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# Value of cardiac enzyme spectrum for the risk assessment of mortality in critically ill children: a single-centre retrospective study

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## ABSTRACT

**Objectives** Identifying high-risk paediatric patients with a poor prognosis and providing timely and adequate treatment are critical. This study aimed to evaluate the effects of different types of cardiac enzyme spectrum within 24 hours of admission on the short-term prognosis of patients in paediatric intensive care units.

**Design** A retrospective study.

**Setting** A single-centre, tertiary care hospital in China, with patient data from 2010 to 2018.

**Participants** A total of 4343 critically ill children were enrolled.

**Intervention** None.

**Primary and secondary outcome measures** The main outcome measure was in-hospital mortality, which was defined as death from any cause during hospitalisation. The secondary outcome was 30-day mortality, intensive care unit (ICU) length of stay (LOS) and total LOS.

**Results** Using the local polynomial regression fitting method, an approximately linear increase in in-hospital mortality was detected for creatine kinase (CK), creatine kinase MB (CK-MB), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH). Among the different types of cardiac enzyme spectrum, LDH had the highest area under the curve value (0.729), followed by AST (0.701), CK-MB (0.613) and CK (0.557). The Kaplan–Meier analysis showed that the patients in the high LDH group had higher 30-day mortality. The multivariate logistic regression revealed that high LDH was independently associated with in-hospital mortality (OR 2.45, 95% CI 1.84 to 3.24). After propensity score matching (PSM) and sensitivity analysis, the results remained consistent.

**Conclusions** LDH is a reliable outcome predictor in critically ill children, including those with various comorbidities.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The sample size of this study was relatively large, and adequate confounding factors were included that might interact with admission temperature.
⇒ The reliability of the results was demonstrated by applying multiple statistical methods.
⇒ It was a single-centre retrospective study.
⇒ Due to database limitations, we had no data on some relatively important variables.

## INTRODUCTION

With the gradual development of medical technology, paediatric intensive care units (PICUs) that treat emergency conditions have been established successively in various regions worldwide. Although the paediatric mortality rate has been reduced to some extent, it is still at a relatively high level, especially in developing countries. This is mainly attributed to the fact that critically ill children have a complex and rapidly changing condition, and the symptoms are often atypical or insidious, which can easily cause a missed diagnosis or a misdiagnosis clinically. The timely identification of critically ill children at high risk of mortality is not only helpful for making scientific treatment decisions but is also important for conserving medical resources.

Although much effort has been invested in studying sensitive biomarkers, identifying these high-risk patients remains challenging. Some critical scoring systems, such as the Paediatric Risk of Mortality (PRISM) III score, have been widely used in PICUs and have been shown to provide an accurate assessment of illness severity and case fatality in critically ill children.[1 2] However, the PRISM III score involves many indicators, cumbersome operations and an unstable prediction accuracy, resulting in limited practical application, especially in some poor countries and regions.

The classic cardiac enzyme spectrum assays mainly include creatine kinase (CK), creatine kinase MB (CK-MB), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH).[3] These cardiac enzymes exist not only in cardiac muscle but also in the

skeletal muscle, brain, kidney and muscle tissues of the whole body. They can reflect the functional impairment of the heart and various organs and can be abnormal in various diseases.[4] Studies have shown that cardiac enzyme spectrum can be used as biomarkers for the prognostic prediction of diseases such as COVID-19,[5–7] peritoneal dialysis,[8] trauma[9] and various cancers.[10 11] Compared with adult patients, children have immature organ development and poor body regulation and compensatory ability. Meanwhile, there is a large amount of interindividual variation in paediatric patients, and paediatric patients are more likely to have cardiac dysfunction and multiple organ dysfunction. Therefore, abnormalities in cardiac enzyme spectrum are common in PICU patients. However, the impact of abnormal cardiac enzyme spectrum on the prognosis of critically ill children is still unclear, and there is a lack of simple and efficient clinical tools for evaluating prognosis. This study aimed to investigate the relationship between early cardiac enzyme spectrum levels and prognosis in PICU patients and to provide clues for the early detection of high-risk children and timely intervention.

## MATERIALS AND METHODS

### Source of patients

The paediatric intensive care (PIC) database, developed by the Children's Hospital, Zhejiang University School of Medicine, is an open data repository dedicated to paediatric critically ill patients.[12] The database contains hospitalisation information for a total of 12 881 different paediatric patients admitted between 2010 and 2018. This project was approved by the Institutional Review Committee of the Children's Hospital, Zhejiang University School of Medicine. Because this study was retrospective, did not affect clinical decision-making and did not contain personal or medical information that could identify an individual, the ethics committee has waived the necessity for obtaining informed consent from parents or guardians. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### Inclusion and exclusion criteria

The inclusion criteria for patients were as follows: (1) intensive care unit (ICU) hospitalisation; (2) if multiple hospitalisations occurred in the ICU, only the information of the first hospitalisation was counted. The exclusion criteria were as follows: (1) patients in the neonatal ICU; (2) patients in the cardiac ICU with congenital heart disease or who required surgical treatment; and (3) lack of cardiac enzyme spectrum data.

### Data extraction, missing value processing and grouping methods

The extracted demographic informatics data included age, sex, ICU type and causes for admission; the analysed laboratory test data were the initial values within 24 hours of ICU admission. The comorbidities were all diagnosed within 48 hours of admission to the ICU, and the definitions of comorbidities are shown in online supplemental table 1. The primary outcome measure was in-hospital mortality, defined as death from any cause that occurred during the hospital stay. The secondary outcomes were 30-day mortality, ICU length of stay (LOS) and total LOS.

The proportions of missing values for all covariates were less than 10%. We provided a detailed description of missing values for relevant variables in online supplemental table 2, including the specific number and proportion of missing values. Depending on the type of variable, the mean or median was used in place of the missing values.

### Statistical analysis

Measurement data conforming to a normal distribution are expressed as the mean±SD, and non-normally distributed measurement data are expressed as the median (IQR). Student's t test or Mann–Whitney U test was used to compare the differences between two groups according to the type of distribution. Enumeration data were expressed as the number of patients (percentage), and $X^2$ test was used to compare differences between the two groups.

The local polynomial regression fitting method was used to detect the approximate relationship between the different types of cardiac enzyme spectrum and in-hospital mortality. Receiver operator characteristic (ROC) curves were drawn to evaluate the predictive value of the different types of cardiac enzyme spectrum on in-hospital mortality. The Youden index (the sum of the sensitivity and specificity minus 1) was calculated, and the value corresponding to the largest Youden index was determined as the cut-off value. The Z test was used to compare differences in the AUC values of different indicators.

The type of cardiac enzyme spectrum (LDH) with the largest AUC value was selected as the index for further in-depth analysis, and the children were grouped according to their cut-off value. Thirty-day survival curves of different cardiac enzyme spectrum levels were established by Kaplan–Meier analysis and compared by log-rank test. The variables with $p<0.05$ in the univariate logistic regression analysis were included in the multivariate logistic regression equation. Covariate adjustment was performed using an extended model approach: model 1, LDH; model 2, model 1+demographic informatics data (age and sex); model 3, model 2+laboratory tests (peripheral blood leukocytes, platelets, serum sodium, potassium, ionised calcium, glucose, arterial pH, lactate, activated partial thromboplastin time and albumin); and model 4, model 3+complications [anaemia, acute kidney injury (AKI), malignancy, diabetic ketoacidosis (DKA), liver dysfunction, pneumonia and central nervous system (CNS) infection]. The variables of laboratory tests were transformed into dichotomous variables (ie, normal laboratory tests and abnormal laboratory tests) according to the normal reference range. The relative importance of each covariate in the multivariate logistic regression

model was evaluated by subtracting the degree of freedom of the covariate from the Wald $X^2$ value.[13–15] The larger the difference, the more important the covariate in the logistic regression model. Considering that the type of complications may affect the relationship between cardiac enzyme spectrum and the prognosis of patients and that the cardiac enzyme spectrum values may be affected by the patient's age, the above factors were specified in advance for the subgroup analysis. To verify the interaction between cardiac enzyme spectrum and these factors, a multiplicative interaction term was included in the regression model.

Propensity score matching (PSM) analysis was used to minimise the influence of the confounding factors that could bias the results. Propensity scores were assigned according to the probability of different LDH groups in children and estimated using a multivariate logistic regression model. The nearest neighbour matching algorithm for 1:1 matching was applied for matching, and the calliper value was set to 0.05.

p<0.05 was considered statistically significant. Statistical analysis was performed with STATA V.16, SPSS V.24 and MedCalc V.18.2.1.

### Patient and public involvement

There were no patients involved in the current study. Additionally, participants and members of the public were not involved in the design, conduct, reporting or dissemination plans of the current research.

## RESULTS

### General information of the selected children

The process of screening research subjects is shown in online supplemental figure 1. Table 1 lists the baseline characteristics of the patients. A total of 4343 critically ill children were included, comprising 2540 males (58.5%) with a median age of 22 months. There were 973 patients (22.4%) in the general ICU, 1262 patients (29.1%) in the PICU and 2108 patients (48.5%) in the surgical ICU. Of the patient complications, 2938 cases (67.6%) of anaemia, 459 cases (10.6%) of AKI, 750 cases (17.3%) of liver dysfunction, 250 cases (5.8%) of malignancy, 171 cases (3.9%) of DKA, 456 cases (10.5%) of pneumonia and 206 cases (4.7%) of CNS infections were reported. The median ICU LOS was 1.9 days, and the median total LOS was 10 days. There were 297 patients (6.8%) who had in-hospital deaths and 326 patients (7.5%) who were grouped in the 30-day mortality.

Compared with the survivor group, the nonsurvivor group had higher CK (174 vs 141, p=0.001), CK-MB (40 vs 27, p<0.001), AST (82 vs 37, p<0.001) and LDH (567 vs 326, p<0.001) values.

### The approximate relationship between different types of cardiac enzyme spectrum and in-hospital mortality

The local polynomial regression fitting method was used to detect the approximate relationship between the different types of cardiac enzyme spectrum and in-hospital mortality. As shown in figure 1, CK, CK-MB, AST and LDH all showed an approximately linear increasing relationship with in-hospital mortality.

### Predictive value of different types of cardiac enzyme spectrum on in-hospital mortality

The ROC analysis results are shown in figure 2 and online supplemental table 3. CK, CK-MB, AST and LDH all have certain predictive values for in-hospital death in critically ill children (p<0.05), with AUC values of 0.557, 0.613, 0.701 and 0.729, respectively. Among all the types of cardiac enzyme spectrum, LDH had the highest predictive value for in-hospital mortality, and it had a higher predictive value than AST (Z=2.581, p=0.001).

### Comparison of the clinical data of children in different LDH groups

The LDH with the largest AUC value was selected as the index for further analysis. The children were divided into a low LDH group (≤408) and a high LDH group (>408) according to the cut-off value of LDH. The clinical data of the children in the high LDH group were compared with those in the low LDH group. As shown in online supplemental table 4, age, white blood cell count, serum potassium, lactate and the proportions of patients with AKI, liver dysfunction, DKA and pneumonia in the high LDH group were higher than those in the low LDH group. Platelet count, albumin, ionised calcium, pH and the proportion of patients with CNS infections were lower than those in the low LDH group.

In terms of the clinical outcome indicators, the high LDH group had a higher ICU LOS (3.4 vs 1.4, p<0.001) and total LOS (10.8 vs 10.0, p<0.001) than the low LDH group. Meanwhile, the 30-day mortality rate of the high LDH group was 4.3 times higher than that of the low LDH group (13.7% vs 3.2%, p<0.001), and the in-hospital mortality rate was 4.1 times higher than that of the low LDH group (14.9% vs 3.6%, p<0.001).

### Survival analysis in different LDH groups

The Kaplan–Meier curves of the relationship between the different LDH levels and 30-day mortality of critically ill children are shown in online supplemental figure 2. At different time periods, compared with the children in the low LDH group, the survival rate of children in the high LDH group was decreased (p<0.001).

### Further relationship between LDH and in-hospital mortality and 30-day mortality

As shown in table 2, in step-by-step expanded multivariate logistic regression models that used low LDH as reference, high LDH was significantly associated with increased in-hospital mortality. The ORs of all the covariates in model 4 are shown in online supplemental table 5. Similar results were obtained for the association of LDH with 30-day mortality. When LDH was included as a continuous variable in the multivariate logistic regression model in model 4, each one SD increase in LDH

Table 1 Comparison of clinical data between the survival and death groups

| Variable | All (n=4343) | Survival group (n=4017) | Death group (n=326) | P |
|---|---|---|---|---|
| Age, months | 22 (6–69) | 23 (6–70) | 16 (5–48) | 0.002 |
| Male, n (%) | 2540 (58.5) | 2333 (58.1) | 207 (63.5) | 0.056 |
| ICU type, n (%) | | | | <0.001 |
| General ICU | 973 (22.4) | 825 (20.5) | 148 (45.4) | |
| Paediatric ICU | 1262 (29.1) | 1126 (28.0) | 136 (41.7) | |
| Surgical ICU | 2108 (48.5) | 2066 (51.4) | 42 (12.9) | |
| Cause for admission, n(%) | | | | <0.001 |
| Respiratory system | 750 (17.3) | 650 (16.2) | 100 (30.7) | |
| Circulatory system | 235 (5.4) | 187 (4.7) | 48 (14.7) | |
| Digestive system | 920 (21.2) | 898 (22.4) | 22 (6.7) | |
| Nervous system | 1339 (30.8) | 1270 (31.6) | 69 (21.2) | |
| Urogenital system | 189 (4.4) | 186 (4.6) | 3 (0.9) | |
| Hematologic system | 333 (7.7) | 276 (6.9) | 57 (17.5) | |
| Other | 577 (13.3) | 550 (13.7) | 27 (8.3) | |
| Vital signs | | | | |
| Body temperature, ℃ | 36.9 (36.4–37.4) | 36.9 (36.5–37.4) | 36.9 (36.0–37.6) | 0.464 |
| Heart rate, beats/min | 126 (108–144) | 126 (108–144) | 139 (113–158) | 0.001 |
| Respiratory rate, breaths/min | 28 (24–32) | 28 (24–32) | 35 (28–48) | <0.001 |
| Systolic pressure, mmHg | 106 (96–117) | 106 (96–118) | 92 (83–113) | <0.001 |
| Diastolic pressure, mmHg | 63 (54–72) | 63 (54–72) | 56 (45–67) | <0.001 |
| Laboratory data | | | | |
| White blood cell, $10^9$ /L | 9.63 (6.46–14.17) | 9.63 (6.46–13.98) | 10.14 (6.73–16.59) | 0.022 |
| Platelet, $10^9$ /L | 297 (206–384) | 297 (213–386) | 253 (109–359) | <0.001 |
| Sodium, mmol/L | 137 (134–139) | 137 (134–139) | 137 (133–141) | 0.081 |
| Potassium, mmol/L | 3.8 (3.4–4.1) | 3.8 (3.4–4.1) | 3.9 (3.4–4.5) | <0.001 |
| Glucose, mmol/L | 6.7 (5.6–8.7) | 6.7 (5.7–8.6) | 6.7 (5.2–10.9) | 0.662 |
| Albumin, g/L | 36.8 (32.6–40.8) | 36.8 (32.9–40.8) | 35.5 (29.6–40.2) | <0.001 |
| APTT, s | 33.9 (28.8–43.2) | 33.9 (28.8–42.9) | 33.9 (30.1–46.5) | 0.079 |
| Ionised calcium, mmol/L | 1.21 (1.12–1.28) | 1.21 (1.13–1.28) | 1.12 (1.03–1.21) | <0.001 |
| PH | 7.375 (7.317–7.428) | 7.377 (7.321–7.430) | 7.336 (7.195–7.398) | <0.001 |
| Lactate, mmol/L | 1.7 (1.2–2.7) | 1.7 (1.2–2.5) | 3.2 (1.7–7.2) | <0.001 |
| Comorbidities, n (%) | | | | |
| Anaemia | 2938 (67.6) | 2711 (67.5) | 227 (69.6) | 0.426 |
| Acute kidney injury | 459 (10.6) | 377 (9.4) | 82 (25.2) | <0.001 |
| Liver dysfunction | 750 (17.3) | 624 (15.5) | 126 (38.7) | <0.001 |
| Malignancy | 250 (5.8) | 224 (5.6) | 26 (8.0) | 0.074 |
| Diabetic ketoacidosis | 171 (3.9) | 140 (3.5) | 31 (9.5) | <0.001 |
| Pneumonia | 456 (10.5) | 390 (9.7) | 66 (20.2) | <0.001 |
| CNS infection | 206 (4.7) | 183 (4.6) | 23 (7.1) | 0.041 |
| Cardiac enzymes, U/L | | | | |
| Creatine kinase | 143 (73–346) | 141 (73–332) | 174 (75–668) | 0.001 |
| Creatine kinase isoenzyme | 28 (19–43) | 27 (19–42) | 40 (21–91) | <0.001 |
| Aspartate aminotransferase | 39 (27–68) | 37 (26–63) | 82 (40–261) | <0.001 |
| Lactate dehydrogenase | 334 (256–497) | 326 (252–468) | 567 (356–1077) | <0.001 |

APTT, activated partial thromboplastin time; CNS, central nervous system; ICU, intensive care unit.

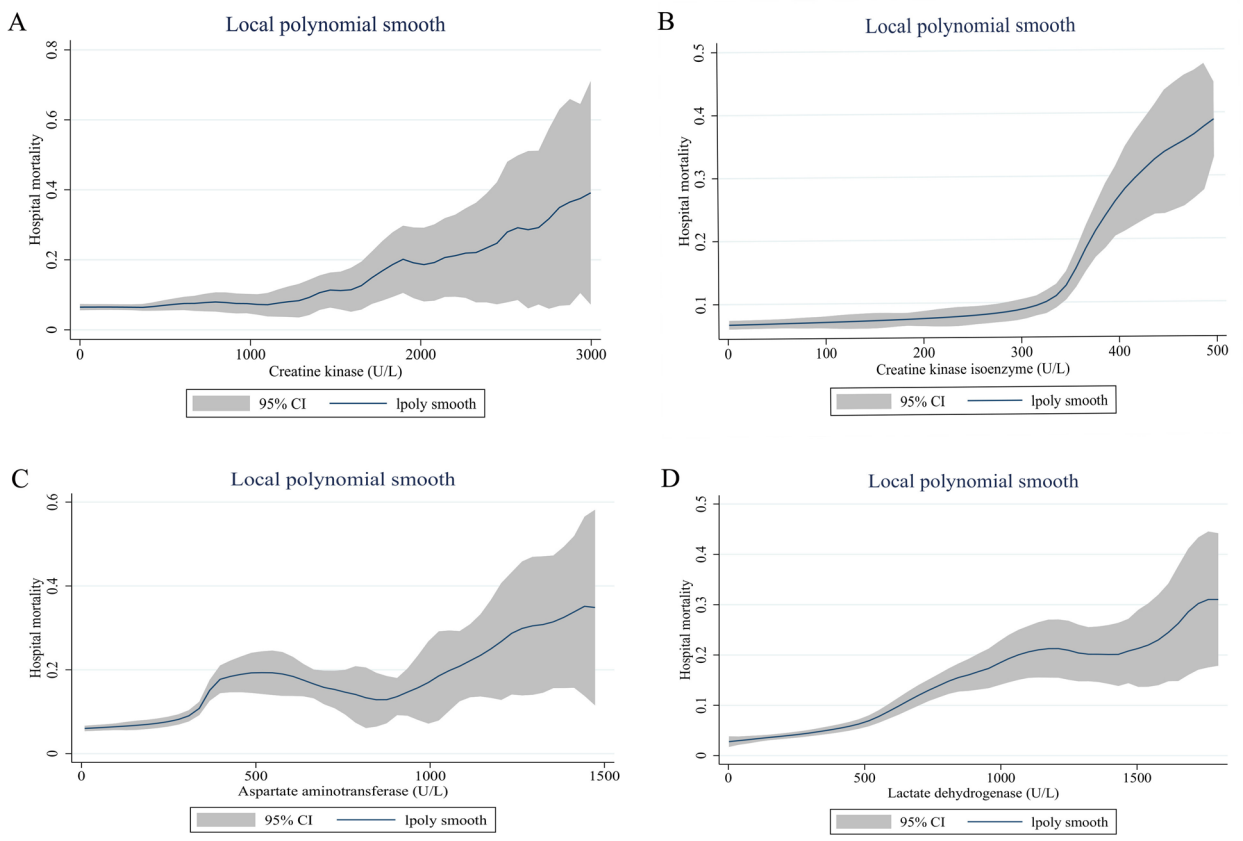


**Figure 1** Relationship between cardiac enzyme spectrum and in-hospital mortality in critically ill children using the local polynomial regression fitting method. (A) creatine kinase; (B) creatine kinase MB; (C) aspartate aminotransferase; (D) lactate dehydrogenase.

was associated with an 11.0% increase in the in-hospital mortality (p=0.005) and a 12.0% increase in the 30-day mortality (p=0.004). When ICU LOS or hospital LOS was used as the outcome variable, higher LDH was an independent risk factor only when ICU LOS was the outcome variable (online supplemental table 6).

The statistical results of the Wald $X^2$ value minus the DF are shown in online supplemental figure 3 and table 7. The results showed that LDH was the second most important covariate in predicting in-hospital death after lactate (value 37.7), followed by pneumonia and AKI.

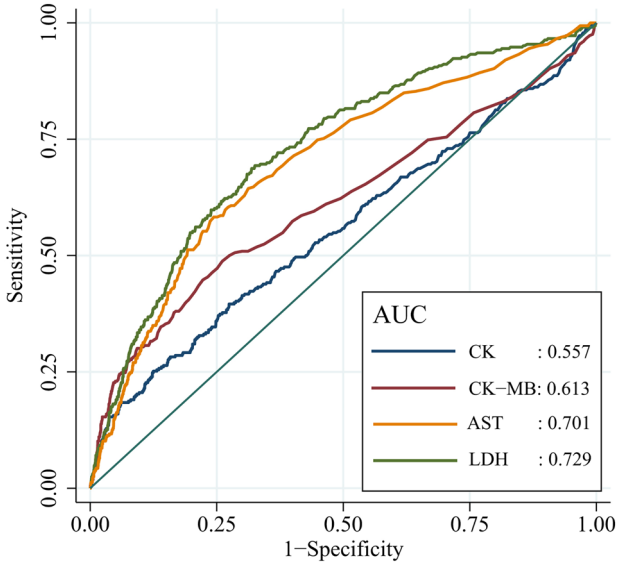


**Figure 2** The predictive value of different types of cardiac enzyme spectrum on in-hospital mortality. AST, aspartate aminotransferase; AUC, area under the curve; CK, creatine kinase; CK-MB, creatine kinase MB; LDH, lactate dehydrogenase.

## Subgroup analysis

A multiplicative interaction term was introduced into the regression model to verify the interaction between LDH and age or complications. However, there was no interaction between LDH and age or complications (*P*-interaction >0.05). This showed that the results of logistic regression were stable.

## PSM results

Based on the baseline data sheet, the variables with statistically significant differences between the high and low LDH groups were selected to generate propensity scores. The overall quality of the matched sample was assessed by examining the propensity scores between the groups (online supplemental figure 4). As shown in table 3, 1015 patients were matched in each group, and all covariates were balanced between the two groups. The difference in the total LOS between the two groups was not

Table 2 Stepwise expansion of the multivariate logistic regression model (lactate dehydrogenase as a dichotomous variable or continuous variable)

| | High lactate dehydrogenase (>408 U/L) | | |
|---|---|---|---|
| | OR | 95% CI | P |
| In-hospital mortality | | | |
| Model 1 | 4.69 | 3.67 to 5.98 | <0.001 |
| Model 2 | 4.64 | 3.63 to 5.94 | <0.001 |
| Model 3 | 2.85 | 2.19 to 3.72 | <0.001 |
| Model 4 | 2.45 | 1.84 to 3.24 | <0.001 |
| 30-day mortality | | | |
| Model 1 | 4.78 | 3.70 to 6.17 | <0.001 |
| Model 2 | 4.75 | 3.67 to 6.16 | <0.001 |
| Model 3 | 2.93 | 2.22 to 3.87 | <0.001 |
| Model 4 | 2.51 | 1.87 to 3.37 | <0.001 |
| | **Lactate dehydrogenase (per SD increase)** | | |
| | OR | 95% CI | P |
| In-hospital mortality | | | |
| Model 1 | 1.32 | 1.22 to 1.43 | <0.001 |
| Model 2 | 1.32 | 1.22 to 1.43 | <0.001 |
| Model 3 | 1.17 | 1.09 to 1.25 | <0.001 |
| Model 4 | 1.11 | 1.03 to 1.20 | 0.005 |
| 30-day mortality | | | |
| Model 1 | 1.32 | 1.22 to 1.42 | <0.001 |
| Model 2 | 1.31 | 1.22 to 1.42 | <0.001 |
| Model 3 | 1.17 | 1.09 to 1.26 | <0.001 |
| Model 4 | 1.12 | 1.04 to 1.21 | 0.004 |

statistically significant. ICU LOS (3.3 vs 2.4, p<0.001), 30-day mortality (9.3% vs 5.6%, p=0.002) and in-hospital mortality (10.1% vs 6.2%, p=0.001) were significantly higher in the high LDH group than in the low LDH group.

To test the reliability of the results after PSM, we included all covariates in the sensitivity analysis. After the sensitivity analysis, each covariate was balanced between the two groups, and the results remained stable (online supplemental table 8 and figure 5).

### Sensitivity analysis

To verify the stability of our results, we conducted sensitivity analyses using three different methods. These methods included performing multivariate logistic regression analysis after excluding surgical ICU patients, conducting multivariate logistic regression analysis with multiple comorbidities as a separate covariate and incorporating a time variable for multivariate Cox regression analysis. Across all these sensitivity analyses, LDH remained an independent risk factor for in-hospital mortality (online supplemental tables 9–11).

## DISCUSSION

The main purpose of this study was to evaluate the prognostic value of early cardiac enzyme spectrum levels in critically ill children. Our results showed that CK, CK-MB, AST and LDH all showed an approximately linear increasing relationship with in-hospital mortality. Among the different types of cardiac enzyme spectrum, the AUC value of LDH was the highest, followed by AST, CK-MB and CK. The Kaplan–Meier analysis showed that the high LDH group had a higher 30-day mortality rate. The multivariate logistic regression revealed that LDH was an independent risk factor for in-hospital mortality. LDH is suggested to be a promising biomarker for predicting the prognosis of patients in the PICU.

The results of our study showed that the activities of CK, CK-MB, AST and LDH in the nonsurvival group were higher than those in the survival group. In critically ill children, tissue ischaemia and hypoxia are caused by various pathogenic factors, and cell energy metabolism is transformed from aerobic oxidation to anaerobic glycolysis. There is an insufficiency of cell energy supply in this condition, with impaired cell membrane function and hyperpermeability, causing the release of cardiac enzyme spectrum into the blood. Meanwhile, the rupture of mitochondria and lysosome membranes causes a large number of hydrolytic enzymes to enter the cytoplasm, further aggravating the cell membrane damage. In addition, pathogenic microorganisms and toxins can directly damage the cell membrane and aggravate the entry of cardiac enzyme spectrum into the blood.

CK mainly exists in the cytoplasm of skeletal muscle, myocardium and smooth muscle cells and is directly related to intracellular energy transport, muscle contraction and ATP regeneration.[16 17] It is an important tool for the evaluation of neuromuscular diseases in children. In addition to disease factors, CK significantly increases after some nondisease factors, such as strenuous exercise, an intramuscular injection, major surgery, electromyography or muscle biopsy. CK isozymes exist in three different forms in the cytoplasm: CK-MM (muscle type), CK-BB (brain type) and CK-MB (heart type).[18] CK-MB is mainly distributed in the myocardium and is a specific and sensitive index of myocardial injury. The serum CK-MB activity increases sharply 2–12 hours after myocardial injury. AST is a pyridoxal-5-phosphate-dependent enzyme widely distributed in the heart, liver, skeletal muscle, kidney and brain, with the highest concentration in cardiomyocytes. It plays a key role in amino acid metabolism, purine/pyrimidine base synthesis, urea and protein synthesis and gluconeogenesis.[19] In a single-centre study involving 331 COVID-19 patients, the researchers found that critically ill patients had high CK levels at admission and that high CK (>200 U/L) was an independent prognostic factor [OR 2.70, 95% CI 1.24 to 5.86, p=0.010].[20] In a case–control study of 180 children with sepsis, the prognosis of patients was associated with CK-MB and cardiac troponin I using Cox proportional hazard regression analysis, and the AUC of CK-MB predicting 30-day death was 0.778.[21]

Table 3 Comparison of clinical data between high lactate dehydrogenase (LDH) group and low LDH group after propensity score matching

| Variable | All (n=2030) | Low LDH (n=1015) | High LDH (n=1015) | P |
|---|---|---|---|---|
| Age, months | 17 (4–50) | 17 (5–49) | 16 (4–50) | 0.628 |
| Laboratory data | | | | |
| White blood cell, $10^9$ /L | 9.63 (6.32–14.20) | 9.63 (6.43–14.25) | 9.63 (6.14–14.13) | 0.726 |
| Platelet, $10^9$ /L | 296 (182–390) | 297 (198–379) | 294 (164–404) | 0.832 |
| Potassium, mmol/L | 3.8 (3.4–4.2) | 3.8 (3.4–4.2) | 3.8 (3.4–4.2) | 0.347 |
| Albumin, g/L | 36.0 (31.8–40.0) | 36.1 (31.5–40.1) | 35.9 (32.2–40.0) | 0.789 |
| Ionised calcium, mmol/L | 1.19 (1.10–1.27) | 1.19 (1.10–1.27) | 1.19 (1.10–1.28) | 0.668 |
| PH | 7.375 (7.316–7.429) | 7.375 (7.324–7.428) | 7.373 (7.309–7.429) | 0.147 |
| Lactate, mmol/L | 1.7 (1.2–2.6) | 1.7 (1.2–2.7) | 1.7 (1.2–2.6) | 0.838 |
| Comorbidities, n (%) | | | | |
| Acute kidney injury | 227 (11.2) | 108 (10.6) | 119 (11.7) | 0.439 |
| Liver dysfunction | 334 (16.5) | 171 (16.8) | 163 (16.1) | 0.632 |
| Diabetic ketoacidosis | 91 (4.5) | 48 (4.7) | 43 (4.2) | 0.592 |
| Pneumonia | 296 (14.6) | 152 (15.0) | 144 (14.2) | 0.615 |
| CNS infection | 83 (4.1) | 44 (4.3) | 39 (3.8) | 0.575 |
| Clinical outcome | | | | |
| ICU LOS, days | 2.9 (1.0–8.1) | 2.4 (0.9–7.2) | 3.3 (1.0–9.4) | <0.001 |
| Hospital LOS, day | 11.0 (5.6–18.5) | 10.9 (5.9–17.5) | 11.0 (5.0–19.1) | 0.947 |
| 30-day mortality, n (%) | 151 (7.4) | 57 (5.6) | 94 (9.3) | 0.002 |
| Hospital mortality, n (%) | 166 (8.2) | 63 (6.2) | 103 (10.1) | 0.001 |

CNS, central nervous system; ICU, intensive care unit; LOS, length of stay.

In addition, studies have shown that high AST (>99 IU/L) is independently associated with hospital death in PICU patients (OR 4.80, 95% CI 1.78 to 13.86, p=0.001).[22]

However, in our study, although CK, CK-MB and AST were higher in the death group, their prognostic accuracy was significantly lower than that of LDH, and these three were not the best prognostic indicators. It is worth noting that in some studies, CK, CK-MB and AST were not significantly associated with the prognosis of critically ill patients.[23–25] Chen *et al* analysed indicators affecting disease severity and prognosis in a multicentre retrospective study of 482 patients with COVID-2019.[26] In the univariate analysis, AST, CK and LDH were different between the survival group and nonsurvival group. However, after adjusting for many covariates, AST (OR 0.980, 95% CI 0.952 to 1.009, p=0.171) and CK (OR 1.000, 95% CI 0.996 to 1.003, p=0.953) were not significantly associated with in-hospital death, only LDH (OR 1.011, 95% CI 1.005 to 1.017, p=0.001) was an independent risk factor for hospital death.

LDH is a tetramer composed of two different subunits and exists widely in human tissues, such as the heart, liver and kidney. LDH includes five isozymes, among which LDH1 and LDH2 mainly exist in the myocardium, accounting for more than 50% of the total myocardial LDH activity.[27] As a glycolytic enzyme, LDH can assist in the conversion of pyruvate to lactic acid and can promote lactic acid accumulation in the cell metabolism process. When cells undergo lysis or the cell membrane is damaged, cytoplasmic enzymes such as LDH and glutathione reductase are released into the extracellular space. Therefore, an elevation in LDH levels indicates the extent of cell and tissue damage. LDH was reported as a predictive marker in many conditions and diseases such as sepsis, infection, hypoxia, dehydration, injury, malignancies and after ingesting certain drugs and chemical poisonings.[28 29] It is well known that these adverse factors are prevalent among PICU patients. The cumulative effect of these unfavourable factors increases the risk of cytolysis and cell membrane disruption, which further promotes the release of LDH into the extracellular space. Therefore, serum LDH levels may be correlated with the severity of illness in critically ill patients.

The strong correlation between LDH and the prognosis of critically ill patients has been confirmed in adult ICUs. Lu *et al* found that there was a positive correlation between serum LDH levels and lactic acid in patients with sepsis (r=0.560, p<0.001).[30] The AUC for predicting 28-day mortality was 0.783, and LDH was an independent risk factor for 28-day mortality (HR 1.005, 95% CI 1.002 to 1.007, p=0.001). In a study involving 1981 emergency critical care patients, researchers found that elevated LDH levels were significantly associated with higher mortality rates (ICU mortality: Q2 vs Q1: 1.046

[0.622–1.758]; Q3 vs Q1: 1.667 [1.029–2.699]; and Q4 vs Q1: 1.760 [1.092–2.839]).[31] Similar results persisted in patients with different acute physiology and chronic health evaluation IV scores and with or without sepsis. Chen *et al* found that higher levels of CK and LDH were associated with early death in COVID-19 patients, but after univariate and multivariate logistic regression analysis, only LDH (as a continuous variable) was identified as an independent predictor of early death (OR 1.002, 95% CI 1.000 to 1.004).[32]

Although numerous studies have confirmed the prognostic value of LDH in predicting the outcomes of critically ill patients in adult ICUs, the relationship between LDH and critically ill children has been less studied. Lin *et al* developed a nomogram model for predicting hospital mortality in children with pneumonia-associated bacteraemia.[33] The prediction model included three indexes: the first positive time of blood culture, serum albumin and LDH. The AUC of the nomogram model was 0.84 (95% CI 0.77 to 0.91) in the training group and 0.82 (95% CI 0.71 to 0.93) in the verification group, and its clinical practicability was better than that of PRISM III. Mehta *et al* recruited 131 bronchiolitis children from paediatric emergency rooms and PICUs in Texas.[34] Children admitted to the PICU had significantly higher nasal wash LDH levels compared with those sent home from the emergency room or admitted to regular wards (p=0.020). An increase of one unit in nasal wash LDH (log10, mU/L) was associated with an increased likelihood of ICU admission (OR 6.10, 95% CI: 1.28 to 28.99). In our study, LDH demonstrated the highest AUC value in predicting in-hospital mortality. Even after applying multivariable logistic regression, PSM analysis and sensitivity analysis, hyperlactatemia remained a risk factor for in-hospital death. This finding aligns with the results of other studies involving critically ill patients. Compared with other research, our study boasts a larger sample size and more thoroughly controlled confounding factors, making our conclusions more reliable.

Our subgroup analysis revealed that the association between LDH and in-hospital mortality remained consistent across all comorbidity subgroups, with *P* values for interaction of greater than 0.05. This result suggests that the predictive value of elevated LDH for poor prognosis in PICU patients is not limited to specific comorbidities but rather reflects the overall severity of illness. Although we observed a higher incidence of certain comorbidities (such as AKI, liver dysfunction, DKA and pneumonia) in the high LDH group, the role of LDH as an independent prognostic marker was evident across all subgroups. This underscores the importance of LDH in assessing the overall risk of mortality in PICU patients, regardless of their specific clinical presentations.

To our knowledge, this is the largest study to date to explore the relationship between serum cardiac enzyme spectrum and mortality in critically ill children. However, there are some limitations in this study. First, due to the limitations of public databases, we could not accurately obtain certain data, including pupillary reflex, mental status, eye open response, verbal response and motor response; thus, the PRISM III, Paediatric Logistic Organ Dysfunction-2 and other critical scores could not be derived. In this study, we listed some laboratory indicators, such as lactate, white blood cells, platelet and calcium, while some comorbidities, such as AKI and liver dysfunction, also reflect the severity of the disease to some extent. Second, this is a retrospective study, and the impact of troponin, cardiac pyruvate dehydrogenase and cardiac collagen content on the prognosis cannot be assessed in a large sample due to the low testing rate and high percentage of missing values. A prospective study is planned that will evaluate the effect of these indicators on mortality in critically ill children. Third, as a retrospective study, the limitation of this study lies in its reliance on historical data, which may suffer from incomplete information or inaccurate recording. Additionally, retrospective studies may be affected by selection bias.

## CONCLUSIONS

This study showed that LDH is a promising independent prognostic marker in PICU patients and that elevated LDH is significantly associated with poor prognosis. This association remained stable across different comorbidity subgroups, emphasising the value of LDH as a robust tool for assessing the overall risk of mortality in PICU patients. Although further research is needed to determine the exact mechanism of the association between LDH and mortality, this study provides a rationale for considering risk stratification of critically ill children based on LDH levels.

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**Contributors** HW, XC, CS, JW and LG conceived and designed the study; HW extracted the data; HW, CC and JH analysed the data; HW, XC and CS drafted the manuscript; XR and LG critically reviewed and revised the manuscript; LG is responsible for the overall content as the guarantor. All authors approved for submission.

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**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the Institutional Review Committee of the Children's Hospital of Zhejiang University School of Medicine (ethics reference number: 2019-IRB-052). Because this study was retrospective, did not affect clinical decision-making and did not contain personal or medical information that could identify an individual, the ethics committee has waived the necessity for obtaining informed consent from parents or guardians.

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**Data availability statement** Data are available upon reasonable request. The full data set used in this study is available from the first author at wanghb53@mail2.sysu.edu.cn. However, reanalysis of the full data for other use requires approval by the PIC Institute.



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**Supplementary Table 1** Diagnostic criteria for complications

| Complications | Diagnostic criteria |
|---|---|
| Acute kidney injury | We used the pROCK criterion, which defines acute kidney injury as an increase in creatinine levels of ≥ 20 μmol/L and ≥ 30% within 7 days. The pROCK classified AKI stages 2 and 3 as SCr increases of ≥ 40 μmol/L and ≥ 60% and ≥ 80 μmol/L and ≥ 120%, respectively. |
| Anemia | 1-4 months < 90 g/L; 4-6 months < 100 g/L; 6-60minths < 110 g/L; 60-144months < 115 g/L; >144 months < 120 g/L. |
| Pneumonia | Including pneumonia caused by various pathogens. |
| Central nervous system infection | Including central nervous system infection caused by various pathogens. |
| Diabetic ketoacidosis | Blood glucose > 11 mmol/L; venous blood pH < 7.3 or serum bicarbonate < 15 mmol / L; presence of ketone bodies in blood or urine. |
| Liver dysfunction | Total bilirubin > 68.4mmol/L or alanine aminotransferase elevation more than two times the upper value. |
| Malignancy | Including solid malignancies and non-solid malignancies. |

**Supplementary Table 2** Number and proportion of missing values

| Variable | Number of missing values (n) | Ratio of missing values (%) |
|---|---|---|
| **Age** | 0 | 0 |
| **Sex** | 0 | 0 |
| **ICU type** | 0 | 0 |
| **Cause for admission n(%)** | 0 | 0 |
| **Laboratory data** | | |
| White blood cell | 90 | 2.1 |
| Platelet | 89 | 2.0 |
| Sodium | 24 | 0.6 |
| Potassium | 24 | 0.6 |
| Glucose | 114 | 2.6 |
| Albumin | 6 | 0.1 |
| APTT | 418 | 9.6 |
| Ionized calcium | 24 | 0.6 |
| PH | 24 | 0.6 |
| Lactate | 27 | 0.6 |
| **Comorbidities** | | |
| Anemia | 0 | 0 |
| Acute kidney injury | 0 | 0 |
| Liver dysfunction | 0 | 0 |
| Malignancy | 0 | 0 |
| Diabetic ketoacidosis | 0 | 0 |
| Pneumonia | 0 | 0 |
| CNS infection | 0 | 0 |

**Supplementary Table 3** Area under the curve (AUC) values for the prediction of in-hospital mortality by different cardiac enzyme spectrum

| Variables | AUC | P | 95% CI | Cut-off values | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| CK | 0.557 | 0.002 | 0.542-0.572 | 667 | 25.2 | 87.5 |
| CK-MB | 0.613 | <0.001 | 0.598-0.627 | 40 | 48.8 | 73.9 |
| AST | 0.701 | <0.001 | 0.687-0.715 | 63 | 58.3 | 75.6 |
| LDH | 0.729 | <0.001 | 0.715-0.742 | 408 | 68.7 | 68.1 |

AST, aspartate aminotransferase; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase MB; LDH, lactate dehydrogenase.

**Supplementary Table 4** Comparison of clinical data between high lactate dehydrogenase (LDH) group and low LDH group

| Variable | All (n=4343) | Low LDH (n=2837) | High LDH (n=1506) | *P* |
|---|---|---|---|---|
| **Age, months** | 22 (6-69) | 28 (8-79) | 14 (4-44) | 0.002 |
| **Male, n (%)** | 2540 (58.5) | 1638 (57.7) | 902 (59.9) | 0.056 |
| **Laboratory data** | | | | |
| White blood cell, $10^9$/L | 9.63 (6.46-14.17) | 9.47 (6.52-13.56) | 10.19 (6.36-15.12) | 0.022 |
| Platelet, $10^9$/L | 297 (206-384) | 305 (235-386) | 269 (133-380) | <0.001 |
| Sodium, mmol/L | 137 (134-139) | 137 (135-139) | 137 (133-140) | 0.081 |
| Potassium, mmol/L | 3.8 (3.4-4.1) | 3.7 (3.4-4.1) | 3.8 (3.4-4.3) | <0.001 |
| Glucose, mmol/L | 6.7 (5.6-8.7) | 6.7 (5.7-8.4) | 6.7 (5.5-9.3) | 0.662 |
| Albumin, g/L | 36.8 (32.6-40.8) | 37.6 (33.6-41.4) | 35.0 (30.8-39.2) | <0.001 |
| APTT, s | 33.9 (28.8-43.2) | 33.9 (28.9-43.2) | 33.9 (28.7-43.1) | 0.079 |
| Ionized calcium, mmol/L | 1.21 (1.12-1.28) | 1.23 (1.15-1.29) | 1.17 (1.06-1.25) | <0.001 |
| PH | 7.375 (7.317- | 7.381 (7.331- | 7.362 (7.284- | <0.001 |
| Lactate, mmol/L | 1.7 (1.2-2.7) | 1.6 (1.2-2.4) | 2.0 (1.3-3.6) | <0.001 |
| **Comorbidities, n (%)** | | | | |
| Anemia | 2938 (67.6) | 1893 (66.7) | 1045 (69.4) | 0.426 |
| Acute kidney injury | 459 (10.6) | 231 (8.1) | 228 (15.1) | <0.001 |
| Liver dysfunction | 750 (17.3) | 173 (6.1) | 577 (38.3) | <0.001 |
| Malignancy | 250 (5.8) | 128 (4.5) | 122 (8.1) | 0.074 |
| Diabetic ketoacidosis | 171 (3.9) | 76 (2.7) | 95 (6.3) | <0.001 |
| Pneumonia | 456 (10.5) | 256 (9.0) | 200 (13.3) | <0.001 |
| CNS infection | 206 (4.7) | 148 (5.2) | 58 (3.9) | 0.041 |
| **Clinical outcome** | | | | |
| ICU LOS, days | 1.9 (0.9-6.7) | 1.4 (0.9-5.2) | 3.4 (1.0-9.7) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Hospital LOS, day | 10.0 (5.4-17.1) | 10.0 (5.9-16.5) | 10.8 (4.4-19.1) | <0.001 |
| 30-day mortality, n (%) | 297 (6.8) | 91 (3.2) | 206 (13.7) | <0.001 |
| Hospital mortality, n (%) | 326 (7.5) | 102 (3.6) | 224 (14.9) | <0.001 |

APTT, activated partial thromboplastin time; CNS, central nervous system; ICU, intensive care unit; LOS, length of stay.

**Supplementary Table 5** Univariate and multivariable logistic regression results for in-hospital mortality of model 4

| | Crude OR | 95% CI | *P* | Adjusted OR | 95% CI | *P* |
|---|---|---|---|---|---|---|
| Age | 0.997 | 0.994-0.999 | 0.013 | 0.998 | 0.995-1.001 | 0.123 |
| Gender (female) | 0.80 | 0.63-1.01 | 0.057 | | | |
| WBC (< 4 or > 12, $10^9$/L) | 1.91 | 1.52-2.40 | <0.001 | 1.32 | 1.03-1.70 | 0.028 |
| Platelet (< 100, $10^9$/L) | 2.53 | 1.91-3.34 | <0.001 | 1.53 | 1.12-2.09 | 0.008 |
| Sodium (< 135 or > 145, mmol/L) | 1.62 | 1.28-2.03 | <0.001 | 1.07 | 0.83-1.38 | 0.625 |
| Potassium (< 3.5 or > 5.5, mmol/L) | 1.26 | 0.99-1.60 | 0.059 | | | |
| Glucose (< 3.6 or > 6.1, mmol/L) | 1.03 | 0.81-1.31 | 0.799 | | | |
| Ionized calcium (< 1.2 or > 1.3, mmol/L) | 2.69 | 2.04-3.55 | <0.001 | 1.77 | 1.32-2.38 | <0.001 |
| PH (< 7.30 or > 7.50) | 2.60 | 2.07-3.28 | <0.001 | 1.50 | 1.16-1.95 | 0.002 |
| Lactate (≥ 2.0, mmol/L ) | 3.65 | 2.87-4.64 | <0.001 | 2.57 | 1.98-3.34 | <0.001 |
| APTT (< 23 or > 48, s) | 1.15 | 0.90-1.48 | 0.266 | | | |
| Albumin (< 32 or > 52, g/L) | 2.10 | 1.65-2.66 | <0.001 | 1.44 | 1.10-1.89 | 0.008 |
| Anemia | 1.11 | 0.84-1.41 | 0.426 | | | |
| Acute kidney injury | 3.25 | 2.47-4.26 | <0.001 | 2.18 | 1.61-2.95 | <0.001 |
| Liver dysfunction | 3.43 | 2.70-4.35 | <0.001 | 1.41 | 1.06-1.87 | 0.017 |
| Malignancy | 1.47 | 0.96-2.24 | 0.075 | | | |
| Diabetic ketoacidosis | 2.91 | 1.94-4.37 | <0.001 | 1.37 | 0.87-2.16 | 0.176 |
| Pneumonia | 2.36 | 1.77-3.15 | <0.001 | 2.40 | 1.74-3.31 | <0.001 |
| Central nervous system infections | 1.59 | 1.02-2.49 | 0.043 | 2.22 | 1.36-3.65 | 0.002 |
| Lactate dehydrogenase (> 408, U/L) | 4.69 | 3.67-5.98 | <0.001 | 2.45 | 1.84-3.24 | <0.001 |

APTT, activated partial thromboplastin time; CI, confidence interval; OR, odds ratio; WBC, white blood cell.

**Supplementary Table 6** Stepwise extended of the multivariate logistic regression model for secondary outcome

| | High lactate dehydrogenase (>408 U/L) | | |
|---|---|---|---|
| | **β** | **95% confidence interval** | ***P*** |
| **ICU LOS** | | | |
| Model 1 | 2.81 | 1.99-3.63 | <0.001 |
| Model 2 | 2.81 | 1.99-3.63 | <0.001 |
| Model 3 | 2.09 | 1.24-2.94 | <0.001 |
| Model 4 | 1.64 | 0.73-2.54 | <0.001 |
| **Hospital LOS** | | | |
| Model 1 | 0.86 | -0.13-1.85 | 0.089 |
| Model 2 | 0.70 | -0.30-1.70 | 0.172 |
| Model 3 | 0.46 | -0.57-1.49 | 0.381 |
| Model 4 | -0.25 | -1.36-0.87 | 0.665 |

ICU, intensive care unit; LOS, length of stay.

**Supplementary Table 7** The value of the Wald Chi-squared statistic minus the degrees of freedom for different covariates

| Covariates | Wald Chi-squared statistic | Degrees of freedom |
|---|---|---|
| Age | 2.4 | 1 |
| White blood cell | 4.8 | 1 |
| Platelet | 7.1 | 1 |
| Sodium | 0.2 | 1 |
| Ionized calcium | 14.5 | 1 |
| PH | 9.4 | 1 |
| Lactate | 50.3 | 1 |
| Albumin | 7.1 | 1 |
| Acute kidney injury | 25.7 | 1 |
| Liver dysfunction | 5.7 | 1 |
| Diabetic ketoacidosis | 1.8 | 1 |
| Pneumonia | 28.6 | 1 |
| Central nervous system infection | 10.0 | 1 |
| Lactate dehydrogenase | 38.7 | 1 |

**Supplementary Table 8** Comparisons of the covariates after propensity score matching using sensitivity analysis

| Variable | All (n=1986) | Low LDH (*n*=993) | High LDH (*n*=993) | *P* |
|---|---|---|---|---|
| **Age, months** | 17 (4-51) | 18 (5-51) | 17 (4-51) | 0.706 |
| **Male, n (%)** | 1191 (60.0) | 599 (60.3) | 592 (59.6) | 0.749 |
| **Laboratory data** | | | | |
| White blood cell, $10^9$/L | 9.63 (6.26-14.13) | 9.63 (6.39-14.12) | 9.63 (6.10-14.13) | 0.870 |
| Platelet, $10^9$/L | 297 (182-386) | 297 (198-373) | 293 (166-400) | 0.708 |
| Sodium, mmol/L | 137 (134-139) | 137 (134-139) | 137 (134-139) | 0.280 |
| Potassium, mmol/L | 3.8 (3.4-4.2) | 3.8 (3.4-4.1) | 3.8 (3.4-4.2) | 0.669 |
| Glucose, mmol/L | 6.7 (5.6-8.8) | 6.7 (5.6-8.8) | 6.7 (5.6-8.7) | 0.888 |
| Albumin, g/L | 36.0 (31.8-40.2) | 36.0 (31.5-40.4) | 36.1 (32.1-40.0) | 0.800 |
| APTT, s | 33.9 (28.6-41.8) | 33.9 (28.9-41.6) | 33.9 (28.4-41.8) | 0.893 |
| Ionized calcium, mmol/L | 1.19 (1.10-1.27) | 1.20 (1.10-1.27) | 1.19 (1.10-1.27) | 0.442 |
| PH | 7.375 (7.314- | 7.375 (7.318- | 7.375 (7.312- | 0.866 |
| Lactate, mmol/L | 1.7 (1.2-2.7) | 1.7 (1.2-2.7) | 1.7 (1.2-2.6) | 0.864 |
| **Comorbidities, n (%)** | | | | |
| Anemia | 1394 (70.2) | 705 (71.0) | 689 (69.4) | 0.433 |
| Acute kidney injury | 226 (11.4) | 108 (10.9) | 118 (11.9) | 0.480 |
| Liver dysfunction | 312 (15.7) | 169 (17.0) | 143 (14.4) | 0.109 |
| Malignancy | 160 (8.1) | 79 (8.0) | 81 (8.2) | 0.869 |
| Diabetic ketoacidosis | 85 (4.3) | 40 (4.0) | 45 (4.5) | 0.579 |
| Pneumonia | 293 (14.8) | 149 (15.0) | 144 (14.5) | 0.752 |
| CNS infection | 80 (4.0) | 40 (4.0) | 40 (4.0) | 1.000 |
| **Clinical outcome** | | | | |
| ICU LOS, days | 2.9 (1.0-8.1) | 2.1 (0.9-6.6) | 3.6 (1.0-9.5) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Hospital LOS, day | 10.8 (5.5-18.0) | 10.5 (5.9-17.8) | 10.9 (5.0-18.8) | 0.775 |
| 30-day mortality, n (%) | 151 (7.6) | 57 (5.7) | 94 (9.5) | 0.002 |
| Hospital mortality, n (%) | 164 (8.3) | 61 (6.1) | 103 (10.4) | 0.001 |

APTT, activated partial thromboplastin time; CNS, central nervous system; ICU, intensive care unit; LOS, length of stay.

**Supplementary Table 9** Sensitivity analysis: stepwise extended of the multivariate logistic regression model after excluding patients from the surgical intensive care unit

| | High lactate dehydrogenase (>408 U/L) | | |
|---|---|---|---|
| | **Odds ratio** | **95% confidence interval** | ***P*** |
| **In-hospital mortality** | | | |
| Model 1 | 3.25 | 2.48-4.24 | <0.001 |
| Model 2 | 3.14 | 2.40-4.11 | <0.001 |
| Model 3 | 2.12 | 1.59-2.83 | <0.001 |
| Model 4 | 1.90 | 1.41-2.58 | <0.001 |
| **30-day mortality** | | | |
| Model 1 | 3.21 | 2.43-4.25 | <0.001 |
| Model 2 | 3.12 | 2.36-4.12 | <0.001 |
| Model 3 | 2.09 | 1.55-2.81 | <0.001 |
| Model 4 | 1.88 | 1.37-2.58 | <0.001 |

| | Lactate dehydrogenase (per standard deviation increase) | | |
|---|---|---|---|
| | **Odds ratio** | **95% confidence interval** | ***P*** |
| **In-hospital mortality** | | | |
| Model 1 | 1.23 | 1.14-1.33 | <0.001 |
| Model 2 | 1.23 | 1.13-1.33 | <0.001 |
| Model 3 | 1.13 | 1.05-1.23 | 0.002 |
| Model 4 | 1.09 | 1.00-1.18 | 0.040 |
| **30-day mortality** | | | |
| Model 1 | 1.23 | 1.13-1.33 | <0.001 |
| Model 2 | 1.22 | 1.13-1.32 | <0.001 |
| Model 3 | 1.14 | 1.05-1.23 | 0.002 |
| Model 4 | 1.09 | 1.01-1.19 | 0.033 |

**Supplementary Table 10** Sensitivity analysis: stepwise extended of the multivariate logistic regression model including comorbidity status as a separate covariate

| | High lactate dehydrogenase (>408 U/L) | | |
|---|---|---|---|
| | **Odds ratio** | **95% confidence interval** | ***P*** |
| **In-hospital mortality** | | | |
| Model 1 | 4.69 | 3.67-5.98 | <0.001 |
| Model 2 | 4.64 | 3.63-5.94 | <0.001 |
| Model 3 | 2.85 | 2.19-3.72 | <0.001 |
| Model 4 | 2.42 | 1.83-3.22 | <0.001 |
| **30-day mortality** | | | |
| Model 1 | 4.78 | 3.70-6.17 | <0.001 |
| Model 2 | 4.75 | 3.67-6.16 | <0.001 |
| Model 3 | 2.93 | 2.22-3.87 | <0.001 |
| Model 4 | 2.51 | 1.86-3.37 | <0.001 |

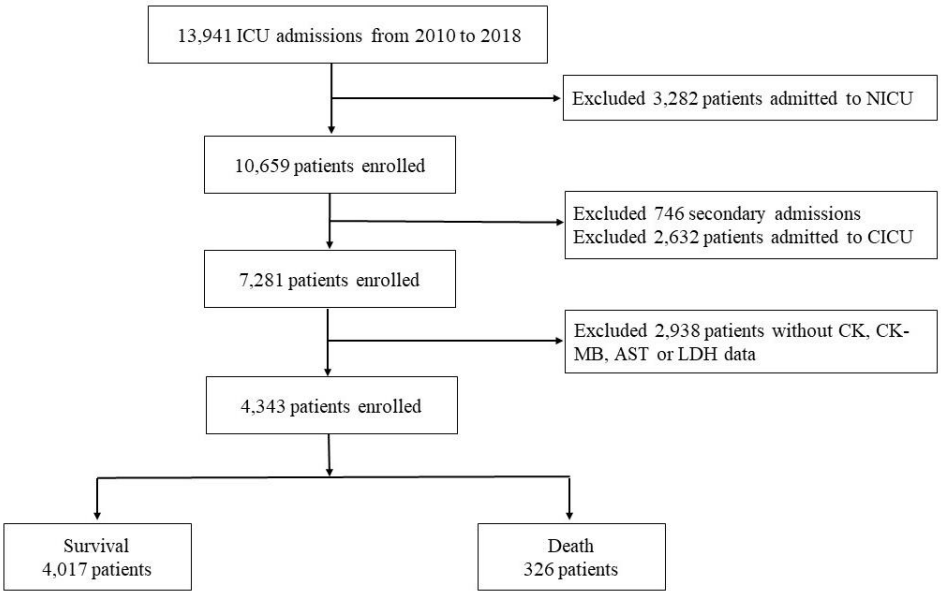
| | Lactate dehydrogenase (per standard deviation increase) | | |
|---|---|---|---|
| | **Odds ratio** | **95% confidence interval** | ***P*** |
| **In-hospital mortality** | | | |
| Model 1 | 1.32 | 1.22-1.43 | <0.001 |
| Model 2 | 1.32 | 1.22-1.43 | <0.001 |
| Model 3 | 1.17 | 1.09-1.25 | <0.001 |
| Model 4 | 1.11 | 1.03-1.20 | 0.005 |
| **30-day mortality** | | | |
| Model 1 | 1.32 | 1.22-1.42 | <0.001 |
| Model 2 | 1.31 | 1.22-1.42 | <0.001 |
| Model 3 | 1.17 | 1.09-1.26 | <0.001 |
| Model 4 | 1.12 | 1.04-1.20 | 0.004 |

The comorbidity status consists of three categories: no comorbidities, one comorbidity, and multiple comorbidities. Multiple comorbidities are defined as having two or more comorbidities.

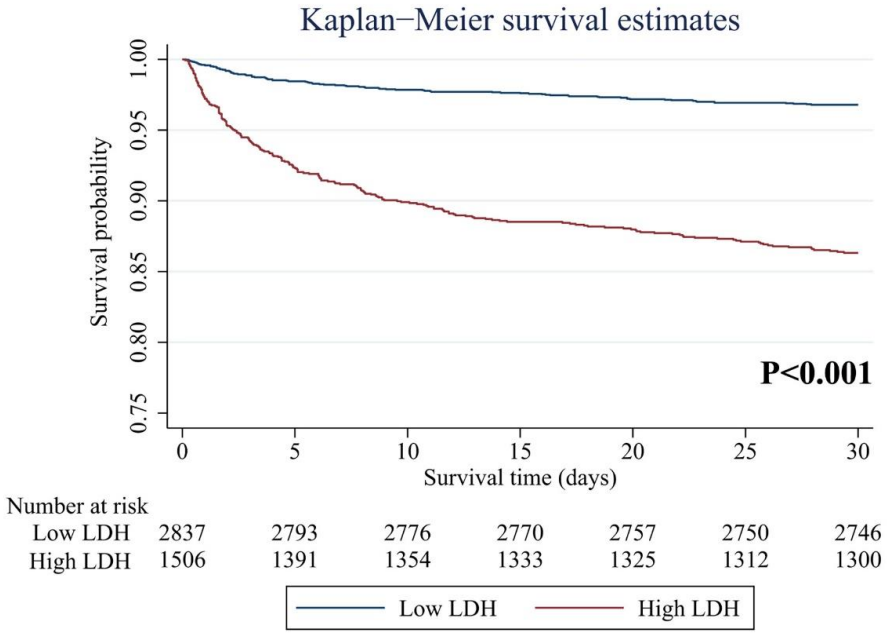
**Supplementary Table 11** Sensitivity analysis: stepwise extended of the multivariate Cox regression model

| | High lactate dehydrogenase (>408 U/L) | | |
|---|---|---|---|
| | **Hazard ratio** | **95% confidence interval** | ***P*** |
| **30-day mortality** | | | |
| Model 1 | 4.52 | 3.53-5.79 | <0.001 |
| Model 2 | 4.50 | 3.50-5.77 | <0.001 |
| Model 3 | 2.77 | 2.12-3.61 | <0.001 |
| Model 4 | 2.36 | 1.78-3.12 | <0.001 |

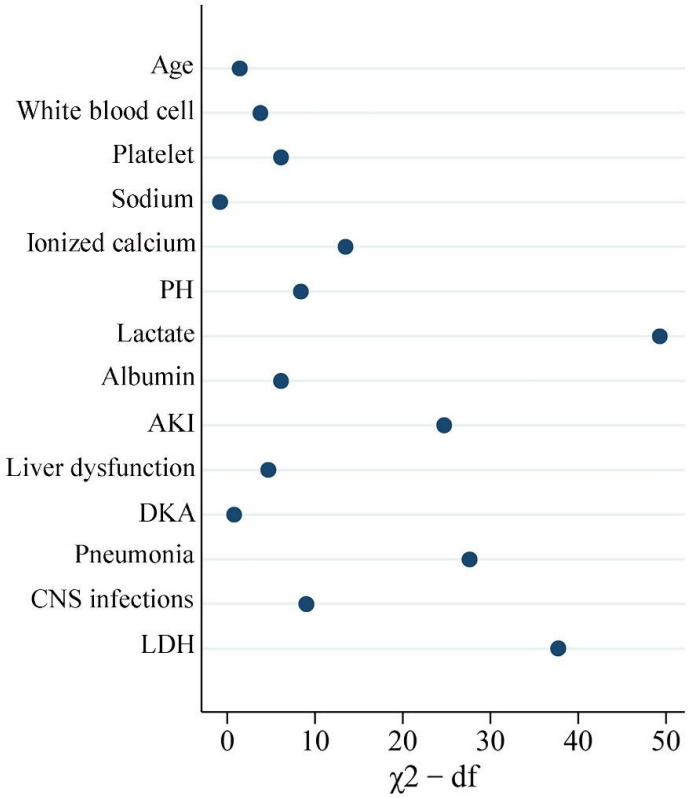
| | Lactate dehydrogenase (per standard deviation increase) | | |
|---|---|---|---|
| | **Hazard ratio** | **95% confidence interval** | ***P*** |
| **30-day mortality** | | | |
| Model 1 | 1.19 | 1.14-1.23 | <0.001 |
| Model 2 | 1.19 | 1.15-1.23 | <0.001 |
| Model 3 | 1.13 | 1.07-1.18 | <0.001 |
| Model 4 | 1.09 | 1.03-1.15 | 0.002 |



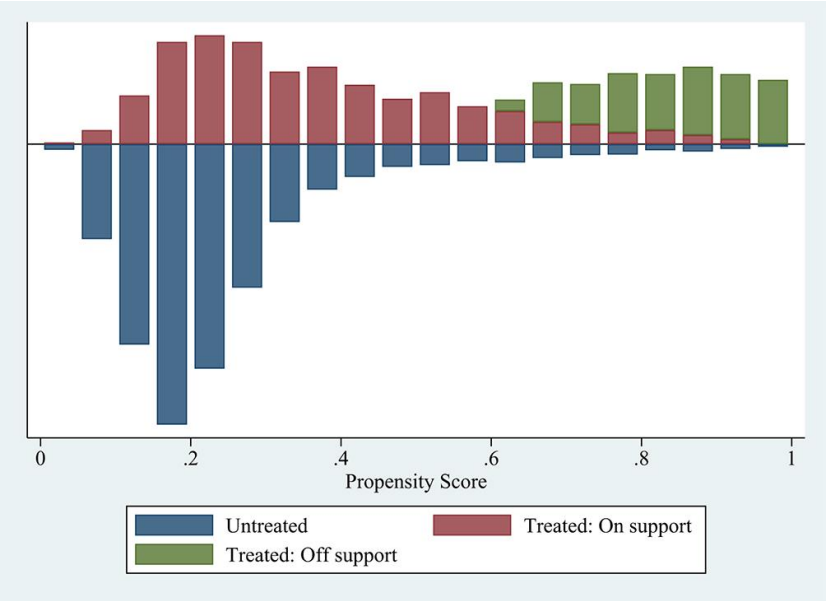

**Supplementary Figure 1** Flow diagram of patient recruitment. AST, aspartate aminotransferase; CICU, cardiac intensive care unit; CK, creatine kinase; CK-MB, creatine kinase MB; ICU, intensive care unit; NICU, neonatal intensive care unit.



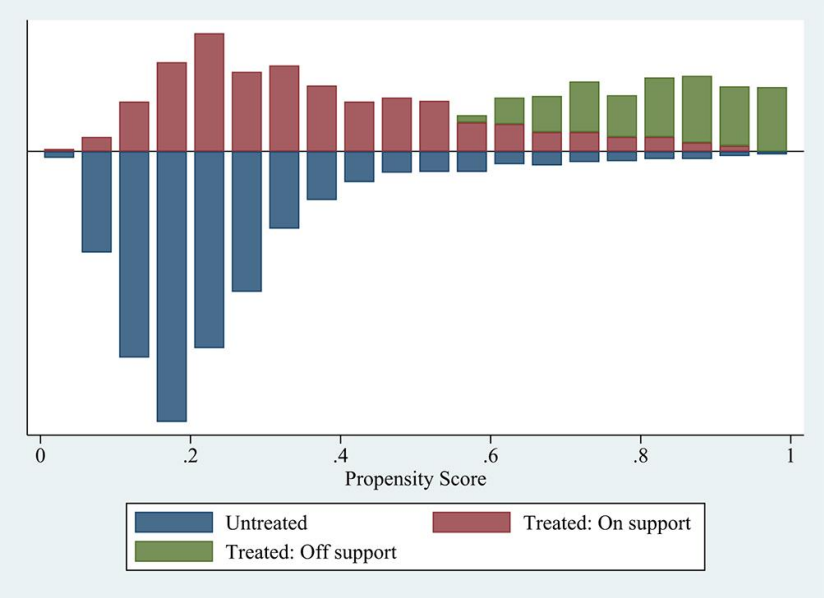

**Supplementary Figure 2** Association between lactate dehydrogenase (LDH) and 30-day overall survival in critically ill children.




**Supplementary Figure 3** The statistical results of the Wald chi-square values minus degrees of freedom for each variable. AKI, acute kidney injury; CNS, central nervous system; DKA, diabetic ketoacidosis; LDH, lactate dehydrogenase.




**Supplementary Figure 4** Propensity scores before sensitivity analysis.




**Supplementary Figure 5** Propensity scores after sensitivity analysis.