Poster #32

# A systematic review of mortality statistics and causes of death in people with congenital hemophilia A (PwcHA)

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## Summary

A current evidence-based understanding of mortality in congenital hemophilia A (HA) is absent.

A total of 17 records from 2010 to 2020 reporting mortality and/or cause of death in people with hemophilia (PwH) were analyzed.

Bleeding, human immunodeficiency virus (HIV), hepatitis C virus (HCV), and liver diseases are leading causes of death among PwH.

Reporting of cause of death was highly diverse and often incomplete; a unified approach is needed to understand mortality in people with congenital HA (PwcHA).

## Study populations

**PwH**: people with hemophilia, including hemophilia A and hemophilia B.
**PwHA**: people with hemophilia A, including congenital and acquired hemophilia A.
**PwcHA**: people with congenital hemophilia A.

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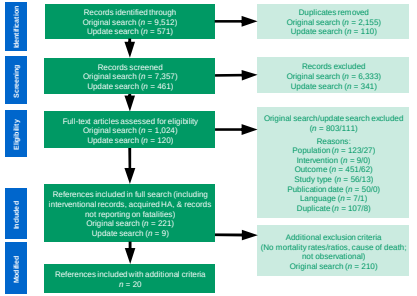
## Introduction

- Due to the development of innovative therapies and adoption of lifelong prophylaxis as standard of care,[1] the life expectancy of PwcHA has substantially improved over recent decades, and causes of death have changed.[2]
- While previous records have reported on mortality in PwcHA,[3,4] there is no current, evidence-based understanding of mortality in PwcHA in the literature.
- This systematic literature review aims to examine the available data on mortality and cause of death in PwcHA, to enable comparisons and monitoring as treatments continue to evolve.

## This systematic literature review identified observational records on mortality and causes of death in PwH published from 2010 to 2020.

- A search of Medline, Embase, the Cochrane Central Register of Controlled Studies, clinicaltrials.gov, and conference abstracts was conducted on March 17, 2020 using the search terms *hemophilia A (HA)*, *therapy*, *mortality* or *cause of death* to identify observational records published between January 2010 and March 2020 (**Figure 1**).
- Interventional records, records not reporting on fatalities, records reporting only on hemophilia B (HB) or acquired HA, and records with populations mixed with other coagulopathies were excluded.
  - The search was updated to include mixed populations of HA and HB and/or acquired and congenital hemophilia, as most historical cohort records were not able to differentiate between hemophilia types.

**Figure 1.** Identifying and screening of relevant literature on mortality in HA.




A total of 10,083 records were identified by searching databases and clinical trial registries. A primary search conducted on February 5, 2020 identified 9,512 of these; an updated search, limited to observational records, was carried out on March 17, 2020, and identified a further 571. After the removal of duplicated records, a total of 7,818 unique records were identified, of which 20 met the eligibility criteria for this review; however, three were not included in the following analyses due to an overlap in record population with another record (1) and only reporting a single death (2). HA, hemophilia A.

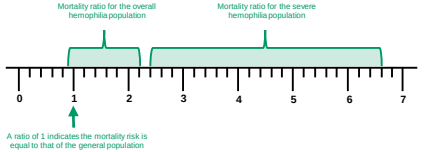
## Inconsistent reporting limits evidence on mortality in PwH.

- Three of the 20 eligible records were not included in this review, due to an overlap in population with another record (1)[5] and only reporting a single death (2).[6,7] The remaining 17 records reported mortality rates/ratios and/or cause of death;[8–24] their data collection periods spanned 1968 to 2018, and most focused on the developed world.
- The records used a range of measures, including crude mortality rates (6),[8–13] and standardized mortality ratios (4)[8,11,15,16] and hazard ratios (1),[14] which compare risk of death in PwH to that of the general population, adjusted for varying age distributions.
- The six published crude mortality rates ranged from 0.2 to 0.6/100 person years for PwH across all severities.

## Published mortality ratios suggest a raised mortality risk for PwH.

- As a ratio, the risk of death in PwH compared with that of the general population ranged from 0.86 (standardized mortality ratio) to 2.2 (hazard ratio) in all PwH,[8,14] and from 2.4 (standardized mortality ratio) to 6.6 (hazard ratio) in people with severe hemophilia.[14,15]
  - These ranges suggest a raised mortality risk, particularly with severe hemophilia (**Figure 2**).

**Figure 2.** Mortality ratios in PwH compared with that of the general population.

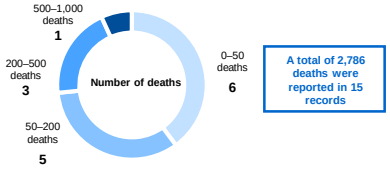



The mortality risk ranges are presented here as standardized mortality ratios. PwH, people with hemophilia.

## Records reporting causes of death in PwH (15) were highly diverse.

- Records varied in size, population (age, comorbidities), location, and time.[8–10, 12–14, 16–24] Incomplete reporting of long-term outcomes limits evidence on mortality in PwH.
  - The number of deaths reported in a single record ranged from 12 to 784[16,17] (**Figure 3**).

**Figure 3.** Range in the number of deaths in the 15 records listing cause of death.




  - Differences in patient management and available treatments across high- and low-income countries are likely to impact mortality in PwH (**Figure 4**).

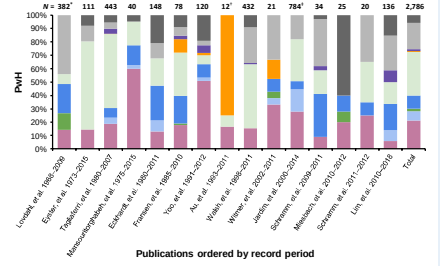
**Figure 4.** Records reported causes of death in PwH from across the world.


Total number of records reporting cause of death included in the analysis was 15; one record spanned both Europe and Australia. PwH, people with hemophilia.

## Bleeding, HIV, and HCV were leading causes of death in PwH.

- The most frequently observed hemophilia-related causes of death were bleeding (23%), HIV (19%), hepatitis C and B viruses (HCV/HBV), and liver disease-related (15%) (**Figure 5**).
- Cancer (10% of deaths) had a similar prevalence to that of the general population.[14,18]

**Figure 5.** Primary cause of death in 15 observational records.

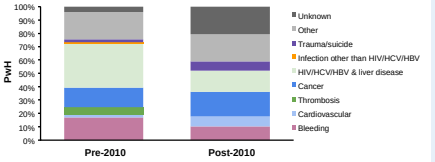



Records were ordered by record period, from least to most recent. Ischemic heart disease and pulmonary embolism were categorized as 'thrombosis', and if exact cause of death was unclear, the death was categorized as 'unknown'.
*Number of deaths was only recorded for the five most frequent causes of death. †Of the nine deaths attributed to fulminant sepsis ('other infection'), all were people with HIV infection. ‡Some people presented with more than one related cause of death.
HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PwH, people with hemophilia.

## Primary cause of death changed over time.

- There were numerous disparities in categorization and reporting of causes of death; nevertheless, broad trends were consistently observed across different records (**Figure 6**).
  - Deaths relating to HIV and hepatitis have been generally decreasing since the 1990s.[8,16,22]
  - Cardiovascular disease is an increasingly prevalent cause of death in PwH, as improved treatment and prophylaxis have increased life expectancy.[13,16]

**Figure 6.** Primary cause of death among records that were conducted pre-2010 versus post-2010.*




Records were divided into those conducted pre- and post-2010. Those with record periods spanning across 2010 were excluded. Ischemic heart disease and pulmonary embolism were categorized as 'thrombosis'; if exact cause of death was unclear, the death was categorized as 'unknown'.
*Includes: Fransen, et al., Lovdahl, et al., and Tagliaferri, et al. pre-2010 and Lim, et al., Miesbach, et al., and Schramm, et al. (2013) post-2010.
HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PwH, people with hemophilia.

## Conclusions

Decreasing mortality rates in PwH were observed in recent decades, likely from advances in treatment and care for hemophilia and its complications. However, the published mortality ratios suggest there is still an excess risk of death in PwH compared with the general population, particularly in severe hemophilia.

The categorization of death in the literature was highly diverse, limiting understanding of mortality in hemophilia.

A unified approach to reporting mortality and cause of death is needed to understand mortality in PwcHA and to monitor changes as treatments continue to progress.

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