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Original Article

Outcomes of adult critically ill patients with hemophagocytic lymphohistiocytosis in united states-analysis from an administrative database from 2007 to 2015

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Abstract: Background: Severe infections caused by the novel coronavirus 2 display similarities to secondary hemophagocytic lymphohistiocytosis (HLH). However, HLH is a rare disease and has not been well described in critically ill patients. Methods: We used the Nationwide Inpatient Sample (NIS), the largest all-payer inpatient care database publicly available in the United States to identify all adult discharges with Hemophagocytic syndrome (ICD-9 CM code 288.4) between 2007 and 2015. Critical illness was considered present if patient had either ICD-9 CM code indicating the requirement of invasive mechanical ventilation or the presence of shock. We used ICD-9-CM codes to identify various infections (inf-HLH), malignancies (mal-HLH) and autoimmune diseases associated with HLH (MAS-HLH) and classified them in their respective groups. Primary outcome was in-hospital mortality in critically ill patients. We developed multivariable regression model to examine variables associated with mortality in critically ill HLH patients. *P* value was kept at < 0.05. Results: Of the 7420 (95% CI 6959-7881) estimated discharges with HLH, 2313 (31%) were critically ill. Of the critically ill patients, 442 (34%) were mal-HLH, 422 (43.3%) were inf-HLH, 403 (30.7%) were MAS-HLH and 1046 (27.3%) were unable to be classified. In hospital mortality rates were 6.4% in non-critically ill and 48.4% in critically ill patients. Among the subtypes of HLH, in-hospital mortality was 53% in mal-HLH, 49.4% in inf-HLH, 26% in MAS-HLH and 54.6% in unclassified group. On multivariable regression analysis, development of acute renal failure requiring hemodialysis (OR 2.06, 95% CI 1.29-3.3, P=0.002) and acute hepatic failure (OR 2.21, 95% CI 1.38-3.52, P=0.001) were significantly associated with higher mortality. Conclusion: Inpatient mortality of critically ill patients is remarkably high. Patients with MAS-HLH had better outcomes when compared to other groups of HLH.

Keywords: Hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, epidemiology, critical illness

Introduction

Severe infections caused by the novel coronavirus 2 (SARS-Cov2) display similarities to secondary hemophagocytic lymphohistiocytosis (HLH) [1-3]. In fact, some COVID-19 patients with high acuities of illness fulfill criteria used to diagnose HLH (H-score criteria). Anecdotally, IL6 receptor inhibitors such as Tocilizumab are used in this subset of patients with COVID-19 in efforts to reverse cytokine storm and improve outcomes [4-6]. HLH is a rare disease and has not been well described in critically ill patients. Classically, two forms of HLH are described - primary and secondary. Primary HLH is associated with a variety of genetic mutations predominantly occurring in children. Secondary HLH is usually associated with infectious, oncologic, and rheumatologic conditions. The final common pathway in both types of HLH comprises a hyper-cytokine state which is mediated by defective natural killer cells and cytotoxic T cell function [7-9].

Manifestations of clinical findings in HLH include high fever, and a systemic inflammatory

response syndrome (SIRS) like response associated with cytopenias affecting at least two cell lineages in the peripheral blood, hypofibrinogenemia, elevated ferritin levels, and hypertriglyceridemia [10]. However, when applied to critically ill patients, these criteria are hampered by the lack of specificity [11].

Often, an intensive care unit (ICU) admission is required because many HLH patients experience multiple organ failure from the underlying cytokine storm state. Delays in diagnosis from lack of specificity of diagnostic criteria combined with the absence of treatment modalities may lead to poor outcomes. Investigations, mostly consisting of case-series have reported mortality rates from 41% to 57% [12-14].

We designed our study to clarify the epidemiology of HLH. We used a large national administrative database maintained by the Agency of Healthcare Quality and Research (AHRQ) for the purposes of our study as it has been used in the past to study rare diseases. The goals of our study were to describe the characteristics and outcomes of patients with HLH particularly those that become critically ill.

Methods

Data source

We used the Nationwide Inpatient Sample (NIS), the largest all-payer inpatient care database publicly available in the United States. This administrative dataset was created by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project and contains data on 5 to 8 million hospital stays from about 1,000 hospitals sampled to approximate a 20-percent stratified sample of U.S. community hospitals but excludes federal hospitals. Each hospitalization is treated as an individual entry in the database and includes International Classification of Diseases-9th Clinical Modification (ICD-9-CM) codes for the principal diagnosis and secondary diagnoses and procedures associated with that stay. NIS includes appropriate weights to allow the production of national estimates. The ICD-9-CM code for HLH was developed in 2007. ICD-10-CM codes started being used from October 1st, 2015. Hence, we used data from the year 2007 to September 30th, 2015 for this study. Each hospitalization record includes common demographic variables, hospital characteristics and clinical data coded using ICD9CM codes. Information about patient race is missing in about one fifth of the study population because some participating states restrict race data. The data within the NIS is publicly available and does not contain any identifying information, making this retrospective study exempt from review by the Institutional Review Board. The retrospective nature of studying de-identified patient data, lack of direct patient contact or intervention also makes this study exempt for ethics committee and from the requirement of patient consent.

Study population

Inclusion criteria-we used ICD-9-CM codes to identify patients 18 years and above who were discharged with Hemophagocytic syndrome (ICD-9 CM code 288.4) between 2007 and 2015 [15]. This code encompasses-Familial hemophagocytic lymphohistiocytosis, Infection associated Hemophagocytic syndrome, Histiocytic syndromes, and Macrophage activation syndrome. We used ICD-9-CM codes to identify various infections, malignancies and autoimmune diseases associated with HLH. We then classified HLH into infection associated HLH (inf-HLH), malignancy associated HLH (mal-HLH) and macrophage activation syndrome (MAS-HLH) as described in previous literature [16]. (See Table S1 for ICD-9-CM codes used). Less than 5% of the patients had concomitant infection and malignancy or autoimmune diagnoses. These were kept into their respective malignancy or autoimmune groups. Patients not categorized in the above groups were kept in “unclassified-HLH” group. Exclusion criteria-patients who did not have the above mentioned diagnosis code.

Definition of variables

We used NIS variables to identify demographic variables such as patient age, gender, and race. We also used ICD-9-CM codes to identify co-morbid conditions and procedure codes (Table S2). Similarly, we identified patients who received blood transfusions, tracheostomy, total parenteral nutrition, and renal failure requiring dialysis (Table S2). We identified NIS

variables for discharge dispositions and classified them as discharge to home, transfers to other healthcare facilities (e.g. skilled nursing facilities, intermediate care, inpatient rehabilitation, psychiatric hospitals, or inpatient hospice), home health care, and others (including against medical advice, unknown, and missing).

Definition of critical illness

We considered patients to be critically ill if they had either ICD-9CM code indicating the requirement of invasive mechanical ventilation (96.70-96.72) or the presence of shock (785.5, 00.17).

Outcomes

Our primary outcome of interest was in-hospital mortality in critically ill patients with HLH, which is recorded as such in the NIS database. Secondary outcomes included length of hospital stay and discharge disposition.

Statistical analysis

We performed all statistical analyses using STATA IC 11.0 (Stata-Corp, College Station, TX). We used the strata and weights with appropriate survey commands to generate national estimates. For our descriptive analyses, we compared demographic and clinical characteristics as well as outcomes of critically ill and non-critically ill patients using Student's t-test for continuous variables and Pearson's chi-square test for categorical variables. Statistical significance was reported if *p* value was found to be less than 0.05. In separate analyses we compared characteristics of patients in the 4 subtypes of HLH using analysis of one-way variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

We constructed several multivariable models to examine characteristics associated with in-hospital mortality. We used single predictor logistic regression to identify significant associations between putative risk factors and mortality. Variables found significant at $P < 0.10$ were candidates for inclusion in our primary model. The different groups of HLH were compared to mal-HLH as reference.

Results

There were 7420 (95% CI 6959-7881) estimated discharges with diagnosis of HLH from years 2007 to 2015. Of these 2313 (31%) met criteria for being critically ill. 422 (43.3%) in inf-HLH, 442 (34%) in mal-HLH and 403 (30.7%) in MAS-HLH were critically ill. We were not able to classify 1046 (27.3%) patients.

Demographical & clinical characteristics-comparison of patients with and without critical illness

Demographic comparisons between critically ill patients with HLH and those without critical illness are shown **Table 1**. A larger proportion of patients discharged with a diagnosis of HLH were admitted to urban teaching hospital as compared to non-teaching and rural hospitals. A larger proportion of critically ill patients as compared to those were not had CHF, CAD, ILD, cirrhosis, stroke, solid organ transplants and lymphoid leukemia (**Table 2**). Patients with CMV infections were also strongly associated with development of critical illness. Organ failure rates and procedures associated with being critically ill were greater in the critically ill cohort as compared to people who were not critically ill (**Table 2**). In hospital mortality rates were 6.4% in non-critically ill and 48.4% in critically ill patients ($P < 0.001$) (**Table 2**).

Demographical & clinical characteristics of critically ill HLH patients-according to HLH subtypes

MAS-HLH had higher proportions of young patients and females. African Americans and Hispanics were disproportionately higher in MAS-HLH group (**Table 3**). Hyperlipidemia was noted to be more often in unclassified group. Other co-morbidities did not differ significantly between the groups. Acute liver failure was seen least often in MAS-HLH group. Blood and platelet transfusions were also observed least often in MAS-HLH group. Rates of tracheostomy was least in mal-HLH group. Inf-HLH group had highest rates of renal failure requiring dialysis and acute liver failure.

Outcomes of critically ill HLH patients

Overall mortality in critically ill patients with HLH was 48.4%. Patients with MAS-HLH had

Table 1. Demographic characteristics of patients with HLH

	Not critically ill	Critically ill	*P*-value
TOTAL	5107	2313	
Age Group* (%)			< 0.001
18-34	39.3	27.7	
35-49	18.4	22.7	
50-64	21.5	29.9	
≥ 65	20.8	19.7	
Female (%)	43.3	42.7	0.83
Race (%)			0.40
White	52.7	49.4	
African American	14.4	16.7	
Hispanic	12.6	11.1	
Asian	5.3	5.6	
Others	3.7	5.5	
Unknown	11.3	11.8	
Insurance (%)			0.23
Private	50.6	44.2	
Medicare	24.1	26.2	
Medicaid	18.5	21.7	
Uninsured	4.0	5.0	
Other	2.9	3.0	
Hospital location-teaching status* (%)			< 0.001
Rural	3.4	1.0	
Urban Non-teaching	14.5	7.1	
Urban Teaching	82.1	91.9	
Hospital Bed size (%)			0.02
Small	10.2	5.7	
Medium	16.5	16.3	
Large	73.3	78	
Hospital region* (%)			0.05
Northeast	25.5	18.6	
Midwest	23.7	24.6	
South	31.2	33.8	
West	19.6	23	

*denotes a *p*-value < 0.05.

significantly lower mortality than other groups (**Table 3**). Length of hospital stay was also significantly lower in MAS-HLH group. After adjusting for demographical and clinical characteristics, MAS-HLH still had significantly lower in-hospital mortality when compared to mal-HLH (OR 0.42; 95% CI 0.20-0.89; P=0.023) (**Table 4**). Other parameters associated with in-hospital mortality were older age, presence of end stage renal disease, development of acute renal failure requiring hemodialysis and acute liver failure. Hyperlipidemia and neutropenia were associated with lower in-hospital mortality.

Female gender had significantly lower odds of mortality when compared to males (OR 0.59, 95% CI 0.37-0.89). Since females have significantly higher rates of MAS-HLH, we examined this association using interaction terms. The results are shown in **Table 5**. We observed that the mortality of females is significantly lower than males only for MAS-HLH. Asian race was associated with higher mortality but did not reach significance of P < 0.05. Median duration of hospitalization was longest in inf-HLH and shortest in MAS-HLH. Of the survivors, 39.8% were discharged to skilled nursing facility.

Discussion

From a large administrative dataset, we report aggregate characteristics and outcomes of patients with HLH which is an uncommon condition; an average of only 825 cases per year were found nationally in the NIS. Thus, the strength of our study lies in analysis of over 7000 patients of which over 2000 were critically ill. This, to our knowledge, is the largest report of critically ill adults with HLH.

We found that at least 31% of patients with HLH become critically ill (develop shock and/or require invasive mechanical ventilation). Further, almost half (48.4%) of those who develop critical illness die in the hospital and of the survivors, 40% are discharged to nursing facilities. The remarkably high mortality compares closely to the in-hospital mortality of septic shock in the same time period of our study (39.3-48.3%) [17]. Although there are differences in the inflammatory pathways between HLH and sepsis, [11] our findings highlight the

Table 2. Clinical characteristics & outcomes of patients with HLH

Clinical characteristics	Not critically ill	Critically ill	*P*-value
TOTAL	5107	2313	
Co-morbidities			
Hyperlipidemia	13.4	17	0.08
Smoking	14.6	12	0.18
Diabetes Mellitus	10.4	12.5	0.21
Hypertension	28.7	31.4	0.28
Coronary Artery Disease*	8.3	12.9	0.01
Morbid Obesity	1.9	1.1	0.28
Congestive heart failure*	6.7	15.6	0.001
Chronic Obstructive Lung Disease	3.2	2.8	0.67
Interstitial lung disease*	4.1	9.8	< 0.001
Cirrhosis*	7.6	12.2	0.004
End Stage Renal Disease	1.5	2.8	0.14
Malnutrition*	14.1	26.6	0.001
Bone Marrow Transplant	3.9	3.0	0.55
Solid Organ Transplant*	1.7	3.7	0.01
Immunodeficiency	3.5	2.8	0.44
Neutropenia	11.4	12.2	0.61
Thrombocytopenia	2.4	4.5	0.30
Non hematological cancers	1.4	1.8	0.59
Hodgkin's lymphoma	2.1	2.8	0.45
Non-Hodgkin's lymphoma	14.7	12.9	0.38
Multiple Myeloma	0.6	1.5	0.06
Lymphoid leukemia*	1.5	3.7	0.02
Myeloid leukemia	0.7	1.3	0.25
Rheumatoid arthritis	9.3	9.1	0.9
Systemic Lupus Erythematosus	6.2	6.0	0.84
Other collagen vascular diseases	2.5	2.2	0.69
Crohn's disease	1.6	1.9	0.62
Infections			
Epstein Barr virus	5.4	7.4	0.16
Cytomegalovirus*	5.2	8.3	0.035
Herpes Simplex Virus	3.0	3.8	0.40
Influenza	1.1	1.9	0.20
Human Immunodeficiency Virus	3.8	4.9	0.40
Tuberculosis	0.2	1.1	0.02
Aspergillus	1.2	2.8	0.04
Other clinical characteristics			
Atrial fibrillation*	5.6	12.6	0.001
Stroke*	1.2	3.9	0.001
Venous embolism and thrombosis*	2.1	5.6	< 0.001
Acute renal failure*	19.7	66.6	< 0.001
Altered mental status*	5.0	28.4	< 0.001
Acute liver failure*	5.7	30	< 0.001
Blood transfusion*	27.8	47.9	< 0.001
Platelet transfusion*	14.3	32.3	< 0.001
Coagulation factor transfusion*	0.9	4.7	< 0.001
Upper Gastrointestinal bleeding requiring upper endoscopy*	4.4	8.3	0.004

Tracheostomy*	0	7.0	< 0.001
Percutaneous endoscopic gastrostomy*	0.4	1.9	0.002
Total Parenteral Nutrition	2.6	4.5	0.07
Acute renal failure requiring hemodialysis*	2.5	28.9	< 0.001
Outcomes			
Mortality* (%)	6.4	48.4	< 0.001
Disposition in survivors* (%)			< 0.001
Home	63.4	35.6	
Home care	16.2	23.8	
Facility	19.4	39.8	
Others	1.0	0.8	
Median Length of Stay in days* (IQR)	7 (4-15)	16 (8-30)	< 0.001

*denotes a *p*-value < 0.05.

Table 3. Demographical and clinical characteristics of critically ill patients with HLH-according to subtypes

	Mal-HLH	Inf-HLH	MAS-HLH	Unclassified	*P*-value
Total (%)	442 (19.1%)	422 (18.2%)	403 (17.4%)	1046 (45.3%)	
Age groups (%)					< 0.001
18-34	16.8	36.3	48.8	20.8	
35-49	23.8	16.2	22.8	24.8	
50-64	31.5	34.8	18.5	31.7	
≥ 65	27.9	12.7	9.9	22.8	
Female (%)	32.3	28	76.3	40	< 0.001
Race (%)					< 0.001
White	51.9	48.1	35.6	54.1	
African American	13.4	19.7	23.1	14.4	
Hispanic	12.2	8.5	14.8	10.3	
Asian	3.4	3.7	9.8	5.7	
Others	5.8	10.6	5.4	3.4	
Unknown	13.2	9.5	11.2	12.3	
Co-morbidities					
Hyperlipidemia	14.3	14.1	9.3	22.2	0.04
Smoking	9.9	12.8	14.7	11.4	0.79
Diabetes Mellitus	13.5	11.9	10	13.4	0.86
Hypertension	28.1	24.6	26.7	37.4	0.08
Coronary Artery Disease	16.9	11.9	7.4	13.7	0.31
Congestive heart failure	14.7	10.7	19.3	16.5	0.53
Chronic Obstructive Lung Disease	3.5	2.2	0	3.4	0.70
Interstitial lung disease	4.7	10.7	7.6	12.4	0.18
Cirrhosis	16.7	8.1	8.5	13.4	0.19
End Stage Renal Disease	0	0	7.1	2.9	0.12
Malnutrition	24.9	33.4	22.2	26.3	0.36
Other Clinical characteristics					
Atrial fibrillation	11.4	13.9	10.1	13.7	0.81
Stroke	3.4	2.6	5.0	3.8	0.95
Venous embolism and thrombosis	5.7	5.9	3.7	6.2	0.86
Acute renal failure	75.1	68.3	56.1	66.3	0.07
Altered mental status	26.9	34.4	25.7	27.6	0.59
Acute liver failure	25.8	35.3	17.2	34.4	0.02
Blood transfusion	53.8	54	39.8	46.1	0.18
Platelet transfusion	49.6	29.4	18.6	31.4	0.001
Coagulation factor transfusion	10.2	2.4	3.7	3.6	0.08
Upper Gastrointestinal bleeding requiring upper endoscopy	5.6	9.3	3.7	10.9	0.15

Tracheostomy	2.1	11.7	9.8	6.2	0.057
Percutaneous endoscopic gastrostomy	1	3.5	3.7	1	0.23
Total Parenteral Nutrition	6.8	7.1	2.4	3.3	0.25
Acute renal failure requiring hemodialysis	29	38.8	17.3	29.4	< 0.001
Outcomes					
Mortality (%)	53	49.4	26	54.6	< 0.001
Disposition in survivors (%)					0.07
Home	40.6	18.4	34.7	41.7	
Home care	28.3	25.6	21	22.8	
Other healthcare Facility	31.1	56	41	35.4	
Others	0	0	3.3	0	
Median Length of Stay, days (IQR)	16 (8-31)	20 (13-38)	13 (7-29)	15 (7-26)	< 0.001

Table 4. Variables associated with mortality in critically ill HLH patients

	OR	95% Confidence Interval	*P*-value
Age Group			
18-34	reference		
35-49*	1.80	1.00-3.22	0.046
50-64*	2.97	1.68-5.24	< 0.001
≥ 65*	2.95	1.52-5.68	0.001
Female*	0.59	0.37-0.89	0.013
Race			
White	reference		
Asian	2.31	0.93-5.67	0.068
Hyperlipidemia*	0.53	0.30-0.94	0.03
End Stage Renal Disease*	2.64	0.74-9.39	0.13
Neutropenia*	0.44	0.23-0.84	0.014
New dialysis*	2.06	1.29-3.3	0.002
Acute Liver failure*	2.21	1.38-3.52	0.001
HLH type			
Mal-HLH	Reference		
Inf-HLH	0.75	0.38-1.45	0.39
Mas-HLH*	0.42	0.20-0.89	0.023
Unclassified	1.00	0.58-1.73	0.99

*denotes a *p*-value < 0.05.

Table 5. Association of in-hospital mortality and Interaction between gender and HLH-type. Adjusting for the other variables in **Table 4**

Gender	HLH type	OR	95% CI	*P*-value
Male	Mal-HLH	Reference		
Male	Inf-HLH	0.95	0.43-2.11	0.91
Male	MAS-HLH	1.06	0.33-3.37	0.91
Male	Unclassified	1.23	0.62-2.43	0.54
Female	Mal-HLH	1.09	0.41-2.90	0.85
Female	Inf-HLH	0.53	0.18-1.52	0.24
Female	MAS-HLH	0.22	0.08-0.55	0.001
Female	Unclassified	0.73	0.35-1.54	0.415

need for expeditious diagnosis and prompt institution of therapies-a strategy that has worked well to decrease the mortality associated with septic shock.

Our mortality rates are similar to other reports. For example, Barba et al. reported a 68% 28-day mortality in 71 ICU patients with HLH [18]. Although limited by sample size, they also found that advancing age, SOFA scores at admission and lymphoma related HLH were associated with increased mortality. In a systematic review of the literature, Ramos-Casals et al. reported a 41% mortality in data collected from 1109 patients [12]. Jumic et al. (2019) over a ten-year period at a single institution reported a 39% in hospital mortality in 41 adult HLH cases [19]. Birndt et al. reported no difference in overall survival between inf-HLH and mal-HLH on long term follow up in 137 patients [20]. Our report adds to this literature. In addition to allowing classification into subtypes our large sample size also allowed for more robust determination of associations with mortality. Like Barba et al. We found that advancing age and worsening organ failure were associated with mortality. Moreover, we observed that patients with MAS-HLH had significantly lower in-hospital mortality when compared to other subtypes. This may perhaps reflect availability of better immunosuppressive therapies for rheumatological conditions leading to MAS-HLH.

We observed that aspergillus infection was more common than other fungal infection. This

has been observed previously by Barba et al. who reported 25% rates of invasive aspergillosis [18]. A significant observation was the association of female gender with improved odds of survival in HLH. We also found significantly higher rates of MAS-HLH in women which led us to examine gender mortality association using interaction terms with sub-types of HLH. The interaction was only significant with MAS-HLH indicating that mortality differences in women were largely driven by this entity. It is likely that since collagen vascular diseases are known to be more common in women, survival advantage is secondary to the advantage conferred by MAS-HLH. Conversely, men had significantly higher rates of HLH other than MAS-HLH.

Acute renal failure and end stage renal disease were observed to be the most important clinical parameter associated with increased in-hospital mortality. Of 66.6% of patient who develop acute renal failure, about half of them end up requiring hemodialysis. Renal failure has been known to adversely affect survival in HLH [21]. Acute liver failure was also associated with poorer outcomes.

Our study has several important limitations. First, we used ICD-9-CM codes to identify HLH and other clinical variables. We cannot discount that variations in coding practices between institutions may have affected the accuracy of our data. Further, HLH is a rare diagnosis and may be often missed secondary to unclear diagnostic criteria. It is likely that true HLH is underrepresented in this database. Second, since primary HLH is predominantly a childhood disease, we assumed that adult cases in the dataset were all secondary and attempted to classify HLH into categories using codes for infections, malignancies and collagen vascular diseases previously known to cause HLH. It was not possible to determine the temporality of these conditions with the diagnosis of HLH. It is possible that cases classified as secondary HLH may have been primary. Further, over half the cases (45.3%) were unclassifiable. We cannot be certain if these cases captured primary HLH accurately or were secondary HLH without known etiologies. Third, our data source did not allow us to determine multiple hospitalizations for the same patient; this may have exaggerated the precision of our estimates. Fourth, we did not have important clinical information such as vital signs, important therapies such as steroids, the degrees of severity of comorbid conditions or the severity of organ failures. For example, different degrees of shock or respiratory failure or thrombocytopenia cannot be distinguished using these codes. If available these would have added more robustness to our multivariable adjustment models. Finally, though we are unable to comment on long term outcomes of our patients especially those discharged to nursing facilities.

Despite these limitations, our study provides important demographic, clinical and outcome information about HLH and its sub-types. This may help in the design of future trials especially given the rarity of this condition.

Disclosure of conflict of interest

None.

Abbreviations

ICU, Intensive Care Unit; HLH, hemophagocytic lymphohistiocytosis; Inf-HLH, Infection associated HLH; Mal-HLH, Malignancy associated HLH; MAS-HLH, Macrophage Activation Syndrome associated HLH; ICD-9-CM, International Classification of Diseases-9th Clinical Modification; NIS, Nationwide Inpatient Sample; AHRQ, Agency of Healthcare Quality and Research; 95% CI, 95% Confidence Interval.

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Table S1. Identification of subtypes of HLH

Hemophagocytic syndrome (HLH)	288.4
Infections: inf-HLH	
Infectious mononucleosis	075
CMV	078.5, 573.1
HSV	054
Tuberculosis	010-018
Influenza	487, 488
SARS-associated coronavirus	480.3
Aspergillus	117.3, 484.6
Human Immunodeficiency Virus	042, 079.53, V08
Malignancy: mal-HLH	
Non hematological cancer	140-175, 179-195, 196-199
Hodgkin's lymphoma	201
Non-Hodgkin's lymphoma	200, 202
Multiple Myeloma	203
Lymphoid leukemia	204
Myeloid leukemia	205, 206
Other leukemias	207, 208
Autoimmune: MAS-HLH	
Rheumatoid diseases	714
SLE	710.0
Other Collagen vascular disease	710.1-710.9
Crohn's disease	555.0-52; 555.9

Table S2. Patient co-morbidities and procedures

Mechanical ventilation	96.70-96.72
Shock	785.5, 00.17
Co-morbidities	
Hyperlipidemia	272.0-272.4
smoking	305.1, V15.82
Diabetes Mellitus	250
Hypertension	401-405
coronary artery disease	410-414
Morbid obesity	278.01, V85.4
Congestive Heart Failure	428
Chronic Obstructive Pulmonary Disease	490, 491, 492, 496
Interstitial lung disease	135, 500, 501, 502, 503, 504, 505, 506.0, 506.4, 507.0, 507.1, 507.8, 508.1, 515, 516.0, 516.1, 516.2, 516.3, 516.8, 516.9, 517.2
Cirrhosis	571.2, 571.5-9, 275.0, 275.1, 39.1, 572.4, 572.2, 572.3, 572.4, 456.0, 456.1, 456.20, 456.21, 567.23
End Stage Renal Disease	585.6, 39.95, V56.0-3, V45.1, V56.2, V56.8
Malnutrition	260-269
Solid organ Transplant	Kidney: V42.0. 996.81, Heart: V42.1, 996.83, Lungs: V42.6, 996.84, Liver: V42.7, 996.82
Bone marrow	41.0, 996.85, V42.81, V42.82, 279.5
Immunodeficiency	279
Neutropenia	288.00
Thrombocytopenia	287.4, 287.5
Other clinical characteristics	
Atrial fibrillation	427.31
Stroke	433, 434, 436, 437.1
Venous embolism and thrombosis (include pulmonary embolism)	453, 415.11, 415.19
Acute renal failure	584
Altered mental status	780.01, 780.09, 348.1, 348.3, 293.0, 293.1
Acute liver failure	570, 572.2, 573.4
Procedures	
Blood transfusion	99.03, 99.04
Platelet transfusion	99.05
Coagulation factor transfusion	99.06
Upper gastrointestinal endoscopy	42.23, 42.24, 42.33, 44.13, 44.14, 44.43, 44.91, 45.13, 45.14, 45.16, 45.30
Tracheostomy	31.1, 31.2, 31.21, 31.29
Percutaneous endoscopic gastrostomy	43.11
Total Parenteral Nutrition	99.15
Acute renal failure requiring hemodialysis	584.5-584.9 AND 39.95