Submitted: 22 February, 2024 Accepted: 29 May, 2024 Published: 08 October, 2024 DOI:10.22514/sv.2024.121

Open Access
Signa Vitae

ORIGINAL RESEARCH

Role of blood lactate levels in kidney suitability for donation after circulatory death: a retrospective analysis

Gabriele Melegari[1,*], Stefano Baroni[1], Federica Arturi[2], Simone Rinaldi[1], Chiara Dallai[1], Dalila Donelli[3], Giacomo Mori[4], Alberto Barbieri[2]

[1]Department of Anaesthesia and Intensive Care, Polyclinic Teaching Hospital of Modena, 41121 Modena, Italy
[2]School of Anaesthesia and Intensive Care, University of Modena and Reggio Emilia, 41121 Modena, Italy
[3]School of Medicine, University of Modena and Reggio Emilia, 41121 Modena, Italy
[4]Nephrology Dialysis and Kidney Transplantation Unit, University Hospital of Modena, 41121 Modena, Italy

***Correspondence**
melegari.gabriele@aou.mo.it
(Gabriele Melegari)

Abstract

This present study aims to investigate the Donation after Circulatory Death (DCD) procedure and the ischemia-reperfusion injury that occurs during organ preservation by examining the correlation between lactate levels during normothermic reperfusion (NrP) and the positive criterion of eligibility and suitability of the organ for DCD transplantation. This retrospective study was approved by the Ethics Committee of our institution. Data were retrieved from DCD kidney donors who were patients admitted to the Intensive Care Unit (ICU) of Ospedale Civile di Baggiovara, Modena (Italy), between 2018 and 2019 and comprised various parameters related to DCD donors, including age, reason for ICU admission, administration of noradrenaline infusion exceeding the dosage of 0.3 mcg/kg/min, duration of ICU stay, lactate levels during normothermic reperfusion (NrP), blood flow during NrP, time of NrP and the criterion of eligibility and suitability of the organ for transplantation as per the Karpinski score. Additionally, when available, short-term information regarding graft complications or organ rejection was also recorded. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Univariate analysis showed that T0 lactates (odds ratio (OR): 2.20, 95% confidence interval (CI) 1.04–4.71; $p = 0.038$) and age (OR: 0.69, 95% CI 0.51–0.93; $p = 0.016$) were significantly associated with the outcome of organ suitability for transplantation. Additionally, lactate levels exhibited a decrease during NrP time, as indicated by a linear mixed model effect, with p-values of 0.004 for the outcome of organ suitability for transplantation and 0.004 for time. Statistical analyses indicate no negative correlation between an increase in lactate levels in the blood during explantation and negative outcomes. Conversely, higher levels of lactate in younger and healthier patients may suggest better mitochondrial function, while a significant decrease in lactate levels may indicate reduced organ damage and increased suitability for transplantation.

Keywords

Lactate level; Organ suitable; Donation after circulatory death

1. Introduction

Organ donation is often the final option for patients with severe organ failure, highlighting the critical shortage of available organs. In this regard, the scientific community is actively exploring alternative sources to address this pressing need. Within the transplant community, concerted efforts are underway to expand the utilization of Donation after Circulatory Death (DCD) donors. As defined by the 6th International Conference on Organs, DCD refers to the complete absence of both circulation and respiration despite the provision of life support through modern medical technology [1].

During the process of DCD, organ preservation induces ischemia-reperfusion injury, resulting in tissue and cell damage upon the restoration of blood flow following ischemia. This damage impacts signal pathways regulating important cellular functions, including inflammation and the management of Oxygen Species-related damage [2, 3]. When tissue blood supply is critically reduced, Adenosine triphosphate (ATP) production decreases, leading to elevated lactate levels, acidosis and limited reactive oxygen species (ROS) production. Conversely, upon blood flow restoration and increased oxygen levels, calpain activation occurs, leading to significant ROS production and mitochondrial dysfunction [4–7]. These trigger a series of cellular events that lead to the activation of the immune system, which may result in organ rejection and, in the long term, chronic graft dysfunction accompanied by fibrosis. Notably, Warm Ischemia Time has been reported to be

an important variable influencing the prognosis of transplant. Panconesi *et al.* [8] reported an elevation in inflammatory mediators, particularly lactate, in DCD livers following 30 and 60 minutes of warm ischemia time but also noted no changes after 15 minutes of ischemia, underscoring the significance of reducing warm ischemia time to enhance transplant survival. However, in the current literature, there are no reliable biomarkers that can be clinically used to identify the success or failure of the procedure [9, 10].

Herein, we designed this study to examine the correlation between lactate levels during normothermic reperfusion (NrP) and the positive criterion of eligibility and suitability of the organ for transplantation from DCD.

2. Materials and methods

2.1 Patient management

All DCD donors classified under Maastricht Classification III were treated with the same protocol and considered suitable for DCD donation. Normothermic reperfusion (NrP) was conducted using Extracorporeal Membrane Oxygenation (ECMO) (Getinge®, Goteborg Sweden) and a hemadsorption cartridge (CytoSorb® cartridge, Aferetica, Italy). Further details are provided in the **Supplementary material**.

2.2 Data collection

Data were collected from patients admitted to the Intensive Care Unit (ICU) who donated kidneys after circulatory death (DCD) between 2018 and 2019. The collected data comprised various parameters related to the DCD donors, including age, reason for ICU admission, administration of noradrenaline infusion exceeding the dosage of 0.3 mcg/kg/min, duration of ICU stay, lactate levels during normothermic reperfusion (NrP), blood flow during NrP, time of NrP and eligibility and suitability of the organ for transplantation according to the Karpinski score. Additionally, whenever feasible, short-term information regarding graft disease or organ rejection was also collected [11–13].

Blood samples were obtained at various perfusion intervals during normothermic reperfusion (NrP), with sequential measurements of plasma creatinine and blood lactates. The initial sample (T0) was collected 15 minutes after NrP initiation to allow for system equilibrium. Subsequent samples were obtained at specific intervals: the second sample (T1) at 60 minutes post-NrP initiation, the third sample (T2) at 120 minutes post-NrP initiation and the fourth sample (T3) either 240 minutes post-NrP initiation or at the conclusion of NrP. Kidneys were assessed based on the clinical condition of the donor and Karpinski's score [14, 15]. Further details regarding Karpinski's score, donor management and the DCD technique are shown in the **Supplementary material**.

2.3 Statistic

The statistical analysis was conducted using the STATA16 program® (STATA Corp, College Station LP 4905 Lakeway Drive, Lakeway, TX 77845, USA). Several tests were employed: the Shapiro-Wilk-Test assessed the normal distribution of continuous data, while the *t*-Test of Student compared continuous variables under a Gaussian distribution curve. Confidence intervals were calculated at 95% and expressed as CI, with standard deviations denoted as ±sd. Non-parametric tests were utilized for data that did not adhere to a Gaussian distribution. Outcome correlation was examined among blood lactates, laboratory exams, blood flow and time of NrP using univariate logistic regression, with the output variable being organ suitability for transplantation. Receiver Operating Characteristic (ROC) analysis of the model was conducted if $p < 0.05$. Laboratory exam values and differences over time were analyzed using the Wilcoxon Signed rank test. Mixed model test repeated measures correlation coefficients (Rrm) were employed for within-patient comparisons, with "cons" representing the constant (Y-intercept) of the model. Specifically, this analysis was conducted to measure lactate and plasma creatinine levels during the time of NrP. The postestimation margin was calculated, and comparisons and correlations were deemed significant when the applied test yielded a p-value < 0.05. *Post hoc* analysis was undertaken to validate the results.

This study was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

3. Results

The study cohort comprised 21 patients, including 13 males and 8 females. The primary reason for ICU hospitalization was post-cardiac arrest syndrome, accounting for 61.90% of all cases, followed by spontaneous intracranial hemorrhage (19.04%), ischemic stroke (14.28%), and no malignant vascular lesion (4.76%). None of the patients received a noradrenaline infusion exceeding 0.3 mcg/kg/min. Graft disease was observed in only one patient, representing 4.76% of all cases. Table 1 provides a comprehensive summary of the principal variables examined in the study.

During NrP, the lactate levels were found to decrease from T0 to T1 (11.89 ± 2.78 to 9.92 ± 3.18; $p = 0.017$), from T0 to T2 (11.89 ± 2.78 to 9.29 ± 4.63; $p = 0.045$), and from T0 to T3 (11.89 ± 2.78 to 8.19 ± 5.13; $p = 0.009$).

The plasma creatinine levels increased from T0 to T1 (1.2 ± 1.00 to 1.33 ± 1.06; $p < 0.001$), from T0 to T2 (1.200 ± 1.00 to 1.39 ± 1.06; $p < 0.001$), and from T0 to T3 (1.200 ± 1.00 to 1.66 ± 1.33) (Fig. 1). Additionally, the Karpinski score of the right kidney was found to be negatively correlated with the T0 lactate level, with a coefficient of −0.577 ($p = 0.006$), and the T0 lactate level was similarly negatively correlated with the Karpinski score of the left kidney, with a coefficient of −0.554 ($p = 0.009$). No further measurements were correlated with the Karpinski score (**Supplementary Figs. 1,2**).

Univariate logistic regression analysis (Table 2) revealed an odds ratio (OR) of 2.20 (95% CI 1.04–4.71; prob > chi^2 0.022; ROC CURVE 0.819) for T0 lactates, with a p-value of 0.038 (**Supplementary Fig. 3**). Similarly, age exhibited an OR of 0.69 (95% CI 0.51–0.93; prob > chi^2 0.002; ROC CURVE 0.914) with a p-value of 0.016 (**Supplementary Fig. 4**). Lactate levels demonstrated a decrease during NrP time following a linear mixed model effect for the outcome of organ suitability, with p-values of 0.004 for both time and

TABLE 1. Resumes the principal examined variables.

Variables	Mean	Std. Dev.	Min	Max	p1	p99	Skew.	Kurt.	Swilk coeff	*p*-value
Age	63.14	8.248	44.00	79.00	44.00	79.00	−0.115	2.905	0.966	0.661
Right Karpinski	4.71	1.901	1.00	8.00	1.00	8.00	−0.250	2.460	0.980	0.931
Left Karpinski	4.71	2.004	1.00	9.00	1.00	9.00	–0.017	2.513	0.987	0.991
T0 lactates mmol/L	11.89	2.718	6.60	17.00	6.60	17.00	0.008	2.931	0.977	0.891
T1 lactates mmol/L	9.92	3.18	4.30	16.00	4.30	16.00	0.031	2.287	0.977	0.885
T2 lactates mmol/L	9.29	4.643	1.50	17.00	1.50	17.00	0.236	2.069	0.969	0.734
T3 lactates mmol/L	8.19	5.153	2.00	18.00	2.00	18.00	0.438	2.171	0.931	0.411
Blood Flow T0	2648.38	627.234	1500.00	3680.00	1500.00	3680.00	−0.186	1.744	0.917	0.071
Blood Flow T1	2585.09	587.054	1700.00	3607.00	1700.00	3607.00	−0.221	1.686	0.882	0.016
Blood Flow T2	2607.55	567.167	1600.00	3589.00	1600.00	3589.00	−0.292	1.895	0.916	0.085
Blood Flow T3	2524.00	580.421	1730.00	3520.00	1730.00	3520.00	0.107	1.783	0.926	0.342
T0 creatinine mg/dL	1.20	1.00	0.36	4.17	0.36	4.17	2.340	7.155	0.600	<0.001
T1 creatinine mg/dL	1.33	1.03	0.45	4.31	0.45	4.31	2.248	6.719	0.670	<0.001
T2 creatinine mg/dL	1.39	1.06	0.42	4.33	0.42	4.33	2.036	5.938	0.934	0.416
T3 creatinine mg/dL	1.66	1.33	0.43	4.46	0.43	4.46	1.275	3.078	0.754	0.003
Normothermic reperfusion (NrP) minutes	182.33	62.64	0.84	373.00	84.00	373.00	1.175	5.146	0.912	0.061

Std. Dev.: standard deviations; Skew.: Skewness; Kurt.: Kurtosis.

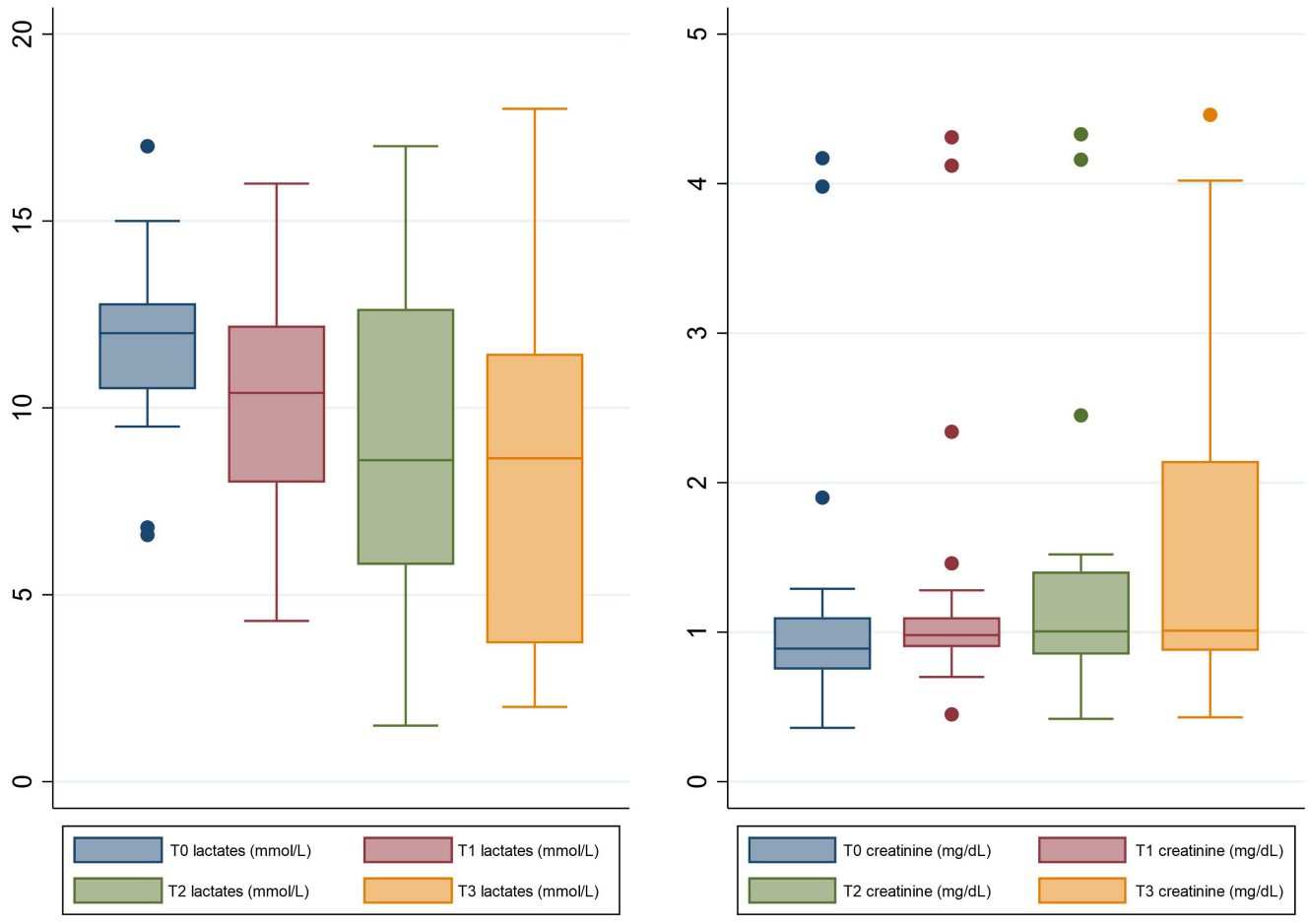

FIGURE 1. Principal variations in lactate levels and plasma creatinine during NrP.

TABLE 2. Univariate logistic analysis for kidney suitable donation: the output variable is organ suitable for transplantation.

Variables	OR to be suitable	*p*-value
T0 lactates mmol/L	2.20 (95% CI 1.04–4.71)	0.038
T1 lactates mmol/L	1.02 (95% CI 0.77–1.36)	0.842
T2 lactates mmol/L	0.95 (95% CI 0.78–1.16)	0.668
T3 lactates mmol/L	1.04 (95% CI 0.82–1.31)	0.714
T0 creatinine mg/dL	9.82 (95% CI 0.22–432.19)	0.236
T1 creatinine mg/dL	16.74 (95% CI 0.17–1612.83)	0.227
T2 creatinine mg/dL	2.58 (95% CI 0.52–12.68)	0.241
T3 creatinine mg/dL	1.73 (95% CI 0.59–5.02)	0.310
Blood flow T0	1.00 (95% CI 0.99–1.00)	0.163
Blood flow T1	1.00 (95% CI 0.99–1.00)	0.220
Blood flow T2	1.00 (95% CI 0.99–1.00)	0.194
Blood flow T3	1.00 (95% CI 0.99–1.00)	0.438
Age	0.69 (95% CI 0.51–0.93)	0.016
NrP minutes	1.00 (95% CI 0.98–1.01)	0.823

OR: odds ratio; CI: confidence interval; NrP: normothermic reperfusion.

outcome (Rrm lactate 10.032, Time −0.013, Outcome −3.05, Cons 13.89) (Fig. 2). The model exhibited a prob > chi^2 value of 0.000 (**Supplementary Tables 1 and 2**). Creatinine did not reach the significance of the statistics test.

4. Discussion

This study highlights the important role of mitochondrial damage during the ischemia-reperfusion process [16] and the importance of reducing lactate levels rather than only focusing on their absolute values. Several studies have investigated mitochondrial metabolism throughout various stages of DCD, with mitochondrial dysfunction suggested as a contributing factor to ischemia-reperfusion injury [17–19]. Lesnefsky *et al.* [17] examined the biochemical mechanisms within cardiomyocyte mitochondria during ischemia, including membrane alterations, oxidant molecule generation and signaling pathway activation, all of which may lead to cell death. According to some research, mitochondrial damage during ischemia may initiate succinate accumulation, resulting in increased flavin mononucleotide levels and subsequent release of reactive oxygen species [18, 19]. The duration of the ischemic period influences the nature of mitochondrial damage, which can either be transient or become permanent [20, 21]. Additionally, Quader *et al.* [22] elucidated the disparity between *in-vivo* and *ex-vivo* ischemia in rat heart models, demonstrating higher mitochondrial damage levels in both subsarcolemmal and interfibrillar mitochondria during *ex-vivo* ischemia. The role of mitochondrial damage has also been explored in liver transplantation. Schlegel *et al.* [23] discovered succinate and flavin mononucleotide release during the early stages of liver reperfusion [24]. However, this response is attenuated under colder conditions. Thus, exposing ischemic livers to a cold, oxygenated solution can mitigate mitochondrial damage during reperfusion [25]. After transplantation, an elevation in blood lactate levels during the post-ischemic phase has been observed. Lactate serves a pivotal role in metabolism, acting as a bridge between glycolysis and aerobic oxidative phosphorylation [26–29]. There is evidence suggesting a link between oxygen homeostasis and the expression of hypoxia-inducible factor 1 (HIF-1). Elevated lactate levels have been shown to increase HIF-1 expression, supporting this association [30, 31].

Arnold *et al.* [27] conducted a study in 2021 using rat heart models of DCD and reported some interesting findings demonstrating that organs with elevated pre-ischemic lactate levels experience delayed recovery of contractility and an increased risk of cardiomyocyte death. This effect is likely attributed to increased intracellular calcium and cytochrome c levels, leading to mitochondrial damage. Despite this, lactate levels tend to decrease after reperfusion, hinting at its potential utilization for ATP energy production, a process hindered when lactate levels are zero [32]. Lactate is recognized as an indicator of organ perfusion, and a gradual rise in serum levels, without an apparent cause, may signal inadequate organ perfusion and thus justify kidney refusal [33]. According to our statistical analyses, no negative correlation was observed between increased blood lactate levels during explantation and adverse outcomes. Elevated lactate levels in younger and healthier individuals may signify enhanced mitochondrial function. Moreover, a significant decrease in lactate levels may indicate organs suitable for transplantation and a reduction in organ damage, highlighting the importance of preventing and mitigating organ damage, especially in cases of prolonged ischemic time [34]. Although limited evidence exists, some studies have reported positive outcomes with cytokine hemadsorption [35, 36]. Currently, only a limited number of studies have explored DCD biomarkers related to organ suitability, among which plasmatic creatinine levels did not exhibit any correlation.

Niederberger *et al.* [37] assessed the influence of pre-

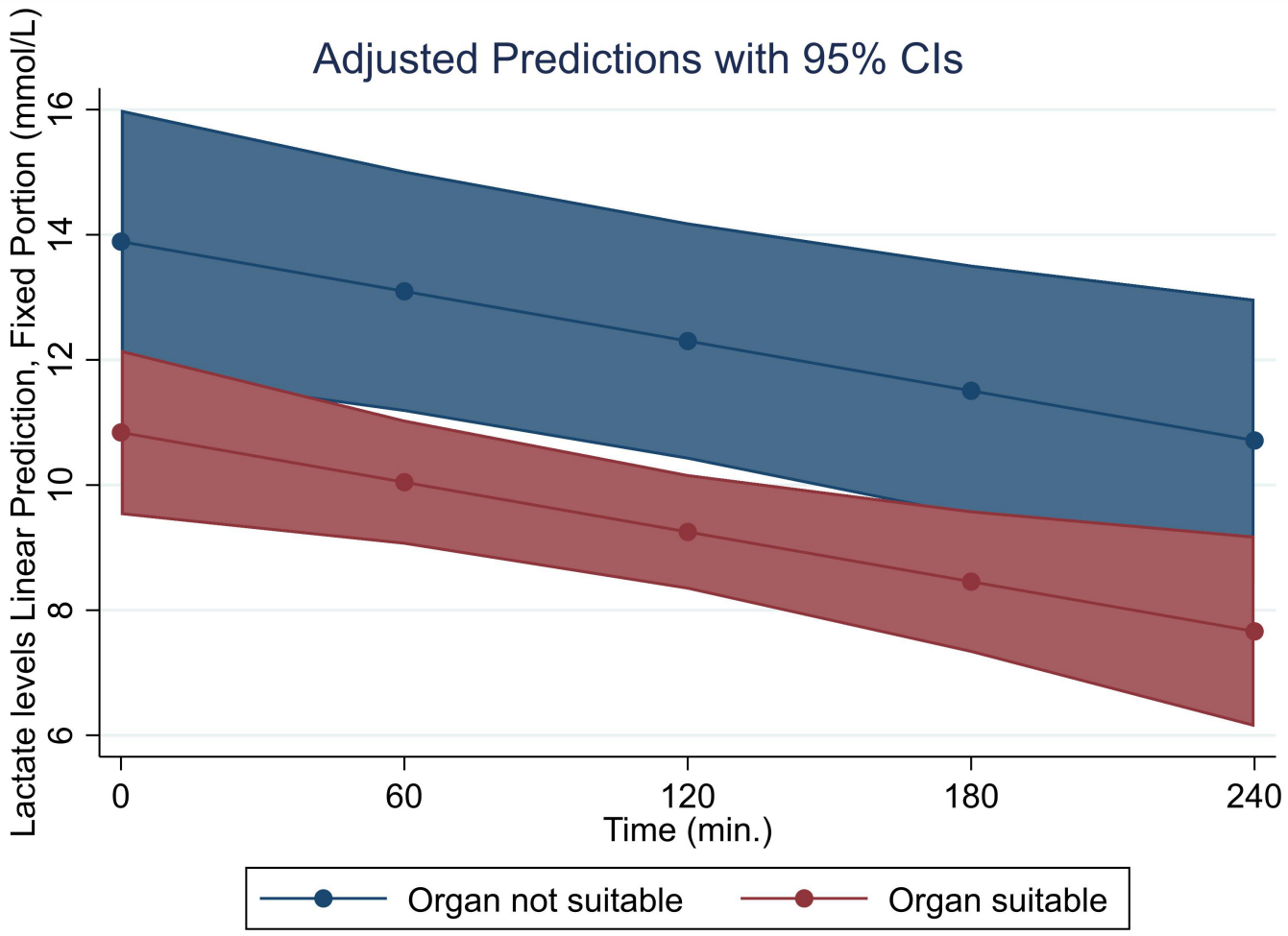

FIGURE 2. The decline in lactate levels over time according to the mixed model for organ suitability during NrP. CI: confidence interval.

ischemic fatty acid levels on rat heart donation and reported that elevated levels of fatty acids just before the warm ischemia phase may hinder circulation resumption during the post-ischemic period, possibly due to the rapid restoration of fatty acid metabolism following reperfusion, leading to the suppression of glucose metabolism, which adversely affects hemodynamic recovery in the post-ischemic phase.

In a recent study, Kadowaki *et al.* [38] investigated the potential role of Glucagon-like peptide 1 (GLP-1) agonists, such as Exenatide, a medication commonly used in diabetes management, has shown promise in preventing ischemia-reperfusion injury. Researchers utilized pig heart models to investigate the impact of Exenatide on myocardial damage, diastolic activity and metabolism. The findings revealed that Exenatide mitigated the risk of myocardial damage and enhanced diastolic activity and metabolism, suggesting potential cardio-protection [38].

The role of certain interleukins (IL) has also been investigated. Quader *et al.* [39] conducted a study suggesting that IL-1 and IL-18 may contribute to the injury induced by DCD. Their findings showed that genetically modified mice lacking these interleukins exhibited reduced susceptibility to DCD damage and demonstrated improved cardiac function post-procedure. Additionally, they noted a similar response when utilizing molecules that inhibited these interleukins, highlighting their potential beneficial role, particularly during the reperfusion phase [40].

Lastly, Aceros *et al.* [41] investigated the influence of Heat Shock Protein on ischemia-reperfusion injury in rat heart DCD models. Their study revealed that inhibiting this protein can offer cardioprotective advantages by improving both ventricular relaxation and contractility while concurrently reducing the risk of ischemic injury [41]. Given the ongoing demand for transplantable organs, larger datasets and studies are imperative to identify DCD biomarkers. Lactate levels could serve as a feasible and rapidly assessable parameter for organ assessment and restoration.

5. Strengths and limitations

This research presents both strengths and limitations. Its primary strength lies in the analysis of two potential biomarkers, lactates and creatinine, for identifying suitable organs for transplantation. However, a notable limitation is the small sample size, consisting of only a small cohort of patients. Consequently, conducting multiple variables analysis was not feasible due to insufficient data. Despite being readily accessible and commonly used in clinical practice, the sample size was inadequate to support such an analysis. Larger datasets are

required to validate these initial findings. Limited available data for predicting organ suitability underscores the need for further exploration of DCD biomarkers [17].

6. Conclusions

In conclusion, this study suggests that higher blood lactate levels might not be a negative predictor for organ suitability, and a greater decrease over time may indicate organ recovery. Rapid identification of suitable organs for transplantation could facilitate strategies to minimize organ damage, thereby enhancing the success rate of transplantation.

AVAILABILITY OF DATA AND MATERIALS

Data are available upon request to the authors.

AUTHOR CONTRIBUTIONS

GaM and SB—designed and conducted the research and performed the statistical analysis. FA—wrote the draft paper. SR, DD and CD—collected data. GiM—collected data of Karpinski score. AB—revised the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study was approved by the Ethics Committee of Azienda Ospedaliera Universitaria (AOU, Modena, Italy) (code 1217-2020) and conducted in compliance with the principles outlined in the Declaration of Helsinki. In accordance with Italian regulations governing data (Italian law, D.Lgs 196/2003 and Italian Data Protection regulation 146/2019), written consent was waived for patients unable to provide it.

ACKNOWLEDGMENT

We would like to thank Annamaria Montrone, Elisa Lori, Aurelia Cocilio and Elisa Davolio for their kind help and assistance during the research.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1840665679392325632/attachment/Supplementary%20material.docx.

REFERENCES

[1] Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. British Journal of Anaesthesia. 2012; 108: i108–i121.

[2] Chazelas P, Steichen C, Favreau F, Trouillas P, Hannaert P, Thuillier R, *et al*. Oxidative stress evaluation in ischemia reperfusion models: characteristics, limits and perspectives. International Journal of Molecular Sciences. 2021; 22: 2366.

[3] Zhou M, Yu Y, Luo X, Wang J, Lan X, Liu P, *et al*. Myocardial ischemia-reperfusion injury: therapeutics from a mitochondria-centric perspective. Cardiology. 2021; 146: 781–792.

[4] Nieuwenhuijs-Moeke GJ, Pischke SE, Berger SP, Sanders JSF, Pol RA, Struys MMRF, *et al*. Ischemia and reperfusion injury in kidney transplantation: relevant mechanisms in injury and repair. Journal of Clinical Medicine. 2020; 9: 253.

[5] Koyama T. Postconditioning with lactate-enriched blood for reducing lethal reperfusion injury in humans. Journal of Cardiovascular Translational Research. 2023; 16: 793–802.

[6] Casiraghi G, Poli D, Landoni G, Buratti L, Imberti R, Plumari V, *et al*. Intrathecal lactate concentration and spinal cord injury in thoracoabdominal aortic surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2011; 25: 120–126.

[7] Liu GY, Xie WL, Wang YT, Chen L, Xu ZZ, Lv Y, *et al*. Calpain: the regulatory point of myocardial ischemia-reperfusion injury. Frontiers in Cardiovascular Medicine. 2023; 10: 1194402.

[8] Panconesi R, Carvalho MF, Eden J, Fazi M, Ansari F, Mancina L, *et al*. Mitochondrial injury during normothermic regional perfusion (NRP) and hypothermic oxygenated perfusion (HOPE) in a rodent model of DCD liver transplantation. EBioMedicine. 2023; 98: 104861.

[9] Callaghan CJ, Charman SC, Muiesan P, Powell JJ, Gimson AE, van der Meulen JH; UK Liver Transplant Audit. Outcomes of transplantation of livers from donation after circulatory death donors in the UK: a cohort study. BMJ Open. 2013; 3: e003287.

[10] Silva A, Arora S, Dhanani S, Rochon A, Giorno LP, Jackson E, *et al*. Quality improvement tools to manage deceased organ donation processes: a scoping review. BMJ Open. 2023; 13: e070333.

[11] Bissolati M, Cerchione R, Terulla A, Corsini C, Lee YH, Secchi A, *et al*. Renal resistance trend during hypothermic machine perfusion correlates with preimplantation biopsy score in transplantation of kidneys from extended criteria donors. Transplantation Proceedings. 2021; 53: 1823–1830.

[12] Marletta S, Di Bella C, Catalano G, Mastrosimini MG, Becker J, Ernst A, *et al*. Pre-implantation kidney biopsies in extended criteria donors: from on call to expert pathologist, from conventional microscope to digital pathology. Critical Reviews in Oncogenesis. 2023; 28: 7–20.

[13] Zagni M, Croci GA, Cannavò A, Passamonti SM, De Feo T, Boggio FL, *et al*. Histological evaluation of ischemic alterations in donors after cardiac death: a useful tool to predict post-transplant renal function. Clinical Transplantation. 2022; 36: e14622.

[14] Mori G, Cerami C, Facchini F, Fontana F, Alfano G, Giovanni R, *et al*. Kidney transplantation from circulatory death donors: monocentric experience. Transplantation Proceedings. 2019; 51: 2865–2867.

[15] Ruberto F, Lai Q, Piazzolla M, Brisciani M, Pretagostini R, Garofalo M, *et al*. The role of hypothermic machine perfusion in selecting renal grafts with advanced histological score. Artificial Organs. 2022; 46: 1771–1782.

[16] Ma H, Guo X, Cui S, Wu Y, Zhang Y, Shen X, *et al*. Dephosphorylation of AMP-activated protein kinase exacerbates ischemia/reperfusion-induced acute kidney injury via mitochondrial dysfunction. Kidney International. 2022; 101: 315–330.

[17] Lesnefsky EJ, Chen Q, Tandler B, Hoppel CL. Mitochondrial dysfunction and myocardial ischemia-reperfusion: implications for novel therapies. Annual Review of Pharmacology and Toxicology. 2017; 57: 535–565.

[18] Kim M, Stepanova A, Niatsetskaya Z, Sosunov S, Arndt S, Murphy MP, *et al*. Attenuation of oxidative damage by targeting mitochondrial complex I in neonatal hypoxic-ischemic brain injury. Free Radical Biology & Medicine. 2018; 124: 517–524.

[19] Stepanova A, Kahl A, Konrad C, Ten V, Starkov AS, Galkin A. Reverse electron transfer results in a loss of flavin from mitochondrial complex

I: potential mechanism for brain ischemia reperfusion injury. Journal of Cerebral Blood Flow and Metabolism. 2017; 37: 3649–3658.

[20] Chen Q, Hoppel CL, Lesnefsky EJ. Blockade of electron transport before cardiac ischemia with the reversible inhibitor amobarbital protects rat heart mitochondria. The Journal of Pharmacology and Experimental Therapeutics. 2006; 316: 200–207.

[21] Lesnefsky EJ, Tandler B, Ye J, Slabe TJ, Turkaly J, Hoppel CL. Myocardial ischemia decreases oxidative phosphorylation through cytochrome oxidase in subsarcolemmal mitochondria. The American Journal of Physiology. 1997; 273: H1544–H1554.

[22] Quader M, Akande O, Toldo S, Cholyway R, Kang L, Lesnefsky EJ, *et al*. The commonalities and differences in mitochondrial dysfunction between *ex vivo* and *in vivo* myocardial global ischemia rat heart models: implications for donation after circulatory death research. Frontiers in Physiology. 2020; 11: 681.

[23] Schlegel A, Mergental H, Fondevila C, Porte RJ, Friend PJ, Dutkowski P. Machine perfusion of the liver and bioengineering. Journal of Hepatology. 2023; 78: 1181–1198.

[24] Panconesi R, Widmer J, Carvalho MF, Eden J, Dondossola D, Dutkowski P, *et al*. Mitochondria and ischemia reperfusion injury. Current Opinion in Organ Transplantation. 2022; 27: 434–445.

[25] Schlegel A, Muller X, Mueller M, Stepanova A, Kron P, de Rougemont O, *et al*. Hypothermic oxygenated perfusion protects from mitochondrial injury before liver transplantation. EBioMedicine. 2020; 60: 103014.

[26] Ferguson BS, Rogatzki MJ, Goodwin ML, Kane DA, Rightmire Z, Gladden LB. Lactate metabolism: historical context, prior misinterpretations, and current understanding. European Journal of Applied Physiology. 2018; 118: 691–728.

[27] Arnold M, Méndez-Carmona N, Wyss RK, Joachimbauer A, Casoni D, Carrel T, *et al*. Comparison of experimental rat models in donation after circulatory death (DCD): *in-situ vs. ex-situ* ischemia. Frontiers in Cardiovascular Medicine. 2020; 7: 596883.

[28] Brooks GA. The science and translation of lactate shuttle theory. Cell Metabolism. 2018; 27: 757–785.

[29] Parente A, Flores Carvalho M, Schlegel A. Endothelial cells and mitochondria: two key players in liver transplantation. International Journal of Molecular Sciences. 2023; 24: 10091.

[30] Hunt TK, Aslam RS, Beckert S, Wagner S, Ghani QP, Hussain MZ, *et al*. Aerobically derived lactate stimulates revascularization and tissue repair via redox mechanisms. Antioxidants & Redox Signaling. 2007; 9: 1115–1124.

[31] Nalbandian M, Takeda M. Lactate as a signaling molecule that regulates exercise-induced adaptations. Biology. 2016; 5: 38.

[32] Arnold M, Segiser A, Graf S, Méndez-Carmona N, Sanz MN, Wyss RK, *et al*. Pre-ischemic lactate levels affect post-ischemic recovery in an isolated rat heart model of donation after circulatory death (DCD). Frontiers in Cardiovascular Medicine. 2021; 8: 669205.

[33] Takahashi K, Jafri SR, Safwan M, Abouljoud MS, Nagai S. Peri-transplant lactate levels and delayed lactate clearance as predictive factors for poor outcomes after liver transplantation: a propensity score-matched study. Clinical Transplantation. 2019; 33: e13613.

[34] Baroni S, Melegari G, Brugioni L, Gualdi E, Barbieri A, Bertellini E. First experiences of hemoadsorption in donation after circulatory death. Clinical Transplantation. 2020; 34: e13874.

[35] Saemann L, Hoorn F, Georgevici AI, Pohl S, Korkmaz-Icöz S, Veres G, *et al*. Cytokine adsorber use during DCD heart perfusion counteracts coronary microvascular dysfunction. Antioxidants. 2022; 11: 2280.

[36] Baroni S, Marudi A, Rinaldi S, Ghedini S, Magistri P, Piero Guerrini G, *et al*. Cytokine mass balance levels in donation after circulatory death donors using hemoadsorption: case series report. The International Journal of Artificial Organs. 2022; 45: 642–646.

[37] Niederberger P, Farine E, Arnold M, Wyss RK, Sanz MN, Méndez-Carmona N, *et al*. High pre-ischemic fatty acid levels decrease cardiac recovery in an isolated rat heart model of donation after circulatory death. Metabolism. 2017; 71: 107–117.

[38] Kadowaki S, Siraj MA, Chen W, Wang J, Parker M, Nagy A, *et al*. Cardioprotective actions of a glucagon-like peptide-1 receptor agonist on hearts donated after circulatory death. Journal of the American Heart Association. 2023; 12: e027163.

[39] Quader M, Mezzaroma E, Kenning K, Toldo S. Modulation of interleukin-1 and -18 mediated injury in donation after circulatory death mouse hearts. The Journal of Surgical Research. 2021; 257: 468–476.

[40] Quader M, Chen Q, Akande O, Cholyway R, Mezzaroma E, Lesnefsky EJ, *et al*. Electron transport chain inhibition to decrease injury in transplanted donation after circulatory death rat hearts. Journal of Cardiovascular Pharmacology. 2023; 81: 389–391.

[41] Aceros H, Der Sarkissian S, Borie M, Pinto Ribeiro RV, Maltais S, Stevens LM, *et al*. Novel heat shock protein 90 inhibitor improves cardiac recovery in a rodent model of donation after circulatory death. The Journal of Thoracic and Cardiovascular Surgery. 2022; 163: e187–e197.

How to cite this article: Gabriele Melegari, Stefano Baroni, Federica Arturi, Simone Rinaldi, Chiara Dallai, Dalila Donelli, *et al*. Role of blood lactate levels in kidney suitability for donation after circulatory death: a retrospective analysis. Signa Vitae. 2024; 20(10): 16-22. doi: 10.22514/sv.2024.121.