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Prognostic death factors in secondary hemophagocytic lymphohistiocytosis children with multiple organ dysfunction syndrome receiving continuous renal replacement therapy: A multicenter prospective nested case-control study

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Abstract

Introduction: Multiple organ dysfunction syndrome (MODS) with secondary hemophagocytic lymphohistiocytosis (SHLH) causes significant mortality. We aimed to identify the predictor factors for death in pediatric patients with SHLH-associated MODS receiving continuous renal replacement therapy (CRRT).

Methods: This multicentered nested case–control study was conducted from 2016 to 2020. The characteristics were compared between survivors and non-survivors. Logistic regression was applied to identify the risk factors for death. The cutoff values were assessed by receiver operating characteristics curves.

Results: Fifty two patients were enrolled in this study. Interleukin-6 level ($p = 0.018$) and the number of organ dysfunction ($p = 0.047$) were independent risk factors for death. The cutoff value of 13.12 pg/ml interleukin-6 and three organs dysfunction at CRRT initiation presented a high sensitivity and specificity.

Conclusion: The number of organ dysfunction and interleukin-6 at CRRT initiation are independent risk factors for death in pediatric patients with SHLH-associated MODS.

KEYWORDS

continuous renal replacement therapy, death, IL-6, pediatric intensive care unit, secondary hemophagocytic lymphohistiocytosis

Yun Cui and Jingyi Shi are co-first authors and contributed equally to this work.

1 | INTRODUCTION

Secondary hemophagocytic lymphohistiocytosis (SHLH), a rare hyperinflammatory syndrome without familial history or known genetic defect, is considered an overwhelming and life-threatening disease. The occurrence of SHLH is associated with persistent activation of the mononuclear-phagocytic system and would ultimately result in an uncontrolled inflammatory response. Particularly, patients with internal organ involvement would progressively develop to multiple organ dysfunction syndrome (MODS), which would cause irreversible organ damage and subsequent death [1, 2]. Despite previous studies have depicted the association between the pathogenetic development of SHLH and viral infection, malignancies, and autoimmune disease [3, 4], the pathogenesis of SHLH is yet to be comprehensively understood.

Abrupt onset of MODS is common in HLH patients [5]. The mortality rate in SHLH with MODS patients has remained unacceptably high [6–8]. In children, SHLH may present with more acute fulminant manifestations and the incidence of MODS was higher than adults [9, 10]. Poor outcomes in children with SHLH-associated MODS have led to an urgent need for improvement in promising treatment and early diagnosis.

Continuous renal replacement therapy (CRRT) has become an emerging treatment for severe SHLH patients owing to its effectiveness in removal of inflammatory mediators, ability to maintain the fluid balance, and the hemodynamic stability for critical ill patients [11–13]. Moreover, aggressive application of CRRT has been found to decrease the mortality rate in patients with septic shock and MODS [14]. In addition, DiCarlo et al. [15] demonstrated the utility of continuous hemofiltration in attenuating the consequences of excess cytokine activity and the degree of lactate in three HLH patients with MODS. In such instance, this technique has been applied at some institutions in China for pediatric patients who suffered from SHLH with MODS. Therefore, it is important for physicians to identify the risk factors that might lead to death in pediatric SHLH patients with MODS who underwent CRRT.

To the best of our knowledge, there were only an extremely sparse number of case report/series studies discussed the relevant prognostic factors in critically ill children with SHLH and MODS receiving CRRT [7, 16, 17]. We previously assessed the dynamic changes in biomarkers during hemofiltration therapy and speculated a potential prognostic effect of cytokine level and other laboratory characteristics in those critical ill children [12]. Herein, in this multicenter study, we prospectively collected a cohort of pediatric patients with SHLH and MODS to be treated with CRRT, and retrospectively reviewed their data to assessed and identified the predictive factors that might associated with death.

2 | MATERIALS AND METHODS

2.1 | Study design

We performed a multicenter nested case control study between August 2016 and July 2020 from four tertiary care pediatric ICUs (PICUs) in Shanghai. The protocol was approved by each institution's ethics/investigation review board (2016R011-F01). Informed consent of participation in the study was obtained from the guardians of the patients. Eligibility criteria for this study were as follows: (1) aged between 1 month and 18 years, (2) meet HLH-2004 for HLH and diagnostic criteria of MODS, (3) treated with HLH-2004 protocol, (4) receiving CRRT during the pediatric ICU stay. Exclusion criteria were (1) had familiar hemophilic cell syndrome, (2) had a history of biofilm or hemofilter allergy. Data from enrolled patients were entered into standardized electronic case report forms (CRF). MODS was defined as the underlying primary disease process leading to at least two organ system dysfunctions at any time during PICU stay [18].

2.2 | Selection of cases and controls

The cohort were followed up until the earliest date of death, transfer to another practice, or the study end date (July 31, 2020). Case and control patients were differentiated by whether they were pronounced dead during hospitalization. For the accuracy of this analyses, the data of case and controls patients were only considered valid if they had stayed in the PICU for at least 48 h.

2.3 | CRRT treatment

The indications for CRRT in our study were as follow: (1) hypercreatinemia or azotemia (creatinine levels of >2 mg/dl; (2) blood urea nitrogen levels of >40 mg/dl); (3) oliguria (urine output of <0.5 ml/kg/h); (4) fluid overload >10%; (5) acute liver failure complicated with hepatorenal syndrome or hyperammonemia; (6) severe electrolyte imbalance which did not respond immediately to conventional therapy (hyperkalemia > 7 mmol/L; hypernatremia > 160 mmol/L or hyponatremia < 110 mmol/L). Vascular access was obtained with 5F dual-lumen (Arrow, Teleflex Inc, Limerick, PA, USA), 6.5F–12F central venous catheters (GamCath; Gambro, Colombes, France) in the right internal jugular or femoral vein, according to patient body weight.

Patients were commonly treated with a Prismaflex machine (Gambro Renal Products) in continuous venovenous hemofiltration (CVVH) mode. While in patients with acute kidney injury, continuous venovenous hemodiafiltration (CVVHDF) was performed. Polyacrylonitrile AN69 or polysulfone hollow-fiber hemofilters were used, depending on the body surface area (BSA) of the patient and on the pump that been employed. M10 filters (Gambro Renal Products, France) were used in children weighing less than 5 kg, M60 (Gambro Renal Products, France) in patients weighing between 5 and 35 kg, and M100 (Gambro Renal Products, France) in children weighing over 35 kg. Hemofilters changes were scheduled every 24 h or whenever clot was observed.

Initiation of CRRT and prescription of replacement and dialysis doses were based on the decisions of the PICU attending intensivist. The dosage of heparin was 5–20 U/kg h to maintain activated partial thromboplastin time (APTT) with 1.5–2 folds of normality during CRRT. The regional citrate anticoagulation (RCA) procedure was conducted according to the guidelines from the Prismaflex operator's manual. When sodium citrate was used as anticoagulation, the target post-filter ionized calcium level of 0.25–0.35 mmol/L was maintained. The citrate effect was neutralized using a continuous calcium infusion of 10% calcium gluconate to maintain ionized calcium blood levels between 1.0 and 1.2 mmol/L.

2.4 | Data collection

Except from the CRRT, all children were treated according to the 2004-HLH protocol, including glucocorticoids, immunosuppressive agents (cyclosporine A), etoposide, etc. Children with infection-associated hemophagocytic syndrome (IAHS) were treated according to clinical and laboratory examinations to determine the responsible pathogen for anti-infection treatment. Data on patients' demographics and laboratory investigations during the first 3 days of PICU admission were prospectively collected by the attending intensivists according to standard practice in each PICU. In addition, during the PICU stay, data regarding onset, duration, and types of organ dysfunction were recorded. Pediatric Risk of Mortality III (PRISM III) scores that assessed whether the observed effect was independent to severity of illness were registered by the same intensivist daily. The following data were also recorded: age, sex, reasons for PICU admission, primary disease, comorbidities, and family history of HLH.

At the time of starting CRRT, the following data were gathered prospectively: reasons for CRRT initiation, days in PICU until CRRT initiation, total fluid intake and output from admission to the PICU until initiation of CRRT, mechanical ventilation and the number of vasoactive drugs to support respiratory and circulation. During CRRT therapy, a daily record was kept for the maximum dose of heparin, ultrafiltration rate, life of each filter, CRRT-related complications and PICU mortality. Reasons to terminate CRRT were as follows: patient death/withdrawal of support, inability to continue CRRT, or regained organ function. Laboratory values were recorded when patients were admitted to the PICU and within 72 h after diagnosis of SHLH.

2.5 | Statistical methods

The statistical analyses were performed with IBM SPSS Statistics V.22.0 (IBM, Armonk, NY). Continuous variables were summarized as means ± SDs for normal distribution data, and as median (interquartile range) for abnormal distribution data. Independent-samples t test (for normal distribution data), Mann–Whitney U tests (for abnormal distribution data), or Chi-square (for categorical variables) was used to compare parameters in the two groups. Univariate and multivariate logistic regression were performed to analyze the influence of each factor on PICU mortality. The ability of factors to predict hospital mortality was tested using receiver operating characteristic (ROC) curve by STATA 15.0 MP (College Station, TX, USA). The cutoff values were identified according to the highest Youden index (sensitivity + specificity − 1) [19]. A p value less than 0.05 is considered significant.

3 | RESULTS

3.1 | Patient's characteristics

Over the 5-year study period, a total of 114 patients were screened for eligibility and 52 patients were eventually enrolled in this analysis (Figure S1). The average age was 24.5 (IQR: 12–89) months and 28 patients (53.8%) were boy. Thirty-three patients (63.5%) received CVVH, and nineteen patients (36.5%) received CVVHDF. Infection associated hemophagocytic syndrome (IAHS) was the most frequently type of SHLH (n = 46, 88.5%), among which 40 cases were Epstein–Barr virus-triggered. The average length of CRRT was 43 (IQR: 24–86.5) h. The overall PICU mortality among the included cases was 46.2% (24/52). There was no significant difference between survivors and non-survivors with respect to age, sex, PRISM III score at PICU admission, and the type of SHLH. Length of PICU stay, number of organ dysfunction,

usage of mechanical ventilation, and usage of vasoactive agents were significantly differed between survivors and non-survivors. Details of the characteristics were shown in Table S1.

3.2 | Risk factors for PICU mortality

Of the laboratory characteristics tested at CRRT initiation, serum lactate dehydrogenase (LDH), lactic acid (LAC), triglyceride and interleukin-6 (IL-6) were found to be significantly higher in patients who were non-survivor (Table 1, All $p < 0.05$). No difference was observed in serum IL-1, IL-10, TNF-a, SCD25, IL-8, IL-12, and IL-18 between patients discharged alive from PICU and those who died during PICU stay (All $p > 0.05$).

Logistic regression analysis using PICU mortality as the endpoint was performed (Table 2). Regression modeling identified two independent risk factors associated with death: the number of organ dysfunction (OR: 3.464; 95% CI: 1.018–11.788, $p = 0.047$), and the serum IL-6 level at CRRT initiation (OR:1.388; 95% CI: 1.058–1.821, $p = 0.018$). The most discriminative cutoff points were assessed by the highest Youden index in the ROC curves. 13.12 pg/ml serum IL-6 and three organs dysfunction at CRRT initiation were identified as the cutoff points with promising sensitivity and specificity for the prediction of death, which can also be illustrated by the AUC values (IL-6: 0.896, 95%CI: 0.806–0.986; organ dysfunction: 0.964, 95% CI: 0.913–1.000, Tables 3 and 4).

Our study has some limitations. First, gene sequencing was not performed in all patients, so that the proportion of FHL remained uncertain. Second, although this study was based on a multicentered prospective study, only a relatively small number of patients was enrolled owing to the extreme rarity of the disease. Third, even if

TABLE 1 The laboratory variables for survivors vs. non-survivors

Biological parameters median (IQR)	ALL ($n = 52$)	Survivor ($n = 28$)	Non-survivor ($n = 24$)	p
TBIL, μmol/L	25.18 (8.09, 56.73)	15.53 (5.76, 51.76)	44.02 (11.47, 72.89)	0.128
DBIL, μmol/L	13.99 (4.08, 40.66)	8.66 (3.03,28.03)	34.37 (5.23, 43.84)	0.061
ALT, μmol/L	121.5 (68.96, 256.06)	147.0 (74.25, 256.18)	83.96 (39.18, 318.78)	0.313
ALB, g/L	28.39 (24.89, 32.74)	29.42 (25.05, 33.75)	26.75 (24.75, 32.69)	0.245
LDH, IU/L	1030.5 (720.25, 1868)	982.7 (692, 1461)	1404.5 (713.252793)	0.037
BUN, mmol/L	4.14 (2.96, 7.53)	3.84 (2.79, 5.28)	4.80 (2.79, 10.11)	0.163
CR, μmol/L	24.77 (18.45, 41.8)	23.38 (18.15, 35.75)	26.68 (17.78, 81.08)	0.409
PT, s	14.6 (13.75, 18.6)	14.2 (12.45,18.23)	16.85 (14.03, 20.2)	0.057
FIB, g/L	0.59 (0.35, 1.19)	0.54 (0.32, 1.68)	0.66 (0.34, 0.91)	0.666
LAC, mmol/L	1.7 (1.15, 2.93)	1.65 (0.80, 2.45)	1.90 (1.30, 4.53)	0.034*
WBC, 10^9/L	3.30 (1.29, 7.01)	3.62 (1.45, 7.11)	2.94 (1.02, 8.22)	0.441
Hemoglobin, g/L	85 (73, 96.5)	81.5 (68.25, 99)	89 (77.25, 97.5)	0.797
Platelets, 10^9/L	63 (34.25, 84.75)	66 (27, 85.75)	59 (35.75, 96.75)	0.582
Triglyceride, mmol/L	2.65 (1.81, 3.67)	2.41 (1.63, 3.32)	2.88 (1.94, 5.08)	0.024
Ferritin > 1500 ng/ml, n (%)	43 (82.69)	22 (78.57)	21 (87.5)	0.082
IL-6, pg/ml	5.27 (0.62, 23.08)	0.98 (0.10, 4.63)	28.66 (17.77, 113.63)	<0.001
IL-1, pg/ml	1.045 (0.12, 2.33)	0.92 (0.11, 2.36)	1.22 (0.11, 2.61)	0.852
IL-10, pg/ml	4.06 (0.1, 39.18)	3.43 (0.29, 21.22)	10.35 (0.1, 182.74)	0.081
TNF-a, pg/ml	1.45 (0.10, 10.45)	1.44 (0.10, 10.31)	1.45 (0.1, 12.75)	0.383
SCD25, pg/ml	30426.5 (15950.46, 52028.6)	29074.39 (12526.45, 56262.46)	36862.5 (21893.18, 47356.85)	>0.999
IL-8, pg/ml	3.72 (0.10, 32.39)	3.72 (0.10–34.68)	4.09 (0.1, 66.24)	0.662
IL-12, pg/ml	0.77 (0.10, 6.25)	0.76 (0.10, 5.09)	0.93 (0.1, 6.31)	0.286
IL-18, pg/ml	344.15 (95.73, 1626.42)	542.1 (88.01, 2259.71)	326.16 (98.96, 1422.04)	0.857

Abbreviations: ALT, alanine transaminase; BUN, blood urea nitrogen; DBIL, direct bilirubin; FIB, fibrinogen; IL, interleukin; LAC, lactic acid; LDH, lactate dehydrogenase; PT, prothrombin time; TBIL, total bilirubin; WBC, white blood cell.

*$p < 0.05$.

TABLE 2 Predictive capacity for PICU mortality of the selected variables in patients with SHLH and MODS receiving CRRT

Variables	Odds ratio	95% CI	*p*
IL-6	1.388	1.058–1.821	0.018*
Number of organ dysfunction	3.464	1.018–11.788	0.047*
LAC	0.773	0.194–3.084	0.715
Triglyceride	1.633	0.814–3.279	0.168
LDH	1.732	0.528–3.252	0.232
Age	0.997	0.968–1.028	0.863

Note: Only factors with statistical significance in the univariate analyses were included, *$p < 0.05$.

TABLE 3 ROC analysis of IL-6 and number of organ dysfunction in the PICU mortality of patients with SHLH and MODS

Variables	Cutoff point	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Number of Organ dysfunction	3.0	95.8	75.0	23/30 (76.7)	21/22 (95.5)
IL-6	13.12	91.7	100.0	22/22 (100.0)	28/30 (93.3)

Note: The highest Youden Index determined the most discriminative cutoff point for the number of Organ dysfunction and the serum IL-6 level at PICU admission.

TABLE 4 ROC analysis of IL-6 and number of organ dysfunction in the PICU mortality of patients with SHLH and MODS

				95% confidence interval	
Variables	AUC	SE	*p*	Upper limit	Lower limit
Number of organ dysfunction	0.896	0.046	<0.001*	0.806	0.986
IL-6	0.964	0.026	<0.001*	0.913	1.000

*$p < 0.05$.

the number of patients were similar between survivors and non-survivors, yet the total number of patients were too small to apply matching in this analysis, which might bring a certain level of bias in this result.

4 | DISCUSSION

To our knowledge, our study is the largest, multicenter, prospective study of CRRT conducted in critically ill children with SHLH-associated MODS. Our data demonstrated that the number of organ dysfunction and serum IL-6 level at CRRT initiation are independent risk factors of initial PICU mortality. Specifically, serum IL-6 higher than 13.12 pg/ml and more than three organs dysfunction at CRRT initiation had a distinguished predictive effect to death. We also observed that children with SHLH and MODS received CRRT in PICU was associate ed with a high PICU mortality at 46.2% (22/52).

The prognostic significance of cytokines for early death has been extensively reported in prior researches [20, 21]. Particularly, previous study in patients with HLH showed a higher level of IL-6, IFN-γ, and IL-10 in the non-survivor group [22]. IL-6 levels are usually significantly elevated in patients with sepsis, which is considered to be the major cause of morbidity and mortality in pediatric SHLH patients [23]. Besides, the abrupt onset of MODS that often occurred at the advanced stage of SHLH is considered correlating with abnormally higher concentrations of hypercytokinemia including interferon-γ (IFN-γ), tumoral necrosis factor-α (TNF-α), interleukin-10 (IL-10) and IL-6 [24]. It is worth noting that IL-6 amplifies TLR-induced inflammatory response also in cells originating from inflammatory site. In vitro, Caiello et al. demonstrated that prolonged exposure of human macrophages to IL-6 leads to increased production of cytokines, including chemokine (C-X-C Motif) Ligand 8 (CXCL-8) and TNF-α [25]. A single-center study also reported that renal failure was related to abnormally high concentrations of nephrotoxic interleukin-6 (IL-6) in serum [26]. Similarly, our data consists with the previous results that elevated serum IL-6 levels at baseline was significantly associated with subsequent death. We further found that highly elevated IL-6 level (>13.12 pg/ml) was an independent risk factor of hospital death in critically SHLH-associated MODS pediatric patients. However, the

level of other cytokines at baseline including IL-10 and TNF-α were not statistically different between survivors and non-survivors, suggesting no predictive value for death among children with SHLH-associated MODS. Therefore, it might be reasonable to consider IL-6 level greater than 13.12 pg/ml as a prognostic factor to death in our population.

Aside from the laboratory characteristics, the number and severity of organ dysfunctions is also the leading prognostic factor of hospital death in SHLH patients. Numerous studies reported over half of deaths occur within 30 days after SHLH diagnosis due to MODS or secondary infection [27, 28]. Leow et al. [29] previously assessed the survival outcome of pediatric patients with HLH admitted to the cardiac ICU, they found that patients with a higher mortality index score at admission, higher serum lactate levels, the need for mechanical ventilation, vasoactive and CRRT had an increased risk of death. These results are rather comparative to our analysis in the pediatric patients with SHLH. We demonstrated a correlation between the number of organ dysfunctions and mortality and found that the rate of organ support (mechanical ventilation, vasoactive agents) usage was significantly higher in the non-survival group. In terms of the organ dysfunction, the additional analysis for the types of organ dysfunction identified a significantly higher percentages of respiratory, cardiovascular, and gastrointestinal dysfunctions among non-survivors.

The overall mortality rate of HLH ranges across studies from 22% to 59% based on a recent published epidemiological review [30]. In recent years, a myriad of studies has begun to pay meticulous attention to the mortality among critically ill patients, especially in pediatric patients, with SHLH admitted to the ICU. In 2018, Gregory and colleagues described a single center experience of HLH in a PICU over a 10-year period, which including 42 patients. They reported an overall initial PICU hospitalization mortality and the 1-year mortality of 21% and 42%, respectively [9]. Owing to the prompt improvement in chemotherapy, multiple organ support technology and intensive care management, the survival of critical ill patients has been extensively prolonged. Nevertheless, there is no published literature reporting mortality in SHLH-associated MODS patients required CRRT. In our registry, total initial PICU hospitalization mortality for our patient cohort was 46.2% (22/52), which is higher compared to the data in other reports. Medications, such as corticosteroids and immunosuppressants, are recommended in SHLH treatment to suppress the inflammatory response and control cell proliferation [31, 32]. However, corticosteroids and immunosuppression leave many SHLH patients susceptible to infection which might trigger reactivation of the underlying hyperinflammatory response and lead to additional morbidity and mortality. This poor prognosis suggested an urgent need of novel therapies in the future for patients with SHLH and MODS who need CRRT.

In summary, the number of organ dysfunction (≥3), and increased IL-6 (≥13.2 pg/ml) at CRRT initiation are independent prognostic factors for the prediction of early death in children with SHLH and MODS who underwent CRRT. These findings may help guide the treatment decision making for this disease to avoid insufficient therapy. In addition, IL-6 can be designated as a particular cytokine biomarker for SHLH-associated MODS patients. Inhibiting IL-6 may be a potential therapeutic strategy to reverse the course of disease.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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SUPPORTING INFORMATION

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