Poor Outcomes in People with Hemophilia: Physician and Subject Matter Expert Perspectives

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Background

The American Thrombosis and Hemostasis Network (ATHN) is the steward of extensive hemostasis and thrombosis data and analytic resources. The ATHN Affiliate Network consists of over 145 health care entities providing programs and services to individuals impacted by these conditions. Through its partnership with ATHN Affiliates, ATHN routinely collects demographic, clinical, and genetic data for the ATHNdataset, a de-identified, voluntary data set. The ATHNdataset is a rich source of data available for clinicians and clinical researchers to identify, explore, and advance knowledge around issues affecting the inherited bleeding disorders community with the goal of transforming care. Recently, ATHN received a grant to determine whether data contained in the ATHNdataset could be utilized, in conjunction with machine learning and artificial intelligence, to predict those people with hemophilia (PwH) who may experience a poor outcome. Over the past decade, as therapies for hemophilia have rapidly improved, both in both clinical efficacy and convenience, no consensus as to the definition of "poor outcome" exists.

Purpose

To develop a contemporary consensus definition of "poor outcome" for PwH to use in developing our machine learning and artificial intelligence modelling of data within the ATHNdataset.

Methods

Physicians: A link to a SurveyMonkey® poll was sent via email to all physicians associated with ATHN-affiliated centers in the United States. Physicians were allowed 7 days to complete the survey. Based on the European Haemophilia Safety Surveillance (EUHASS), physicians were asked to rank the following outcomes from most (1) to least (14) dire: cardiovascular event, death, excessive bleeding, hospitalization, inhibitor development, intracranial hemorrhage, malignancy, neurologic event, target joint development, thrombosis, transfusion-transmitted infection, unexpected poor efficacy, other adverse event possibly related to therapy, and other events.

Subject matter experts (SMEs): In collaboration with staff from the National Hemophilia Foundation (NHF), a five-question survey was developed then sent out to individuals with a self-reported diagnosis of hemophilia and their self-identified caregivers, also known as SMEs, who participate in Community Voices in Research (CVR). CVR is a community-powered registry assisting researchers to understand how current treatments and policies affect the inherited bleeding disorders community. CVR collects information from people directly affected by inherited bleeding disorders, including people with bleeding disorders, their parents, siblings, partners, and caregivers. The confidential, de-identified aggregate data gathered through CVR contributes to the goal of improving clinical outcomes and quality of life.

The five free-text questions asked of CVR participants were:

1. **Are you a patient or caregiver?**
2. **What is your age?**
3. **What is your diagnosis?**
4. **What do you consider to be the upsides of living with hemophilia?**
5. **What do you consider to be the challenges of living with hemophilia?**

The survey was pushed via email to CVR participants on June 18, 2021. A total of two reminders were sent every 5-6 days. The survey remained open for 14 days.

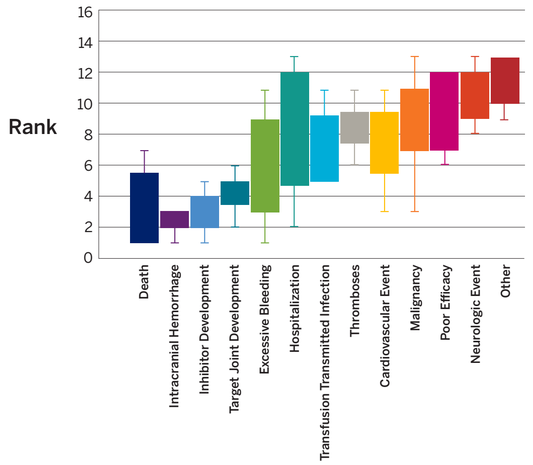
Because the responses to the CVR survey were submitted as free text, a qualitative approach to the analysis was undertaken. Each response was independently reviewed and assigned certain categories based on what was mentioned (see figure 2). Categories varied across reviews and included but were not limited to the following: access to care, arthropathy, career/school, everything, finances, insurance, joint bleeding, lack of support,limitations in activities, medication, menstruation, mental health, pain,physical health, reproductive choices, stigma, transfusion-transmitted infections, travel, and none. Categories across the authors' reviews were compared and subsequently consolidated based on similarity. Afterwards, groupings were discussed and finalized over emails and teleconferences.

Results

Physicians: An invitation to participate in the survey along with a link to the survey was emailed to 386 physicians providing care at ATHN-affiliated centers. A total of 14 physicians responded for a response rate of 3.6%. Of the 14 respondents, 8 (57%) were female and 6 (43%) were male. All were practicing pediatric hematologists. All responded within two days of the initial email. There were no additional responses generated by the follow-up, reminder emails.

Figure 1 represents the physician rankings of the EUHASS outcomes. There was a clear demarcation between the events ranked in the top four (death, intracranial hemorrhage, inhibitor development, and target joint development) and the remaining 10 potential poor outcomes. Therefore, based on the data collected and the purposes of our project, our current physician-derived definition of poor outcome for PwH will be limited to death, intracranial hemorrhage, inhibitor development, and target joint development (Table 1).

Figure 1: Physician ranking of poor outcome for PwH



Subject matter experts: An invitation to participate in the CVR survey was pushed to 732 SMEs. A total of 64 responded, 44 with hemophilia A, 11 with hemophilia B, and 9 caregivers, for a response rate of 8.74%. The average age of the responding SMEs was 50 years with a range from 22 to 80 years.

Figure 2 represents the number of SME mentions of challenges associated with living with hemophilia. As with the physicians' responses, there was a clear demarcation between the top three challenge categories and the remaining 13 categories as determined by qualitative analysis. Therefore, based on data collected directly through CVR, the current SME-derived definition of poor outcome for PwH will be restricted to a limitation in activity, the presence of arthropathy, and the presence of chronic pain (Table 1).

Discussion

In order to determine a consensus definition of "poor outcome" in PwH, physicians at ATHN-affiliated centers and SMEs were surveyed. For the physicians, the options for poor outcomes were limited to those defined by EUHASS. For SMEs, the survey was designed to allow free text answers, therefore a qualitative analysis approach was taken to assess the responses. Based on these methodologies, the physician-derived and SME-derived consensus definition of poor outcomes in PwH is listed in Table 1.

Figure 2: SME mentions of challenges of living with hemophilia

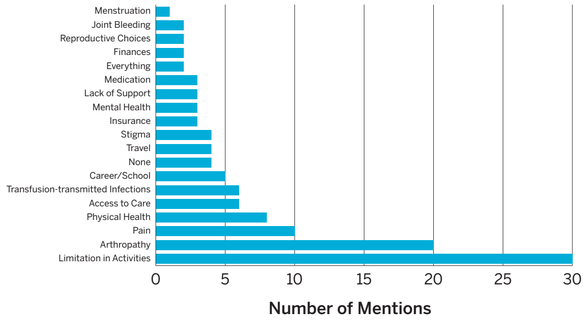


Table 1. Consensus definition of poor outcome in PwH

PHYSICIAN-DERIVED DEFINITION	SME-DERIVED DEFINITION
Death	Limitations in activities
Intracranial hemorrhage	Arthropathy
Inhibitor development	Chronic pain
Target joint development	

This approach to the development of a consensus definition of poor outcomes in PwH has several strengths. First, all physicians at ATHN-affiliated centers in the United States were given the opportunity to respond. Although the response rate was low and limited to pediatric providers, there was overwhelming consensus as to the definition of poor outcome. Second, this was the first collaboration between ATHN and NHF in utilizing CVR to directly query SMEs and incorporate the voice of those who experience hemophilia on a daily basis for an ATHN project.

Although there were similarities in the themes of the outcomes identified by the two groups, there was seemingly a lack of overlap in the precise events defined as poor outcomes. This lack of accord between the physicians and SMEs could be due to issues related to how the data was collected as well as the respondents' differing perspectives. First, the choices of poor outcomes presented to physicians was prescriptive in nature as we wanted to ensure our ability to harmonize our definition of poor outcomes with data collected within ATHN Systems and EUHASS. For SMEs, we were interested in obtaining a more holistic understanding of the daily challenges associated with living with hemophilia. In addition, despite several revisions by multiple people, asking about the "challenges of living with hemophilia" may not have completely harmonized with the question to physicians with a limited number of poor outcomes from which to choose. That said, as physicians and SMEs do not have or use the same vocabulary, what appears to be a discordance, may, in truth, reflect the ability of respondents in the two populations to communicate equivalent ideas using different vernacular. For example, the physicians' choice of "target joint development" may represent the SMEs' identification of "chronic pain" and "limitation in activity" as physicians approached this task from a biologic perspective and SMEs approached the task from a psychosocial perspective.

Our approach to arriving at this consensus definition of poor outcome had several limitations, however. The response rate for both physicians and SMEs was low. The physicians were all pediatric providers, potentially affecting the ability to generalize the responses as no input from medical hematologists was obtained. In addition, there was no potential for the physician respondents to add alternative choices of potential poor outcomes to the list of choices they were provided. Finally, we did not get input from other multi-disciplinary hemophilia center team members, limiting the diversity of input as well as the diversity of background and experience of the respondents.

While time-efficient, utilizing CVR as a mechanism to obtain input from SMEs as compared to going through ATHN-affiliated centers or offering a public survey through social media, may have negatively impacted our ability to recruit higher numbers of SME respondents. In addition, neither the physician nor SME surveys were open for long periods of time, leading to limitations of recruitment and scope. Finally, we did not collect demographic information such as sex at birth, gender, race, and ethnicity, from either the physician or SME respondent population, impacting our ability to assess the inclusion of an appropriately diverse population of respondents from either group. Finally, as both data acquisition approaches required the ability to access and use the internet, we missed collecting input from those individuals who lack such access, are not savvy in the use of technology, or choose not to share opinions in such forums.

Conclusion

Despite the potential limitations discussed above, this is the first consensus opinion as to the definition of poor outcome in PwH based on perspectives from both physicians and SMEs. ATHN will use these definitions as proof-of-concept in the planned machine learning/artificial intelligence project. If these definitions lead to a predictive model of poor outcome, we will be to take a more inclusive approach to determining a final definition of poor outcome for PwH.