

## SHORT REPORT

# Epidemiology of haemophagocytic lymphohistiocytosis at the population level in Germany

David Kuron<sup>1</sup> | Jakob Christoph Voran<sup>2</sup> | Friedrich Alexander von Samson-Himmelstjerna<sup>3</sup> | Claudia Baldus<sup>1</sup> | Ulrich Kunzendorf<sup>3</sup> | Kevin Schulte<sup>3</sup> | Benedikt Kolbrink<sup>3</sup> 

<sup>1</sup>Department of Medicine II, Hematology and Oncology, University Hospital Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany

<sup>2</sup>Department of Medicine III, Cardiology, University Hospital Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany

<sup>3</sup>Department of Nephrology and Hypertension, University Hospital Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany

## Correspondence

Benedikt Kolbrink, Department of Nephrology and Hypertension, University Hospital Schleswig-Holstein, Christian-Albrechts-University, 24105 Kiel, Germany. Email: [benedikt.kolbrink@uksh.de](mailto:benedikt.kolbrink@uksh.de)

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## Summary

We retrospectively analysed all German inpatient cases of haemophagocytic lymphohistiocytosis (HLH) from 2014 to 2020 to describe the epidemiology, clinical course, and underlying diseases of 4065 HLH patients. The age-standardized incidence rate of HLH in Germany was 0.52/100 000 people in 2014 and steadily increased by 10% per year to 0.97/100 000 in 2020 (mean 0.70/100 000). Inpatient deaths related to HLH increased from 0.84/1 000 000 people in 2014 to 2.32/1 000 000 people in 2020, caused by rising numbers of older HLH patients. Overall, HLH is more frequent than previously expected and incidence as well as HLH-related deaths increased significantly.

## KEY WORDS

epidemiology, haemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS)

## INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome driven by excessive activation of macrophages, cytotoxic T-lymphocytes, and natural killer cells. This pathological inflammation either originates from an underlying genetic cause, often referred to as primary HLH, or it can be driven by a multitude of inflammatory disorders, then often termed secondary HLH. The range of triggering diseases mainly includes innate immunodeficiencies, autoimmune disorders, malignancies and infectious diseases.<sup>1</sup> Diagnosis is often delayed or missed entirely because HLH can show a broad spectrum of symptoms, and is often indistinguishable from systemic inflammatory

response syndrome or sepsis, leading to high mortality rates of 40%–70%.<sup>1–3</sup>

Given the difficulty of diagnosis and the associated poor outcomes, it is of enormous importance to understand the epidemiology of HLH. In addition, potential triggers of HLH are becoming more common in the general population due to improved therapy of malignant and autoimmune diseases and increased life expectancy.<sup>4,5</sup> However, currently available epidemiologic data on HLH are either outdated, from smaller cohorts, or focused on specific subpopulations and treatments, hence insufficient to provide a broader picture by design.<sup>3,6</sup> Comprehensive and up-to-date studies on the epidemiology of HLH are therefore of great interest.

**Abbreviations:** HLH, haemophagocytic lymphohistiocytosis; ICD-10-GM, International Classification of Diseases 10th Revision German Modification; OPS, Operation and Procedure Classification System.

David Kuron, Jakob Christoph Voran, Kevin Schulte and Benedikt Kolbrink contributed equally to this study.

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In this population-based cohort study, we analysed data of all German inpatient cases from 2014 to 2020 to describe epidemiologic characteristics, potential triggers, and clinical course of HLH patients.

## STUDY DESIGN

For this study, we used the Diagnosis-Related Groups statistics of the German Federal Statistical Office. The database covers records of all German inpatient cases and can be accessed for research purposes. Reported data mandatorily include basic hospital and patient characteristics and one main diagnosis for every case. In addition, up to 89 subsidiary diagnoses according to the International Classification of Diseases 10th Revision German Modification (ICD-10-GM) can be included, as well as up to 100 German Operation and Procedure Classification System (OPS) key codes per individual case.

We conducted a database query of all German inpatient cases from 1 January 2014 to 31 December 2020 and identified patients diagnosed with HLH according to the respective ICD-10-GM codes (D76.1 and D76.2). We used additional ICD-10-GM codes as well as OPS key codes to identify possible triggering diseases and to describe the course and complications of HLH recorded for the respective patient cases (see the Supplementary Data for details). A triggering disease was defined as any diagnosis from [Table S1](#) that co-occurred

with a diagnosis of HLH during the patient's hospital stay. Incidence rates were calculated based on Germany's historical population of the corresponding year.<sup>7</sup> If not stated otherwise, incidence rates are given as age-standardized incidence and were calculated using the 2013 European standard population as reference.<sup>8</sup> The  $\chi^2$  test was used to analyse group differences and we performed a Bonferroni correction to adjust the local significance level by dividing the global significance level by the number of categories. A two-sided Cochran–Armitage test was performed to assess trends in incidence and mortality case numbers. Data were analysed using the statistical environment R (Version 4.2.0); *p*-values <0.05 or <0.0071 after Bonferroni correction for multiple testing performed in [Table 1](#) were considered statistically significant.

## RESULTS

Between 2014 and 2020, the Federal Statistical Office recorded almost 136 million inpatient cases in more than 1900 German hospitals. We identified 4065 cases of HLH, accounting for a mean incidence rate of 0.70 per 100 000 people. We noticed nearly a doubling in HLH cases from 414 in 2014 (incidence rate 0.52/100 000) to 820 in 2020 (incidence rate 0.97/100 000), reflecting a yearly increase of about 10% per year ([Figure 1A](#)). A Cochran–Armitage test revealed a

**TABLE 1** Baseline characteristics and outcomes of patients with HLH in Germany

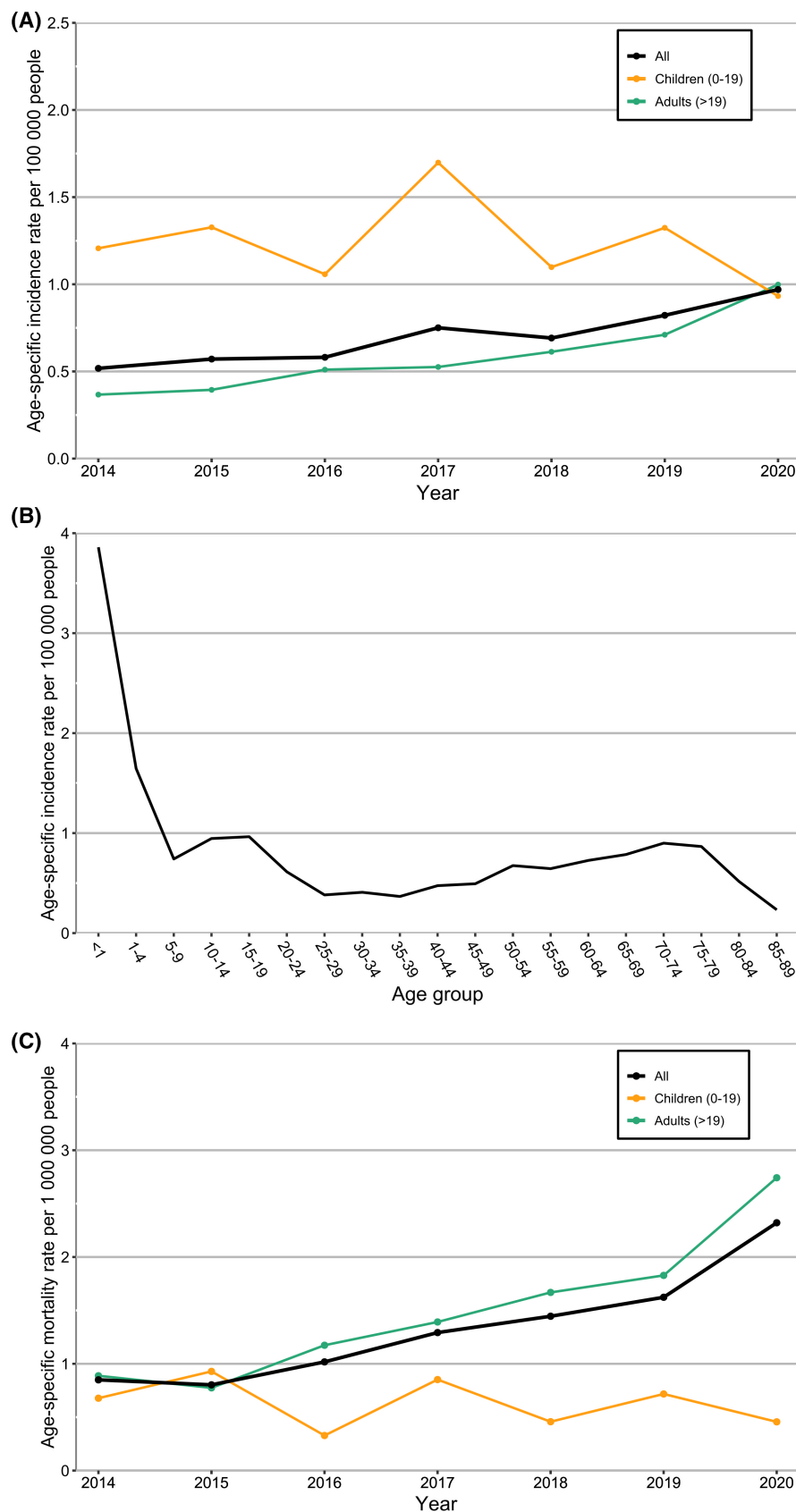
	Children (age ≤ 19)	Adults (age > 19)	All	<i>p</i> -value <sup>a</sup>
Total number, <i>n</i> (%)	1312 (32.3)	2753 (67.7)	4065 (100)	
Male	710 (54.1)	1684 (61.2)	2394 (58.9)	<b>0.00002</b>
Female	602 (45.9)	1069 (38.8)	1671 (41.1)	<b>0.00002</b>
Triggering diseases, <i>n</i> (%)				
Lymphoma	29 (2.2)	373 (13.5)	402 (9.9)	<b>&lt;0.00001</b>
Leukaemia	88 (6.7)	214 (7.7)	302 (7.4)	0.22
Other malignancy	11 (0.8)	80 (2.9)	91 (2.2)	<b>0.00003</b>
Autoimmune	205 (15.7)	359 (13.0)	564 (13.9)	0.03
Infectious disease	201 (15.4)	230 (8.4)	431 (10.6)	<b>&lt;0.00001</b>
More than one	167 (12.8)	744 (27.0)	911 (22.4)	<b>&lt;0.00001</b>
No known specific trigger	607 (46.4)	753 (27.4)	1360 (33.5)	<b>&lt;0.00001</b>
Clinical course, <i>n</i> (%)				
Intensive care unit	286 (21.8)	952 (34.6)	1238 (30.5)	<b>&lt;0.00001</b>
Invasive ventilation	208 (15.9)	682 (24.8)	890 (21.9)	<b>&lt;0.00001</b>
Renal replacement	63 (4.8)	515 (18.7)	578 (14.2)	<b>&lt;0.00001</b>
Multi-organ failure	289 (22.0)	1153 (41.9)	1442 (35.5)	<b>&lt;0.00001</b>
Death	85 (6.5)	707 (25.7)	792 (19.5)	<b>&lt;0.00001</b>
Median stay time, days	25	26	25	
Incidence rate (per 100 000)	1.19 <sup>b</sup>	0.59 <sup>b</sup>	0.70 <sup>c</sup>	

Abbreviation: HLH, haemophagocytic lymphohistiocytosis.

<sup>a</sup>Chi-squared test, children versus adults, *p*-values <0.0071 were considered statistically significant and are marked in bold.

<sup>b</sup>Age-specific incidence rate.

<sup>c</sup>Age-standardized incidence rate.



**FIGURE 1** Epidemiological characteristics of HLH in Germany. Incidence rate of HLH in children/adults (A) and by age groups (B) per 100 000 people in Germany. (C) Inpatient age-specific mortality rates per 1 000 000 people in Germany. HLH, haemophagocytic lymphohistiocytosis

significant increase in the number of adult HLH patients ( $p < 0.0001$ ) whereas no directed trend was found in children ( $p = 0.094$ ). While HLH was nearly evenly distributed between sexes in children, in adults 61.2% of HLH cases were found in men (Table 1; Figure S1). We calculated age-specific incidence rates and found the highest incidence of HLH in children less than one year old (3.86/100 000) and the lowest in 35- to 39-year-old and 85- to 89-year-old adults. We observed a second peak in the 70- to 79-year-old age group (0.9/100 000) (Figure 1B).

To identify potential underlying diseases or triggers, we examined the database and were able to attribute 1794 of the 4065 HLH cases to a single triggering factor (44.1%, Figure S2A). The most abundant among these were malignancies (795 cases, 19.6%), followed by autoimmune disorders (564 cases, 13.9%) and infectious diseases (431 cases, 10.6%). More than one potential triggering factor was present in 911 (22.4%) HLH cases. This group included patients with a lymphoma and a concomitant Epstein–Barr virus (EBV) infection, for example. In 1360 cases (33.5%), we could not identify a specific trigger for HLH. Children accounted for 607 (46.4%) cases in this group, most likely due to a higher portion of primary HLH cases (Figure S2B).

In concordance with the increased incidence, we found an increase of in-hospital deaths from 69 deceased in 2014 (0.84 per million people) to 193 deceased in 2020 (2.32 per million people) ( $p < 0.0001$ ) (Figure 1C). This is the result of a significant increase in adult HLH cases, while the in-hospital mortality of nearly 25% in this cohort was sustained over that period (Figure S3A). The in-hospital mortality in children was significantly lower (6.5%). In addition, adult HLH patients were more often in need of intensive-care treatment and suffered more frequently from multi-organ failure than children (Table 1).

## DISCUSSION

To our knowledge, this is one of the largest population-based cohorts of HLH patients ever analysed. Previous studies and a meta-analysis of 2197 patients with data from Sweden, Italy, Japan and the United States have estimated annual incidence rates of around 0.125/100 000 people and up to 1/100 000 in children while acknowledging a broad geographical variability.<sup>1,6,9–11</sup>

We suspect the following main reasons for the variation in published incidence rates and our findings:

- First, the previous studies were largely based on disease registries and questionnaire surveys. For lack of alternatives, these methods are often used to describe the prevalence of rare diseases, although they are subject to selection and reporting bias. In contrast, the major advantage of our methodology is that it covered all cases treated in German hospitals. Nevertheless, our analysis missed cases that were not diagnosed correctly by physicians, which is a limitation common to all epidemiological studies.

- Second, socioeconomic and sociodemographic differences may contribute to varying case numbers of HLH. Recently, a Chinese study noticed significant differences in the number of HLH cases depending on region and per capita gross domestic product, with incidence rates ranging from 0.06 to 0.47/100 000.<sup>12</sup> With economic performance as an indicator of a region's development, the diagnosis of HLH may be influenced by available medical resources. It is therefore likely that a good medical infrastructure will increase the number of cases reported.

We noticed a steady increase in HLH cases from 2014 to 2020, driven by elderly patients. Possible factors contributing to this could be the increasing prevalence of HLH triggers worldwide, particularly malignant and autoimmune diseases due to the ageing population and improved therapies.<sup>4,5</sup> Taking this development into account, the strong increase in HLH diagnoses in German hospitals still seems disproportionate. Hence, we suspect that efforts in recent years, such as implementation of state-wide registries or the 2014 and 2020 revised German HLH guidelines increased awareness of HLH as an important differential diagnosis.<sup>3,13</sup>

Regarding the inpatient course of HLH patients, the in-hospital mortality of adult patients diagnosed with HLH was stable at approximately 25% and in line with published data.<sup>14</sup> However, the increase in HLH cases led to a substantial increase in age-specific inpatient deaths related to HLH, resulting in nearly three times as many recognized HLH-related deaths in 2020 as in 2014. In-hospital mortality in children in our cohort appeared to be lower than in published studies and showed no directional trend.<sup>9,15</sup>

This study has some limitations: we performed a secondary data analysis using data that were not primarily collected for scientific purposes. Therefore, we cannot directly confirm the diagnosis of HLH, or the coded secondary diagnoses reported by hospitals. However, both hospitals and health insurers have a financial interest in the accuracy of the data, so regular reviews by both parties ensure data quality.

In summary, HLH is diagnosed more frequently than expected and the number of cases and HLH-related deaths in Germany has increased strongly in recent years. Although clinician awareness of this disease seems to have increased as well, inpatient mortality is still high. This underscores the importance of monitoring trends in HLH patients, as well as providing information on the disease, especially considering the ever-increasing number of recognized cases.

## AUTHOR CONTRIBUTIONS

David Kuron designed and performed research, analysed data and wrote the paper. Jakob Christoph Voran designed and performed research and analysed data. Friedrich Alexander von Samson-Himmelstjerna designed research and analysed data. Claudia Baldus designed research and analysed data. Ulrich Kunzendorf designed research and analysed data. Kevin Schulte designed research and analysed data. Benedikt Kolbrink designed research, analysed data

and wrote the paper. All authors revised the paper critically and approved of the submitted version.

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## CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

## DATA AVAILABILITY STATEMENT

The datasets analysed during the current study were provided by the German Federal Statistical Office and are available to researchers upon request.

## PATIENT CONSENT STATEMENT

Neither the researchers nor the German Federal Statistical Office have any contact with individual patient data or patients themselves, as the data processed are aggregated and anonymized secondary data. Patients' informed consent is therefore not applicable.

## PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No excerpts from copyrighted works owned by third parties are included, therefore not applicable.

## ORCID

Benedikt Kolbrink  <https://orcid.org/0000-0002-6331-8388>

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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