

Characteristics and Prognostic Value of Pleural Effusion in Secondary Hemophagocytic Lymphohistiocytosis

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Research

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Abstract

Background: Secondary hemophagocytic lymphohistiocytosis (sHLH) is a pathologic immune activation syndrome characterized by immune-mediated multiple organ system damage. Pleural effusion can occur as a specific manifestation of sHLH, however, has rarely been evaluated. This study aimed to describe the clinical characteristics of pleural effusion in sHLH and assess whether it affects prognosis.

Methods: We retrospectively analysed 203 newly diagnosed sHLH patients from July 2015 to July 2019 according to the HLH-2004 protocol. Baseline characteristics, laboratory results, and imaging materials were reviewed

Results: Pleural effusion was found in 58.6% of the studied sHLH population, and imaging findings were characterized by minimal amounts and bilaterality. Multivariate analyses showed that sCD25 level and $PLT \leq 65 \times 10^9/L$ were significant risk factors for developing pleural effusion in sHLH. Regarding prognostic value, survival analysis showed a lower survival probability for patients with pleural effusion than for those without pleural effusion (median OS, 90 vs. 164 days, $p = 0.028$). In the multivariate analysis, pleural effusion was an independent prognostic factor for OS (HR = 2.68; 95% CI 1.18–6.11, $p = 0.019$).

Conclusions: Pleural effusion is frequently found in patients with sHLH and is associated with a higher inflammatory state and worse outcomes.

Background

Hemophagocytic lymphohistiocytosis (HLH), caused by cytokine-dependent accumulation and aberrant activation of macrophages and cytotoxic T cells, is a life-threatening and severe hyperinflammatory syndrome^[1]. It is seen in both children and adults and is recognized as primary HLH (pHLH) or secondary HLH (sHLH)^[2]. pHLH is accompanied by inherited mutations affecting lymphocyte cytotoxicity and immune regulation. sHLH is triggered by various pathologies, mainly infections, malignancies, autoimmune disorders or unknown aetiologies, without a family history or known genetic predisposition^[3].

Clinically, sHLH symptoms is characterised by sustained fever, cytopenia, coagulopathy, and hepatosplenomegaly that may rapidly progress to terminal multiple organ failure^[4]. Early recognition of sHLH is essential to prevent irreversible organ damage and subsequent death, but it is difficult because of the nonspecific clinical manifestations and rapid disease progression. In the most serious cases, cytokine storms can result in progressive multiple organ failure involving the neurologic, cardiovascular, hepatic, and/or respiratory systems^[5]. Experimental and epidemiological data suggest that the spleen and liver are the most frequently involved organs, and nearly 60% of HLH patients have altered liver tests^[6]. Recent clinical studies have shown that pulmonary involvement is also frequent, and symptoms can include cough, dyspnoea, pleural effusion, and respiratory failure^[7]. Moreover, the COVID-19 pandemic has drawn attention to virally induced hyperinflammatory lung injury, and sometimes severe COVID-19 may be considered part of the HLH spectrum^[8]. However, little is known about pleural effusion involvement in sHLH, and relatively few

studies have addressed the clinical significance of pleural effusion. The pathophysiology and prognostic significance of pleural effusion in patients with sHLH remain unknown.

To the best of our knowledge, few studies to date have investigated the association between sHLH and pleural effusion before treatment. The incidence, distribution, possible mechanisms and significance of pleural effusion in sHLH have not been elucidated. Here, we aimed to show the characteristics of pleural effusion in sHLH and the biomarker performance associated with the development of pleural effusion. We further show the prognostic value of pleural effusion in sHLH patients

Methods

Study design and data collection

Patients who enrolled in this retrospective study fulfilled the criteria shown in Fig. 1. In total, 203 newly diagnosed sHLH patients were admitted to the First Affiliated Hospital of Nanjing Medical University from July 2015 to July 2019, with 162 individuals meeting the inclusion criteria. Patients were divided into the positive pleural effusion (PE+) group and the negative pleural effusion (PE-) group according to the presence or absence of pleural effusion at the initial diagnosis of sHLH.

Baseline clinical characteristics and laboratory data, such as age, gender, highest recorded temperature, splenomegaly, aetiologies, absolute neutrophil count (ANC), haemoglobin (HB), platelet (PLT), fibrinogen (FIB), triglyceride (TG), lactate dehydrogenase (LDH), albumin (ALB), ferritin, serum soluble interleukin-2 receptor (sIL-2R, sCD25), β 2-microglobulin (β 2-MG), and Epstein-Barr virus (EBV) infection, were collected by reviewing their medical records. Blood samples were obtained on admission, and the tests were performed by laboratory technologists at Nanjing Medical University Hospital. The results of chest X-ray, computed tomography (CT), positron emission tomography/computed tomography (PET-CT), ultrasonography, and thoracentesis were also evaluated.

Diagnosis and definitions

The diagnosis of HLH was established based on the 2004 HLH Diagnostic Criteria^[9]. PET-CT, combined with biopsy of suspicious lesions, revealed lymphoma-associated hemophagocytic lymphohistiocytosis (LHLH) and hemophagocytic lymphohistiocytosis of unknown origin (NHLH)^[10].

The diagnosis of pleural effusion was based on chest X-ray, CT, PET-CT, thoracic ultrasound, and thoracentesis. As there are no accepted definitions to describe the extent of pleural effusion, we decided to use the following criteria: minimal: a small amount of liquid, below the fourth rib level; moderate: liquid involves the fourth to second anterior ribs without clinical symptoms, or a crescent-shaped low density area is observed on chest CT, with mild compression of local lung tissue; massive: liquid involves the upper part of the second anterior rib, accompanied by clinical symptoms, or pleural effusion causes significant compression of lung tissue, a reduction in volume, close to the lung door, and a mediastinal shift to the

opposite side. In addition, early-onset effusion was defined as effusion occurring at the time of sHLH diagnosis or during the first chemotherapy cycle. Late-onset effusion was defined as any effusion occurring after the first cycle of chemotherapy.

Outcome and follow-up

Overall survival (OS) was defined as the time between the first day of diagnosis and the date of death from any cause or the last follow-up until June 2020. Follow-up was conducted by reviewing inpatient medical records and making phone calls.

Treatment

Any of the following regimens were adopted as the initial therapy: HLH-04, HLH-94 regimen, CHOP-like chemotherapy, glucocorticoid (GC), GC+intravenous immunoglobulins (IVIg) or supportive care therapy. In our 94 malignancy-associated hemophagocytic lymphohistiocytosis (MHLH) patients, 56 patients had received systemic combination chemotherapy, such as EPOCH, CHOP, and DEP; 24 patients were treated with HLH-94 or HLH-04 as the initial therapy; and 12 patients were treated with only GC+IVIg. In our 68 non-MHLH patients, 13 patients were given HLH-94 first-line treatment, GC+IVIg was administered in 12 patients, GC was administered in 10 patients, GS+IVIg+cyclophosphamide was administered in 3 patients, GC+etoposide was administered in 2 patients, and GS+IVIg+cyclosporine was administered in 2 patients. No statistically significant difference was observed in treatment regimen between the PE+ group and the PE-group.

Statistical analysis

Data analysis was performed using SPSS version 22.0 (Chicago, IL, USA), GraphPad Prism 6 (GraphPad Software, La Jolla, CA), and STATA/MP statistical software (version 16.0; StataCorp, TX, USA). Quantitative variables are reported as medians with interquartile ranges (IQRs), and categorical data are presented as frequencies and percentages. X-tile was conducted to assess biomarkers and calculate the optimal survival cut-off level. Survival functions were estimated by the Kaplan-Meier method, and subgroups were compared using a log-rank test. Univariable Cox regression analysis was applied to test baseline variables for effects on overall survival. Variables found to have significant predictive outcome were then entered in a stepwise forward multivariable Cox regression model within respective categories to adjust for potential confounding effects. A two-sided $P < 0.05$ was used to define statistical significance for all comparisons.

Results

Incidence and risk factors for pleural effusion

From July 2015 to July 2019, a total of 162 subjects with sHLH were enrolled in this retrospective study, of whom 95 (58.6%) patients developed pleural effusion at the time of diagnosis. The median time between sHLH onset and pleural effusion onset was 2 days (0-3.5 days). To determine the risk of pleural effusion, we retrospectively analyzed the demographic, clinical and laboratory characteristics of subjects with and

without pleural effusion (Table 1). For demographic and clinical parameters, there was no significant difference in age, gender, aetiology, maximum temperature, splenomegaly or treatment regimen between the PE + group and PE- group. Regarding laboratory examinations, patients with pleural effusion had lower PLT counts, HB and ALB levels and higher sCD25 levels than those without pleural effusion (all p values < 0.05). Of significance, $\lg(\text{sCD25})$ ($p = 0.011$; OR = 13.27; 95% CI: 1.81–97.11) and $\text{PLT} \leq 65 \times 10^9/\text{L}$ ($p = 0.027$; OR = 4.03; 95% CI: 1.17–13.88) were found to be risk factors for developing pleural effusion. These results were confirmed using a reduced model multivariate analysis.

Table 1
Baseline demographic, clinical, and laboratory characteristics of sHLH patients with or without pleural effusion

	Total (N = 162)	PE+ (N = 95)	PE- (N = 67)	P values
Gender				0.695
Male (%)	90 (55.6)	54 (56.8)	36 (53.7)	
Female (%)	72(44.4)	41(43.2)	31(46.3)	
Age (years)	53.5 (13–86)	54.0 (13.0–86.0)	52.0 (17.0–84.0)	0.934
Etiologies (%)				0.322
Infection	49 (30.2)	31 (32.6)	18 (26.8)	
Malignancy	94 (58.0)	52 (54.7)	42 (62.7)	
Autoimmune	9 (5.6)	4 (4.2)	5 (7.5)	
Unknown reason	10 (6.2)	8 (8.5)	2 (3.0)	
Maximum temperature (°C)	39.4 (39–40)	39.5 (39–40)	39.0 (38.9–40.0)	0.209
Splenomegaly (%)	124 (76.5)	72 (75.8)	52 (77.6)	0.149
ANC (×10 ⁹ /L)	0.91 (0.56–1.25)	0.92 (0.53–1.26)	0.91 (0.61–1.24)	0.848
HB (g/L)	80.0 (64–88.5)	76.5 (60–88)	81(69–92)	0.047
PLT (×10 ⁹ /L)	36.0 (21.0–59.0)	35 (17–53.5)	46(26.5–80.5)	0.005
ALT (U/L)	77.8 (38.5–148.6)	78.4 (41.08–164.3)	67.9 (31.0–137.6)	0.618
AST (U/L)	83.1 (48.2–197.85)	93.6 (49.6–200.3)	77.3(40.5–197.6)	0.388
LDH (U/L)	763(495.8–1226.3)	739 (485.5–1333.0)	763 (498.0–1014.0)	0.708
ALB (U/L)	26.1 (22.85–29.4)	25.2(22.08–27.95)	27.6(24.8–30.0)	0.001
TG (mmol/L)	2.91 (2.18–3.91)	2.97 (2.46–4.08)	2.74 (2.04–3.5)	0.118
ADA (U/L)	61.3 (46.0–111.0)	60.7 (46.4–110.6)	63.2 (43.2–117.9)	0.819
Fib (g/L)	1.29 (0.95–1.74)	1.24 (0.96–1.73)	1.36 (0.91–1.75)	0.566
β2-MG (mg/L)	5.22 (3.96–7.74)	5.06 (3.94–8.15)	5.27 (4.14–7.26)	0.866
Ferritin (ug/L)	3,360(1,501–11,105)	3,370(1,500–12,017)	3,360(1,505–9,203)	0.729
sCD25 (ng/L)	40,311(20,442–52,462)	44,926(25,590–58,515)	29,190(15,177–45,819)	0.006

	Total (N = 162)	PE+ (N = 95)	PE- (N = 67)	P values
EBV infection (%)	73 (45.1)	41 (43.1)	32 (47.8)	0.562
Treatment				0.052
Chem ± HLH- 94 ± HLH- 04(%)	107 (66.0)	64 (67.4)	42 (62.7)	
GC ± IVIg (%)	34 (25.3)	23 (67.6)	11 (32.4)	
Support (%)	14 (8.7)	4 (4.2)	10 (14.9)	

ANC, absolute neutrophil count; HB, hemoglobin; PLT, platelet; ALT, alanine transaminase; AST, aspartate transaminase; LDH, lactic dehydrogenase; ALB, albumin; TG, triglyceride; ALP, alkaline phosphatase; ADA, adenosine deaminase; Fib, fibrinogen; β 2-MG, β 2-microglobulin; sCD25: soluble interleukin-2 receptor; EBV: Epstein-Barr virus.

Distribution of pleural effusion

We reviewed the radiological reports at the diagnosis of 95 sHLH patients with pleural effusion and found that the most common radiologic findings were small amounts of bilateral pleural effusion with no specific pattern. In the PE + group, there were 68 (71.6%) cases of minimal pleural effusion, 19 (20.0%) cases of moderate, 8 (8.4%) cases of massive, 73 (76.8%) cases of bilateral pleural effusion, 11 (11.6%) cases of left and 11 (11.6%) cases of right. In addition, we further explored the correlations between pleural effusion levels and other laboratory data parameters, as shown in Table 2. There were significant correlations between pleural effusion levels and HB, PLT, ALB, and sCD25. Another analysis showed that there was a statistically significant difference in the incidence of pelvic effusion, pericardial effusion and ascites between the PE + group and the PE- group, indicating that patients with pleural effusion have a higher probability of pelvic effusion, pericardial effusion, and ascites (Table 3).

Table 2
Correlation analysis between pleural effusion level and other laboratory data parameters

Variables	r	P values
ANC ($\times 10^9/L$)	-0.041	0.554
HB (g/L)	-0.130	0.039
PLT ($\times 10^9/L$)	-0.205	0.001
Fib (g/L)	-0.022	0.744
$\beta 2$ -MG (mg/L)	0.073	0.401
Ferritin (ug/L)	0.025	0.717
sCD25 (ng/L)	0.279	0.002
TG (mmol/L)	0.123	0.090
ADA (U/L)	-0.049	0.524
ALB (g/L)	-0.202	0.001

Table 3
Distribution of pelvic effusion, pericardial effusion, and ascites in 162 patients with sHLH

group	pelvic effusion (%)	pericardial effusion (%)	ascites (%)
PE+	49 (51.6%)	40 (42.1%)	26 (27.4%)
PE-	19 (28.4%)	9 (13.4%)	6 (9.0%)
χ^2	8.698	15.310	8.404
P values	0.003	< 0.001	0.004

Prognostic value of pleural effusion in sHLH

After a median follow-up of 107 (interquartile range 36–425) days, 66 (69.5%) deaths occurred in the PE + group, whereas 40 (59.7%) deaths occurred in the PE- group. In the Kaplan-Meier analysis (Fig. 2), OS was significantly worse in the PE + group than in the PE- group (median OS, 90 vs. 164 days, $p = 0.028$). Table 4 summarizes the univariate and multivariate Cox regression analyses of OS for potential risk predictors in sHLH. By univariate analysis, age > 72 years, EBV infection, PLT < $30 \times 10^9/L$, FIB ≤ 1.3 g/L, TG ≥ 3.0 mmol/L, ALB < 31.7 g/L, ADA > 134.3 U/L, $\beta 2$ -MG > 6.7 mg/L, ferritin > 1500 ng/ml, and LHLH were also associated with a worse outcome. Upon multivariable adjustment, pleural effusion (HR 2.68; 95% CI 1.18–6.11), PLT <

$30 \times 10^9/L$ (HR 2.78; 95% CI 1.41–5.49), and EBV infection (HR 2.36; 95% CI 1.18–4.74) were significantly associated with poor survival.

Table 4
Univariate and multivariate Cox regression analyses of survival in 162 patients with sHLH

Variables	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P values	HR (95% CI)	P values
With pleural effusion	1.55 (1.05–2.22)	0.028	2.68(1.18–6.11)	0.019
Male	1.46 (1.00–2.13)	0.054		
Age > 72 years	2.19 (1.06–4.51)	0.003		
ANC < $1.0 \times 10^9/L$	0.94 (0.64–1.38)	0.735		
HB < 98 g/L	1.65 (1.01–2.68)	0.086		
PLT < $30 \times 10^9/L$	1.97(1.29–3.02)	< 0.001	2.78(1.41–5.49)	0.003
Fib \leq 1.3 g/L	1.93 (1.29–2.90)	< 0.001		
TG \geq 3.0 mmol/L	1.60 (1.05–2.45)	0.030		
ALB < 31.7 g/L	1.98 (1.20–3.28)	0.034		
LDH > 1000 U/L	1.30 (0.82–2.08)	0.233		
ADA > 134.3 U/L	1.94 (1.05–3.58)	0.034		
β 2-MG > 6.7 mg/L	1.83 (1.05–3.20)	0.007		
Ferritin > 1500 ng/ml	1.86 (1.01–3.42)	0.047		
EBV infection	1.51 (1.03–2.21)	0.029	2.36(1.18–4.74)	0.016
LHLH	1.61 (1.11–2.35)	0.013		

Subgroup analysis on the predictive power of pleural effusion in sHLH

We performed subgroup analyses to eliminate the effect of confounding factors, including age, gender, pathogenesis, EBV infection, neutrophils, haemoglobin, platelets, fibrinogen, and albumin. As shown in Fig. 3, the positive associations between pleural effusion and poor survival were stronger among males and patients with ANC < $1.0 \times 10^9/L$. Nevertheless, in the overall subgroup analysis, the predictive efficiency of pleural effusion combined with baseline characteristics showed no significant change.

Discussion

To our knowledge, this retrospective study is the first systematic study on the incidence, risk factors, distribution and outcome of pleural effusion in sHLH. In the present study, we observed the distribution and possible mechanism of pleural effusion in sHLH. Furthermore, we demonstrated that pleural effusion on admission was associated with worse survival in sHLH.

Pleural effusion was found in 58.6% of the studied sHLH population at diagnosis, a higher percentage than the range of previously reported data for critical illness and haematologic malignancies^[11, 12]. The higher incidence of pleural effusion in sHLH patients, similar to that of previous imaging characteristic analyses, may be due to their high inflammatory state.^[13] In recent years, mounting evidence has indicated that pleural effusion is common in paediatric or adult patients with HLH^[7, 14]. Our findings suggest that pleural effusion developed more often in patients with lower PLT counts, HB and ALB levels and higher sCD25 levels. Moreover, through multivariate analyses, we determined that $PLT \leq 65 \times 10^9/L$ and high levels of sCD25 were associated with an increased risk of pleural effusion.

It is well known that platelets and sCD25 play an important role when evaluating sHLH and are the diagnostic criteria set in the HLH-2004 criterion^[15]. On the one hand, cytopenia, especially persistent severe thrombocytopenia, is a key laboratory marker of HLH and is mainly related to severe cytokine-mediated inflammation^[6, 16]. Reportedly, the rapid onset of cytopenia suggests a consumptive process critically driven by TNF- α and INF- γ . At the same time, uncontrolled activation of macrophages will result in phagocytosis of platelets and other haematopoietic components by macrophages^[16, 17]. Furthermore, previous studies have suggested that persistent thrombocytopenia is significantly associated with death^[18]. On the other hand, sCD25 is the most studied cytokine/cytokine receptor to date in HLH and is considered a sensitive diagnostic test and disease marker^[19]. Indeed, a high level of sCD25 linked the diagnosis of adult HLH with the defining features of hypercytokinemia^[20]. Platelets and sCD25 can serve as diagnostic and disease markers in sHLH, and it is reasonable to presume that pleural effusion at diagnosis may be associated with higher inflammation in sHLH. Additional pleural effusion can develop during sHLH, especially at initial diagnosis, and should be considered when evaluating individual patients. Its elevation accompanied the severity of the disease. Therefore, maintaining awareness of the possibility of pleural effusion is important, especially in sHLH patients with significantly decreased haemoglobin, platelet, and albumin and significantly elevated sCD25.

Although the pathogenesis of sHLH-induced pleural effusion remains to be systematically investigated, three different theories have been proposed to offer some mechanistic insights. One theory, to which the authors subscribe, holds that the onset of pleural effusion is caused by excessive inflammatory cytokines resulting from HLH, though the association between pleural effusion and a higher inflammatory state was not sufficiently substantiated. In this theory, the release of a large number of inflammatory factors leads to widespread increases in vascular permeability that can result in progressive subcutaneous and body cavity oedema, including pleural effusion^[21]. Previous studies have suggested that cytokines and other inflammatory mediators could induce gaps between endothelial cells by disassembling intercellular

junctions, altering the cellular cytoskeletal structure, or directly damaging the cell monolayer. This creation of gaps can result in microvascular leak and pleural effusion^[21-23]. Moreover, HLH was also described in severely ill patients during the COVID-19 pandemic, presenting with vascular injury resulting from hyperinflammation in the alveoli^[24]. In one study, Weaver et al^[25] reported that hyperinflammation, rather than hemophagocytosis, appears to be the driving cause of HLH pathology. As fluid retention events have been more frequently reported in pleural effusion patients, the second theory holds that it is tempting to attribute the occurrence of pleural effusion to a class effect on fluid overload, especially hypoproteinaemia^[26]. However, an immune-mediated mechanism is more likely responsible for the sHLH-related pleural effusion, as our multivariate analysis has reported. The third theory holds that EB virus plays a role in the pathogenesis of pleural effusion, either by a direct cytopathic effect or uncontrolled immune response^[27]. Instead, we obtained evidence that the incidence of pleural effusion in patients with different aetiologies of sHLH was not statistically significant.

We reviewed the radiological reports at diagnosis of 162 patients with sHLH, noting any presence of pleural effusion and its extent (minimal, moderate, or massive). A notable observation in our study was that pleural effusion often occurs early in the disease, and the incidence of early-onset effusion (58.6%) was higher than that of late-onset effusion (11.7%). Pleural effusion may be the first presentation of sHLH or may develop during the course of the disease. Although these findings need to be further validated, our results suggest that the early onset of pleural effusion and its association with HLH severity support a direct link to HLH or suggest that pleural effusion is in part due to HLH itself. A second finding in our study was the observation that pleural effusion at diagnosis in sHLH is characterized by minimal amounts and bilaterality. The present results were consistent with two paediatric HLH studies indicating that bilateral lung infiltrates and pleural effusions were the most common findings in HLH according to chest imaging^[13, 28]. Additionally, the incidence of pelvic effusion, pericardial effusion, and ascites in sHLH patients with pleural effusion was higher than that in patients without pleural effusion. Moreover, only three of the 95 patients with pleural effusion in this study underwent pleural puncture and drainage. The reason was that most patients with sHLH were accompanied by severe hypofibrinogenemia and coagulation dysfunction, which increased the risk of bleeding. According to Light's standard, the effusion samples of the three patients with sHLH was exudative effusion. There were no obvious abnormalities in biochemical, tumor markers, tuberculosis, bacterial culture and exfoliated cells of pleural effusion. Due to the small sample size, this paper cannot summarize the biochemical indexes and cytological characteristics of sHLH combined with pleural effusion.

More recent studies have shown that pleural effusion is an important prognostic factor for overall survival in critically ill patients and those with haematologic malignancies^[29, 30], and at face value, this appeared to offer a more logical explanation for our present findings. It is generally believed that the prognosis of sHLH is known to be heavily dependent on the aetiology and treatment. However, based on fragmentary evidence, it appears that pleural effusion was an ominous sign^[31]. Obviously, the relationships between pleural effusion and outcome are poorly understood, and only a few cases have been reported^[32]. Benmiloud et al^[33] described a boy presenting with HLH as an initial manifestation of Hodgkin's lymphoma whose state worsened with the onset of pleural effusion. Our study showed that the presence of pleural effusion was independently associated with worse survival among patients with sHLH, and therefore, deeper knowledge

of pleural effusion in sHLH is important for guiding physicians to evaluate the condition and formulate treatment in these patients. In addition, the results strongly imply that patients with moderate to massive amounts of pleural effusion have worse survival than patients with minimal amounts of pleural effusion, although no significant difference was present. Currently, there is no specific treatment for pleural effusion in sHLH, and active treatment of primary disease based on fluid therapy is a key measure. In our study, all 95 patients with pleural effusion received active treatment for the primary diseases and appropriate supplementation with diuretics, oxygen therapy, colloidal fluid and crystalloids. Furthermore, after the initial effective treatment of HLH, pleural effusion can be improved or disappear.

Our study also suffers from some limitations. First, the results are a retrospective cohort study from a single center, which may not be representative of the general sHLH population. Nevertheless, this also implies an advantage in terms of consistency in diagnosis, treatment and follow-up. Second, pleural effusion levels are a dynamic process, and their analyses did not account for development over time. Thus, our results must be interpreted with some caution.

Conclusion

In summary, our data indicate that the incidence of pleural effusion is relatively high in sHLH patients (58.6%) and suggest that thrombocytopenia and high levels of sCD25 were predictive risk factors for the development of pleural effusion in sHLH patients. We propose that the pathogenesis of pleural effusion may be directly related to excessive inflammatory cytokines in sHLH. Additionally, sHLH patients with pleural effusion had a higher inflammatory state and poor prognosis.

Abbreviations

sHLH, secondary hemophagocytic lymphohistiocytosis; HLH, hemophagocytic lymphohistiocytosis;

95% CI, 95% confidence interval; PE+, positive pleural effusion; PE-, negative pleural effusion;

ANC, absolute neutrophil count; HB, hemoglobin; PLT, platelet; ALT, alanine transaminase;

AST, aspartate transaminase; LDH, lactic dehydrogenase; ALB, albumin; TG, triglyceride;

ALP, alkaline phosphatase; ADA, adenosine deaminase; Fib, fibrinogen; β 2-MG, β 2-microglobulin;

sCD25: soluble interleukin-2 receptor; EBV: Epstein-Barr virus;

LHLH, lymphoma-associated hemophagocytic lymphohistiocytosis;

NHLH, hemophagocytic lymphohistiocytosis of unknown origin

Declarations

Ethics approval and consent to participate

It was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Number: 2019-SR-446) and registered on the Chinese Clinical Trial Registry (ChiCTR2000032421).

Consent for publication

Consent for publication was obtained from all participants.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study concepts: WYC, HXQ. Study design: WYC, XG. Data acquisition: WYC, GLY, JYH, CFM, JX. Quality control of data: LMD, TT. Data analysis and interpretation: WYC, XG. Manuscript preparation: WYC, HXQ. Manuscript editing: WYC. Manuscript review: JJW, HXQ.

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Figures

A total of 203 consecutive sHLH patients in our study were admitted to the First Affiliated Hospital of Nanjing Medical University Hospital between July 2015 and July 2019

Totally 41 case were excluded:

- a) Comorbidities conditions which could directly cause pleural effusion: severe hepatic disease (liver cirrhosis or a Model for End-Stage Liver Disease score >20), renal failure(estimated creatinine clearance <15 mL/min per 1.73 m²), pulmonary embolism, acute pancreatitis**
- b) History of drugs and operation known to cause pleural effusion at admission: amiodarone, dasatinib, methotrexate, post-cardiac surgery, lung operation and/or radiation**
- c) Previous severe cardiopulmonary disease**
- d) Under 18 years or Refuse to any treatment or HScore < 90**
- e) No detailed Chest imaging report**

Data available for analysis:

PE+ group(n=95)

PE- group(n=67)

Figure 1

The patient selection flowchart

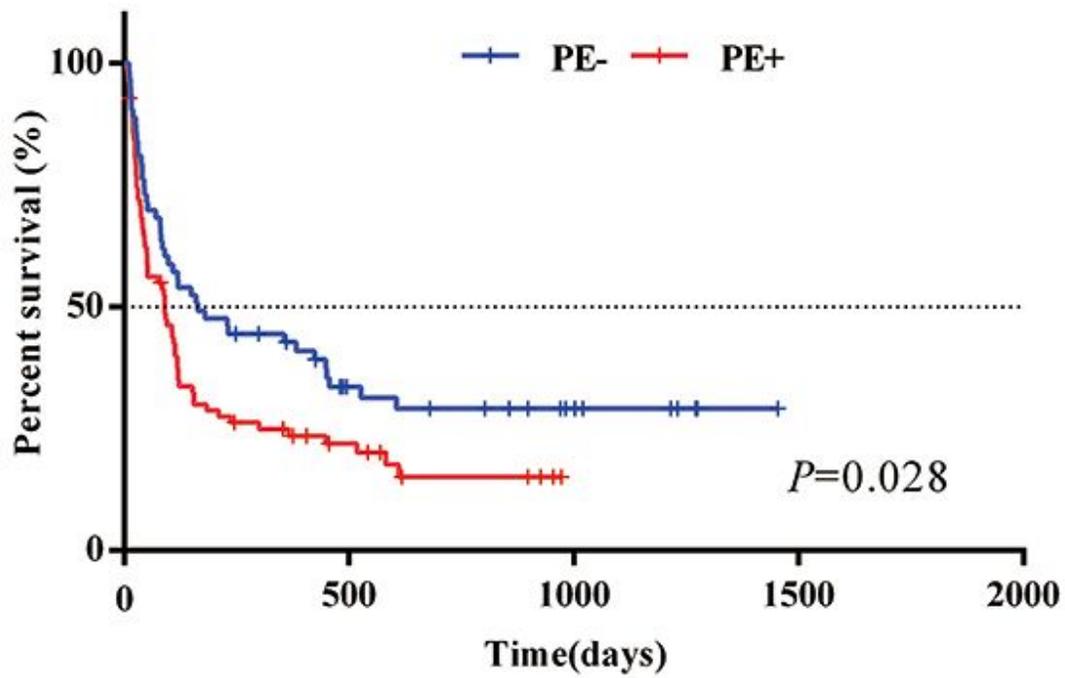


Figure 2

Survival curves of sHLH patients according to pleural effusion

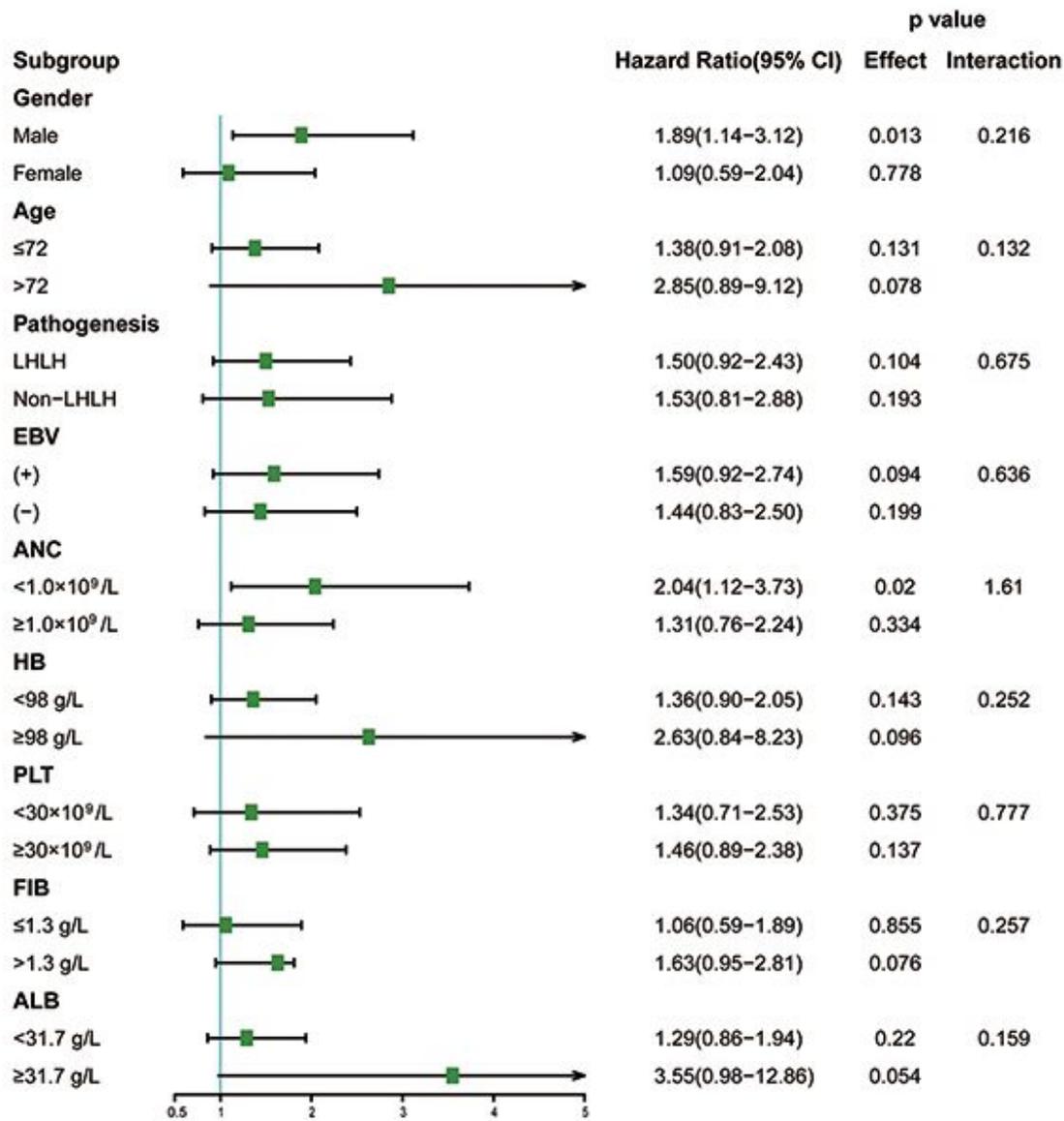


Figure 3

Cox proportional hazards analysis for OS and subgroup analysis: impact of pleural effusion.