# Association between lactic acidosis and multiple organ dysfunction syndrome after cardiopulmonary bypass

**Dan Zheng** [1] , **Guo-Liang Yu** [1] , **Yi-Ping Zhou** [1] , **Qiao-Min Zhang** [1] , **Chun-Guo Wang** [2] , **Sheng Zhang** [Corresp. 1]

[1] Department of Critical Care Medicine, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Linhai, China

[2] Department of Cardiothoracic Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Linhai, China

Corresponding Author: Sheng Zhang
Email address: 13676655525@163.com

**Background:** The relationship between hyperlactatemia and prognosis after cardiopulmonary bypass (CPB) is controversial, and some studies ignore the presence of lactic acidosis in patients with severe hyperlactacemia. This study explored the association between lactic acidosis (LA) and the occurrence of multiple organ dysfunction syndrome (MODS) after cardiopulmonary bypass (CPB). **Methods:** This study was a post hoc analysis of patients who underwent cardiac surgery between February 2017 and August 2018 and participated in a prospective study at Taizhou Hospital. The data were collected at: ICU admission (H0), and 4, 8, 12, 24, and 48 h after admission. Blood lactate levels gradually increased after CPB, peaking at H8 and then gradually decreasing. The patients were grouped as LA, hyperlactatemia (HL), and normal control (NC) based on blood test results 8 h after ICU admission. B asic preoperative, perioperative, and postoperative conditions were compared between the three groups, as well as postoperative perfusion and oxygen metabolism indexes. **Results:** There were 22 (19%), 73 (64%), and 19 (17%) patients in the LA, HL, and NC groups, respectively. APACHE II (24h) and SOFA (24h) scores were the highest in the LA group (P<0.05). ICU stay duration was the longest for the LA group [48.5 (42.5, 50) h], compared with the HL [27 (22, 48) h] and NC [27 (25, 46) h] groups (P=0.012). The LA group had the highest incidence of MODS (36%), compared with the HL (14%) and NC (5%) groups (P=0.015). In the LA group, the oxygen extraction ratio ($O_2ER$) was lower [21.5 (17.05, 32.8) %] than in the HL [31.3 (24.8, 37.6) %] and the NC group [31.3 (29.0, 35.4) %] (P=0.018). In the univariable analyses, patient age (OR=1.054, 95% CI: 1.003-1.109, P=0.038), the LA group ( vs. the NC group, (OR=10.286, 95% CI: 1.148-92.185, P=0.037), and ΔPCO2 at H8 (OR=1.197, 95% CI: 1.022-1.401, P=0.025) were risk factor of MODS after CPB. **Conclusions:** There is a correlation between lactic acidosis and MODS after CPB, so LA should be monitored closely after CPB .

1 **Association between lactic acidosis and multiple organ dysfunction syndrome after**

2 **cardiopulmonary bypass: a post hoc analysis of oxygen metabolism after CPB and 48-h**

3 **organ dysfunction**

5 **Running title:** lactic acidosis and multiple organ dysfunction syndrome

7 Dan Zheng[1], Guo-Liang Yu[1], Yi-Ping Zhou[1], Qiao-Min Zhang[1], Chun-Guo Wang[2], Sheng

8 Zhang[1]

9 [1] Department of Critical Care Medicine, Taizhou Hospital of Zhejiang Province, Wenzhou

10 Medical University, Linhai, 317000 China

11 [2] Department of Cardiothoracic Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou

12 Medical University, Linhai, 317000 China

14 **Corresponding author**

15 Sheng Zhang

16 Department of Critical Care Medicine, Taizhou Hospital of Zhejiang Province, Wenzhou

17 Medical University, Linhai, 317000 China

18 E-mail: zhangs@enzemed.com

19 Tel: +86-13515869796

22 **ABSTRACT**

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25 with severe hyperlactacemia. This study explored the association between lactic acidosis (LA)

26 and the occurrence of multiple organ dysfunction syndrome (MODS) after cardiopulmonary

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29 February 2017 and August 2018 and participated in a prospective study at Taizhou Hospital. The

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31 lactate levels gradually increased after CPB, peaking at H8 and then gradually decreasing. The

32 patients were grouped as LA, hyperlactatemia (HL), and normal control (NC) based on blood test

33 results 8 h after ICU admission. Basic preoperative, perioperative, and postoperative conditions

34 were compared between the three groups, as well as postoperative perfusion and oxygen

35 metabolism indexes.

36 **Results:** There were 22 (19%), 73 (64%), and 19 (17%) patients in the LA, HL, and NC groups,

37 respectively. APACHE II (24h) and SOFA (24h) scores were the highest in the LA group

38 (P<0.05). ICU stay duration was the longest for the LA group [48.5 (42.5, 50) h], compared with

39 the HL [27 (22, 48) h] and NC [27 (25, 46) h] groups (P=0.012). The LA group had the highest

40 incidence of MODS (36%), compared with the HL (14%) and NC (5%) groups (P=0.015). In the

41 LA group, the oxygen extraction ratio ($O_2ER$) was lower [21.5 (17.05, 32.8) %] than in the HL

42 [31.3 (24.8, 37.6) %] and the NC group [31.3 (29.0, 35.4) %] (P=0.018). In the univariable

43 analyses, patient age (OR=1.054, 95% CI: 1.003-1.109, P=0.038), the LA group (vs. the NC

44 group, (OR=10.286, 95% CI: 1.148-92.185, P=0.037), and $\Delta PCO2$ at H8 (OR=1.197, 95% CI:

45   1.022-1.401, P=0.025) were risk factor of MODS after CPB.

46   **Conclusions:** There is a correlation between lactic acidosis and MODS after CPB, so LA should

47   be monitored closely after CPB.

48

49   **Key words:** cardiopulmonary bypass; lactic acidosis; hyperlactatemia; multiple organ

50   dysfunction syndrome.

51

52  **INTRODUCTION**

53     Cardiac surgery comes with a significant risk of major adverse events, with an overall

54  mortality rate of 2%-3% (Senst et al. 2022). Major complications include bleeding, stroke,

55  kidney injury, mesenteric ischemia, atrial fibrillation, cardiogenic shock, and respiratory distress

56  (Senst et al. 2022). Multiple organ dysfunction syndrome (MODS) occurs in about 5% of

57  patients after cardiac surgery, with cardiopulmonary bypass (CPB) being the procedure with the

58  highest risk (D'Agostino et al. 2018; Liu et al. 2021). The 28-day mortality rate of MODS is 23%

59  (Stoppe et al. 2016), and MODS can persist for as long as 28 days in 15% of patients (Stoppe et

60  al. 2016). MODS after cardiac surgery is associated with high morbidity and mortality.

61  Predicting the risk of MODS after cardiac surgery could help screen patients requiring closer

62  management.

63     Hyperlactatemia occurs in 10%-20% of patients following cardiac surgeries (Minton &

64  Sidebotham 2017), as it can result from hypoxic and nonhypoxic causes such as drug therapy,

65  cardioplegia, hypothermia, and CPB. Severe hyperlactatemia can lead to lactic acidosis (LA;

66  Garcia-Camacho et al. 2020; Greenwood et al. 2021; Teloh et al. 2017), which can then lead to

67  vascular hyporeactivity, decreased peripheral vascular resistance, decreased myocardial

68  contraction force, and reactivation of the heart and exogenous catecholamines, causing

69  myocardial injury, severe arrhythmia, inflammation, and impaired immune cell function (Azad et

70  al. 2019; Kimmoun et al. 2015; Rudnick et al. 2020). The relationship between hyperlactatemia

71  and prognosis after CPB remains controversial, however, and the limits of lactic acid values for

72  hyperlactacemia are not uniform in published research (Joudi et al. 2014; Mak et al. 2016;

73  Minton & Sidebotham 2017). Normal lactate is generally defined as blood lactate <2.0 mmol/L

74  (Foucher & Tubben 2022), but because there is no standard definition for hyperlactatemia, it has

75    been variably defined as blood lactate >3 or >4 mmol/L, or even >10 mmol/L (Bhardwaj et al.

76    2017; Kedziora et al. 2020; Renew et al. 2016). LA is a well-known marker of poor tissue

77    perfusion and multiorgan dysfunction, and LA can predict mortality in patients with severe sepsis

78    and septic shock and the incidence of MODS in hospitalized patients (Doshi et al. 2018;

79    Gattinoni et al. 2019). LA and a longer time to lactic acid normalization are also associated with

80    an increased risk of death (Bullock & Benham 2022; Gillies et al. 2019; Radelfahr & Klopstock

81    2019). However, there are few studies on the effect of LA on MODS after CPB. This study

82    aimed to determine the association between LA and the occurrence of MODS after CPB. The

83    results of this study could help improve the management of CPB patients.

84

85    **MATERIALS & METHODS**

86    **Study design and participants**

87      This study was a post hoc analysis of the clinical data from all patients who underwent

88    cardiac surgery between February 2017 and August 2018 and participated in a prospective study

89    (monitoring oxygen metabolism after cardiopulmonary bypass and 48-h organ dysfunction,

90    ChiCTR-ROC-1701072; Zhang et al. 2021). This study was approved by the ethics committee of

91    Taizhou Hospital (Zhejiang Province, China) and was carried out according to the tenets of the

92    Helsinki Declaration of 1975 and good clinical practice. Written informed consent was obtained

93    from all patients in the original study (Zhang et al. 2021), including consent to the use of study

94    data for post hoc analyses.

95      The study inclusion criteria were: 1) ≥18 years of age, 2) admission to the ICU

96    immediately after CPB, and 3) ICU stay of more than one day. The exclusion criteria were: 1)

97    received $NaHCO_3^-$, 2) emergency surgery, 3) pregnancy, 4) chronic renal insufficiency with

98    dialysis, 5) preoperative acute or chronic liver failure, 6) hematologic diseases, 7) central venous

99    catheter dislocation, or 8) death within 48 h. Intraoperative and postoperative ICU management

100   was conducted in accordance with local protocols and international guidelines (Carl et al. 2010;

101   Zhang et al. 2021).

102

103   **Data collection and definitions**

104        Intraoperative and ICU management was performed using the same methods as the

105   original study (Zhang et al. 2021). The following data were collected: basic patient

106   characteristics before surgery, intraoperative conditions, postoperative vital signs, and blood test

107   results. The data were collected at: ICU admission (H0), and 4 (H4), 8 (H8), 12 (H12), 24 (H24),

108   and 48 hours (H48) after admission. The Acute Physiology and Chronic Health Evaluation II

109   (APACHE II) and sequential organ failure (SOFA) scores were assessed between 24 and 48

110   hours after ICU admission. A blood gas analysis of arteries and veins were performed at ICU

111   admission, and at H4, H8, H12, and H24 using an automated analyzer (ABL800 Flex,

112   Radiometer Medical Aps, Bronshoj, Denmark).

113        Blood lactate levels gradually increased after CPB, peaking at H8 and then gradually

114   decreasing **(Figure 1)**. In animal studies, lactic acid level increased after CPB, peaking at 8-12 h

115   and gradually decreasing to the normal range 24 h after surgery (Chiang et al. 2001). A previous

116   clinical study found that lactic acid level peaked 6-9 h after surgery and then gradually

117   decreased, with most levels returning to normal within 24 h (Aktar et al. 2020). Based on these

118   results, H8 was selected for grouping. Patients were divided into three groups according to blood

119   lactate level, $HCO_3^-$, and pH measurement at H8: the lactic acidosis group (LA group; blood

120   lactate levels $\geq$5 mmol/L, pH <7.35, and $HCO_3^-$ <20 mmol/L), the hyperlactatemia group (HL

121    group; blood lactate levels >2 mmol/L, without pH <7.35 and $HCO_3^-$ <20 mmol/L), and the

122    normal control group (NC group; blood lactate levels ≤2 mmol/L, without pH <7.35 and $HCO_3^-$

123    <20 mmol/L(Kraut & Madias 2014)..

124

125    **Outcomes**

126    The primary outcome was the occurrence of MODS at H48. The diagnostic indexes of

127    organ dysfunction used in this study refer to the same criteria as the original study, and MODS

128    was defined as the dysfunction of two or more organs (Zhang et al. 2021). Organ dysfunction

129    within 48 h after surgery was diagnosed in accordance with the following criteria: the diagnostic

130    criteria for acute respiratory distress syndrome (ARDS) was a PaO2/FIO2 of <300 mmHg

131    requiring non-invasive ventilation or invasive mechanical ventilation support; acute kidney

132    injury was defined according to Kidney Disease Improving Global Outcomes (KDIGO): Clinical

133    Practice Guideline for Acute Kidney Injury; additional criteria included total bilirubin levels ≥32

134    μmmol/L, platelet count <100×$10^9$/L, and acute tissue hypoperfusion (presence of tachycardia

135    and hypotension, with central venous oxygen saturation ($ScvO_2$) level of <65% and cardiac index

136    of ≤2.2 L/min/m$^2$), cardiac arrest, arrhythmia (ventricular tachycardia and ventricular

137    fibrillation), and acute neurological dysfunction (stroke, seizure, persistent delirium, and

138    Glasgow coma score below 12).

139

140    **Statistical analysis**

141    The statistical analysis was conducted using SPSS 2.0 (IBM Corp., Armonk, NY, USA).

142    The Kolmogorov-Smirnov test was used to evaluate the normality of the continuous variables

143    and the results showed that many continuous variables were non-normally distributed. All

144   continuous variables were expressed as median (range) and analyzed using the Mann-Whitney

145   U-test, the Kruskal-Wallis test (intergroup comparisons), or repeated-measures ANOVA

146   (intragroup comparisons). Categorical variables were presented as m (%) and analyzed using the

147   chi-square test. The factors associated with MODS at H48 were analyzed using a multivariable

148   logistic regression analysis. Variables with $P<0.10$ in the univariable regression analyses were

149   included in the multivariable regression analysis. GraphPad Prism version 8.0.2 (GraphPad

150   Software Inc., San Diego, CA, USA) was used for the boxplot charts.

151

152   **RESULTS**

153   **Clinical characteristics and prognosis of the patients**

154       The original study enrolled 139 patients, but 25 were excluded based on the exclusion

155   criteria of the present study, and eight patients were excluded due to incomplete data. Therefore,

156   114 patients were included in this study: 22 (19%) in the LA group, 73 (64%) in the HL group,

157   and 19 (17%) in the NC group **(Figure 2)**. There were no significant differences in the

158   preoperative and intraoperative variables among the three groups (all $P>0.05$). The APACHE II

159   (H24) and SOFA (H24) scores were the highest in the LA group ($P<0.05$). The ICU stay

160   duration was the longest for the LA group, at 48.5 h (42.5 h, 50 h), compared with 27 h (22 h, 48

161   h) for the HL group and 27 h (25 h, 46 h) for the NC group ($P=0.012$). The patients in the LA

162   group had the highest incidence of MODS (36%), compared with 14% in the HL group and 5%

163   in the NC group ($P=0.015$; $P<0.05$ for LA vs. HL and LA vs. NC**; Table 1)**.

164

165   **Vital signs and perfusion variable at H8**

166       The pH, $HCO_3^-$, and lactate levels were all significantly different between the three groups

167 (all P<0.001). The LA group had lower BE [-7.6 (-9.25, -6.05) vs. -2.3 (-4.4, -1.05) vs. -1.35 (-

168 2.5, 0.75)], lower $SaO_2$-$SvO_2$ [21.0 (16.5, 32.5) vs. 31.0 (23.75, 37.0) vs. 31.0 (29.0, 36.5)] and

169 lower $O_2ER$ [21.5 (17.05, 32.8) vs. 31.3 (24.8, 37.6) vs. 31.3 (29.0, 35.4)] compared with the HL

170 and NC groups (all P<0.05). The LA group had higher $ScvO_2$ compared with the NC group [76

171 (66.5, 81) vs. 68 (64, 70), P=0.024] **(Table 2).**

172

173 **Risk factors associated with MODS**

174 In the univariable analyses, patient age (OR=1.054, 95% CI: 1.003-1.109, P=0.038), the LA

175 group (vs. NC, OR=10.286, 95% CI: 1.148-92.185, P=0.037), and $\Delta PCO_2$ at H8 (OR=1.197,

176 95% CI: 1.022-1.401, P=0.025) were associated with MODS after CPB **(Table 3)**.

177

178 **DISCUSSION**

179 This post hoc analysis of a previous prospective study aimed to determine the association

180 between LA and the occurrence of MODS after CPB. The LA group had long ICU stays and a

181 high incidence of MODS, suggesting that LA was associated with MODS after CPB.

182 Tissue hypoperfusion and lactic acid accumulation can occur during cardiac surgery

183 (Chiang et al. 2001; Kanazawa et al. 2015; Naik et al. 2016; Teloh et al. 2017). When tissue

184 perfusion is restored after CPB, lactic acid displays a washout effect, and a large amount of lactic

185 acid is released into the blood, leading to apparent hyperlactatemia, but that lactic acid is cleared

186 rapidly if the heart and vital organs recover well after surgery, preventing LA (Kanazawa et al.

187 2015). LA occurs when the body fails to compensate (Kanazawa et al. 2015). Some studies

188 suggest that high lactacidemia during operation is related to CPB time and aortic occlusion time

189 (Naik et al. 2016; Ranucci et al. 2006). In this study, lactic acid levels were grouped eight hours

190 after surgery, and there was no difference in cardiopulmonary bypass time and aortic occlusion

191 time among the three groups. This may be because the patients were stable before surgery and

192 the operations were performed by the same surgeon, so there was no difference in time of CPB

193 and aortic occlusion. Naik et al. (2016) reported that the incidence of hyperlactatemia (blood

194 lactate levels ≥4 mmol/L) was 42.7%, and these patients had an increased incidence of

195 postoperative atrial fibrillation and extended ICU stays. Renew et al. (2016) observed that severe

196 hyperlactatemia (blood lactate level >10 mmol/L) was associated with increased mortality. Zante

197 et al. (2018) reported that blood lactate levels >4.0 mmol/L, combined with a BE <6.7 mmol/L,

198 could predict mortality, whereas blood lactate levels >4.0 mmol/L alone did not affect mortality

199 after cardiac surgery. However, these studies ignored the presence of lactic acidosis in patients

200 with severe hyperlactacemia, especially when the blood lactate levels were >5 mmol/L. In the

201 present study, the blood lactate levels were 6.8 (5.6, 9.6) mmol/L in the LA group and 4.1 (3.0,

202 5.4) mmol/L in the HL group. The LA group tended to be severely ill, had a prolonged ICU stay,

203 and a high incidence of MODS. Hyperlactemia alone did not affect prognosis.

204       Clinically, $ScvO_2$, $O_2ER$, $\triangle PCO_2$, and $\triangle PCO_2/Ca\text{-}vO_2$ are often used to evaluate tissue

205 perfusion (Janotka & Ostadal 2021). The $O_2ER$ is the amount of oxygen taken out of the blood

206 by the tissues. Normal $O_2ER$ is about 25%-30%. In this study, $O_2ER$ was calculated as 1-

207 $ScvO_2/SaO_2$. In sepsis, because oxygen free radicals and inflammatory mediators damage the

208 structure of the mitochondria, the number and function of mitochondria declines. The longer

209 severe sepsis lasts, the more irreversible mitochondrial structure and function changes occur,

210 resulting in mitochondrial dysfunction and microcirculation disorders, decreased oxygen use,

211 decreased oxygen consumption, increased $ScvO_2$, and reduced $O_2ER$ (Gong & Li 2013; Pope et

212 al. 2010). In a study of patients with septic shock, the hospital mortality rate was 41.7% in the

213  low $O_2ER$ group, which was higher than the normal and high $O_2ER$ groups. $O_2ER$ was

214  negatively correlated with $ScvO_2$ ($R^2=0.878$, $P<0.001$), and high $ScvO_2$ combined with low

215  $O_2ER$ was associated with mitochondrial dysfunction (Park et al. 2015). In the present study,

216  there was no difference in mean arterial pressure between the three groups, but the LA group had

217  decreased urine volume, increased $ScvO_2$, and decreased $O_2ER$, due to the SIRS produced by

218  CPB, and the oxygen free radicals and various chemia-reperfusion injuries leading to

219  mitochondrial dysfunction, causing lactic acidosis (Balzer et al. 2015; Janotka & Ostadal 2021;

220  Stephens et al. 2020). Dekker et al. (2019) found persistent microcirculation perfusion disorders

221  through hypoglossal flow dark field microcirculation imaging technology in the first three days

222  after CPB. A separate study found that microcirculation disorders persisted 24 h after CPB

223  through the reduction of functional capillary density (FCD), perfusion vessel density (PVD), or

224  perfusion vessel proportion (PPV), even when general circulation was stable (den Os et al.

225  2020). A single-center study analyzed the relationship between microcirculation heterogeneity

226  and hemodynamics and found that $SaO_2$-$SvO_2$ and $O_2ER$ decreased in microcirculation perfusion

227  disorders after CPB (Koning et al. 2014). In the present study, there were high $ScvO_2$ and low

228  $O_2ER$ in the LA group, suggesting that LA after CPB may be accompanied by microcirculation

229  and mitochondrial dysfunction. MODS can be the result of both hypoperfusion and hypo-

230  oxygenation (Rixen & Siegel 2005), or the result of microcirculation and mitochondrial

231  dysfunction, reflected by LA (Garcia-Camacho et al. 2020; Greenwood et al. 2021; Teloh et al.

232  2017). Even if the patient's circulation is stable after CPB, there might be mitochondrial

233  dysfunction and microcirculation disorders, resulting in organ dysfunction. However, this study

234  was a retrospective analysis, and the indicators of mitochondrial function could not be analyzed

235  with LA. Therefore, future studies are needed to evaluate this relationship.

236    In this study, patient age and ∆PCO2 were risk factors for MODS, but the OR value of

237  age and ∆PCO2 were close to 1, and were of little clinical significance. The research team

238  previously found that ∆PCO2 and ∆PCO2/Ca-vO2 levels are not reliable predictors of organ

239  dysfunction occurrence at H48 (Lefering et al. 2013; Zhang et al. 2021). LA is a prognostic

240  factor for MODS in sepsis (Bakker et al. 1996; Doshi et al. 2018; Gattinoni et al. 2019), trauma

241  with massive hemorrhage (Lefering et al. 2013), and cardiogenic shock (Jentzer et al. 2022). The

242  occurrence of MODS leads to longer ICU stays, higher hospital expenses, and increased

243  morbidity and mortality (Asim et al. 2020; Zhao et al. 2022). In this study, LA was associated

244  with MODS. However, due to the insufficient number of cases in this study, no further multi-

245  factor analysis was done. Because LA can be detected quickly through a blood gas analysis, LA

246  could be used as a monitoring indicator of MODS after CPB. There are many causes of lactic

247  acidosis, including tissue hypoperfusion, hyperglycemia, and endogenous catecholamines caused

248  by the stress response during cardiac surgery. The liver accounts for 60% of lactic acid

249  metabolism, and the kidney accounts for 30% (Lefering et al. 2013; Stephens et al. 2020). Lactic

250  acidosis could be avoided by controlling blood glucose and body temperature, shortening the

251  time of aortic blood flow blockade during operation, optimizing volume management, supporting

252  organ function treatment, and ensuring the perfusion of macrocirculation and microcirculation

253  after operation. LA could be used as a reference index for the occurrence of MODS after CPB,

254  better guiding clinical treatment for post-surgical patients.

255

256  **Limitations**

257    This study has some limitations. First, this was a post hoc analysis of a completed

258  prospective study. The sample size of the original study was limited, and some patients had to be

259   excluded from the present analysis. This small sample size likely led to the wide 95% CI

260   observed in the association between LA and MODS in the univariate analysis. Therefore, no

261   further multivariate regression analysis was performed. Second, it was a single-center study, and

262   generalizability might be limited. Third, this study did not include data on whether LA after

263   cardiac surgery was only caused by increasing lactic acid levels or by other factors. Therefore, a

264   future prospective multicenter study is planned, with a larger sample size, to collect relevant data

265   with MODS as the outcome indicator, monitoring mitochondrial function indexes and

266   investigating the relationship between LA and MODS.

267

268   **Conclusion**

269       This study identified a correlation between lactic acidosis and MODS after CPB. LA is

270   an easy-to-obtain clinical indicator, so LA should be closely monitored after CPB to help

271   improve patient prognosis after CPB.

272

273

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276

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415

416 **Figure legend**

417 **Figure 1.** Blood lactate level trends during the 24-h observation period. H8 lactate (Lac), H12

418 Lac, and H0 Lac were statistically significant (P=0.001, 0.007).

419 **Figure 2. Flowchart.** CKD: Chronic kidney disease.

Patients' clinical characteristics and prognosis

APACHE II: Acute Physiology and Chronic Health Evaluation II; ALT: alanine aminotransferase; AST= aspartate aminotransferase ; BMI: body mass index; BE: base excess; BUN: Urea nitrogen; CPB: cardiopulmonary bypass; DBIL: direct bilirubin; H24: 24 h after entering the ICU; H48: 48 h after entering the ICU; HB: hemoglobin; PLT: platelet; SCr: serum creatinine; SOFA: Sequential Organ Failure Assessment; TBIL: total bilirubin. [a] P<0.05 between the LA and HL groups; [b] P<0.05 between the LA and NC groups; [c] P<0.05 between the HL and NC groups.

1    **Table 1. Patients' cClinical characteristics and prognosis ~~of the patients~~**

| Subject | LA group (n=22; H8) | HL group (n=73; H8) | NC group (n=19; H8) | P |
|---|---|---|---|---|
| **Preoperative** | | | | |
| Age (years) | 59.50 (55.75, 68.25) | 57.00 (48.50, 64.00) | 60.00 (50.00, 66.00) | 0.421 |
| Sex (male/female) | 6/16 | 34/39 | 12/7 | 0.068 |
| Body mass index (kg/m$^2$) | 22.59 (19.56, 24.57) | 22.77 (20.83, 25.38) | 23.07 (20.85, 24.23) | 0.633 |
| Smoking (yes/no) | 3/19[b] | 26/47 | 10/9 | 0.029 |
| Diabetes (yes/no) | 0/22 | 6/67 | 2/17 | 0.336 |
| Hypertension (yes/no) | 8/14 | 27/46 | 10/9 | 0.437 |
| Tumor (yes/no) | 1/21 | 3/70 | 0/19 | 0.658 |
| COPD (yes/no) | 1/21 | 1/72 | 1/18 | 0.527 |
| Coronary heart disease (yes/no) | 4/18 | 4/69 | 0/19 | 0.052 |
| Cerebrovascular disease (yes/no) | 2/20 | 3/70 | 1/18 | 0.657 |
| EF (%) | 59.5 (54,64.25) | 63 (57,67) | 64 (53,67) | 0.196 |

| | | | | |
|---|---|---|---|---|
| pH | 7.41 (7.39, 7.42) | 7.40 (7.38, 7.42) | 7.40 (7.39, 7.41) | 0.551 |
| BE (mmol/L) | - 0.5 ( - 1.6, 1.3) | - 1.0 ( - 1.9, 0.5) | 1.0 ( - 0.9, 1.8) | 0.351 |
| Hb (g/L) | 136 (126, 148) | 135 (126, 149) | 139 (128, 149) | 0.743 |
| PLT count ($10^9$/L) | 222 (165, 264) | 211 (171, 245) | 204 (161, 254) | 0.385 |
| ALT (U/L) | 25 (14, 36) | 20 (12, 40) | 25 (16, 35) | 0.796 |
| AST (U/L) | 22 (20, 27) | 22 (20, 31) | 29 (24, 33) | 0.054 |
| TBIL (μmol/L) | 15 (10.5, 16.6) | 12.2 (8.6, 17.4) | 9.7 (7.5, 16.2) | 0.287 |
| DBIL (μmol/L) | 4.6 (3.8, 5.6) | 4.3 (2.9, 5.8) | 3.3 (2.4, 6.0) | 0.486 |
| Albumin (g/L) | 40 (37.5, 44.6) | 42.9 (39.9, 46.3) | 43 (39.3, 44.4) | 0.165 |
| SCr (μmol/L) | 69 (61, 87) | 79 (72, 85) | 74.5 (61.5, 84) | 0.351 |
| BUN (mmol/L) | 5.9 (4.6, 8.7) | 6.2 (4.8, 7.7) | 7.5 (5.8, 8.3) | 0.538 |
| GLU (mmol/L) | | | | |
| **Surgery** | | | | |
| Valve replacement | 14 | 56 | 13 | 0.43 |
| Others | 8 | 17 | 6 | |

| | | | | |
|---|---|---|---|---|
| Duration of surgery (h) | 4.5 (3.5, 5.0) | 4.0 (3.5, 5.0) | 3.6 (3.1, 4.2) | 0.354 |
| CBP duration (min) | 110 (60, 135) | 105 (85, 140) | 110 (75, 134) | 0.911 |
| Aortic clamping duration (min) | 60 (42, 75) | 65 (50, 85) | 55 (30, 82.5) | 0.829 |
| **Prognosis** | | | | |
| APACHEII (H24) score | 10 (9, 13)[a, b] | 7 (4,9) | 7 (5, 10) | 0.003 |
| SOFA (H24) score | 7 (5, 8) [a, b] | 5 (3, 7) | 5 (4, 6) | 0.005 |
| Ventilation duration (h) | 16.5 (13.5, 17.5) | 16.6 (13.5, 17.5) | 17 (13.5, 18) | 0.369 |
| ICU stay duration (h) | 48.5 (42.5, 50)[a] | 27 (22, 48) | 27 (25, 46) | 0.012 |
| Hospital stay duration (d) | 11 (8, 13) | 10 (9, 13) | 11.5 (8.5, 17) | 0.456 |
| Organ dysfunction (yes/no) | 11/11 | 31/42 | 6/13 | 0.489 |
| Multiple organ dysfunction (yes/no) | 8/14 [a, b] | 10/63 | 1/18 | 0.015 |

2   APACHE II: Acute Physiology and Chronic Health Evaluation II; ALT: alanine aminotransferase; AST= aspartate aminotransferase;

3   BMI: body mass index; BE: base excess; BUN: Urea nitrogen; CPB: cardiopulmonary bypass; DBIL: direct bilirubin; H24: 24 h after

4   entering the ICU; H48: 48 h after entering the ICU; HB: hemoglobin; PLT: platelet; SCr: sSerum creatinine; SOFA: Sequential Organ

5   Failure Assessment; TBIL: total bilirubin.

6    [a] P<0.05 between the LA and HL groups; [b] P<0.05 between the LA and NC groups; [c] P<0.05 between the HL and NC groups.

Vital signs and perfusion variable at H8

BE: base excess; CVP: central venous pressure; Ca-vO$_2$: arterial-to-central venous oxygen content difference; DBP: diastolic blood pressure; MAP: mean arterial pressure; O$_2$ER: oxygen extraction ratio; $\triangle$PCO$_2$: central venous-to-arterial carbon dioxide difference; $\triangle$PCO2/C(a-cv)O$_2$: $\triangle$PCO$_2$-to-arterial-to-central venous oxygen content difference rate: SBP: systolic blood pressure; ScvO$_2$: central venous oxygen saturation; SaO$_2$-SvO$_2$: arterial-to-central venous oxygen saturation difference; VIS: vasoactive-inotropic score. [a] P<0.05 between the LA and HL groups; [b] P<0.05 between the LA and NC groups; [c] P<0.05 between the HL and NC groups.

1    **Table 2. Vital signs and perfusion variable at H8**

| | LA group (n=22; T8) | HL group (n=73; T8) | NC group (n=19; T8) | P |
|---|---|---|---|---|
| SBP (mmHg) | 100.00 (92.5, 112.5) | 106.00 (100.00, 112.25) | 98.5 (93.5, 111.25) | 0.106 |
| DBP (mmHg) | 55.0 (49.5, 60.5) | 59.0 (52.75, 64.0) | 57.5 (51.25, 63.25) | 0.169 |
| MAP (mmHg) | 72.0 (63.5, 79.0) | 74.0 (68.75, 79.0) | 69.5 (67.00, 75.75) | 0.196 |
| CVP (mmHg) | 10 (7.5, 12.0) | 7.0 (6.0, 9.25) | 9.0 (7.5, 10.0) | 0.033 |
| VIS | 4.00 (0.00, 8.00) | 3.0 (0.00, 9.00) | 8.0 (2.00, 9.00) | 0.377 |
| Intake (mL) | 1184 (1057.5, 1592.5) | 1085 (861.75, 1445) | 1150 (860.0, 1551.25) | 0.394 |
| Output (mL) | 871 (721.5, 1266)[b] | 952.5 (843.75, 1226.25) | 1242 (768.75, 1707.5) | 0.028 |
| Urine volume (mL) | 655 (544.0, 1033.5)[b] | 782.5 (550.00, 973.75) | 1062.5 (653.5, 1367.5) | 0.012 |
| Fluid balance (mL) | 340.0 (-153.75, 623.5) | 33.0 (-187.0, 367.5) | -20 (-395, 185) | 0.093 |
| pH | 7.29 (7.23, 7.31) [a, b] | 7.39 (7.36, 7.43) | 7.39 (7.37, 7.44) | <0.001 |
| BE (mmol/L) | -7.6 (-9.25, -6.05) [a, b] | -2.3 (-4.4, -1.05) | -1.35 (-2.5, 0.75) | 0.001 |
| $HCO_3$ (mmol/L) | 19.2 (18.5, 20.5) [a, b] | 22.0 (20.3, 23.6)[c] | 24.1 (22.4, 25.6) | <0.001 |
| Lactate (mmol/L) | 6.8 (5.6, 9.6) [a, b] | 4.1 (3.0, 5.4)[c] | 1.7 (1.3, 1.9) | <0.001 |

| | | | |
|---|---|---|---|
| ScvO$_2$ (%) | 76 (66.5, 81)[b] | 68 (61.0, 74.5) | 68 (64, 70) | 0.024 |
| SaO$_2$-SvO$_2$ (%) | 21.0 (16.5, 32.5) [a, b] | 31.0 (23.75, 37.0) | 31.0 (29.0, 36.5) | 0.016 |
| O$_2$ER (%) | 21.5 (17.05, 32.8) [a, b] | 31.3 (24.8, 37.6) | 31.3 (29.0, 35.4) | 0.018 |
| $\triangle$PCO$_2$ (mm Hg) | 10.00 (6.50, 11.50) | 9.50 (7.75, 11.00) | 9.00 (5.00, 11.00) | 0.417 |
| $\triangle$PCO$_2$/Ca-vO$_2$ (mm Hg/mL) | 2.1 (1.8, 3.7) | 2.0 (1.6, 2.3) | 1.8 (1.3, 2.1) | 0.084 |

2  BE: base excess; CVP: central venous pressure; Ca-vO$_2$: arterial-to-central venous oxygen content difference; DBP: diastolic blood

3  pressure; MAP: mean arterial pressure; O$_2$ER: oxygen extraction ratio; $\triangle$PCO$_2$: central venous-to-arterial carbon dioxide difference;

4  $\triangle$PCO2/C(a-cv)O$_2$: $\triangle$PCO$_2$-to-arterial-to-central venous oxygen content difference rate: SBP: systolic blood pressure; ScvO$_2$: central

5  venous oxygen saturation; SaO$_2$-SvO$_2$: arterial-to-central venous oxygen saturation difference; VIS: vasoactive-inotropic score.

6  [a] P<0.05 between the LA and HL groups; [b] P<0.05 between the LA and NC groups; [c] P<0.05 between the HL and NC groups.

Risk factors associated with MODS

The risk factors of MODS and the perfusion index at the H8 time point were analyzed by binary logistic regression. P<0.05 was considered statistically significant. MODS: multiple organ dysfunction syndrome; OR: odds ratio; CI: confidence interval; NC: normal control; HL: hyperlactatemia; LA: lactic acidosis; $ScvO_2$: central venous oxygen saturation; $SaO_2$-$SvO_2$: arterial-to-central venous oxygen saturation difference; $O_2ER$: oxygen extraction ratio, $\triangle PCO_2$: central venous-to-arterial carbon dioxide difference, $\triangle PCO2/C(a$-$cv)O_2$: $\triangle PCO_2$-to-arterial-to-central venous oxygen content difference rate.

**Table 3.** **Risk fF̶actors associated with MODS**

| Subject | Univariate | |
| --- | --- | --- |
| | OR (95%CI) | P |
| Group | | |
|   NC | Reference | |
|   HL vs. NC | 2.857 (0.342-23.835) | 0.332 |
|   LA vs. NC | 10.286 (1.148-92.185) | 0.037 |
| Age | 1.054(1.003-1.109) | 0.038 |
| $ScvO_2$ (H8) | 0.953 (0.908-1.000) | 0.051 |
| $O_2ER$ (H8) | 1.023 (0.995-1.052) | 0.108 |
| $\triangle PCO_2$ (H8) | 1.197 (1.022-1.401) | 0.025 |
| $\triangle PCO_2/Ca\text{-}vO_2$ (H8) | 1.218 (0.849-1.746) | 0.283 |

The risk factors of MODS ~~were analyzed,~~ and the perfusion index at the H8 time point

w~~ere~~as̲ analyzed by binary logistic regression.

P<0.05 was considered̲ statistically significant.

MODS: multiple organ dysfunction syndrome; OR: odds ratio; CI: confidence interval;

NC: normal control; HL: hyperlactatemia; LA: lactic acidosis; $ScvO_2$: central venous

oxygen saturation; $SaO_2$-$SvO_2$: arterial-to-central venous oxygen saturation difference;

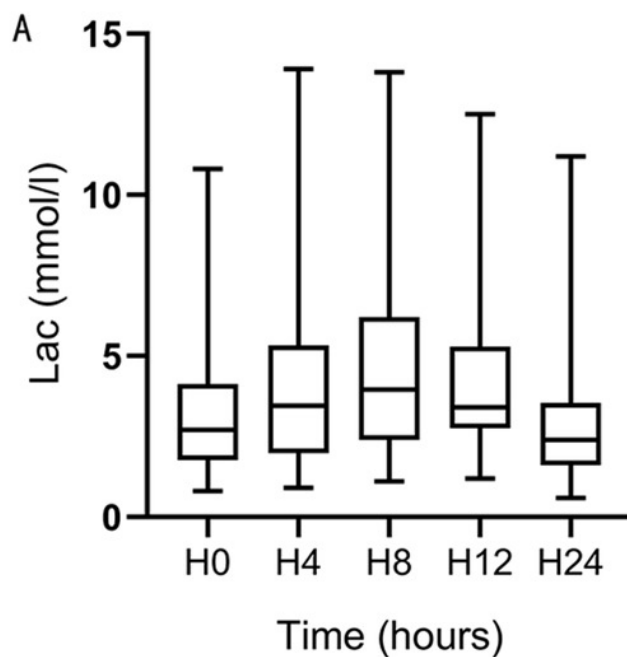
$O_2ER$: oxygen extraction ratio, $\triangle PCO_2$: central venous-to-arterial carbon dioxide

difference, $\triangle PCO2/C(a\text{-}cv)O_2$: $\triangle PCO_2$-to-arterial-to-central venous oxygen content

difference rate.

# Figure 1

Blood lactate level trends during the 24-h observation period.

H8 lactate (Lac), H12 Lac, and H0 Lac were statistically significant (P=0.001, 0.007).

| B observation time point | blood lactate level(mmol/l) |
|---|---|
| H0 Lac | 2.7 (1.8, 4.1) |
| H4 Lac | 3.5 (2.0, 5.3) |
| H8 Lac | 4.0 (2.4, 6.2) |
| H12 Lac | 3.4 (2.8, 5.3) |
| H24 Lac | 2.4 (1.6, 3.6) |

# Figure 2

Flowchart

CKD: Chronickidney disease