only included patients treated with VA-ECMO but also intra-aortic balloon pump. The authors demonstrated in a retrospective analysis of 412 HTX patients that patients who survived and were treated with intra-aortic balloon pump or VA-ECMO due to PGD have the same long-term conditional survival rate at 5 years after surgery as patients who have not suffered from PGD.[11]

Definition of days alive and out of hospital

Regarding the current literature, two forms to calculate DAOH have been suggested. The difference consists in the evaluation of death within the study period. While the first definition by Ariti *et al*. counts every day patients were alive and not in hospital regardless of death within the observation period,[15] the second definition by Myles *et al*. assigns DAOH of 0 days if patients die.[18] In this study, we decided to choose the definition by Ariti *et al*. as this approach was employed in heart failure patients and thus in a cohort that is more comparable with HTX patients. Furthermore, 1 year mortality after HTX is reported to be ~15%[19] and is therefore higher than in perioperative non-cardiac surgery settings.[20] Overall mortality in our study was 20.8%. We decided to use the definition by Ariti *et al*. to calculate DAOH, as the definition by Myles *et al*. might underestimate DAOH after HTX. Nevertheless, we performed a sensitivity analysis using the definition by Myles *et al*., which revealed that the results were comparable (Supporting Information, *Figure S1*).

Impact of veno-arterial extracorporeal membrane oxygenation on days alive and out of hospital

The findings of our study regarding impact of VA-ECMO on mortality are in line with the mentioned literature and confirm that weaned VA-ECMO patients seem to have similar 1 year survival chances as non-VA-ECMO patients after HTX. However, in recent years, serious concerns have been raised if 'surviving the procedure' is the only meaningful measure of outcome. In this context, there might be other factors from a patient's point of view such as quality of life or functionality in daily life. Therefore, more patient-centred outcomes have been suggested recently. In the present study, DAOH was chosen as a measure of life impact. Data on DAOH after HTX do not exist yet so that the results of our study add new information to the current literature. First, we could show that DAOH are significantly lower in patients surviving VA-ECMO due to PGD compared with non-VA-ECMO patients after HTX. A multivariate linear regression revealed that after adjustment for age, neurological complications, renal replacement therapy, and duration of surgery, impact of VA-ECMO on DAOH was still significant. The only variable that also revealed a significant association with DAOH was 'neurological complications'. This clarifies that despite similar survival rates, VA-ECMO therapy has a relevant life impact in this cohort. Furthermore, we investigated not only the absolute number of DAOH at 1 year but also the duration of hospital stays for specific reasons. As presented in *Table 2*, a significant finding was that patients with VA-ECMO had a longer initial hospital stay compared with patients not treated with VA-ECMO. This suggests that impact of VA-ECMO therapy due to PGD after HTX on DAOH is mainly driven by prolonged initial hospital stay in these patients. The finding is supported by the fact that important variables such as age, duration of surgery, duration of cardiopulmonary bypass, and total ischaemia time of the donor heart were also significantly higher in patients who received VA-ECMO therapy afterwards. Most of these factors are associated with PGD. However, these findings were not associated with increased 1 year mortality in this study but with notable life impact, which seems surprising. This depicts the need for new concepts, especially in cases where long ischaemia or cardiopulmonary bypass times cannot be avoided and risk for PGD is high.

Referring to the existing literature, several studies came to similar conclusions. For example, Jalowiec *et al*. found in a retrospective study with 269 HTX patients that the length of the initial HTX hospital stay is the third strongest predictor for rehospitalizations during the first year after surgery.[21] Another large retrospective cohort study by Crawford *et al*. included 16 723 HTX patients and revealed that the risk for a prolonged hospital stay can already be determined at the time of HTX as it is mainly influenced by preoperative and intraoperative factors such as cold ischaemic time.[22] But despite the fact that prolonged HTX surgery (including the other intraoperative variables) could be a marker for adverse clinical outcomes, our linear regression model could not detect significant association with DAOH.

Finally, for the first time, this study provides epidemiological data on DAOH after HTX that might serve as a basis for future clinical trials investigating new methods in the prevention of PGD using DAOH as primary endpoint.

Limitations

This study has several limitations. First, this is a retrospective single-centre study. However, the majority of our data has been extracted from a prospectively conducted database. This ensures high data quality. Unfortunately, relevant parameters as SOFA score, SAVE score, or maximum lactate levels could not be assessed retrospectively as they were

not recorded in this database. Future studies should investigate the impact of VA-ECMO on outcome after HTX with a prospective design. Second, to assess the influence of covariates, multivariate linear regression was used. Nevertheless, other covariates that have not been included into analysis may have influenced our results. Third, we cannot guarantee that every hospitalization was reported as patients may have entered another hospital without our knowledge. However, HTX patients represent a cohort that is closely connected to our centre, and it is very unlikely that these patients are hospitalized elsewhere within the first year after HTX. Fourth, the sample size of 154 patients in a 10 year period is rather small, which raises concerns of a potential centre bias in regard of the overall experience with HTX patients. However, all our HTX patients are treated by the same specialized team so that expertise in this area may be regarded as good. Fifth, patients with other mechanical circulatory support devices such as combined VA-ECMO and Impella were not excluded in this study. Future studies should consider if the use of further devices might have an influence on DAOH.

Conclusions

Despite similar survival rates, VA-ECMO due to PGD after HTX has a relevant life impact as these patients spend significantly more time in hospital during the first year after surgery. Thus, DAOH may contribute to a more comprehensive assessment of outcome in this cohort.

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Conflict of interest

The authors report no conflict of interest or financial disclosures related to the current research project.

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Supporting information

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

Figure S1. DAOH analysis according to the alternative definition of DAOH.
Figure S2. Mortality analysis for the period 2010-2014.
Figure S3. DAOH analysis for the period 2010-2014.
Figure S4. Mortality analysis for the period 2015-2020.
Figure S5. DAOH analysis for the period 2015-2020.
Table S1. Multivariate logistic regression for association of selected variables with mortality in subgroup of VA-ECMO patients.
Table S2. Multivariate logistic regression for influence of selected variables on successful weaning in subgroup of VA-ECMO patients.
Table S3. Multivariate linear regression for influence of selected variables on DAOH in subgroup of VA-ECMO patients.

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Risk Factors for Acute Kidney Injury Requiring Renal Replacement Therapy after Orthotopic Heart Transplantation in Patients with Preserved Renal Function

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Abstract: Acute kidney injury (AKI), requiring renal replacement therapy (RRT). is a serious complication after orthotopic heart transplantation (HTX). In patients with preexisting impaired renal function, postoperative AKI is unsurprising. However, even in patients with preserved renal function, AKI requiring RRT is frequent. Therefore, this study aimed to identify risk factors associated with postoperative AKI requiring RRT after HTX in this sub-cohort. This retrospective cohort study included patients $\geq$ 18 years of age with preserved renal function (defined as preoperative glomerular filtration rate $\geq$ 60 mL/min) who underwent HTX between 2010 and 2021. In total, 107 patients were included in the analysis (mean age 52 $\pm$ 12 years, 78.5% male, 45.8% AKI requiring RRT). Based on univariate logistic regression, use of extracorporeal membrane oxygenation, postoperative infection, levosimendan therapy, duration of norepinephrine (NE) therapy and maximum daily increase in tacrolimus plasma levels were chosen to be included into multivariate analysis. Duration of NE therapy and maximum daily increase in tacrolimus plasma levels remained as independent significant risk factors (NE: OR 1.01, 95%CI: 1.00–1.02, p = 0.005; increase in tacrolimus plasma level: OR 1.18, 95%CI: 1.01–1.37, p = 0.036). In conclusion, this study identified long NE therapy and maximum daily increase in tacrolimus plasma levels as risk factors for AKI requiring RRT in HTX patients with preserved renal function.

Keywords: heart failure; cardiac surgery; prognosis; vasopressors; tacrolimus; calcineurin inhibitors

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1. Introduction

Acute kidney injury (AKI) is a common complication after orthotopic heart transplantation (HTX) [1,2]. A recent meta-analysis showed that incidences of AKI (according to KDIGO criteria) and AKI requiring renal replacement therapy (RRT) after HTX were 62.8% and 11.8%, respectively [3]. AKI post-HTX was associated with reduced long-term and 1-year patient survival [3,4]. In addition, AKI requiring RRT led to massive impairments

regarding the patient's quality of life [4,5]. Even in patients with preserved renal function, the occurrence of postoperative AKI requiring RRT was common [6]. Although some risk factors for postoperative AKI were previously identified, predictors for AKI in patients with preserved renal function undergoing HTX are underexplored [3]. Therefore, the aim of this study was to identify predictors for AKI requiring early RRT after HTX in patients with preserved renal function.

2. Materials and Methods

The present study was a retrospective, single-center cohort study and was conducted in compliance with the declaration of Helsinki and the International Society for Heart and Lung Transplantation (ISHLT) ethics statement. Ethical approval was obtained from the University of Duesseldorf's ethic committee (Reference-number: 4567). All patients were registered in the local dedicated prospective heart transplantation database and gave written informed consent to be registered. This report follows the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines for cohort studies.

2.1. Participants

All patients $\geq$ 18 years of age who underwent HTX at the University Hospital Duesseldorf, Germany, between 2010 and 2021 were screened for this study. The main inclusion criterium was preserved renal function before surgery. This was defined as a glomerular filtration rate (GFR) of $\geq$60 mL/min calculated from creatinine clearance on the day of HTX using the "Chronic Kidney Disease Epidemiology Collaboration" (CKD-EPI) formula, according to our local laboratory standards [7]. Patients with creatinine GFR $\geq$ 60 mL/min but preoperative AKI requiring RRT or preoperative CKD requiring hemodialysis were excluded. Patients with missing preoperative GFR values and incomplete medical records regarding the primary endpoint were also excluded.

2.2. Outcome Assessment and Data Collection

The primary endpoint of this study was AKI requiring RRT within 72 h after HTX. AKI was defined according to the Kidney Disease Improving Global Outcome (KDIGO) criteria. RRT was performed as continuous veno-venous hemodialysis (CVVHD). For data collection, the local prospective HTX database was screened. Data from this database or the patient's medical records were extracted by members of the study team. All data were double-checked by two persons trained in the study protocol.

2.3. Intraoperative and Postoperative Management

In our center, HTX patients are treated according to standard operating procedures. Additionally, to ensure a high quality of care, all HTX patients are treated by a small specialized team. In terms of AKI and RRT, volume management and infusion regimes may have a strong impact. Infusion regimes did not change during the study period. All patients received crystalloids as first line infusion therapy. Colloids such as hydroxyethyl starch or gelatin were not administered after heart transplantation. Albumin was only administered if the albumin plasma level was low, with a target area of 2.5–4.5 g/dL. Fresh frozen plasma, platelets and erythrocytes were given according to the cross-sectional guidelines of therapy with blood components and plasma derivatives by the German Medical Association.

2.4. Choice of Candidate Variables

To identify candidate variables for analysis, all variables relating to the patient, diagnosis, or associated organ dysfunction available in our database were considered. As an additional variable explored beyond the standard database contents, a maximum daily increase in tacrolimus plasma levels was separately calculated from daily tacrolimus levels. Firstly, all of these variables were assessed in a univariate analysis. As we observed

49 events in this study, a maximum of 5 covariables could be included into multivariate analysis [8]. Therefore, only significant variables in univariate analysis with good evidence of association with AKI after cardiac surgery were included into this model.

2.5. Statistical Analysis

All statistical analyses were performed using IBM SPSS version 25. Continuous variables are presented as means with standard deviation or median with interquartile range as appropriate. Categorical variables are presented as counts and percentages. Fisher's exact test and *t*-tests were used to compare categorical or continuous variables for descriptive statistics. Binary logistic regression was used for univariate analysis screening of continuous or dichotomous variables, respectively. For multivariate analysis, binary multivariate logistic regression was performed to assess independent associations between chosen variables and AKI requiring RRT. A p-value of <0.05 was considered as significant.

3. Results

3.1. Study Cohort

A total of 206 patients were screened for this study. A sum of 13 patients had haemodialysis prior to HTX and 86 patients had baseline GFR < 60mL/min. Based on the inclusion and exclusion criteria, 107 patients were used in the statistical analysis. Figure 1 displays selection process. The mean age of the study cohort was 52 ± 12 years and 84 patients (78.5%) were male. A total of 49 patients (45.8%) received RRT due to AKI after HTX. Detailed patient characteristics are presented in Table 1.

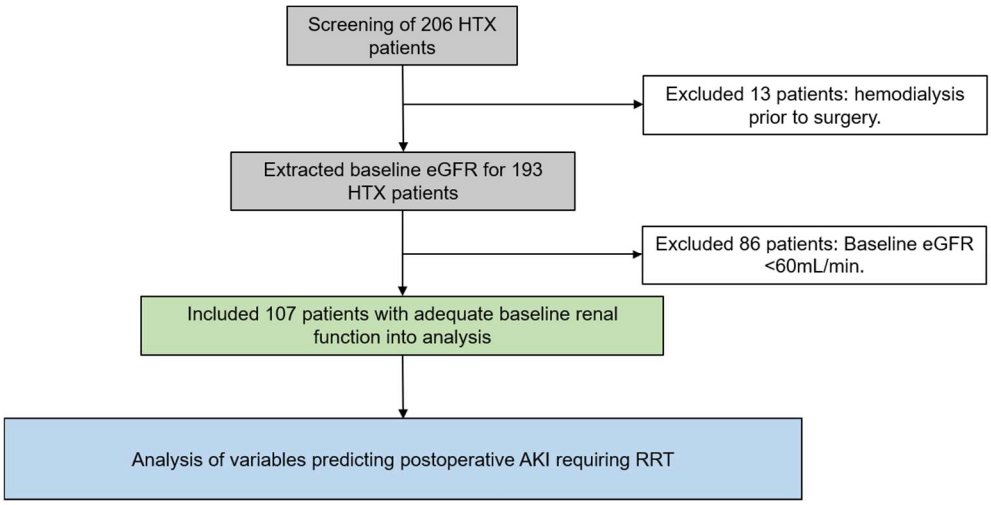

Figure 1. Study flow chart.

Table 1. Patient characteristics.

	All HTX Patients with Preserved Renal Function (N = 107)	HTX Patients without AKI Requiring RRT (N = 58)	HTX Patients with AKI Requiring RRT (N = 49)	*p*-Value
Baseline characteristics				
Male sex no. (%)	84 (78.5)	46 (79.3)	38 (77.6)	0.999
Age (years)	56 ± 12	51 ± 13	53 ± 11	0.356
Body mass index (kg/m^2)	25.2 ± 4.9	24 ± 5	26 ± 5	0.100
Comorbidities no. (%)				
Arterial hypertension	62 (57.9)	34 (58.6)	28 (57.1)	0.999
Diabetes	19 (17.8)	9 (15.5)	10 (20.4)	0.614
Pulmonary hypertension	11 (10.3)	5 (8.6)	6 (12.2)	0.751
COPD	10 (10.3)	7 (12.1)	3 (6.1)	0.338
During surgery				
Cold ischemia time (min)	153 ± 46	156 ± 38	152 ± 54	0.635
Warm ischemia time (min)	64 ± 15	63 ± 15	65 ± 14	0.551
Overall ischemia time (min)	218 ± 46	219 ± 37	216 ± 54	0.829
Cumulative Blood product transfusion (L)	6.2 ± 4.1	5.8 ± 4.3	6.4 ± 3.9	0.492
PRBC transfusion (L)	3.8 ± 2.9	3.6 ± 2.8	3.8 ± 2.3	0.675
FFP transfusion (L)	1.5 ± 1.8	1.2 ± 1.5	1.5 ± 1.5	0.278
Thrombocyte transfusion (L)	1.1 ± 0.9	1.0 ± 0.8	1.1 ± 0.7	0.848
Duration of surgery (min)	444 ± 115	431 ± 114	459 ± 116	0.224
Duration of CPB (min)	265 ± 78	253 ± 70	279 ± 85	0.083
Duration of Reperfusion (min)	132 ± 51	126 ± 49	140 ± 53	0.165
After surgery				
VA-ECMO no. (%)	33 (30.8)	9 (15.8)	24 (49.0)	<0.0001
CVVHD no. (%)	49 (45.8)	0 (0)	49 (100)	<0.0001
All-cause Infection no. (%)	21 (19.6)	6 (10.9)	15 (30.6)	0.015
Resternotomy no. (%)	29 (27.1)	13 (23.6)	16 (33.3)	0.380
Days on ICU	14 (8–27)	10 (6–17)	26 (13–36)	0.002
Length of mechanical ventilation (h)	63 (25–166)	32 (18–76)	155 (49–310)	<0.0001
Cumulative Blood product transfusion (L)	9.5 ± 12.7	5.1 ± 5.4	14.6 ± 16.3	<0.0001
PRBC transfusion (L)	3.5 ± 4.3	2.1 ± 3.3	4.9 ± 5.4	0.002
FFP transfusion (L)	5.7 ± 7.1	2.6 ± 2.1	8.1 ± 9.8	<0.0001
Thrombocyte transfusion (L)	1.0 ± 2.0	0.4 ± 0.7	1.4 ± 1.9	0.001
Medication at ICU				
Levosimendan no. (%)	23 (21.5)	5 (9.6)	18 (40.0)	0.001
Length of epinephrine therapy (h)	134 ± 126	99 ± 87	163 ± 145	0.043
Length of norepinephrine therapy (h)	134 ± 163	73 ± 58	205 ± 57	<0.0001
Peak tacrolimus plasma level (ng/mL)	12.9 ± 5.8	12.3 ± 5.1	13.6 ± 6.6	0.281
Steepest Increase in tacrolimus plasma level (ng/mL)	6.4 ± 5.1	4.4 ± 2.4	6.8 ± 6.6	0.037
Laboratory parameters at baseline				
GFR (mL/min)	82.3 ± 21.8	85.8 ± 20.6	78.1 ± 22.6	0.070
Bilirubin (mg/dL)	0.7 ± 0.6	0.59 ± 0.47	0.83 ± 0.64	0.072
Albumin (g/L)	4.0 ± 0.8	3.9 ± 0.7	4.0 ± 0.8	0.787
LDH (mg/dL)	308.8 ± 222.2	281 ± 182	339 ± 258	0.210
Quick (%)	49.6 ± 26.7	51 ± 30	47 ± 22	0.456
aPTT (s)	37.9 ± 10.6	37 ± 9	39 ± 12	0.354
Hemoglobin (g/dL)	11.9 ± 2.2	12.1 ± 2.0	11.7 ± 2.3	0.309
Hematocrite (%)	36.7 ± 5.9	37.1 ± 5.5	36.2 ± 6.5	0.450

HTX = Heart Transplantation; COPD = Chronic Obstructive Pulmonary Disease; PRBC = packed red blood cells; FFP = Fresh frozen plasma; CPB = Cardiopulmonary Bypass; VA-ECMO = Veno-Arterial Extracorporeal Membrane Oxygenation; CVVHD = Continuous Veno-Venous Hemodialysis; ICU = Intensive Care Unit; GFR = Glomerular Filtration Rate; LDH = Lactate Dehydrogenase; aPTT = Activated Partial Thromboplastin Time.

3.2. Univariate Analysis

From our local HTX database, we could assess 41 variables in univariate analysis (see Table A1). The following 9 variables were significantly associated with AKI requiring RRT in this first part of analysis (see Table 2): Post-HTX use of extracorporeal membrane

oxygenation (ECMO) (OR 5.12, 95%CI: 2.07–12.67, p = 0.0004), post-HTX new onset of any infection (OR 3.60, 95%CI: 1.27–10.22, p = 0.016), post-HTX levosimendan therapy (OR 6.27, 95%CI: 2.09–18.79, p = 0.001), post-HTX duration of norepinephrine (NE) therapy (OR 1.01, 95%CI: 1.00–1.02, p = 0.002), post-HTX amount of blood products on ICU (OR 1.00, 95%CI: 1.00–1.00, p = 0.0004), post-HTX length of ICU stay (OR 1.04, 95%CI: 1.01–1.08, p = 0.008), post-HTX length of mechanical ventilation (OR 1.02, 95%CI: 1.01–1.02, p = < 0.0001), peak tacrolimus plasma level within first 72 h (OR 1.15, 95%CI: 1.03–1.27, p = 0.011), and maximum daily increase in tacrolimus plasma levels within first 72 h post-HTX (OR 1.14, 95%CI: 1.01–1.29, p = 0.041).

Table 2. Univariate logistic regression for significant variables associated with acute kidney injury requiring renal replacement therapy after heart transplantation.

Variables for Univariate Logistic Regression	OR	95%CI	*p*-Value
ECMO after surgery	5.12	2.07–12.67	0.0004
All cause infection after surgery	3.60	1.27–10.22	0.016
Days at ICU	1.04	1.01–1.08	0.008
Length of mechanical ventilation	1.02	1.01–1.02	<0.0001
Cumulative blood product transfusion at ICU	1.00	1.00–1.00	0.0004
Levosimendan therapy	6.27	2.09–18.79	0.001
Duration of norepinephrine therapy	1.01	1.00–1.02	0.002
Max. daily increase in Tacrolimus plasma levels first 72 h	1.14	1.01–1.29	0.041
Tacrolimus peak concentration first 72 h	1.15	1.03–1.27	0.011

ECMO = Extracorporeal Membrane Oxygenation; ICU = Intensive Care Unit; OR = Odds Ratio; CI = Confidence Interval.

3.3. Multivariate Analysis

Based on the literature research, the following five of the nine significant variables were included into multivariate binary logistic regression (see Table 3): ECMO [9–11], all cause infection after surgery [12,13], levosimendan [14–16], duration of NE therapy [17–19] and increase in Tacrolimus plasma levels [18,20,21]. Evidence for the choice to include these five variables can be found as references next to each variable. Multivariate analysis revealed an independent significant influence of duration of NE therapy and maximum daily increase in tacrolimus plasma levels on AKI requiring RRT (NE: OR 1.01, 95%CI: 1.00–1.02, p = 0.005; increase in tacrolimus plasma level: OR 1.18, 95%CI: 1.01–1.37, p = 0.036). In addition, there was a nonsignificant trend for VA-ECMO due to primary graft dysfunction after HTX [OR 4.54, 95%CI: 0.96–21.43; p = 0.056].

Table 3. Multivariate logistic regression for variables predicting acute kidney injury requiring renal replacement therapy after heart transplantation.

Variables for Multivariate Logistic Regression	Regression Coefficient	Standard Error	OR	95%CI	*p*-Value
ECMO after surgery	1.513	0.792	4.54	0.96–21.43	0.056
All cause infection after surgery	−0.339	0.948	0.71	0.11–4.57	0.720
Duration of norepinephrine therapy	0.013	0.005	1.01	1.00–1.02	0.005
Levosimendan therapy	0.154	0.870	1.17	0.21–6.42	0.860
Max. daily increase in Tacrolimus plasma level first 72 h	0.162	0.077	1.18	1.01–1.37	0.036

ECMO = Extracorporeal Membrane Oxygenation; OR = Odds Ratio; CI = Confidence Interval.

4. Discussion

With our results we could show that prolonged NE therapy and maximum daily increase in tacrolimus plasma levels seem to be associated with early postoperative AKI requiring RRT after HTX in patients with preserved renal function.

4.1. Risk Factors for AKI Requiring RRT after HTX in the Literature

According to a recent meta-analysis, incidence of AKI is high, with up to 62.8% after HTX. Therefore, its prevention is a topic of interest for clinicians as AKI is associated with higher mortality rates [3]. Hence, the identification of risk factors for AKI after HTX was the focus of previous research. However, predictors for patients with preserved renal function is lacking. Previous cohort studies investigating HTX patients identified several patient related peri- and post-operative risk factors for AKI, as reported in the meta-analysis of Thongprayoon et al. [3]. Most of these variables were available in our database and therefore were included into univariate analysis (Table A1). Besides these variables, Euroscore, levels of Troponin I, use of Cyclosporine, right ventricular failure with higher right atrial pressure and high pulmonary vascular resistance or cardiac tamponade were reported to have association with postoperative AKI after HTX [3]. However, these variables were not accessible in our database. Only a few variables could be identified as associated with early onset AKI requiring RRT in patients with preserved renal function undergoing HTX. In line with the current literature, we can confirm that postoperative VA-ECMO therapy [22], high tacrolimus levels [20], the amount of transfusions [23], therapy with levosimendan for right ventricular failure [24], and duration of mechanical ventilation [25] were associated with AKI requiring RRT. However, out of all variables only the duration of NE therapy and maximum daily increase in tacrolimus plasma levels remained significant in our multivariable logistic regression.

4.2. The Role of Tacrolimus in Early AKI Requiring RRT

Tacrolimus is a crucial component of immunosuppressive therapy after HTX and is commonly started directly after surgery. However, nephrotoxicity by reduced renal blood flow is an adverse side effect, which can potentially aggravate the risk for early onset AKI [26,27]. Previous studies have already shown that high peak concentrations, above the therapeutic window of 8–12 ng/mL, are associated with AKI in post-transplant patients [18,20,21]. Sikma and co-authors demonstrated, in a retrospective cohort study including 110 patients, that supratherapeutic tacrolimus concentrations are independently associated with the development of AKI in adult HTX patients [20]. Miano and co-authors investigated early tacrolimus concentrations in 484 lung transplant recipients and also found that early tacrolimus exposure was an independent risk factor for AKI [21]. However, utility of this marker in predicting AKI is unclear as tacrolimus concentrations can be influenced by metabolic disorders which are also associated with AKI. Postoperative organ failure due to infection or sepsis could lead to impaired metabolization of tacrolimus, resulting in high plasma levels. In this context, a previous study of Percy et al. could show elevated Tacrolimus plasma levels in patients transplanted with a kidney and concomitant infection [28]. In our study, we demonstrated that tacrolimus peak plasma concentration within the first 72 h after HTX was associated with early onset AKI. Additionally, we showed that high maximum daily increase in tacrolimus plasma levels within the first 72 h was an independent predictor of AKI after HTX. In this study, postoperative infection was also associated with AKI but max. daily increase in tacrolimus plasma levels showed an independent association with AKI in multivariable logistic regression. This aspect, in addition to avoiding peak plasma concentration outside the therapeutic window, might have a significant impact in the clinical prevention of AKI after HTX. Our findings complement the limited literature in this field and should be investigated in larger, prospective trials. To avoid early postoperative AKI, alternative concepts for postoperative immunosuppressive therapy were previously proposed. In this context, calcineurin inhibitor-free induction therapy with basiliximab or anti-thymocyte globulin (ATG) showed reduced incidence of

postoperative AKI after HTX as compared to calcineurin inhibitors [29]. Another concept to avoid high Tacrolimus peak plasma concentrations is use of extended-release tacrolimus. The extended release of the substance decreases the maximum concentrations while immunosuppressive effects seem to be non-inferior to regular Tacrolimus [30]. However, impact on early acute kidney injury after HTX is underexplored and should be investigated in future trials.

4.3. The Role of Norepinephrine in Early AKI Requiring RRT

In the present study, we found that duration of NE therapy was associated with AKI requiring RRT in patients with preserved renal function after HTX. Nephrotoxic properties of vasoactive agents by constriction of afferent renal blood vessels are critically discussed. In this context, Jocher et al. showed that elevated vasoactive inotropic score at 24 h after surgery was an independent risk factor for early onset AKI in 228 HTX patients [17]. The vasoactive inotropic score is used to objectively quantify the cardiovascular support of different vasoactive drugs. A high vasoactive inotropic score is associated with poor outcomes [31]. Interestingly, mean arterial blood pressure did not differ between AKI and non-AKI patients in the study of Jocher et al. This could lead to the conclusion that use of vasoactive drugs such as NE may directly impair renal blood flow leading to AKI. Nevertheless, adequate mean arterial blood pressure, resulting from vasoactive support, only insufficiently reflects cardiac output and organ perfusion. Microvascular perfusion can be affected by excessive vasopressors therapy to achieve mean arterial pressure goals while cardiac output remains low [32]. This aligns with our findings, where we showed an association between duration of NE therapy and AKI. Unfortunately, we were not able to assess vasoactive inotropic score. However, a major limit of vasoactive inotropic score is that it can only depict vasoactive support at one specific time point. Hence, the incidence of AKI could depend on dosing and duration of NE infusion and needs further investigation. Another study could reveal that use of dopamine, another vasoactive drug, was associated with AKI after liver transplantation [18]. However, these results are contradicting as Carrier et al. could not show any association between use of vasopressors and AKI requiring RRT after liver transplantation [33]. Once again, the postoperative use of vasoactive drugs such as NE can modify fluid balance or arise from low intravascular volume after HTX, resulting in decreased renal blood flow and therefore marks another risk factor for AKI [33,34].

4.4. Limitations

This study has several limitations that need to be addressed. Firstly, the incidence of early onset AKI requiring RRT in this study was high. This must be taken into account when interpreting our results. Secondly, as our sample size was rather small, we were not able to include all significant variables of the univariate model into multivariate analysis. However, some of these variables, such as prolonged ICU stay, might rather be associated with AKI than being a predictor for AKI. Thus, a larger sample size might enable the identification of more independent risk factors for AKI requiring RRT. Thirdly, this study had a retrospective design, therefore data assessment was limited to our database. Unfortunately, we could not assess vasoactive inotropic score. However, a huge amount of our data could be extracted from this prospectively conducted database, which should ensure a higher quality of data. Nevertheless, further studies should re-investigate our findings with a prospective design.

5. Conclusions

This study identified prolonged vasopressor therapy and high maximum daily increase in tacrolimus plasma concentrations as independent risk factors for early onset AKI requiring RRT after HTX in patients with preserved renal function. These results are clinically relevant and new therapeutic approaches for HTX patients are urgently needed. In this context, the role of calcineurin inhibitor free induction therapy or extended-release tacrolimus should be investigated.

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Informed Consent Statement: As this study was a retrospective study, no separate informed consent was necessary. All patients gave written informed consent in the past to be registered in the local HTX database and that these data can be used for research purposes.

Data Availability Statement: All generated data can be made available on reasonable request by the first author R.M.

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

Appendix A

Table A1. Univariate logistic regression for identification of variables associated with acute kidney injury requiring renal replacement therapy after heart transplantation.

Variables for Univariate Logistic Regression	OR	95%CI	*p*-Value
ECMO after surgery	5.12	2.07–12.67	0.0004
All cause infection after surgery	3.60	1.27–10.22	0.016
Days at ICU	1.04	1.01–1.08	0.008
Length of mechanical ventilation	1.02	1.01–1.02	<0.0001
Cumulative blood product transfusion at ICU	1.00	1.00–1.00	0.0004
Levosimendan therapy	6.27	2.09–18.79	0.001
Duration of norepinephrine therapy	1.01	1.00–1.02	0.002
Max. daily increase in Tacrolimus plasma level first 72 h	1.14	1.01–1.29	0.041
Tacrolimus peak concentration first 72 h	1.15	1.03–1.27	0.011
Duration of epinephrine therapy	1.00	1.00–1.01	0.057
Age (Recipient)	1.02	0.98–1.05	0.353
Sex (Recipient)	1.11	0.44–2.80	0.825
BMI (Recipient)	1.07	0.99–1.16	0.103
Bilirubin (Recipient)	2.27	0.92–5.58	0.075
Hemoglobin (Recipient)	0.91	0.76–1.09	0.307
Albumin (Recipient)	1.11	0.53–2.34	0.782
Prior cardiac surgery (Recipient)	1.50	0.64–3.52	0.349
Prior ventricular assist device (Recipient)	1.22	0.56–2.66	0.624
Prior resuscitation (Recipient)	1.22	0.42–3.53	0.715
Diabetes (Recipient)	1.40	0.52–3.77	0.511
Hypertension (Recipient)	0.94	0.44–2.03	0.877
Pulmonary hypertension (Recipient)	1.48	0.42–5.18	0.540

Table A1. *Cont.*

Variables for Univariate Logistic Regression	OR	95% CI	*p*-Value
COPD (Recipient)	0.48	0.12–1.95	0.301
Age (Donor)	1.01	0.98–1.05	0.417
Sex (Donor)	0.93	0.43–2.00	0.852
BMI (Donor)	0.94	0.86–1.02	0.140
Hypertension (Donor)	1.14	0.35–3.72	0.834
Diabetes (Donor)	0.64	0.10–3.95	0.631
Creatine kinase peak (Donor)	1.00	1.00–1.00	0.461
Hemoglobin (Donor)	1.13	0.96–1.34	0.141
LVEF (Donor)	0.98	0.93–1.03	0.403
IABP after surgery	1.54	0.33–7.25	0.584
Graft rejection after surgery	0.36	0.07–1.85	0.22
CMV after surgery	0.56	0.05–6.42	0.644
Resternotomy	1.62	0.68–3.83	0.277
Duration of CPB	1.01	0.99–1.01	0.089
Duration of Reperfusion	1.01	0.99–1.01	0.172
Duration of surgery	1.00	0.99–1.01	0.224
Cold ischemic time	0.99	0.99–1.01	0.632
Warm ischemic time	1.01	0.98–1.03	0.547
Total ischemic time	0.99	0.99–1.01	0.822

ECMO = Extracorporeal Membrane Oxygenation; ICU = Intensive Care Unit; BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; LVEF = Left Ventricular Ejection Fraction; IABP = Intra-Aortic Balloon Pump; CMV = Cytmegalovirus; CPB = Cardiopulmonary Bypass; OR = Odds Ratio; CI = Confidence Interval.

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Impact of Cardiopulmonary Resuscitation of Donors on Days Alive and Out of Hospital after Orthotopic Heart Transplantation

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Abstract: Background: The number of patients waiting for heart transplantation (HTX) is increasing. Optimizing the use of all available donor hearts is crucial. While mortality seems not to be affected by donor cardiopulmonary resuscitation (CPR), the impact of donor CPR on days alive and out of hospital (DAOH) is unclear. Methods: This retrospective study included adults who underwent HTX at the University Hospital Duesseldorf, Germany from 2010–2020. Main exposure was donor-CPR. Secondary exposure was the length of CPR. The primary endpoint was DAOH at one year. Results: A total of 187 patients were screened and 171 patients remained for statistical analysis. One-year mortality was 18.7%. The median DAOH at one year was 295 days (interquartile range 206–322 days). Forty-two patients (24.6%) received donor-CPR hearts. The median length of CPR was 15 (9–21) minutes. There was no significant difference in DAOH between patients with donor-CPR hearts versus patients with no-CPR hearts (CPR: 291 days (211–318 days) vs. no-CPR: 295 days (215–324 days); $p = 0.619$). Multivariate linear regression revealed that there was no association between length of CPR and DAOH (unstandardized coefficients B: −0.06, standard error: 0.81, 95% CI −1.65–1.53, $p = 0.943$). Conclusions: Donor CPR status and length of CPR are not associated with reduced DAOH at one year after HTX.

Keywords: heart failure; heart transplantation; cardiopulmonary resuscitation; patient centered outcomes; quality of life; mortality

1. Introduction

The number of patients waiting for heart transplantation (HTX) is constantly increasing due to factors such as demographic shift and improved medical treatment [1–8]. The

number of available donor hearts, however, does not match the high demand for these organs. According to Eurotransplant's annual report for Germany, 329 donor hearts were transplanted in the year 2021, while 727 patients remained on the waiting list for HTX at the end of the year [9]. To maximize the benefit from available donor organs, it is crucial to optimize the allocation of potential donor hearts.

One criterion to consider in the allocation is a status of cardiopulmonary resuscitation (CPR) of the donor. Recent studies showed that mortality was not altered by the usage of donor CPR hearts after HTX, even when adjusted for longer durations of CPR and no-flow-time [10–13]. However, from a patient point of view, there might be other important factors next to solely survive and it is unclear how donor CPR affects patient quality of life. Days alive and out of hospital (DAOH) has been suggested as an alternative endpoint to quantify life impact, as it captures mortality, re-hospitalizations, and quality of life to an extent [14–17]. In this study, we evaluated the impact of donor CPR on DAOH in patients undergoing HTX. Our primary hypothesis was that, consistent with the existing mortality data, there might be no difference in DAOH after HTX when donor-CPR hearts were used compared with donor hearts without CPR. Another objective was to analyze the effect of CPR length on DAOH.

2. Materials and Methods

This study was conducted as a retrospective cohort study at the University Hospital Duesseldorf in accordance with the declaration of Helsinki and the guidelines for good clinical practice. The ethical review board of the Heinrich Heine University Duesseldorf approved the study protocol (reference number 4567). As all patients gave their written informed consent to be included in the prospective heart transplantation database of the University Hospital Duesseldorf, the need for additional written informed consent for this retrospective analysis could be waived. The present analysis complements a recent analysis by M'Pembele et al. (under review) which investigated life impact of perioperative variables after HTX. All included variables in this study were based on a meta-analysis [18]. As donor-CPR was not included into this meta-analysis (and consequently not included into the study), this separate analysis was performed.

This report was written according to the "Strengthening the Reporting of Observational studies in Epidemiology" (STROBE) guidelines [19].

2.1. In- and Exclusion Criteria/Study Participants

Inclusion criteria for this study were defined as HTX from September 2010 to December 2020 at our institution and age $\geq$18 years. Exclusion criteria were: incomplete medical records and missing data regarding the main exposures and/or the primary endpoint. Patients were then divided into two groups according to their main exposure: patients receiving hearts of donors that underwent cardiopulmonary resuscitation (donor-CPR-group) and patients receiving CPR-naive hearts (no-CPR-group). As a secondary exposure, we analyzed the length of CPR. All data were extracted from the local HTX database, as well as from electronic medical charts and included patient characteristics, medical history, and hospitalizations within one year.

2.2. Measurement of Endpoint DAOH

The primary endpoint of this study was days alive and out of hospital (DAOH) at one year after HTX. The calculation of DAOH was performed in the same manner as reported previously [16,17]. Briefly, DAOH is equal to the sum of days in hospital for one patient, subtracted from 365 days. In the case that a patient did not survive until one year after HTX, 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 day in hospital. As all HTX patients are very closely connected to our center, it is very unlikely that there were external hospitalizations without

our knowledge. As a secondary endpoint, we analyzed mortality at one year after HTX to oppose this endpoint with DAOH.

2.3. Statistical Analysis

Statistical analysis was performed using GraphPad Prism© (Version 8.02, LaJolla, CA, USA) and IBM SPSS© (Version 26.0, Armonk, NY, USA). Continuous variables are reported as mean ± standard deviation (SD) or as median with interquartile ranges (IQR) whenever appropriate, while categorical variables are presented as absolute numbers and percentages.

To compare DAOH depending on the donor-CPR status, we performed a Mann–Whitney U test. In order to assess the impact of the CPR length, we stratified the donor-CPR group by quartiles of CPR duration in four groups (<9 min, 9–14 min, 15–21 min, and >21 min) of similar size. Group comparison was performed with a Kruskal–Wallis test adjusted for multiple comparisons. Further, we conducted univariable linear regression to quantify the potential correlation between donor-CPR duration and DAOH. This was expanded by a multivariate linear regression model adjusting for donor age, mechanical ventilation, and renal replacement therapy based on M'Pembele et al. 2022 (under review). Finally, univariate survival analysis of donor-CPR- and no-CPR patients was conducted by computing Kaplan–Meier curves.

3. Results

In total, 187 patients underwent HTX at out center from September 2010 to December 2020. After exclusion of 16 (6.4%) patients due to missing data regarding CPR length or DAOH, 171 eligible patients were identified and analyzed, of which 42 (24.6%) received hearts from donors that underwent cardiopulmonary resuscitation (see Figure 1).

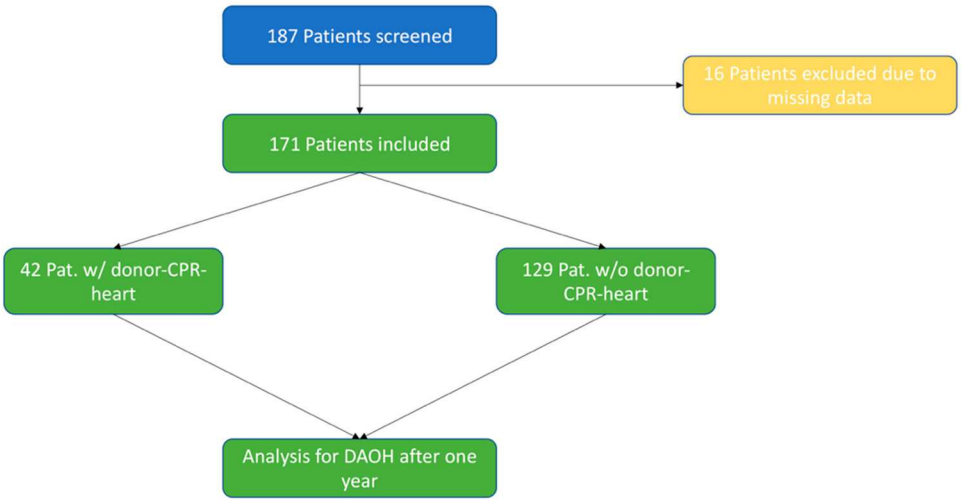

Figure 1. Study flow chart.

Mean age for recipients was 54 ± 11 years, 74 out of 171 (43%) patients were female. Mean age for donors was 43 ± 13 years. The median length of CPR was 15 min (IQR: 9–21 min). The inotropic dobutamine was administered to 21% of the donors with CPR status and to 9% of the no-CPR donors. Recipients and donor characteristics are specified in detail in Table 1. Overall, 32 (18.7%) patients had died after one year. Median DAOH after one year for the entire cohort was 295 (interquartile range (IQR) 206–322 days).

Table 1. Patient characteristics.

	All (n = 171)	Donor-CPR (n = 42)	No-CPR (n = 129)
Baseline Characteristics of Recipients in Mean ± SD/n (%)			
Male/female	97/74	32/10	65/64
Age (years)	54 ± 11	56 ± 10	54 ± 12
BMI (kg/m^2)	26 ± 5	27 ± 5	25 ± 5
Creatinine (mg/dL)	1.4 ± 1.0	1.4 ± 0.7	1.4 ± 1.1
Diabetes present	34 (20)	8 (19)	26 (20)
Baseline characteristics of donors in mean ± SD/n (%)			
Male/female	97/74	32/10	65/64
Mismatched sex	51 (30)	6 (14)	45 (35)
Age (years)	43 ± 13	38 ± 12	44 ± 13
BMI (kg/m^2)	26 ± 4	26 ± 5	26 ± 3
Diabetes present	11 (6)	1 (2)	10 (8)
Last dosage of norepinephrine (µg/kg/min)	0.13 ± 0.2	0.08 ± 0.08	0.14 ± 0.23
Donors with dobutamine	20 (12)	9 (21)	11 (9)
Last dosage of dobutamine (µg/kg/min)	3.51 ± 1.42	3.32 ± 0.81	3.67 ± 1.75
Preoperative morbidities			
Requirement of LVAD	88 (51)	23 (55)	65 (50)
Arterial hypertension	102 (60)	31 (74)	71 (55)
Pulmonal hypertension	18 (11)	5 (12)	13 (10)
Previous cardiothoracic surgeries	110 (64)	30 (71)	80 (62)
CMV IgG present	83 (49)	18 (43)	65 (50)
Intraoperative conditions			
total ischemic time (min)	219 ± 52	219 ± 40	219 ± 55
Postoperative conditions			
Dialysis	100 (58)	26 (62)	
VA-ECMO	51 (30)	15 (36)	36 (28)
Assisted ventilation (h)	151 ± 194	177 ± 207	142 ± 188
Underlying diseases requiring HTX			
DCM	91 (53)	19 (45)	72 (56)
ICM	67 (40)	19 (45)	48 (37)
HCM	3 (2)	1 (2)	2 (2)
ARVCM	6 (4)	1 (2)	5 (4)
Others	4 (2)	2 (5)	2 (2)
Endpoints			
DAOH	295 (206, 322)	291 (211, 318)	295 (215, 324)

BMI = Body mass index, LVAD = left ventricular assist device, DCM = dilated cardiomyopathy, ICM = ischemic cardiomyopathy, HCM = hypertrophic cardiomyopathy, ARVCM = arrhythmogenic right ventricular cardiomyopathy, VA-ECMO = veno-arterial extracorporeal membrane oxygenation, DAOH = days alive and out of hospital.

There was no significant difference in DAOH after one year between donor-CPR patients: 291 days (IQR: 211–318 days) vs. no-CPR patients: 295 days (IQR: 215–324 days; $p = 0.619$, see Figure 2). There was also no difference in DAOH when stratified by CPR duration (see Figure 3).

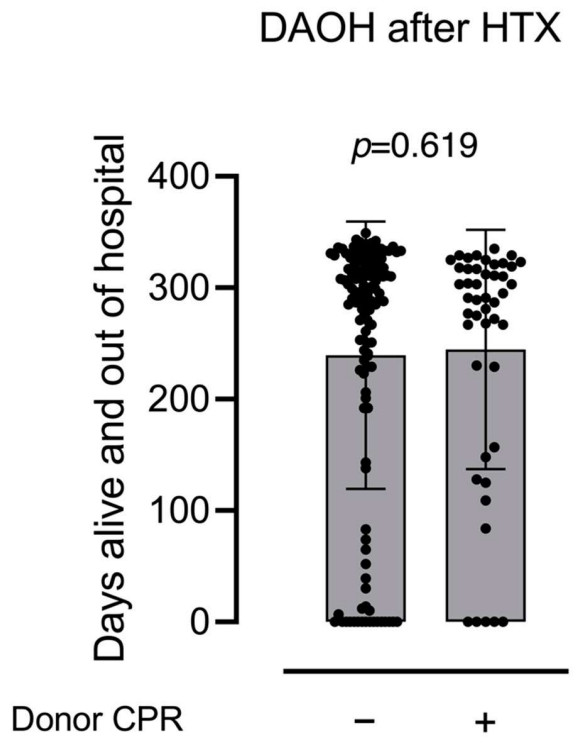

Figure 2. Comparison of days alive and out of hospital at one year after heart transplantation between patients who received donor hearts with and without history of cardiopulmonary resuscitation.

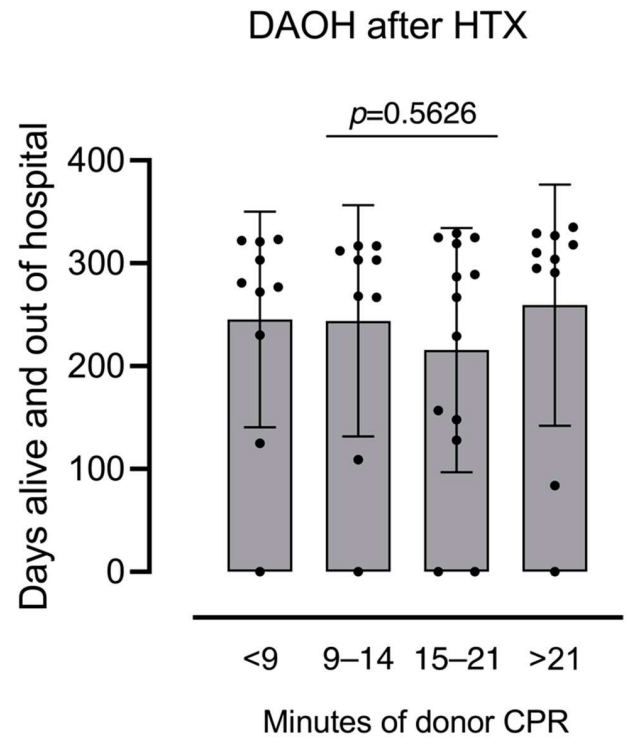

Figure 3. Days alive and out of hospital at one year after heart transplantation by quartile of cardiopulmonary resuscitation duration of donor hearts.

3.1. Univariate and Multivariate Linear Regression

Univariate linear regression showed that there was no association between length of CPR and DAOH (unstandardized coefficients B: −0.208, standard error: 1.42, 95% CI −3.078–2.662, $p = 0.884$). According to multivariate linear regression, the association between length of donor-CPR and DAOH was still not significant (unstandardized coefficients B: −0.06, standard error: 0.81, 95% CI −1.65–1.53, $p = 0.943$), whereas significant associations of known risk factors for low DAOH were unaffected (see Table 2).

Table 2. Multivariate linear regression for the association between length of donor-CPR and DAOH at one year after heart transplantation.

Variables	Unstandardized B	Std. Error	Standardized Beta	Lower Bound 95% CI	Upper Bound 95% CI	*p*-Value
Donor age	−2.26	0.61	−0.25	−3.47	−1.05	<0.0001
Length of mechanical ventilation	−0.23	0.04	−0.38	−0.32	−0.14	<0.0001
Postoperative RRT	−50.84	17.18	0.21	−84.76	−16.91	0.004
Length of Donor CPR	−0.06	0.81	−0.005	−1.65	1.53	0.943

Std = Standard; CI = Confidence Interval; RRT = Renal Replacement Therapy; CPR = Cardiopulmonary Resuscitation.

3.2. Kaplan–Meier Analysis

Survival analysis by Kaplan–Meier method revealed that there was no significant difference between donor-CPR- and no-CPR-patients regarding survival rates at one year after HTX (donor-CPR patients = 79.9% versus no-CPR patients = 85.8%; hazard ratio = 1.39 (95% CI 0.62 to 3.10, $p = 0.41$) (see Figure 4).

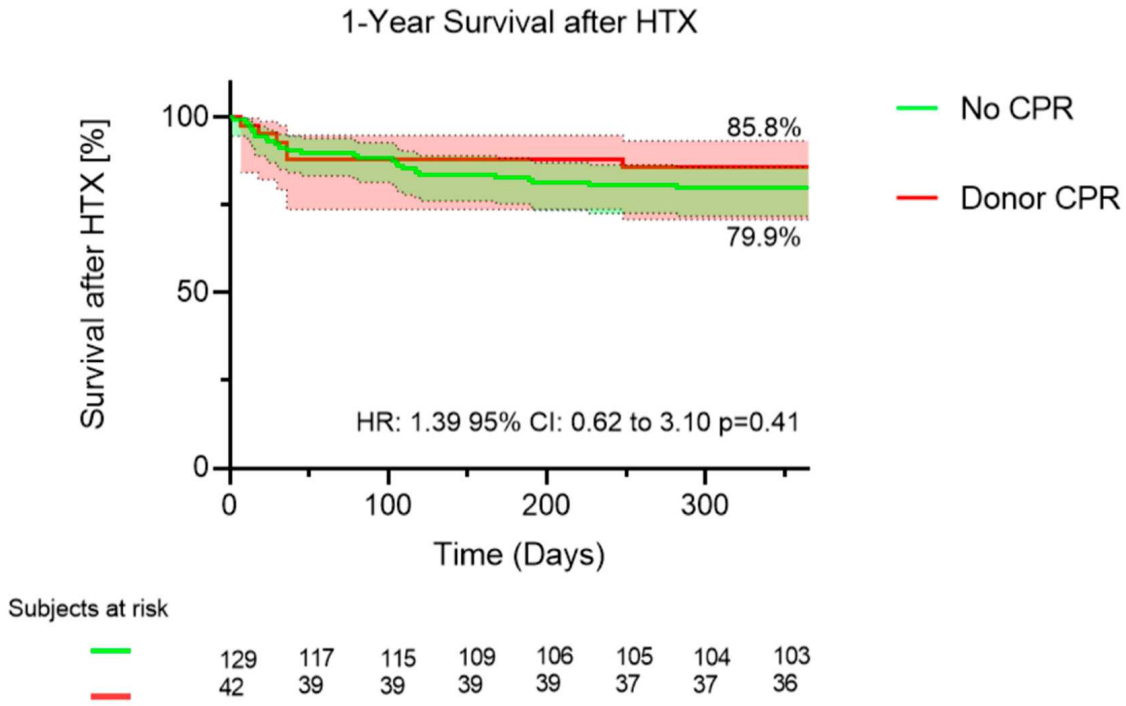

Figure 4. Comparison of survival at one year after heart transplantation between patients who received donor hearts with and without history of cardiopulmonary resuscitation.

4. Discussion

The current study aimed to analyze the impact of donor-CPR on DAOH after HTX. Our findings are in line with data on survival and suggest that a status of donor-CPR as well as the length of CPR do not negatively affect DAOH after one year.

Mehdiani and colleagues have shown in a retrospective study that postoperative morbidity and one-year mortality are not affected by CPR prior to organ donation in heart transplant patients [10]. From this, the authors drew the conclusion that donor hearts should not be rejected due to a history of CPR. Cheng et al. examined whether different durations of CPR prior to organ donation affected postoperative outcomes and survival [11]. Although a trend towards lower survival rates for longer CPR times prior to organ donation seemed to emerge from their data, this trend did not reach statistical significance.

Even earlier than that, the group around Quader and colleagues conducted a retrospective analysis of a large number of cases of HTX in the USA (n = 29,242, n = 1396 with history of CPR), reaching the conclusion that cardiac arrest and subsequent cardiopulmonary resuscitation did not induce poorer outcomes for the recipients [20]. Interestingly, a possible explanation cited by Quader et al. for why these CPR-positive hearts do not negatively affect mortality is the lack of comorbidities and generally younger age of these donors. In our cohort, donors in the donor-CPR group were not significantly younger, but were not more likely to have diabetes mellitus.

Literature on quality of life after HTX is abundant and consensually agrees that organ transplant positively affects most aspects commonly assessed in surveys (see for example, the reviews of Rosenberger et al., and more recently, Tackmann and Dettmer) [21,22]. However, such studies seldomly assess donor characteristics for their analyses and are, thus, not useful to determine the impact of CPR status of the donor on recipient QOL. To the best of our knowledge, at the time of writing this report, there are no studies comparing QOL between recipients from CPR-subjected donors vs. CPR-naive donors. We also could not find any report on DAOH for these two groups.

Seeing the scarcity of data on patient-centered outcomes, our study could further assist physicians when making choices on donor eligibility and organ allocation. Of course, clinicians primarily have to answer the question if suitable patients for HTX are able to survive when receiving a donor heart with a history of CPR. However, after successful HTX, this focus might change and factors related to functional capacity and QOL might get more and more important. From our point of view, being in hospital is not compatible with good QOL. Consequently, the number of days patients are alive and not hospitalized (=DAOH) after HTX might be an appropriate measure of long-term life impact and QOL to an extent. Referring to our data, the lack of significant difference in DAOH between our study cohorts thus might be interpreted as an additional measure of safety and suitability for CPR-positive donor hearts in regard to patient quality-of-life. Additionally, fewer days in hospital means less financial burden on healthcare systems, and DAOH might be used as a surrogate marker for healthcare costs.

Strengths and Limitations

Our current study is subject to the usual limitations that incur for retrospective analyses. However, our center's HTX database is collected prospectively, which can serve to ensure the quality of the data we analyzed. This study also suffers from being limited to a single center and having a modest sample size. Another limitation is the impossibility of including hospitalizations outside of our university hospital into the DAOH calculation. Although patients that underwent HTX at our center are closely connected and normally referred to us for care, we cannot exclude missing data on hospital stays, which might alter the results of our calculations.

On the other hand, the usage of DAOH as our endpoint bears the strength of including an objective quantification of QOL and healthcare costs, in addition to the standard assessment of mortality alone. A further strength of this study is the one year follow-up period.

5. Conclusions

With this study, we were able to show that donor CPR status and length of CPR are not associated with a reduction of DAOH at one year after HTX. Our findings emphasize

the approach that CPR status might be regarded as a less important factor when deciding on donor eligibility and allocation, even for extended durations of CPR. Importantly, the results of this study should be reproduced in larger cohorts with a prospective design before final conclusions can be drawn.

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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 number 4567).

Informed Consent Statement: All patients gave their written informed consent to be included in the prospective heart transplantation database 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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Validation of days alive and out of hospital as a new patient-centered outcome to quantify life impact after heart transplantation

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The number of patients waiting for heart transplantation (HTX) is increasing. Thus, identification of outcome-relevant factors is crucial. This study aimed to identify perioperative factors associated with days alive and out of hospital (DAOH)—a patient-centered outcome to quantify life impact—after HTX. This retrospective cohort study screened 187 patients who underwent HTX at university hospital Duesseldorf, Germany from September 2010 to December 2020. The primary endpoint was DAOH at 1 year. Risk factors for mortality after HTX were assessed in univariate analysis. Variables with significant association were entered into multivariable quantile regression. In total, 175 patients were included into analysis. Median DAOH at 1 year was 295 (223–322) days. In univariate analysis the following variables were associated with reduced DAOH: recipient or donor diabetes pre-HTX, renal replacement therapy (RRT), VA-ECMO therapy, recipient body mass index, recipient estimated glomerular filtration rate (eGFR) and postoperative duration of mechanical ventilation. After adjustment, mechanical ventilation, RRT, eGFR and recipient diabetes showed significant independent association with DAOH. This study identified risk factors associated with reduced DAOH at 1-year after HTX. These findings might complement existing data for outcome of patients undergoing HTX.

Abbreviations

ARVC	Arrhythmogenic right ventricular cardiomyopathy
BMI	Body mass index
CMV	Cytomegalovirus
DAOH	Days alive and out of hospital
eGFR	Estimated glomerular filtration rate
GCP	Good clinical practice
HCM	Hypertrophic cardiomyopathy
HTX	Heart transplantation
IQR	Interquartile range
RRT	Renal replacement therapy

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SD	Standard deviation
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation

Orthotopic heart transplantation (HTX) is a complex procedure which is carried out at specialized centers[1]. As the number of patients waiting for HTX is constantly increasing, efficient perioperative resource management and a careful selection of donors and suitable patients for HTX are highly relevant[2]. To optimize perioperative resource management, the identification of outcome-relevant perioperative factors in HTX patients is crucial. Previous studies tried to identify factors associated with poor outcome and mostly focused on hard endpoints such as mortality[3,4]. A high-quality meta-analysis by Foroutan et al. investigated influence of different recipient-, donor- and transplant-associated variables on 1-year mortality after HTX[5]. Donor and recipient age, creatinine concentration, mechanical ventilation, recipient diabetes and mechanical circulatory support were identified to be significantly associated with 1-year mortality in HTX patients[5].

Recently, more patient centered outcomes have been investigated in HTX patients as traditional mortality analysis might be insufficient to measure life impact. Days Alive and Out of hospital (DAOH) is a statistically efficient patient-centered outcome to measure life impact of a procedure[6,7]. Further advantages of DAOH are that it is easy to measure, readily available and it can be regarded as a composite of multiple clinically relevant outcomes including mortality, length and number of (re-)hospitalization and—indirectly—health care costs due to hospitalizations. A previous study showed that veno-arterial extracorporeal membrane oxygenation (VA-ECMO) therapy due to primary graft dysfunction has critical life impact at 1-year after HTX measured by DAOH[8]. Interestingly, patients who could be successfully weaned from VA-ECMO showed lower DAOH as compared to patients without primary graft dysfunction whilst 1-year mortality did not differ between groups in this study. This finding illustrates utility of DAOH and emphasizes clinical importance of this outcome beyond traditional endpoints.

Beside VA-ECMO therapy further important factors might be associated with reduced DAOH in HTX patients. However, evidence on prognostic factors for DAOH after HTX is very limited. Identification of those risk factors is crucial to complement survival data. Therefore, the present study aimed to identify donor-, recipient- and procedure-related prognostic variables for DAOH at 1-year after HTX.

Patients and methods

Study design and ethical statement. This retrospective single-center cohort study was conducted in compliance with the Declaration of Helsinki, guidelines for good clinical practice (GCP) and the International society for Heart and Lung Transplantation (ISHLT) ethics statement. Ethical approval for this retrospective study was obtained on 25th of January 2021 from the University of Duesseldorf's ethics committee (reference number: 4567). All patients gave written informed consent to be registered in a local prospective HTX database in the past so that the ethics committee waived the need for additional written informed consent for this retrospective analysis. The "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines were used for standardized reporting of the study results[9].

Participants. All consecutive patients aged ≥ 18 years who underwent HTX at the University Hospital Duesseldorf, Germany from September 2010 to December 2020 were included. Patients with missing data and incomplete medical records regarding the primary endpoint were excluded.

Outcome assessment. DAOH at 1 year after HTX was the primary endpoint of this study. Calculation of DAOH was performed as previously described[8,10]. In brief, all days of hospitalization in the first year after HTX were summed up and subtracted from 365 days. Outpatient visits and emergency department visits not exceeding 24 h were excluded from DAOH analysis. In case of mortality within the first year after HTX, days the patient did not survive were added to days of hospitalization before subtracting them from 365 days. Notably, DAOH does include the time spent in cardiac rehabilitation centers or similar institutions patients were transferred to after hospital discharge. All HTX patients are closely connected to our center so that external hospitalizations without our knowledge are very unlikely.

Data collection. Data of patients were derived from the continuously updated local prospective HTX database and the patient's electronic medical records. These data consisted of patient characteristics, comorbidities, information on treatment and complications during hospital stay, as well as date of mortality and days of hospital stay during the first year after HTX.

Identification of included variables. We primarily based the choice of variables on a meta-analysis by Foroutan et al. which summarized risk factors for 1-year mortality after HTX[5]. We considered all variables which were included into the final forrest-plot, regardless of significant association with 1-year mortality. Selected variables which were available in our prospective HTX database were included into analysis. Accordingly, the following 19 predefined recipient-, donor- and transplant-related variables were included: (1) preoperative variables: recipient age, recipient sex, underlying disease, recipient diabetes, recipient estimated glomerular filtration rate (eGFR), recipient arterial hypertension, recipient body mass index (BMI), recipient pulmonary hypertension, recipient cytomegalovirus (CMV) status, previous cardiothoracic surgery, left ventricular assist device before HTX, donor age, donor sex, donor diabetes, sex mismatch between donor and recipient, total ischemic time; (2) postoperative: recipient renal replacement therapy (RRT), duration of mechanical ventilation, use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Data on influence of VA-ECMO therapy on

DAOH has been published previously by our group[8]. The present study complements these data, as sample size was smaller in the previously published report.

Statistical analysis. Statistical analysis was performed in GraphPad Prism© version 8.02 (La Jolla, California, USA) and IBM SPSS© software version 25.0 (Armonk, NY, USA). Patient characteristics were presented as mean ± standard deviation (SD) or as median and interquartile ranges (IQR, 25–75%), as appropriate, for continuous variables and numbers (n) with corresponding percentages (%) in brackets for categorical variables. Boxplots were created for categorical variables to visualize DAOH and Mann–Whitney-U-test was used to compare DAOH between groups. Continuous variables were categorized into quartiles or according to international classifications if feasible and presented as boxplots. Association between continuous variables and DAOH was analyzed using Kruskal–Wallis test. Variables with significant association with DAOH in univariate analysis were included in a multivariable model. For multivariate analysis, we chose a quantile regression model which accounts for non-linear associations between independent variables and DAOH as dependent variable. In this model, all percentiles of DAOH were investigated. At each level the associations of independent variables with DAOH were investigated in a multivariable model. We predefined that factors affecting DAOH in 10th and 20th DAOH percentile as relevant based on the current literature[7]. These quantiles represent patients with the lowest DAOH from the total patient cohort. According to our statistical protocol, we entered following variables into our multivariable quantile regression model: Recipient diabetes, RRT, ECMO, Donor DM, recipient BMI, Recipient eGFR and duration of mechanical ventilation. Sensitivity analysis was performed for univariate analysis by excluding all patients who died during the first year after HTX. For all results of statistical analysis, a p-value < 0.05 was considered as significant.

Results

In the time period from September 2010 to December 2020, 187 patients underwent HTX at the University hospital Duesseldorf, Germany. According to the inclusion and exclusion criteria, 12 patients had to be excluded as DAOH could not be computed. Therefore, 175 HTX patients were included into our analysis. Mean age was 54 ± 11 years and 134 patients (76.6%) were male. Detailed patient characteristics are presented in Table 1. Median DAOH at 1 year was 295 days (IQR 223–322). Reasons for rehospitalization are presented in Table 2. Overall, 32 patients (18.3%) died during the study period. Eleven patients died out of hospital from unknown causes. In-hospital causes of death were: sepsis (8 patients), intracranial hemorrhage (3 patients), mesenteric ischemia (3 patients), graft failure (2 patients), cerebral hypoxia (3 patients), bleeding (1 patient) and multiple organ failure (1 patient).

Univariate association of categorical variables with DAOH. After univariate analysis of the 13 categorical variables, four variables were significantly associated with DAOH. As preoperative factors we identified recipient and donor diabetes to be associated with lower DAOH [recipient diabetes: 303 (247–323) days vs. 272 (97–293) days $p = 0.0314$; donor diabetes: 308 (229–323) days vs. 211 (65–303) days $p = 0.0329$]. As postoperative variables, renal replacement therapy (RRT) and VA-ECMO therapy were identified [RRT: 316 (295–329) days vs. 267 (75–305) days $p = < 0.0001$; VA-ECMO: 309 (273–327) days vs. 243 (0–290) days $p = < 0.0001$] (Fig. 1, Table 3).

Univariate association of continuous variables with DAOH. Association of 6 prespecified continuous variables with DAOH was investigated by using non-parametric Kruskal–Wallis test for column comparison, after variables were stratified by median and IQR or international classification. Out of these variables, recipient eGFR, recipient BMI and postoperative duration of mechanical ventilation were significantly associated with lower DAOH [recipient eGFR: < 45 ml/min = 260 (90–303) days vs. 45-62 ml/min = 289 (226–317) days vs. 63-80 ml/min = 310 (255–329) days vs. > 80 ml/min = 311 (210–329) days; $p = 0.01$; recipient BMI: < 19 kg/m^2 = 282 (159–332) days vs. 19–25 kg/m^2 = 308 (253–327) days vs. 25–29 kg/m^2 = 290 (228–317) days vs. > 30 kg/m^2 = 250 (23–295) days; $p = 0.011$ mechanical ventilation: < 28 h = 318 (299–334) days vs. 28–78 h = 311 (285–326) days vs. 78–182 h = 289 (229–311) days vs. > 182 h = 199 (0–277) days; $p = < 0.0001$]. Kruskal–Wallis test for column comparison did not show significant difference between columns for donor and recipient age regarding DAOH, despite clear visual trend (Fig. 2, Table 3).

Independent association of variables with DAOH in multivariable analysis. All variables which were significantly associated with DAOH in univariate analysis were included into a multivariable quantile regression model and the 10th and 20th percentile of this model were investigated for association of variables with DAOH. The pseudo-R^2 of the final model reached from 0.39 to 0.41 for the selected quantiles, indicating a moderate goodness of fit. In this model recipient diabetes, recipient eGFR, duration of mechanical ventilation and postoperative RRT had independent impact on DAOH in patients with low DAOH (Fig. 3).

Sensitivity analysis without 1-year mortality. To ensure that our findings in univariate analysis of risk factors and DAOH were not mainly influenced by 1-year mortality we performed a sensitivity analysis. In this analysis we excluded all patients who died during the first year after HTX and reanalyzed univariate association of risk factors and days out of hospital. Most of the significant associations remained after analysis except from donor diabetes, recipient age and donor age. For detailed results please see supplementary figures (Figs. S1 and S2).

	HTX patients (N = 175)
Baseline characteristics recipients mean ± S.D. or No. (%)	
Age (years)	54 ± 11
BMI (kg/m^2)	25.6 ± 4.6
male	134 (76.6)
Creatinine (mg/dl)	1.4 ± 1.0
Underlying disease	
ICM	69 (39.4)
DCM	93 (53.1)
ARVC	6 (3.4)
HCM	3 (1.7)
others	4 (2.3)
Preoperative conditions	
Arterial hypertension	105 (60.0)
Pulmonary hypertension	18 (10.3)
Diabetes mellitus	37 (21.1)
Cytomegalovirus IgG status	101 (57.7)
LVAD	92 (52.6)
Previous cardiothoracic surgeries	114 (65.1)
Postoperative conditions	
Mechanical ventilation (h)	151 ± 13
RRT	102 (58.3)
VA-ECMO	52 (29.7)
Length of hospital stay (d)	46 ± 35
Length of ICU stay (d)	25 ± 28
Donor characteristics	
Age (years)	43 ± 13
BMI (kg/m^2)	25.9 ± 3.9
male	101 (57.7)
Sex mismatch	51 (29.1)
diabetes	12 (6.9)
LVEF (%)	59 ± 12
History of CPR	42 (24.6%)
Length of CPR (min)	15 (9–21)
Intraoperative conditions	
Total ischemic time (min)	218 ± 51
Duration of surgery (min)	445 ± 116
Outcome	
DAOH	295 (223–322)
1-year mortality	32 (18.3)
Mean survival (d)	313 ± 116
Numbers of hospital readmissions	3 (1–4)
Time from HTX to death (d)	36 (17–115)

Table 1. Characteristics of HTX recipients and donors. *BMI* Body mass index, *ICM* ischemic cardiomyopathy, *DCM* dilated cardiomyopathy, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *HCM* hypertrophic cardiomyopathy, *LVAD* left ventricular assist device, *RRT* renal replacement therapy, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *DAOH* days alive and out of hospital.

Independent association of preoperative variables with DAOH. We additionally performed the quantile regression model including only preoperative parameters (recipient BMI, recipient eGFR, donor diabetes and recipient diabetes). In this model, only donor and recipient diabetes showed influence on DAOH in the 10th and 20th percentile of the model. However, model performance was poor. Detailed results are presented in the supplements (Fig. S3).

Reason for hospital admission	No. of patients	Days of hospital stay (mean ± S.D.)
HTX	175	48 ± 39
Endomyocardial biopsy	126	7 ± 4
Gastrointestinal disorders	15	14 ± 12
Respiratory infections	18	20 ± 14
Wound infection/impaired wound healing	14	25 ± 30
Urinary tract infections	5	16 ± 18
Other infections	22	23 ± 20
Acute kidney injury	13	10 ± 5
Graft rejection reaction	24	16 ± 18
Bleeding complications	6	21 ± 12
Hematological disorders	3	16 ± 13
Epileptic seizure	3	14 ± 10
Non-cardiac surgery	14	13 ± 12
Other reasons	10	25 ± 34

Table 2. Reasons for hospital admission and corresponding mean days of hospital stay. *HTX* Heart transplantation.

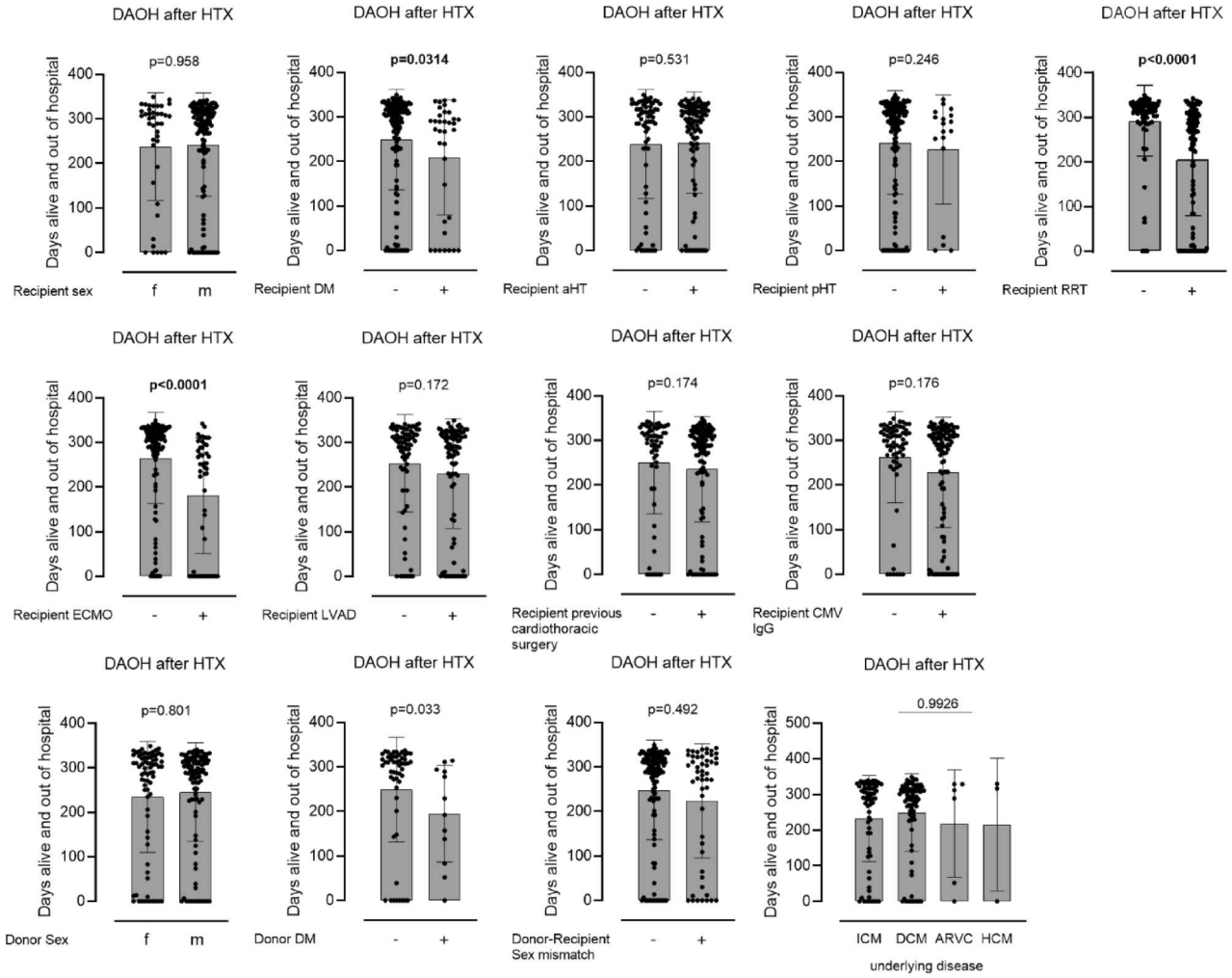

Figure 1. Influence of categorical variables on DAOH. Univariate analysis for the association of 13 categorical variables with days alive and out of hospital (DAOH) at 1 year after heart transplantation (HTX).

Categorical variables	Total No. of patients	No. of patients per subgroup	Univariate association with DAOH
Recipient sex	175	Male: 134	No
		Female: 41	
Recipient diabetes	175	Yes: 35	Yes
		No: 140	
Recipient arterial hypertension	175	Yes: 105	No
		No: 70	
Recipient pulmonary hypertension	175	Yes: 18	No
		No: 157	
Recipient RRT	175	Yes: 102	Yes
		No: 73	
Recipient ECMO	175	Yes: 50	Yes
		No: 125	
Recipient LVAD	175	Yes: 92	No
		No: 83	
Recipient previous cardiothoracic surgery	175	Yes: 114	No
		No: 61	
Recipient CMV status	175	Positive: 110	No
		Negative: 65	
Donor sex	175	Male: 101	No
		Female: 74	
Donor diabetes	66*	Yes: 12	Yes
		No: 54	
Donor-recipient sex mismatch	175	Yes: 51	No
		No: 124	
Underlying disease	171**	ICM: 69	No
		DCM: 93	
		ARVC: 6	
		HCM: 3	
Continuous variables Recipient age	175	01:44	No
		02:43	
		03:51	
		04:37	
Recipient BMI	175	01:08	Yes
		0.1382	
		0.1681	
		04:26	
Recipient eGFR	175	01:40	Yes
		02:53	
		03:40	
		04:42	
Duration of mechanical ventilation	175	01:41	Yes
		02:43	
		03:43	
		04:48	
Total ischemic time	175	01:43	No
		02:44	
		03:45	
		04:43	
Donor age	175	01:43	No
		02:39	
		03:49	
		04:44	

Table 3. Variables investigated for association with days alive and out of hospital in univariate analysis. *BMI* Body mass index (kg/m^2), *CMV* cytomegalovirus, *ECMO* extracorporeal membrane oxygenation, *eGFR* estimated glomerular filtration rate, *LVAD* left ventricular assist device, *RRT* Renal replacement therapy. *Missing data from donors' hospital. **4 Missing patients with other underlying diseases.

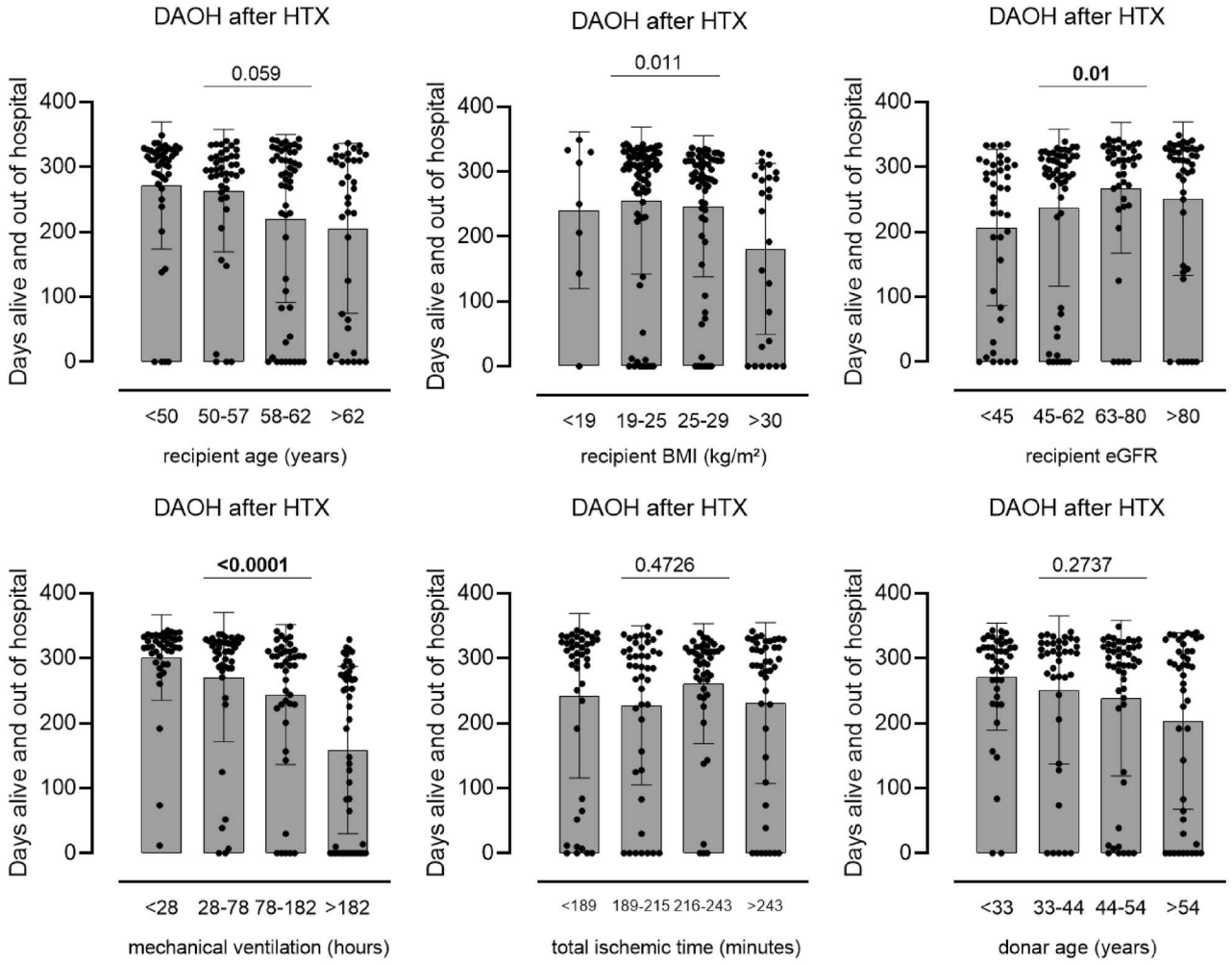

Figure 2. Influence of continuous variables on DAOH. Univariate analysis for the association of 6 continuous variables with days alive and out of hospital (DAOH) at 1 year after heart transplantation (HTX). To visualize distribution of DAOH, all continuous variables were stratified by quartiles.

Discussion

This study aimed to identify recipient-, donor- and procedure-related risk factors which might have an influence on postoperative outcome at 1-year after HTX as measured by DAOH. We could identify that recipient diabetes, donor diabetes, RRT, VA-ECMO therapy, recipient BMI, recipient eGFR and postoperative duration of mechanical ventilation were associated with lower DAOH according to univariate analysis. Only recipient diabetes, recipient eGFR, mechanical ventilation and postoperative RRT remained independently associated with reduced DAOH after multivariate analysis.

Variables associated with mortality within the first year after HTX. A previous meta-analysis of Foroutan et al. investigated variables associated with 1-year mortality in patients after HTX, as mortality is highest in the first year after surgery in these patients. This meta-analysis included results of 62 studies including 282.367 HTX patients. Recipient age, congenital etiology of heart failure, recipient diabetes, kidney function, dialysis, mechanical ventilation, mechanical circulatory support, donor age, and sex mismatch (especially transplantation from female donor to male recipient) were identified to be associated with 1-year mortality in this study[5]. This meta-analysis served as a basis for the present analysis.

Variables associated with reduced DAOH within the first year after HTX. In the present study we could confirm that recipient diabetes, RRT and mechanical ventilation have a significant and independent life impact as measured by DAOH. In our study cohort we did not show significant influence of other variables, e.g. congenital heart failure. This is likely due to the fact that we did only include 6 patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), 3 patients with hypertrophic cardiomyopathy (HCM) and no patients with other congenital heart failure as underlying diseases into our analysis. Therefore, sample size is very limited to show any effect on DAOH, in line with the findings for 1-year mortality, there was no difference in DAOH between patients representing with ischemic and dilated cardiomyopathy[5,11–13]. We could also not show

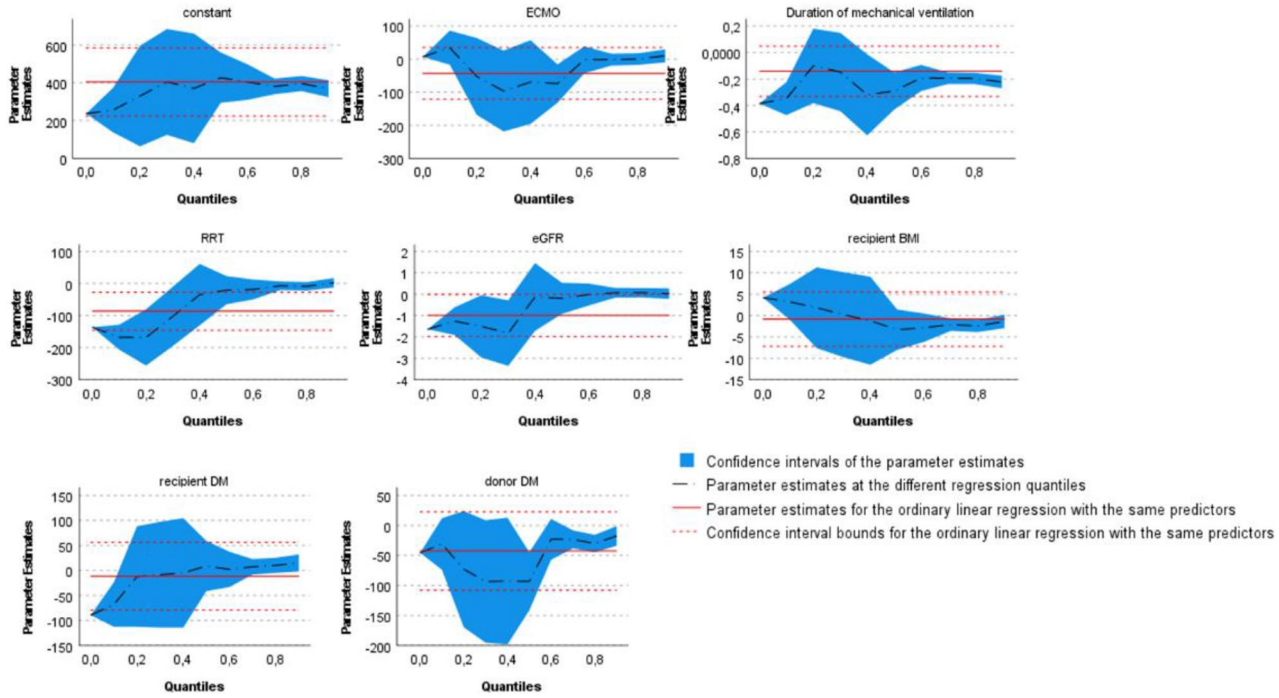

Figure 3. Association of variables with DAOH in multivariable quantile regression model. The figure shows the influence of selected variables on DAOH in a multivariable quantile regression model. Y-axis shows DAOH estimates while X-axis shows different quantiles. The black line represents parameter estimates at different regression quantiles. The Confidence intervals of quantile regression are presented in blue. Red lines represent parameter estimates and confidence interval of an ordinary linear regression with same variables. Duration of mechanical ventilation, renal replacement therapy (RRT), estimated glomerular filtration rate (eGFR), recipient diabetes mellitus (DM) were significantly associated with lower DAOH in the 10th and 20th percentile in this quantile regression model.

an association for sex mismatch which might again be related to our limited sample size as a visual trend can be seen within boxplots. Interestingly, we showed in our sensitivity analysis of the endpoint that at least some risk factors (eGFR, VA-ECMO, RRT, mechanical ventilation, donor diabetes) showed significant impact on DAOH independent from 1-year mortality, while impact of other risk factors was mainly driven by 1-year mortality. This underlines the strength of the endpoint as it combines both, days out of hospital and 1-year mortality and therefore might be more sensitive to measure life impact as sole mortality analysis as described previously[7,14].

Risk factors which showed association with DAOH but not with mortality. Notably, we identified a univariate association between donor diabetes and reduced DAOH in our study. This is interesting as findings of two previous studies show contradicting results concerning influence of donor diabetes on 1-year mortality[15,16]. However, within the meta-analysis no influence could be detected[5]. As those results are based on only two studies and data is very limited, quality of this result is indicated as moderate. In this case DAOH might be a more sensitive parameter to measure life impact. A previous study in HTX patients could show that mortality analysis and DAOH analysis can differ significantly[8]. In cases of donor diabetes this might reflect that patients had longer hospital stay without increased mortality. Additionally, we could identify in our study that patients with BMI ≥ 30 kg/m^2 had lower DAOH as compared to patients with BMI < 30 kg/m^2 according to univariate analysis. In a previous study BMI was identified to be associated with mortality in female recipients but not in male recipients[17]. Another data registry study including 38.498 patients showed that underweight and obese patients had significantly higher risk for mortality[18]. In this context another recent registry study confirmed the results for obese patients[19]. However, previous evidence on influence of BMI on 1-year mortality is contradicting as other studies showed similar 1-year survival of obese patients compared to normal BMI patients[13,20,21].

Regarding the results of our analysis, we can see that there was a visually clear trend for some variables without showing statistical significance. E.g. the DAOH in recipients receiving donor hearts < 33 years appear relevantly lower than the DAOH in recipients receiving donort hearts > 54 years. From a clinical/patient point of view, this difference might be of importance as recipients receiving older donor hearts may have similar (or even lower) DAOH in comparison with LVAD patients. First data suggest that older patients initially might benefit more from LVAD implantation, than from older donor hearts which consequently raises further interesting and relevant questions[22]. In this context, it is important to mention that the sample size in this study was rather small so that several results might become statistically significant when increasing the sample size. Therefore, our data can only serve as a first basis for further investigations. In the future, DAOH as a new patient-centered measure after

HTX may be implemented in existing registries so that more data will be available to complement and validate the findings of this study.

Strengths and limitations of this study. This was a retrospective single-center cohort study with a limited sample size, limiting the external applicability of the results. However, most patient characteristics and outcomes of our cohort correspond to the current literature and thus may be regarded as representative. As mentioned above, this study included only a selected number of predefined variables. The choice was based on a meta-analysis to ensure adequate choice of variables. Hence, it is possible that not all risk factors with influence on DAOH were included into this study. To cover as many relevant variables as possible, we performed analyses for further variables not included in the meta-analysis. The results can be found in the supplements (Fig. S4). A strength of this study is the endpoint DAOH which might be more suitable to measure life impact of recipient, donor and transplant associated risk factors as compared to mortality. We also showed in our sensitivity analysis that most variables not only have impact on 1-year mortality but also on hospital stay and hospital readmissions. We performed a 365-day follow-up in this study. Due to the retrospective nature of the study, we cannot guarantee that every hospitalization was reported within this year. However, HTX patients are closely connected to our center. Therefore, it is very unlikely that these patients were hospitalized at another hospital without our knowledge within the first year after HTX. Finally, it is important to mention that the results of this analysis regarding postoperative VA-ECMO support differ from our previously published work[8]. This discrepancy can be explained by the fact that the sample size as well as the choice of covariables were different between both works.

Conclusions

This study identified recipient- and donor-associated risk factors with influence on DAOH—a more patient centered outcome to quantify life impact after HTX. Our findings support previous evidence for mortality analysis and complement the existing data. Our results may help to improve perioperative resource management and to optimize careful donor and recipient selection of patients undergoing HTX. Further studies with a prospective design are needed to validate our results in a variety of larger cohorts.

Data availability

All relevant data are included in the present manuscript or in the supplements. Raw data are available upon reasonable request by the first author R.M.

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Author contributions

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RESEARCH

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Postoperative high-sensitivity troponin T predicts 1-year mortality and days alive and out of hospital after orthotopic heart transplantation

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Abstract

Background Orthotopic heart transplantation (HTX) is the gold standard to treat end-stage heart failure. Numerous risk stratification tools have been developed in the past years. However, their clinical utility is limited by their poor discriminative ability. High sensitivity troponin T (hsTnT) is the most specific biomarker to detect myocardial cell injury. However, its prognostic relevance after HTX is not fully elucidated. Thus, this study evaluated the predictive value of postoperative hsTnT for 1-year survival and days alive and out of hospital (DAOH) after HTX.

Methods This retrospective cohort study included patients who underwent HTX at the University Hospital Duesseldorf, Germany between 2011 and 2021. The main exposure was hsTnT concentration at 48 h after HTX. The primary endpoints were mortality and DAOH within 1 year after surgery. Receiver operating characteristic (ROC) curve analysis, logistic regression model and linear regression with adjustment for risk index for mortality prediction after cardiac transplantation (IMPACT) were performed.

Results Out of 231 patients screened, 212 were included into analysis (mean age 55 ± 11 years, 73% male). One-year mortality was 19.7% (40 patients) and median DAOH was 298 days (229–322). ROC analysis revealed strongest discrimination for mortality by hsTnT at 48 h after HTX [AUC = 0.79 95% CI 0.71–0.87]. According to Youden Index, the cutoff for hsTnT at 48 h and mortality was 1640 ng/l. After adjustment for IMPACT score multivariate logistic and linear regression showed independent associations between hsTnT and mortality/DAOH with odds ratio of 8.10 [95%CI 2.99–21.89] and unstandardized regression coefficient of −1.54 [95%CI −2.02 to −1.06], respectively.

Conclusion Postoperative hsTnT might be suitable as an early prognostic marker after HTX and is independently associated with 1-year mortality and poor DAOH.

Keywords Heart failure, Heart transplantation, IMPACT score, Risk prediction, Patient-centered outcomes

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Introduction

Orthotopic heart transplantation (HTX) is still the gold standard therapy for end-stage heart failure. Unfortunately, there is an ongoing donor shortage which limits the number of HTX and leads to an increasing number of patients on HTX waiting lists [1]. In addition, the treatment of end-stage heart failure is continuously improving so that the patients undergoing HTX are getting older and have more comorbidities with an increased risk for postoperative complications [2, 3]. To optimize perioperative risk stratification and early re-estimation of risk, the development of risk prediction models and the identification of perioperative prognostic factors became more and more important [4, 5, 6]. Numerous risk stratification tools have been developed in the past years, but their clinical use is often limited by insufficient predictive values [5]. In this context, the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score was introduced as validated tool for prediction of 1-year mortality after HTX [7, 8]. However, some studies report poor-to-moderate discrimination for mortality in their cohorts [9–11].

Previously biomarkers were established as another possibility to support perioperative stratification and early re-estimation of risk. A sensitive biomarker for myocardial cell injury is high-sensitivity troponin T (hsTnT) [12]. Postoperative troponin release has been investigated extensively in cardiac and non-cardiac surgery and is associated with adverse events [13, 14, 15]. Recently, Devereaux et al. investigated the prognostic value of high-sensitivity troponin I (hsTnI) in patients undergoing cardiac surgery and showed that levels of hsTnI were independently associated with mortality [16]. The role of hsTnT as a prognostic factor after HTX, however, is not clear and recent literature is ambiguous [17]. Therefore, we conducted this analysis to evaluate whether hsTnT is a suitable marker for risk stratification and prognosis after HTX.

Methods

This retrospective single-center cohort study was approved by the University of Duesseldorf's ethics committee (reference number: 4567) and complies with the International Society for Heart and Lung Transplantation (ISHLT) ethics statement. Data were extracted from the local prospective HTX database. All patients had given written informed consent to be registered in this database. Reporting of this work corresponds to the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines [18].

Patient population

All patients aged ≥ 18 years who underwent HTX at the University Hospital Duesseldorf, Germany, in a time period from September 2010 to August 2021 were considered for inclusion. Patients with missing data regarding survival, DAOH and hsTnT measurements, as well as patients without completed 1-year follow-up were excluded from analysis. In all patients HTX was conducted using bicaval technique and traditional cold storage was used for donor organ preservation.

High-sensitivity troponin T measurements

Main exposure was postoperative hsTnT measured in ng/L after HTX at different time points. At our institution hsTnT is routinely measured preoperatively, within the first 12 h, day 1, day 2 and day 3 after HTX. Measurements were performed in the central laboratory of the University hospital Duesseldorf.

IMPACT score calculation

The risk index for mortality prediction after cardiac transplantation (IMPACT) is a score validated to predict 1-year mortality after HTX from preoperative recipient risk factors. This score assigns varying points for 10 variables: age, serum bilirubin, creatinine clearance, dialysis, sex, heart failure etiology, preoperative infection, race, circulatory support and type of ventricular assist device. The score was calculated for each HTX patient as described before with a maximum of 50 points [7, 8].

Outcomes

The primary outcome of this study was mortality during the first year after HTX. Days alive and out of hospital (DAOH) at 1 year after HTX was the secondary endpoint of this study. Calculation of DAOH was conducted by summing up all days of hospitalization in the first year after HTX and subtracting them from 365 days, as described before [19–21]. In case of mortality, the number of days the patient did not survive and of days spent in hospital were subtracted from 365 days.

Statistical analysis

Statistical analysis was performed using IBM SPSS© software version 25.0 (Armonk, NY, USA), GraphPad Prism© version 8.02 (La Jolla, California, USA), MedCalc® Statistical Software version 20.114 (MedCalc Software Ltd, Ostend, Belgium) and R Statistical Software (v4.1.2; R Core Team 2021). Patients characteristics with continuous variables were presented as mean ± standard deviation (SD) or as median and interquartile ranges (IQR, 25–75%), as appropriate. Categorical variables were presented as numbers (n) with corresponding percentages (%) in brackets. Fisher's exact test or unpaired t-tests

Table 1 Characteristics of survivors and non-survivors after HTX

	Survivors ($N=172$)	Non-survivors ($N=40$)	*p*-value[a]
Preoperative characteristics			
Male sex	128 (74)	27 (68)	0.429
Age (years)	55 ± 11	57 ± 11	0.140
BMI (kg/m^2)	25.6 ± 4.5	25.8 ± 5.1	0.861
Smoker	41 (24)	8 (20)	0.681
Diabetes	34 (20)	14 (35)	0.058
Arterial hypertension	106 (62)	21 (53)	0.286
Pulmonary hypertension	14 (8)	5 (13)	0.368
Donor–recipient sex mismatch	45 (26)	14 (35)	0.327
Prior cardiothoracic surgery	108 (63)	29 (73)	0.276
LVAD	86 (50)	25 (63)	0.164
Preoperative ECMO	5 (3)	3 (8)	0.175
Preoperative mechanical ventilation	7 (4)	3 (8)	0.405
Preoperative dialysis	7 (4)	4 (10)	0.127
Serum creatinine (mg/dl)	1.4 ± 1.0	1.3 ± 0.5	0.649
Creatinine clearance (ml/min)	65 ± 24	64 ± 31	0.793
Bilirubin (mg/dl)	0.8 ± 0.9	1.2 ± 1.2	0.080
IMPACT score	8 ± 5	10 ± 5	0.003
Donor characteristics			
Male sex	99 (58)	19 (48)	0.290
Age (years)	41 ± 12	50 ± 10	< 0.0001
BMI (kg/m^2)	26 ± 5	25 ± 4	0.365
Smoker	93 (54)	17 (43)	0.220
Arterial hypertension	40 (23)	16 (40)	0.045
Diabetes	11 (6)	3 (8)	0.731
Cardiopulmonary resuscitation	55 (32)	8 (20)	0.179
Intraoperative characteristics (min)			
Duration of surgery	424 ± 105	484 ± 144	0.017
Duration of CPB	250 ± 64	301 ± 99	0.003
Total ischemia time	212 ± 49	228 ± 52	0.070
Reperfusion time	126 ± 45	151 ± 69	0.044
Postoperative characteristics			
ECMO	38 (22)	23 (58)	< 0.0001
Renal replacement therapy	87 (53)	31 (80)	0.003
Neurological complication	20 (12)	17 (43)	< 0.0001
Days in ICU	23 ± 22	30 ± 38	0.116
Duration of mechanical ventilation (hours)	119 ± 168	268 ± 236	0.001

BMI body mass index, *CPB* cardiopulmonary bypass, *ECMO* extracorporeal membrane oxygenation, *IMPACT* risk index for mortality prediction after cardiac transplantation, *ICU* intensive care unit, *LVAD* left ventricular assist device

were used to test for differences between dichotomous or continuous variables between groups defined by survival status. For analysis of the primary endpoint, receiver operating characteristic (ROC) analyses were performed for hsTnT levels within 12 h, 24 h, 48 h and 72 h after HTX. Cutoff values for troponin levels were determined by Youden index. The cutoff of the hsTnT time point with the strongest discrimination for 1-year mortality in ROC analysis was added to a logistic regression model, with adjustment using the continuous IMPACT score. The net reclassification improvement (NRI) and the net absolute reclassification improvement (NARI) of the mortality prediction model by adding the postoperative troponin cutoff were assessed. Discrimination (ROC-AUC) of the models with and without postoperative hsTnT was quantified and compared using Delong test. To compare net benefit of using these models to detect patients' risk for

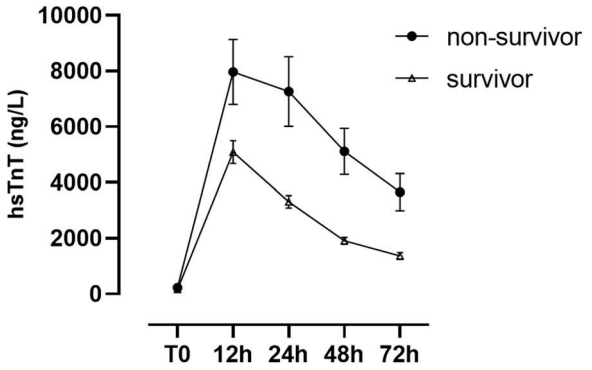

Fig. 1 Postoperative levels of hsTnT of survivors and non-survivors. The graphs depict high-sensitivity troponin (hs-TnT) concentrations for survivors (triangles) and non-survivors (dots) across different time points with corresponding standard errors. Preoperative hs-TnT values did not differ significantly between groups [baseline hsTnT—survivors 165 ± 687 ng/L vs. non-survivors 228 ± 906 ng/L, $p = 0.638$]. Postoperative values at timepoints 12 h, 24 h, 48 h and 72 h after surgery were significantly higher in non-survivors as compared to survivors [hsTnT 12 h—survivors 5089 ± 5305 ng/L vs. non-survivors 7972 ± 7419 ng/L, $p = 0.005$; hsTnT 24 h—survivors 3309 ± 2934 ng/L vs. non-survivors 7266 ± 7942 ng/L, $p \leq 0.0001$; hsTnT 48 h—survivors 1911 ± 1598 ng/L vs. non-survivors 5115 ± 5196 ng/L, $p \leq 0.0001$; hsTnT 72 h—survivors 1363 ± 1565 ng/L vs. non-survivors 3651 ± 4126 ng/L, $p \leq 0.0001$]

1-year mortality, a decision curve analysis was performed for both models.

For analysis of DAOH patients were classified by hsTnT cutoff. DAOH was compared using non-parametric Mann–Whitney U test. Association of continuous hsTnT elevation per 100 ng/L with DAOH was adjusted by the continuous IMPACT score using multivariable linear regression. For all statistical tests, a $p < 0.05$ was considered significant.

Results

Study cohort and characteristics

In total 231 patients underwent HTX at the University Hospital Duesseldorf during the time period of September 2010 and December 2021. Thereof, 19 (8%) patients had to be excluded according to the exclusion criteria. Among the 212 included patients, mean age was 55 ± 11 years and 155 (73%) were male. During first year after HTX, 40 patients (19%) died. Causes of death were: graft dysfunction (7 patients), septic shock (9 patients), major bleeding complications (6 patients with intracranial hemorrhage, 1 patient with gastrointestinal bleeding, 1 patient with ECMO cannulation site bleeding), bowel ischemia (3 patients), cerebral hypoxia (3 patients) and unknown causes (10 patients who died out of hospital). Overall median DAOH was 298 days (229–322). Detailed patient characteristics for survivors and non-survivors are presented in Table 1 (Additional file 1: Figure S1, Table 1).

HsTnT levels of survivors and non-survivors after HTX

Baseline levels of hsTnT did not differ significantly between survivors and non-survivors. In contrast, postoperative hsTnT levels were significantly higher in patients who died as compared to survivors at 12 h, 24 h, 48 h and 72 h after HTX. Detailed results are presented in Fig. 1.

ROC analysis for postoperative hsTnT and 1-year mortality

We performed ROC analysis for hsTnT levels and 1-year mortality at sampling time points 12 h, 24 h, 48 h and 72 h after HTX, respectively. All postoperative hsTnT showed a significant discrimination for 1-year mortality [$hsTnT_{12h}$—AUC = 0.66, 95% CI 0.56–0.75; $hsTnT_{24h}$—AUC = 0.74, 95% CI 0.66–0.82; $hsTnT_{48h}$—AUC = 0.79, 95% CI 0.71–0.87; $hsTnT_{72h}$—AUC = 0.77, 95% CI 0.68–0.86]. The hsTnT levels at 48 h after HTX showed numerically strongest discrimination for 1-year mortality regarding the AUC. Youden Index determined a cutoff of 1640 ng/L for hsTnT at 48 h after HTX (Fig. 2).

Binary logistic regression model for hsTnT and 1-year mortality

Binary logistic regression model was performed with hsTnT cutoff at 48 h after HTX as independent variable and 1-year mortality as dependent variable. In univariate analysis hsTnT levels at 48 h after HTX showed significant association with 1-year mortality [OR 8.84 95% CI 3.31–23.66, $p \leq 0.0001$]. After adjustment for continuous IMPACT score, association of hsTnT with mortality remained significant [$hsTnT_{48h}$—OR 8.10 95% CI 2.99–21.89, $p \leq 0.0001$; IMPACT score—OR 1.09 95% CI 1.01–1.18, $p = 0.025$]. We analyzed in how far risk prediction for 1-year mortality by IMPACT score was improved by the addition of hsTnT levels at 48 h after HTX are added to the logistic regression model. The NRI for the model including hsTnT was 7.6% (95% CI 4.1–12.6) for non-events and 27.5% (95% CI 14.6–43.9) for events. Regarding NARI, the model was able to identify 114/1000 patients more at risk for 1-year mortality. Corresponding reclassification tables were added to the supplements. In ROC analysis the AUC for the model including troponin was significantly higher as compared to the model only including IMPACT score [IMPACT score—AUC = 0.65 95% CI 0.56–0.74; IMPACT score with $hsTnT_{48h}$—AUC = 0.77 95% CI 0.70–0.84; difference between areas: 0.12, 95% CI 0.04–0.19, $p = 0.0016$]. The net benefit curve suggested highest net benefit for the

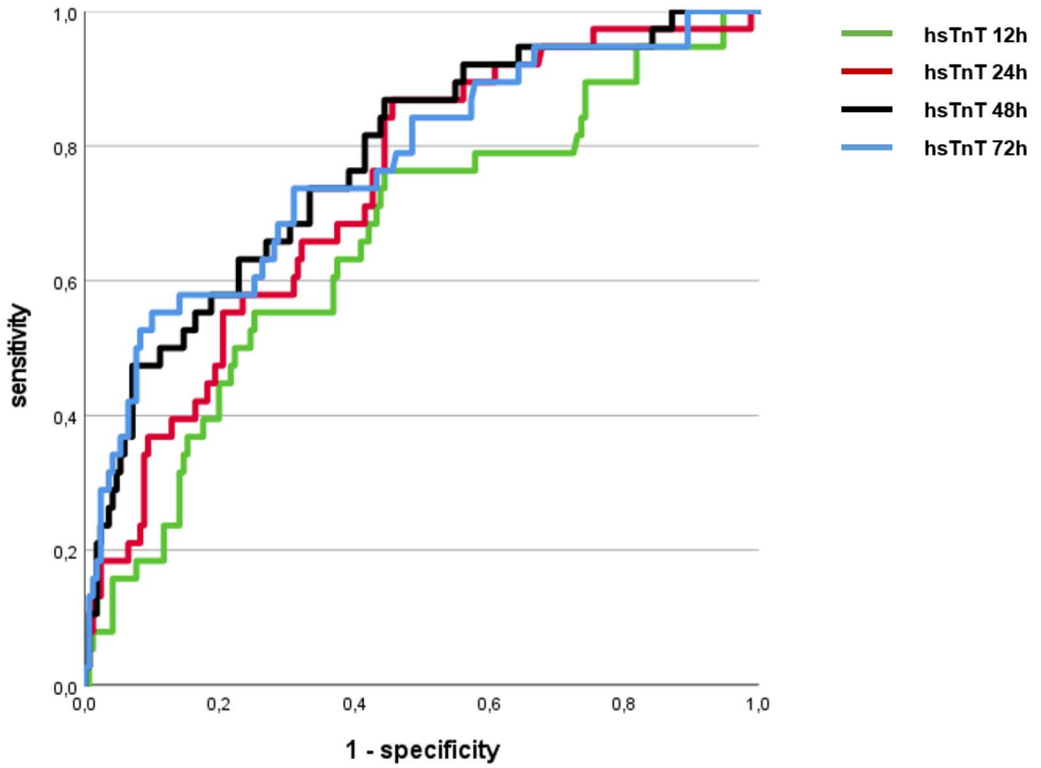

Fig. 2 Receiver operating characteristic curves of postoperative hsTnT and 1-year mortality. The figure shows the receiver operating characteristics (ROC) curves for association of different hs-TnT sampling time points with 1-year mortality after heart transplantation. The areas under the curves (AUC) are as follows: hsTnT 12 h AUC = 0.66 (CI 0.56–0.75); hsTnT 24 h AUC = 0.74 (CI 0.66–0.82); hsTnT 48 h AUC = 0.79 (CI 0.71–0.87); hsTnT 72 h AUC = 0.77 (CI 0.68–0.86). The numerically strongest discrimination ability is given for hsTnT values at 48 h after heart transplantation

combined use of IMPACT and hsTnT (Figs. 3, 4, Additional file 1: Table S1).

Association of postoperative hsTnT and DAOH

In univariate analysis hsTnT levels higher than predefined cutoff by Youden Index were associated with lower DAOH at 48 h after HTX [$hsTnT_{48h}$—below cutoff 317 (283–328) days vs. above cutoff 278 (14–308) days, $p \leq 0.0001$]. Results for other hsTnT sampling timepoints are presented in the supplements. In a multivariable linear regression model, association of continuous hsTnT elevation (per 100 ng/L) and DAOH remained significant when adjusted for points on the IMPACT score [per 100n g/L hsTnT elevation—regression coefficient: -1.54, 95% CI −2.02 to −1.06, $p \leq 0.0001$; IMPACT score—regression coefficient: −4.79, 95% CI −7.83 to −1.76, $p = 0.002$] (Fig. 5, Additional file 1: Figure S2, Table 2).

Discussion

The present study suggested that early hsTnT levels at 48 h after HTX are independently associated with mortality and DAOH after HTX. Moreover, this study showed that the addition of hsTnT improved risk prediction for mortality and DAOH over IMPACT score.

Referring to the current literature, the prognostic value of troponin after HTX is underexplored. A recent systematic review by Liu and colleagues identified only three studies including a total of 372 patients that investigated the association between elevated troponin levels and mortality. As these studies revealed significant heterogeneities, the authors decided not to perform a meta-analysis [17]. Labarrere et al. investigated the value of persistent troponin I (TnI) levels in 110 HTX patients during first year after HTX. They found that persistent TnI levels greater than 0.5 ng/ml were associated with development of coronary artery disease and graft failure. However, as patients were only included if they had survived the first year after HTX, association of postoperatively elevated TnI and early mortality was not investigated [22]. Another study investigated the prognostic value of postoperative hsTnT for 1-year mortality in 141 HTX patients. They identified that elevated hsTnT levels at 6 weeks after HTX were highly associated with 1-year mortality. Again, association of early postoperative levels of hsTnT was not investigated by the authors [23].

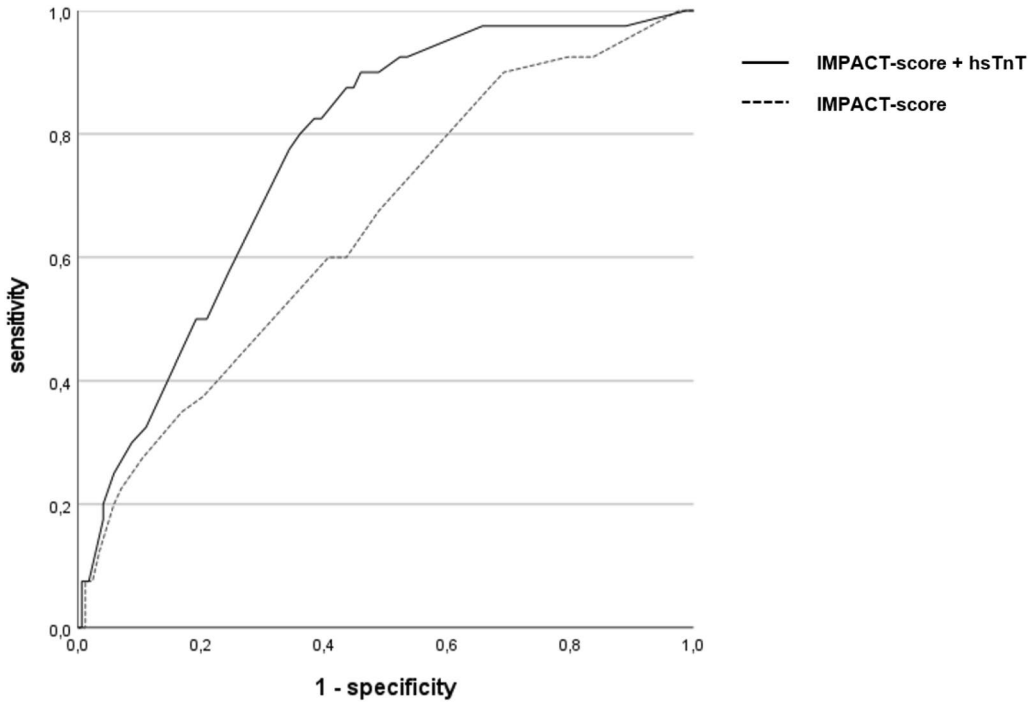

Fig. 3 Receiver operating characteristic curves of two prediction models for 1-year mortality. The figure shows the receiver operating characteristics (ROC) curves of risk prediction models for 1-year mortality. While on its own the IMPACT score has a ROC- a moderate discrimination ability (AUC = 0.65 95% CI 0.56–0.74), adding hsTnT levels at 48 h after heart transplantation to the model improves its performance (AUC = 0.79; CI 0.71–0.87)

The last study by Franeková et al. demonstrated an association of hsTnT levels at 10 days after HTX and 1-year mortality [24]. However, an earlier postoperative assessment of risk might be favorable as it might change clinical practice for patients at risk.

Postoperative troponin release has been extensively studied in non-cardiac surgery before [25, 26]. In these studies, early postoperative troponin elevation above the upper limit of normal was associated with major adverse events like mortality. In cardiac surgery however, this upper limit of normal troponin concentration is frequently exceeded by myocardial trauma due to surgery, with not necessarily higher risk for mortality [13]. Therefore, Devereaux et al. defined new cutoffs for association of troponin and 30-day mortality after cardiac surgery corresponding with an hsTnI level 218 times the upper reference limit [16]. Our recent study now adds data for association of early hsTnT with 1-year mortality after HTX. Patients who died within the first year after HTX had significantly higher troponin values at each timepoint of measurement. These findings were independently associated when adjusted for the IMPACT score. IMPACT score showed weak-to-moderate association with 1-year mortality in our cohort. This goes in line with previous reports, describing similar AUC in ROC analysis [9, 11]. Addition of hsTnT level at 48 h improved the discrimination ability of IMPACT score. The net benefit using the combined model was also higher to identify patients at risk for 1-year mortality. Recently, similar risk prediction models and decision curve analyses for mortality were presented as effective to guide palliative care consultation [27, 28]. Additionally, hsTnT levels were independently associated with low DAOH. This is an important finding, as this complements the current knowledge on more patient-centered outcomes in the field of end-stage heart failure and HTX surgery [21, 29, 30].

In the Eurotransplant area, the responsible parties discuss the implementation of a cardiac allocation score (CAS) which is supposed to optimize the allocation of the limited donor organs. In the lung transplantation setting, a similar score already exists (Lung allocation score (LAS)) which is also used to prioritize waiting list candidates 12 years and older based on a combination of waitlist urgency and post-transplant survival. Based on the data of this study, postoperative hsTnT may also be included into such a score for early re-estimation of postoperative risk and prognosis. Further studies should focus on potential interventions depending on hsTnT values that might be able to prevent complications and

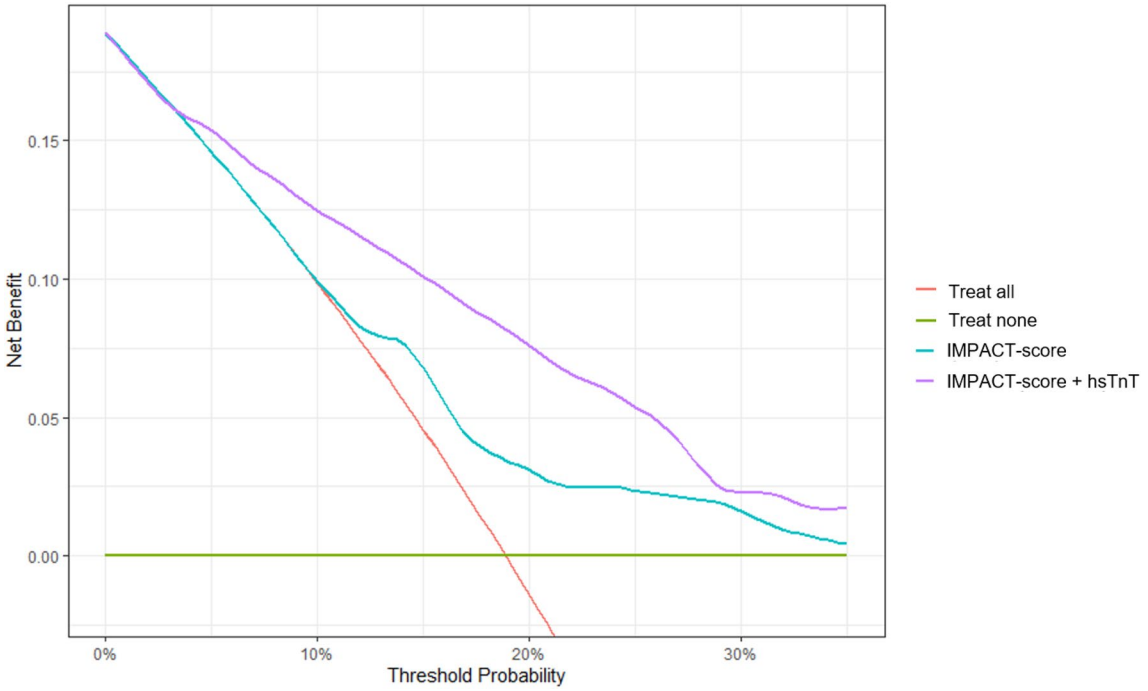

Fig. 4 Decision curves for different models of risk prediction after HTX. The figure shows a decision curve analysis for mortality prediction model with IMPACT score (turquoise) and IMPACT score with hsTnT (purple). The x-axis shows the threshold probability for 1-year mortality while the y-axis shows the net benefit of the models. Beyond a threshold of 5% the combined model of IMPACT and hsTnT shows the greatest net benefit. The red line depicts a model in which all patients would be treated and the green line represents a model in which none patient will be treated

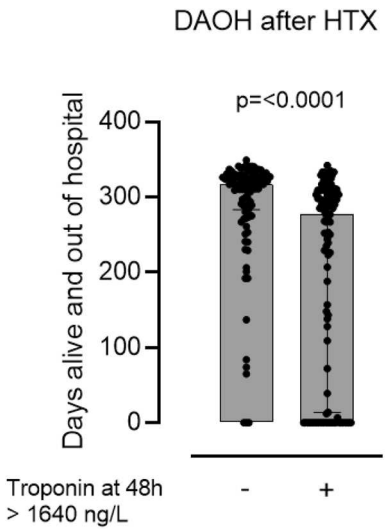

Fig. 5 Association of hsTnT levels above cutoff and days alive and out of hospital. The box-plot shows significantly fewer DAOH for patients above the determined cutoff of hs-TnT at 48 h after heart transplantation [hsTnT 48 h—below cutoff 317 (283–328) days vs. above cutoff 278 (14–308) days, $p \leq 0.0001$]. Black dots represent individual DAOH values of patients, the upper end of the boxes shows the median while error bars depict interquartile ranges. The hsTnT cutoff was determined by Youden index

finally to reduce mortality after HTX. These may include intensified monitoring or standardized protocols for strict follow-up of these patients.

Strengths and limitations

Strengths of the presented data include first, standardized troponin measurement at multiple time points with high data completeness; second, complete 12-month follow-up. Further, we did not only address mortality but also DOAH, a more patient-centered endpoint to quantify life impact [19]. We are aware of the following limitations. First, as a single-center study, sample size and number of events was limited. However, only 2 variables (troponin and IMPACT) were included into the logistic model that can therefore be considered robust. Second, we cannot exclude that any external hospitalization took place. However, HTX patients are very closely connected to our center so that we consider the risk of misclassification bias was very limited. Further, although DAOH is a measure of life impact, we did not collect data on quality of life, another relevant patient-centered outcome. Finally, we chose hsTnT at 48 h after HTX as primary biomarker for our analysis as it showed the numerically strongest discrimination for 1-year mortality. However,

Table 2 Multivariable linear regression model for influence of postoperative troponin on days alive and out of hospital

Variables for multivariable linear regression	Unstandardized coefficients B	Standard error	Standardized coefficients beta	95% CI	*p*-value
Per 100 ng/L hsTnT elevation	−1.54	0.25	−0.39	−2.02 to −1.06	< 0.0001
IMPACT score	−4.79	1.54	−0.19	−7.83 to −1.76	0.002

hsTnT high-sensitivity troponin T, *IMPACT* risk index for mortality prediction after cardiac transplantation

ROC-AUC did not significantly differ from values at 24 h and 72 h. In this context an earlier timepoint like 24 h after HTX might be favorable for early re-estimation of postoperative risk in the clinical setting. Therefore, optimal cutoff and sampling time point should be investigated in a larger cohort.

The generalizability of these findings may be hampered by the single-center design. However, characteristics such as 1-year mortality were in line with the current literature.

Conclusion

Early hsTnT levels after HTX surgery are independently associated with poor 1-year survival and reduced DAOH. Therefore, early hsTnT concentrations might be useful for early risk reassessment to tailor postoperative therapy or decision-making in the intensive care unit.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-022-00978-4.

Additional file 1: Figure S1. Study Flowchart. **Figure S2.** Association of hsTnT levels at different timepoints above cutoff and days alive and out of hospital. **Table S1.** Reclassification tables of a 1-year mortality prediction model using IMPACT compared to a model using IMPACT and hsTnT.

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None.

Author contributions
RM: concept/design, data collection, data analysis/interpretation, statistics, writing of article. SR: concept/design, data collection, data analysis/interpretation, critical revision of article. AN: data collection, data analysis, writing and critical revision of article. AS: data collection, data analysis, critical revision of article. TT: data collection, data analysis, critical revision of article. GLB: statistics and methodology, critical revision of article. FB, DS, CB, IT, HA: data collection, critical revision of article. AL: drafting article, data collection, critical revision of article. RH and UB: concept/design, data interpretation, critical revision of article. All authors have read and approved the final manuscript.

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Availability of data and materials
All relevant data are included in the present manuscript or in the supplements. Raw data are available upon reasonable request by the first author R.M.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethical Committee of the University Hospital Duesseldorf (Chair: Professor Thomas Hohlfeld; reference number: 4567; date of approval: 25.01.2021).

Consent to participate
Not applicable.

Competing interests
The authors declare no competing or financial competing interest.

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Association between early postoperative hypoalbuminaemia and outcome after orthotopic heart transplantation

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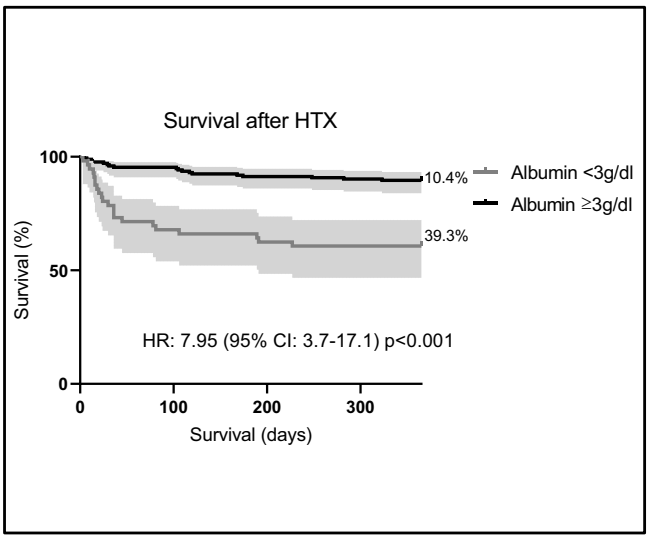
Association between early postoperative hypoalbuminemia and outcome after orthotopic heart transplantation

Summary

We retrospectively investigated association of early postoperative hypoalbuminemia <3 g/dl with mortality and days alive and out of hospital in 229 heart transplant patients. Early postoperative hypoalbuminemia was independently associated with poor outcomes after heart transplantation.



Legend: Survival of heart transplant patients according to postoperative albumin levels

Abstracts including data from the same data set have been submitted to the annual meeting 2023 of the European Association for Cardio-Thoracic Surgery (EACTS; no presentation) and to the annual meeting 2023 of the European Society of Anaesthesiology and Intensive Care (ESAIC; oral presentation).

Abstract

OBJECTIVES: In patients undergoing heart transplantation (HTX), preoperative liver impairment and consecutive hypoalbuminaemia are associated with increased mortality. The role of early postoperative hypoalbuminaemia after HTX is unclear. This study investigated the association between early postoperative hypoalbuminaemia and 1-year mortality as well as 'days alive and out of hospital' (DAOH) after HTX.

METHODS: This retrospective cohort study included patients who underwent HTX at the University Hospital Duesseldorf, Germany, between 2010 and 2022. The main exposure was serum albumin concentration at intensive care unit (ICU) arrival. The primary endpoints were mortality and DAOH within 1 year after surgery. Receiver operating characteristic (ROC) curve analysis was performed and logistic and quantile regression models with adjustment for 13 a priori defined clinical risk factors were conducted.

RESULTS: Out of 241 patients screened, 229 were included in the analysis (mean age 55 ± 11 years, 73% male). ROC analysis showed moderate discrimination for 1-year mortality by postoperative serum albumin after HTX [AUC = 0.74; 95% confidence interval (CI): 0.66–0.83]. The cutoff for serum albumin at ICU arrival was 3.0 g/dl. According to multivariate logistic and quantile regression, there were independent associations between hypoalbuminaemia and mortality/DAOH [odds ratio of 4.76 (95% CI: 1.94–11.67) and regression coefficient of −46.97 (95% CI: −83.81 to −10.13)].

CONCLUSIONS: Postoperative hypoalbuminaemia <3.0 g/dl is associated with 1-year mortality and reduced DAOH after HTX and therefore might be used for early postoperative risk re-assessment in clinical practice.

Keywords: cardiac surgery • biomarkers • prognosis • risk stratification • liver function

INTRODUCTION

Postoperative hypoalbuminaemia is frequent after cardiac surgery with the use of cardiopulmonary bypass (CPB) and can result from intraoperative blood loss, dilution, increased inflammatory response or postoperative capillary leak amongst other reasons [1]. Recent studies showed an association of postoperative hypoalbuminaemia with poor short- and long-term survival in patients undergoing cardiac surgery with and without CPB [2]. In patients undergoing heart transplantation (HTX), preoperative risk assessment is crucial to identify patients with poor prognosis. In this context, preoperative liver impairment was identified as a factor which is associated with increased mortality after HTX. Therefore, biomarkers of liver impairment are included in risk prediction tools like the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score [3, 4]. Recently, the use of the model for end-stage liver disease (MELD) score was proposed for preoperative risk assessment in heart transplant patients [5]. Preoperative serum albumin is another biomarker that is decreased when liver function is impaired. Previous research showed that low preoperative albumin levels as the sole marker or when added to the MELD score were a strong predictor of poor outcome in HTX and heart failure patients [6–9]. However, the role of early postoperative hypoalbuminaemia in risk re-assessment and prognosis after HTX is unclear. Therefore, the aim of this study was to investigate the association between early postoperative hypoalbuminaemia and 1-year mortality as well as 'days alive and out of hospital' (DAOH) as a patient-centred outcome after HTX. Furthermore, the additional predictive value of postoperative hypoalbuminaemia for 1-year mortality was assessed as compared to the postoperative MELD score, as a measure for early postoperative liver dysfunction, and the preoperative IMPACT score.

MATERIALS AND METHODS

Ethics statement

This analysis was conducted as a retrospective single-centre cohort study. Approval was obtained from the institutional review board of the University of Duesseldorf (reference number: 4567). The extracted data for this analysis were available in the local prospective HTX database. All patients included in this database had given written informed consent to be enrolled. Reporting of the results follows STROBE guidelines [10].

Patient population and inclusion criteria

Consecutive adult patients (≥18 years) undergoing HTX at a tertiary care University Hospital in Duesseldorf, Germany, from September 2010 to April 2022 with completed 1-year follow-up were screened for inclusion. Patients with missing data regarding the primary endpoints or postoperative serum albumin measurements were excluded from the analysis.

Perioperative fluid and transfusion management

Perioperative fluid and transfusion management of HTX patients is highly standardized in our institution and guided by continuous haemodynamic monitoring. Intraoperative blood management during and post CPB targets haemoglobin levels around 10 g/dl. Serum albumin levels of 2.0 g/dl or below are used as a threshold for albumin substitution. Albumin substitution is considered at serum albumin levels below 2.5 g/dl if the patient shows signs of peripheral oedema.

Serum albumin measurements

Main exposure was the first postoperative serum albumin concentration measured in g/dl within the first 12 h at ICU. Albumin values were determined by the local central laboratory.

IMPACT score calculation

The risk index for IMPACT was calculated for each patient as described previously [3, 4, 11]. It assigns varying points for the variables age, serum bilirubin, creatinine clearance, dialysis, sex, heart failure aetiology, preoperative infection, race, circulatory support and type of ventricular assist device and was calculated

for a previously published analysis [11]. Data were received by the prospective local database that stored manually extracted information from electronic clinical charts by trained personnel.

MELD score calculation

The MELD score was calculated for each patient as described previously using the following formula: $10 \times [0.957 \times \text{Ln}(\text{Creatinine}) + 0.378 \times \text{Ln}(\text{total bilirubin}) + 1.12 \times \text{Ln}(\text{international normalized ratio}) + 0.643]$ [12]. For calculation, immediate postoperative values of these biomarkers were used.

Outcomes

The primary endpoint was all-cause mortality during the first year after surgery. The secondary endpoint was the number of DAOH within the first year after HTX. DAOH were calculated by subtraction of all days spent in the hospital from 365 days. In case of death, the days the patient did not survive were added to the time spent in the hospital which was then subtracted from 365 days [13, 14]. DAOH is a more patient-centred outcome as it includes mortality, length of hospital stay and hospital readmissions and is known for its correlation with measures of quality of life [11].

Statistical analysis

Statistical software used for the present analysis were IBM SPSS software version 25.0 (Armonk, NY, USA), GraphPad Prism version 8.02 (La Jolla, CA, USA) and MedCalc Statistical Software version 20.114 (MedCalc Software Ltd, Ostend, Belgium). Descriptive statistics are presented as number (*n*) with corresponding percentages (%) in brackets for categorical variables and as mean ± standard deviation (SD) for continuous variables. Fisher's exact test or unpaired *t*-tests were used to compare continuous or dichotomous variables between groups. To evaluate the prognostic value of postoperative albumin receiver operating characteristic curve (ROC) analysis was conducted (dependent variable: 1-year mortality). The Youden index was used to determine a cutoff value for albumin level. Kaplan–Meier curves were conducted for survival analysis depending on albumin cutoff value. Univariate logistic regression was conducted for postoperative albumin level and 1-year mortality. In a multivariate logistic regression model, odds ratios (ORs) were adjusted for clinical risk factors from baseline characteristics that might be associated with 1-year mortality. To evaluate if postoperative albumin could improve risk stratification of mortality prediction models, the net reclassification improvement (NRI) and the net absolute reclassification improvement (NARI) of two mortality prediction models adding postoperative albumin level to either MELD score or IMPACT score were calculated as previously performed [11]. Discrimination of these models with and without the addition of albumin was assessed (ROC-AUC) and compared using the Delong test. DAOH of patients with albumin values higher and lower than Youden index derived cutoff were compared in univariate analysis using Mann–Whitney *U* test. In a multivariate quantile regression model of the lowest DAOH centile, association of continuous postoperative albumin values with DAOH was adjusted for clinical risk factors from baseline characteristics. For all statistical tests, a *P*-value of <0.05 was considered significant. Similar methods were used in previous publications [11].

RESULTS

Study cohort and characteristics

A total of 241 patients underwent HTX from 2010 to 2022 at the University Hospital of Duesseldorf and completed 1-year follow-up. Based on the inclusion and exclusion criteria 12 patients had to be excluded and 229 patients were included in the analysis. Mean age of the study group was 55 ± 11 years. Overall 1-year mortality was 17.4% (40 patients) and 30-day mortality was 7.8% (18 patients). Median DAOH were 299 (230–322) at 1 year after HTX. Detailed patient characteristics are presented in Table 1 (Supplementary Table S1, Figure S1).

Pre- and postoperative serum albumin levels in survivors and non-survivors

There was no significant difference in preoperative serum albumin levels between survivors and non-survivors (survivors: 3.9 ± 0.7 g/dl vs non-survivors: 3.7 ± 0.7 g/dl, $P = 0.084$). Postoperative serum albumin levels were significantly lower in patients who died in the first year after HTX (survivors: 3.3 ± 0.6 g/dl vs non-survivors: 2.8 ± 0.6 g/dl, $P < 0.001$) (Fig. 1).

Discrimination and association of postoperative albumin and 1-year mortality

In ROC analysis, postoperative albumin levels showed a significant discrimination for 1-year mortality with an area under the curve (AUC) of 0.75 and 95% CI of 0.66–0.83. Youden index determined a cutoff of 2.95 g/dl for postoperative albumin levels. In a univariate logistic regression model, there was a significant association between postoperative serum albumin values and 1-year mortality (OR: 4.54, 95% CI: 2.34–8.78, $P \leq 0.001$). In Kaplan–Meier analysis, patients with postoperative albumin levels below cutoff showed lower survival rates as compared to controls (hazard ratio 7.95, 95% CI: 3.7–17.1, $P < 0.001$). Of note, preoperative hypoalbuminaemia occurred in 19 patients (8%) and was not associated with the incidence of postoperative hypoalbuminaemia. After adjustment for 13 covariables in multivariate logistic regression analysis, only postoperative albumin and donor age remained independently associated with 1-year mortality (postoperative albumin—OR: 4.76, 95% CI: 1.94–11.67, $P = 0.001$ and donor age—OR: 1.11, 95% CI: 1.05–1.17, $P \leq 0.001$] (Figs 2 and 3, Table 2).

Improvement of risk prediction models by postoperative albumin

We analysed if risk prediction of either IMPACT or MELD score for 1-year mortality could be improved by the addition of postoperative albumin levels to the prognostic models (based on logistic regression). The NRI for the model including IMPACT and albumin was 15.87% (95% CI: 9.43–23.53) for non-events and 5% (95% CI: 1.64–11.28) for events. The NRI for the model including MELD and albumin was 4.23% (95% CI: 1.64–9.93) for

Table 1: Patient characteristics by postoperative albumin levels

	Albumin ≥3 g/dl (*N* = 173)	Albumin <3 g/dl (*N* = 56)	*P*-value
Preoperative recipient characteristics			
Male sex	129 (74.6)	38 (67.9)	0.387
Age (years)	55.1 ± 10.8	55.3 ± 11	0.904
BMI (kg/m^2)	25.8 ± 4.5	25.4 ± 4.7	0.614
Smoker	45 (26.2)	12 (21.4)	0.594
Diabetes	32 (18.7)	18 (32.1)	**0.042**
Arterial hypertension	98 (57)	32 (57.1)	>0.999
Pulmonary hypertension	14 (8.1)	7 (12.5)	0.424
Prior cardiothoracic surgery	101 (58.4)	44 (78.6)	**0.007**
LVAD	78 (45.1)	37 (66.1)	**0.009**
ICM	73 (42.4)	25 (44.6)	0.877
DCM	81 (47.1)	28 (50)	0.759
ARVC	7 (4.1)	1 (1.8)	0.683
RCM	0 (0)	1 (1.8)	0.246
HCM	3 (1.7)	1 (1.8)	>0.999
Myocarditis	2 (1.2)	0 (0)	>0.999
Preoperative dialysis	10 (5.8)	2 (3.7)	0.736
IMPACT score	8.1 ± 4.7	9.4 ± 4.1	0.096
Albumin (g/dl)	3.9 ± 0.7	3.7 ± 0.7	0.185
MELD score	14.3 ± 7.6	13.7 ± 6.5	0.652
Donor characteristics			
Male sex	98 (56.6)	28 (50)	0.441
Age (years)	43.1 ± 12.2	44.3 ± 12.4	0.526
BMI (kg/m^2)	26.1 ± 4.9	26.0 ± 3.7	0.945
Cardiopulmonary resuscitation	53 (30.6)	15 (26.8)	0.618
Intraoperative characteristics (min)			
Duration of surgery	401 ± 95	490 ± 148	**<0.001**
Duration of CPB	240 ± 57	294 ± 94	**<0.001**
Total ischaemia time	212 ± 48	220 ± 51	0.330
PRBC (l)	2.9 ± 2.4	4.9 ± 3.2	**<0.001**
Platelets (l)	1.0 ± 0.8	1.5 ± 1.1	**0.001**
FFP (l)	1.5 ± 1.6	1.9 ± 2.3	0.218
Postoperative laboratory values			
Creatinine (mg/dl)	1.5 ± 0.8	1.3 ± 0.5	0.230
Bilirubin (mg/dl)	2.6 ± 1.9	2.5 ± 1.3	0.576
INR	1.2 ± 1.9	1.3 ± 2.2	0.280
Albumin (g/dl)	3.5 ± 0.4	2.4 ± 0.4	**<0.001**
Postoperative characteristics			
ECMO	33 (19.2)	28 (50)	**<0.001**
Renal replacement therapy	90 (57.7)	35 (62.5)	0.635
MELD score	14.6 ± 5.3	14.3 ± 5.1	0.711
Albumin substitution within first 24 h	47 (28.7)	29 (54.7)	**0.001**
Days in ICU	24 ± 25	25 ± 26	0.677
Duration of mechanical ventilation (hours)	110 ± 167	223 ± 216	**0.001**
30-day mortality	6 (3.5)	12 (21.4)	**<0.001**
1-year mortality	18 (10.4)	22 (39.3)	**<0.001**

ARVC, arrhythmogenic right ventricular cardiomyopathy; BMI, body mass index; CPB, cardiopulmonary bypass; DCM, dilative cardiomyopathy; ECMO; extracorporeal membrane oxygenation; FFP, fresh frozen plasma; HCM, hypertrophic cardiomyopathy; ICM, ischaemic cardiomyopathy; IMPACT, risk index for mortality prediction after cardiac transplantation; ICU, intensive care unit; INR, international normalized ratio; LVAD, left ventricular assist device; MELD, model for end-stage liver disease; PRBC, packed red blood cells; RCM, restrictive cardiomyopathy [11].

Significant results are marked in bold.

non-events and 25% (95% CI: 16.88–34.66) for events. The assessment of NARI showed that both models including postoperative albumin were able to detect 139/1000 and 78/1000 patients more at risk for 1-year mortality, respectively. ROC analysis showed that the models including postoperative albumin levels had significantly higher AUC as compared to the two baseline models only including IMPACT score (IMPACT score—AUC = 0.65, 95% CI: 0.57–0.74; IMPACT score with albumin—AUC = 0.77, 95% CI: 0.70–0.84; difference between areas: 0.12, 95% CI: 0.02–0.21, $P = 0.016$) or MELD score (MELD score—AUC = 0.60, 95% CI: 0.50–0.70; MELD score with albumin—AUC = 0.78, 95% CI: 0.70–0.85; difference between areas: 0.17, 95% CI: 0.06–0.29, $P = 0.002$) (Fig. 4, Supplementary Tables S2 and S3).

Association of postoperative albumin with DAOH

In univariate analysis, DAOH of patients with postoperative albumin levels ≥3 g/dl were significantly higher than DAOH of patients with albumin levels <3 g/dl [albumin—above cut-off 308 (271–325) days vs below cutoff 253 (0–305) days, $P \leq 0.001$]. Of note, after the exclusion of patients who died during 1-year follow-up, univariate findings for DAOH remained significant in a sensitivity analysis (Supplementary Figure S2). A multivariate quantile regression model was performed in which postoperative albumin levels were independently associated with poor DAOH after adjustment for 13 covariables (postoperative albumin—coefficient: −46.97, 95% CI: −83.81 to −10.13, $P = 0.013$) (Table 3, Supplementary Figure S3).

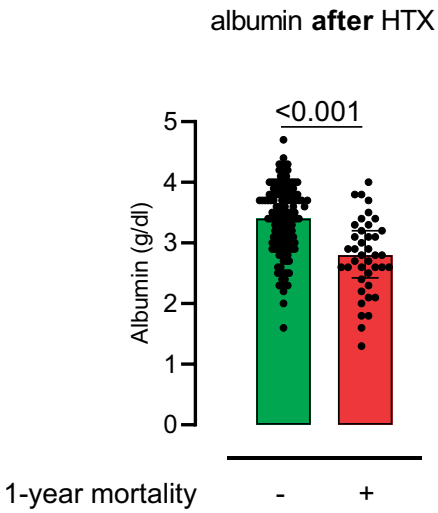


Figure 1: Postoperative serum albumin levels. The figure shows postoperative serum albumin levels after heart transplantation in survivors compared with non-survivors 1-year follow-up (survivors: 3.3 ± 0.6 g/dl vs non-survivors: 2.8 ± 0.6 g/dl; $P < 0.001$)

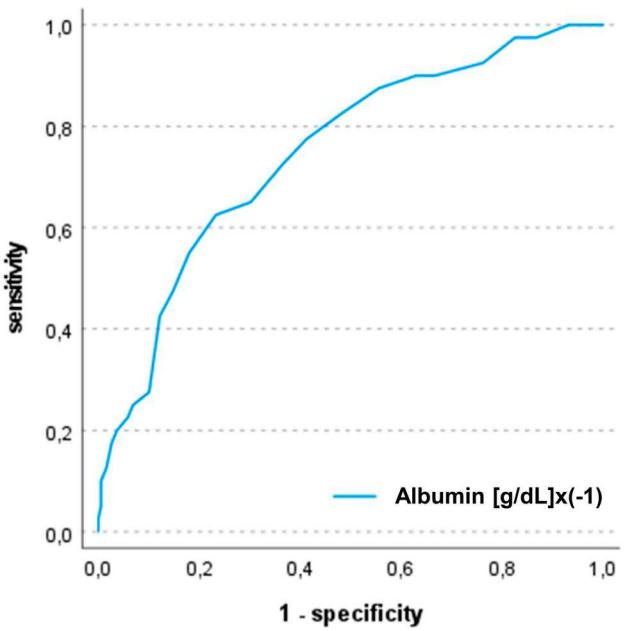


Figure 2: Receiver operating characteristic curves of postoperative albumin levels and 1-year mortality. The figure shows the ROC curves for association of postoperative albumin levels with 1-year mortality after heart transplantation. The AUC was 0.75 (95% CI: 0.66–0.83)

DISCUSSION

This study revealed an independent association between low postoperative serum albumin levels and increased 1-year mortality as well as poor DAOH after HTX. Additionally, risk prediction for mortality by IMPACT score or MELD score was significantly improved when postoperative albumin was added to the models.

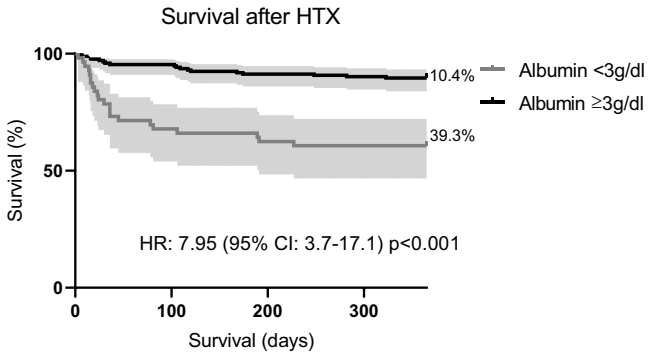


Figure 3: Postoperative survival of patients based on albumin levels. The figure shows the Kaplan–Meier curves of patients after HTX classified by postoperative albumin levels above and below cutoff of 3 g/dl. Survival in patients with postoperative albumin levels >3 g/dl was higher as compared to controls (HR 7.95, 95% CI: 3.7–17.1; $P<0.001$)

Table 2: Multivariate binary logistic regression for the association of postoperative albumin and 1-year mortality

Parameter	Adjusted odds ratio	95% CI	P-value
Albumin (g/dl) × (−1)	4.76	1.94–11.67	**0.001**
IMPACT	1.04	0.91–1.19	0.549
Postoperative MELD	1.05	0.94–1.17	0.424
Recipient diabetes	1.09	0.31–3.78	0.892
Prior LVAD	0.86	0.20–3.77	0.838
Prior cardiothoracic surgery	1.50	0.31–7.33	0.618
Donor age (years)	1.11	1.05–1.17	**<0.001**
Duration of surgery (min)	0.99	0.98–0.99	**0.015**
Duration of CPB (min)	1.01	0.99–1.02	0.221
mechanical ventilation (h)	1.00	1.00–1.01	0.073
Postoperative RRT	1.78	0.47–6.68	0.396
Postoperative ECMO	1.96	0.54–7.07	0.305
PRBC transfusion (ml)	1.00	1.00–1.00	0.774
Platelet transfusion (ml)	1.00	1.00–1.00	0.154

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; IMPACT, risk index for mortality prediction after cardiac transplantation; LVAD, left ventricular assist device; MELD, model for end-stage liver disease; PRBC, packed red blood cells; RRT, renal replacement therapy [11].

The role of preoperative serum albumin in patients undergoing HTX

Previous investigations described that preoperative serum albumin levels were associated with unfavourable outcome after HTX. Kato *et al.* [8] showed in a retrospective analysis of 822 HTX patients that preoperative serum albumin levels <3.5 g/dl were associated with increased 1-year mortality. Additionally, the authors used the same cutoff for analysis of data of 13 671 HTX patients from the united network of organ sharing database. Again preoperative serum albumin levels below cutoff were associated with poor 1-year survival in a parametric survival model [15]. Other studies showed similar associations between preoperative albumin levels and 1-year mortality after HTX [6]. Previously preoperative albumin levels were also included in risk scores to assess postoperative survival after HTX. In this context, Schulze *et al.* [16] proposed the CARRS score including prior stroke, albumin, retransplantation, glomerular filtration rate and prior thoracic surgeries. This score showed a

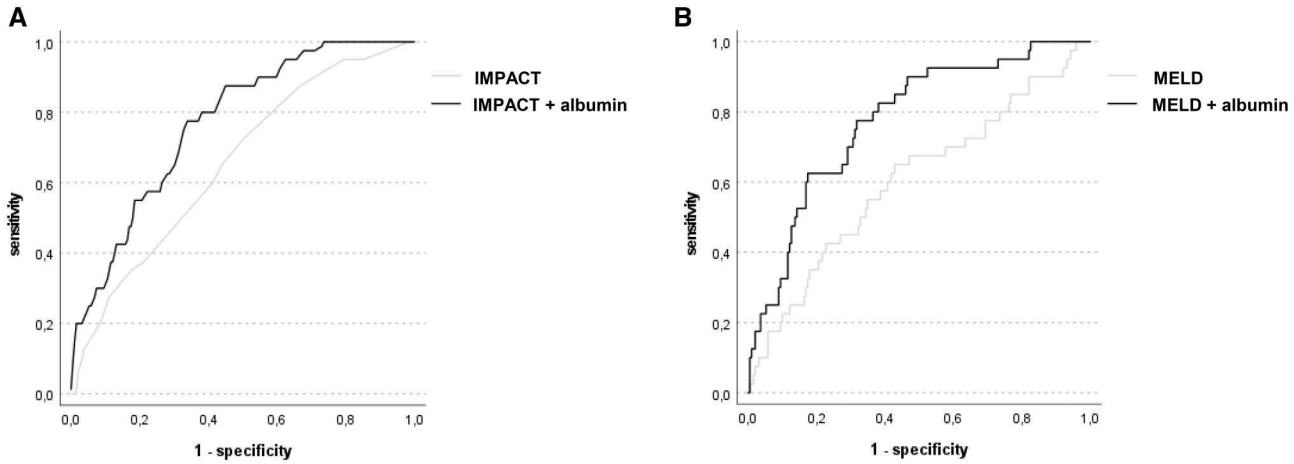


Figure 4: Receiver operating characteristic curves of two different prediction models for 1-year mortality including postoperative albumin. ROC curves using the IMPACT score (**A**) or the MELD score (**B**) alone compared to models which added postoperative albumin levels (dependent variable: 1-year mortality). Models including postoperative albumin showed better discrimination for 1-year mortality (IMPACT score—AUC = 0.65, 95% CI: 0.57–0.74 vs IMPACT score with albumin—AUC = 0.77, 95% CI: 0.70–0.84; difference between areas: 0.12, 95% CI: 0.02–0.21, $P = 0.016$; MELD score—AUC = 0.60, 95% CI: 0.50–0.70 vs. MELD score with albumin—AUC = 0.78, 95% CI: 0.70–0.85; difference between areas: 0.17, 95% CI: 0.06–0.29, $P = 0.002$)

Table 3: Multivariate quantile regression model for the association of postoperative albumin with Days alive and out of hospital

Parameter	Coefficient	Standard error	95% CI	P-value
Constant	163.39	95.20	−24.49 to 351.27	0.088
Albumin (g/dl) × (−1)	−46.97	18.67	−83.81 to −10.13	**0.013**
MELD	−0.09	0.39	−0.86–0.68	0.821
IMPACT	−3.42	2.67	−8.70 to 1.85	0.202
Recipient diabetes	−73.40	25.26	−123.24 to −23.56	**0.004**
Prior LVAD	13.75	30.82	−47.07 to 74.58	0.656
Prior cardiothoracic surgery	18.73	31.40	−43.25 to 80.70	0.552
Donor age (years)	−2.80	0.81	−4.40 to −1.20	**<0.001**
Duration of surgery (min)	0.08	0.15	−0.21 to 0.37	0.607
Duration of CPB (min)	0.21	0.23	−0.24 to 0.67	0.355
mechanical ventilation (h)	−0.14	0.07	−0.28 to 0.01	0.056
Postoperative RRT	−120.91	22.59	−165.49 to −76.34	**<0.001**
Postoperative ECMO	−3.60	29.22	−61.26 to 54.05	0.902
PRBC transfusion (ml)	−0.016	0.01	−0.03 to −0.01	**0.006**
Platelet transfusion (ml)	0.01	0.02	−0.02 to 0.05	0.405

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; IMPACT, risk index for mortality prediction after cardiac transplantation; LVAD, left ventricular assist device; MELD, model for end-stage liver disease; PRBC, packed red blood cells; RRT, renal replacement therapy [11].

good discriminative ability with an ROC-AUC of 0.77. Another study by Chokshi *et al.* [7] investigated the role of liver dysfunction on outcome after HTX. Therefore, preoperative serum albumin values were added to the MELD score. Higher modified MELD score and lower albumin values were associated with poor survival.

The role of postoperative serum albumin after HTX

The role of postoperative serum albumin levels after HTX has not been investigated until now. Our current data suggest that low postoperative serum albumin values are strongly associated with poor outcome regarding 1-year survival and DAOH after HTX. This is in line with the findings of previous studies for cardiac and non-cardiac surgery [2, 17]. Berbel-Franco *et al.* [1] showed a strong association of low postoperative serum albumin levels (within the first 24 h at ICU) with in-hospital and long-term mortality in 2818 cardiac surgery patients. Interestingly risk for mortality was not linear but showed a progressively steeper increase when serum albumin levels were below 3.0 g/dl which goes in line with the cutoff from our ROC analysis [1]. However, heart transplant patients were not included in the above-mentioned study. It is well known that postoperative serum albumin mimics intra- and postoperative course as it is influenced by numerous factors like increased inflammatory response resulting from surgical trauma, long CPB times or ischaemia reperfusion injury and postoperative liver dysfunction, making it a suitable biomarker for postoperative prognosis [1, 2, 18–20]. Within our patient cohort, we could show that patients with serum albumin levels below the cutoff of 3 g/dl had significantly longer durations of surgery and CPB, as well as significantly higher transfusion requirements,

supporting this relationship. This might be the reason why postoperative albumin showed a strong independent association with mortality and DAOH in our cohort. Additionally, we adjusted our findings for postoperative MELD score, which shows that low albumin values are not solely influenced by postoperative liver dysfunction and impaired synthesis after HTX. Although, preoperative factors are more useful for risk prediction than postoperative variables, postoperative albumin can be used for early risk re-assessment after HTX, as a widely available biomarker in clinical practice. If low serum albumin levels themselves have negative effects on patient's prognosis after HTX is unclear, but could be an interesting therapeutic approach for upcoming investigations. Targeting postoperative serum albumin levels >3.0 g/dl after HTX by substitution of human albumin might be a feasible approach and should be investigated in prospective trials, as data concerning this topic are lacking. However, as in our cohort patients with low albumin levels had higher rates of albumin substitution but also higher mortality, benefit of this therapeutic approach is questionable and cannot be drawn from our data, as negative effects should also be considered.

Strengths and limitations

This work has several limitations that we are aware of. First, this was a retrospective single-centre study with a limited number of patients and events. However, data were obtained from the local HTX database and we had a full dataset regarding the endpoints and covariates in 95% of all patients. As our patients are closely connected to our centre we could provide not only data on mortality but also DAOH which represents a more patient-centred outcome. Nevertheless, we cannot be sure if patients were hospitalized externally during 1-year follow-up, although the risk is very limited. Finally, we had to assess the postoperative albumin values during the first 12 h after arrival ICU, as albumin was not measured systematically at arrival in ICU in all patients. Regarding our statistical approach, all analyses were exploratory in nature and 95% CIs were not adjusted for multiple comparisons, hence inferences drawn from them may not be reproducible.

CONCLUSIONS

Early postoperative hypoalbuminaemia <3.0 g/dl is associated with 1-year mortality and poor DAOH after HTX. This makes postoperative albumin a suitable marker for early risk re-assessment after HTX.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Conflict of interest: None declared.

DATA AVAILABILITY

All relevant data are included in the present manuscript or in the supplements. Raw data are available upon reasonable request by the first author R.M.

Author contributions

René M'Pembele: Conceptualization; Formal analysis; Investigation; Writing—original draft. **Sebastian Roth:** Conceptualization; Investigation; Writing—original draft; Writing—review & editing. **Freya Jenkins:** Investigation; Writing—review & editing. **Vincent Hettlich:** Conceptualization; Investigation; Writing—review & editing. **Anthony Nucaro:** Data curation; Investigation; Writing—review & editing. **Alexandra Stroda:** Investigation; Writing—review & editing. **Theresa Tenge:** Investigation; Writing—review & editing. **Amin Polzin:** Investigation; Writing—review & editing. **Bedri Ramadani:** Investigation; Writing—review & editing. **Giovanna Lurati Buse:** Investigation; Methodology; Supervision; Writing—review & editing. **Hug Aubin:** Investigation; Writing—review & editing. **Artur Lichtenberg:** Investigation; Supervision; Writing—review & editing. **Ragnar Huhn:** Investigation; Supervision; Writing—review & editing. **Udo Boeken:** Conceptualization; Investigation; Supervision; Writing—review & editing.

Reviewer information

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