Association of Mitochondrial Respiratory Chain Enzymes with the Risk and Mortality of Sepsis Among Chinese Children

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Abstract

Background: Sepsis is a leading cause of pediatric morbidity and mortality worldwide. The aim of this study was to explore the association of mitochondrial respiratory chain enzyme activities with the risk for pediatric sepsis, and interrogate their association with hospitalized mortality among affected children.

Methods: A total of 50 incident cases with sepsis and 49 healthy controls participated in this study. Logistic regression models were used to estimate odds ratio (OR) and 95% confidence interval (CI).

Results: The levels of CoQ10, complex II, complex I+III and FoF1-ATPase were significantly higher in controls than in cases. In children with sepsis, levels of CoQ10 and complex I+III were significantly higher in survived cases than in deceased cases. Per 0.05 μmol/L, 50 nmol/min.mg and 100 nmol/min.mg increment in CoQ10, complex I+III and FoF1-ATPase were associated with significantly lowered risk of having sepsis, even after adjusting for confounding factors (OR=0.85, 0.68 and 0.04, P: 0.001, <0.001 and <0.001, respectively). Per 0.05 μmol/L and 50 nmol/min.mg increment in CoQ10 and complex I+III was associated with significantly lowered risk of dying from sepsis during hospitalization, and significance retained after adjustment (OR=0.73 and 0.76, 95% CI: 0.59 to 0.90 and 0.64 to 0.89, P=0.004 and 0.001, respectively) in sepsis children.

Conclusion: Our findings indicate the promising predictive contribution of serum CoQ10 and complex I+III to the risk of pediatric sepsis and its associated mortality during hospitalization among Chinese children.

Background

Sepsis is a leading cause of morbidity and mortality in children worldwide, with the case-fatality rate of 31.7% in developing countries and 19.3% in developed countries [1, 2]. In China, the incidence rate of pediatric sepsis was estimated to be 181/100,000 in 2014 [3]. The resolution of the World Health Assembly in 2017 has stressed the importance of developing more tools for sepsis diagnosis and treatment [4]. Current diagnostic strategies in identifying patients with sepsis mainly rely on clinical presentations and markers of end-organ dysfunction, including lactate and global measurements of tissue oxygen supply and demand [5–7]. Hence, early detection of sepsis using powerful tools or sensitive biomarkers and individualized close monitoring of patients at risk are of clinical and public health importance.

Mitochondrial dysfunction is a feature of many pathologies, including sepsis [8–10]. Recent studies have shown that mitochondrial respiration was acutely decreased in peripheral blood mononuclear cells in pediatric sepsis [11]. Moreover, mitochondrial dysfunction is also associated with kidney and liver injuries in patients with sepsis [12–14]. Besides, animal studies have shown that the reduction of mitochondrial calcium uptake was associated with the survival rate of rats [15]. Currently, most mitochondrion-sepsis correlation studies have focused on mitochondrial respiration or mitochondrial DNA, yet few studies examined the enzymes and complexes on respiratory chains.

To fill this gap in knowledge and yield more information for future studies, we enrolled children suffering sepsis and healthy controls and assayed the activities of major mitochondrial respiratory chain enzymes in circulation, aiming to explore the association of mitochondrial respiratory chain enzyme activities with the risk for pediatric sepsis, and interrogate their association with hospitalized mortality among affected children.

Methods

Study Subjects

All study subjects were recruited from the Children's Hospital Affiliated to the Capital Institute of Pediatrics during the period from March 2013 to August 2014. This study received approval from the Ethics Committee of this hospital, and was

conducted in compliance with the Declaration of Helsinki.

A total of 50 children who were clinically confirmed to have sepsis were classified as the case group, and 49 age- and sex-matched healthy controls who had no signs of sepsis formed the control group. All study subjects had no physical discomfort and abnormal indexes in blood routine or biochemical examinations.

Tissue Collection and Diagnosis

Children aged 1 month to 192 months who were admitted to the Pediatric Intensive Care Unit (PICU) diagnosed with sepsis (as defined by International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics [16]) were consecutively enrolled. Children were excluded due to the following reasons: (i) taking medications affecting mitochondrial function, such as adenosine, ATP, CoQ10 inhibitors or modeling inhibitors; (ii) using immunosuppressant or immunomodulator within 4 weeks; (iii) congenital organ dysfunction; (iv) congenital and acquired immunodeficiency diseases; (v) not being of Han nationality.

Baseline Characteristics and Clinical Biomarkers

Baseline information was abstracted from the medical record system. Blood samples were collected from all affected children in the first 24 h of admission and stored with ethylenediaminetetraacetic acid (EDTA) at 4℃. Then blood samples were centrifuged at 2000 rpm for 10 min to separate the serum frozen at -80℃ within 4 hours.

The following markers were assayed from blood samples: blood routine examination, biochemistry detection, immune parameters, serum coenzyme Q10 level (using high-performance liquid chromatography), and mitochondrial complex activities in WBC (using spectrophotometric method). PCIS was tested at the time of the first diagnosis of sepsis, and vital status was determined at the time of discharge from PICU. Blood samples of healthy controls were collected on the date of physical examination. Serum coenzyme Q10 concentration levels and mitochondrial complex activities were assayed at the Institute of Experimental Science.

Statistical Analyses

The χ^2 tests for categorical data and Wilcoxon rank-sum tests for continuous data were used to assess whether baseline characteristics differed between patients with sepsis and healthy controls, as well as between survived and deceased children during hospitalization. Logistic regression analyses were conducted to assess the association of serum coenzyme Q10 and mitochondrial complex activities with the risk and mortality risk of sepsis at a significance level of 5% before and after adjusting for age and gender. Effect size estimates are expressed as odds ratio (OR) and 95% confidence interval (95% CI).

To test the performance of Logistic regression model, statistical indexes from calibration and discrimination aspects were adopted. Calibration capability was evaluated using the − 2 log-likelihood ratio test, Akaike information criterion (AIC), and Bayesian information criterion (BIC) [17] to see how closely the prediction probability for the addition of serum coenzyme Q10 and mitochondrial complex activities reflected the actual observed risk and the global fit of modified risk model. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [18, 19] were calculated to judge the discrimination capability of serum coenzyme Q10 and mitochondrial complex activities. Receiver operating characteristic (ROC) curves [20] were plotted based on the basic model and the plus of each enzyme detection index.

Finally, a prediction nomogram model was constructed based on factors of significance using the “rms” package in the open-source R software, version 3.5.1 (available at the website: https://www.r-project.org).

Unless otherwise indicated, STATA software Release 14.1 (Stata Corp, TX, USA) was used for statistical analyses. A P value of less than 0.05 was considered statistically significant, and for multiple comparisons, Bonferroni correction method was used.

Results

Baseline Characteristics

Distributions and comparisons of the activities of mitochondrial respiratory chain enzymes between healthy controls and children with sepsis, as well as between deceased and survived children during hospitalization, are shown in Table 1. The levels of CoQ10, complex II, complex I + III and FoF1-ATPase were significantly higher in controls than in cases (P: <0.001, 0.004, < 0.001 and < 0.001, respectively). In children with sepsis, levels of CoQ10 and complex I + III were significantly higher in survived cases than in deceased cases (both P < 0.001).

Table 1
The comparisons of circulating biomarkers between children with sepsis and controls, as well as between survived and deceased in children with sepsis.

Biomarkers	Controls	Children with sepsis			P_1	P_2
		All	Deceased	Survived		
CoQ10 (μmol/L)	1.0 (0.8 to 1.2)	0.7 (0.5 to 1.0)	0.5 (0.4 to 0.6)	0.8 (0.6 to 1.1)	< 0.001	< 0.001
Complex □ (nmol/min.mg)	107.7 (95.2 to 120.8)	107.1 (98.8 to 124.4)	113.8 (98.5 to 125.0)	106.2 (98.8 to 124.4)	0.460	0.371
Complex □ (nmol/min.mg)	99.6 (88.0 to 108.1)	88.2 (78.8 to 100.7)	87.1 (70.1 to 98.5)	91.3 (79.9 to 101.4)	0.004	0.499
Complex □+□ (nmol/min.mg)	186.3 (170.2 to 202.7)	184.9 (158.8 to 199.8)	186.8 (132.2 to 207.5)	182.3 (163.6 to 199.6)	0.260	0.606
Complex □ (nmol/min.mg)	136.3 (123.1 to 155.7)	143.6 (88.1 to 166.6)	149.2 (88.8 to 164.1)	132.3 (88.1 to 166.8)	0.521	0.983
Complex □+□ (nmol/min.mg)	898.1 (806.9 to 1083.1)	622.8 (384.7 to 811.9)	236.8 (132.6 to 592.5)	731.7 (563.4 to 823.4)	< 0.001	< 0.001
FoF1-ATPase (nmol/min.mg)	751.9 (605 to 903.3)	356.6 (222.8 to 544.7)	383.9 (215.3 to 710.8)	335.2 (222.8 to 535.1)	< 0.001	0.486

P values are calculated by t-test for normal variables and nonparametric Wilcoxon rank sum tests for non-normal data expressed as median (interquartile range). P_1: Children with sepsis versus controls; P_2: Survived versus deceased. Abbreviations: CoQ10, Coenzyme Q10.

The baseline characteristics between decreased and survived children with sepsis are presented in Table 2.

Table 2
Baseline characteristics of study participants in this study.

Characteristics	Deceased	Survived	P
Age, months	26 ± 37.13	27.32 ± 35.23	0.835
Male, n (%)	11 (68.8%)	25 (73.5%)	0.726
SOFA, n (%)			0.047
0 to 10	3 (18.8%)	19 (55.9%)	
10 to 20	11 (68.8%)	13 (38.2%)	
> 20	2 (12.5%)	2 (5.9%)	
PCIS, n (%)			0.005
80 to 100	2 (12.5%)	19 (55.9%)	
71 to 80	4 (25%)	8 (23.5%)	
0 to 70	10 (62.5%)	7 (20.6%)	
MODS > 4 Organs, n (%)	14 (87.5%)	14 (41.2%)	0.002
MOF > 3 Organs, n (%)	11 (68.8%)	9 (26.5%)	0.004
DIC, n (%)	14 (87.5%)	22 (64.7%)	0.094
Shock, n (%)	13 (81.3%)	23 (67.6%)	0.318
ARDS, n (%)	12 (75%)	19 (55.9%)	0.194
Brain Failure, n (%)	14 (87.5%)	21 (61.8%)	0.064
Respiratory Failure, n (%)	13 (81.3%)	26 (76.5%)	0.704
Heart Failure, n (%)	11 (68.8%)	8 (23.5%)	0.002
Liver Failure, n (%)	12 (75%)	6 (17.6%)	< 0.001
Kidney Failure, n (%)	6 (37.5%)	5 (14.7%)	0.07
Stomach Failure, n (%)	12 (75%)	14 (41.2%)	0.026
Pancreas Failure, n (%)	3 (18.8%)	1 (2.9%)	0.055
Metabolic Acidosis, n (%)	12 (75%)	16 (47.1%)	0.063
Th1 cell (n/μl)	4.2 (1.9 to 6.5)	2.3 (1.9 to 2.6)	0.308
Th2 cell (n/μl)	0.3 (0.1 to 0.6)	0.1 (0.1 to 0.2)	0.075
CD3 (n/μl)	60 (53 to 71)	60 (40 to 73)	0.721
CD4 (n/μl)	32.5 (22 to 44)	23 (17 to 41)	0.251

P values are calculated by nonparametric Wilcoxon rank sum tests for continuous variables expressed as median (interquartile range) and χ^2 tests for categorical variables expressed as count and percent. Abbreviations: SOFA, Sequential organ failure score; PCIS, Pediatric critical illness score; MODS, Multiple organ dysfunction syndrome; MOF, Multiple organ failure; DIC, Disseminated intravascular coagulation; ARDS, Acute respiratory distress syndrome; TRIG, Triglyceride; HDL, High-density lipoprotein; LDL, Low density lipoprotein; ALT, Alanine transaminase; AST, Aspartate aminotransferase; LD, Lactate dehydrogenase; HBDH, Hydroxybutyrate dehydrogenase; CK, Creatine Kinase; CKMB, Creatine phosphokinase-Mb; WBC, White blood cell; CRP, C-Reactive Protein; PCT, Procalcitonin.

Characteristics	Deceased	Survived	P
CD8 (n/μl)	21.5 (17 to 27)	23 (18 to 33)	0.818
CD4/CD8	1.55 (0.87 to 2.19)	1 (0.68 to 1.5)	0.284
CD19 (n/μl)	27.4 (24.4 to 41)	28 (9 to 46)	0.858
CD16/CD56	6.5 (3 to 13)	9 (3 to 22)	0.294
IgG (g/L)	8.86 (6.46 to 13.76)	14.47 (10.26 to 23.61)	0.039
IgA (g/L)	0.8 (0.31 to 1.28)	0.36 (0.19 to 0.81)	0.260
IgM (g/L)	0.84 (0.53 to 1.09)	0.53 (0.35 to 0.76)	0.061
TRIG (mmol/L)	1.51 (0.97 to 2.39)	2.22 (1.5 to 2.69)	0.105
HDL (mmol/L)	0.81 (0.59 to 1.03)	0.69 (0.41 to 0.96)	0.173
LDL (mmol/L)	2.21 (1.63 to 2.79)	3.1 (2.17 to 3.79)	0.038
ALT (U/L)	28 (17.45 to 68.55)	168.5 (37.3 to 181.1)	0.003
AST (U/L)	50.15 (30.95 to 121.9)	104.1 (65.45 to 188.2)	0.105
LD (U/L)	320 (260 to 828)	874 (660 to 1089)	0.016
HBDH (U/L)	293.5 (199 to 741)	539 (413 to 749)	0.118
CK (U/L)	44.5 (32 to 77.5)	59 (20 to 142)	0.836
CKMB (ng/mL)	18 (12 to 27)	23.5 (18 to 38)	0.075
Glucose (mmol/L)	5.61 (4.81 to 6.74)	5.6 (3.2 to 8.15)	0.639
Ca (mmol/L)	2.26 (2.08 to 2.35)	1.96 (1.81 to 2.28)	0.015
WBC (10^9/L)	12.9 (8.14 to 16.65)	11.8 (7.02 to 16.96)	0.920
CRP (mg/mL)	8 (2 to 54)	23 (15 to 34)	0.116
PCT (ng/mL)	1.38 (0.27 to 2.55)	1.7 (0.1 to 2.89)	0.958

P values are calculated by nonparametric Wilcoxon rank sum tests for continuous variables expressed as median (interquartile range) and χ^2 tests for categorical variables expressed as count and percent. Abbreviations: SOFA, Sequential organ failure score; PCIS, Pediatric critical illness score; MODS, Multiple organ dysfunction syndrome; MOF, Multiple organ failure; DIC, Disseminated intravascular coagulation; ARDS, Acute respiratory distress syndrome; TRIG, Triglyceride; HDL, High-density lipoprotein; LDL, Low density lipoprotein; ALT, Alanine transaminase; AST, Aspartate aminotransferase; LD, Lactate dehydrogenase; HBDH, Hydroxybutyrate dehydrogenase; CK, Creatine Kinase; CKMB, Creatine phosphokinase-Mb; WBC, White blood cell; CRP, C-Reactive Protein; PCT, Procalcitonin.

Sepsis Risk and Mortality Risk

The risk for sepsis development and associated mortality risk of the activities of mitochondrial respiratory chain enzymes are shown in Table 3 before and after confounding adjustment. Per 0.05 μmol/L, 50 nmol/min.mg and 100 nmol/min.mg increment in CoQ10, complex I + III and FoF1-ATPase was associated with significantly lowered risk of having sepsis, even after adjusting for age and sex (OR = 0.85, 0.68 and 0.53, P: 0.001, < 0.001 and < 0.001, respectively), yet the association of complex II and complex II + III with sepsis risk was only marginally significant.

Table 3
Risk prediction of circulating biomarkers for the risk of sepsis, as well as the mortality risk.

Significant risk factors	cOR	95% CI	P	aOR	95% CI	P*
Children with sepsis versus controls						
CoQ10 (+ 0.05 µmol/L)	0.88	0.82 to 0.95	0.001	0.85	0.77 to 0.93	0.001
Complex Ⅱ (+ 20 nmol/min.mg)	1.19	0.75 to 1.89	0.456	1.02	0.59 to 1.78	0.942
Complex Ⅰ (+ 50 nmol/min.mg)	0.29	0.10 to 0.85	0.025	0.29	0.10 to 0.85	0.025
Complex Ⅰ+Ⅲ (+ 50 nmol/min.mg)	0.71	0.39 to 1.28	0.258	0.42	0.20 to 0.90	0.026
Complex Ⅳ (+ 100 nmol/min.mg)	0.69	0.23 to 2.10	0.517	0.25	0.06 to 1.04	0.057
Complex Ⅱ+Ⅲ (+ 50 nmol/min.mg)	0.71	0.61 to 0.83	< 0.001	0.68	0.57 to 0.82	< 0.001
FoF1-ATPase (+ 100 nmol/min.mg)	0.53	0.42 to 0.68	< 0.001	0.53	0.40 to 0.70	< 0.001
Children with sepsis: deceased versus survived						
CoQ10 (+ 0.05 µmol/L)	0.74	0.61 to 0.90	0.003	0.73	0.59 to 0.90	0.004
Complex Ⅱ (+ 20 nmol/min.mg)	1.35	0.71 to 2.58	0.364	1.38	0.71 to 2.65	0.340
Complex Ⅰ (+ 50 nmol/min.mg)	1.30	0.36 to 4.80	0.690	1.32	0.35 to 4.96	0.678
Complex Ⅰ+Ⅲ (+ 50 nmol/min.mg)	0.81	0.37 to 1.77	0.598	0.79	0.33 to 1.85	0.580
Complex Ⅳ (+ 100 nmol/min.mg)	1.15	0.29 to 4.59	0.841	1.14	0.27 to 4.80	0.857
Complex Ⅱ+Ⅲ (+ 50 nmol/min.mg)	0.79	0.68 to 0.91	0.001	0.76	0.64 to 0.89	0.001
FoF1-ATPase (+ 100 nmol/min.mg)	1.08	0.87 to 1.35	0.478	1.08	0.87 to 1.35	0.481

Abbreviations: cOR, crude odds ratio; aOR, adjusted odds ratio; 95% CI, 95% confidence interval. *P was calculated after adjusting for age and sex. Data are expressed as odds ratio, 95% confidence interval, P value.

In children with sepsis, per 0.05 µmol/L and 50 nmol/min.mg in CoQ10 and complex I + III was associated with significantly lowered risk of dying from sepsis during hospitalization, and significance retained after controlling for age and sex (OR = 0.73 and 0.76, 95% CI: 0.59 to 0.90 and 0.64 to 0.89, P = 0.004 and 0.001, respectively). No signs of significance were noted for the other biomarkers.

Accuracy Appraisal of Mortality Prediction

The prediction accuracy gained by adding mitochondrial respiratory chain enzymes individually to the basic model is summarized in Table 4. As reflected by both calibration and discrimination statistics, only CoQ10 and complex I + III exhibited significant contribution to the mortality risk of hospitalized children with sepsis. Prediction accuracy was reinforced after adding both biomarkers simultaneously to the basic model.

Table 4
Prediction accuracy for sepsis mortality risk gained by adding each circulating biomarker to basic model.

Statistics	Basic Model	Basic Model Plus							
		CoQ10	Complex □	Complex □+□	Complex □+□	Complex □	Complex □+□	FoF1-ATPase	CoQ10 and Complex □+□
Calibration									
AIC	56.67	44.57	50.70	49.36	49.04	50.49	43.06	49.84	39.96
BIC	68.14	57.95	64.08	62.74	62.43	63.87	56.44	63.23	55.25
LR	Ref.	14.1	7.97	9.31	9.62	8.18	15.61	8.82	20.71
LR (P)	Ref.	< 0.001	0.005	0.002	0.002	0.004	< 0.001	0.003	< 0.001
Discrimination									
NRI	Ref.	0.032	0.317	0.083	0.157	0.498	0.046	0.632	0.005
IDI	Ref.	0.003	0.808	0.265	0.575	0.392	0.006	0.377	< 0.001
ROC curve	Ref.	2.15	0.74	0.03	0.29	0.12	1.75	0.26	7.11
ROC curve P	Ref.	0.143	0.389	0.864	0.593	0.731	0.185	0.613	0.008

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; LR, likelihood ratio; NRI, net reclassification improvement; IDI, integrated discrimination improvement; ROC, Relative operating characteristic curve; Ref., reference group. Basic model included age, gender, Pediatric critical illness score (Day 1), number of multiple organ failure, and shock.

Nomogram Prediction Model

In light of the significant contribution of serum CoQ10 and complex I + III to mortality risk, a nomogram prediction model incorporating age, PCIS, CoQ10 and complex I + III was constructed (Fig. 1). The accuracy of this model reached as high as 92.3% (P < 0.001).

Discussion

The aim of this study was to explore the association of mitochondrial respiratory chain enzyme activities with the risk of sepsis and its associated mortality risk among hospital-based children. The key findings are the promising predictive contribution of serum CoQ10 and complex I + III to the risk of pediatric sepsis and its associated mortality during hospitalization, highlighting the importance of mitochondrial respiratory chain enzymes in the development and progression of pediatric sepsis. To the best of our knowledge, this is the first study that has evaluated the association of circulating mitochondrial respiratory chain enzyme activities with sepsis risk in the literature.

Currently, the biological implications of mitochondrial dysfunction in sepsis have been widely evaluated [8, 21, 22]. Mitochondria produce ATP by transferring electrons from substrates sequentially across four respiratory chain complexes (I to IV) and two mobile carriers (coenzyme Q and cytochrome C) to final electron acceptors [23]. Mitochondrial dysfunction is deemed as a key cellular event involved in the pathogenesis of multi-organ failure in sepsis, and it is secondary to tissue hypoxia and involves various toxins or mediators of inflammation that impair oxygen utilization (cytopathic hypoxia) [23, 24]. There is evidence that damaged mitochondria contribute to NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome-related sepsis [21]. In addition, hydrogen was found to alleviate mitochondrial dysfunction and cytokine release via autophagy-mediated NLRP3 inflammasome inactivation [11]. On the

basis of above evidence, it is reasonable to hypothesize that mitochondrial dysfunction plays a contributory role in the development of sepsis, especially the abnormal expressions of mitochondrial respiratory chain complexes and mobile carriers. In support of this hypothesis, Donnino and colleagues conducted a randomized, double-blind, placebo-controlled, pilot trial, by showing that plasma CoQ10 levels were increased in patients with severe sepsis or septic shock, with the administration of oral ubiquinol [25]. However, the contribution of mitochondrial respiratory chain complexes and mobile carriers to the development and progression of sepsis has been rarely reported. To shed some light, we assayed the activities of mitochondrial respiratory chain enzymes in circulation among children with and without clinically-confirmed sepsis to examine their association with the risk and mortality of pediatric sepsis.

After a comprehensive analysis, we interestingly found that high CoQ10 and complex I + III levels were significantly associated with the reduced risk of having pediatric sepsis, as well as the reduced risk of dying from sepsis during hospitalization. CoQ10 has been proposed as an effective agent for reducing the deleterious effects of septic shock by acting as an oxygen free radical scavenger and thus stabilizing mitochondrial membranes, as well as by inhibiting the arachidonic acid metabolic pathway and the formation of various prostaglandins. There is evidence that CoQ10 is effective in alleviating histological organ damage in sepsis via mortality statistics of mice model [26]. In addition, animal studies indicated that complex I + III activity was higher in the sepsis groups than healthy controls in septic mice models caused by lipopolysaccharide, and after treatment with Simvastatin, mitochondrial complex I + III expression was increased [27]. Given the significant association observed in this present study and strong biological implications, it would be tempting to speculate that dysregulation of mitochondrial respiratory chain, in particular CoQ10 and complex I + III, is attributable to the pathogenesis of pediatric sepsis. Moreover, considering the high mortality rate of sepsis in children, identification of circulating biomarkers is of great importance in sanitary science and public health.

Several limitations should be acknowledged for this study. First, the small sample size involved may limit the power to detect small contributions. Second, all study participants are of Chinese descent, which may limit the extrapolation of our findings to other ethnic groups. Third, only a death-or-discharge outcome was recorded during hospitalization and further follow-up evaluation was not available for us. Fourth, mitochondrial respiratory chain enzyme activities were assayed only once, and their dynamic monitoring is of added interest.

Conclusion

Our findings indicate the promising predictive contribution of serum CoQ10 and complex I + III to the risk of pediatric sepsis and its associated mortality during hospitalization among Chinese children. Given the aforementioned limitations, we agree that further investigations on the molecular mechanisms linking mitochondrial respiratory chain enzymes and pediatric sepsis are warranted.

Abbreviations

CoQ10: coenzyme Q10; PICU: Pediatric Intensive Care Unit; SOFA: Sequential organ failure score; PCIS: Pediatric critical illness score; ARDS: Acute respiratory distress syndrome; LD: Lactate dehydrogenase; HBDH: Hydroxybutyrate dehydrogenase; AIC: Akaike information criterion; BIC: Bayesian information criterion; NRI: Net reclassification improvement; IDI: integrated discrimination improvement; ROC: Receiver operating characteristic; OR: odds ratio; CI: confidence interval; I^2: inconsistency index

Declarations

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Availability of data: Data are available upon reasonable request.

Author Contribution Statement:

Q.Z. planned and designed the study, and directed its implementation.

Q.Z. drafted the protocol.

N.L., L.Z. and X.L. obtained statutory and ethics approvals.

D.H., N.L., and X.C. contributed to data acquisition.

D.H., Y.C., L.G., and W.N. conducted statistical analyses.

D.H., Z.S., W.L., and G.S. did the data preparation and quality control.

D.H., W.N., and Q.Z. wrote the manuscript.

All authors read and approved the final manuscript prior to submission.

Ethics approval and consent to participate: Our study design received approval from ethics committee of Children's Hospital Affiliated to the Capital Institute of Pediatrics. Written informed consent was obtained from a parent or guardian for all study participants. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication: Not applicable.

Competing Interest: The authors declare no competing interests.

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Figures

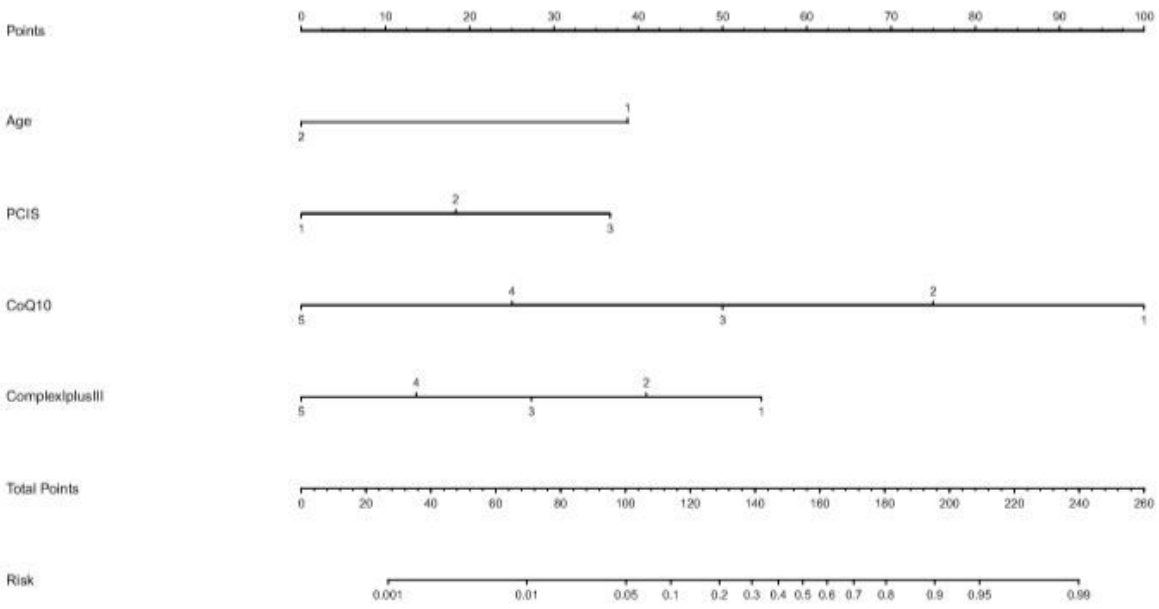

Figure 1

Nomogram prediction model of significant attributes for mortality risk in children with sepsis.