Submitted: 20 August, 2024 Accepted: 05 December, 2024 Published: 08 March, 2025 DOI:10.22514/sv.2025.034

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ORIGINAL RESEARCH

Severe pneumonia complicated by hemophagocytic lymphohistiocytosis in adults: a retrospective and exploratory clinical analysis

Ling Zhang[1,*,†], Qi-Gang Yang[1,†], Min Shao[1,*]

[1]Department of Critical Care Medicine, The First Affiliated Hospital of Anhui Medical University, 230022 Hefei, Anhui, China

***Correspondence**
zhangling1702@126.com
(Ling Zhang);
shaomin@ahmu.edu.cn
(Min Shao)

[†] These authors contributed equally.

Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening complication that can arise in adults with severe pneumonia (SP). This retrospective study analyzed the clinical characteristics, diagnostic approaches and treatment outcomes of adult patients diagnosed with SP complicated by HLH. **Methods**: The clinical data of 9 related adult patients were collected from the Department of Critical Care Medicine and analyzed. **Results**: The mean age of the patients was 41.11 $\pm$ 13.02 years, with 88.9% (8/9) being male. Comorbidities included post-renal transplantation, lymphoma, pregnancy, hepatitis E, syphilis and hypertension. The observed 28-day mortality rate was 22.2% (2/9), while the 60-day to 1-year mortality rates were both 77.8% (7/9). The etiological agents responsible for SP included bacteria (16%), viruses (52%), fungi (28%) and chlamydia (4%). Chest computed tomography revealed bilateral multiple exudative lesions. All patients met the 2004 HLH diagnostic criteria and had a mean HScore of 246.78 $\pm$ 44.11 and median ferritin level of 2828 μg/L (Inter Quartile Range (IQR) 2284–5152). Bone marrow cytology revealed mononuclear-phagocytic histiocytes in 8 of 9 patients. Lymphocyte subpopulations, including total lymphocyte count, cluster of differentiation (CD)4^+ and $CD8^+$ cells, were found to be significantly reduced ($p < 0.01$), while serum levels of interleukin (IL)-6 and IL-8 were markedly elevated ($p < 0.001$). Therapeutic interventions included targeted anti-infective treatment, with glucocorticoids administered to 5 patients, low-dose etoposide to 4 patients, intravenous immunoglobulin to 7 patients, and plasma exchange in 6 patients. Despite these interventions, mortality remained high. **Conclusions**: Routine monitoring of HLH diagnostic indicators in patients with SP is crucial, and anti-infective and supportive therapies, as well as immunosuppressive and cytotoxic agents, may offer potential benefits for critically ill patients.

Keywords

Severe pneumonia; Hemophagocytic lymphohistiocytosis; Adults; Clinical characteristics

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening complication that can occur in adults with severe pneumonia (SP) and may significantly increase their mortality risks [1, 2]. Despite its clinical significance, the occurrence of HLH in adults with SP remains poorly studied, posing challenges in understanding its effective treatment and prognosis.

SP is a significant global health issue caused by progressive lung tissue inflammation due to various pathogens [3]. It has been associated with organ dysfunction and life-threatening conditions. The mortality rates for SP in adults range from 25% to 50% [4], with even higher rates of 50%–65% reported for critically ill patients with severe coronavirus disease 2019 (COVID-19) requiring intensive care unit (ICU) admission [5].

HLH is characterized by dysregulated immune responses resulting from excessive activation and proliferation of lymphocytes, macrophages and monocytes [6], which can lead to uncontrolled inflammation and the release of large quantities of pro-inflammatory cytokines. HLH is classified as either primary (pHLH), which is genetically inherited, or secondary (sHLH), which is triggered by infections, malignancies or autoimmune conditions [7]. The diagnosis of HLH in critically ill patients, particularly in the ICU, can be challenging due to its clinical similarity to other inflammatory conditions, such as sepsis. To address this diagnostic challenge, Fardet *et al.* [8] developed the HScore, a tool for estimating the likelihood of sHLH in patients.

This study aims to retrospectively analyze the clinical characteristics, diagnostic approaches, and treatment outcomes of adult patients with SP complicated by sHLH. By improving our understanding of this condition, the study seeks to enhance management strategies and improve prognosis in critically ill patients.

2. Materials and methods

2.1 Study population

This study comprised 9 adult patients diagnosed with SP (including both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP)) complicated by sHLH admitted to the Department of Critical Care Medicine at the First Affiliated Hospital of Anhui Medical University between February 2020 and May 2022. This study was conducted in accordance with ethical standards for medical research and received approval from the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (approval number: Quick-PJ2022-06024).

2.1.1 Diagnostic criteria for SP

The diagnosis of SP in adults was based on the 2007 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) criteria [9]. The definition includes the following: Major criteria: ① Requirement for invasive mechanical ventilation; ② Septic shock necessitating vasopressor support. Minor criteria: ① Respiratory rate $\geq$30 breaths/min; ② Arterial partial pressure of oxygen (PaO_2)/Fraction of inspired oxygen (FiO_2) ratio $\leq$250 mmHg; ③ Multilobar infiltrates on imaging; ④ Confusion or disorientation; ⑤ Uremia (blood urea nitrogen level $\geq$20 mg/dL); ⑥ Leukopenia (white blood cell count $<4 \times 10^9$/L); ⑦ Thrombocytopenia (platelet count $<100 \times 10^9$/L); ⑧ Hypothermia (core temperature $<$36 °C); ⑨ Hypotension requiring aggressive fluid resuscitation. For a diagnosis of SP, patients had to meet at least one major criterion or three minor criteria.

2.1.2 Diagnostic criteria for HLH

The diagnosis of HLH was based on the revised criteria established by the International Histiocyte Society in 2004 [7]. A diagnosis of HLH could be confirmed if one of the following conditions was met: ① A molecular diagnosis consistent with HLH; ② Fulfillment of at least five of the following eight clinical and laboratory criteria: (A) Initial diagnostic criteria: fever; splenomegaly; cytopenias affecting at least two of three blood cell lineages: Hemoglobin $<$90 g/L (in infants $<$4 weeks: hemoglobin $<$100 g/L), platelets $<100 \times 10^9$/L, and neutrophils $<1.0 \times 10^9$/L; Hypertriglyceridemia (fasting triglycerides $\geq$3.0 mmol/L or $\geq$265 mg/dL) and/or hypofibrinogenemia (fibrinogen $\leq$1.5 g/L); Hemophagocytosis observed in bone marrow, spleen or lymph nodes without evidence of malignancy; (B) New diagnostic criteria: Decreased or absent natural killer (NK) cell activity, as per local laboratory reference; Ferritin levels $\geq$500 mg/L; Soluble CD25 (*i.e.*, soluble IL-2 receptor) $\geq$2400 U/mL.

2.2 Data collection

Clinical data, laboratory findings, imaging results, therapeutic interventions and outcomes of the study population were retrospectively collected. All test results were obtained within 72 hours of hospitalization and provided by the Department of Medical Laboratory and Imaging at the First Affiliated Hospital of Anhui Medical University.

2.2.1 Basic clinical information

Data collected included gender, age, comorbidities, oxygenation index (OI) at ICU admission, primary etiological factors and their detection methods, use of vasoactive drugs, mode of respiratory support, disease severity score and duration of invasive mechanical ventilation (IMV).

2.2.2 Chest imaging data

Chest imaging was performed using either X-ray (Digital Radiography Imaging System, MobiEye 700T, Mindray healthcare, Shenzhen, China) or computed tomography (CT) plain scan (GE Revolution 256-row wide-body detector CT, GE healthcare, Fairfield, CT, USA). The imaging data were automatically transmitted to a computer workstation for visualization and analysis.

2.2.3 Diagnosis and treatment of sHLH

Data related to the diagnosis and treatment of sHLH included the number of diagnostic criteria met, HScore values, and therapeutic interventions. The HScore, which calculates a cumulative score from nine variables, was used to assess the probability of HLH (https://saintantoine.aphp.fr/score/) [10]. Therapeutic measures recorded included targeted anti-infection treatment, glucocorticoids, etoposide, intravenous immunoglobulin (IVIG) and plasma exchange.

2.2.4 Cellular immune function

Cellular immune function was evaluated through the following parameters: (1) Neutrophil count: Assessed using automated hematology analyzers (XN-9000 Series, Sysmex, Kobe, Japan); (2) Lymphocyte subsets and ratios: Determined using clinical flow cytometry (BD FACSCanto™); (3) Cytokine levels: Measured using a multiplex bead-based flow fluorescent immunoassay (RAISECARE). All tests were performed according to the manufacturer's protocols and standardized procedures.

2.2.5 Follow up

The prognosis of all patients was assessed through follow-up at 28 days, 60 days and 1 year post-hospitalization. Follow-up was conducted by trained professionals via telephone interviews.

2.3 Statistical analysis

The statistical analyses were conducted using SPSS 23.0 software (IBM, Armonk, NY, USA). Qualitative data were expressed as absolute values. The Shapiro-Wilk Test was used to determine whether quantitative data were normally distributed. For normally distributed, the data were described as mean $\pm$ standard deviation ($\bar{x} \pm s$), and comparisons between two

groups were made using the independent student *t*-test; otherwise the data were described as median (P25, P75), and the differences between two groups were expressed using the Mann-Whitney U test. Missing quantitative data were replaced by adjacent linear trends. $p < 0.05$ was considered statistically significant.

3. Results

3.1 Demographic characteristics and basic clinical information

This study included 9 adult patients with SP complicated by sHLH, comprising 8 males and 1 female. The mean age of the patients was 41.11 ± 13.02 years, the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 22.67 ± 4.10, and the mean Sequential organ failure assessment (SOFA) score was 11.78 ± 1.64, as detailed in Table 1.

Regarding comorbidities, 5 had undergone kidney transplantation, while 1 had lymphoma. Three patients (3/9) presented with syphilis and hypertension, pregnancy and hepatitis E, respectively. At ICU admission, the mean OI was 93.81 ± 34.83 mmHg. Of the 9 patients, 1 required VV-ECMO (veno-venous extracorporeal membrane oxygenation), 1 received non-invasive respiratory support, and the remaining 7 patients were managed with IMV. The mean duration of IMV was 20.00 ± 17.85 days. The demographic characteristics and pathological findings of the nine patients are summarized in Fig. 1.

3.2 Chest imaging findings

Chest imaging revealed multiple exudative lesions in both lungs of all 9 patients, which appeared as patchy, solid, ground-glass, lattice-like, nodular or cavernous shadows, depending on the underlying etiology. One patient presented with pneumothorax, and 6 exhibited a small amount of pleural effusion. Representative chest CT scans are shown in Fig. 2, highlighting different etiologies: PCP (Pneumocystis carinii) combined with CMV (cytomegalovirus), *Aspergillus fumigatus* co-infection with CMV, and *Chlamydia psittaci*.

3.3 Diagnosis, treatment and prognosis of sHLH

All 9 patients met the diagnostic criteria for HLH as outlined in the 2004-HLH guidelines. The mean HScore was 246.78 ± 44.11, and the median ferritin level was 2828 μg/L (IQR 2284–5152) (Fig. 3). Of note, Patient 4 did not undergo ferritin testing.

All patients underwent bone marrow aspirations. The morphological examination revealed a state of active bone marrow proliferation, accompanied by the presence of mononuclear and phagocytic histiocytes in 8 patients (Fig. 4).

All 9 patients received targeted anti-infection treatments. Additional therapies included glucocorticoids (administered to 5 patients), low-dose etoposide (VP-16, administered to 4 patients), IVIG (administered to 7 patients), and plasma exchange (performed in 6 patients). The detailed treatment regimens are outlined in Table 2.

In terms of prognosis, the 28-day mortality rate was 22.2% (2/9), with Patients 8 and 9 succumbing to the disease within this period. Long-term follow-up revealed that only two patients (Patients 3 and 5) survived beyond 60 days and 1 year, corresponding to a 1-year mortality rate of 77.8% (7/9). Notably, Patient 3 did not exhibit recurrence of sHLH during a subsequent successful pregnancy occurring one year after hospitalization.

3.4 Cellular immune function

As shown in Table 3, lymphocyte counts and their subpopulations were markedly reduced across all patients. The median total lymphocyte count was 0.25 × 10^9/L (IQR: 0.13–0.45 × 10^9/L), the $CD4^+$ T cell count was 51 cells/μL (IQR: 43–184 cells/μL), and the $CD8^+$ T cell count was 72 cells/μL (IQR: 45–131.5 cells/μL). The $CD4^+/CD8^+$ ratio was 1.23 ± 0.95, and the NK cell count was 29 cells/μL (IQR: 17–300 cells/μL). The total lymphocyte count, as well as $CD4^+$ and $CD8^+$ T cell counts, were significantly below the lower limit of the normal range ($p < 0.01$).

Moreover, the levels of serum cytokines (IL-1β, IL-6, IL-8, IL-10, tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ)) exhibited varying degrees of alteration. Among them, the serum levels of IL-6 and IL-8 were significantly elevated, with IL-6 measured at 770 (40.99, 9207.61) pg/mL and IL-8 measuring 285.40 (42.98, 9153.33) pg/mL, both exceeding the upper limit of the normal range ($p < 0.001$).

4. Discussion

SP in adults is a severe condition of acute respiratory infection and represents a significant global health challenge for healthcare systems. HLH is characterized by excessive inflammatory responses, leading to the benign proliferation of tissue cells and widespread phagocytosis of hematopoietic cells [7]. sHLH is more commonly observed in adults and is often triggered by immune system activation due to underlying conditions such as infections [11]. When SP is complicated by sHLH, it becomes a fatal condition, further complicating the effective management of critically ill patients [12]. However, there is limited research addressing SP complicated by sHLH in adult ICU populations.

Mortality rates in adult patients with sHLH admitted to the ICU are alarmingly high. Lachmann *et al.* [13] reported a mortality rate of 44%, while Nyvlt *et al.* [14] observed a comparable rate of 43.3%. Meng *et al.* [10] found that mortality among COVID-19 patients suspected of being sHLH-positive was significantly higher than in the suspected sHLH-negative group (100% *vs.* 34.77%, $p < 0.001$). Additionally, the 1-year survival rate for HLH patients has been reported at 50%, highlighting the urgent need for advancements in HLH treatment strategies [15]. In our study, the mortality rates were 22.2% at 28 days and 77.8% at 60 days to 1 year post-hospitalization. These findings underscore the severity of sHLH in the context of SP. The high mortality observed in our study may be influenced by several factors, including the small study population, elevated APACHE II and SOFA scores, and the severity of the underlying trigger conditions.

TABLE 1. Demographic characteristics and basic clinical data of the 9 assessed patients.

Number	1	2	3	4	5	6	7	8	9
Age (yr)	50	45	27	36	31	46	33	69	33
Gender	Male	Male	Female	Male	Male	Male	Male	Male	Male
Complication	Renal transplantation	Syphilis Hypertension	Pregnant	Renal transplantation	Renal transplantation	Lymphoma	Renal transplantation	Hepatitis E	Renal transplantation
Origin of SP	CAP	CAP	CAP	HAP	CAP	HAP	CAP	HAP	CAP
OI (mmHg)	102.0	46.7	68.0	88.1	94.8	52.9	105.0	142.2	144.6
Main etiology	EBV CMV PCP SM	AB HPVB19 HSV1	Chlamydia psittaci	PAE EBV CMV Mucor	PCP CMV TTV	PAE EBV	PCP CMV BKV	Aspergillus CMV EBV	Mucor Aspergillus
Detection method	BALF mNGS + DNA	BALF + Blood mNGS	BALF + Blood mNGS	BALF mNGS + DNA	BALF mNGS	BALF + Blood mNGS	BALF mNGS + DNA	BALF mNGS + DNA	BALF + Blood mNGS
Vasopressor	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Respiratory support	IMV NIPPV	VV-ECMO IMV	IMV HFNO	IMV	NIPPV HFNO	IMV	HFNO IMV	IMV	IMV HFNO
APACHE II	29	24	21	24	17	17	27	24	21
SOFA	10	14	11	12	10	10	13	14	12
CPIS	8	7	11	9	8	9	8	10	11
MV days (d)	27	57	28	5	0	18	30	11	4

Abbreviations: OI: Oxygenation index; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential organ failure assessment; CPIS: Clinical pulmonary infection score; EBV: EB virus; CMV: cytomegalovirus; PCP: Pneumocystis carinii; HPVB19: human parvovirus B19; HSV1: herpes simplex virus 1; SM: Serratia marcescens; AB: Acinetobacter baumannii; PAE: Pseudomonas aeruginosa; TTV: human parvovirus; BKV: BK virus; BALF: bronchoalveolar lavage fluid; mNGS: macro genomic sequencing; NIPPV: non-invasive positive pressure ventilation; VV-ECMO: veno-venous extracorporeal membrane oxygenation; HFNO: nasal high flow oxygen therapy; SP: severe pneumonia; CAP: community-acquired pneumonia; HAP: hospital-acquired pneumonia; IMV: invasive mechanical ventilation; MV: mechanical ventilation.

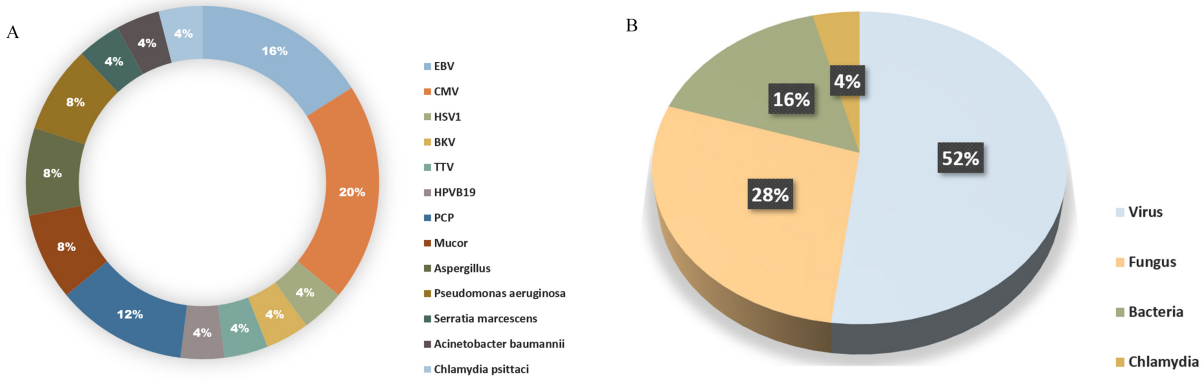

FIGURE 1. Etiology of severe pneumonia in the 9 investigated patients. (A) Detailed etiology of severe pneumonia. (B) Etiological classification of severe pneumonia. EBV: EB virus; CMV: cytomegalovirus; HSV1: herpes simplex virus 1; BKV: BK virus; TTV: human parvovirus; HPVB19: human parvovirus B19; PCP: Pneumocystis carinii.

TABLE 2. Treatments of the 9 sHLH patients.

Treatments	1	2	3	4	5	6	7	8	9
Anti-infection	Ganciclovir	Tigecycline Ganciclovir	Doxycycline	Amphotericin B liposome	SMZ Ganciclovir	Meropenem	SMZ Ganciclovir	Voriconazole Ganciclovir	Amphotericin B liposome
Glucocorticoid	MP	No	DXM	DXM	MP	MP	No	No	No
VP-16	No	No	Yes	Yes	Yes	No	Yes	No	No
IVIG	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
PE	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No

VP-16: etoposide; IVIG: intravenous immunoglobulin; SMZ: sulfamethoxazole; PE: plasma exchange.

Shi *et al.* [16] identified male gender as a risk factor for poor prognosis in severe COVID-19 patients, with literature confirming male predominance in HLH [11]. A nationwide study in England by West *et al.* [15], which analyzed HLH cases from 2003 to 2018, reported a higher prevalence of males (56.51% *vs.* 43.49%). Furthermore, the study highlighted that one-year survival rates for HLH varied significantly by gender, with males exhibiting worse outcomes compared to females [15]. In our study, 88.9% of the patients were male (8 out of 9), suggesting that gender may be a potential risk factor for poor prognosis in SP complicated by sHLH. However, confirmation of this association requires further investigation using larger sample size cohorts.

The pathogens responsible for SP are influenced by factors such as environmental exposure, local epidemiology and individual immune status. Previous studies have demonstrated that bacteria are the most frequent pathogens in severe respiratory infections among immunosuppressed patients, followed by RNA and DNA viruses and invasive fungi [17, 18]. Ren *et al.* [19] described 18 cases of cytomegalovirus (CMV) pneumonia in patients with inflammatory bowel disease, with half of the cases complicated by sHLH. Bichon *et al.* [20] conducted a retrospective analysis of a large cohort of ICU patients with HLH, identifying infections as the primary trigger. The implicated pathogens included extracellular bacteria, fungi, Epstein-Barr virus (EBV), influenza virus, COVID-19 and mycobacteria [20]. Despite varying etiologies and specific treatments, the mortality rate of ICU-related HLH remained high at 57% [20]. In our study, the most common pathogens included DNA viruses (*e.g.*, EBV, HSV (herpes simplex virus), CMV) and fungi (*e.g.*, PCP), generally consistent with previous studies.

Viral infections are particularly prevalent in severely immunosuppressed patients with T-cell deficiencies [21, 22]. Griffin *et al.* [23] reviewed the occurrence of HLH in adults with severe combined immunodeficiency and in those undergoing chemotherapy or immunosuppressive therapy for inflammatory diseases. They identified intracellular pathogens, particularly viruses, as the predominant infectious triggers for HLH [23]. In this study, 6 of the 9 cases were immunosuppressed, 5 of whom were post-renal transplant recipients. While only a few cases of HLH secondary to viral infection following renal transplantation have been reported in literature [24, 25], and no large-scale studies have systematically explored this association in adults. Based on our findings, it is plausible to speculate that the immunosuppressive state following renal transplantation may represent a risk factor for SP complicated by sHLH. Additionally, 1 pregnant patient in our study, who presented with SP complicated by sHLH involving the central nervous system, was infected with *Chlamydia psittaci*. To our knowledge, no prior cases of *Chlamydia psittaci* infection in a pregnant patient leading to sHLH with central nervous system involvement have been documented. We hypothesize that the *Chlamydia psittaci* infection and pregnancy status may act as independent risk factors for sHLH and central nervous system involvement in such cases.

HLH is characterized by an uncontrolled inflammatory response mediated by hypercytokinemia, with elevated levels

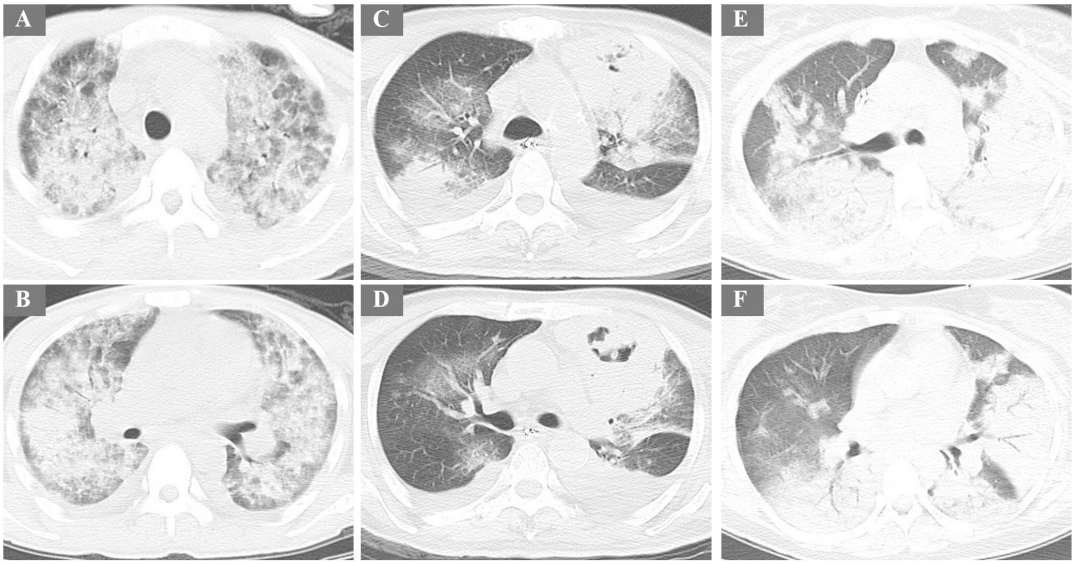

FIGURE 2. Chest CT findings. (A,B) In the case of PCP combined with CMV, the chest CT scan (lung window) revealed patchy and reticular exudation in both lungs, predominantly in the upper lobes. (C,D) For *Aspergillus fumigatus* co-infection with CMV, the chest CT scan (lung window) showed consolidation in the upper left lung with an air crescent sign. Additionally, patchy ground-glass opacities were observed in the right lung, accompanied by bilateral pleural effusion. (E,F) For *Chlamydia psittaci*, the chest CT scan (lung window) demonstrated patchy shadows and consolidation in both lungs, with a bronchial inflation sign present.

TABLE 3. Cellular immune function of the 9 patients.

Number	1	2	3	4	5	6	7	8	9
Neutrophil and lymphocyte subsets count									
NEUT (10^9/L) (1.8∼6.3)	0.11	2.55	11.02	3.91	1.23	1.34	1.74	11.28	0.02
LY (10^9/L) (1.1∼3.2)	0.11	0.34	1.30	0.22	0.25	0.32	0.15	0.55	0.11
$CD3^+$ (cells/μL) (690∼2540)	—	285	647	98	123	158	112	279	82
$CD4^+$ (cells/μL) (410∼1590)	84	184	364	36	27	44	43	79	51
$CD8^+$ (cells/μL) (190∼1140)	27	88	238	68	72	80	59	175	31
$CD4^+/CD8^+$ (0.9∼2.1)	3.11	2.10	1.53	0.52	0.38	0.54	0.73	0.45	1.68
NK (cells/μL) (78∼756)	—	97	300	9	7	570	17	29	28
$CD45^+$ (cells/μL)	—	422	1111	—	135	737	135	393	123
NLR	1.00	7.50	8.47	17.77	4.92	4.19	11.60	20.51	0.18
Serum cytokine level (pg/mL)									
IL-1β (≤12.4)	35.22	1.77	27.28	—	<5.00	35.21	17.37	14.72	9.09
IL-6 (≤5.4)	770.00	9929.15	39.00	2360.00	10.40	42.98	9261.89	194.62	9153.33
IL-8 (≤20.6)	1267.00	318.79	158.00	—	61.60	282.17	136.61	285.40	1492.04
IL-10 (≤12.9)	25.09	18.86	<5.00	143.00	13.28	3130.65	2.64	19.87	4.74
TNF-α (≤16.5)	48.40	2.78	33.37	1.13	75.29	20.70	2.42	2.94	<1.58
IFN-γ (≤23.1)	—	6.44	—	26.90	—	>10,000.00	418.91	13.36	83.58

Remarks: NEUT: neutrophil count; LY: lymphocyte count; NLR: neutrophil count/lymphocyte count ratio; CD: cluster of differentiation; NK: natural killer; IL: interleukin; TNF-α: tumor necrosis factor α; IFN-γ: interferon γ.

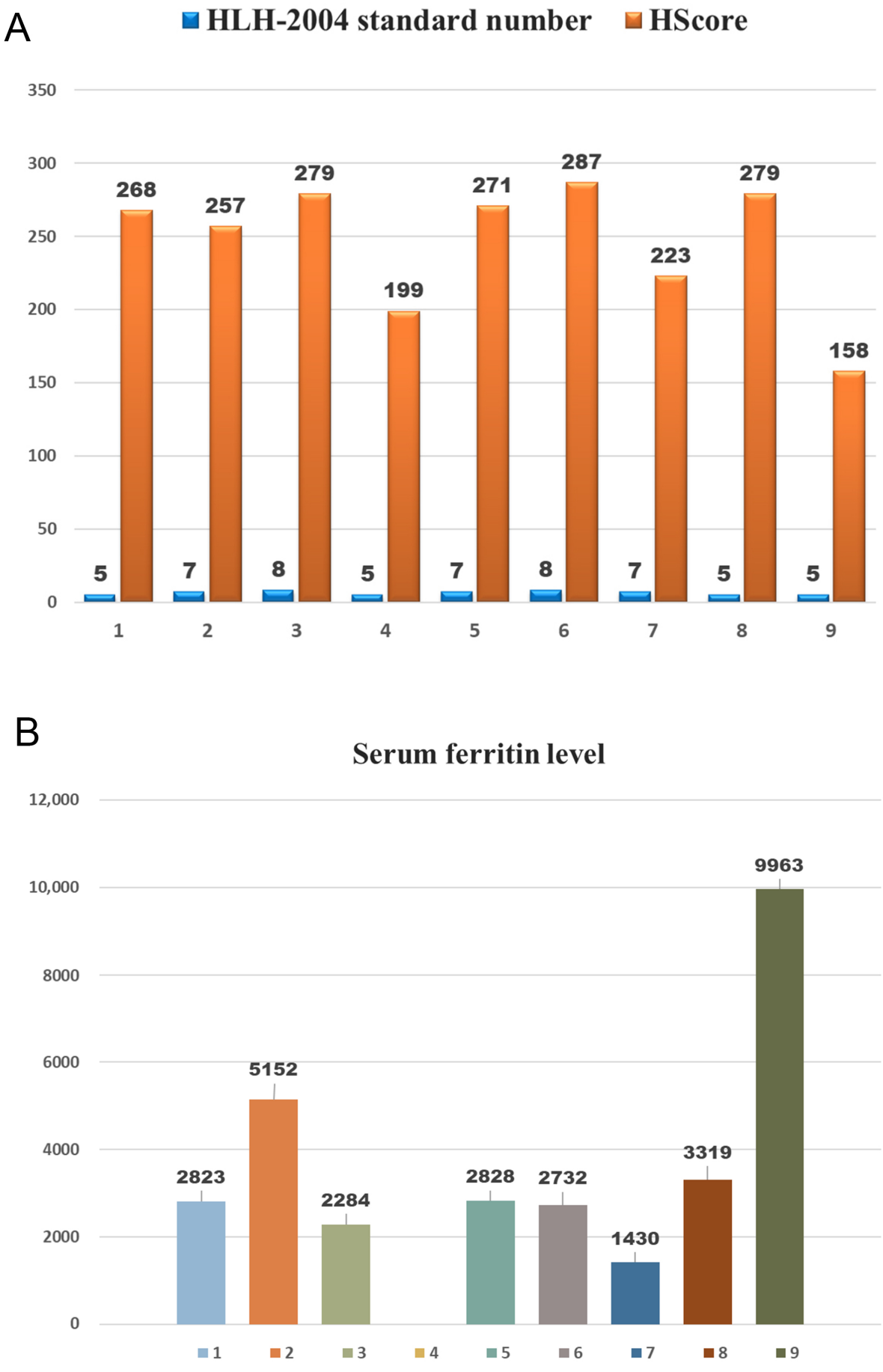

FIGURE 3. The HLH standard numbers, HScore and serum ferritin level of the investigated patients. (A) HLH standard number and Hscore of each patient. (B) Serum ferritin level of each patient. HLH: Hemophagocytic lymphohistiocytosis.

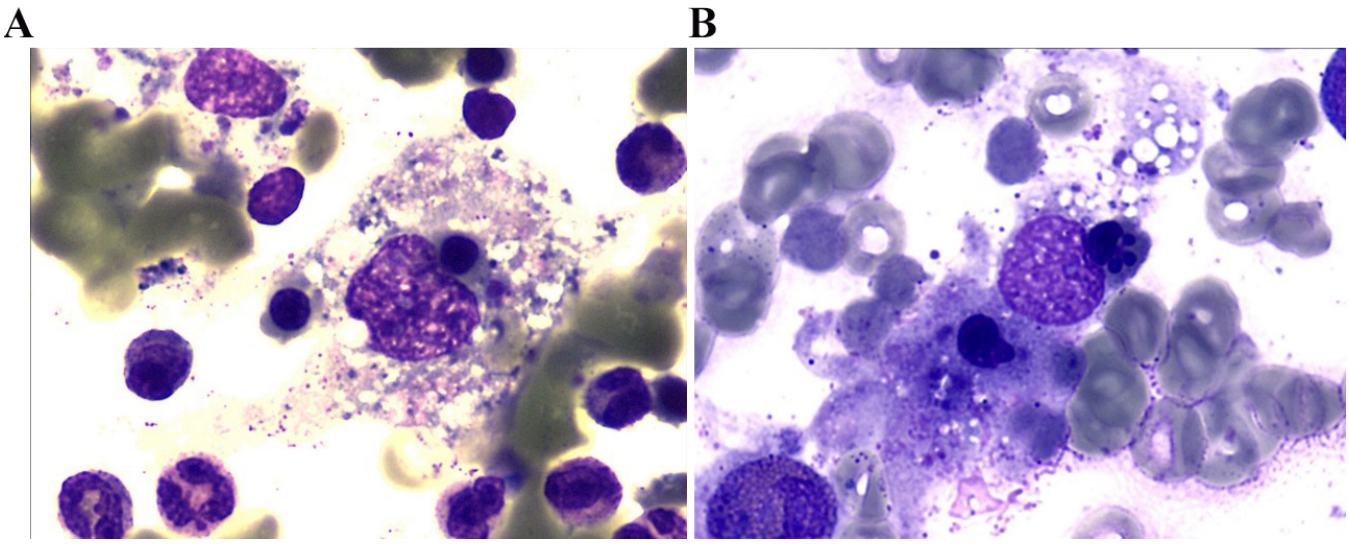

FIGURE 4. Monocyte-phagocytic cells in bone marrow cytological smear. Morphological examination of bone marrow cells demonstrated the presence of mononuclear and phagocytic histiocytes. (A) Monocytes phagocytosing platelets and mature erythrocytes. (B) Monocytes phagocytosing lymphocytes, neutrophils and mature erythrocytes. Staining was performed using Wright-Giemsa, captured at 10 × 100 magnification.

of cytokines such as IL-1β, IL-6, IL-18, IFN-γ and TNF-α, driven by dysregulated cellular immune responses [26]. T cells, particularly $CD4^+$ and $CD8^+$ subsets, are essential for modulating and suppressing excessive innate immune activation [27]. In severe COVID-19, the depletion of $CD4^+$ and $CD8^+$ T cells has been associated with increased inflammatory responses, cytokine storm activation, and worse clinical outcomes [28]. In our study, serum levels of IL-6 and IL-8 were markedly elevated, significantly exceeding the upper limit of the normal range. Concurrently, the total lymphocyte count, as well as $CD4^+$ and $CD8^+$ T cell counts, were significantly below the normal lower limit. These findings suggest that the patients were experiencing uncontrolled cellular immunity driven by severe infections, potentially influenced by underlying viral and fungal infections and immunosuppressive states. Moreover, the 2 survivors in our cohort had lymphocyte subset counts that were generally within the normal range.

The clinical manifestations and organ dysfunction caused by severe infections can closely resemble those of HLH, potentially leading to an underestimation of sHLH incidence in ICU settings. Due to the common presence of severe leukopenia in these patients, NK cell count and functional assays are not routinely recommended [8]. However, ferritin levels $\geq$3095 μg/L have demonstrated a sensitivity of 100% and specificity of 82.6% for diagnosing sHLH in ICU patients. In addition to the HLH-2004 criteria, the HScore has proven to be a valuable diagnostic tool, with an HScore $>$169 yielding sensitivity and specificity of 93% and 86%, respectively [8]. Furthermore, combining the HLH-2004 criteria with an HScore $>$168 has been shown to provide optimal diagnostic accuracy [29]. High HScore values may also predict both the diagnosis and mortality risk associated with HLH [10, 30]. Consistent with these findings, all nine patients in our study met at least five HLH-2004 criteria, and their HScore values were $\geq$158, aligning with previous studies.

The treatment of sHLH generally encompasses three main strategies [7, 26]: controlling the underlying disease, managing excessive inflammation, and providing symptomatic supportive care. Hansen *et al.* [31] reported successful outcomes using ruxolitinib to treat four patients with sHLH. In our study, all patients received targeted anti-infective therapies and comprehensive supportive care, with 5 also treated with glucocorticoids. Although etoposide (VP-16) has shown potential in treating HLH secondary to infection by inhibiting macrophage activation, restoring immune homeostasis, and clearing infected cells, only four patients in this cohort received low doses of the drug. Notably, neither of the 2 surviving patients experienced recurrence during the 1-year follow-up, suggesting the potential efficacy of these treatments. Nevertheless, individualized treatment remains essential for critically ill patients. For patients unable to tolerate glucocorticoids or cytotoxic therapies, alternative strategies such as IVIG, plasma exchange [32], or cytokine adsorption may be beneficial by mitigating excessive inflammatory cytokines [33]. In this study, 7 patients received IVIG, and 6 underwent plasma exchange. However, these interventions did not significantly improve survival outcomes, indicating the need for further investigation into the effectiveness of these treatments for sHLH.

This study has several limitations. First, it is a single-center study with a small sample size, which may limit the generalizability of the findings. Validation of the results through larger sample sizes and multicenter studies is warranted. Second, the retrospective design relied on data collected from electronic medical records, which may have introduced minor gaps or inconsistencies in the data.

5. Conclusions

In conclusion, sHLH is a severe complication of adult SP characterized by rapid progression, high mortality and poor prognosis. Early monitoring of HLH-related indicators, including

the use of HScore, could be essential for the timely detection and confirmation of sHLH in adult SP patients, particularly those with viral or other specific pathogenic infections. In addition to targeted anti-infective and supportive therapies, immunosuppressive and cytotoxic medications may play an important role in severe cases by mitigating cytokine storms and improving clinical outcomes. Future research should aim to further elucidate the pathophysiological mechanisms underlying sHLH and explore more effective therapeutic options to improve the prognosis of these critically ill patients.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

LZ—Investigation, material preparation, data collection and writing-original draft were performed. QGY—Methodology and formal analysis were performed. LZ, MS—The Writing-review draft of the manuscript was written. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors contributed to the study conception and design.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with ethical standards for medical research and received approval from the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (approval number: Quick-PJ2022-06024). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This work was supported by the Provincial Natural Science Foundation of Education Department of Anhui (Key project) (Grant No. KJ2021A0309) and Anhui Medical University research fund project (Grant No. 2021xkj151).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay EJC. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. Chest. 2016; 149: 1294–1301.

[2] Song R, Zhang Q, Wu T, Pan Y, Wei A, Shi Y, *et al*. SARS-CoV-2 reactivates fungal-associated hemophagocytic lymphohistiocytosis: case report and review of the literature. International Immunopharmacology. 2024; 142: 113141.

[3] Martin-Loeches I, Torres A, Nagavci B, Aliberti S, Antonelli M, Bassetti M, *et al*. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. The European Respiratory Journal. 2023; 61: 2200735.

[4] Cillóniz C, Torres A, Niederman MJB. Management of pneumonia in critically ill patients. British Medical Journal. 2021; 375: e065871.

[5] Bhatraju P, Ghassemieh B, Nichols M, Kim R, Jerome K, Nalla A, *et al.* Covid-19 in critically ill patients in the Seattle region—case series. The New England Journal of Medicine. 2020; 382: 2012–2022.

[6] Lafarge A, Chean D, Whiting L, Clere-Jehl R. Management of hematological patients requiring emergency chemotherapy in the intensive care unit. Intensive Care Medicine. 2024; 50: 849–860.

[7] Henter J, Horne A, Aricó M, Egeler R, Filipovich A, Imashuku S, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatric Blood & Cancer. 2007; 48: 124–131.

[8] Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, *et al*. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis & Rheumatology. 2014; 66: 2613–2620.

[9] Mandell L, Wunderink R, Anzueto A, Bartlett J, Campbell G, Dean N, *et al*. Infectious diseases society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical Infectious Diseases. 2007; 44: S27–S72.

[10] Meng M, Chen L, Zhang S, Dong X, Li W, Li R, *et al*. Risk factors for secondary hemophagocytic lymphohistiocytosis in severe coronavirus disease 2019 adult patients. BMC Infectious Diseases. 2021; 21: 398.

[11] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta M, Bosch XJL. Adult haemophagocytic syndrome. The Lancet. 2014; 383: 1503–1516.

[12] Prilutskiy A, Kritselis M, Shevtsov A, Yambayev I, Vadlamudi C, Zhao Q, *et al*. SARS-CoV-2 infection-associated hemophagocytic lymphohistiocytosis. American Journal of Clinical Pathology. 2020; 154: 466–474.

[13] Lachmann G, Spies C, Schenk T, Brunkhorst FM, Balzer F, La Rosée P. Hemophagocytic lymphohistiocytosis: potentially underdiagnosed in intensive care units. Shock. 2018; 50: 149–155.

[14] Nyvlt P, Schuster FS, Ihlow J, Heeren P, Spies C, Hiesgen J, *et al*. Value of hemophagocytosis in the diagnosis of hemophagocytic lymphohistiocytosis in critically ill patients. European Journal of Haematology. 2024; 112: 917–926.

[15] West J, Stilwell P, Liu H, Ban L, Bythell M, Card T, *et al*. 1-year survival in haemophagocytic lymphohistiocytosis: a nationwide cohort study from England 2003–2018. Journal of Hematology & Oncology. 2023; 16: 56.

[16] Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng JJCc. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Critical Care. 2020; 24: 108.

[17] Rafeq R, Igneri LA. Infectious pulmonary diseases. Infectious Disease Clinics of North America. 2024; 38: 1–17.

[18] Di Pasquale M, Sotgiu G, Gramegna A, Radovanovic D, Terraneo S, Reyes L, *et al.* Prevalence and etiology of community-acquired pneumonia in immunocompromised patients. Clinical Infectious Diseases. 2019; 68: 1482–1493.

[19] Ren K, Yong C, Wang Y, Wei H, Zhao K, He B, *et al*. Cytomegalovirus pneumonia in inflammatory bowel disease: literature review and clinical recommendations. Infection and Drug Resistance. 2023; 16: 6195–6208.

[20] Bichon A, Bourenne J, Allardet-Servent J, Papazian L, Hraiech S, Guervilly C, *et al*. High mortality of HLH in ICU regardless etiology or treatment. Frontiers in Medicine. 2021; 8: 735796.

[21] Yunis J, Short KR, Yu D. Severe respiratory viral infections: T-cell functions diverging from immunity to inflammation. Trends in Microbiology. 2023; 31: 644–656.

[22] Azoulay E, Russell L, Van de Louw A, Metaxa V, Bauer P, Povoa P, *et al*. Diagnosis of severe respiratory infections in immunocompromised patients. Intensive Care Medicine. 2020; 46: 298–314.

[23] Griffin G, Shenoi S, Hughes GC. Hemophagocytic lymphohistiocytosis:

an update on pathogenesis, diagnosis, and therapy. Best Practice & Research Clinical Rheumatology. 2020; 34: 101515.

[24] Steffen CJ, Koch N, Eckardt KU, Amann K, Seelow E, Schreiber A. Hemophagocytic lymphohistiocytosis and thrombotic microangiopathy after parvovirus B19 infection and renal transplantation: a case report. BMC Nephrology. 2021; 22: 337.

[25] Choi E, Lee S, Oh C, Kim Y, Bang JB. Cytomegalovirus-associated hemophagocytic syndrome diagnosed by liver biopsy in a kidney transplant recipient. Yonsei Medical Journal. 2021; 62: 274–277.

[26] Wu Y, Sun X, Kang K, Yang Y, Li H, Zhao A, *et al*. Hemophagocytic lymphohistiocytosis: current treatment advances, emerging targeted therapy and underlying mechanisms. Journal of Hematology & Oncology. 2024; 17: 106.

[27] Sun L, Su Y, Jiao A, Wang X, Zhang B. T cells in health and disease. Signal Transduction and Targeted Therapy. 2023; 8: 235.

[28] Boechat JL, Chora I, Morais A, Delgado L. The immune response to SARS-CoV-2 and COVID-19 immunopathology—current perspectives. Pulmonology. 2021; 27: 423–437.

[29] Knaak C, Nyvlt P, Schuster F, Spies C, Heeren P, Schenk T, *et al*. Hemophagocytic lymphohistiocytosis in critically ill patients: diagnostic reliability of HLH-2004 criteria and HScore. Critical Care. 2020; 24: 244.

[30] Khare N, Jinkala SR, Kanungo S. Performance of HScore in reactive hemophagocytic lymphohistiocytosis. Indian Journal of Hematology & Blood Transfusion. 2021; 37: 256–263.

[31] Hansen S, Alduaij W, Biggs CM, Belga S, Luecke K, Merkeley H, *et al.* Ruxolitinib as adjunctive therapy for secondary hemophagocytic lymphohistiocytosis: a case series. European Journal of Haematology. 2021; 106: 654–661.

[32] Shi YF, Shi XH, Zhang Y, Chen JX, Lai WX, Luo JM, *et al*. Disseminated tuberculosis associated hemophagocytic lymphohistiocytosis in a pregnant woman with Evans syndrome: a case report and literature review. Frontiers in Immunology. 2021; 12: 676132.

[33] Cheng S, Yan Z, Ma H, Liu Y. Lymphoma-associated hemophagocytic syndrome: a retrospective, single-center study of 86 patients. Annals of Hematology. 2024; 103: 3649–3656.

How to cite this article: Ling Zhang, Qi-Gang Yang, Min Shao. Severe pneumonia complicated by hemophagocytic lymphohistiocytosis in adults: a retrospective and exploratory clinical analysis. Signa Vitae. 2025; 21(3): 36-45. doi: 10.22514/sv.2025.034.