Original Article

Assessment of continuous neutrophil CD64 index measurement for diagnosing sepsis and predicting outcome in a Chinese pediatric intensive care unit: a prospective study

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Background: The high affinity immunoglobulin-Fc fragment receptor I CD64 on neutrophils is widely assumed to be a useful biomarker in the early identification of sepsis, and it improves outcomes. We aimed to determine its ability to diagnose sepsis and predict its prognosis with continuous measurements.

Methods: A total of 335 patients admitted to a Chinese PICU were prospectively stratified into two groups according to the presence of sepsis (defined by clinical criteria for sepsis) between 2018 and 2019. Serum concentrations of the nCD64 index, C-reactive protein (CRP), and procalcitonin (PCT) were measured. Sensitivity, specificity and receiver operating characteristic (ROC) curves were calculated to evaluate the diagnostic value for sepsis. A multiple logistic regression model was used to estimate the prognostic value of continuous nCD64 index measurement for in-hospital death.

Results: The baseline nCD64 index and levels of PCT and CRP were significantly higher in septic children than in nonseptic children (P<0.05). The nCD64 index presented a higher sensitivity (0.90), specificity (0.78) and area under the ROC curve [0.91 (0.90, 0.93)] than CRP and PCT in discriminating septic children with an optimal cutoff value of 5.78. The nCD64 index decreased with the progression of sepsis, and the baseline nCD64 index was strongly associated with in-hospital death (OR: 2.18, 95% CI: 1.02–4.74). Moreover, the more rapidly the nCD64 index declined, the lower the in-hospital death rate was (OR: 0.89, 95% CI: 0.63–1.35) after adjusting for the baseline nCD64 index and other confounders.

Conclusions: The nCD64 index was not only effective for the early diagnosis of childhood sepsis but also positively associated with the prognosis of sepsis. Moreover, the nCD64 decline was inversely associated with the in-hospital death rate.

Keywords: Sepsis; childhood; neutrophil CD64 index; diagnosis; outcome

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Introduction

Sepsis is the response of the immune system to invasive infection, which is the main cause of morbidity and mortality in the intensive care unit (ICU) globally, and the disease burden is extremely high (1-3). Although early identification and appropriate immediate management of sepsis were reported to be associated with better prognosis and outcomes (4), early diagnosis of this syndrome remains challenging. Hundreds of studies have investigated possible promising early diagnostic biomarkers for sepsis (5-7). In fact, the early biomarkers of sepsis reported in the literature have exceeded 100 and continue to increase, but none were proven to be consistently useful in the early diagnosis of sepsis. Among them, the most commonly mentioned biomarkers were C-reactive protein (CRP), procalcitonin (PCT) and in particular, the neutrophil CD64 index (nCD64 index).

CD64 is also called high-affinity immunoglobulin Fc-γ receptor I (8). The nCD64 index has been investigated for years as a biomarker of infection and sepsis, given its reported low baseline expression and quick increase after inflammation (9). Moreover, several authors have also reported its value as an indicator of sepsis severity, prognosis and outcomes. Dai *et al.* (10) performed the diagnostic value of the neutrophil CD64 index for neonatal sepsis in 7 studies, and the pooled sensitivity and specificity were 80% (95% CI: 69–88%) and 83% (95% CI: 71–90%), respectively. Thiriet *et al.* (11) performed a prospective analysis in adults in the ICU and showed that the nCD64 index was a possible diagnostic marker of sepsis with good sensitivity and specificity (78% and 70%, respectively). Moreover, the author performed repeated measurements of the nCD64 index, which showed that it may help improve the accuracy of the diagnosis of sepsis. El Shimi *et al.* (12) observed significantly higher baseline neutrophil CD64 levels in deceased patients than those in recovered neonates, which indicated its predictive value for disease outcomes. However, most studies have focused on populations of neonates and adults, and childhood sepsis has seldom been observed. Moreover, few studies have focused on the change in the nCD64 index during treatment and its influence on disease prognosis.

The aim of this paper was to assess the role of the nCD64 index in establishing the diagnosis criteria of childhood sepsis, comparing the sensitivity, specificity and AUC of PCT, CRP and nCD64 in the diagnosis of childhood sepsis. Moreover, continuous measurement of the nCD64 index was performed to observe the changes in the nCD64 index during treatment and to evaluate its effect in predicting sepsis outcomes.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-21-63).

Methods

Study design and population

This prospective study was implemented on participants admitted to the PICU of Anhui Provincial Children's Hospital between 2018 and 2019. Patients who exhibited the clinical signs of sepsis at admission were enrolled as the sepsis group. The nonsepsis group included those with no symptoms or signs of infection. Two pediatricians independently classified the diagnosis as sepsis or no sepsis at the time of admission.

In the present study, sepsis was defined as systemic inflammatory response syndrome (SIRS) caused by suspected or confirmed infection. The diagnosis of SIRS was based on at least two clinical criteria: hyperthermia (rectal temperature >38 ℃) or hypothermia (rectal temperature <36 ℃), tachycardia, tachypnea, and white blood cell (WBC) count $<4\times10^9$/L or $>12\times10^9$/L. Furthermore, a child with sepsis had damaged function of at least one organ, such as consciousness changes, hypoxemia, increased levels of serum lactic acid and a fast pulse.

We excluded patients who were neonates or those >18 years old. Patients with chromosomal abnormalities, congenital anomalies and/or surgical problems were also excluded from the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Anhui Provincial Children's Hospital, Hefei, China (NO. EYLL-2017-29) and informed consent was taken from all individual participants.

Neutrophil CD64 index

The neutrophil CD64 index was evaluated by flow cytometry (Becton Dickinson, FACS Canto II, USA). Briefly, 100 μL peripheral blood samples were mixed with 20 μL fluorescein isothiocyanate (FITC)-labeled CD64 monoclonal antibody, followed by gentle vortexing and incubation in the dark for 15 min. Then, 1 mL diluted hemolysin solution for flow cytometry was added to the

blood samples. The samples were vortexed and incubated for 15 min in the dark, and then they were subjected to flow cytometry on a FACS Canto II platform (Becton Dickinson, USA) to evaluate the mean FITC intensity from neutrophils and lymphocytes; the ratio of the two was calculated as the nCD64 index. During hospitalization, we performed three nCD64 index measurements in the sepsis group. The first was performed within 12 hours after admission as baseline; the second was performed on day 3 after admission, and the third measurement was taken the day before discharge. For the nonsepsis group, the nCD64 index was only measured once within 12 hours after admission.

Laboratory assays

Peripheral blood samples were collected under complete aseptic conditions on ethylenediaminetetraacetic acid (EDTA) (1.2 mg/mL) for blood cell count and immunophenotyping. WBC count was performed on an automatic blood cell Coulter Sysmex XN-350 (Beckman Coulter, Inc., Fullerton, CA). Serum was obtained from clotted samples by centrifugation at 1,000 ×g for 15 min and used for biochemical analysis of CRP and PCT. High sensitivity CRP and PCT levels were analyzed on an automatic biochemical analyzer (7600-020, Hitachi, Japan) with a turbidimetric CRP assay kit (Fuji, Japan) and an automatic electrochemiluminescence immunoanalyzer (Cobas E411, Roche Diagnostics, Germany), respectively.

Statistical analysis

Participant characteristics were stratified into different groups and presented as the mean [standard deviation (SD)] or median [interquartile range (IR)] for continuous variables and frequency (proportion) for categorical variables. The differences in population characteristics were compared using a *t*-test, the Wilcoxon-Mann-Whitney test, or the chi-square test.

Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic value of these biomarkers, and Youden's index was calculated to determine the optimal cutoff values of the biomarkers, together with the area under the ROC curve (AUC, with 95% CI), sensitivity, specificity, positive and negative likelihood ratios and predictive values. Generalized linear models with a logit link were used to evaluate the predictive value of the baseline nCD64 index and its change from admission for in-hospital death rates with crude or full models adjusted for age, sex, sepsis group, pediatric critical illness score (PCIS) and other biomarkers.

A two-tailed P value <0.05 was considered to be statistically significant in all analyses. All statistical analyses were performed using R software (http://www.R-project.org).

Results

Study participants and baseline characteristics

Within a two-year period, a total of 335 participants were involved in the final analysis (*Figure 1*). Participants were divided into two groups (the sepsis group and nonsepsis group) according to the presence of sepsis. In this population, 120 (35.0%) patients were classified into the sepsis group by two independent pediatric physicians according to clinical sepsis diagnostic criteria. The sepsis group had lower PCIS scores and higher baseline concentrations of the nCD64 index. Moreover, PCT, CRP and WBC counts were also positively higher in the sepsis group than in the nonsepsis group. The total in-hospital mortality was 2.4% in this study, with 4.2% and 1.4% in the sepsis group and nonsepsis group, respectively. Other general characteristics of the study participants are presented by sepsis status in *Table 1*. No significant differences were observed in age, sex or other variables.

Clinical performance of biomarkers in the diagnosis of sepsis

Baseline serum concentrations of the nCD64 index, CRP, PCT, and the WBC count were determined to assess their diagnostic value for sepsis. Overall, all four biomarkers were positively higher in the sepsis group (P<0.05). Areas under the ROC curves (AUCs) differed among these four biomarkers, with CD64 index at 0.91 (0.90, 0.93), PCT at 0.79 (0.77, 0.81), CRP at 0.68 (0.66, 0.71), and WBC count at 0.60 (0.57, 0.63). The nCD64 index had the highest AUC value, which showed the best diagnostic value for sepsis among these biomarkers (*Figure 2*).

The nCD64 index presented a sensitivity of 0.90 and a specificity of 0.78 with a cutoff value of 5.78. The positive and negative likelihood ratios were 4.08 and 0.13, respectively, and the positive and negative predictive values were 70% and 93%, respectively. We observed that the other three biomarkers did not perform better than the nCD64 index (*Table 2*).

We also performed a multiple logistic regression model

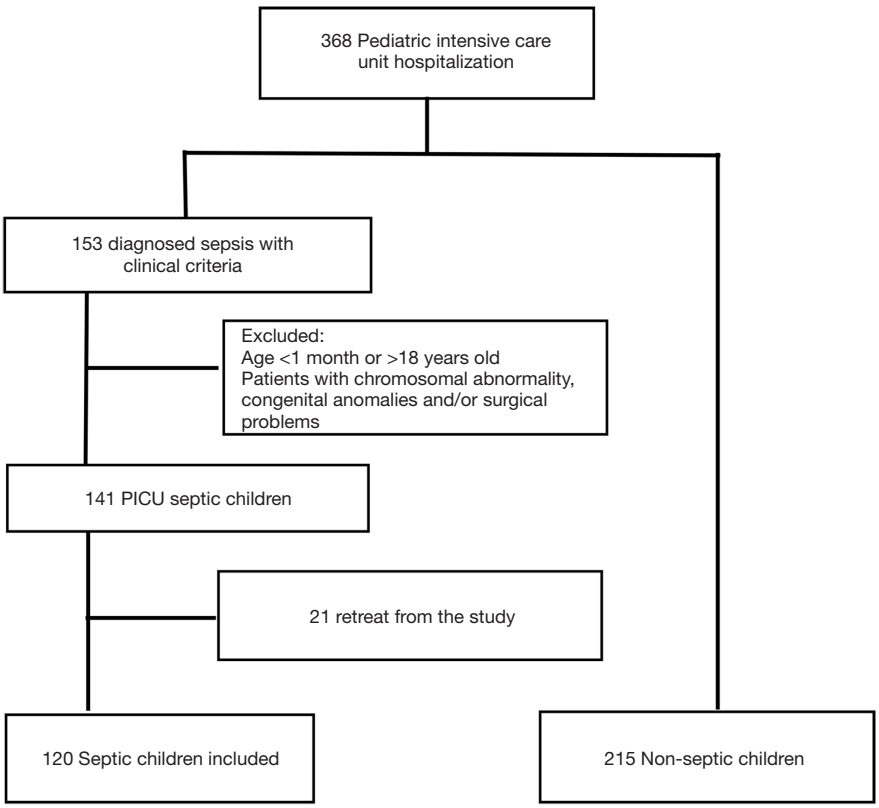

Figure 1 Diagram of participants included in the study.

Table 1 Baseline characteristics of two groups at admission

	Non-sepsis (n=215)	Sepsis (n=120)	Total (n=335)	P value
Age, yrs	1.37 (0.62, 3.44)	1.23 (0.52, 3.21)	1.3 (0.58, 3.34)	0.852
Boys	119 (55.3)	72 (60.1)	191 (57.0)	0.436
Death	3 (1.4)	5 (4.2)	8 (2.4)	0.223
LOS, days	6 (4.5, 8)	6 [5, 8]	6 [5, 8]	0.114
PCIS score	83.88±4.01	79.97±3.09	82.47±4.15	<0.001
Baseline nCD64 index	4.09±2.15	6.06±2.14	4.8±2.35	<0.001
CRP, mg/L	11 (6.12, 24.3)	20.9 (12.3, 29.6)	14.8 (8.56, 26.7)	<0.001
PCT, ng/mL	0.33 (0.25, 0.42)	0.49 (0.41, 0.58)	0.33 (0.25, 0.42)	<0.001
WBC, 10^9/L	9.16 (6.38, 14)	11.31 (8.2, 16)	9.21 (6.34, 14)	<0.001

Results are presented as n (%), mean (SD), or median (interquartile range). LOS, length of stay; PCIS, pediatric critical illness score; SD, standard deviation; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count.

to evaluate the predictive value of these biomarkers for the identification of sepsis. We observed a significantly increased risk of sepsis with an increased nCD64 index (OR: 2.35, 95% CI: 2.15–2.60). Moreover, we also observed a significant effect of PCT (OR: 2.18, 95% CI: 1.44–3.17), CRP (OR: 1.05, 95% CI: 1.03–1.07) and WBC count (OR:

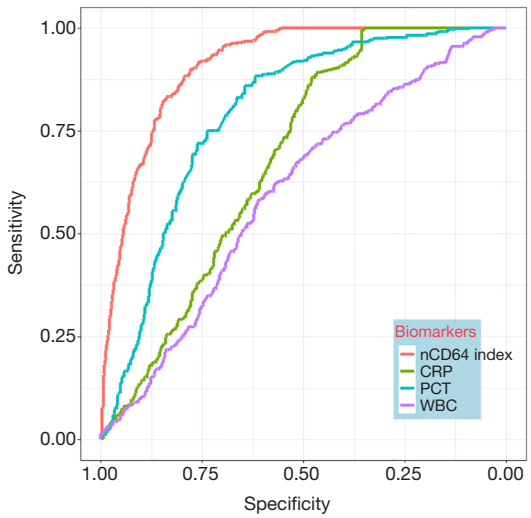

Figure 2 Receiver Operating Characteristic (ROC) curves of different biomarkers.

1.03, 95% CI: 1.00–1.05) for sepsis prediction, but with lower odds ratio (*Table 3*).

The performance of continuous CD64 index determination for death

In the present study, significant differences were observed between the baseline nCD64 index and those assessed afterwards in the sepsis group (P<0.05). Moreover, a gradual decline in the nCD64 index was observed during treatment (*Figure 3*).

We also performed multiple logistic regression to evaluate the risk factors for in-hospital death. Overall, there was a significant association between nCD64 index concentrations and in-hospital death. We observed that the increase in the baseline nCD64 index was associated with a 118% increase in the adjusted risk of death (OR: 2.18, 95%

Table 2 Comparison of clinical performance of biomarkers in diagnosing sepsis

Biomarker	AUC	Optimal Cut-off value	Sensitivity	Specificity	PLR	NLR	PPV	NPV
Baseline nCD64 index	0.91 (0.90, 0.93)	5.78	0.90	0.78	4.08	0.13	0.70	0.93
CRP	0.68 (0.66, 0.71)	8.05	0.61	0.79	3.12	0.88	0.71	0.66
PCT	0.79 (0.77, 0.81)	0.37	0.86	0.63	2.31	0.22	0.57	0.37
WBC	0.60 (0.57, 0.63)	10.6	0.58	0.61	1.49	0.69	0.46	0.39

CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Table 3 Multiple-logistic regression of these biomarkers for differentiating sepsis and non-sepsis children.

Variables	Crude	Adjusted*
	OR (95% CI)	OR (95% CI)
Baseline nCD64 index	2.38 (2.18, 2.62)	2.35 (2.15, 2.60)
CRP	1.05 (1.04, 1.06)	1.05 (1.03, 1.07)
PCT	1.21 (0.92, 1.59)	2.18 (1.44, 3.17)
WBC	0.99 (0.98, 1.101)	1.03 (1.00, 1.05)
Second nCD64 index	1.19 (1.12, 1.27)	1.19 (1.12, 1.28)
Third nCD64 index	1.02 (0.96, 1.09)	1.04 (1.01, 1.05)

*, Adjusted for: age, gender, PCIS score and these biomarkers. CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; OR, odds ratio.

CI: 1.02–4.74). We also observed an increasing trend of the second (OR: 1.29, 95% CI: 0.93–1.65) and third nCD64 index measurements (OR: 1.12, 95% CI: 0.74–1.54) with in-hospital death, although a nonsignificant association was observed.

To evaluate the association between the decrease in CD64 index during hospitalization and outcomes, we defined dCD64 as the baseline nCD64 index minus the third nCD64 index measurement. In the crude model, the increase in dCD64 was significantly associated with increased in-hospital death (OR: 1.31, 95% CI: 1.07–1.58). However, after adjustments for the baseline CD64 index and other confounders, the associations reversed (OR: 0.89, 95% CI: 0.63–1.35), even though the P value was not significant (*Table 4*).

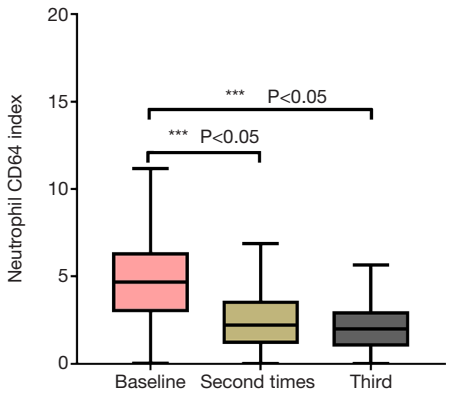

Figure 3 Evolution of continuous neutrophil CD64 index measurement among sepsis patients.

Discussion

To our knowledge, this is the first prospective analysis in children to evaluate the early diagnostic value of nCD64 in sepsis and to examine the predictive value of continuous nCD64 index measurement for in-hospital death. We found that nCD64 had a better diagnostic value for sepsis than PCT, CRP and WBC count. We also determined that the baseline nCD64 index was associated with higher in-hospital mortality. Moreover, the more rapid the decline in the nCD64 index during treatment was, the lower the risk of in-hospital death.

The treatment of sepsis is a dilemma without a definite early diagnosis. On the one hand, the overuse of antibiotics may lead to antimicrobial resistance and higher healthcare costs; on the other hand, it may aggravate the disease and increase mortality without timely treatment. Thus, the early diagnosis of sepsis is extremely important in clinical practice. In fact, the early diagnostic value of the nCD64 index for sepsis has been demonstrated in many studies focusing on elderly adults and neonates with promising results (13), but few studies have reported this topic in childhood (9). For example, Dai *et al.* (10) performed a meta-analysis including 7 studies in neonates with pooled

Table 4 Risk factors of hospital death rate

Variables	Crude	Adjusted*
	OR (95% CI)	OR (95% CI)
Age	1.02 (0.74, 1.29)	0.93 (0.60, 1.26)
Boys	1.34 (0.32, 5.70)	1.31 (0.28, 5.92)
PCIS Score	0.81 (0.68, 0.98)	1.36 (0.76, 2.29)
Baseline nCD64 index	1.39 (1.15, 1.68)	2.18 (1.02, 4.74)
Second nCD64 index	1.29 (0.93, 1.65)	1.31 (0.93, 1.72)
Third nCD64 index	1.12 (0.74, 1.54)	1.13 (0.74, 4.60)
CRP	1.01 (0.95, 1.07)	0.99 (0.91, 1.06)
PCT	0.83 (0.03, 2.67)	0.26 (0.00, 2.44)
WBC	1.08 (0.97, 1.18)	1.11 (1.00, 1.24)
dCD64 index	1.31 (1.07, 1.58)	0.89 (0.63, 1.35)

*, adjusted for: age, gender, PCIS score and other biomarkers. dCD64 index, Baseline nCD64 index- Third nCD64 index. CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; OR, odds ratio.

sensitivity and specificity of 80% (95% CI: 69–88%) and 83% (95% CI: 71–90%), respectively. Ye *et al.* (14) reported a sensitivity of 83% and specificity of 88% in diagnosing sepsis in 62 adult ICU patients. Groselj-Grenc *et al.* (15) reported the diagnostic performance of the nCD64 index with a sensitivity of 86% and specificity of 100% in children. In the present study, we evaluated the early diagnostic value of the nCD64 index with a sensitivity of 0.90 and specificity of 0.78 with an optimal cutoff value of 5.78, which showed better effectiveness than PCT, CRP and WBC count with the highest AUC of 0.91 (0.90, 0.93) and was consistent with the results of a previous meta-analysis. In this study, we observed an optimal cutoff value of 5.78, which is higher than that in neonates (16-18). These discrepancies may be explained by differences in methodology, time of sampling, and age of participants.

Thiriet *et al.* (11) reported a repeated measurement of the nCD64 index in adults and correctly classified 85% of sepsis cases on day 2 versus 74% on day 1, which showed that repeated measurements may help improve the accuracy of sepsis diagnosis. In the present study, continuous measurement of the nCD64 index was performed over the course of disease, and a gradual decline in the nCD64 index was observed throughout treatment, which indicated that the nCD64 index can be used as a potential indicator for evaluating treatment effectiveness and progression. The result was consistent with the result in adults (19). We also determined the low diagnostic value of the second and third nCD64 indices with sensitivities of 77% and 54%, respectively, which may be explained by the timely use of antibiotics.

We also evaluated the performance of the continuous nCD64 index in predicting death, and a significant association between the baseline nCD64 index and in-hospital death was observed (OR: 2.18, 95% CI: 1.02–4.74), which is consistent with previous studies in neonates (12,20). In this study, a positive significant association between nCD64 index decline and death was observed (OR: 1.31, 95% CI: 1.07–1.58) in the crude model. Interestingly, after adjustments of the baseline nCD64 index and other confounders, the associations reversed (OR: 0.89, 95% CI: 0.63–1.35), even though the P value was not significant. The inverse result not only revealed the core value of the baseline nCD64 index in predicting death but also indicated that the nCD64 index decline was negatively associated with in-hospital death rates.

In the present study, although the potential value of early discrimination and prediction of death for sepsis of nCD64 index were observed, its application in some primary hospital may be limited due to the use of flow cytometer is required. There were two alternatives for this situation. Firstly, the correlation between the nCD64 index and other markers (WBC, PCT and CRP) were calculated to evaluate its possibility to be able to instead of nCD64. In this study, although these biomarkers were inferior to nCD64 index in early diagnosing sepsis and predicting hospital death, its potential value were observed; we also calculated the correlation coefficient between these indicators and nCD64 index and found these markers were positively correlated with nCD64 index (WBC: 0.31; PCT: 0.32; CRP: 0.28) and could be used as a substitute for nCD64 index. Secondly, with the development of microfluidic affinity cells separation system, the simple and multi-parameter combined microfluidic chip for early diagnosis of sepsis were exploited, including culture-negative sepsis and culture-positive sepsis, and excellent diagnosis performance were observed (and AUC value of single CD64 index was 0.90 and the combination of CD64 and CD69 for sepsis diagnosis had the AUC of 0.98) (21-23).

Several potential concerns or limitations are worth mentioning. First, the diagnosis of sepsis was based on clinical criteria rather than blood culture tests in this study. In fact, some studies have demonstrated the difference in the nCD64 index between culture-positive sepsis patients and clinical sepsis patients with negative cultures, and no significant difference was observed (24,25). Second, our current study defined in-hospital death as the study outcome and did not conduct further follow-up after discharge; thus, it is possibly unable to demonstrate the long-term effect of sepsis. Third, we calculated the PCIS score rather than the acute physiology and chronic health evaluation (APACHE) score and Sepsis-related Organ Failure Assessment (SOFA) score in the current study, as the PCIS score is generally acknowledged as an excellent tool in China for judging the severity of childhood diseases and predicting the risk of death. Finally, our study was conducted in Chinese children. Whether the results can be extrapolated to other populations requires further verification. Due to these limitations, further confirmation is greatly needed.

Conclusions

In this prospective analysis of Chinese children with sepsis, the nCD64 index could be helpful for the early discrimination of childhood sepsis. We observed a significant association between baseline nCD64 index concentrations and in-hospital death. Moreover, an inverse

association was observed between nCD64 index decline and in-hospital death rates.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/tp-21-63

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-21-63). The authors have no conflicts of interest to declare.

Ethical Statement: 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Anhui Provincial Children's Hospital, Hefei, China (NO. EYLL-2017-29) and informed consent was taken from all individual participants.

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