

## Infection-associated Hemophagocytic Syndrome in Critically Ill Patients with COVID-19

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**Summary:** Infection-associated hemophagocytic syndrome (IAHS), a severe complication of various infections, is potentially fatal. This study aims to determine whether IAHS occurs in critically ill patients with coronavirus disease 2019 (COVID-19). We conducted a retrospective observational study on 268 critically ill patients with COVID-19 between February 1st, 2020 and February 26th, 2020. Demographics, clinical characteristics, laboratory results, information on concurrent treatments and outcomes were collected. A diagnosis of secondary hemophagocytic lymphohistiocytosis (sHLH) was made when the patients had an HScore greater than 169. Histopathological examinations were performed to confirm the presence of hemophagocytosis. Of 268 critically ill patients with confirmed SARS-CoV-2 infection, 17 (6.3%) patients had an HScore greater than 169. All the 17 patients with sHLH died. The interval from the onset of symptom of COVID-19 to the time of a diagnosis of sHLH made was 19 days and the interval from the diagnosis of sHLH to death was 4 days. Ten (59%) patients were infected with only SARS-CoV-2. Hemophagocytosis in the spleen and the liver, as well as lymphocyte infiltration in the liver on histopathological examinations, was found in 3 sHLH autopsy patients. Mortality in sHLH patients with COVID-19 is high. And SARS-CoV-2 is a potential trigger for sHLH. Prompt recognition of IAHS in critically ill patients with COVID-19 could be beneficial for improving clinical outcomes.

**Key words:** severe acute respiratory coronavirus 2; coronavirus disease 2019; infection-associated hemophagocytic syndrome

As of Dec. 26, 2020, the number of global fatal cases due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection had surged past 1 759 000, far exceeding the deaths caused by severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS) coronavirus infections<sup>[1]</sup>. More troubling, however, is that the risk factors for mortality are not

completely clear. It has been reported that several factors, such as old age, underlying disease, secondary infection, coagulation abnormalities, hyperinflammation and acute respiratory distress syndrome (ARDS), are predictors of mortality<sup>[2-4]</sup>. Even when corresponding treatments are provided, a desired response is still hard to obtain in a proportion of patients with severe COVID-19 disease. This raises an important question: are any diagnoses being missed?

Hemophagocytic syndrome, also called hemophagocytic lymphohistiocytosis (HLH), is a rare syndrome involving pathologic immune activation that is often fatal<sup>[5]</sup>. It is characterized by prolonged fever, splenomegaly, hemophagocytosis in the bone

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marrow and abnormalities in laboratory parameters, including cytopenia, hyperferritinemia, low or absent natural killer (NK)-cell activity, elevated soluble CD25 (soluble interleukin 2 receptor, sIL-2R), and hypertriglyceridemia and/or hypofibrinogenemia<sup>[6]</sup>. Hemophagocytic syndrome comprises a primary and a secondary form. The primary form is a familial disorder due to genetic mutation<sup>[7]</sup>. The secondary form is mainly due to infections, malignancies, or autoimmune diseases<sup>[8, 9]</sup>. Infection-associated hemophagocytic syndrome (IAHS) has been associated with a variety of pathogen triggers, including Epstein-Barr virus (EBV), influenza virus, bacteria and fungi<sup>[10–13]</sup>. Surprisingly, it has been reported that 44% of cases with fatal influenza A (H1N1) infection met diagnostic criteria for HLH<sup>[11]</sup>. There was a concern that HLH was under-recognized in a fairly large number of patients with H1N1 infection. The same situation may take place in SARS-CoV-2 infection. It is reported that white blood cells and platelets significantly decreased while serum ferritin dramatically increased in a proportion of non-survivors with severe COVID-19 disease<sup>[4]</sup>. Cytokine storm syndromes and immunosuppression should be considered in patients with severe COVID-19 disease<sup>[14]</sup>. In this study, we attempted to document IAHS in critically ill patients with COVID-19 and raise awareness of IAHS to prompt early treatment.

## 1 MATERIALS AND METHODS

### 1.1 Study Design and Participants

From February 1st to February 26th, 2020, 268 critically ill patients with confirmed SARS-CoV-2 pneumonia admitted to Jinyintan Hospital and Tongji Hospital were enrolled in this study. This study was approved by the Ethics Commission of Jinyintan Hospital (KY-2020-15.01) and the Ethics Commission of Tongji Hospital (TJ-C20200125).

### 1.2 Data Collection

The case data of all patients, including demographics, clinical characteristics, laboratory results, treatments, and clinical outcomes, were obtained from electronic records. Incomplete information was supplemented by the principal physicians. All data were reviewed by two physicians.

### 1.3 Diagnostic Criteria

SARS-CoV-2 infection was confirmed by reverse transcription polymerase chain reaction (RT-PCR) testing of throat swab specimens<sup>[15]</sup>. EBV infection was diagnosed when EBV DNA was detected in serum by PCR. Influenza A infection was diagnosed when antibody IgM was detected in serum. Diagnosis of *Klebsiella pneumoniae* and *Acinetobacter baumannii* infection was made by a positive sputum culture and blood culture, respectively. The assessment of disease severity at admission was based on the

WHO interim guidance on clinical management of severe acute respiratory infection when COVID-19 was suspected<sup>[15]</sup>. The diagnosis of sHLH was based on the HScore (<http://saintantoine.aphp.fr/score/>). Coagulopathy was defined as a 3-second extension of prothrombin time or a 5-second extension of activated partial thromboplastin time. Disseminated intravascular coagulation (DIC) was defined according to scoring algorithm criteria established by the Japanese Association for Acute Medicine (JAAM)<sup>[16]</sup>. Sepsis and multiple organ dysfunction syndrome (MODS) were defined according to the 2016 Third International Consensus Definition for Sepsis<sup>[17]</sup>. ARDS was diagnosed according to the Berlin Definition<sup>[18]</sup>.

### 1.4 Pathology

Post-mortem microscopic (cytomorphologic) examinations were performed on the liver and spleen of 3 sHLH patients who died from SARS-CoV-2 infection. The liver and spleen tissues were sectioned and then fixed in a 4% formaldehyde/saline solution (pH 7.4) for at least 48 h. The tissues were processed routinely into paraffin, sectioned and stained successively with hematoxylin-eosin (HE) as per standard clinical laboratory protocol. Cytomorphologic analyses were performed independently by two pathologists. The images were captured by an Eclipse E600 upright microscope (Nikon, Japan) using imaging software at room temperature. Images captured were combined into one figure and marked with arrows and letters, using Adobe Photoshop CC2019 (Adobe, USA) without any further adjustment.

### 1.5 Statistical Analysis

We presented continuous measurements as medians [interquartile range (IQRs)] and categorical variables as counts (%). Continuous variables were compared with the Mann-Whitney-Wilcoxon test, and categorical variables were expressed as numbers (%) and compared by the  $\chi^2$  test or Fisher's exact test. SPSS (version 25.0) was used for all analyses.

## 2 RESULTS

### 2.1 Incidence of IAHS and Its Triggers

Of the 268 patients, 17 (6.3%) patients were scored greater than 169 (HScore). Notably, 10 sHLH patients were infected with only SARS-CoV-2. The other 7 were co-infected with EBV, influenza A, *Acinetobacter baumannii* or *Klebsiella pneumoniae*. Of the 17 sHLH patients, two patients had malignancies, including active liver cancer and angioimmunoblastic T-cell lymphoma (AITL). The triggers of IAHS are shown in table 1.

### 2.2 Clinical Characteristics and Laboratory Findings

Of the 17 sHLH patients, the mean age was 65 years (IQR, 55–71; range, 41–78 years), and 10 patients (59%) were men. The mean time from the

**Table 1 Summary of laboratory results, clinical features, and treatments of 17 patients infected with SARS-CoV-2 at onset of HLH**

	Normal range	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15*	Patient 16*	Patient 17*	
<b>Demographics, clinical features</b>																			
Age, year		60	65	73	69	72	71	41	51	70	59	77	78	56	55	53	53	66	
Sex		M	M	F	M	M	M	M	M	M	M	F	F	F	M	F	F	F	
Malignancy		-	-	-	-	-	-	+(AITL)	-	-	-	-	-	-	+(HCC)	-	-	-	
AID		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
SARS-CoV-2		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Other pathogens		-	+(Kp)	-	-	-	-	+(EBV)	+(Kp, IAV)	+(IAV)	-	-	-	-	-	+(Ab)	-	-	
Trigger		SARS-CoV-2	SARS-CoV-2/Kp	SARS-CoV-2	SARS-CoV-2	SARS-CoV-2	SARS-CoV-2	SARS-CoV-2/EBV/AITL	SARS-CoV-2/Kp/IAV	SARS-CoV-2/IAV	SARS-CoV-2	SARS-CoV-2	SARS-CoV-2	SARS-CoV-2	SARS-CoV-2/HCC	SARS-CoV-2/Ab	SARS-CoV-2	SARS-CoV-2	
BT <sub>max</sub> (°C)	36.1-37.2	38.5	39.5	39.5	38.9	39.4	39.5	40.0	38.5	38.6	38.9	38.5	38.7	38.5	38.5	39.7	39.0	39.0	
WBC (×10 <sup>9</sup> /L)	3.5-9.5	19.5	3.41	18.76	18.27	7.83	13.66	1.04	6.55	16.65	4.11	17.99	12.04	14.05	16.64	19.4	6.06	19.88	
HGB (g/L)	130-175	89	80	87	86	89	88	63	50	89	93	89	86	86	53	89	69	65	
PLT (×10 <sup>9</sup> /L)	125-350	54	47	89	77	41	55	41	16	58	33	72	21	71	71	84	62	106	
TG (mmol/L)	<1.7	2.00	3.10	4.35	2.09	2.61	2.00	7.12	2.00	2.89	2.73	5.02	2.44	9.32	2.40	5.57	4.36	4.65	
FIB (g/L)	2-4	1.60	1.30	10.30	2.10	1.50	1.02	2.01	1.09	1.03	1.59	0.96	2.50	3.23	0.91	1.30	7.10	1.70	
SF <sup>a</sup> (ng/mL)	30-400	>2000.0	>2000.0	>2000.0	>2000.0	>2000.0	3372.4	7663.8	2664.3	2395.6	>2000.0	1245.8	2200.0	2566.8	2393.5	>2000.0	>2000.0	>2000.0	
AST (U/L)	≤40	556	100	30	57	418	32	55	71	32	93	78	53	463	127	69	26	75	
Known Immunosuppression		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
HScore		185	211	191	185	201	201	246	185	185	185	170	185	175	185	221	191	205	
ALT (U/L)	≤41	206	63	27	8	75	24	18	19	24	39	27	24	434	15	55	4	46	
ALB (g/L)	35-52	23.7	25.3	23.5	24.8	19	24.4	24.7	16.9	22	22.1	33.6	23.6	17.1	20.1	35.6	35.7	27.3	
TBIL (μmol/L)	≤26	28	34.40	56.7	31.3	10.3	79.8	15.3	22.2	26.2	16.4	32.2	10.6	15.1	66.9	9.1	9.8	16.5	
LDH (U/L)	135-225	3335	496	322	525	3320	643	515	302	862	718	1222	905	736	974	1095	362	600	
CRP <sup>b</sup> (mg/L)	<1	60.0	>160.0	>160.0	>160.0	110.0	180.0	58.8	124.4	207.3	211.7	115.2	103.6	259.8	78.0	49.2	86.0	24.3	
PT (s)	11.5-14.5	14.7	12.4	16.0	18.3	26.8	18.0	14.1	32.5	23.6	17.3	20.2	17.8	23.9	29.7	11.1	16.1	14.4	
D-dimer** (μg/mL)	<0.5	1.20	17.54	56.44	26.45	20.00	>21.00	2.72	21.00	6.61	>21.00	>21.00	>21.00	1.46	14.38	80.00	1.03	34.06	
PCT (ng/mL)	<0.05	5.52	0.52	3.44	5.40	2.70	2.22	0.58	0.20	0.31	0.16	1.63	ND	6.14	0.92	1.05	0.24	0.48	
IL-2R <sup>a</sup> (U/mL)	223-710	ND	ND	ND	ND	ND	ND	>5000	225	>5000	996	1124	ND	2925	2780	ND	ND	ND	
IL-6 (pg/mL)	<7	3.97	6.98	40.63	24.95	5.03	68.00	7.78	130.90	568.00	35.50	124.50	ND	736.00	2934.00	10.09	27.90	10.36	

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Treatments	Normal range	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15 <sup>a</sup>	Patient 16 <sup>a</sup>	Patient 17 <sup>a</sup>
Antiviral Tx		Y	Y	Y	N	N	Y	Y	N	N	Y	N	Y	N	Y	Y	Y	Y
Antibiotics Tx		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
GCC Tx		N	Y	N	N	N	Y	Y	N	N	Y	N	Y	N	N	Y	N	Y
IVIg		N	N	Y	Y	N	Y	N	Y	N	Y	N	Y	N	N	Y	N	Y

<sup>a</sup>Hemophagocytosis was found in tissues at autopsy. <sup>b</sup>For serum ferritin (SF), the upper limit of detection was 2000.0 ng/mL for the patients admitted in Wuhan Jinyintan Hospital. However, it was not applied for the patients admitted in Tongji Hospital due to the different brands and models of analyzers used. <sup>c</sup>For C-reactive protein (CRP), the upper limit of detection was 160.0 mg/L for the patients admitted in Wuhan Jinyintan Hospital. However, it was not applied for the patients admitted in Tongji Hospital. <sup>d</sup>For D-dimer, the upper limit of detection was 21.00 µg/mL for the patients admitted in Tongji Hospital. However, it was not applied for the patients admitted in Wuhan Jinyintan Hospital. <sup>e</sup>For interleukin-2 receptor (IL-2R), the upper limit of detection was 5000 U/mL for all patients. Ab. *Acinetobacter baumannii*; AID, autoimmunity disease; AITL, angioimmunoblastic T-cell lymphoma; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BT<sub>max</sub>, maximum body temperature; CRP, C-reactive protein; EBV, Epstein-Barr virus; F, female; FIB, fibrinogen; GCC, glucocorticoid; HCC, hepatocellular carcinoma; HGB, hemoglobin; IAV, Influenza A virus; IL-2R, interleukin-2 receptor; IL-6, interleukin-6; IVIG, intravenous immunoglobulin; Kp, *Klebsiella pneumoniae*; M, male; Myco, mycoplasma; LDH, lactate dehydrogenase; N, no; ND, no data; PCT, procalcitonin; PLT, platelet; PT, prothrombin time; SF, serum ferritin; TBIL, total bilirubin; TG, triglyceride; Tx, therapy; WBC, white blood cell; Y, yes. SI conversion factors: to convert alanine aminotransferase to µkat/L, multiplied by 0.0167; aspartate aminotransferase to µkat/L, multiplied by 0.0167; lactate dehydrogenase to µkat/L, multiplied by 0.0167; D-dimer to nmol/L, multiplied by 5.476; serum ferritin to µg/L, multiplied by 1

onset of COVID-19 to the time of a diagnosis of sHLH made was 19 days (IQR, 15–23; range, 7–40 days). All patients had fever over 38.4°C. Although no rash was observed, petechiae were found in 6 (35%) patients. Three (18%) patients developed DIC. Fifteen (88%) patients developed coagulopathy. Fourteen (82%) patients developed MODS (table 1). Neurologic manifestations, including meningeal irritation and cognitive impairment, were difficult to evaluate since the patients were under oxygen therapy and mechanical ventilation.

Of the 17 HLH patients, two (12%) patients experienced leukopenia ( $<5.0 \times 10^9/L$ ), and 16 (94%) patients developed anaemia (haemoglobin  $<92$  g/L) and all patients developed thrombocytopenia (PLT  $<110 \times 10^9/L$ ). At diagnosis of sHLH, the mean serum level for fasting triglycerides was 2.89 mmol/L (IQR, 2.40–4.65) and that for fibrinogen was 1.59 g/L (IQR, 1.09–2.10). All patients developed hyperferritinemia ( $>500$  ng/mL) with a median serum ferritin of 2000.0 ng/mL (IQR, 2000.0–2395.6 ng/mL; range, 1245.8–7663.8 ng/mL). Thirteen patients (76%) presented with elevated aspartate aminotransferase (AST) ( $>40$  U/L). In addition to the diagnostic criteria findings, an elevated serum lactate dehydrogenase (LDH) level was observed in all patients, with a median of 718 U/L (IQR, 515–974 U/L; range, 302–3335 U/L). Fifteen patients (88%) had hypoalbuminemia (albumin  $<35$  g/L). In all patients, D-dimer increased (median, 21 µg/mL; IQR, 6.61–21 µg/mL). Increased serum level of interleukin-6 (IL-6) was observed in all patients (median, 31.70 pg/mL; IQR, 8.93–127.70 pg/mL). The data of sIL-2R were not available for every patient but showed an increased level ( $>2400$  U/mL) in 5 patients.

### 2.3 Pathological Findings

Of the 268 patients, 6 patients underwent autopsy. The pathological changes were found not only in lungs but also in other organs of autopsy patients. Notably, hemophagocytosis in the liver and spleen as well as a large amount of lymphocyte infiltration in the hepatic portal areas was observed in three sHLH patients (fig. 1).

### 2.4 Treatment and Clinical Outcomes

There are currently no approved treatments for COVID-19. Patients received various supportive care treatments, including antiviral treatment, antibiotic treatment, antifungal treatment, glucocorticoid treatment and intravenous immunoglobulin (IVIg) treatment. Seven sHLH patients received glucocorticoid treatment. One patient received dexamethasone (10 mg daily) and 6 patients received methylprednisolone sodium succinate (40 mg twice daily).

Of the 268 critically ill patients enrolled in this study, 70 patients were discharged, and 198 patients died. All 17 sHLH patients died. The interval from the onset of symptoms of COVID-19 to death was 21 days



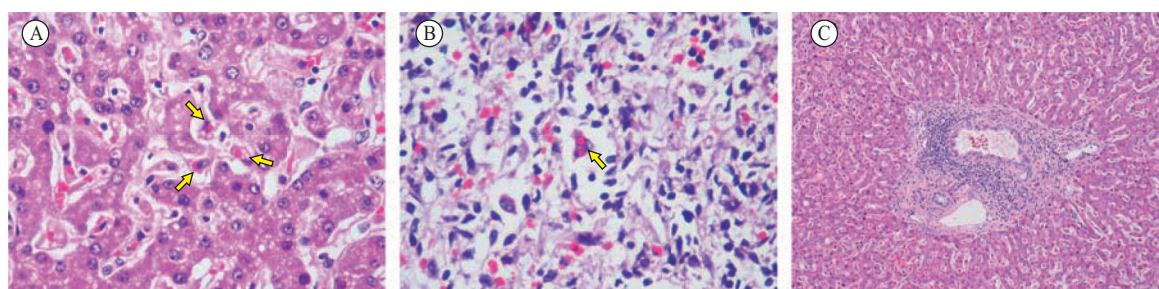
(IQR, 16–30 days; range, 10–49 days). And the interval from the diagnosis of sHLH to death was 4 days (IQR, 2–7 days; range, 1–22 days) (fig. 2).

### 3 DISCUSSION

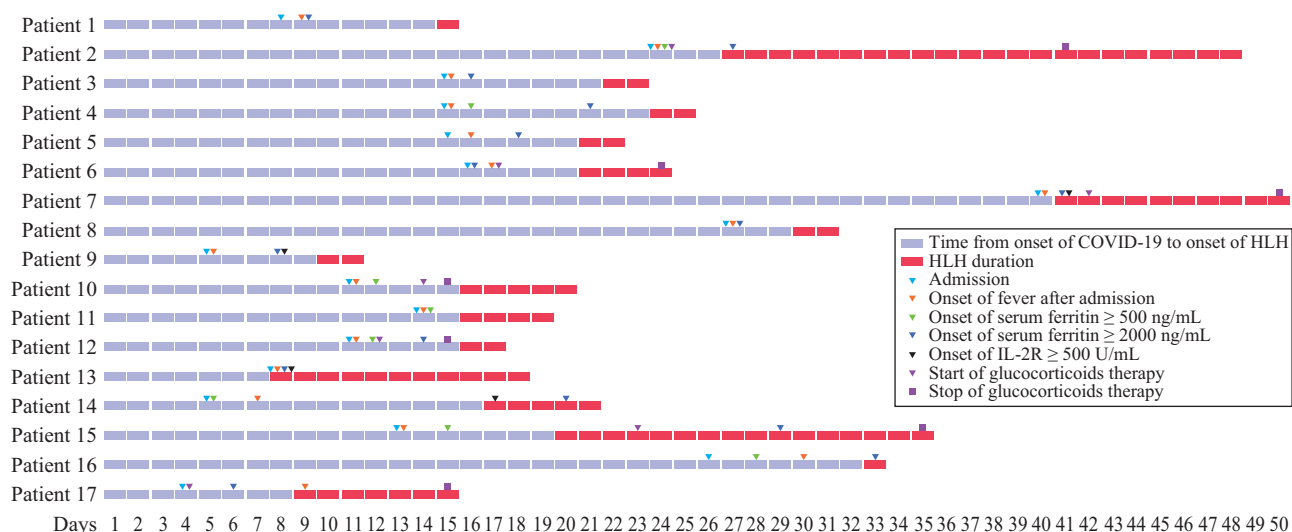
In this case series, we reported that IAHS occurred in critically ill patients with COVID-19. Based on the analyses of the clinical characteristics, laboratory findings, and histopathological results of autopsy specimens, we confirmed that 6.3% (17/268) of patients with laboratory-confirmed SARS-CoV-2 infection developed IAHS. Ten patients who were infected with only SARS-CoV-2 developed sHLH, which indicated that the virus may be a trigger of sHLH. In this study, none of the 17 sHLH patients survived. It suggested that IAHS may be a risk factor for mortality of critically ill patients with COVID-19.

Increased awareness is required to timely diagnose IAHS in critically ill patients with COVID-19 since mortality in sHLH patients with COVID-19 is high. However, there are several challenges in diagnosis of sHLH. In this study, HScore was used to confirm the

diagnosis of sHLH<sup>[19]</sup>, which revealed a sensitivity of 100% and a specificity of 94.1% with a cutoff of 168<sup>[20]</sup>. HLH-2004 diagnostic criteria were not used because they are developed for children but not validated for adults<sup>[6]</sup>. Another challenge is that sHLH patients may present with a phenotype indistinguishable from sepsis or MODS<sup>[6]</sup>. Herein, more characteristic parameters of sHLH, such as hyperferritinemia, pronounced cytopenias, hypofibrinogenemia and hypertriglyceridemia, as well as LDH, AST, albumin and pathological changes were evaluated in patients in this study. Of note, organomegaly (hepatomegaly or splenomegaly) was not recorded in electronic records. And there were other 4 patients who had hyperferritinemia >4420 ng/mL<sup>[21]</sup> at the time of admission and presented with similar clinical manifestations to those of 17 HLH patients. Tissue biopsies in these critically ill patients were challenging. Therefore, they might have a higher HScore and fulfill the diagnosis of sHLH. It is reported that IAHS may be a frequent complication of severe 2009 influenza A (H1N1) infection and represents an important contributor to multiorgan failure and death<sup>[22]</sup>. The



**Fig. 1** Representative examples of hemophagocytosis in fatal cases of SARS-CoV-2 infection  
 Representative examples of hemophagocytosis were characterized by histiocytes with engulfed red blood cells in the liver (A) and spleen (B) (HE, ×400). Lymphocytes infiltration was seen in the hepatic portal areas (C) (HE, ×100). The yellow arrows indicated hemophagocytosis in tissues.



**Fig. 2** Timeline of disease course and treatment of patients with sHLH  
 The clinical course of each patient with the key indicators

same scenario may happen in SARS-CoV-2 infection.

Although hemophagocytic syndrome associated with a variety of viral, bacterial, fungal, and parasitic infections has been reported<sup>[11–13, 23]</sup>, there is a lack of evidence demonstrating that SARS-CoV-2 is a trigger of IAHS. In this study, 10 patients who were infected with only SARS-CoV-2 without any other pathogen infection, malignancy or autoimmune disease developed hemophagocytic syndrome. Moreover, 5 sHLH patients who were concomitantly infected with other pathogens, such as EBV, influenza A, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, also developed hemophagocytic syndrome. Although the trigger of hemophagocytic syndrome in these cases is difficult to be identified, SARS-CoV-2 cannot be excluded as a potential trigger of IAHS. We thus provide evidence that SARS-CoV-2 serves as a potential trigger of hemophagocytic syndrome.

Early and adequate treatment is crucial for improving the clinical outcome of patients with COVID-19 who develop IAHS. The principal goal is to suppress the inflammatory process that underlies IAHS<sup>[24]</sup>. Recently, results from a preliminary study suggested that low dose dexamethasone, a commonly used steroid drug listed in the protocol of sHLH treatment, reduces risk of death in patients with severe COVID-19<sup>[25]</sup>. Moreover, it has been reported that blockade of IL-6 (tocilizumab) and Janus kinase (JAK) inhibition could be potential treatments for COVID-19<sup>[26, 27]</sup>. These clinical trials echoed the findings of this study.

This study has several limitations. First, in light of the emergency conditions, it was challenging to obtain the data regarding genetic mutations and assessments of cytotoxicity of NK cells. However, these missing parameters are helpful for timely diagnosis. Second, treatment recommendations cannot be provided in this retrospective study since none of the 17 sHLH patients survived. Nevertheless, immunosuppressive treatment should be considered when a patient is highly suspected. Last, the sample size of HLH patients identified in this study is small. Further large-scale studies are still needed.

In summary, our findings provided evidence that IAHS occurred in critically ill patients with COVID-19 and it is a potential risk factor for mortality. Physicians caring for critically ill patients with COVID-19 should be aware of the possibility of IAHS and pay attention to important indicators. Prompt recognition of the clinical and laboratory features of IAHS and immediate therapeutic intervention are critical.

#### Conflict of Interest Statement

The authors have no conflicts of interest relevant to this article to disclose.

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