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Doctor of Philosophy

Preoperative Hyperlactatemia and Early Mortality after Liver Transplantation: An Application of Random Survival Forest Analysis

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Preoperative Hyperlactatemia and Early Mortality after Liver Transplantation: An Application of Random Survival Forest Analysis

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Abstract

Background: Hyperlactatemia is a common finding in critically ill patients, including patient with septic shock, cardiogenic, hypovolemic shock, trauma and liver failure. In liver transplantation (LT) patients, postoperative lactate and lactate clearance rate are considered as good surrogate markers of early graft function and outcome. The objectives of this study are to identify variables that are most important for preoperative hyperlactatemia, to see if there are modifiable factors, and to examine the effect of preoperative hyperlactatemia on early mortality after LT using random forest method.

Method: The data from Asan LT registry of all patients who underwent LT between January 2008 and February 2019 at the Asan Medical Center were analyzed. The most important variable for preoperative hyperlactatemia and the effect of preoperative hyperlactatemia on 30-day and 90-day mortality were identified by random forest method. Survival analysis for groups divided by preoperative lactate and modifiable factor was assessed and pairwise comparison between groups was calculated.

Results: A total of 2036 patients were included in this study and median (interquartile range) of preoperative lactate level was 1.9 (1.4-2.4) mmol/L. The five most important variables for preoperative lactate level after comparing minimal depth and VIMP rankings were MELD, use of preoperative ventilator, hemoglobin, troponin I, and use of preoperative vasopressor. Mortality rate at 90 days and 30 days were 5.3% and 2.7%, respectively. Preoperative lactate level was important variables for predicting 30-day and 90-day mortality, and the 30-day mortality and 90-day mortality increased with increasing the concentration of lactate. Survival analysis for groups divided by preoperative lactate and hemoglobin levels revealed that the group with preoperative lactate $\geq$ 4.0 mmol/L and preoperative hemoglobin < 9.35 g/dL showed lower survival probability and higher cumulative hazard than other groups ($p < 0.001$).

Conclusion: Preoperative hyperlactatemia is important factor to predict early mortality after LT. Among the important variables predicting this preoperative hyperlactatemia, hemoglobin is a modifiable factor. Considering lactate and hemoglobin together, high preoperative lactate and low preoperative hemoglobin are associated with higher early mortality after LT. Correcting low preoperative hemoglobin may play a role in preventing elevation of preoperative lactate level and lowering early mortality after LT.

Keywords: lactate, early mortality, prognostic, liver transplantation

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Introduction

Lactate is produced from pyruvate in various organs. Glucose is converted to pyruvate and adenosine triphosphate (ATP) through glycolysis. Pyruvate is primarily converted into acetyl CoA by aerobic oxidation. Under stressful condition such as anoxia and dysoxia, conversion of pyruvate to lactate is increased[1)]. Lactate is eliminated by gluconeogenesis, and the liver shows a higher lactate clearance up to 70%. Therefore, serum lactate levels may be elevated due to decreased metabolism of lactate in the patients with acute liver failure and chronic liver disease[2)].

Hyperlactatemia is a common finding in critically ill patients, including patient with septic shock, cardiogenic or hypovolemic shock, trauma and liver failure. Hyperlactatemia is considered as a marker of impaired organ perfusion in these patients[3)], and blood lactate level and lactate clearance are correlated with outcomes[3-6)].

Postoperative hyperlactatemia is described as a good predictor of patient outcome after liver resection[7)]. Serum lactate level and lactate clearance after transplantation are considered as predictors for early graft function and short-term outcomes in liver transplantation (LT) patents[8-11)]. Pretransplant lactate level was reported to be the independent factor associated with post-transplant mortality in the patients with acute liver failure and acute-on-chronic liver failure requiring ICU care prior to LT[12)]. Finding and evaluating the causes of preoperative hyperlactatemia is important but previously unknown.

Random forests (RF) are the machine learning technique using ensemble learning method for classification, regression, survival and other tasks[13, 14]. In RF, bootstrap sampling (bagging) from the original data was used to make a random subset for training. A large number of decision trees are generated from these random subsets and learned. The results are derived from ensemble method. The remaining sample after bootstrap sampling, the Out-of-Bag (OOB) sample, was used as a test set for each tree. Variable importance (VIMP) and minimal depth are used to select variables in RF. VIMP is the difference in OOB prediction error before and after permutation. A large VIMP value indicates that the variable is predictive. VIMP close to zero indicates that the variable contributes noting to predictive accuracy, and negative value indicates that the predictive accuracy improves without the variable. Minimal depth simply determines variable importance by the position of the variables in the decision trees and assumes that variables with high impact on the prediction are those that most frequently spilt nodes nearest to the root node, where they partition the largest samples of the population. Thus, the smaller minimal depth value indicates that the variable separates large group of observation and has a large impact for prediction.

The objectives of this study are to identify variables that are most important for preoperative hyperlactatemia, to see if there are modifiable factors, and to examine the effect of preoperative hyperlactatemia on early mortality after LT using random forest method.

Subjects and methods

Study population

All 4641 patients on Asan LT registry of all patients who received LT for end-stage liver disease between January 2008 and February 2019 at the Asan Medical Center were included in this study. We excluded patients under 18 years of age (N = 232). We also excluded patients with toxic hepatitis (N=131) and fulminant hepatitis (N = 243). Lastly, we excluded patient without preoperative blood lactate level (N = 1822). Serum laboratory tests during the preoperative period were included, and only the tests closest in time to operation were considered.

Important variable for preoperative lactate level

A random forest for preoperative serum lactate levels was generated by creating 1000 trees using ggRandomForest R-software package. The following variables were assessed for predicting preoperative hyperlactatemia: sex, age, body mass index (kg/m^2), coronary artery disease, cerebrovascular accident, chronic renal failure, diabetes mellitus, hypertension, previous varix bleeding, previous spontaneous bacterial peritonitis, intractable ascites, hydrothorax, hepatic encephalopathy, sepsis, preoperative use of vasopressor, preoperative use of ventilator, preoperative use of renal replacement therapy, serum hemoglobin (g/dL), serum platelet (x1000/uL), brain natriuretic peptide (pg/mL), troponin I (ng/mL), correct QT interval (msec), left ventricular ejection fraction, and model for end-stage liver disease (MELD) score. Missing data were imputed using adaptive tree imputation by ramdomForestSRC R−software package.

The most important variables were identified by VIMP and minimal depth ranks. Variable dependence plots for important variables were used to show the predicted response as a function of a covariate of interest.

Survival analysis

Random forest survival analysis was applied to the data using ggRandomForest R−software package. Two random forest for survival were generated for 30−day survival and 90−day survival by creating 1000 trees. The following variables were assessed for prognostic value: sex, age, body mass index (kg/m2), diabetes mellitus, hypertension, previous varix bleeding, previous spontaneous bacterial peritonitis, intractable ascites, hydrothorax, hepatic encephalopathy, sepsis, preoperative use of vasopressor, preoperative use of ventilator, preoperative use of renal replacement therapy, serum hemoglobin (g/dL), serum lactate (mmol/L), brain natriuretic peptide (pg/mL), left ventricular ejection fraction, and model for end−stage liver disease (MELD) score. Missing data were imputed using adaptive tree imputation by ramdomForestSRC R−software package.

Important variables for survival were identified by VIMP and minimal depth ranks.

According to the Surviving Sepsis Campaign (SSC) bundle, if lactate is increased to 4 mmol/L or more, rapid administration of crystalloid is recommended[15)]. Based on this bundle, we divided the subjects into two groups according to concentration of lactate (greater than or equal to 4 mmol/L and less than 4 mmol/L). Random forest predicted survival plots for each group were used to find the difference of survival in two groups.

Variable dependence plots of survival were used to investigate the trend of survival over the change in the variables. Conditional dependence plots (coplots) are used to visualize how the predicted survival depends on multiple variables.

Receiver operating characteristic (ROC) curve analysis for 30-day mortality were applied to determine cut-off values for lactate and modifiable important variables. The subjects were divided into subgroups by SSC bundle and cut-off value. Survival probability and cumulative hazard plots for different group were assessed and pairwise comparison between groups was calculated.

Statistical analysis

Data were expressed as median with interquartile range (IQR) for continuous variables, and numbers and percentages for categorical variables. All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing). R-software packages of randonForestSRC, ggRandomForests, ggplot2, survival, survminer and pROC were used. P-value of less than 0.05 was considered statistically significant.

Results

Recipient characteristic and post-transplant outcomes

A total of 2036 patients were included in this study. Most LT patients were male (74.5%) and median (IQR) age was 53 (48–58) years old. Median (IQR) preoperative lactate level was 1.9 (1.4–2.4) mmol/L (Table 1, Fig. 1). Overall mortality rate was 18.5% and mortality rate at 90 days and 30 days were 5.3% and 2.7%, respectively.

Important variable for preoperative lactate level

The important variables by VIMP match were troponin I, use of preoperative vasopressor, MELD, use of preoperative ventilator, hemoglobin, use of preoperative renal replacement therapy, varix bleeding, diabetes mellitus, and hepatic encephalopathy. The important variable by minimal depth were MELD, use of preoperative ventilator, hemoglobin, troponin I, preoperative vasopressor, use of preoperative renal replacement therapy, correct QT (QTc) interval on ECG, platelet count and body mass index. The five most important variables after comparing minimal depth and VIMP rankings were MELD, use of preoperative ventilator, hemoglobin, troponin I, and use of preoperative vasopressor (Fig. 2).

Variable dependence plots showed that high MELD, low hemoglobin, high troponin I, use of preoperative ventilator and use of preoperative vasopressor were associated with preoperative hyperlactatemia (Fig. 3).

Table 1. Baseline characteristics in study population

Parameters	N=2036
Sex (Male, n)	1516 (74.5%)
Age (y)	53.0 [48.0;58.0]
Weight (kg)	66.3 [59.0;74.2]
Height (cm)	166.9 [160.8;171.6]
BMI (kg/m2)	24.0 [21.7;26.4]
SMI (kg/m2)	45.2 [39.0;51.3]
Re-transplantation (n)	92 (4.5%)
OLT (n)	393 (19.3%)
CAD (n)	88 (6.6%)
CVA (n)	17 (1.0%)
CRF (n)	34 (1.9%)
DM (n)	502 (24.7%)
HTN (n)	310 (15.2%)
Atrial Fibrillation (n)	30 (1.5%)
Varix bleeding (n)	478 (23.5%)
SBP (n)	129 (6.3%)
Intractable Ascites (n)	532 (26.1%)
Hydrothorax (n)	316 (15.5%)
HEP (n)	443 (21.8%)
Sepsis (n)	36 (1.8%)
MELD	16.0 [10.0;26.0]
CTP	9.0 [7.0;11.0]

Table. 1. Continued

Parameters	N=2036
Hemoglobin (g/dL)	10.2 [8.7;12.1]
Platelet (x1000/ul)	58.0 [40.0;85.0]
Albumin (g/dL)	3.1 [2.7;3.5]
AST (U/L)	45.0 [31.0;69.0]
ALT (U/L)	27.0 [17.0;42.0]
Sodium (mEq/L)	138.0 [135.0;141.0]
Lactic Acid (mmol/L)	1.9 [1.4;2.4]
Total bilirubin (mg/dL)	2.6 [1.3;11.0]
Creatinine (mg/dL)	0.8 [0.7;1.1]
Prothrombin time (INR)	1.5 [1.2;1.9]
BNP (pg/mL)	53.0 [23.0;135.0]
TnI (ng/mL)	0.0 [0.0;0.0]
QTc (msec)	451.0 [430.0;475.0]
LVEF (%)	64.5 [61.4;67.4]
Preoperative vasopressor (n)	115 (5.7%)
Preoperative ventilator (n)	222 (10.9%)
Preoperative RRT (n)	267 (13.1%)

Data were expressed as median with interquartile range (IQR) for continuous variables, and numbers and percentages for categorical variables. CAD, coronary artery disease, CRF, chronic renal failure, CTP, Child−Turcotte−Pugh score, CVA, cerebrovascular accident, DM, diabetes mellitus, HEP, hepatic encephalopathy, HTN, hypertension, LVEF, left ventricular ejection fraction, MELD, model for end−stage liver disease, OLT, orthotopic liver transplantation, QTc, corrected QT interval, RRT, renal replacement therapy, SMI, skeletal muscle index, SBP, spontaneous bacterial peritonitis, TnI, troponin I

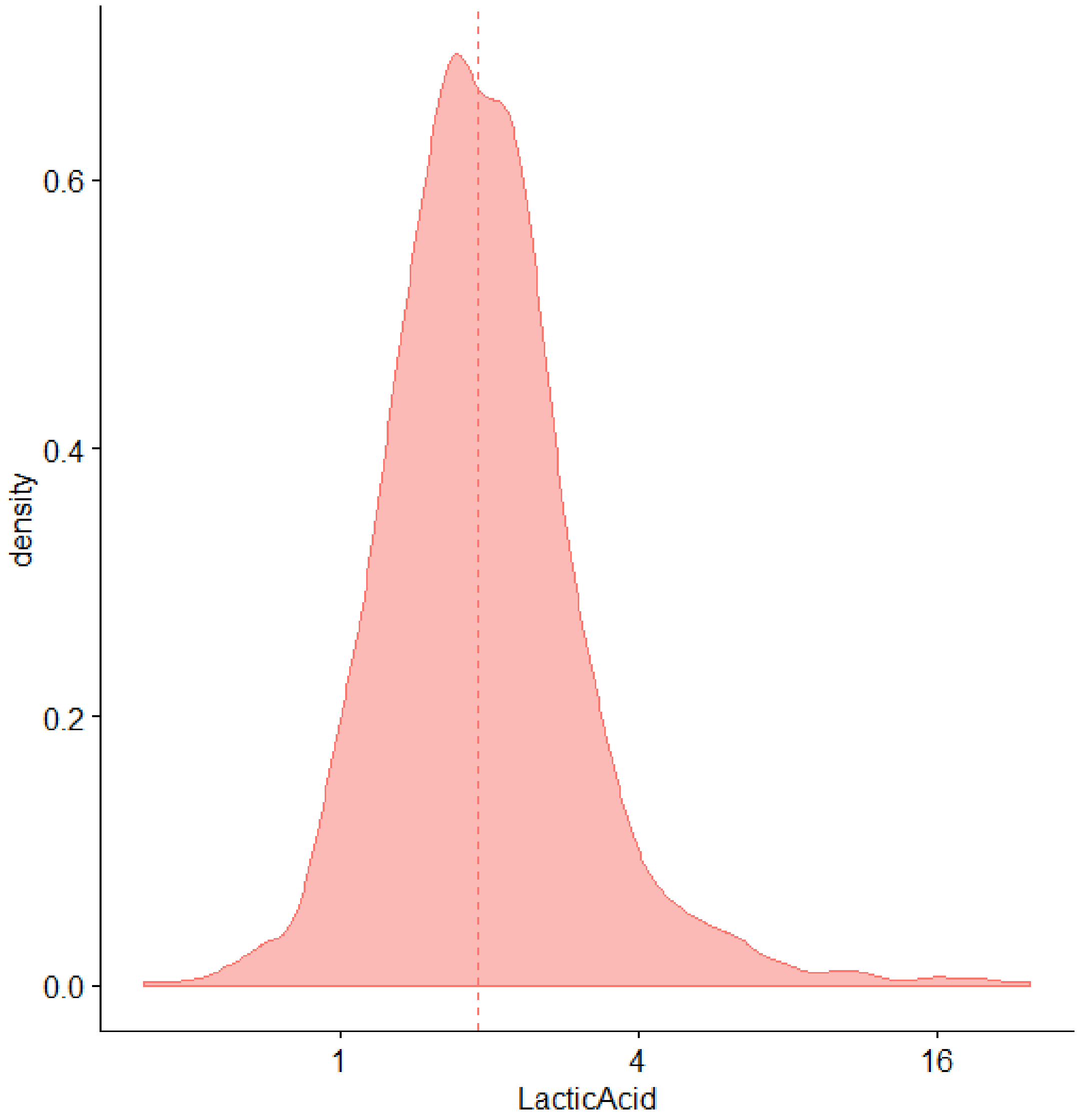


Fig. 1. A density plot for lactate. Vertical dashed line shows the median value of lactate (1.9 mmol/L).

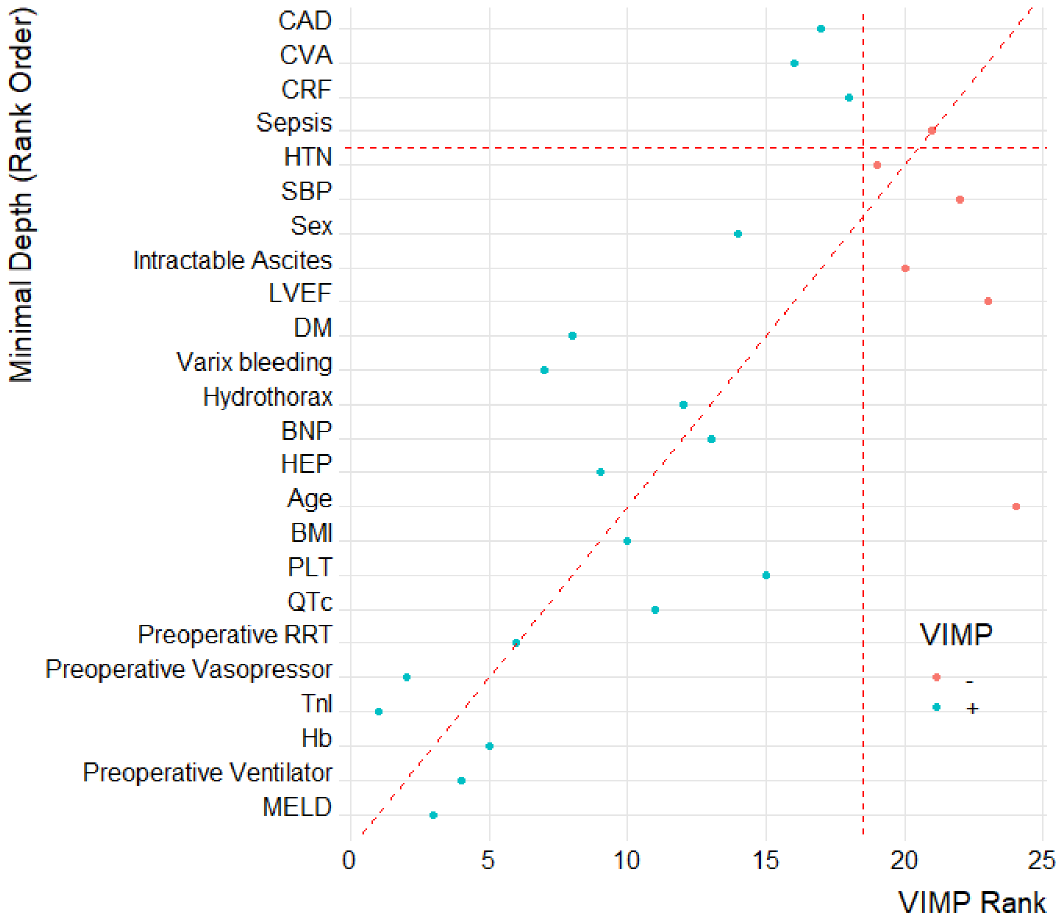
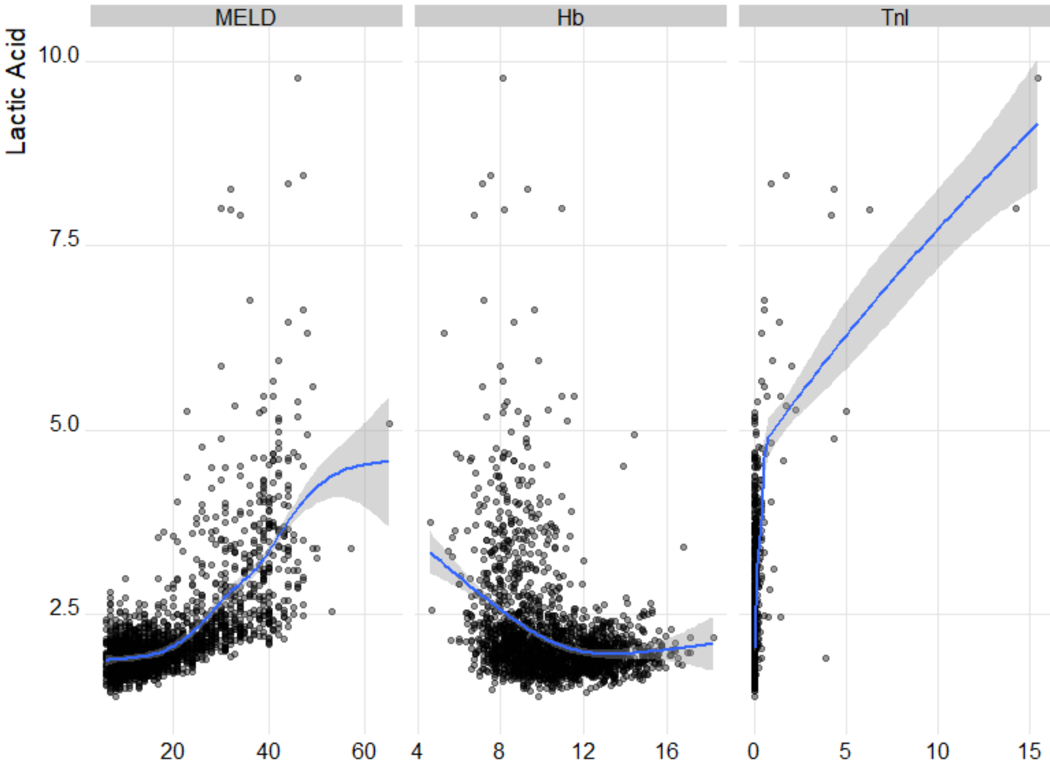
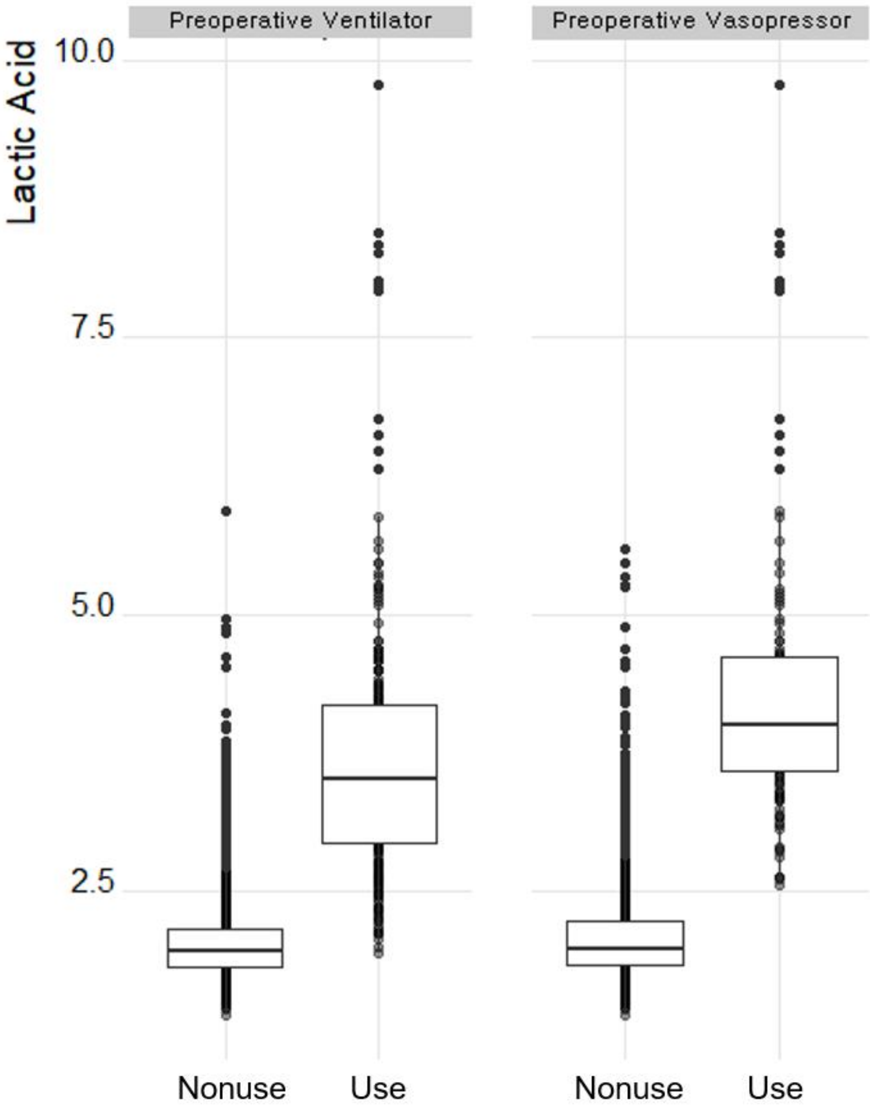


Fig. 2. Comparing minimal depth and variable importance (VIMP) rankings for preoperative lactate level. Low minimal depth and low VIMP rankings indicate important variables. Points on the red dashed line are ranked equivalently, points above have higher VIMP ranking, those below have higher minimal depth ranking.



(A)



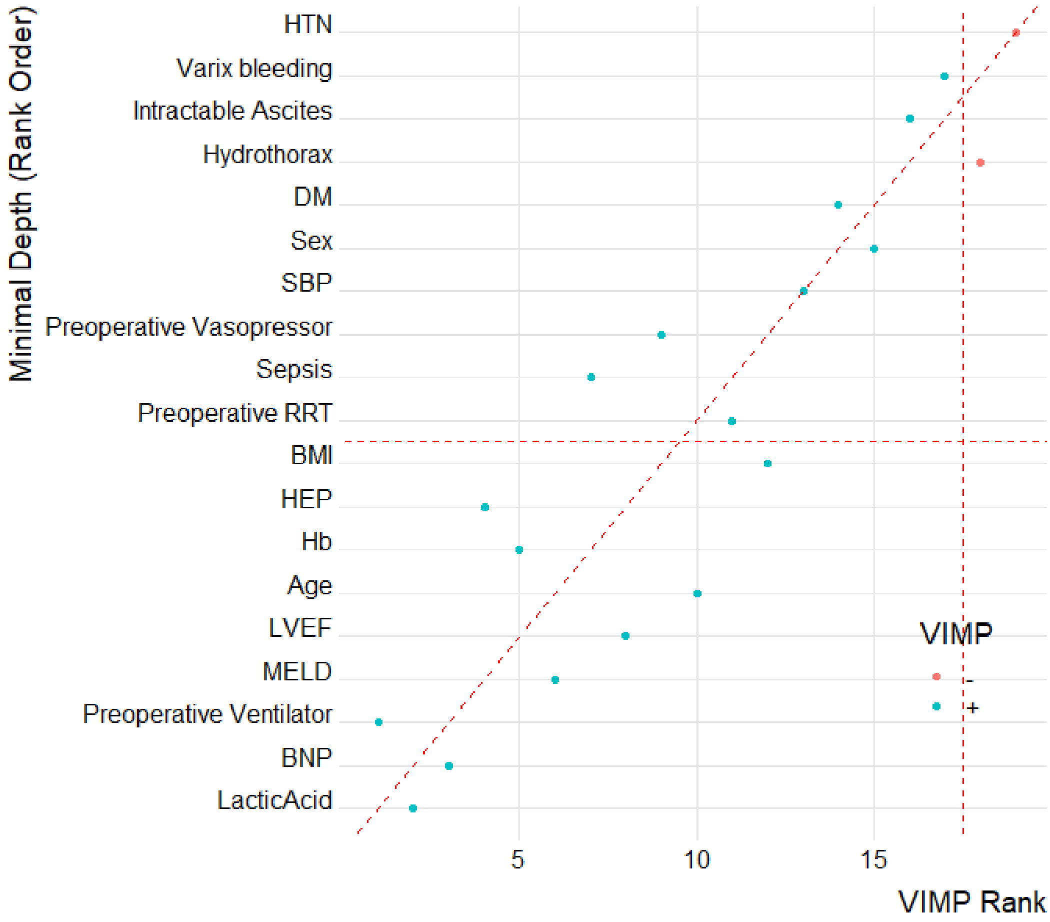
(B)

Fig. 3. Variable dependence plot for preoperative lactate level: (A) MELD, hemoglobin and troponin I, (B) preoperative use of ventilator and vasopressor. Blue curve indicates the trend as the variables increase with shaded 95% confidence band. MELD, model for end−stage liver disease, Hb, hemoglobin, TnI, troponin I

Early mortality rate following liver transplantation

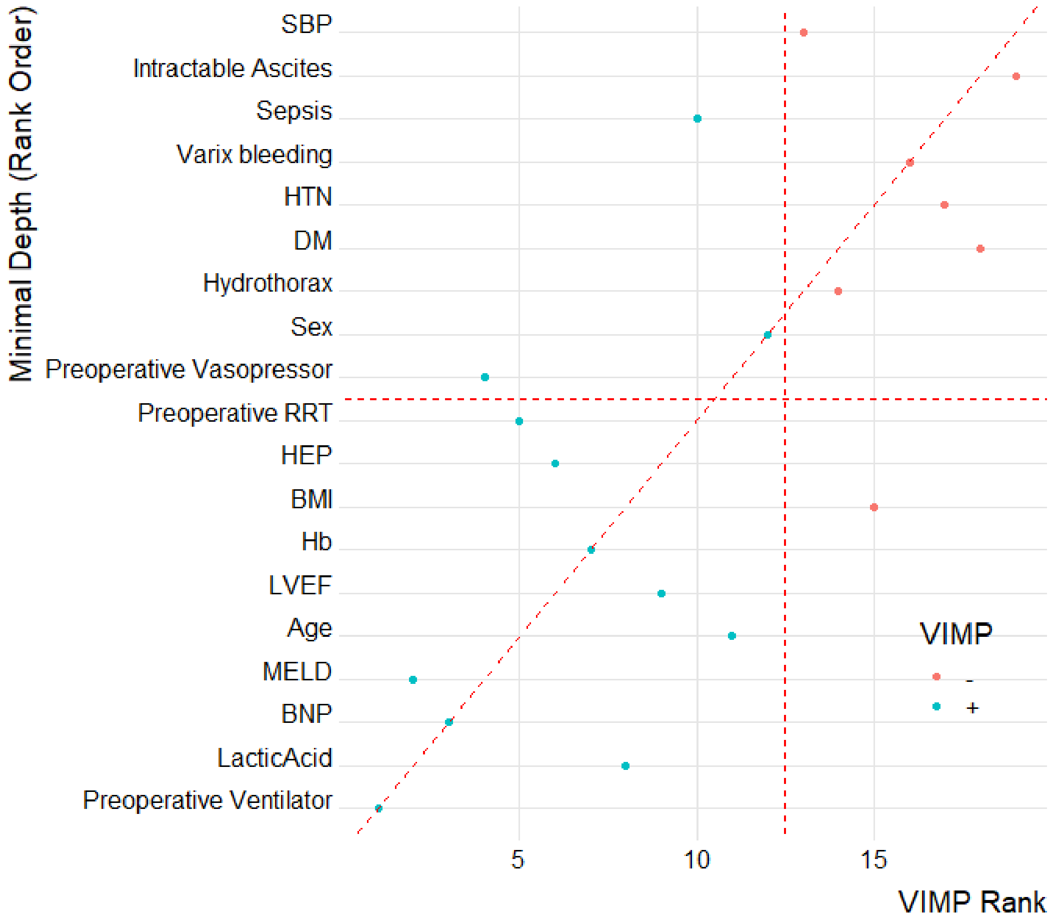
The important variables for 30−day mortality after comparing minimal depth and VIMP rankings were preoperative lactate, BNP, use of preoperative ventilator, MELD and hemoglobin. The important variables for 90−day mortality after comparing minimal depth and VIMP rankings were use of preoperative ventilator, BNP, MELD, hemoglobin, and preoperative lactate (Fig. 4). Considering the order of importance, lactate was more important for 30−day mortality than 90−day mortality.

Random forest predicted survival for lactate group showed that the patient with concentration of lactate greater than or equal to 4 mmol/L had lower survival probability (Fig. 5) Variable dependence of survival on lactate indicated that the 30−day mortality and 90−day mortality increased with increasing the concentration of lactate (Fig. 6). Variable dependence of survival on hemoglobin showed that the 30−day mortality and 90−day mortality increased with decreasing hemoglobin in the range of hemoglobin less than 16g/dL. (Fig. 7) Variable dependence coplot of survival at 30 days against lactate, conditional on hemoglobin interval group membership indicated that the probability of survival decreased with increasing lactate and decreased within groups of decreasing hemoglobin. (Fig. 8)



Minimal Depth (Rank Order)
HTN
Varix bleeding
Intractable Ascites
Hydrothorax
DM
Sex
SBP
Preoperative Vasopressor
Sepsis
Preoperative RRT
BMI
HEP
Hb
Age
LVEF
MELD
Preoperative Ventilator
BNP
LacticAcid
5
10
15
VIMP Rank
VIMP
-
+

(A)



(B)

Fig. 4. Comparing minimal depth and variable importance (VIMP) rankings for 30−day mortality (A) and 90−day (B) mortality. Points on the red dashed line are ranked equivalently, points above have higher VIMP ranking, those below have higher minimal depth ranking.

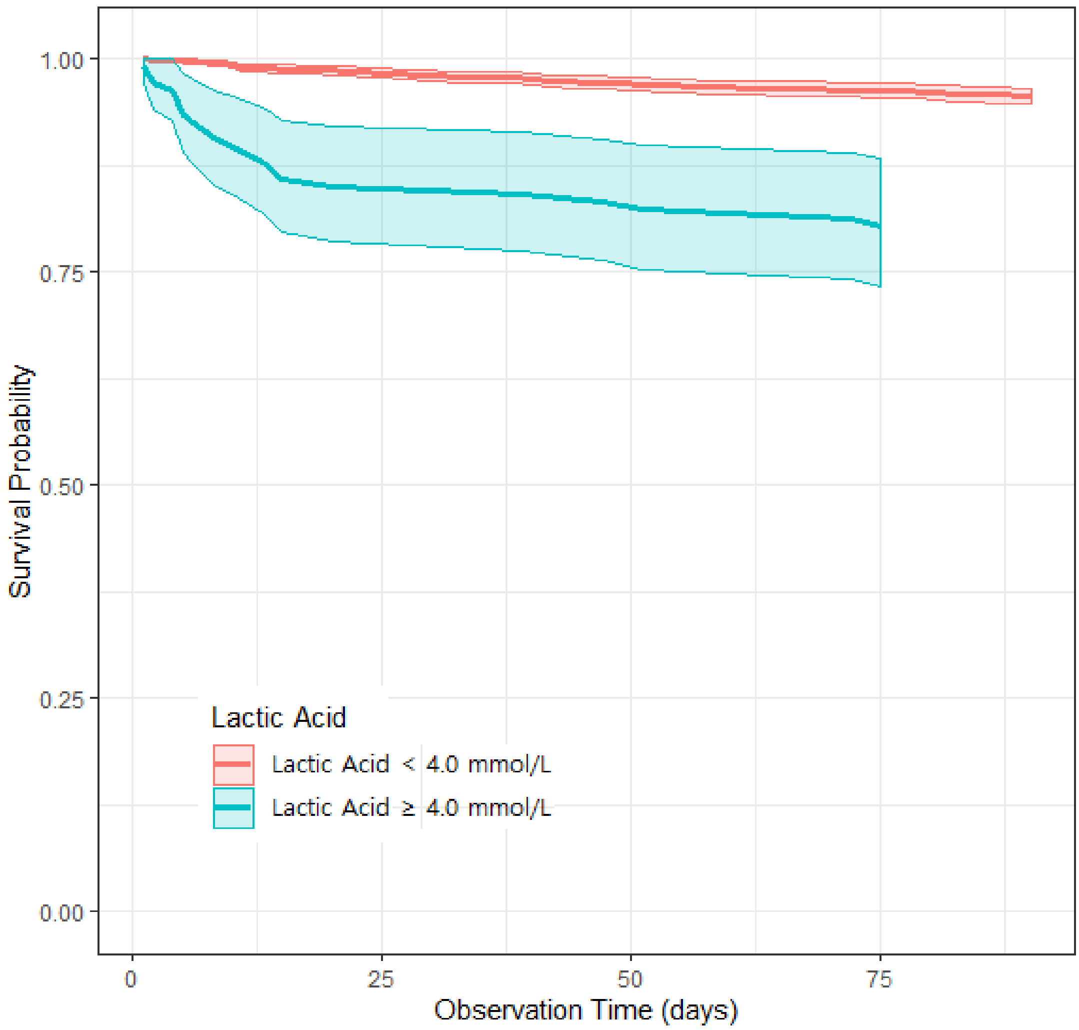


Fig. 5. Random forest predicted survival stratified by lactate group. Shaded areas are 95% confidence bands.

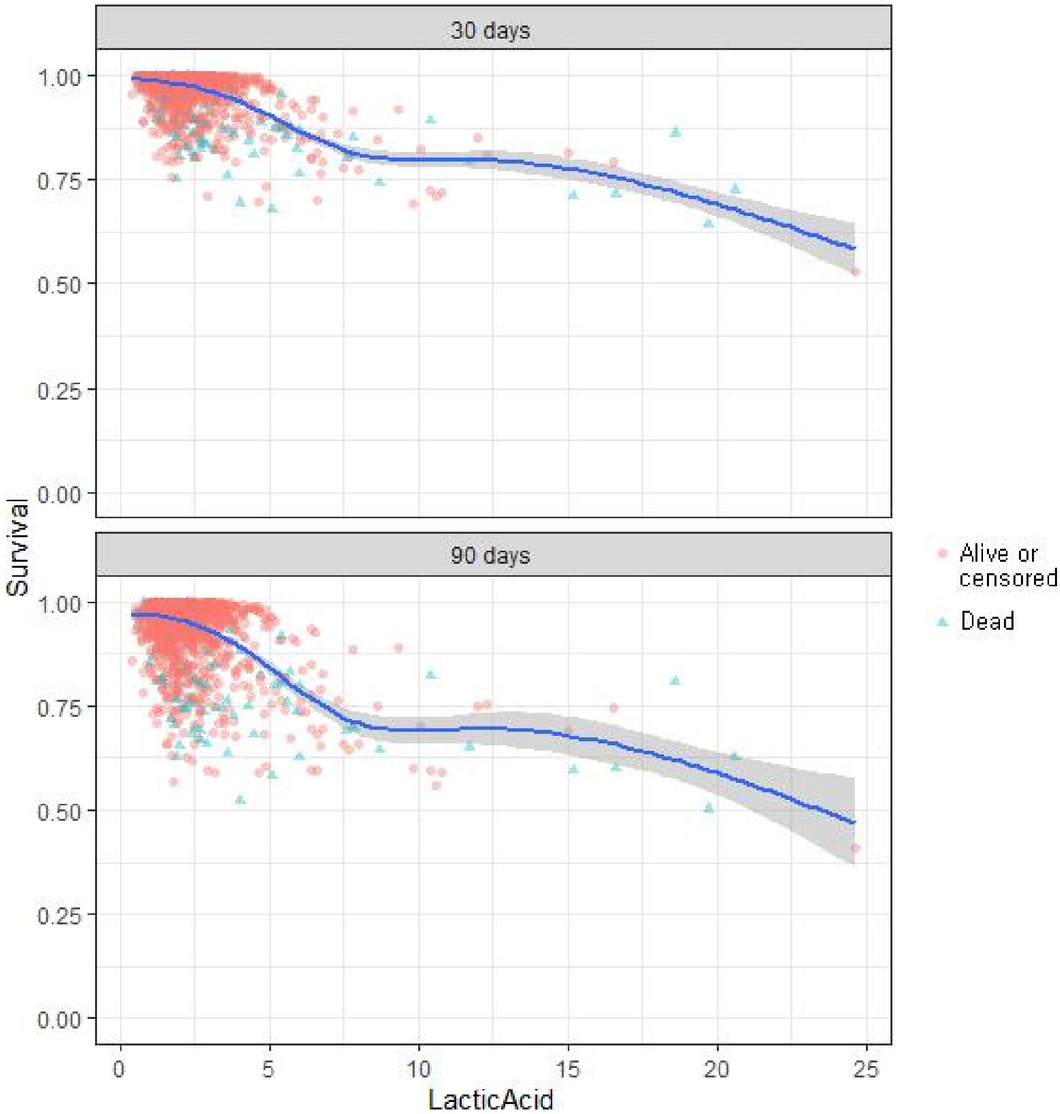


Fig. 6. Variable dependence of survival at 30 and 90 days on lactate variable. Individual cases are marked with red circle (alive or censored) and blue triangle (dead). Blue curve with shaded 95% confidence band indicates decreasing survival with increasing lactate.

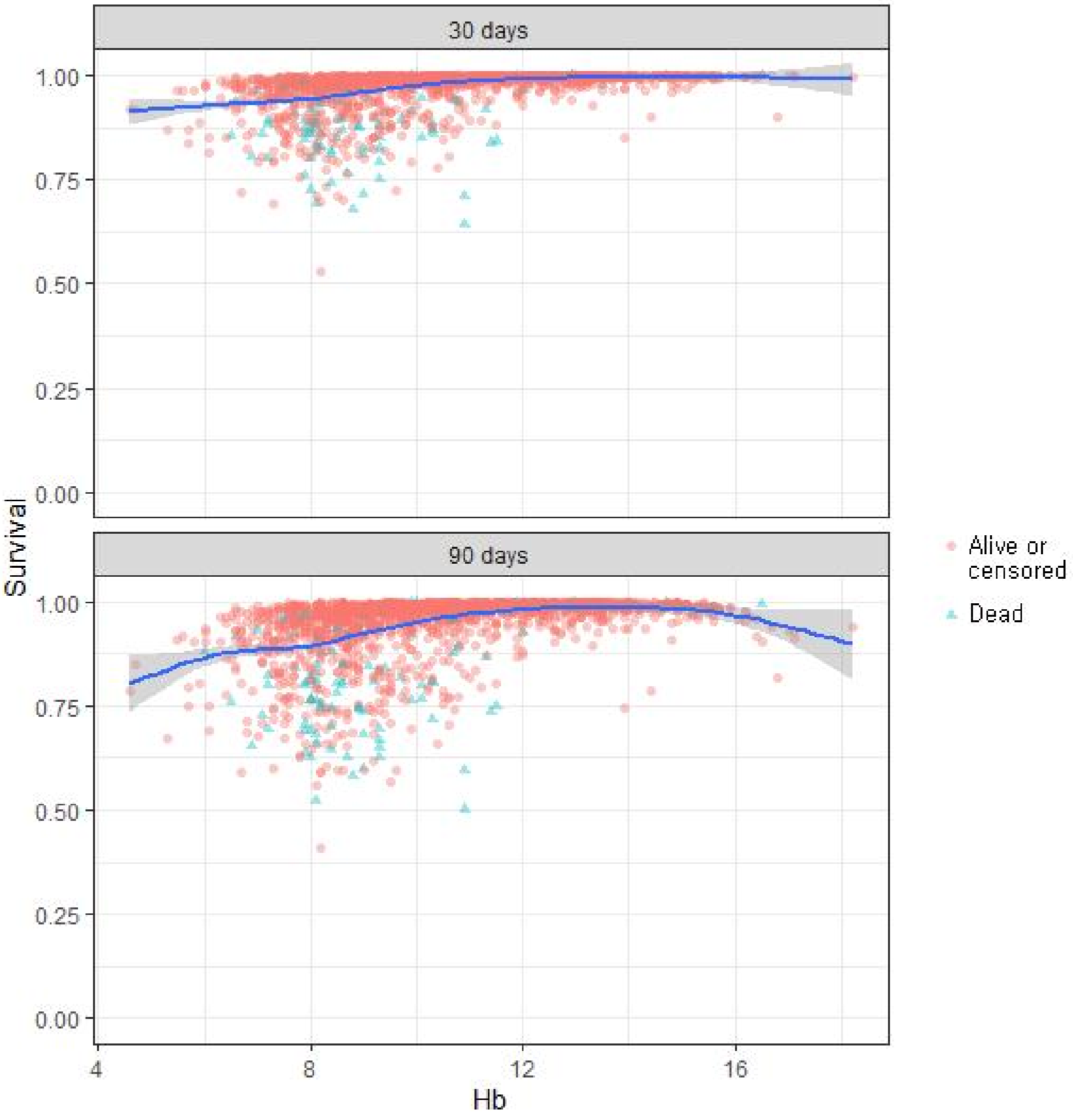


Fig. 7. Variable dependence of survival at 30 and 90 days on hemoglobin (Hb) variable. Individual cases are marked with red circle (alive or censored) and blue triangle (dead). Blue curve with shaded 95% confidence band indicates decreasing survival with decreasing hemoglobin in the range of hemoglobin less than 16g/dL.

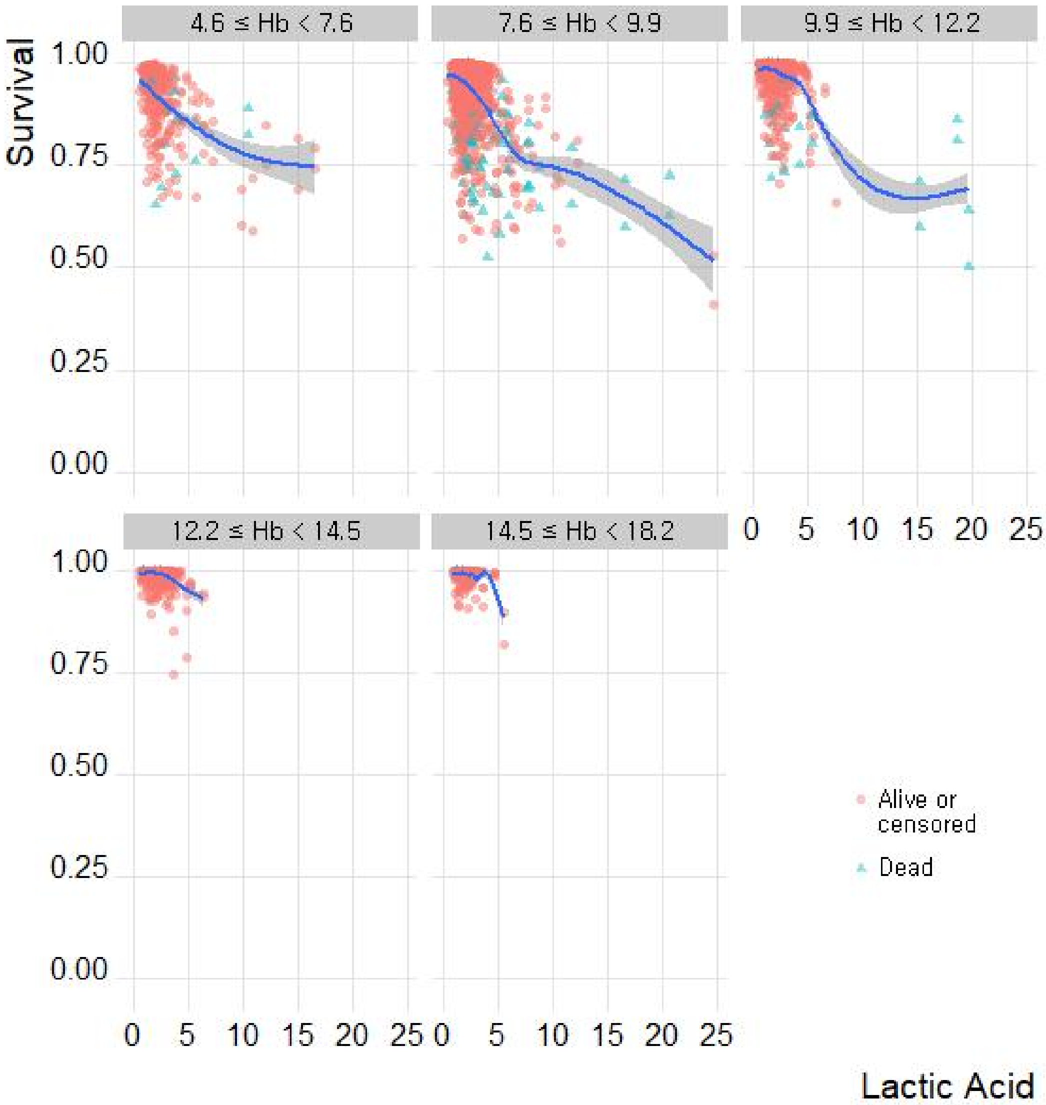


Fig. 8. Variable dependence coplot of survival at 30 days against lactate, conditional on hemoglobin (Hb) interval group membership. Individual cases are marked with red circle (alive or censored) and blue triangle (dead). Blue curve with shaded 95% confidence band indicates that the probability of survival decreased with increasing lactate and decreased within groups of decreasing hemoglobin.

ROC curve analysis determined cut-off values to predict the 30-day mortality (Fig. 9). The cut-off levels of preoperative lactate and hemoglobin levels were 2.15 mmol/L and 9.35 g/dL, respectively (AUC [95% confidence interval], 0.752 [0.6803, 0.824] and 0.738 [0.6846, 0.7917], respectively).

By using hemoglobin cut-off level, survival probability and cumulative hazard plots for different lactate group were assessed and pairwise comparison between group was calculated (Fig. 10). Compared to the group with lactate < 4.0 mmol/L and hemoglobin ≥ 9.35 g/dL, the groups with lactate ≥ 4.0 mmol/L, hemoglobin < 9.35 g/dL, or both showed low survival probability and high cumulative hazard ($p < 0.001$). Among the groups with lactate ≥ 4.0 mmol/L, the group with hemoglobin < 9.35 g/dL showed low survival probability and high cumulative hazard ($p < 0.001$).

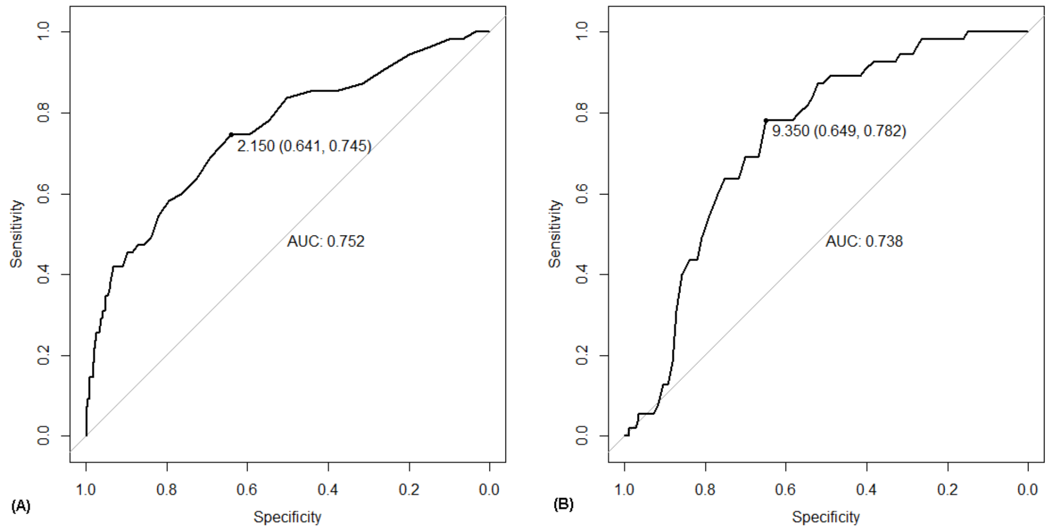
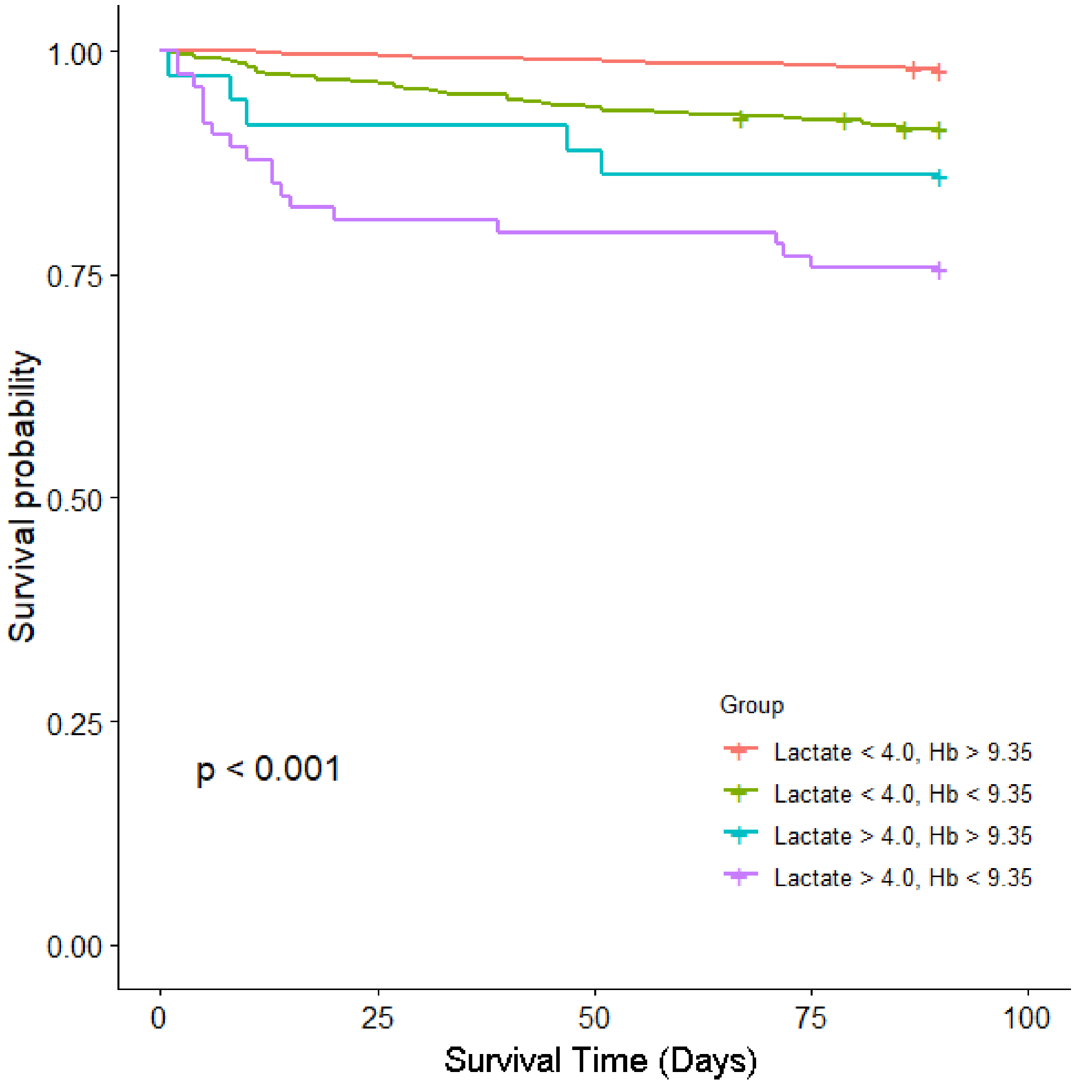
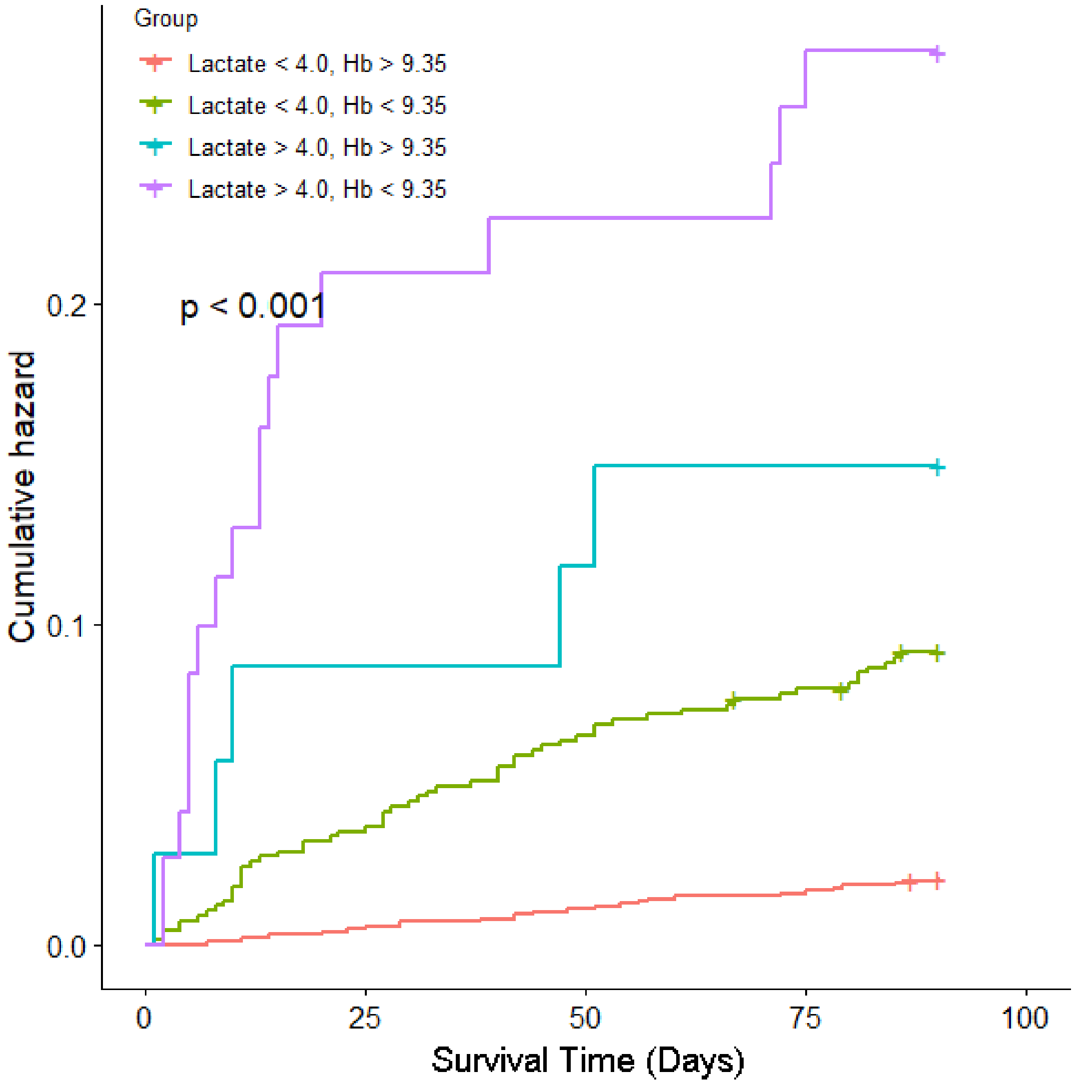


Fig. 9. Receiver operating characteristic (ROC) of lactate (A) and hemoglobin (B) level for 30–day mortality. AUC, area under the curve



Survival probability
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
Survival Time (Days)
p < 0.001
Group
Lactate < 4.0, Hb > 9.35
Lactate < 4.0, Hb < 9.35
Lactate > 4.0, Hb > 9.35
Lactate > 4.0, Hb < 9.35

(A)



(B)

Fig. 10. Survival probability (A) and cumulative hazard (B) plots of different lactate and hemoglobin (Hb) groups.

Discussion

In the present study, we investigated the important variables for preoperative hyperlactatemia and a relation between preoperative hyperlactatemia and early outcome after LT by using random forest survival analysis.

The important variables related to hyperlactatemia were MELD, use of preoperative ventilator, hemoglobin, troponin I, and use of preoperative vasopressor in the order of importance.

MELD score is useful for estimating disease severity and predicting survival in the patient with liver disease, and MELD score is associated with increasing severity of hepatic dysfunction[16]. High MELD score may be related to hepatic dysfunction and thereby reduced metabolism of lactate. Variable dependence plot showed that increasing MELD score was associated with increased lactate level.

Preoperative use of mechanical ventilation means respiratory failure with impairment of oxygenation, which can cause hypoxemia[17]. Red blood cells (RBCs) carry oxygen linked to hemoglobin from the lungs to tissue capillaries. Oxygen is then released from hemoglobin according to the characteristics of the oxyhemoglobin dissociation curve[18]. Impaired oxygen delivery related to anemia may cause hypoxic condition in peripheral tissue. These hypoxic conditions may be associated with increased lactate production[19].

Troponin-I elevation is an indicator of myocardial cell injury and is considered the most specific biomarker for myocardial necrosis. Cardiac troponin can be increased in cardiac disease, but it can also be increased in critically ill patients, sepsis and septic shock, and renal failure without heart disease[20]. Vasopressors are indicated for hypotension and hypoperfusion[21]. Elevated troponin−I and use of vasopressors can mean circulatory problem and decreased perfusion of end−organ. Hypoperfusion of liver and kidney which are responsible for lactate metabolism, can lead to hyperlactatemia.

This study presented that preoperative hyperlactatemia is important variable to predict early mortality after LT. And variable dependence plots showed the trend of the survival prediction over the change in the preoperative lactate level.

There are some papers that studied the relationship between preoperative parameters and outcome after LT using scoring systems. MELD score was commonly used but has low predictive value[22, 23]. Survival outcome following liver transplantation (SOFT)[24] and balance of risk (BAR)[25] scores use pretransplant parameters with donor and surgery risk, and have some predictive value for outcome after LT. These scoring system do not use lactate level as a preoperative parameter.

Most of existing studies on lactate and outcome after LT are related to postoperative lactate level and lactate clearance. Isolated postoperative hyperlactatemia[9] and low lactate clearance[8, 10, 11] are early predictors for early allograft dysfunction and short−term prognosis in LT. Postoperative lactate with other scoring systems such as MELD−lactate[9] have a predictive value for outcome following LT.

Previous studies with preoperative lactate and post−transplant outcome have shown opposite results. A retrospective study compared the preoperative parameters between two groups, those who were survivors and those who were nonsurvivors 30 days after orthotopic LT. Lactate level did not differ significantly between groups before surgery[26]. However, other retrospective study that studied post-transplant mortality rate of patient with acute liver failure and acute-on-chronic liver failure showed that pretransplant lactate level was one of the independent factors associated with post-transplant mortality[12]. Although the subjects are limited to critically ill patients, these findings are consistent with our findings.

Lastly, the presented study suggests that pretransplant hemoglobin is possible modifier associated with early mortality after LT and survival probability according to hemoglobin is significantly different in high lactate group. Anemic hypoxia can lead to hyperlacatatemia[19], and a prospective randomized study showed that RBC transfusion decreased lactate levels in the patients with hypoperfusion regardless of their baseline hemoglobin levels[27]. The randomized controlled study about the correction of preoperative anemia in patients with hemoglobin below 9 g/dL and short-term prognosis following LT is needed.

Random forest is a robust, non-parametric statistical method of machine learning[13, 14] and has several advantages over conventional statistical methods. By using random forest, we can identify risk factors without prior knowledge of any possible parametric relationship, identify complex interactions, and overcome barriers such as high amounts of missing data[28]. Random forest also has no overfitting problem[29].

Our study has several limitations. This is a retrospective and single center study. Therefore, our results need to be validated through data from other centers or prospective studies. However, we included a large number of patients and used missing data with properly imputation. Another limitation is that random forest method did not provide adequate criteria for early mortality risk. To compensate for this, we tried to find the appropriate reference point by performing subgroup analysis using cut−off value through ROC curve and previous known lactate level.

Conclusion

Preoperative hyperlactatemia is important factor to predict early mortality after LT. The important variables predicting this preoperative hyperlactatemia are MELD, use of preoperative ventilator, hemoglobin, troponin I, and use of preoperative vasopressor. Among them, hemoglobin is a modifiable factor. Considering lactate and hemoglobin together, high preoperative lactate and low preoperative hemoglobin are associated with higher early mortality after LT. Correcting low preoperative hemoglobin may play a role in preventing elevation of preoperative lactate level and lowering early mortality after LT.

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국문요약

연구제목: 수술 전 고젖산혈증과 간이식 후 조기 사망률: 랜덤 포레스트 생존 분석의 적용

연구배경 및 목적: 고젖산혈증은 패혈 쇼크, 심장성 쇼크, 저혈량 쇼크, 외상, 간부전과 같은 중환자에서 흔한 소견이다. 간이식 환자에서 수술 전 젖산과 젖산 제거율은 초기 이식 기능 및 예후에 대한 좋은 대리 표지자로 간주된다. 본 연구의 목적은 랜덤 포레스트 기법을 이용하여 수술 전 고젖산혈증의 중요한 인자를 확인하고, 수정 가능한 요인을 찾고, 수술 전 고젖산혈증이 간이식 후 조기사망률에 미치는 영향을 평가하는 것이다.

연구대상 및 방법: 2008 년 1 월부터 2019 년 2 월까지 서울아산병원에서 간이식수술을 받은 환자의 레지스트리의 자료를 분석하였다. 랜덤 포레스트 기법을 이용하여 수술 전 고젖산혈증의 중요한 인자를 확인하고, 수술 전 고젖산혈증이 간이식 후 30 일, 90 일 사망률에 미치는 영향을 평가하였다. 수술 전 젖산과 수정 가능한 요인으로 나눈 군의 생존 분석을 평가하고, 군 간의 차이를 통계 처리하였다.

결과: 총 2036 명의 환자가 연구에 포함되었고, 수술 전 젖산의 중앙값(사분범위)은 1.9 (1.4–2.4) mmol/L 였다. 랜덤 포레스트의 VIMP 와 minimal depth 를 비교하여 확인한 수술 전 고젖산혈증에 가장 중요한 다섯 가지 인자는 MELD, 수술 전 기계 환기의 사용, 헤모글로빈, 트로포닌 I, 수술 전 혈압상승제의 사용이었다. 90 일, 30 일 사망률은 각각 5.3%, 2.7% 였다. 수술 전 젖산의 농도는 30 일 사망률과 90 일 사망률을 예측하는 중요한 인자였고, 수술 전 젖산의 농도가 증가함에 따라 30 일 사망률과 90 일 사망률이 증가하였다. 수술 전 젖산 및 헤모글로빈 수치로 나눈 군의 생존 분석에 따르면

수술 전 젖산이 4.00 mmol/L 이상이고, 수술 전 헤모글로빈이 9.35 g/dL 인 군은 다른 군에 비해 생존 확률이 낮고 누적 위험도가 더 높았다(p<0.001).

결론: 수술 전 고젖산혈증은 간이식 후 조기사망률을 예측하는 중요한 인자이다. 수술 전 고젖산혈증을 예측할 수 있는 중요한 변수 중 헤모글로빈은 수정 가능한 요인이다. 젖산과 헤모글로빈을 함께 고려할 때, 높은 수술 전 젖산 및 낮은 수술 전 헤모글로빈은 간이식 후 높은 사망률과 관련이 있다. 수술 전 낮은 헤모글로빈을 교정하는 것은 수술 전 젖산의 상승을 예방하고 간이식 후 조기사망률을 낮추는데 역할을 할 수 있을 것이다.