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***Retrospective Study***

**Intensive care unit complications and outcomes of adult patients with hemophagocytic lymphohistiocytosis: A retrospective study of 16 cases**

Kapoor S *et al*. ICU complications and outcomes of HLH patients

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**Abstract**

***AIM***

To study the management, complications and outcomes of adult patients admitted with hemophagocytic lymphohistiocytosis (HLH) in the intensive care unit (ICU).

***METHODS***

We performed a retrospective observational study of adult patients with the diagnosis of “HLH” admitted to the two academic medical ICUs of Baylor College of Medicine between 01/01/2013 to 06/30/2017. HLH was diagnosed using the HLH-2004 criteria proposed by the Histiocyte Society.

***RESULTS***

Sixteen adult cases of HLH were admitted to the medical ICUs over 4 years. Median age of presentation was 49 years and 10 (63%) were males. Median Sequential Organ Failure Assessment (SOFA) score at the time of ICU admission was 10. Median ICU length of stay (LOS) was 11.5 d and median hospital LOS was 29 d. Septic shock and acute respiratory failure accounted for majority of diagnoses necessitating ICU admission. Septic shock was the most common ICU complication seen in (88%) patients, followed by acute kidney injury (81%) and acute respiratory failure requiring mechanical ventilation (75%). Nine patients (56%) developed disseminated intravascular coagulation and eight (50%) had acute liver failure. 10 episodes of clinically significant bleeding were observed. Multi system organ failure was the most common cause of death seen in 12 (75%) patients. The 30 d mortality was 37% (6 cases) and 90 d mortality was 81% (13 cases). There was no difference in mortality based on age (above or less than 50 years), SOFA score on ICU admission (more than or less than 10), immunosuppression, time to diagnose HLH or direct ICU admission versus floor transfer.

***CONCLUSION***

HLH is a devastating disease associated with poor outcomes in ICU. Intensivists need to have a high degree of clinical suspicion for HLH in patients with septic shock/multi system organ failure and progressive bi/pancytopenia who are not responding to standard management in ICU.

**Key words:** Lymphohistiocytosis; Cytopenia; Hypercytokinemia; Hemophagocytosis; Shock

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**Core tip:** Hemophagocytic lymphohistiocytosis is a serious disorder in intensive care unit (ICU) with high morbidity and mortality. Septic shock, acute kidney injury and respiratory failure are the most common manifestations in ICU. We observed high incidence of bleeding complications and bloodstream infections. High index of suspicion is necessary for ICU patients with severe septic shock and multi organ failure who do not respond to standard treatment.

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**INTRODUCTION**

 “Hemophagocytic lymphohistiocytosis” or HLH, first described in 1952 by Farquhar and Claireux, is a rare fatal disorder of dysregulated immune activation of natural killer cells and cytotoxic T cells, leading to hypercytokinemia, hemophagocytosis, multiple organ dysfunction and failure[1]. Clinically, the syndrome presents as a constellation of fever, cytopenias (anemia, leukopenia, thrombocytopenia), hepatosplenomegaly, high ferritin and triglyceride levels, low fibrinogen levels and histologic evidence of hemophagocytosis in various organs[2-6]. HLH is classified into two types, primary (familial) and secondary (reactive). Primary or familial HLH is a genetic disorder seen in pediatric population, usually fatal within 2 mo if left untreated. Secondary or reactive HLH is more often diagnosed in adults and usually due to underlying immunosuppression from lymphoid malignancy, infection, connective tissue disorder or idiopathic causes[2-6].

There has been an improved awareness in recent years amongst physicians with regard to HLH presentation, diagnosis and management. Due to the nature of disease to cause multiple organ dysfunctions, the number of intensive care unit (ICU) admissions and management by Intensivists in collaboration with hematologists and immunologists has increased over the last few years[7]. Management of HLH in ICU is very challenging for an intensivist for a variety of reasons. First, the patients are critically ill with multiple organ involvement and failure, putting them at highest risk of mortality. Previous studies have investigated predictors of poor outcomes and reported hospital mortality in the range of 20%-75% and ICU mortality between 50%-80%[7-27]. The most common causes of death include multiple system organ failure (MSOF), bleeding and sepsis[23]. Second, the disease is rare in occurrence and the true incidence, course, complications and risk factors for poor outcomes in ICU are still not clear. Third, the disease is often under recognized in ICU as suggested by the autopsy studies[28]. The reasons include non-specific presentation of disease, lack of specific biomarker and absence of a validated HLH diagnostic criteria in ICU. HLH has many clinical and laboratory features in common with septic shock which inevitably leads to delayed diagnosis and treatment[25,29]. A recent paper by Halacli *et al*[30] emphasized to keep HLH in the differential diagnosis of patients with severe sepsis/septic shock who develop bicytopenia and are resistant to treatment. Hemophagocytosis and macrophage activation, a histologic feature of HLH, is also seen in septic shock, with the incidence of 0.8% and 4% respectively, making it sensitive but less specific for the diagnosis of HLH[29,31-33]. HLH-2004 criteria proposed by Histiocyte Society and H-score have been used to diagnose HLH in ICU but are not well validated in ICU setting[7,8,10,34-37]. Also, there is no specific biomarker for this disease. Ferritin, an acute phase reactant, can be elevated in other infections and acute and chronic inflammatory conditions in ICU and is not specific for HLH[38-43].

Although much research in recent years has focused on hospital complications and outcomes of HLH patients, few researchers have addressed the problem in ICU[1,6-10,25-27]. Buyse *et al*[8] published the first retrospective review on HLH patients in ICU in 2010. Since then, only two other studies (with sample sizes of more than 10 patients) have described ICU course and outcomes of HLH patients in the critical care setting[7,10]. More evidence to guide Intensivists manage these complex patients with rare, fatal and under diagnosed syndrome in ICU is warranted. The present paper examines the ICU course, complications, management and outcomes of HLH patients admitted to the academic medical ICUs of a tertiary medical center over the last 4 years.

**MATERIALS AND METHODS**

The present study is a retrospective observational study of patients with the diagnosis of “HLH” admitted to the two academic medical ICUs of Baylor College of Medicine between January 1, 2013 to June 30, 2017. The research project was approved by the Institutional Review Board of the Baylor College of Medicine and need for written informed consent was waived. All adult patients above 18 years of age admitted to the two medical ICUs with the diagnosis of HLH were included in the study. HLH was diagnosed using the HLH-2004 criteria proposed by the Histiocyte society. Patients were identified using ICD-9 and ICD-10 codes for HLH and data was extracted from EPIC electronic health record with the help of clinical analytics team at Baylor College of Medicine. Data regarding patient demographics [age, sex, Sequential Organ Failure Assessment (SOFA) score on ICU admission, underlying immunodeficiency, precipitating factors *etc*.], most extreme pertinent laboratory values and ICU complications [30 d and 90 d mortality, septic shock, need for mechanical ventilation, acute kidney injury (AKI) *etc*.] was collected. Data analysis was performed using STATA 15 software and descriptive statistics were expressed as median and interquartile range except where mentioned otherwise. For the subgroup analysis in table 4, Fisher’s exact test was used to compare categorical variables and calculate “*P*” value since the sample size was less than 20.

**RESULTS**

***Demographics***

Sixteen adult patients were admitted to our medical ICUs over the study period with the diagnosis of HLH, 3 of them had a prior history of HLH. Four patients had established diagnosis of HLH before ICU admission and rest were diagnosed during ICU stay. The baseline characteristics of patients are presented in Table 1. The median age of presentation was 49 years and ten (63%) were males. Median SOFA score on ICU admission was ten. Median time from hospital to ICU admission was half day with interquartile range of zero to seven days. Eleven patients (69%) had a known immunodeficiency in the form of underlying malignancy, autoimmune disease or human immunodeficiency virus (HIV) infection. Precipitating factors for HLH included infectious causes in five (31%), malignancy related in two (13%), both infection and malignancy related in five (31%) and idiopathic in four (25%) cases.

***Clinical presentation***

Severe sepsis/shock and acute respiratory failure accounted for up to 80% diagnoses for ICU admission. Median ICU length of stay (LOS) was 11.5 d and median hospital LOS was 29 d. Table 2 lists relevant laboratory parameters observed at the time of ICU admission and most extreme values. Thirteen bone marrow biopsies were performed of which, ten (77%) showed evidence of hemophagocytosis. Septic shock was the most common ICU complication seen in fourteen (88%) patients, followed by AKI (81%) and acute respiratory failure requiring mechanical ventilation (75%). Majority of the patients with acute renal failure required continuous renal replacement therapy (CRRT). Nine patients (56%) developed features of disseminated intravascular coagulation (DIC) and eight (50%) had acute liver failure. Of note, ten episodes of clinically significant bleeding requiring intervention were observed in our series. Because most of our patients (94%) were initiated on eight week regimen of standard chemotherapy with dexamethasone and etoposide per HLH-94 protocol they were prone to infectious complications. Six cases of pneumonia (including 3 fungal) and ten cases of blood stream infections (bacteremia in nine and fungemia in one) were observed. One patient developed intra-abdominal abscess and required interventional radiology guided drainage procedure. Of note, the ICU complications occurred both before and after starting chemotherapy. Table 3 lists the ICU complications.

***Outcomes***

Multi system organ failure was the most common cause of death seen in twelve (75%) patients. The 30 d mortality was 37% (six cases) and 90 d mortality was 81% (thirteen cases).

We also performed subgroup analysis comparing categorical variables listed in Table 4 and found no difference in mortality based on age of presentation (above or less than 50 years), SOFA score on ICU admission (above or less than 10), presence of underlying immunosuppression at the time of HLH diagnosis, time to diagnose HLH ( more than or less than 3 d) and whether patients were directly admitted to the ICU versus from the floor.

**DISCUSSION**

HLH is a rare disease, annual incidence being one per 800000 people and one to ten per 1 million children in Italy, Sweden, and the United States[2]. Secondary or reactive HLH usually affects adults who may have underlying immunosuppression from malignancy, HIV infection or autoimmune disorders[2-6]. Usually, the disease is precipitated by factors like infection, malignancy or idiopathic causes. Malignancy associated HLH usually has a poorer prognosis compared to infectious or idiopathic causes[44].

Multiple studies have investigated morbidity, mortality and predictors of poor outcomes in patients with HLH but very few have been conducted in an ICU setting[7-27]. Since HLH is a rare and under diagnosed syndrome in ICU, there are only three retrospective studies reported in literature on ICU patients with sample sizes of 10 or more (ranging from 10 to 71 patients)[7,8,10]. HLH in ICU affects all age groups including young adults, median age varying from 25 to 57 years[7,8,10]. The disease is associated with massive systemic inflammatory response due to cytokine storm, leading to multiple organ failure and circulatory shock[45]. Shock and acute respiratory failure with need for mechanical ventilation are the major reasons for ICU admission in literature, accounting for up to 80% of principal diagnoses in our series[1,7,8,10,25,27]. Other reasons include acute encephalopathy, acute kidney failure, acute liver failure, bleeding complications or MSOF[46]. Distributive shock (septic shock) due to intense vasodilation is the most common form of shock in ICU with reported incidence in literature from 50%-80%[1,7,8,10,25,27]. In our case series, 88% patients developed septic shock and one had concomitant cardiogenic shock requiring mechanical circulatory support with intra-aortic balloon pump.

Patients can develop acute hypoxemic respiratory failure requiring mechanical ventilatory support, incidence of which varies from 58% to 100%[1,7,8,10,25,27]. Various etiologies include pneumonia (infectious/aspiration), acute respiratory distress syndrome, sepsis related respiratory failure, cardiogenic pulmonary edema, atelectasis *etc*[47].

A retrospective study by Aulagnon *et al*[48] reported a high incidence of AKI in HLH patients (62%) and majority of them (59%) needed renal replacement therapy. Main etiologies of AKI in their study included acute tubular necrosis, hypo perfusion, tumor lysis syndrome and HLH related glomerulopathies[48]. Many patients in ICU with AKI require CRRT due to hemodynamic instability with incidence from 30% to 54%.

Patients with HLH in ICU are prone to develop infectious/nosocomial complications like pneumonias, blood stream infections as they are usually immunocompromised. The largest retrospective study in ICU by Barba *et al*[7] with 71 confirmed cases of HLH found out that the incidence of invasive aspergillosis was 25%, another study reported 10% incidence of invasive mucormycosis[10]. We saw 3 cases of invasive fungal infections with 2 due to aspergillosis and 1 from mucormycosis. All three patients died from invasive Pneumonia. There was a high incidence of bacteremias in our patients with incidence of 62%, none with Catheter related bloodstream infections (CRBSI). Only one previous ICU study reported 10% incidence of CRBSI[10].

Severe coagulopathy and DIC add to the morbidity in HLH patients. None of the previous ICU studies have reported any clinically significant bleeding complications in ICU. We observed 10 serious bleeding complications in our case series. In a report by Valade *et al*[49], thrombocytopenia was seen in all patients, coagulation abnormalities in 68% and DIC in 50% patients. 22% of their patients developed severe bleeding complications and 5 of them died from hemorrhagic shock. Low fibrinogen < 2 g/L and elevated PT value were associated with higher mortality[49].

Multi system organ failure was the most common cause of death in our patients, incidence being 75% which is similar to previous ICU studies (56% to 70%)[7,8,10].

None of the diagnostic criteria including HLH-2004 (proposed by Histiocyte society), H-score proposed by Fardet *et al*[36] or Delphi study criteria have been validated in an ICU setting[34-37]. Of the three major retrospective studies in ICU, two used HLH-2004 criterion and one used H score ≥ 169 to diagnose HLH in ICU[7,8,10]. H-score might have higher specificity compared to HLH-2004 criteria and HLH-2004 criteria suffer from some intrinsic problems[40]. Serum ferritin, an acute phase reactant, has been utilized as a diagnostic and prognostic marker for HLH[38-43]. Higher cutoff value of ferritin level above > 10000 μg/L may increase sensitivity to 90% and specificity to 96% in ICU but still can be positive in many conditions other than HLH, thereby lowering specificity[38-43,50]. The incidence of hypertriglyceridemia in HLH is estimated to be between 60%-70%[51]. Improvement of triglyceride level with chemotherapy might be an important predictor of response to treatment[51]. Intensivists should have a high index of suspicion for HLH in patients with septic shock/multi system organ failure and progressive bi/pancytopenia[52]. There should be a low threshold to obtain simple tests like serum ferritin, triglyceride and fibrinogen in patients with suspected HLH. Hemophagocytosis, a pathologic marker for HLH, is a fairly sensitive but not specific criterion for diagnosis. It can be observed in other conditions like sepsis, hemolytic anemias and malignancy[29,31-33]. Its incidence in ICU varies between 70%-80% in pathologic specimens with our case series showing incidence of 77%[32,33]. The results can be false negative based on the experience of the pathologist and is usually seen in the advanced stage of the disease.

In addition to the treatment of the underlying trigger, early diagnosis and treatment with chemotherapy per HLH-94 protocol with 8 wk course of etoposide and dexamethasone is associated with good outcomes[53-57]. Optimal duration of treatment in ICU is unclear and not being studied as patients become prone to infectious complications due to immunosuppression by prolonged chemotherapy. ICU mortality for HLH patients varies between 38% to 70%[1,7,8,10,25,27]. Buyse *et al*[8] reported ICU mortality of 39% and hospital mortality of 52%. Factors associated with higher mortality included shock on ICU admission and presence of thrombocytopenia (platelet count less than 30 gm/L). The largest retrospective study by Barba *et al*[7] reported 28 d ICU mortality of 38% and hospital mortality of 68%. SOFA score on admission, advanced age and lymphoma related HLH were factors associated with higher mortality. Our case series had 30 d ICU mortality of 37% and 81% 90 d mortality. We did not see any mortality difference based on SOFA scores (above or less than 10), age (above or less than 50 years), presence or absence of immunosuppression at the time of HLH diagnosis, time to diagnose HLH (more than or less than 3 d) and direct ICU admission versus transfer from floors. This might be attributable to the overall sickness of our population and the aggressive nature of the disease per se. The median SOFA score at the time of ICU admission in our series was 10 while previous ICU studies reported median SOFA score in the range of 6-8. Larger multi center studies targeting HLH population in ICU and need to create HLH registry are essential in future to improve our understanding of this syndrome.

The major limitations of our study are single center population, retrospective design and relatively small sample size. Our retrospective study reported data over 4 years whereas previous ICU studies reported data over 10-12 years, thereby explaining our small sample size. The major strength of our study is that the HLH population comes from medical ICUs of general medical-surgical hospital and not specialized hematology/oncologic centers, thereby mimicking setup of most of the adult North American ICUs.

In conclusion, HLH is a devastating disease with dismal outcomes. Septic shock, AKI and acute respiratory failure with need for mechanical ventilation were the most common ICU complications in our study. We observed high incidence of clinically significant bleeding and bloodstream infections in our series. Most patients died of MSOF with 80% 90 d mortality.

**ARTICLE HIGHLIGHTS**

***Research background***

Hemophagocytic lymphohistiocytosis (HLH) is a rare, fatal syndrome increasingly being recognized in intensive care unit (ICU) now. Not many studies have been conducted in an ICU setting to study the complications and outcomes of this patient population.

***Research motivation***

There is an urgent need for more evidence in literature to help guide Intensivists identify and manage these sick and complicated patients in ICU. This will help to improve their outcomes and decrease complications.

***Research objectives***

The objective of our research is to study the ICU course, complications and outcomes of adult patients admitted with HLH over the period of 4 years.

***Research methods***

It is a retrospective observational study of adult patients with HLH admitted to the two academic medical ICUs from January 1, 2013 to June 30, 2017. The diagnosis of HLH was established using HLH-2004 criteria. Data was collected using ICD 9 and 10 codes. Statistical analysis was performed using STATA 15 software.

***Research results***

Sixteen adult patients were admitted to ICUs over 4 years with HLH with median age of 49 years. Median ICU LOS was 11.5 days and median hospital LOS was 29 d. Septic shock, acute kidney injury (AKI) and acute respiratory failure were the most common ICU complications. Multi system organ failure was the most common cause of death with high mortality of 80% over 90 days. Age (above or below 50 years), Sequential Organ Failure Assessment score on ICU admission, time to diagnose HLH and immune status of patient did not predict mortality.

***Research conclusions***

Our study showed that HLH in ICU is associated with mortality of 80% over 90 d periods. Most common complications include septic shock, respiratory failure and AKI. Multi system organ failure is the most common cause of death. Clinically significant bleeding and bloodstream infections were also observed in our case series.

***Research perspectives***

Presentation of HLH in ICU mimics severe sepsis/septic shock. High index of suspicion for HLH is warranted in patients with septic shock and bi/pan cytopenia, not responding to standard treatment. Tests like serum ferritin, fibrinogen, triglycerides, bone marrow/lymph node biopsies help in diagnosis of HLH. Early diagnosis and treatment with chemotherapy is crucial for improved outcomes.

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**Table 1 Descriptive statistics of 16 intensive care unit patients with hemophagocytic Lymphohistiocytosis [expressed as median (IQR)] *n* (%)**

|  |  |
| --- | --- |
| **Parameter** | **Value** |
| Age (yr) | 49 (26-61) |
| Sex |  |
| Male | 10 (63) |
| Female  | 6 (37) |
| SOFA Score on ICU admission | 10 (7-15) |
| Time from Hospital to ICU admission  | 0.5 (0-7) |
| Time to diagnose HLH (d) | 3 (1-7) |
| Immunodeficiency  | 11 (69) |
| HIV infection  | 2 |
| Malignancy | 7 |
| Autoimmune (SLE, autoimmune hemolytic anemia)  | 2 |
| Precipitating factors |  |
| Infection only | 5 (31) |
| Pneumonia  | 2 |
| EBV | 2 |
| Typhoid fever  | 1 |
| Malignancy only | 2 (13) |
| Diffuse Large B cell lymphoma  | 1 |
| T cell lymphoma | 1 |
| Infection and Malignancy combined  | 5 (31) |
| EBV and plasmablastic lymphoma | 1 |
| EBV and Hodgkin lymphoma  | 1 |
| EBV and Diffuse large B cell Lymphoma | 1 |
| EBV and NK cell leukemia  | 1 |
| EBV associated lymphoproliferative disorder | 1 |
| Idiopathic  | 4 (25) |
| Number of HLH criteria met | 5 (5-6) |
| Principal Reason for ICU Admission |  |
| Severe sepsis/septic shock  | 9 (56) |
| Acute respiratory failure | 4 (25) |
| GI Bleed  | 2 (13) |
| Acute encephalopathy | 1 (6) |
| ICU Length of Stay (d) | 11.5 (5-29) |
| Hospital Length of Stay (d) | 29 (17-40) |
| Prior history of HLH | 3 (19) |
| Biopsies performed  | 23 |
| Bone marrow  | 13 |
| Liver | 4 |
| Lymph node | 3 |
| Skin  | 2 |
| Lung  | 1 |
| Bi/Pancytopenia on ICU admission | 10 (63) |
| Hemophagocytosis seen on bone marrow biopsy (out of total) | 10 (77) |
| Chemotherapy received  | 15 (94) |

HLH: Hemophagocytic lymphohistiocytosis; ICU: Intensive care unit; SOFA: Sequential organ failure assessment; HIV: Human immunodeficiency virus; SLE: Systemic lupus erythematosus; EBV: Epstein-Barr virus; NK: Natural killer.

**Table 2 Laboratory tests in patients with hemophagocytic lymphohistiocytosis [expressed as median (IQR)]**

|  |  |
| --- | --- |
| **Laboratory test** | **Value** |
| Hemoglobin on ICU Admission (gm/dL) | 9.3 (8.4-11.35) |
| Lowest Hemoglobin during ICU stay (gm/dL) | 6 (4.4-6.7) |
| Platelet count on ICU admission (K/cubic mm) | 89 (37-159) |
| Lowest platelet count (K/cubic mm) | 7.5 (4-22) |
| White blood cell count on ICU admission (K/microL) | 3.75 (1.75-5.4) |
| Lowest White blood cell count (K/microL) | 0.1 (0.1-0.7) |
| Fibrinogen on ICU admission (mg/dL) | 263 (86-312) |
| Lowest Fibrinogen (mg/dL) | 70 (50-176) |
| First Ferritin level in ICU on clinical suspicion of HLH (microgram/L) | 17728 (7689-37981) |
| Highest ferritin (microgram/L) | 40000 (16500-55000) |
| Triglycerides (mg/dL) | 350 (269-556) |

ICU: Intensive care unit.

**Table 3 Intensive care unit complications in patients with hemophagocytic lymphohistiocytosis (Total number of patients = 16)**

|  |  |
| --- | --- |
| **ICU complications** | ***n* (%)** |
| Mechanical ventilation | 12 (75) |
| Septic shock | 14 (88) |
| AKI | 13 (81) |
| With renal replacement therapy | 10 |
| Without renal replacement therapy | 3 |
| Acute liver failure | 8 (50) |
| Clinically significant Bleeding | 10 (62) |
| GI Bleed | 4 |
| Intracerebral bleed | 2 |
| Hemoptysis | 1 |
| Retroperitoneal bleed | 1 |
| Epistaxis | 1 |
| Hematoma-Neck | 1 |
| DIC | 9 (56) |
| ARDS | 4 (25) |
| With ECMO | 2 |
| Without ECMO | 2 |
| Pneumonia | 6 (37) |
| Bacterial | 3 |
| Fungal | 3 |
| Viral/others | 0 |
| Acute encephalopathy | 5 (31) |
| Stress cardiomyopathy | 2 (12) |
| Arrythmias (Atrial, ventricular) | 4 (25) |
| Bloodstream infections | 10 (62) |
| Bacteremia | 9 |
| Gram positive organisms | 2 |
| Gram negative organisms | 7 |
| Fungemia | 1 |
| MSOF | 12 (75) |
| Tracheostomy | 3 (19) |
| Mortality |  |
| 30 d  | 6 (37) |
| 90 d | 13 (81) |
| Miscellaneous (Seizures, perforated viscus, cardiogenic shock requiring IABP, intra-abdominal abscess) | 5 (31) |

ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome; AKI: Acute kidney injury; DIC: Disseminated intravascular coagulation; ECMO: Extracorporeal support; MSOF: Multi system organ failure.

**Table 4 Differences in mortality based on various categorical variables**

|  |  |  |
| --- | --- | --- |
| **Categorical variable** | **Categorical variable**  | ***P* value** |
| Age above 50 yr (8 patients) | Age less than or equal to 50 yr (8 patients) | 0.50 |
| SOFA score on ICU admission above 10 (7 patients) | SOFA score on ICU admission less than or equal to 10 (9 patients) | 0.60 |
| Underlying Immunosuppression (11 patients) | No underlying immunosuppression (5 patients) | 0.70 |
| Direct admission to ICU (8 patients) | Transfer from floor to ICU (8 patients) | 0.50 |
| Time to diagnose HLH more than 3 d (7 patients) | Time to diagnose HLH less than or equal to 3 d (9 patients) | 0.40 |

HLH: Hemophagocytic lymphohistiocytosis; ICU: Intensive care unit; SOFA: Sequential organ failure assessment.