Prognostic death factors in SHLH children with MODS receiving CRRT: a multicenter prospective nested case-control study

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Research

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Abstract

Background: Multiple organ dysfunction syndrome (MODS) with secondary hemophagocytic lymphohistiocytosis (SHLH) causes significant mortality, while continuous renal replacement therapy (CRRT) is commonly conducted. The objective is to identify the predictor factors associated with poor outcomes in pediatric patients with SHLH -associated MODS who received CRRT.

Methods: A multicenter prospective nested case-control study in four PICUs of tertiary university children's hospital in Shanghai from September 2013 to August 2018.We prospectively studied 52 SHLH-associated MODS pediatric patients receiving CRRT.

Results: Overall PICU mortality rate was 46.15%(24/52). Less respiratory (28.6% vs. 87.5%, P <0.001) or cardiovascular dysfunction (25% vs. 83.3%, P <0.001) caused in survivors at CRRT initiation, as well as reduced demands of mechanical ventilation and vasoactive agents (28.6% vs. 87.5%,17.9 % vs. 66.7 %, both P <0.001). Non-survivors had higher levels of serum lactate dehydrogenase (1404.5 (713.25, 2793) vs. 982.7 (692, 1461) (U/L), P = 0.037), lactic acid (1.9 (1.3, 4.53) (mmol/L) vs. 1.65 (0.8, 2.45) , P=0.034), triglyceride (2.88 (1.94, 5.08) (mmol/L) vs. 2.41 (1.63, 3.32), P=0.032) and IL-6 (28.66 (17.77, 113.63) (pg/ml) vs.0.98 (0.1, 4.63) P=0.000). More than 3 organ dysfunction (Odd ratio [OR] : 3.464; 95% confidence interval [CI] [1.018-11.788], P = 0.047), and the serum IL-6 level higher than 13.12 pg/mL (OR :1.388; 95% CI [1.058-1.821], P = 0.018) were two independent risk factors for mortality.

Conclusions: The number of organ dysfunction and IL-6 levels at CRRT initiation are the independent risk factors for mortality in SHLH-associated MODS patients.

Background

Secondary hemophagocytic lymphohistiocytosis (SHLH) without familial history or known genetic predisposition is considered an overwhelming and life-threatening systemic inflammatory syndrome. SHLH can be related to infectious diseases (IAHS), associated with autoimmune diseases (MAS), or due to malignancies (M-HLH). Over half of all the SHLH cases culminate in multiple organ failure, with up to 86% requiring admission to the intensive care unit (ICU). Among ICU patients, SHLH are usually triggered by infection disease and sepsis[1].

Appling initial chemotherapy including etoposide combined with steroids and cyclosporine A in a timely fashion is important for survival. However, despite advances and improvements in chemotherapy, in 20% of cases, SHLH patients do not respond to conventional treatment, many of these patients die of rapid deterioration due to severe sepsis and MODS[2]. The mortality rate in SHLH with MODS patients has remained unacceptably high, at greater than 50% in some studies[3]. In children, SHLH may present with more acute fulminant manifestations and the incidence of MODS was higher than adults[4, 5]. Poor outcomes in children with SHLH-associated MODS have led to a call for action to improve early diagnosis, institute new preventive measures, and develop new treatments to improve clinical outcomes.

Recently, Continuous renal replacement therapy (CRRT) has evolved from standard renal replacement therapy into an especially unique role in “mutiple-organ support technology” for MODS patients. CRRT is very effective in removal of inflammatory mediators, as well as maintaining fluid balance and hemodynamic stability for critical ill patients[6]. Aggressive application of CRRT was found to decrease mortality in adult patients with septic shock and MODS[7]. SHLH patients may need CRRT for renal replacement, inflammatory mediator or cytokine removal. Similarly, CRRT is an important treatment for severe SHLH patients, although there are insufficient studies regarding the efficacy and indications for CRRT in the pediatric HLH ICU population. We previously found that high-volume hemofiltration may improve organ function by decreasing tumor necrosis factor-α and interleukin-6, which might be an effective adjunctive treatment in secondary hemophagocytic lymphohistiocytosis[8]. The mortality among children with MODS requiring CRRT continues to be very high. Therefore, it is important for physicians to identify patients in whom aggressive treatment may offer recovery or those who may benefit from CRRT.

To the best of our knowledge, there are no available data on outcomes of critically ill children with SHLH and MODS receiving CRRT and identifying relevant prognostic factors. In this study, we initially analyzed survival outcomes among 52 pediatric patients with SHLH and MODS receiving CRRT. Then we assessed predictive factors for survival outcome. PRISM scores were used to assess whether the observed effect was independent of severity of illness.

Methods

Design and setting

We performed a prospective multicentre observational cohort study between August 2013 and July 2018 from 4 tertiary care PICUs in Shanghai. Fifty-two critically ill children were enrolled in this study. The protocol was approved by each institution's ethics/investigation review board (2016R011-F01).Informed to participation in the study consent 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 and MODS diagnostic criteria, 3) treated with HLH-2004 protocol, 4) receiving CRRT during the PICU stay[9]. MODS was defined as the underlying primary disease process leading to at least two organ system dysfuction at any time during PICU stay[10]. Patients with familial history or known genetic predisposition(primary HLH)were excluded from analysis. Data from enrolled patients were entered into standardized electronic case report forms (CRF).

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 hyperammonaemia;

6) severe electrolyte imbalance which did not respond immediately to conventional therapy (hyperkalaemia > 7 mmol/L; hypernatraemia > 160 mmol/L or hyponatraemia < 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.

Two CRRT devices were used, including the Plasauto iQ21 (Asahi KASE, Japan), and PRISMA flex (Gambro Renal Products, France). Polyacrylonitrile AN69 or polysulfone hollow-fibre haemofilters were used, depending on the body surface area of the patient and on the pump employed. M10 filters (Gambro Renal Products, France) or AEF-03(Asahi KASE, Japan) were used in children weighing less than 5 kg; M60 (Gambro Renal Products, France) or (Asahi KASE, Japan) was used in patients weighing between 5 and 35 kg, and M100 (Gambro Renal Products, France) or AEF-10 (Asahi KASE, Japan) in children weighing over 35 kg. Thirty-three patients (63.5%) received CVVH, and nineteen patients (36.5%) received continuous venovenous hemodiafiltration (CVVHDF) with an ultrafiltrate flow rate of 35–50 mL/kg/hr. Hemofilters changes were scheduled every 24 h or when clotted.

The dosage of was 5-20U/kg.h to maintain activated partial thromboplastin time (APTT) with 1.5-2 folds of normality during CRRT. Anticoagulation was achieved with heparin adjusted to a target activated partial thromboplastin time (APTT) of 41.5- to 2-fold of normal value. 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.

Data collect

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 PICU stay, data regarding onset, duration and type of organ dysfunction, Pediatric Risk of Mortality III (PRISM III) scores were registered by the same intesivist daily. The following data were also recorded: age, sex, reasons for PICU admission, primary disease, comorbidities and family history of HLH.

Initiation of CRRT and prescription of replacement and dialysis doses were based on the decisions of the PICU attending intensivist. 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.

CRRT is performed either as continuous venovenous hemofiltration (CVVH) or haemodiafiltration (CVVHDF). During CRRT therapy, a daily record was kept of 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 upon admission to the hospital, admission to the PICU, and initiation of CRRT.

Statistical Methods

The statistical analyses were performed with IBM SPSS Statistics V.22.0 (SPSS Inc, Chicago). 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. Proportions were compared using the $\chi 2$ test or by linear-by linear $\chi 2$ association test in case of ordinal categorical variables. Univariate and multivariate analyses 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 performed using STATA 15.0 MP (College Station, Texas, USA). Cut-off values were identified using the highest Youden index (sensitivity + specificity^{-1})[11]. Significance was taken as a P value less than 0.05.

Result

Patient’s characteristics

Baseline Characteristics of Pediatric Patients With SHLH

Over the 5-year study period, a total of 114 patients were screened and 52 cases were enrolled. (Fig. 1). Among these patients, the mean age was 24.5 months (12–89 mo) and 28 patients (53.8%) were male. Of 52 patients with SHLH required CRRT, 24 patients died and overall hospital mortality was 46.15%. The characteristics of the patients included are shown in Table 1The etiology of the SHLH disease was most frequently infection-related (n = 46, 88.5%), among which 87.0% was EBV-SHLH (n = 40). The common indications for PICU admission was hypoxemia (34.6%, n = 18), cardiovascular dysfunction (28.9%, n = 15), recurrent seizures (18.9%, n = 10) or AKI (17.3%, n = 9) .The main reasons for CRRT were fluid overload (FO) (42.3%, n = 22), hepatic dysfunction (30.8%, n = 16), acute kidney injury (AKI) (17.3%, n = 9), and severe electrolyte imbalance (7.5%, n = 4). The femoral vein was catheterized in 69.2% of patients (36/52), and the jugular vein in 30.8%(16/52). At the time of starting CRRT, mechanical ventilation required in 44.1% (33/52) patients, vasoactive drugs continuously infused in 28.8% (14/52) patients, and 23.1% (12/52) of them received diuretics. Anticoagulation was achieved using heparin in 69% of patients (36/52) and citrate in 31% of patients (16/52). The mean length of CRRT was 43 (24, 86.5) hours.

Risk factors for PICU mortality

Overall PICU mortality for all admissions was 46.2% (24/52). There were no significant difference between survivors and nonsurvivors with respect to age, sex, EBV infection, Pediatric Risk of Mortality III (PRISM III) score at PICU admission, and the type of SHLH. For all patients, the factors that were

significantly different between survivors and nonsurvivors were the length of PICU stay, number of organ dysfunction, mechanical ventilation, and vasoactive agents needed.

Table 2 lists data comparing laboratory variables for survivors versus non-survivors. TBIL, DBIL, ALT, AST, ALB, PT, FIB, BUN and CR, as well as WBC, HB, PLT level at CRRT initiation were no different for survivors compared to non-survivors. In contrast, non-survivors had significantly higher levels of serum LDH (1404.5 (713.25, 2793) vs. 982.7 (692, 1461) (U/L), P = 0.037), LAC(1.9 (1.3, 4.53) (mmol/L) vs. 1.65 (0.8, 2.45), P = 0.034), triglyceride (2.88 (1.94, 5.08) (mmol/L) vs. 2.41 (1.63, 3.32), P = 0.032) at CRRT initiation.

Table 1
Demographic and clinical data at CRRT initiation

	ALL (n = 52)	Survivor (n = 28)	Non-survivor (n = 24)	p
Male, n (%)	28 (53.8)	18 (64.3)	10 (41.7)	0.103
Age,month,median (IQR)	24.5 (12.0, 89.0)	22.0 (13.5, 89.0)	26.5 (11.5, 75.5)	0.985
Length of PICU stay, day, median (IQR)	24.0(14.0, 33.0)	30.5(22.5, 40.5)	15.0(6.0, 23.0)	0.000
Expenses of PICU RMB, median (IQR)	83810 (54678, 16047)	88946.35 (59844, 122177)	78759 (45493, 130566)	0.941
PRISM score, median (IQR)	15(13, 21)	14(11, 21)	17(12, 23)	0.427
Type of SHLH				
IAHS, n (%)	46(88.5)	23(82.1)	23(95.8)	0.123
EBV-SHLH, n (%)	40(76.9)	19(67.9)	21(87.5)	0.094
MAS, n (%)	6(11.5)	5(17.9)	1(4.2)	0.123
Organ dysfunction at CRRT, n (%)				
Respiratory	29(55.8)	8(28.6)	21(87.5)	< 0.001
Cardiovascular	27(51.9)	7(25.0)	20(83.3)	< 0.001
Gastrointestinal	20(38.5)	3(10.7)	17(70.8)	< 0.001
Hepatic	45(86.5)	24(85.7)	21(87.5)	0.851
Hematologic	48(92.3)	26(92.9)	22(91.7)	0.872
Renal	16(30.8)	7(25.0)	9(37.5)	0.330
Neurologic	16(30.8)	7(25.0)	9(37.5)	0.330
Number of Organ dysfunction, median (IQR)	4.0(2.5, 5.0)	3.0(2.0, 3.5)	5.0(5.0, 5.0)	0.000
Mechanical ventilation, n (%)	23(55.8)	8(28.6)	15(87.5)	0.000

	ALL (n = 52)	Survivor (n = 28)	Non-survivor (n = 24)	p
vasoactive agents, n (%)	21(40.4)	5(17.9)	16(66.7)	0.000
Indication for CRRT, n (%)				
AKI	12(22.2)	6(21.4)	6(25.0)	0.761
FO	9(17.3)	5(17.9)	4(16.7)	0.910
Remove Inflammatory Mediators	52(100)	28(100)	24(100)	1.000
CRRT mode, n (%)				
CVVH	14(26.9)	9(32.1)	5(20.8)	0.359
CVVHDF	38(73.1)	19(67.9)	19(79.2)	0.359
Interval time of CRRT initiation after SHLH diagnosis ≥ 3days, n(%)	51(98.1)	28(100)	23(95.8)	0.275
mean length of CRRT (h), median (IQR)	43(24, 86.5)	34(12,71)	45.5(30.25 82.5)	0.344

Table 2

The laboratory variables for survivors versus nonsurvivors.

Biological Parameters median (IQR)	ALL n = 52	Survivor n = 28	Nonsurvivor n = 24	p
TBIL, umol/L	25.18(8.09, 56.73)	15.53(5.76, 51.76)	44.02(11.47, 72.89)	0.128
DBIL, umol/L	13.99(4.08, 40.66)	8.66(3.03,28.03)	34.37(5.23, 43.84)	0.061
ALT, umol/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(713.25,2793)	0.037
BUN, mmol/L	4.14(2.96, 7.53)	3.84(2.79, 5.28)	4.8(2.79, 10.11)	0.163
CR, umol/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(0.8, 2.45)	1.9(1.3, 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)	0.000
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

Total bilirubin (TBIL); Direct bilirubin (DBIL); Lactate dehydrogenase (LDH); Alanine transaminase (ALT); Blood Urea Nitrogen (BUN); Prothrombin Time (PT); fibrinogen (FIB); Lactic acid (LAC); white blood cell (WBC); interleukin (IL)

*$p < 0.05$

Biological Parameters median (IQR)	ALL n = 52	Survivor n = 28	Nonsurvivor n = 24	p
SCD25, pg/mL	30426.5(15950.46, 52028.6)	29074.39(12526.45, 56262.46)	36862.5(21893.18, 47356.85)	1.000
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
Total bilirubin (TBIL); Direct bilirubin (DBIL); Lactate dehydrogenase (LDH); Alanine transaminase (ALT); Blood Urea Nitrogen (BUN); Prothrombin Time (PT); fibrinogen (FIB); Lactic acid (LAC); white blood cell (WBC); interleukin (IL)				
*p < 0.05				

Table 3
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
Only factors with statistical significance in the univariate analyses were included, *P < 0.05			

In addition, patients with SHLH and MODS who died during their hospital displayed a significantly higher IL-6 (28.66 (17.77, 113.63) (pg/ml) vs.0.98 (0.1, 4.63) P = 0.000) at CRRT initiation when compared to those who survived. 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.

Logistic regression analysis using PICU mortality as the endpoint was performed on categorical and continuous variables. Regression modeling identified two independent risk factors of mortality: the number of Organ dysfunction (OR: 3.464; 95% CI [1.018–11.788], P = 0.047), and the serum IL-6 level (OR:1.388; 95% CI [1.058–1.821], P = 0.018). Receiver Operating Characteristic (ROC) curve was used to evaluate the power of the two independent variables. The number of Organ dysfunction and the serum IL-

6 level at PICU admission were found high discriminative power with AUC values respectively of 0.896 (SE 0.046, 95% CI 0.806–0.986) and 0.964 (SE 0.026, 95% CI 0.913-1.00).

Furthermore, we used the highest Youden Index to determine the most discriminative cut-off point for the number of Organ dysfunction and the serum IL-6 level at PICU admission to predict PICU mortality (Table 4–5, Fig. 2). A value of serum IL-6 level of 13.12 pg/ml and the number of Organ dysfunction of 3 at CRRT initiation have been identified as cut-off points.

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

Variables	Cut-off 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)
The highest Youden Index determined the most discriminative cut-off point for the number of Organ dysfunction and the serum IL-6 level at PICU admission					

Table 5
ROC analysis of IL-6 and number of organ dysfunction in the PICU mortality of patients with SHLH and MODS

Variables	AUC	SE	P	95% confidence interval	
				upper limit	lower limit
Number of Organ dysfunction	0.896	0.046	0.000*	0.806	0.986
IL-6	0.964	0.026	0.000*	0.913	1.000
*p < 0.05					

Discussion

To our knowledge, our study is the largest, multicenter, prospective study of CRRT conducted in critically ill children with SHLH-associated MODS. Furthermore, we additionally reported the first data on detailing the PICU course and outcome of these patients. We observed that patients with SHLH and MODS received CRRT in PICU was associated with a high PICU mortality at 46.2% (22/52). Our data also demonstrated that the number of organ dysfunction and serum IL-6 level at CRRT initiation higher than 3 and 13.12 pg/ml are independent risk factors of initial PICU mortality.

The overall mortality rate from HLH ranges across studies from 22 to 59%[12]. In recent years, a trend to a reduction in mortality among critically ill patients with SHLH admitted to the ICU was observed. In the sub-group of pediatric patients, the same trend was also found. In 2018, Gregory and colleagues described a single center experience of HLH in a PICU over a 10-year period, which including 42 patients, overall initial PICU hospitalization mortality and 1-year mortality was 21% and 42% respectively[13]. This outcome benefits may be owed to improvement in chemotherapy, multiple organ support technology and better intensive care management. 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). This may shed light onto the quite poor outcomes among patients with SHLH and MODS who need CRRT. Thus, the development of therapies targeted at preventing or limiting the progress of MODS is urgently needed.

MODS is the leading cause of hospital death in SHLH patients and the prognosis depends mainly on the number and severity of organ dysfunctions. Numerous studies reported over half of deaths occur within 30 days after SHLH diagnosis due to MODS or second infection[14, 15]. Leow et al[16], assessed poor prognostic factors and mortality for pediatric patients with HLH admitted to the cardiac ICU, they found patients with a higher mortality index score at admission, higher serum lactate levels, the need for mechanical ventilation, vasoactives and CRRT were associated with higher mortality. Indeed, we demonstrated a correlation between the number of organ dysfunctions and mortality. Significantly, nonsurvivors had more respiratory, cardiovascular and gastrointestinal dysfunctions. Likewise, the use of organ support (mechanical ventilation, vasoactive agents) was also higher in the nonsurvivors.

Abrupt onset of rapid progress to MODS is common in fatal HLH patients[17] MODS is often reported at the advanced stage of SHLH and is related to abnormally higher concentrations of hypercytokinemia including interferon-γ(IFN-γ), tumoral necrosis factor-α (TNF-α), interleukin-10 (IL- 10), IL-6 and so on[18]. IL-6 amplifies TLR-induced inflammatory response also in cells originating from inflammatory site. In vitro, Claudia et al. demonstrated that, prolonged exposure of human macrophages to IL-6 leads to increased production of cytokines, including (C-X-C Motif) Ligand 8 (CXCL-8) and Tumor Necrosis Factor-α (TNF-α)[19]. A single-center study reported, renal failure was related to abnormally high concentrations of nephrotoxic interleukin-6 (IL-6) in serum[20]. Our data demonstrated that serum IL-6 levels was positively associated with the number of dysfunction organs on correlational analysis which corroborated similar findings from previous studies.

The prognostic significance of cytokines for early death has once been reported[21]. Tang et al[22] found high IFN-γ and IL-10 levels were associated with early death. It is worth noting that, in our study serum IL-6 levels at PICU admission was higher in the non-survivor group than survivor group. 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. This result was consistent with previous study of HLH, which showed patients in the non-survivors group had higher IL-6, IFN-γ and IL-10 levels[23]. IL-6 levels are usually significantly elevated in patients with sepsis, which is considered to be the major cause of mobility and mortality in pediatric SHLH patients[24]. This may partially explain the phenomenon of

higher level of IL-6 in SHLH patients with death. As a result, it may be reasonable to consider IL-6 levels greater than13.12 pg/ml as a prognostic factor maker of SHLH.

Current management of SHLH-associated MODS includes prompt clinical stabilization with ICU-level organ supportive care, applying specific measures to control the hyperinflammation, identification and treatment of the underlying cause of SHLH and infectious complications. From the onset, aggressive interventions for the treatment of multiorgan dysfunction are usually conducted to stabilize the patient's status while allowing time for other therapeutic strategy to treat SHLH. Management of the hyperinflammatory response focuses on blocking excessive cytokine production and eliminating the triggers are also important[14, 25]. Medications, such as corticosteroids and immunosuppressants, are recommended in SHLH treatment to suppress the inflammatory response and control cell proliferation[9, 26]. However, corticosteroids and immunosuppression leave many SHLH patients susceptible to infection, as well as secondary infections can trigger reactivation of the underlying hyperinflammatory response leading to additional morbidity and mortality.

CRRT as a new type of renal replacement, is being used more often in critically ill children with MODS. CRRT has been also recommended as an effective therapeutic for the treatment of systemic inflammatory syndromes. With regard to severe sepsis adjunctive therapies, inflammatory mediator modulation can be achieved through hemofiltration (HF) based CRRT mode, such as continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodiafiltration (CVVHDF). One of the mechanisms for the beneficial effect of HF in sepsis may be the convective clearance of soluble inflammatory mediators. Over the last few years, animal experiments and human studies have shown that, CVVH/CVVHDF can remove soluble inflammatory mediators of sepsis, as well as attenuate the severity of the response to sepsis. DiCarlo et al[27] 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. Our previous single-center nonrandomized concurrent control trial showed high-volume hemofiltration (HVHF) may be an effective adjunctive treatment in SHLH/MAS by improving organ function and decreasing serum level of TNF-α and IL-6[8]. There are several small reports of treatment of SHLH with alternative therapeutics directed against IL-1, IL-6 and TNF-α in serum, which have demonstrated clinical benefits for these patients[28].

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 multi-centered prospective study, relatively small number of patients was warranted to validate the results.

Conclusion

In summary, highly number of organ dysfunction (≥ 3), and highly increased IL-6 (≥ 13.2 pg/mL) at CRRT initiation are independent prognostic factors for predicting early death in children with SHLH and MODS. 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 for reversing these cases.

Abbreviations

MODS
Multiple organ dysfunction syndrome
PICU
pediatric intensive care unit
ICU
intensive care unit
SHLH
secondary hemophagocytic lymphohistiocytosis
CRRT
continuous renal replacement therapy
IAHS
infection-associated hemophagocytic
MAS
macrophage activation syndrome
M-HLH
malignancy-associated hemophagocytic lymphohistiocytosis
CRF
case report forms
CVVH
continuous venovenous hemodialysis
CVVHDF
continuous venovenous hemodiafiltration
CRRT
continuous renal replacement therapy
APTT
activated partial thromboplastin time
RCA
regional citrate anticoagulation
PRISM III
pediatric risk of mortality III
IQR
interquartile range
ROC
receiver operating characteristic
FO

fluid overload
HVHF
high-volume hemofiltration
HF
hemofiltration
TBIL
total bilirubin
DBIL
direct bilirubin
ALB
albumin
PLT
platelet counts
PT
prothrombin time
FIB
fibrinogen
BUN
serum urea nitrogen
CR
serum creatinine
HB
hemoglobin
NK
natural kill cell
OR
odd ratio
AKI
acute kidney injury
IL-1
interlukin-1
IL-6
interlukin-6
TNF-α
tumor necrosis factor-α
IFN-γ
interferon-γ
IL-10
interlukin-10

Declarations

- **Ethics approval and consent to participate**

Not applicable.

- **Consent for publication**

Not applicable.

- **Availability of data and materials**

The datasets generated and/or analysed during the current study are not publicly available due to the datasets are now having secondary analysis but are available from the corresponding author on reasonable request.

- **Competing interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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- **Authors' contributions**

YCZ and YC designed the study. JYS, YJS, YNZ, GFY and HR managed data and its quality. JYS, YJS and CXW performed the statistical analysis. YC and JYS drafted the manuscript. CXW and YCZ contributed substantially to its revision. All authors read the manuscript carefully and approved the final version.

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Not applicable.

References

1. Tothova Z, Berliner N. Hemophagocytic syndrome and critical illness: New insights into diagnosis and management. J Intensive Care Med. 2015, 30:401-412.
2. Apodaca E, Rodríguez-Rodríguez S, Tuna-Aguilar EJ, Demichelis-Gómez R. Prognostic Factors and Outcomes in Adults With Secondary Hemophagocytic Lymphohistiocytosis: A Single-center

Experience. Clin Lymphoma Myeloma Leuk. 2018;18: e373-e380.

3. Créput C, Galicier L, Buyse S, Azoulay E. Understanding organ dysfunction in hemophagocytic lymphohistiocytosis. Intensive Care Med. 2008; 34:1177-187.
4. Gregory J, Greenberg J, Basu S. Outcomes Analysis of Children Diagnosed With Hemophagocytic Lymphohistiocytosis in the PICU. Pediatr Crit Care Med. 2019;20: e185-e190.
5. Karapinar B, Yilmaz D, Balkan C, Akin M, Ay Y, Kvakli K. An unusual cause of multiple organ dysfunction syndrome in the pediatric intensive care unit: hemophagocytic lymphohistiocytosis. Pediatr Crit Care Med. 2009;10: 285-290.
6. Ronco C, Ricci Z, De Backer D, Kellum JA, Taccone FS, Joannidis M, et al. Renal replacement therapy in acute kidney injury: controversy and consensus. Crit Care. 2015;19:146.
7. Wu C, Wang X, Yu W, Li P, Liu S, Li J, et al. Short-term consequences of continuous renal replacement therapy on body composition and metabolic status in sepsis. Asia Pacific journal of clinical nutrition. 2016,25(2):300-7.
8. Cui Y, Zhang Y C, Kang Y L, Ren YQ, Miao HJ, Wang F. High-Volume Hemofiltration in Critically Ill Patients With Secondary Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome: A Prospective Study in the PICU. Pediatr Crit Care Med. 2016;17:e437-e443.
9. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007, 48(2): 124-131.
10. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International Consensus Conference on Pediatric Sepsis International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005, 6:2-8.
11. Youden WJ. Index for rating diagnostic tests. All statistical analyses were performed using SPSS (version 19, IBM-SPSS, SPSS Inc. New York, USA software. Cancer. 1950;3:32-35.
12. Al-Samkari H. Hemophagocytic Lymphohistiocytosis. Annu Rev Pathol. 2018;13:27-49.
13. Gregory J, Greenberg J. Outcomes Analysis of Children Diagnosed With Hemophagocytic Lymphohistiocytosis in the PICU. Pediatr Crit Care Med. 2019;20: e185-e190.
14. Bin Q, Gao JH. Prognostic factors of early outcome in pediatric hemophagocytic lymphohistiocytosis: an analysis of 116 cases. Ann Hematol. 2016;95:1411-1418..
15. Arca, L. Fardet L. Galicier L, Rivière S, Marzac C, Aumont C, et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. Br J Haematol. 2015, 168 (1): 63-68.
16. Leow EH, Soh SY, Tan AM, Mok YH, Chan MY, Lee JH. Critically ill children with hemophagocytic lymphohistiocytosis: A case series of 14 patients. J Pediatr Hematol Oncol. 2017, 39:e303–e306.
17. Nahum E, Ben-Ari J, Stain J, Schonfeld T. Hemophagocytic lymphohistiocytic syndrome: Unrecognized cause of multiple organ failure. Pediatr Crit Care Med. 2000, 1:51-54.

18. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood. 2004,104:735-43.
19. Caiello I, Minnone G, Holzinger D, Vogl T, Prencipe G, Manzo A, et al. IL-6 amplifies TLR mediated cytokine and chemokine production: implications for the pathogenesis of rheumatic inflammatory diseases. PLoS One. 2014; 9(10):e107886.
20. Aulagnon F, Lapidus N, Canet E, Galicier L, Boutboul D, Peraldi MN, et al. Acute kidney injury in adults with hemophagocytic lymphohistiocytosis. Am J Kidney Dis. 2015, 65(6):851-9.
21. Brisse E, Wouters CH, Matthys P. Hemophagocytic lymphohistiocytosis (HLH): A heterogeneous spectrum of cytokine-driven immune disorders. Cytokine Growth Factor Rev. 2015, 26(3):263-80.
22. Yang SL, Xu XJ, Tang YM, Song H, Xu WQ, Zhao FY, et al. Associations between inflammatory cytokines and organ damage in pediatric patients with hemophagocytic lymphohistiocytosis. Cytokine. 2016,85 :14-17.
23. Tang YM. Advances in hemophagocytic lymphohistiocytosis: pathogenesis, early diagnosis/differential diagnosis, and treatment. Scientific World Journal. 2011;11:697-708.
24. Tang Y, Xu X, Song H, Yang S, Shi S, Wei J, et al. Early diagnostic and prognostic significance of a specific Th1/Th2 cytokine pattern in children with haemophagocytic syndrome. British journal of haematology. 2008, 143(1):84-91.
25. Chandrakasan S, Filipovich AH. Hemophagocytic Lymphohistiocytosis: Advances in Pathophysiology, Diagnosis, and Treatment. The Journal of pediatrics. 2013, 163(5):1253-1259.
26. Bode SF, Lehmberg K, Maul-Pavicic A, Gera R. Recent advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis. Arthritis Res Ther. 2012;14:213.
27. DiCarlo J, Lui WY, Frankel L, Howell W, Schiffman J, Alexander S. The hemophagocytic syndrome: Titrating continuous hemofiltration to the degree of lactic acidosis. Pediatr Hematol Oncol. 2006, 23:599-610.
28. Mostaza-Fernández JL, Guerra Laso J, Carriedo Ule D, Ruiz de Morales JM. Hemophagocytic lymphohistiocytosis associated with viral infections: Diagnostic challenges and therapeutic dilemmas. Rev Clin Esp. 2014;214:320-327.

Figures

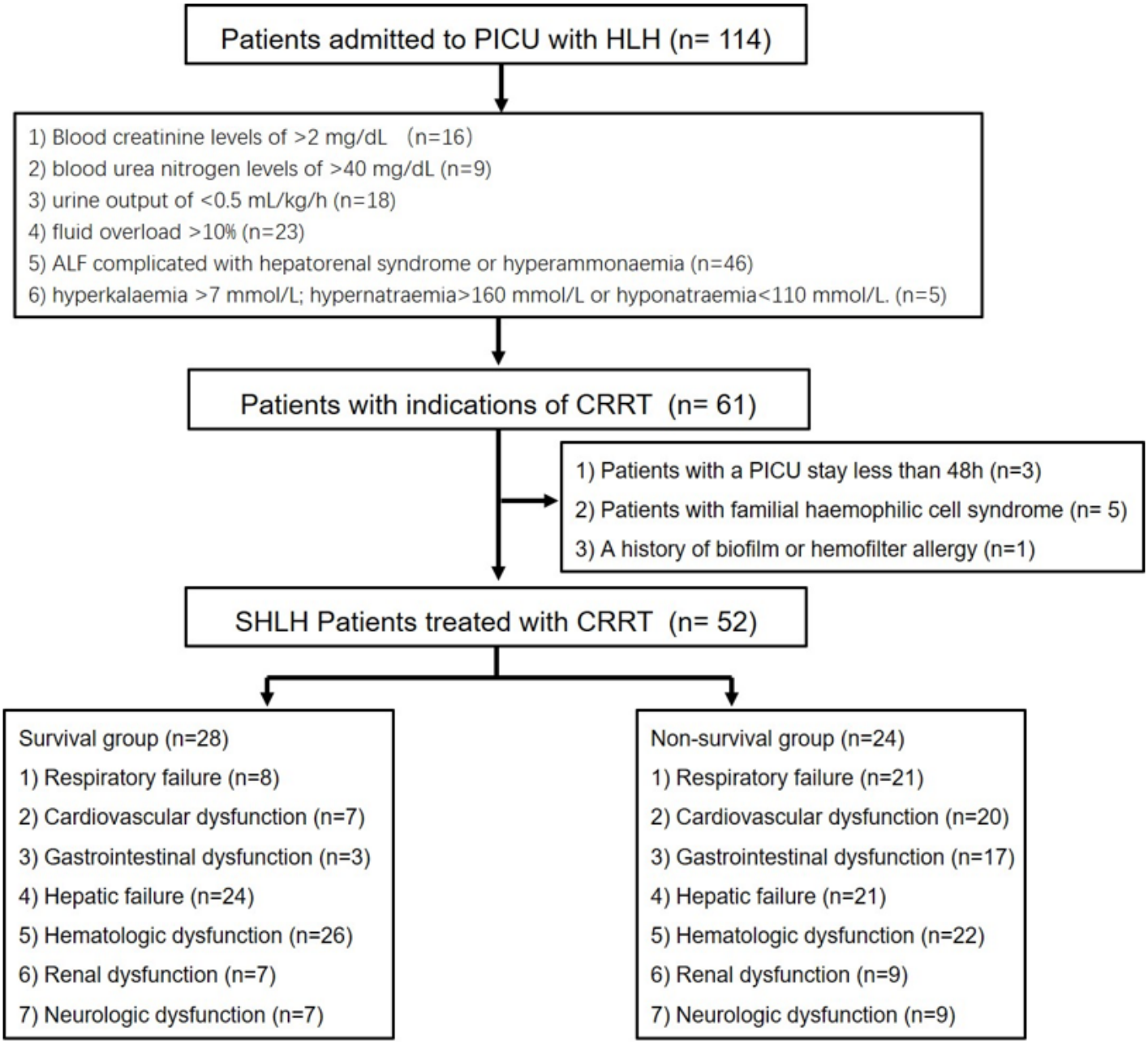

Figure 1

Flowchart of patients with SHLH enrolled in this multicenter study.

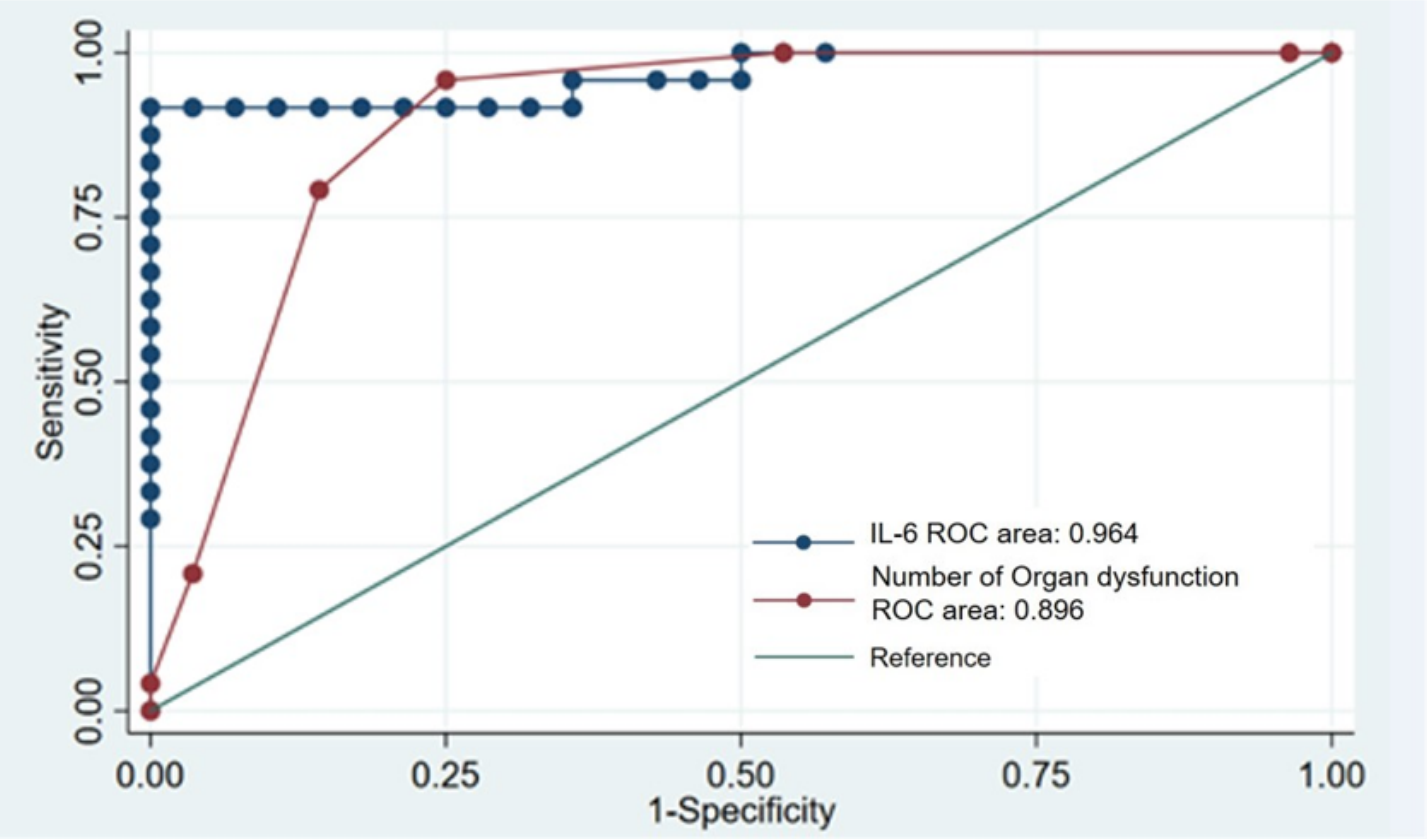

Figure 2

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

Supplementary Files

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- STROBEchecklistSHLH0206.docx