Arterial Lactate Concentration At The End of Liver Transplantation is Independently Associated with One-Year Mortality

Sean Coeckelenbergh
Université Libre de Bruxelles
Leonard Drouard
Université Libre de Bruxelles
Brigitte Ickx
Université Libre de Bruxelles
Valerio Lucidi
Cliniques Universitaires de Bruxelles, Université Libre de Bruxelles
Dessy Germanova
Cliniques Universitaires de Bruxelles, Université Libre de Bruxelles
Olivier Desebbe
Sauvegarde Clinic
Maya Moussa
Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Université Paris-Saclay, Paul Brousse Hospital, Assistance Publique Hôpitaux de Paris (APHP)
Salima Naili
Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Université Paris-Saclay, Paul Brousse Hospital, Assistance Publique Hôpitaux de Paris (APHP)
Eric Vibert
Hôpitaux Universitaires Paris-Sud, Université Paris- Sud, Université Paris-Saclay, Paul Brousse Hospital, Assistance Publique Hôpitaux de Paris (APHP)
Didier Samuel
Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Université Paris-Saclay, Paul Brousse Hospital, Assistance Publique Hôpitaux de Paris (APHP)
Jacques Duranteau
Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Université Paris-Saclay, Paul Brousse Hospital, Assistance Publique Hôpitaux de Paris (APHP)
Jean-Louis Vincent
Université Libre de Bruxelles
Joseph Rinehart
University of California Irvine

Philippe Van der Linden
Université Libre de Bruxelles
Alexandre Joosten
joosten-alexandre@hotmail.com

Université Libre de Bruxelles

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Abstract

BACKGROUND

Liver transplant patients who develop hyperlactatemia are at increased risk of postoperative morbidity and mortality, but there are few data on longer-term outcomes. We therefore investigated whether arterial lactate concentration obtained immediately after surgery, at the time of admission to the intensive care unit (ICU), was associated with 1-year mortality.

METHODS:

In this retrospective cohort study, all patients who underwent liver transplant surgery between September 2013 and December 2019 were screened for inclusion. Patients who underwent combined transplantation surgery and those with a history of previous liver transplantation (i.e., redo surgery) were not included. Logistic regression modeling included univariate and multivariate analyses. Receiver operating characteristic (ROC) curves and areas under the curves (AUROCs) were calculated. Lactate thresholds and association with outcome were analyzed for specificity, sensitivity, and Youden's index.

RESULTS: Of 226 patients included, 18.4% died within 1-year of liver transplantation. Immediate postoperative lactate concentration was independently associated with 1-year mortality with an odds ratio (OR) of 1.35 (95% CI: 1.16 to 1.59; p<0.001) per mEq/L increase in lactate and an AUROC of 0.80 (95% CI: 0.72 to 0.87; p<0.001). A lactate concentration of 2.25 mEq/L (cut-off determined using Youden's index) was associated with increased 1-year mortality with a sensitivity of 0.71 and a specificity of 0.72.

CONCLUSION: Increased arterial lactate concentration on admission to the ICU immediately after orthotopic liver transplantation is independently associated with increased 1-year mortality.

Trial Registration: Not Applicable

Background

Blood lactate concentrations reflect an imbalance between systemic oxygen delivery and tissue oxygen demand, which results in anaerobic metabolism.[1] Because about 60% of lactate is cleared by the liver, blood lactate concentrations also provide an indication of hepatic blood flow and function.[2] Raised blood lactate concentrations may therefore reflect intra-operative tissue dysoxia and graft dysfunction in liver transplant patients.[3–6] Rarer causes of hyperlactatemia include enzymatic (e.g., pyruvate dehydrogenase) alterations, pharmacologic effects (e.g., metformin), and hypothermia.[1] Hyperlactatemia is often associated with metabolic acidosis, which can alter a patient's hemostasis and hemodynamics, worsen hemorrhage, exacerbate postoperative complications, and ultimately increase mortality.[1, 7] Normal arterial lactate concentrations are around 1 mEq/L and values greater than 1.5 mEq/L have been associated with increased mortality in various studies of surgical and critically ill patients.[8–10] Blood lactate levels may therefore represent a useful predictor of complications and outcomes in liver transplant patients.[10]

Although the presence of hyperlactatemia at the end of liver transplantation has been shown to be associated with postoperative mortality within the first [11] and third [4] months after liver transplantation, there are few data on its relationship with long-term mortality. The primary objective of this cohort study was therefore to test the hypothesis that increased lactate concentration on after liver transplantation is associated with increased 1-year mortality.

Methods

The Erasme Hospital Institutional Review Board approved this monocenter study on December 14, 2018 (reference P2018/555), and waived the need for patient informed consent because of the study's retrospective nature. Using our anesthetic electronic records software (Innovian, Drager, Germany), we identified all patients who had had an orthotopic liver transplant between September 2013, date of implementation of the software, and December 2019. We reviewed the electronic medical records (MediView, IMMJ Systems, United Kingdom) of all these patients and included those for whom operating room planning dedicated software (TrackPro, UltraGenda, Belgium) had been used. Exclusion criteria included incomplete records, combined surgeries (e.g., simultaneous lung and liver transplant), and previous liver transplantation.

Anesthesia protocol

Anesthesia was standardized according to our institutional protocol. After arrival in the operating room, patients and were placed under an infrared heating lamp. Standard non-invasive monitoring consisted of a 5-lead EKG, non-invasive blood pressure, temperature, frontal processed electroencephalogram, diuresis, and neuromuscular blockade monitoring. Vascular access consisted of one or two large bore peripheral venous catheters, right femoral artery and vein catheters, and right jugular vein catheter. The left femoral and internal jugular veins were left at the surgeon's disposal for possible veno-venous bypass. A pulmonary artery (Swan-Ganz) catheter was inserted, and hemodynamic management was guided using calibrated cardiac index, central venous oxygen saturation, inferior vena cava pressure, central venous pressure, and arterial pressure. Hemodynamic targets were left to the discretion of the attending anesthesiologist. Rapid infusers, perfusion heaters, and an intraoperative blood product salvage system were ready for use prior to induction. In case of massive bleeding, it was recommended that the anesthesiologist should use ROTEM technology to guide blood product administration. Anesthesia was induced with propofol or etomidate and neuromuscular blockade with rocuronium or succinylcholine, depending on the patient's history, and maintained with cisatracurium. Anti-nociception was maintained with remifentanil and unconsciousness with sevoflurane or desflurane. Rapid sequence intubation was performed if patients had not fasted or had abdominal ascites.

Surgical procedure

The standard approach for orthotopic liver transplantation was recipient hepatectomy with a vena cava–sparing technique, piggy-back reconstruction, and no venous-venous bypass. Liver reperfusion began with the portal vein and then arterial reperfusion. End-to-end choledochectomy without a T-tube assured

biliary reconstruction. Portal ischemia (i.e., cold ischemia) time was defined as the time from donor aortic clamping to portal unclamping of the recipient. Arterial ischemia (i.e., warm ischemia) was defined as the time from recipient portal unclamping to hepatic artery unclamping. Immunosuppression consisted of tacrolimus with mycophenolate mofetil and prednisone. Tacrolimus levels were targeted at 5–10 ng/mL and steroids were maintained for the first 3 months post liver transplantation.

At our institution all patients are transferred to the ICU immediately after liver transplantation.

Data collection and outcomes

Preoperative demographics, intraoperative and postoperative (at patient arrival in the ICU) arterial lactate concentrations, postoperative major and minor complications, 30-day mortality, and 1-year mortality were collected from the medical records for each patient.

The primary objective was to test the hypothesis that postoperative lactate concentration at ICU admission was associated with long-term mortality (i.e., death within one year of transplantation). Secondary objectives included the association between lactate concentration and 30-day mortality and between lactate and major postoperative complications (defined in **Appendix 1**).

Statistical Analysis

Data are reported as mean ± standard deviation or median [25th -75th percentiles] depending on the normality of the distribution as tested by the Shapiro-Wilk test. Results for counts are reported as number (% of group). Baseline, intraoperative, and outcome data were first compared groupwise with a Student's t-test or a Mann-Whitney U for normal and skewed data, respectively, or a chi-square test for counts. Univariate testing identified potential contributors to mortality. All variables with a p value < 0.10 were introduced into a multivariate analysis and a backwards feature selection process removed variables with a p value > 0.05 in the model.

Receiver operating characteristic (ROC) curves were established for 1-year mortality, 30-day mortality, and postoperative complications; 95% confidence intervals were calculated using the DeLong method. Lactate concentration thresholds and the mortality or morbidity risk were calculated, with 2000 bootstrapped Monte-Carlo samples for specificity, sensitivity, and Youden's Index

Results

A total of 276 liver transplant procedures were performed during the study period; 28 patients had incomplete anesthesia medical records, 10 had had combined surgery, and 10 had had a previous liver transplant. Accordingly, 228 patients were included in the analysis **(**Fig. 1**).** Forty-two patients (18.6%) patients died within the year after transplantation

The American Society of Anesthesiology (ASA) score, Child-Pugh score, Model for End-stage Liver Disease (MELD) score, duration of anesthesia, duration of surgery, crystalloid volume, blood product transfusion, platelet transfusion, total infused volume, fluid balance, portal ischemia time, mean end tidal CO_2, and immediate postoperative lactate concentration were associated with 1-year mortality in

univariate analysis (Tables 1 and 2). Postoperative events associated with 1-year mortality were: sepsis, postoperative bleeding requiring transfusions, atrial fibrillation, encephalopathy, acute respiratory distress syndrome, reoperation, renal replacement therapy, and acute kidney injury (stages II and III) (Table 3).

Table 1
Baseline Characteristics

	Deceased at 1-year (N = 42)	Alive at 1-year (N = 184)	P-value
Male (%)	29 (69.0%)	131 (71.2%)	0.93
Age (years)	56.9 ± 9.64	54.9 ± 10.4	0.24
Donor Age (years)	56.7 ± 16.6	53.9 ± 15.8	0.33
Weight (Kg)	82.7 ± 22.7	79.7 ± 19.1	0.43
Height (cm)	172 ± 9.59	171 ± 11.3	0.71
BSA (m^2)	1.95 ± 0.27	1.91 ± 0.25	0.37
ASA score			**0.0048**
1	0 (0%)	0 (0%)	
2	1 (2.4%)	5 (2.7%)	
3	12 (28.6%)	105 (57.1%)	
4	27 (64.3%)	72 (39.1%)	
5	2 (4.8%)	2 (1.1%)	
Child-Pugh Score	10.6 ± 3.44	9.11 ± 3.20	**0.017**
MELD Score	24.4 ± 12.5	19.4 ± 10.7	**0.031**
Etiology of liver failure			0.14
Acute hepatic failure	7 (16.7%)	8 (4.3%)	
Biliary disease	4 (9.5%)	12 (6.5%)	
Thrombotic	0 (0%)	3 (1.6%)	
Cirrhosis	13 (31.0%)	73 (39.7%)	
Malignancy	12 (28.6%)	70 (38.0%)	
NASH	5 (11.9%)	5 (2.7%)	
Benign tumor	0 (0%)	3 (1.6%)	
Hepato-pulmonary syndrome	0 (0%)	2 (1.1%)	

Data are presented as mean ± SD or number (%). statistically significant values are in bold

ASA American Society of Anesthesiology *BSA* Body Surface Area *MELD* Model for End-stage Liver Disease

	Deceased at 1-year (N = 42)	Alive at 1-year (N = 184)	P-value
Polycystic disease	0 (0%)	1 (0.5%)	
Other	0 (0%)	1 (0.5%)	
Unknown	1 (2.4%)	7 (3.8%)	
Data are presented as mean ± SD or number (%). statistically significant values are in bold			
ASA American Society of Anesthesiology *BSA* Body Surface Area *MELD* Model for End-stage Liver Disease			

Table 2
Intraoperative events

	Deceased at 1-year (N = 42)	Alive at 1-year (N = 184)	P-value
Key durations			
Duration of anesthesia	566 ± 202	500 ± 106	**0.046**
Duration of surgery	402 ± 132	367 ± 85.6	0.10
Duration of portal ischemia	453 ± 116	411 ± 104	**0.037**
Duration of arterial ischemia	40.1 ± 24.0	35.2 ± 20.1	0.23
Infused fluids			
Crystalloid	3540 ± 3000	2680 ± 1720	0.078
Colloid	1060 ± 889	867 ± 885	0.2
Bicarbonate	81.2 ± 237	31.2 ± 70.8	0.18
Pack Red Blood Cells	2790 ± 2680	1830 ± 2230	**0.036**
Plasma	1190 ± 1170	875 ± 1150	0.12
Platelets	350 ± 397	184 ± 308	**0.014**
Cell Saver Return	623 ± 1050	646 ± 1040	0.89
Total in	10900 ± 8210	7900 ± 5610	**0.029**
Fluid loss			
Estimated Blood Loss	4350 ± 4670	3140 ± 3100	0.11
Urine Output	386 ± 363	378 ± 362	0.89
Total Out	4740 ± 4670	3520 ± 3130	0.11
Net fluid balance	6150 ± 5760	4380 ± 4260	0.066
Organ Perfusion Parameters			
Average MAP	72.2 ± 7.22	73.3 ± 7.09	0.38
Time with MAP < 65mmHg	33.3 ± 20.3	28.1 ± 20.4	0.14
End-Tidal CO_2	29.5 ± 3.88	30.7 ± 3.61	0.063

Data are presented as mean ± SD. Statistically significant values are in bold

ICU Intensive Care Unit *MAP* mean arterial pressure

	Deceased at 1-year (N = 42)	Alive at 1-year (N = 184)	P-value
Lactate on ICU admission	6.6 ± 5.9	2.3 ± 2.11	**0.00004**
Data are presented as mean ± SD. Statistically significant values are in bold			
ICU Intensive Care Unit *MAP* mean arterial pressure			

Table 3
Complications and outcomes

	Deceased at 1-year (N = 42)	Alive at 1-year (N = 184)	P-value
Major complications			
Biliary dysfunction	12 (28.6%)	40 (21.7%)	0.46
Anastomotic leakage	8 (19.0%)	11 (6.0%)	0.014
Peritonitis	3 (7.1%)	4 (2.2%)	0.24
Sepsis	13 (31.0%)	13 (7.1%)	**< 0.001**
Primary graft failure	3 (7.1%)	7 (3.8%)	0.59
Bleeding requiring reoperation	25 (59.5%)	43 (23.4%)	**< 0.001**
Atrial fibrillation	9 (21.4%)	16 (8.7%)	**0.036**
Acute coronary syndrome	1 (2.4%)	1 (0.5%)	0.81
Stroke	0 (0%)	1 (0.5%)	> 0.99
Graft thrombosis	6 (14.3%)	13 (7.1%)	0.22
DVP/PE	2 (4.8%)	5 (2.7%)	0.84
Encephalopathy	16 (38.1%)	16 (8.7%)	**< 0.001**
ARDS	12 (28.6%)	15 (8.2%)	**< 0.001**
Heart failure	4 (9.5%)	13 (7.1%)	0.82
Reoperation (Any Cause)	21 (50.0%)	36 (19.6%)	**< 0.001**
Renal replacement therapy	23 (54.8%)	19 (10.3%)	**< 0.001**
AKI KDIGO II	2 (4.8%)	29 (15.8%)	0.10
AKI KDIGO III	25 (59.5%)	29 (15.8%)	**< 0.001**
Any major complication	5.0 [0.0–10.0]	1.0 [0.0–9.0]	**< 0.001**
Minor Complications			
AKI KDIGO I	7 (16.7%)	42 (22.8%)	0.50

Data are presented as IQR [Q25, Q75] or number (%)

*statistically significant values are in bold

AKI Acute Kidney injury *ARDS* Acute Respiratory Distress Syndrome *KDIGO* Kidney Disease: Improving Global Outcomes ; DVP: deep venous thrombosis; PE: pulmonary embolism

	Deceased at 1-year (N = 42)	Alive at 1-year (N = 184)	P-value
Urinary Infection	1 (2.4%)	8 (4.3%)	0.88
Ileus	9 (21.4%)	23 (12.5%)	0.21
Pleural Effusion	7 (16.7%)	24 (13.0%)	0.71
Pneumonia	4 (9.5%)	8 (4.3%)	0.33
Delirium	13 (31.0%)	25 (13.6%)	0.013
Other infection	10 (23.8%)	17 (9.2%)	**0.0181**
Any Minor Complication	1.0 [0.0–3.0]	0 [0.0–4.0]	**0.0047**
Hospitalization			
ICU Length of stay	5 [1–27]	3 [1–27]	**0.0031**
Hospital Length of stay	23 [2–122]	15 [7–166]	0.16
Readmission within 90 days	5 (11.9%)	12 (6.5%)	0.38
Mortality			
1-Year mortality	42 (100%)	0 (0%)	**< 0.001**
Data are presented as IQR [Q25, Q75] or number (%)			
*statistically significant values are in bold			
AKI Acute Kidney injury *ARDS* Acute Respiratory Distress Syndrome *KDIGO* Kidney Disease: Improving Global Outcomes ; DVP: deep venous thrombosis; PE: pulmonary embolism			

In the multivariate model, ASA score, duration of anesthesia, infused crystalloid volume, total infused volume, and lactate concentration at ICU admission were independently associated with 1-year mortality (Table 4). Lactate concentration at ICU admission was strongly associated with 1-year mortality with an odds ratio (OR) of 1.35 (95% CI: 1.16 to 1.59; $p < 0.001$) per unit increase in lactate. The AUROC was 0.80 (95% CI: 0.72 to 0.87; $p < 0.001$) (Fig. 2), and a lactate concentration of 2.25 mEql/L (cut-off determined using Youden's index) was associated with 1-year mortality with a sensitivity of 0.71 and a specificity of 0.72. Lactate concentration at ICU admission also predicted 30-day mortality, with an AUROC of 0.91 (95% CI: 0.84 to 0.97; $p < 0.0001$). A lactate concentration of 2.65 mEq/L was associated with 30-day mortality with a sensitivity of 0.94 and a specificity of 0.72. Lactate concentration predicted major postoperative complications poorly, with an AUROC of 0.63 (95% CI: 0.56 to 0.71; $p = 0.0013$). A lactate concentration of 2.55 mEq/L was associated with major postoperative complications with a sensitivity of 0.41 and a specificity of 0.80.

Table 4
Factors independently associated with postoperative mortality

Factor	Adjusted Odds Ratio	95% CI	P value
ASA Score	2.4040	1.0703–5.3994	**0.033**
Anesthesia duration (per minute)	1.0037	1.0004–1.0071	**0.030**
Intraoperative crystalloid (per ml)	1.0006	1.0001–1.0010	**0.008**
Intraoperative total infused volume (per ml)	0.9996	0.9992–0.9999	**0.035**
Lactate on ICU Admission (per mEq/L)	1.3568	1.1590–1.5884	**< 0.001**

ASA - American Society of Anesthesiology; *ICU* - Intensive Care Unit

Discussion

Even a moderate increase in blood lactate concentration early after orthotopic liver transplantation was associated with increased long-term mortality. Previous studies have reported an association between postoperative hyperlactatemia and mortality after liver transplantation,[4, 11, 12] but none evaluated long-term mortality. Our study is consistent with the prior observations after liver transplantation[4] liver surgery,[12] major abdominal surgery,[13] cardiac surgery [14–16], and intensive care admission.[9]

There are several potential causes of increased lactate concentration at the end of liver transplant surgery. Liver transplant patients can develop tissue dysoxia and graft failure, both of which have been associated with increased mortality during major abdominal surgery and after liver transplantation.[5, 6] However, the incidence of graft failure in our cohort was similar in survivors and non-survivors, suggesting that tissue hypoperfusion was the predominant cause of the higher lactate concentrations in the non-survivors. Other factors contributing to hyperlactatemia could be compromised hemodynamic status during complex surgery, reflected by increased surgical duration and portal ischemia. Hemodynamic alterations can lead to tissue hypoxia with subsequent development of anaerobic metabolism [17] and followed by multiple organ dysfunction.[18] The significantly higher rates of organ failure, including encephalopathy, acute respiratory distress syndrome, kidney injury, and sepsis in patients who did not survive the first year after transplantation compared to those who did, further suggests that intraoperative tissue dysoxia contributed to the increased lactate concentrations. Patients who died within one year of transplantation had higher preoperative risk (i.e., higher ASA, MELD, and Child-Pugh scores). These scores reflect patient frailty and are linked to hepatic and other organ dysfunctions, which increase the burden of perioperative patient care. [19–21] The ASA score, for example, has been consistently linked with increased postoperative complications and mortality.[21] Our results confirm this finding, as the ASA score was independently associated with postoperative mortality.

Several other factors were independently associated with postoperative mortality, including duration of anesthesia and infused crystalloid volume. Excessive fluid administration has been linked to increased postoperative complications either because this is an indicator of hemodynamic instability or because of an intrinsic effect of fluid.[22–24] These factors attest to the hemodynamic and anesthetic challenges of these patients and strengthen the association between unstable hemodynamics, decreased perfusion, tissue hypoxia, increased lactate, and postoperative mortality. Increased postoperative lactate concentration was also associated with major complications, with good specificity. In addition to tissue hypoxia, other causes of postoperative morbidity after liver transplant, include coagulopathy and biliary complications,) [25, 26] for which increased lactate concentrations may have lower sensitivity.

Liver transplant patients with postoperative hyperlactatemia should be carefully investigated to determine the cause of hyperlactatemia and administer effective treatment. A perioperative goal-directed hemodynamic strategy may help to prevent intraoperative tissue hypoxia and its associated postoperative complications.[27–29] Maintaining optimal hemodynamic goals (e.g.,preload, arterial pressure, and cardiac output), is essential, but clinicians must still recognize that hyperlactatemia may be due to other causes during liver surgery. [12] Regardless of its etiology, hyperlactatemia is linked to increased short- and long-term mortality and its presence should promote close observation and prophylactic measures to prevent postoperative complications and death.

Limitations

This study had several limitations. First, it was a single center, retrospective study, with a relatively small number of patients. Second, although a single arterial lactate concentration was strongly associated with 30-day and 1-year mortality, evaluating the time course of blood lactate levels may give even more information; this should be further studied. Third, our study did not include donor data, which could have an impact on survival. Although invasive hemodynamic monitors were used, future studies should assess the impact of goal-directed hemodynamic strategies on postoperative morbidity and mortality in liver transplant patients. Our study, however, reflects standard of care in an academic center with expertise in liver transplantation anesthesia.

Conclusions

In patients who underwent orthotopic liver transplantation, an increased lactate concentration immediately after surgery was independently associated with increased 1-year mortality.

List Of Abbreviations

ASA
American Society of Anesthesiology
AUC
Area Under the Curve

ICU
Intensive Care Unit
MELD
Model for End-stage Liver Disease
ROC
Receiver Operating Characteristic

Declarations

Ethics approval: Study approved by the Institutional Review Board of Erasme hospital on December 14, 2018 under the reference P2018/555.

Consent for publication: Not Applicable

Availability of data and materials: By request to the corresponding author

Competing interests:

SC is a consultant for Medtronic (Dublin, Ireland)

AJ is a consultant for Edwards Lifesciences (Irvine, California, USA).

OD is a consultant for Medtronic (Dublin, Ireland)

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Authors' contributions: All authors read and approved the final manuscript

S.C.: Designed the study, collected and analyzed the data and drafted the manuscript

L.D: Collected and analyzed the data and edited the final manuscript

B.I: Analyzed the data and edited the final manuscript

V.L: Analyzed the data and edited the final manuscript

D.G: Analyzed the data and edited the final manuscript

O.D: Analyzed the data and edited the final manuscript

M.M: Analyzed the data and edited the final manuscript

S.N: Analyzed the data and edited the final manuscript

E.V: Analyzed the data and edited the final manuscript

D.S: Analyzed the data and edited the final manuscript

J.D: Analyzed the data and edited the final manuscript

JL.V: Analyzed the data and edited the final manuscript

J.R: Statistical analysis of the data and edited the final manuscript.

P.VdL: Statistical analysis of the data and edited the final manuscript.

A.J: Designed the study, collected and analyzed the data and drafted the manuscript.

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Figures

Figure 1

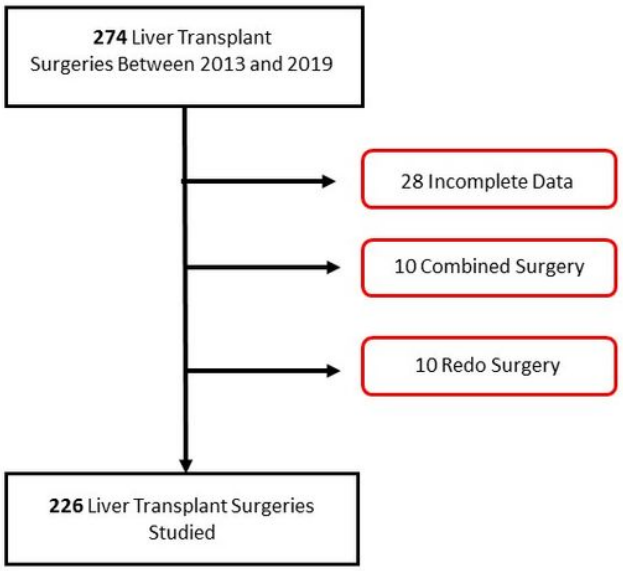

Figure 1

Flow chart of patient inclusion

Figure 2

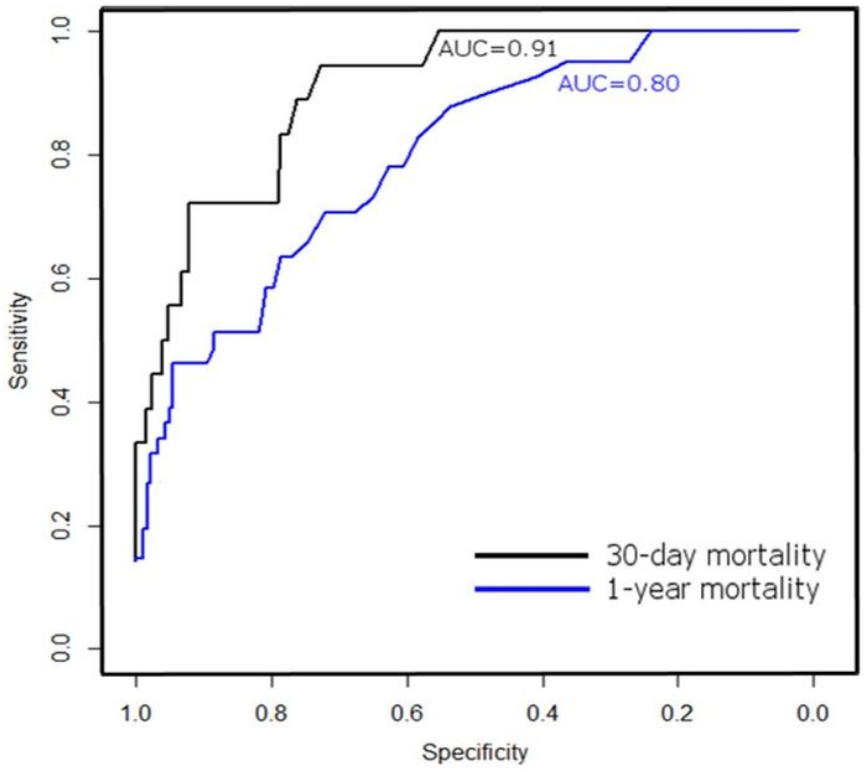

Figure 2

Receiver operating characteristic curves of 30-day and 1-year mortality

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