

# Lactate levels and clearance rate in neonates undergoing mechanical ventilation in Tibet

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## Abstract

**Objective:** This study aimed to examine the characteristics of blood lactate in neonates undergoing mechanical ventilation in Tibet.

**Methods:** We recruited 67 neonates undergoing mechanical ventilation in Naqu People's Hospital as the plateau observation group and 94 neonates undergoing mechanical ventilation in Shengjing Hospital as the control group. We analyzed the differences in lactate levels between the two groups.

**Results:** The lactate clearance rates of neonates with asphyxia and those with respiratory distress syndrome were significantly lower in the plateau group than in the control group. Lactate levels in neonates who died in the plateau group were significantly higher and the lactate clearance rate was significantly lower than those in neonates who survived. The cut-off point for the lactate clearance rate at 6 hours for predicting mortality was 6.09% in the plateau group.

**Conclusion:** The lactate clearance rate of neonates on mechanical ventilation in the plateau area is lower than that in neonates in the non-plateau area. The lactate clearance rate at 6 hours is important for evaluating the prognoses of critical neonates in plateau areas.

## Keywords

Altitude, neonate, mechanical ventilation, lactate clearance rate, plateau area, asphyxia, respiratory distress syndrome

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## Introduction

Properly tested biochemical markers of end-organ perfusion and cellular homeostasis are lacking in neonates, but measurement of lactate may represent a biologically plausible approach. Lactate levels in arterial blood are often used for assessing critical patients. With a severe reduction in oxygen supply, sustaining aerobic metabolism via the Krebs's cycle is not possible. Therefore, tissues increasingly need anaerobic metabolism to meet their energy requirements, resulting in production and accumulation of lactate in the blood. Therefore, hypoxia and tissue hypoperfusion can result in hyperlactatemia.<sup>1</sup> Some scholars regard blood lactate monitoring as an index with which to evaluate the severity and prognosis of tissue hypoxia.<sup>2,3</sup>

If hyperlactatemia cannot be corrected in time, it can cause damage to multiple organs perinatally and increase the mortality and disability rate of neonates.<sup>4</sup> An increase in blood lactate concentrations during hospitalization is considered to represent a significant prognostic indicator for neonates.<sup>5</sup> Moreover, continual measurement of blood lactate concentrations is more useful than a single measurement and can provide more accurate prognostic evaluation.<sup>6</sup> Dynamic monitoring of blood lactate levels in asphyxiated neonates can lead to a dynamic understanding of the internal environment and provide a basis for judging the prognosis of neonates and formulating measures for rescue and treatment.<sup>4</sup> Lactate is the main energy substrate of animals exposed to high altitude and plays an important role in energy production at high altitude.<sup>7</sup> Brooks et al.<sup>8</sup> previously reported that healthy men suffering from acute exposure at 4300 m above sea level had arterial lactate levels that were four times higher than a control group at sea level. However, other studies have

suggested that anaerobic metabolism remains unchanged throughout exposure to high altitude.<sup>9</sup> These previous studies were based on a normal population or animals exposed to hypoxia, or in non-plateau areas. There have been no previous studies on lactate levels and lactate clearance rates of neonates undergoing mechanical ventilation in plateau areas.

Tibet has an average altitude of 4000 m and is the highest geographical region in China and Asia. Naqu has an altitude of 4580 m and a population of approximately 460,000 people. However, little is known about critical neonates undergoing mechanical ventilation in this area. Blood lactate levels may provide an early warning signal and important prognostic information in ill, ventilated neonates, and serial measurements of blood lactate are more useful than a single value.<sup>10</sup> However, whether there are differences in lactate levels and the lactate clearance rate between neonates undergoing mechanical ventilation in plateau areas and those in non-plateau areas is unclear. Therefore, this study aimed to analyze neonates undergoing mechanical ventilation in the Naqu area to examine lactate levels and lactate clearance rates at different time points after mechanical ventilation in a plateau area, and to assess the value of these parameters for predicting prognosis.

## Materials and methods

### *Subjects*

Between 1 May 2017 and 31 December 2018, we recruited neonates who were undergoing mechanical ventilation in the neonatal intensive care unit of Naqu People's Hospital in Tibet (4580 m above sea level) (plateau group). We also recruited a non-plateau control group, which comprised neonates undergoing mechanical ventilation in Shengjing Hospital in

Liaoning (51 m above sea level). The guardians of all patients gave informed consent before mechanical ventilation.

Our inclusion criteria were as follows: (1) neonates who were hospitalized and required mechanical ventilation immediately after birth; (2) the synchronized intermittent mandatory ventilation mode was adopted during mechanical ventilation; and (3) in neonates with respiratory distress syndrome (RDS), chest X-rays were consistent with severe changes in RDS, including ground glass opacity accompanied by bronchial inflation, a blurred cardiac boundary or complete atelectasis, and the newborn did not experience cardiac compression after birth. RDS was defined as the presence of clinical symptoms, such as tachypnea, retractions, flaring of the nasal alae, grunting, and cyanosis shortly after birth, and inadequate pulmonary surfactant was the primary cause. Furthermore, neonates with asphyxia, but without RDS, were provided tracheal intubation, positive pressure ventilation, and resuscitation after birth via chest compression. Asphyxia was defined as the condition during the first and second stages of labor in which impaired gas exchange led to fetal hypoxemia and hypercarbia.

Neonates were excluded from our study if they had hereditary metabolic disease, congenital anomalies of the airways, congenital heart disease, chromosomal anomalies, intrauterine growth restriction, or small for gestational age. Newborns with a survival time of less than 6 hours were also excluded.

The study protocol was reviewed and approved by Shengjing Hospital of China Medical University Ethics Committee (Shenyang, China). The study did not include patient's personal information, fully protected the patient's privacy, had no effect on routine diagnosis and treatment of patients, and patients did not participate in the study for additional tests or

examinations. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. No potentially identifiable human images or data are presented in this study.

### ***Data collection and lactate measurement***

For each subject, approximately 1 mL of blood was collected from the radial artery within 30 minutes (immediately after mechanical ventilation and before using pulmonary surfactant in neonates with RDS), and at 1, 6, and 12 hours after birth. Lactate levels in arterial blood were measured using a blood gas analyzer (see details below).

Clinical data were recorded, including gestational age, sex, birth weight, ethnicity, 1-minute and 5-minute Apgar scores, and arterial blood lactate values within 30 minutes, and at 1, 6, and 12 hours after birth, and outcomes.

The lactate clearance rate was calculated as follows: (initial lactate level – lactate level after mechanical ventilation for several hours) / initial lactate level  $\times$  100%.<sup>11</sup>

### ***Instruments and equipment***

In the plateau group, we used the SV600 ventilator (Mindray Bio-Medical Electronics, Shenzhen, China; altitude was set to 4500 m) and the ABL80 blood gas analyzer (Radiometer Medical, Bronshoj, Denmark; lactate reference value: 0.6–1.5 mmol/L). In the non-plateau group, we used the Babylog VN500 ventilator (Drägerwerk AG, Lubeck, Germany) and the Cobas B 123 blood gas analyzer (Roche, Rotkreuz, Switzerland; lactate reference value: 1.0–1.7 mmol/L).

### **Statistical analysis**

SPSS version 13.0 (SPSS, Chicago, IL, USA) was used for all processing and statistical analysis. Data are presented as mean  $\pm$  standard deviation. The Student's t-test,  $\chi^2$  test, and Fisher's exact test were used for analysis where appropriate. Multivariate logistic regression analysis was used to analyze the medical history data. The receiver operating characteristic (ROC) curve was used to evaluate the values of lactate levels and lactate clearance rates for predicting mortality.  $P < 0.05$  was considered to indicate a statistically significant difference.

## **Results**

### **General characteristics**

Sixty-seven Tibetan neonates were in the plateau group, and 25 died. In the plateau group, there were 33 cases of RDS, 21 cases of asphyxia, 8 cases of meconium aspiration syndrome, 3 cases of sepsis, 1 case of sclerodema, and 1 case of pneumonia. Eighteen of the neonates with RDS used porcine pulmonary surfactant (PS) (240 mg regardless of weight) within 5 to 12 hours of birth. There were 94 neonates in the non-plateau group of Han nationality. Among these, there were 66 cases of RDS, including 1 death, 28 cases of asphyxia, including 4 deaths, and 65 of the neonates with RDS used porcine PS (200 mg/kg) within 1 hour of birth. The distribution of disease and mortality of the two groups is shown in Figure 1.

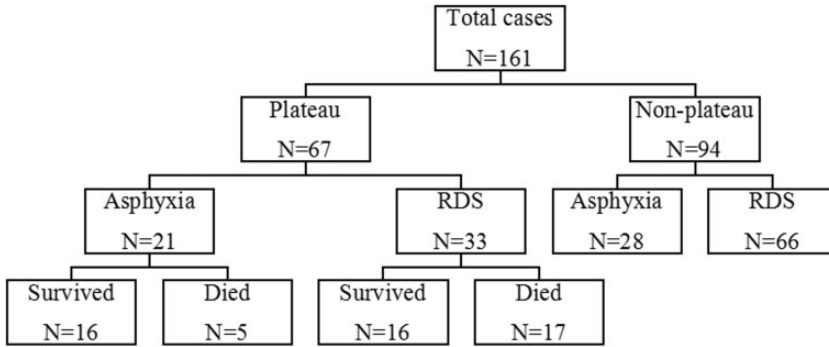
### **Comparison of lactate levels and lactate clearance rates between neonates with asphyxia in the plateau and non-plateau groups at different time points**

The cesarean section rate and Apgar scores of neonates with asphyxia in the plateau

group were significantly lower than those of neonates with asphyxia in the non-plateau group (all  $P < 0.001$ ). There were no significant differences in gestational age, birth weight, sex, and mortality between the two groups. Lactate levels in the plateau group were significantly lower than those in the non-plateau group within 30 minutes of birth, and the lactate clearance rates at 1 and 6 hours after birth were significantly lower than those in the non-plateau group (all  $P < 0.001$ ) (Table 1).

### **Comparison of lactate levels and lactate clearance rates between neonates with RDS in the plateau and non-plateau groups at different time points**

The cesarean section rate and Apgar scores of neonates with RDS in the plateau group were significantly lower than those of neonates with RDS in the non-plateau group (all  $P < 0.05$ , Table 2). However, birth weight was significantly higher in neonates with RDS in the plateau group than that in those in the non-plateau group ( $P = 0.034$ ). Further multivariate logistic regression analysis showed that there was no significant difference in the Apgar score (95% confidence interval [CI]: 0.735–5.790) between the two groups 5 minutes after birth. There was no significant difference in gestational age or sex between the two groups. Lactate levels were significantly higher in neonates with RDS in the plateau group than in those in the non-plateau group at 30 minutes, and 1, 6, and 12 hours after birth (all  $P < 0.001$ ). The lactate clearance rates in the plateau group at 1 and 6 hours after birth were significantly lower than those in the non-plateau group (both  $P < 0.001$ ). The mortality rate in the plateau group was significantly higher than that in the non-plateau group ( $P < 0.001$ ).



**Figure 1.** Flow chart of the plateau and non-plateau groups. RDS, respiratory distress syndrome.

**Table 1.** Comparison of lactate levels and the lactate clearance rate at different time points in neonates with asphyxia between the plateau and non-plateau groups.

	Plateau group	Non-plateau group	t/ $\chi^2$ value	P value
Medical history data				
Gestational age (weeks)	36.1 $\pm$ 2.4	36.2 $\pm$ 2.6	-0.092	0.927
Birthweight (g)	2652.4 $\pm$ 551.0	2583.5 $\pm$ 663.6	0.386	0.701
Sex (male/female)	16/5	14/14	3.467	0.063
Delivery mode (cesarean/natural)	2/19	20/8	18.588	<0.001
Apgar score				
1 minute	1.24 $\pm$ 0.44	2.64 $\pm$ 1.28	-4.803	<0.001
5 minute	4.10 $\pm$ 1.51	6.29 $\pm$ 1.70	-4.681	<0.001
Arterial lactate levels (mmol/L)				
Within 30 minutes after birth	8.67 $\pm$ 3.10	13.64 $\pm$ 4.29	-4.713	<0.001
1 hour after birth	7.83 $\pm$ 3.10	9.71 $\pm$ 5.43	-1.527	0.134
6 hours after birth	6.73 $\pm$ 3.37	7.75 $\pm$ 4.99	-0.847	0.401
12 hours after birth	4.53 $\pm$ 2.14	5.90 $\pm$ 4.76	-1.330	0.191
Lactate clearance rate (%)				
1 hour after birth	10.01 $\pm$ 8.26	33.46 $\pm$ 21.18	-5.341	<0.001
6 hours after birth	23.89 $\pm$ 17.38	46.52 $\pm$ 23.41	-3.883	<0.001
12 hours after birth	45.04 $\pm$ 18.86	57.26 $\pm$ 26.62	-1.751	0.087
Mortality (%)	23.8	14.3		0.470

**Comparison of lactate levels and lactate clearance rates at different time points in neonates who died and those who survived in the plateau group**

Gestational age and birth weight in the group of neonates who died were significantly lower than those in the group of neonates who survived (both  $P < 0.05$ ).

Further multivariate logistic regression analysis showed that there was no significant difference in gestational age (95% CI: 0.477–1.091) or birth weight (95% CI: 0.999–1.003) between the two groups. There were no significant differences in sex, the cesarean section rate, and Apgar scores between the two groups. Lactate levels within 30 minutes, and at 1, 6, and

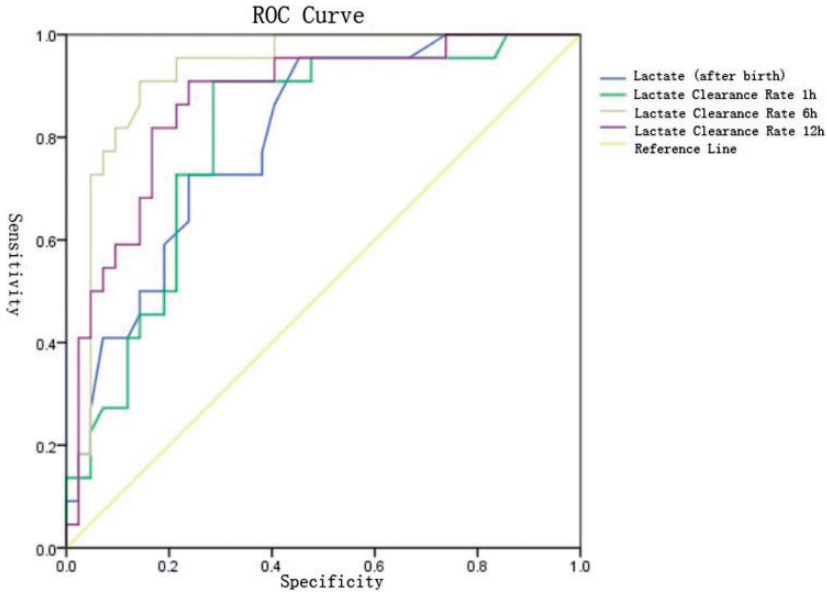
**Table 2.** Comparison of lactate levels and the lactate clearance rate at different time points in neonates with respiratory distress syndrome between the plateau and non-plateau groups.

	Plateau group	Non-plateau group	t/ $\chi^2$ value	P value
Medical history data				
Gestational age (weeks)	30.45 ± 2.2	30.4 ± 2.2	0.235	0.815
Birthweight (g)	1681.8 ± 324.5	1490.4 ± 455.5	2.154	0.034
Sex (male/female)	24/9	50/16	0.107	0.744
Delivery mode (cesarean/natural)	4/25	22/22	26.206	<0.001
Apgar score				
1 minute	4.52 ± 1.91	6.38 ± 1.60	-5.129	<0.001
5 minutes	7.36 ± 1.54	8.14 ± 0.93	-2.656	0.011
Arterial lactate levels (mmol/L)				
Within 30 minutes after birth	9.61 ± 3.11	7.15 ± 3.14	3.692	<0.001
1 hour after birth	8.77 ± 3.24	3.79 ± 2.43	8.577	<0.001
6 hours after birth	7.37 ± 2.80	3.42 ± 1.50	7.478	<0.001
12 hours after birth	5.79 ± 2.73	3.69 ± 1.47	4.023	<0.001
Lactate clearance rate (%)				
1 hour after birth	9.27 ± 8.83	47.21 ± 18.15	-13.992	<0.001
6 hours after birth	21.62 ± 16.45	48.97 ± 16.68	-7.646	<0.001
12 hours after birth	38.11 ± 18.48	43.82 ± 20.70	-1.308	0.194
Mortality (%)	51.5	1.5	36.972	<0.001

**Table 3.** Comparison of lactate levels and the lactate clearance rate between neonates who died and those who survived in the plateau group.

	Neonates who died	Neonates who survived	t/ $\chi^2$ value	P value
Medical history data				
Gestational age (weeks)	31.9 ± 3.5	34.4 ± 4.0	-2.557	0.013
Birthweight (g)	1952.0 ± 539.4	2285.7 ± 709.0	-2.028	0.047
Sex (male/female)	18/7	32/10	0.145	0.703
Delivery mode (cesarean/natural)	4/21	3/39		0.411 <sup>#</sup>
Apgar score				
1 minute	3.68 ± 2.29	3.36 ± 2.50	0.528	0.599
5 minutes	6.48 ± 2.33	6.40 ± 2.20	0.133	0.895
Arterial lactate levels (mmol/L)				
Within 30 minutes after birth	11.14 ± 3.73	7.90 ± 1.96	4.024	<0.001
1 hour after birth	10.56 ± 3.69	6.86 ± 1.84	4.696	<0.001
6 hours after birth	9.59 ± 2.95	5.34 ± 2.17	6.697	<0.001
12 hours after birth	7.66 ± 2.89	3.92 ± 1.69	5.586	<0.001
Lactate clearance rate (%)				
1 hour after birth	5.39 ± 3.93	12.99 ± 9.13	-4.711	<0.001
6 hours after birth	10.75 ± 4.68	32.77 ± 17.52	-7.680	<0.001
12 hours after birth	26.84 ± 12.07	49.95 ± 16.85	7.529	<0.001

<sup>#</sup>Fisher's exact test.



**Figure 2.** Receiver operating characteristic (ROC) curve of initial lactate levels and the lactate clearance rate at different time points for predicting the risk of mortality in neonates undergoing mechanical ventilation in the plateau group.

12 hours after birth were significantly higher in the group of neonates who died than in those who survived (all  $P < 0.001$ ) The lactate clearance rate at 1, 6, and 12 hours was significantly lower in the group of neonates who died than in those who survived (all  $P < 0.001$ ) (Table 3).

### *Best cut-off points for diagnosis of death by initial lactate levels and the lactate clearance rate at different time points in the plateau group*

When the initial lactate level was 7.7 mmol/L, the area under the curve for predicting the neonatal risk of mortality in the plateau group was 0.80, the sensitivity was 95.5%, and the specificity was 54.8%. The cut-off values for the lactate clearance rate to predict death at 1, 6, and 12 hours after birth were 13.86%, 6.09%, and 2.64%, respectively. The sensitivity (90.9%) and

specificity (85.7%) of the lactate clearance rate at 6 hours were the highest (Figure 2).

## **Discussion**

The current study showed the following findings. Lactate levels in arterial blood of neonates with asphyxia in the plateau group were lower than those of neonates with asphyxia in the non-plateau group during the early postnatal period. However, lactate levels in neonates with severe RDS were higher in the plateau group than in the non-plateau group. We are unable to determine the specific reasons for this finding without analysis of a larger sample size. Irrespective of whether we considered asphyxia or RDS, the lactate clearance rate in the plateau group was significantly lower than that in the non-plateau group. In the plateau group, lactate levels in neonates who died were significantly higher at different time points after birth compared

with those who survived, while the lactate clearance rate was significantly lower. The sensitivity (90.9%) and specificity (85.7%) of lactate clearance at 6 hours after birth were the highest. Additionally, the cut-off point of predicting mortality for the initial lactate level and lactate clearance at 6 hours were 7.7 mmol/L and 6.09%, respectively.

The Naqu area of Tibet is 4580 m above sea level, thus representing the highest elevation studied thus far for mechanical ventilation in newborns. Because the time for mechanical ventilation is only short, synchronized intermittent mandatory ventilation is the main mode used at present. Although the mortality rate in this area has been significantly reduced over time, there are still some newborns, especially those with RDS and asphyxia, in whom treatment fails, resulting in death. These events relate to inexperience in adjusting the parameters of the ventilator and the lack of ventilation guidelines for high altitude areas. Neonates who are born at high altitude have a low partial pressure of oxygen inhalation and may require a longer transition period after birth.

A previous study showed that acute exposure to high altitude led to increased glycolysis and a marked increase in plasma lactate levels in mice.<sup>7,12</sup> However, in rats exposed to high altitude, lactate concentrations in the liver and blood did not increase.<sup>13</sup> In neonates with asphyxia, we found that most delivered naturally in the plateau area and their postnatal Apgar scores were lower than those in the non-plateau group. However, arterial blood lactate levels during the early postnatal period were lower in the plateau group than in the non-plateau group. Considering the degree and duration of hypoxia and genetic differences between the two groups, whether there is an increase in neonatal tolerance to hypoxia and delayed anaerobic metabolism at high altitude, are unclear. Further research is required to confirm this

hypothesis. The lactate clearance rate of neonates with asphyxia in the plateau group was lower than that in the non-plateau group. Because setting of mechanical ventilation parameters in plateau areas continues to use guidelines for non-plateau areas, the hypoxic status of neonates cannot be corrected during a short space of time. In our study, in neonates with severe RDS, the mortality rate of neonates was higher in the plateau area than in the non-plateau area. Some previous studies showed that hyperlactatemia was associated with an increased mortality rate in premature infants with RDS.<sup>14</sup> Additionally, we found that lactate levels at different postnatal time points in neonates with RDS were significantly higher in the plateau area than in the non-plateau area, and the lactate clearance rate was lower in the plateau area. Because of the low application rate of PS and insufficient experience in ventilatory parameter setting, hypoxia cannot be corrected during a short period of time. In this study, because of the small sample size, lactate levels were not used to predict the risk of mortality in neonates with RDS.

Neonates who died in the plateau group had a lower gestational age and birth weight compared with those who survived, although there was no significant difference when analyzed by multivariate logistic regression analysis. Lactate levels and the lactate clearance rate are widely used for predicting the treatment effect for neonatal septic shock, resuscitation, and mortality. Lactate is an effective marker of hypoperfusion, resuscitation, and death.<sup>14-16</sup> Furthermore, the lactate clearance rate is closely related to organ failure and death.<sup>17-21</sup> The lactate clearance rate in the early stages, especially within 6 hours after birth, could reflect the curative effect of neonates and evaluate the prognosis of asphyxiated newborns.<sup>22</sup> In this study, we found that lactate levels were significantly higher in neonates who died than in those



who survived at different time points after birth. Additionally, the lactate clearance rate was significantly lower in neonates who died than in those who survived. Therefore, lactate levels and the lactate clearance rate are important for predicting neonatal mortality for mechanical ventilation in plateau areas. Beyond the first 6 hours after birth, lactate concentrations in umbilical arterial blood of healthy term and preterm infants are often  $<2.5$  mmol/L.<sup>6</sup> The lactate cut-off value for predicting adverse outcomes ranges from 3.2 to 10.0 mmol/L.<sup>23–26</sup> In our study, the cut-off point for predicting death at the initial lactate level was 7.7 mmol/L. Nadeem et al.<sup>27</sup> considered that a lactate level  $>5.6$  mmol/L was an independent risk factor for adverse prognosis in premature infants with a gestational age  $<32$  weeks. The differences in cut-off points between different studies are not only related to differences in analysis and the study population, but also to how prognosis was determined in the study. Jones et al.<sup>28</sup> considered that the effect of resuscitation guided by the 6-hour lactate clearance rate was comparable with that of central venous oxygen saturation. Nguyen et al.<sup>29</sup> further found that the 6-hour lactate clearance rate at 10% as a threshold for assessing mortality during hospitalization had good specificity and sensitivity. The current study showed that a 6-hour lactate clearance rate of 6.09% was the most significant predictor of mortality, with the highest sensitivity and specificity. This finding suggests that the cut-off point of the lactate clearance rate for neonates in a plateau region may be different from that in a non-plateau region. Previous studies have also shown an increase in lactate levels in Tibetans with an EPAS1 haplotype, which suggests that an increase in lactate levels might be related to genotype.<sup>30</sup> All patients in this study were Tibetan, but unfortunately, we did not carry out genotype analysis.

Our study indicates that lactate levels and the lactate clearance rate are important for predicting the mortality of neonates undergoing mechanical ventilation in a plateau area and that the level of clinical treatment for RDS in high altitude areas needs to be improved. Further analysis is required to determine how lactate can be effectively removed and how to perform rational use of mechanical ventilation parameters in high altitude areas.

## Limitations

There are some limitations to this study that should be considered. First, there was a smaller number of cases in the plateau group than in the non-plateau group. Second, using lactate levels and lactate clearance rates alone to predict the death of neonates with asphyxia and RDS is not appropriate. Lack of experience in mechanical ventilation in plateau areas may also lead to delays in correcting hypoxia. Third, different lactate measurement techniques might have caused variation in the results.

## Conclusion

The lactate clearance rate and lactate levels during the early postnatal period of newborns undergoing mechanical ventilation in plateau areas are different from those in non-plateau areas. In terms of the cut-off point for prediction of mortality, the lactate clearance rate at 6 hours in a plateau area is different from that in a non-plateau area. Setting ventilatory parameters and ventilation modes appropriately in plateau areas is critical. Studying larger samples to clarify the specific characteristics of lactate levels and the lactate clearance rate in neonates with hypoxia in plateau areas is also necessary.

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## Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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