Annals of Hematology (2023) 102:2989–2996
https://doi.org/10.1007/s00277-023-05271-w

ORIGINAL ARTICLE

Delay in treatment of adult hemophagocytic lymphohistiocytosis is associated with worse in-hospital outcomes

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Received: 17 February 2023 / Accepted: 9 May 2023 / Published online: 1 July 2023

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by uncontrolled activation of the immune system leading to multiorgan failure. Timely initiation of HLH-specific treatment is believed to be essential and lifesaving. Due to the rarity of the condition in adults, there is no data available in the literature to investigate the effects of treatment delay in this age group. We used data from the National Inpatient Sample (NIS) to evaluate the inpatient practices of HLH treatment initiation over 13 years (2007–2019) and their association with clinically relevant inpatient outcomes. Patients were divided into early treatment group (<6 days) and late treatment group (≥ 6 days). We compared outcomes using multivariate logistic regression models adjusting for age, sex, race, and HLH-triggering conditions. There were 1327 and 1382 hospitalizations in the early and late treatment groups, respectively. Hospitalization in the late treatment group had higher rates of in-hospital mortality (OR 2.00 [1.65–2.43]), circulatory shock (OR 1.33 [1.09–1.63]), requiring mechanical ventilation (OR 1.41 [1.18–1.69]), venous thromboembolism (OR 1.70 [1.27–2.26]), infectious complications (OR 2.24 [1.90–2.64]), acute kidney injury (OR 2.27 [1.92–2.68]), and requiring new hemodialysis (OR 1.45 [1.17–1.81]). Additionally, we observed no significant trend in the mean time to treatment over the study period. This study shows the importance of early initiation of HLH treatment and highlights the adverse outcomes of treatment delay.

Keywords Hemophagocytic lymphohistiocytosis · Immune system · Treatment · National inpatient sample

Key Points

- Treatment delay is associated with higher odds of in-hospital mortality and other adverse outcomes in adult patients with HLH.
- There has been no significant improvement in the time to treatment of adult HLH over the period 2007 to 2019.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an inflammatory syndrome where genetic predisposition and/or environmental factors such as severe infections and malignancy lead to uncontrolled T-cell and macrophage activation resulting in severe and sometimes fatal multiorgan damage.[1] Characterized by a distinct constellation of clinical features, patients typically exhibit fever and rapid clinical deterioration, along with signs of multiple organ involvement, such as altered mental status, requirement of respiratory support, hepatitis, splenomegaly, cytopenias, renal dysfunction, hypotension, and rash. Diagnosis is often delayed due to similarities with other febrile and inflammatory illnesses, like sepsis.[2] The HLH-2004 diagnostic guidelines are usually used for diagnosis. They include either the presence of genetic mutations related to HLH or the fulfillment of at least 5 of 8 clinical and laboratory criteria.[3] The mainstay of treatment includes suppression of inflammation and

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the immune system with chemotherapeutic agents such as dexamethasone and etoposide, and intrathecal hydrocortisone and methotrexate if CNS disease is present. This can be followed by hematopoietic stem cell transplant in those with genetic mutations and in those not responding to initial therapy. Other agents that can be added include monoclonal antibodies like rituximab and alemtuzumab.[4] Despite improvement in survival with initial treatment, HLH remains associated with high mortality, and delaying treatment can lead to short and long-term mortality. The effect of treatment delay has received limited evaluation in the pediatric population, but not in adult HLH.[5] This study aims to look at the effects of delay in treatment on inpatient outcomes of adult HLH.

Materials and methods

Data source and study design

The National Inpatient Sample (NIS) is a publicly available all-payer database developed by the Healthcare Cost and Utilization Project (HCUP). The database is built by the weighted sampling of 20% of the hospital discharges from the State Inpatient Databases (SID), amounting to over 7 million entries per calendar year. Clinical and resource utilization data for each hospitalization is derived from the discharge abstracts submitted by HCUP-participating hospitals to different data-gathering organizations. The NIS presents clinical data using the International Classification of Diseases, 9th and 10th revisions, Clinical Modifications (ICD-CM) coding system. ICD-9-CM was in use until October 2015, and ICD-10-CM is used thereafter.

Data sampling

The use of HLH-specific code started in October 2006; therefore, we chose the NIS for the years 2007–2019 for our study. We used ICD-9-CM code 2884 and ICD-10-CM codes D76x to identify patients with HLH. Similarly, ICD codes were used to identify patients who received inpatient antineoplastic chemo or immunotherapy and to identify comorbidities, potential confounders, and clinical outcomes. All utilized codes are provided in the supplementary material (Tables S1 and 2). We included all patients with the diagnosis of HLH who received inpatient HLH-targeted treatment, including chemotherapy and/or monoclonal antibodies. We excluded those who were admitted electively or did not have documentation of the starting day of treatment. Figure 1 summarizes the selection process and the number of hospitalizations in each step.

Endpoints

The primary endpoint of the study was to compare the rate of inpatient mortality between HLH patients who received

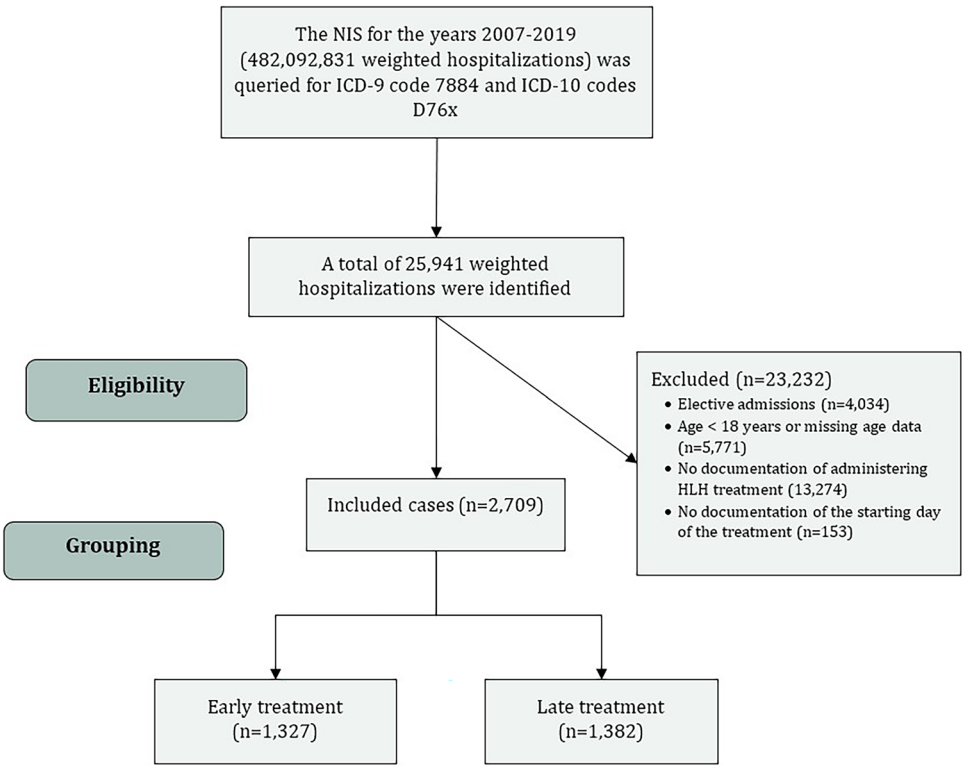


Fig. 1 Sampling, eligibility, and grouping

late HLH treatment (equal to or more than 6 days since admission) and those who received early HLH treatment (before 6 days). The cutoff of 6 days is the median time to treatment in the whole sample. Secondary endpoints included comparing both groups for rates of cardiovascular complications (acute myocardial infarction, acute ischemic stroke, and acute left heart failure), venous thromboembolic complications (acute deep vein thrombosis and acute pulmonary embolism), infectious complications (bacterial pneumonia, urinary tract infections, and sepsis or septicemia), acute kidney injury, and requiring new hemodialysis. We also evaluated the time to treatment initiation trend during the study period. Circulatory shock was defined as carrying the diagnosis of shock (other than anaphylactic) or requiring intravenous vasopressors. New hemodialysis was defined as hemodialysis in patients with no history of end-stage renal disease or chronic kidney disease stage 5.

Primary analysis

Baseline characteristics were calculated at baseline for both groups. These included demographic factors like age, sex, and race; comorbidities commonly associated with the development of adult HLH like malignancies (including lymphomas, leukemias, and solid malignancies), common viral infections (including EBV, CMV, HIV, other herpes viruses, and viral hepatitis), connective tissue diseases, and organ transplant status (including bone marrow transplant, kidney transplant, and other organ transplants); and weekend admission status. Categorical variables were presented as counts with percentages and compared using Pearson's Chi-square and Fischer's exact tests. Continuous variables were presented as means and standard deviations (SD) and compared using Mann-Whitney *U* test. All continuous variables were found to be non-normally distributed; Therefore, we also reported medians and interquartile ranges (IQR) and used non-parametric testing for comparisons. For adjusted comparisons of the outcomes, we constructed multivariate logistic regression models adjusting for multiple covariates. These covariates were similar to the mentioned baseline characteristics. These covariates were chosen based on prior literature review. [6] We found that 6.3% of the hospitalizations were missing race data; these were re-coded with the category "Other" for all comparative analyses. No other variables had missing data. All analysis models were two-tailed with α value of <0.05.

For trend analysis, we computed Spearman's rank-order correlation to assess the relationship between calendar year and time to treatment. The trend was visually illustrated by plotting the mean time to treatment against calendar year.

Sensitivity analyses and respective rationales

For the significant findings, we conducted three different models of sensitivity analysis. Each model tested the robustness of the results against a different assumption. In the first model, we excluded hospitalizations where the treatment was started within 48 h. There is a chance that these patients were admitted electively to receive chemotherapy even though they are documented otherwise. The second model excluded patients with known malignancy. Patients with a concurrent malignancy could have received chemotherapy earlier in their admission for that malignancy. Unfortunately, the NIS does not report the name or indication of the antineoplastic drug in most cases. Therefore, repeating the analysis with restriction to patients with no malignancy was crucial to eliminate this doubt. The third model excluded patients with underlying connective tissue diseases as these patients are usually treated with immunosuppressive regiments (e.g., corticosteroids), and antineoplastic agents are reserved for relapsed/refractory cases.[7, 8] Aside from these changes, all models were conducted using multivariate regression with the same parameters and covariates used in the primary analysis.

Analysis was conducted using IBM SPSS version 26 and R software package version 4.2.

Results

Baseline characteristics

We identified 21,906 weighted hospitalizations with HLH diagnoses from 2007 to 2019. Of these, 2709 hospitalizations met the inclusion and exclusion criteria and were included in the analysis. Baseline characteristics and distribution of potential confounders are presented in Table 1. Hospitalizations in the late treatment group had a significantly higher average age (49.4 vs. 47.9, p=0.029) and significantly higher proportions of solid malignancies, connective tissue diseases, most infectious triggers, and kidney and other organ transplant status than those in the early treatment group.

Results of the primary analysis

Table 2 summarizes the distributions of all primary and secondary outcomes between both groups. Hospitalizations in the late treatment group had higher rates of in-hospital mortality (OR 2.00 [1.65–2.43]), circulatory shock (OR 1.33 [1.09–1.63]), requiring mechanical ventilation (OR 1.41 [1.18–1.69]), venous thromboembolism (OR 1.70 [1.27–2.26]), infectious complications (OR 2.24 [1.90–2.64]), acute kidney injury (OR 2.27 [1.92–2.68]), and requiring new hemodialysis (OR 1.45 [1.17–1.81]). Rates of cardiovascular complications and urinary tract infections were not significantly different between the two groups. Figure 2 summarizes the primary and secondary outcomes.

Table 1 Baseline characteristics SD standard deviation; IQR interquartile range, EBV Epstein-Barr virus, CMV cytomegalovirus, HIV human immunodeficiency virus

		All patients $n = 2709$ count (%)	Early treatment $n = 1327$ count (%)	Late treatment $n = 1382$ count (%)	p value
Age in years					0.029
Mean (SD)		48.7 (17.9)	47.9 (18.2)	49.4 (17.5)	
Median (IQR)		51 (32–63)	2 (1–4)	53 (33–64)	
Sex	Male	1759 (64.9)	864 (65.1)	896 (64.8)	0.880
	Female	950 (35.1)	463 (34.9)	486 (35.2)	
Race	Caucasian	1311 (48.4)	669 (50.4)	642 (46.4)	<0.001
	African American	429 (15.8)	234 (17.6)	195 (14.1)	
	Hispanic	426 (15.7)	164 (12.3)	262 (18.9)	
	Asian or Pacific Islander	180 (6.6)	105 (7.9)	75 (5.4)	
	Native American	-	<11	15 (1.1)	
	Other	174 (6.4)	80 (6.4)	94 (7.3)	
	Missing	169 (6.3)	70 (5.3)	100 (7.2)	
Weekend admission		536 (19.8)	203 (15.3)	333 (24.1)	<0.001
All malignancies		1723 (63.6)	837 (63.0)	886 (64.1)	0.576
Solid malignancies		100 (3.7)	40 (3.0)	60 (4.3)	0.067
Lymphomas		1333 (49.2)	651 (49.1)	682 (49.3)	0.880
Leukemias†		424 (15.7)	215 (16.2)	209 (15.1)	0.440
Connective tissues diseases		244 (9)	95 (7.2)	149 (10.8)	0.001
Common viral infections		664 (24.5)	286 (21.5)	378 (27.3)	<0.001
EBV		296 (10.9)	127 (9.6)	169 (12.2)	0.027
CMV		115 (4.2)	50 (3.7)	65 (4.7)	0.227
HIV		119 (4.4)	34 (2.6)	85 (6.1)	<0.001
Viral hepatitis		135 (5.0)	55 (4.2)	80 (5.8)	0.049
Other herpes viruses		139 (5.1)	50 (3.7)	89 (6.4)	0.002
Organ transplant status		181 (6.7)	81 (6.1)	100 (7.2)	0.236
Bone marrow transplant		116 (4.3)	66 (4.9)	50 (3.6)	0.082
Kidney transplant*		-	<11	20 (1.4)	0.004
Other organs transplant		70 (2.6)	25 (1.9)	45 (3.2)	0.024
Treatment starting day					<0.001
Mean (SD)		8.3 (9.3)	2.2 (1.8)	14.1 (9.8)	
Median (IQR)		6 (2–11)	2 [1–4]	11 [8–17]	

†Includes leukemias, myelodysplastic syndromes (MDS), myeloproliferative disorders (MPD), and plasma cell dyscrasias (PCD)

*HCUP privacy policies recommend against reporting counts less than 11

Results of the sensitivity analyses

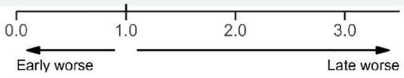
We ran three additional models of sensitivity analysis. The first model excluded cases with treatment within 48 h to exclude HLH cases that may have been electively scheduled for treatment. This model revealed the same outcomes as the main analysis except for circulatory shock and requiring new hemodialysis which became not statistically significant. In the second model, patients with a diagnosed malignancy were excluded to assess the effect of possible confounding. The results of this model also mirrored the main analysis except for acute pulmonary embolism and requiring new hemodialysis which became not statistically significant. In the third model, we excluded patients with underlying connective tissue disease. All primary and secondary outcomes retained statistical significance in this model. Adjusted ORs and 95% CI for these models are reported in the supplementary materials (Table S3).

Trends of time to treatment

We observed no significant trend in the mean time to treatment between the years 2007 and 2019 ($r_s = 0.008$; $p = 0.668$) (Fig. 3).

Table 2 Primary and secondary outcomes rates, with respective *p* values, odds ratios, and 95% confidence intervals

Outcome	Early	Late	Adj p value	Adj OR (95% CI)
All patients (n)	1,327	1,382		
In hospital mortality	259 (19.5)	429 (31.2)	<0.001	2.00 (1.65 to 2.43)
Circulatory shock	224 (16.9)	313 (22.7)	0.005	1.33 (1.09 to 1.63)
Mechanical ventilation	319 (24)	442 (32)	<0.001	1.41 (1.18 to 1.69)
Cardiovascular complications	80 (6)	80 (5.8)	0.716	0.94 (0.66 to 1.33)
Acute myocardial infarction	25 (1.9)	25 (1.8)	0.513	0.81 (0.43 to 1.52)
Acute ischemic stroke	20 (1.5)	25 (1.8)	0.38	1.33 (0.70 to 2.56)
Acute left heart failure	40 (3)	35 (2.5)	0.312	0.77 (0.47 to 1.28)
Venous thromboembolic complications	90 (6.8)	155 (11.2)	<0.001	1.70 (1.27 to 2.26)
Acute deep vein thrombosis	75 (5.7)	130 (9.4)	0.003	1.60 (1.17 to 2.19)
Acute pulmonary embolism	15 (1.1)	40 (2.9)	0.001	2.90 (1.54 to 5.45)
Infectious complications	573 (43.1)	869 (62.9)	<0.001	2.24 (1.90 to 2.64)
Bacterial pneumonia	249 (18.8)	444 (32.1)	<0.001	1.97 (1.63 to 2.38)
Urinary tract infection	69 (5.2)	74 (5.3)	0.859	1.03 (0.72 to 1.48)
Sepsis/septicemia	443 (33.4)	686 (49.6)	<0.001	2.04 (1.73 to 2.41)
Acute kidney injury	487 (36.7)	771 (55.8)	<0.001	2.27 (1.92 to 2.68)
Requiring new hemodialysis	175 (13.2)	254 (18.4)	0.001	1.45 (1.17 to 1.81)



Discussion

The patients in our study all received at least one anti-neoplastic agent and were divided into an early treatment group (treatment received within 6 days of admission) and a late treatment group (treatment received 6 or more days after admission). Our results showed that patients in the late treatment group were more likely to be older (median age 53 compared to 50). Patients in the late treatment group had higher mortality as well as higher association with shock, venous thromboembolism, infectious complications, major bleeding disorders, initiation of hemodialysis, and mechanical ventilation even after adjusting for potential confounders. The risk of associated cardiovascular complications was similar in both groups.

Diagnosis of HLH is challenging, as its presentation can be similar to that of sepsis, malignancies, and autoimmune disorders, and those same conditions can be the triggering factors for HLH.[6, 9] Furthermore, the standard diagnostic criteria, HLH-04, were developed in the pediatric HLH and have not been validated in adults.[1, 3, 10] Therefore, many providers opt to delay the initiation of HLH-directed treatment until the workup is completed, which might take days to weeks. The results of our study underline the harmful effects of treatment delay and provide more supporting evidence for early treatment.

Comparing outcomes across studies is difficult due to differences in the diagnosis of HLH, treatment protocols, and patient populations, but most studies have shown poor outcomes in adult patients. There are no large prospective studies for HLH in adult patients, but retrospective studies have shown mortality ranging from 30 to 75%.[11–14] Overall, our study showed in-hospital mortality of 25.4%. Previous studies have described different poor prognostic factors including malignancy-associated HLH (especially T-cell lymphomas), EBV-associated HLH, older age at onset, male sex, thrombocytopenia, renal insufficiency, low serum albumin, and presence of disseminated intravascular coagulation.[14] Our study shows that delay in treatment is an independent poor prognostic factor, which reflects the highly aggressive nature of the disease and the importance of early intervention to break the cycle of immune dysregulation.[13, 15]

Our trend analysis also ascertained that despite improvements in the treatment modalities, there has been no significant improvement in the early initiation of antineoplastic treatment. However, non-antineoplastic therapies, like anakinra and alemtuzumab, have gained more attention in recent years.[4, 16, 17] It is uncertain how much of an impact this has on our trend analysis since we only focused on antineoplastic treatment for HLH.

The only large prospective trials for HLH were conducted on pediatric patients and showed the efficacy of dexamethasone and etoposide in improving outcomes.[18] Only one study assessed outcomes in HLH patients based on time to treatment. A retrospective study assessing 47 pediatric patients with EBV-associated HLH showed that early initiation of an etoposide-containing regimen (less than 4 weeks since diagnosis of HLH) was associated with improved survival (90% long-term survival) compared to late initiation (after 4 weeks) (56% long-term survival).[5] One other retrospective study assessed the time to diagnosis but did not find

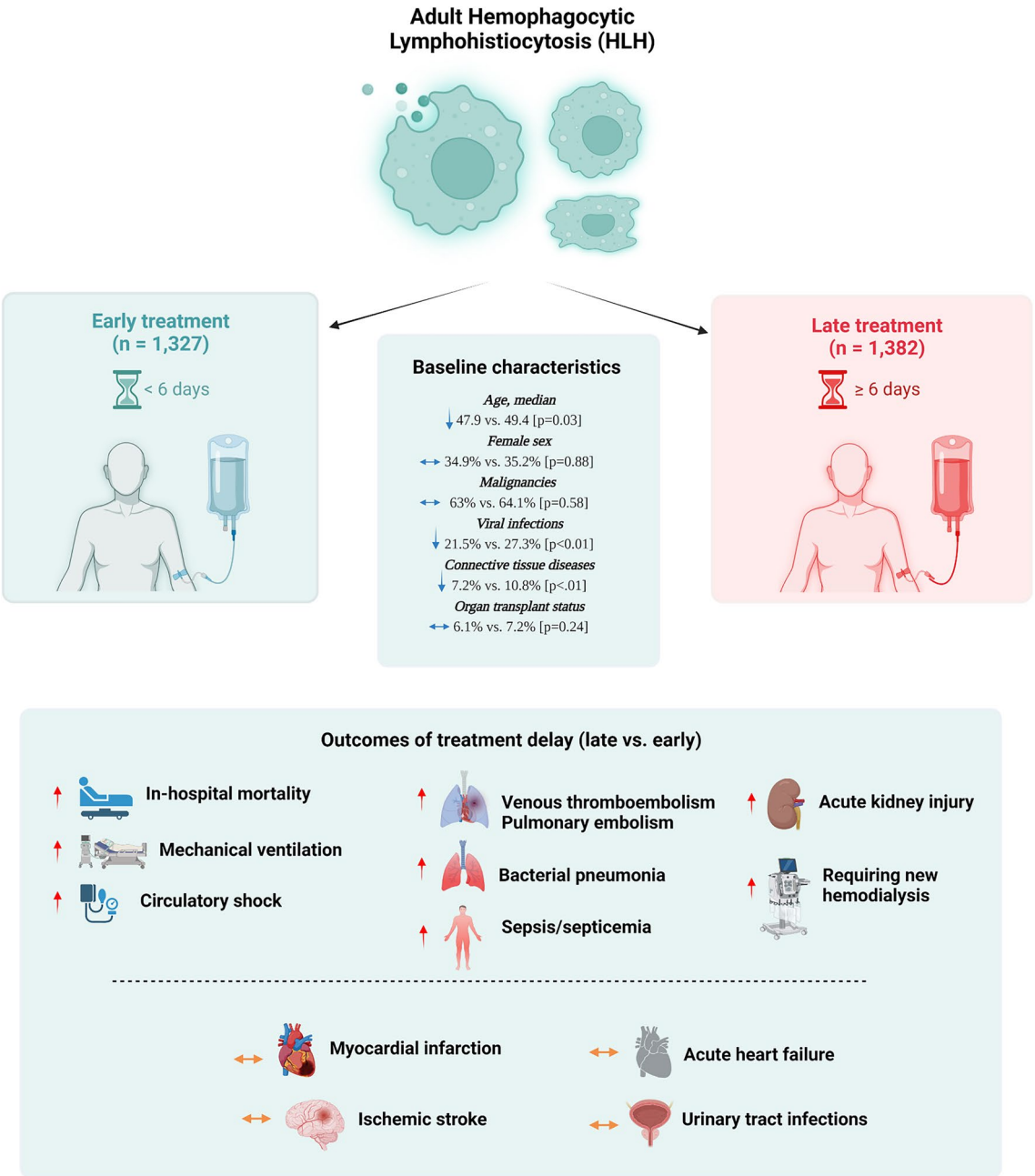


Fig. 2 Central illustration of the primary and secondary outcomes

improved outcomes with early diagnosis.[19] However, that study was limited by a small sample size (18 patients) and high overall mortality. Our study is the first study to assess outcomes related to early vs late administration of therapy in adult HLH patients as well as in patients with different underlying etiologies for HLH.

Our data were drawn from a population-based database using diagnosis codes. This places the study at risk of misclassification bias as we were unable to ascertain the diagnosis of HLH in the included cases. However, we found that our study had a similar demographic distribution to that of the largest published report on adult HLH, suggesting a low impact of misclassification bias.[6] In that study, the authors identified 2197 cases of adult HLH published worldwide. Of these, 37% were females, compared to 35% in our study. Also, patients had a mean age of 49.03 years, compared to 48.7 years in our study. On the other hand, the distribution of associated conditions was markedly different. Our study had higher rates of malignancies (63.6 vs. 47.7) and lower rates of viral infections (24.5 vs. 30.3). This is likely related to different methods of

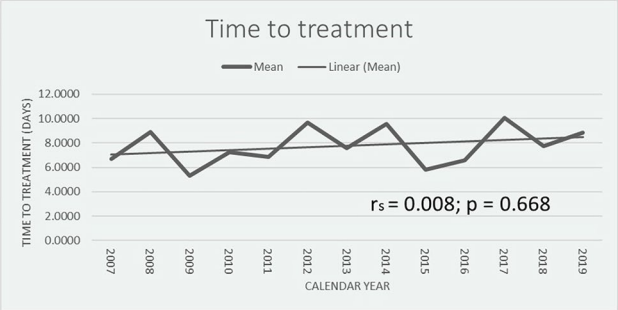


Fig. 3 Trend of in-hospital mean time to treatment of hemophagocytic lymphohistiocytosis from 2007 to 2019

data gathering and different inclusion/exclusion criteria. For instance, rare causes are more likely to be reported in case reports and series; therefore, data compiled from case reports and series are likely to overestimate these causes.

This study used 13 years of nationally representative data from the largest available all-payer hospitalization database. Previous studies and audits have shown sensitivity and specificity in using ICD codes to explore outcomes.[20] The most important limitation of our study is its retrospective nature. However, given the rarity of HLH, it is extremely difficult to do a prospective study, especially at this scale. Other limitations in the study include that we could not confirm the severity of the disease at baseline, the type of anti-neoplastic treatments administered, and the reasons for the delay in treatment. Also, we could not account for the administration of steroids in the excluded or treated groups due to a lack of specific codes.

Mortality in adult patients with HLH remains poor. Our study on the largest nationally representative sample of adult HLH patients shows that early administration of treatment is associated with better outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-023-05271-w.

Author contributions Contributions: A.A., A.M., M.M., T.J., S.E., and O.A. were involved in the conception and design of the manuscript; S.F. and M.A. collected and revised the required ICD codes; A.A. and A.M. analyzed and interpreted the data. All writers were involved in the writing and approval of the final manuscript.

Data availability Data is publicly available upon request from Healthcare Cost and Utilization Project website.

Declarations

Ethics approval As the NIS data is deidentified, the ethics committee at Rochester General Hospital has determined that no specific ethical approval for this research.

Consent to participate As the NIS data is deidentified, the ethics committee at Rochester General Hospital has determined that no patient consent is needed for this research. No elements of this work need permission for reproduction.

Conflict of interest The authors declare no competing interests.

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