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Norepinephrine versus epinephrine for hemodynamic support in post-cardiac arrest shock: A systematic review

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ABSTRACT

Purpose: The preferred vasopressor in post-cardiac arrest shock has not been established with robust clinical outcomes data. Our goal was to perform a systematic review and meta-analysis comparing rates of in-hospital mortality, refractory shock, and hemodynamic parameters in post-cardiac arrest patients who received either norepinephrine or epinephrine as primary vasopressor support.
Methods: We conducted a search of PubMed, Cochrane Library, and CINAHL from 2000 to 2022. Included studies were prospective, retrospective, or published abstracts comparing norepinephrine and epinephrine in adults with post-cardiac arrest shock or with cardiogenic shock and extractable post-cardiac arrest data. The primary outcome of interest was in-hospital mortality. Other outcomes included incidence of arrhythmias or refractory shock.
Results: The database search returned 2646 studies. Two studies involving 853 participants were included in the systematic review. The proposed meta-analysis was deferred due to low yield. Crude incidence of in-hospital mortality was numerically higher in the epinephrine group compared with norepinephrine in both studies, but only statistically significant in one. Risk of bias was moderate to severe for in-hospital mortality. Additional outcomes were reported differently between studies, minimizing direct comparison.
Conclusion: The vasopressor with the best mortality and hemodynamic outcomes in post-cardiac arrest shock remains unclear. Randomized studies are crucial to remedy this.

1. Introduction

Cardiac arrest is associated with significant morbidity and mortality in the United States, with rates of death exceeding 75% for in-hospital cardiac arrest (IHCA) and 90% for out-of-hospital cardiac arrest (OHCA) [1]. Despite high mortality, return of spontaneous circulation (ROSC) is initially achieved in approximately 67% of IHCA patients and sustained to hospital admission in 24% of OHCA patients [2]. Neurologic injury has been attributed to one-fourth of subsequent mortality in IHCA and two-thirds of OHCA [3-5]. The remaining causes of death are due to other sequelae of post-cardiac arrest syndrome, including post-cardiac arrest shock.

Post-cardiac arrest shock occurs in up to 70% of OHCA patients and is characterized by hypotension and hypoperfusion requiring vasopressor support [6]. The 2020 American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) guidelines recommend post-ROSC mean arterial pressure (MAP) goals ≥65 mmHg, however, no specific guidance is provided for the preferred first-line vasopressor [7]. To complicate matters, this is a physiologically unique shock state with features of myocardial dysfunction, hypovolemia, and vasoplegia that are

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secondary to the residual precipitating factor, the complex resuscitation process, and ischemia-reperfusion [6,8].

Norepinephrine and epinephrine are two catecholamine agents used to treat shock. Norepinephrine has been associated with a lower incidence of refractory shock in the cardiogenic shock population and remains the vasopressor of choice in septic shock [9,10]. Epinephrine is associated with increased metabolic demands, myocardial workload, and incidence of arrhythmias compared to norepinephrine and is often used as a secondary vasopressor [9-12]. Despite these associations, links to clinical outcomes specifically in the post-ROSC population are limited to small retrospective studies [13,14].

The purpose of this systematic review was to summarize the literature reporting mortality and hemodynamic outcomes between norepinephrine and epinephrine in post-cardiac arrest shock, including that found within the cardiogenic shock literature.

2. Materials and methods

2.1. Protocol and registration

This systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; protocol CRD42022361120). The study was conducted according to recommendations from the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines and the Cochrane Handbook of Systematic Reviews of Interventions [15,16].

2.2. Search strategy

An electronic search of PubMed, Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases was conducted in collaboration with a medical librarian (CC). The search was limited to the English language and human studies (except in Cochrane Library where these filters are unavailable), and the timeframe was restricted to the years 2000 to 2022 (conducted through December 5, 2022). The authors reasoned that due to changes in vasopressor preferences across multiple shock states over the past 22 years and major updates to the AHA ACLS guidelines in the year 2000, literature prior to this timeframe would be unlikely to capture the comparison proposed in the current meta-analysis and systematic review [17]. The search strategy included key population and intervention terms such as “advanced cardiac life support,” “return of spontaneous circulation,” “epinephrine,” “norepinephrine,” and “vasoactive agents.” Notably, “cardiogenic shock” was used as a search term because cardiogenic shock studies can have high representation of post-cardiac arrest patients [18]. The full search strategy for each database can be found in Supplementary Appendix A.

2.3. Eligibility criteria and selection process

Randomized prospective, prospective cohort, and retrospective cohort study designs were included, along with published abstracts. Population inclusion criteria were adults at least 18 years of age in the emergency department or admitted to the hospital with post-cardiac arrest shock requiring epinephrine or norepinephrine for hemodynamic support. Studies including adults with cardiogenic shock requiring hemodynamic support were also included in case of extractable post-cardiac arrest data. Studies with additional vasopressor groups (e.g., dopamine) were included if data for norepinephrine and epinephrine were extractable. Studies were only included upon full-text review if the outcomes of interest were reported. Exclusion criteria were case reports, case series, expert opinion, animal studies, studies containing the pediatric population, and populations with vasoplegic shock secondary to invasive cardiovascular surgery.

Two investigators (CL, LR) independently screened all titles and abstracts for inclusion and exclusion criteria. All conflicts were resolved through consensus with no need for a third party. Two additional investigators (MR, BF) independently conducted full text review of the initially selected titles and abstracts. Conflicts were resolved through consensus with adjudication by a third investigator (CL).

2.4. Data extraction and outcomes

A single investigator (CL) extracted data from included studies. Abstracted data included: title, first author, year, study design, study time frame, country, study inclusion and exclusion criteria, sample size, primary outcome, secondary outcomes, whether the study was included for extractable data, and variables used for covariate adjustment if retrospective. Where available, extracted demographic data included age, sex, site of cardiac arrest (in-hospital vs out-of-hospital), and presence of an initial shockable rhythm. The primary outcome of interest was in-hospital mortality in patients receiving norepinephrine versus epinephrine post-cardiac arrest. Additional extracted outcomes of interest included 30-day mortality, incidence of arrhythmias, incidence of refractory shock, duration of vasopressor therapy, and incidence of renal replacement therapy (RRT). Extracted surrogate markers of hemodynamics included MAP, cardiac index, heart rate, cardiac double product, serum creatinine, and lactate at 12 or 24 h post-cardiac arrest. Data were abstracted as summary statistics where available unless adjusted effect estimates with covariate corrections were reported in retrospective study designs.

2.5. Quality assessment and risk of bias

Included studies were independently assessed by two investigators (GS, CB) for quality using version 1 of the Cochrane risk-of-bias in non-randomized studies-of interventions (ROBINS-I) assessment tool [19]. Risk of bias was conducted for the primary outcome of interest for each study. Disagreements were resolved through discussion and adjudication by a third investigator (CL).

2.6. Synthesis

Meta-analyses were originally planned for studies reporting the same outcomes in the same timeframe. However, data synthesis was ultimately not pursued due to low yield of included studies and moderate to severe risk of bias. Instead, narrative analysis with critical appraisal was conducted to provide a global assessment of existing literature.

3. Results

3.1. Study selection and inclusion

After removal of duplicates, 2646 individual studies were captured by the search criteria across PubMed, CINHAL, and Cochrane databases. Title and abstract screening resulted in 63 articles eligible for full-text review. Only two of these studies ultimately met criteria for inclusion in the systematic review (Fig. 1). The primary reason for exclusion was lack of comparison between norepinephrine and epinephrine, or inability to extract data directly comparing the two vasopressors. A lack of extractable data in the post-ROSC subgroup in cardiogenic shock studies was the second most common reason for exclusion.

3.2. Study characteristics

Both studies meeting criteria for inclusion were retrospective observational studies. Weiss et al. collected data from the electronic health record at a single institution in the United States, whereas Bougouin et al. used the prospective, population-based Paris Sudden Death Expertise Center Registry spanning five centers in France [13,14,20]. Also notable was the difference in inclusion criteria based on definition of post-cardiac arrest shock. Bougouin et al. captured only patients admitted

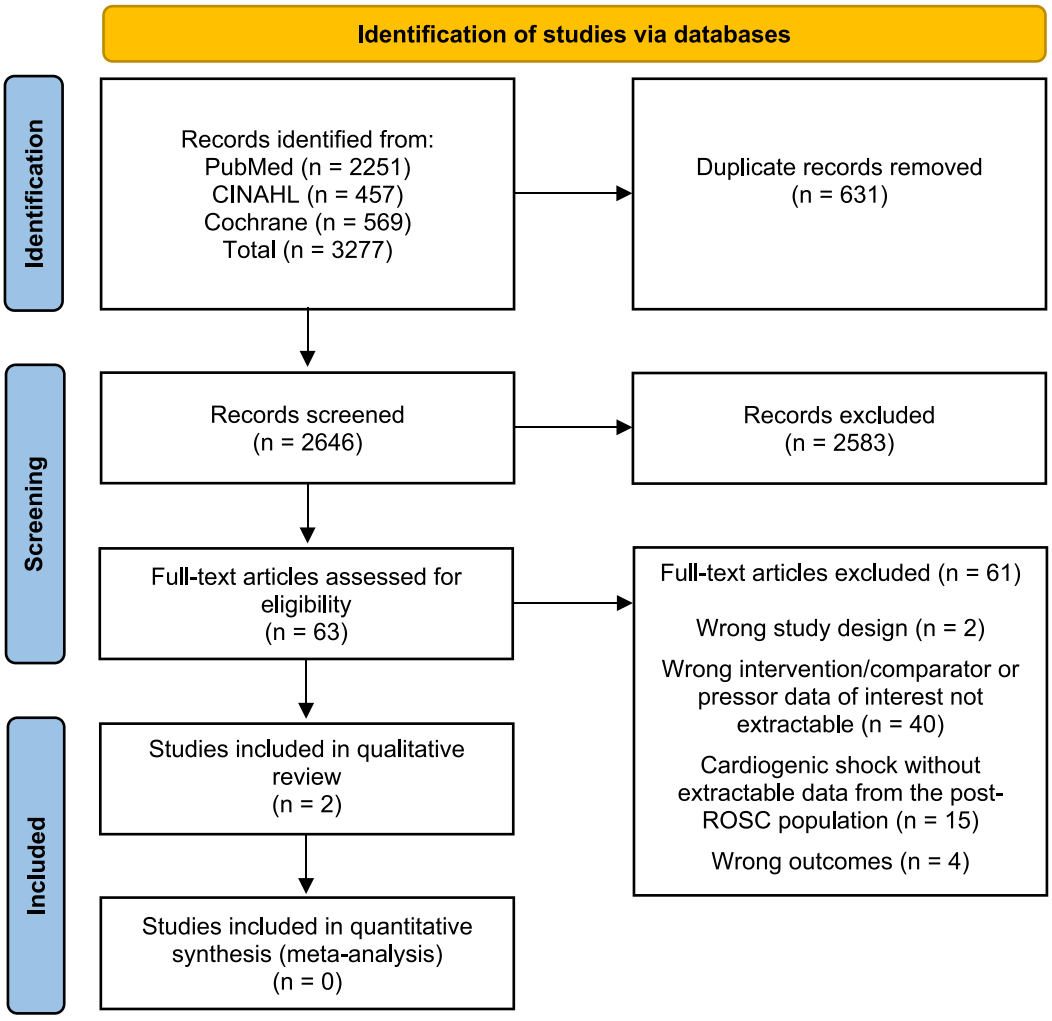

Fig. 1. PRISMA-guided flow diagram.
PRISMA: Preferred reporting items for systematic review and meta-analyses.
CINAHL: Cumulative Index to Nursing and Allied Health Literature.
ROSC: Return of spontaneous circulation.

to the ICU requiring vasopressors for at least six hours, whereas Weiss et al. included patients in the emergency department with sustained ROSC requiring vasopressor support [13,14]. Table 1 summarizes the key characteristics of each study.

3.3. Key clinical outcomes

Crude incidence of in-hospital mortality was numerically higher in the epinephrine group (88% and 83%) compared to norepinephrine

Table 1
Summary of included study characteristics.

Author, Year	Study Design	Time Frame	Country	Inclusion Criteria	Exclusion Criteria	Comparators	Primary Outcome
Weiss et al., 2021	Single-center retrospective chart review	Jan 2015-Aug 2017	USA	Adults with OHCA or in-ED CA and sustained ROSC requiring vasopressors	Patients <18 years-old, incomplete medical record, DNR status, failed to achieve initial ROSC, on a vasoactive prior to arrest, transfer from an outside institution	NE or EPI or DA	Composite of refractory shock (need for second vasopressor), rearrest, or death at 3 different time points: during ED stay, at 6 h, and throughout hospitalization
Bougouin et al., 2022	Multicenter (5) observational study	May 2011–May 2018	France	Patients in the Sudden Death Expertise Center registry admitted alive to the ICU following OHCA and with post--resuscitation shock (need for vasopressors for >6 h despite adequate fluid loading)	Patients with obvious extra-cardiac cause of arrest, refractory CA without sustainable ROSC, refractory shock requiring ECMO, absence of continuous treatment with either NE or EPI, continuous treatment with both NE and EPI	NE or EPI	All-cause in-hospital mortality

Abbreviations: USA = United States of America; OHCA = out-of-hospital cardiac arrest; ED = emergency department; CA = cardiac arrest; ROSC = return of spontaneous circulation; DNR = do not resuscitate; NE = norepinephrine; EPI = epinephrine; DA = dopamine; ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation.

(71% and 61%) in both studies, respectively (Table 2) [13,14]. Covariate correction was only pursued for the composite primary outcome in the study by Weiss et al., meaning an adjusted odds ratio for in-hospital mortality could not be extracted [13]. In an adjusted model, Bougouin et al. reported a statistically significant greater odds of in-hospital mortality in those receiving epinephrine post-ROSC (OR 2.6, 95% CI 1.4 to 4.7) (Table 2) [14]. Refractory shock was defined differently across the two studies and is therefore reported separately according to definition. Individual study reports of in-hospital mortality and other clinical outcomes of interest are summarized in Table 2.

3.4. Surrogate markers

Surrogate hemodynamic markers were only reported by Bougouin et al. [14] The mean maximum heart rate in the first 48 h was 134 ± 36 bpm in the norepinephrine group and 128 ± 34 bpm in the epinephrine group. Clearance of lactate at 12 h was reportedly significant with a median of 47% (IQR 18 to 64) in the norepinephrine group and 13% (IQR −21 to 37) in the epinephrine group. MAP was only reported upon admission. Cardiac index, cardiac double product, and serum creatinine were not reported in either study.

3.5. Quality assessment and risk of bias

Risk of bias assessment was conducted for in-hospital mortality, our primary outcome of interest (Fig. 2). Bias due to confounding was a major driver in overall assessment due to retrospective study design. While both studies accounted for confounding factors in statistical analysis, adjustment was not conducted for the individual outcome of in-hospital mortality in the study by Weiss et al. [13]

4. Discussion

The intended primary outcome of interest in this study was meta-analysis of pooled in-hospital mortality data for adult patients receiving norepinephrine versus epinephrine for vasopressor support post-ROSC. This analysis was not pursued due to low study yield and heterogeneity in reported results. Instead, the findings of two included studies were summarized according to pre-defined outcomes of interest [13,14]. Both studies reported either numerically or statistically significant higher incidence of in-hospital mortality in patients receiving epinephrine compared with norepinephrine. At maximum this can be interpreted as an association due to limitations in observational study design and moderate to severe risk of bias. Even across other shock states, these mortality results are not robustly reflected in prospective randomized studies. Most recently, the OptimaCC study in patients with cardiogenic shock after acute myocardial infarction detected an association between those receiving epinephrine and risk of death or extracorporeal life support at day seven [9]. No other mortality outcomes were significantly different between norepinephrine and epinephrine, however the study was not powered to detect mortality outcomes. Notably, over half of the patients in OptimaCC endured cardiac arrest prior to inclusion [9].

Table 2
Summary of pre-defined clinical outcomes of interest between the included studies.

Study	Weiss et al., 2021		Bougouin et al., 2022	
Sample Size	Total: $n = 87$		Total: $n = 766$	
	NE $n = 45$	EPI $n = 42$	NE $n = 481$	EPI $n = 285$
OHCA	69%	79%	100%	100%
Initial shockable rhythm	31%	21%	57%*	44%*
Crude incidence of in-hospital mortality	71%	88%	61%*	83%*
Adjusted** OR of EPI association with in-hospital mortality	NR		2.6 (95% CI 1.4–4.7)*	
Incidence of arrhythmias	9%	21%	NR	NR
Incidence of refractory shock	53%	64%	NR	NR
Incidence of death due to refractory shock	NR	NR	9%*	35%*
Incidence of RRT in the ICU	NR	NR	30%	32%

Abbreviations: NE = norepinephrine; EPI = epinephrine; OHCA = out-of-hospital cardiac arrest; OR = odds ratio; NR = not reported; CI = confidence interval; RRT = renal replacement therapy; ICU = intensive care unit; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation; TTM = targeted temperature management; PCI = percutaneous coronary intervention.

* Statistical significance reported in original study ($P < 0.05$).

** Method of adjustment: Multiple regression adjusted for sex, age, bystander CPR, initial shockable rhythm, time from collapse to CPR > 5 min, time from CPR to ROSC >22 min, EPI dose prior to ROSC, arterial pH > 7.21, myocardial dysfunction, TTM, and PCI.

Norepinephrine is the first-line vasopressor recommended for various shock states (e.g., septic, cardiogenic shock) due to its favorable safety profile. In the SOAP II trial, patients with shock (predominantly septic shock) had comparable mortality if receiving dopamine compared with norepinephrine, but dopamine was associated with a high rate of arrhythmias, conveying a NNH of 8 [21]. Norepinephrine use increases cardiac index, MAP, and coronary perfusion pressure without an increase in heart rate, myocardial workload, and other increased metabolic demands that have been associated with epinephrine [9,11,22]. In the CAT study, a group of heterogeneous ICU patients requiring vasopressor support achieved comparable vasoactive-free days with norepinephrine compared to epinephrine, but more patients were withdrawn from the epinephrine group due to metabolic effects [23]. The clinical impact of these metabolic differences is unclear. Even OptimaCC was terminated early when patients receiving epinephrine exhibited a five-fold higher incidence of refractory shock than those receiving norepinephrine, despite comparable cardiac index evolution [9].

Incidence of arrhythmias, refractory shock, initiation of RRT and other surrogate cardiac markers were additional outcomes of interest in this review of vasopressors in post-cardiac arrest shock. The two studies summarized in this review did not report the same surrogate or clinical outcomes for synthesis or direct comparison. Only one of the two studies in this review reported on pre-defined surrogate markers (Bougouin et al.), for which lactate was cleared significantly slower in the epinephrine group and is consistent with the previous metabolic findings [9,11,14,22]. This outcome is not surprising and is of limited clinical utility since β_2-adrenergic stimulation increases aerobic glycolysis, pyruvate production, and ultimately lactate production [24]. Refractory shock is an outcome of greater clinical relevance. Weiss et al. reported a higher incidence of refractory shock in post-ROSC patients receiving epinephrine compared to norepinephrine, although not statistically significant, and Bougouin et al. detected a statistically significant association with death due to refractory shock in patients receiving epinephrine compared to norepinephrine [13,14]. Associations with refractory shock in both studies is consistent with that reported in the OptimaCC trial, although they differ in definition and have limited statistical power [9].

Post-cardiac arrest shock is the culmination of a complex pathophysiology involving the inciting pathology of arrest, the resuscitation process, and ischemia-reperfusion [6,8]. There exist components of both cardiogenic shock and sepsis-like features due to myocardial stunning, inflammation, vasoplegia, and relative hypovolemia. Therefore, interpretation of existing literature across various shock states in context of post-cardiac arrest shock is difficult. This is further compounded by existing cardiogenic shock literature including post-ROSC patients [18]. Yet in our review, no extractable post-ROSC data were identified for incorporation into a meta-analysis.

Our study reinforces that vasopressor preference exclusively in the post-cardiac arrest population has been scarcely explored. Possibly the most compelling limitation in interpreting the existing data is the risk of indication bias. Epinephrine could simply be the pressor of choice in patients with worse prognosis. In the Bougouin et al. study, patients in the epinephrine group had multiple factors that may indicate patients

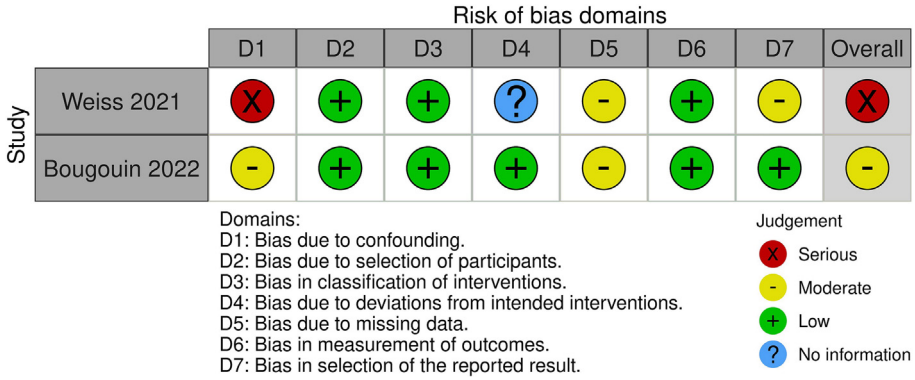

Fig. 2. Risk of bias assessment for the outcome of hospital mortality using the ROBINS-I tool.

were sicker in this group, including a longer time to ROSC from initiation of cardiopulmonary resuscitation, a lower prevalence of initial shockable rhythm, lower pH and higher lactate on admission, and greater prevalence of myocardial dysfunction (also indicated by lower left ventricular ejection fraction) on admission [14]. Despite these differences across groups, it is encouraging that statistical significance of in-hospital mortality remained after correction for these factors. The greatest indication of imbalance in disease severity from Weiss et al. was a higher rate of re-arrest prior to vasopressor initiation in the epinephrine group [13]. The individual outcome of in-hospital mortality was not corrected for this imbalance since this was not the primary outcome for the study. Similar Acute Physiology and Chronic Health Evaluation (APACHE) IV scores were reported between the two groups, but this does not rule out differences in shock severity or predominant shock characteristics present post-ROSC based on inciting etiology. It is crucial for future studies to employ a prospective, randomized design to escape indication bias and better understand this "chicken-or-the-egg" dilemma.

Several limitations must be acknowledged in this study. First, this review did not restrict study design inclusion to prospective randomized trials. This was done with the knowledge that limited literature exists on this topic and meta-analysis was unlikely if only capturing prospective study designs. Second, 55 studies were excluded for inability to extract data of interest. Had unreported data been obtained it is possible there would have been enough data to perform meta-analysis. Third, inclusion criteria limited study capture to those comparing both norepinephrine and epinephrine, meaning data from studies reporting only data for norepinephrine or epinephrine were not collected and included for pooled analyses. Finally, inclusion criteria only included comparison of initial norepinephrine and epinephrine monotherapy, whereas post-ROSC patients may have rapid addition of multiple vasopressors.

5. Conclusion

This systematic review found only two studies comparing mortality and hemodynamic outcomes of interest in adult patients receiving norepinephrine or epinephrine for post-cardiac arrest shock, including cardiogenic shock literature. Despite trends toward increased in-hospital mortality in patients receiving epinephrine, the vasopressor of choice remains unclear in the setting of limited literature and retrospective study design. Our systematic review highlights that randomized studies comparing vasopressor treatments should be a top priority to improve the care of patients with post-cardiac arrest shock.

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Data statement

Search strategies, risk of bias data, and abstracted data sets are available upon request to Christine Lawson, Pharm.D. at clawson@lifespan.org

CRediT authorship contribution statement

Christine K. Lawson: Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft. **Brett A. Faine:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Megan A. Rech:** Conceptualization, Investigation, Methodology, Writing – original draft. **Christopher A. Childs:** Data curation, Investigation, Methodology, Writing – review & editing. **Caitlin S. Brown:** Formal analysis, Resources, Writing – review & editing. **Giles W. Slocum:** Formal analysis, Writing – review & editing. **Nicole M. Acquisto:** Methodology, Writing – review & editing. **Lance Ray:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The following authors report no conflict of interest: CL, CC, NA, LR. The following authors received funding by Spero Therapeutics-provided unrestricted research grant via its Investigator Initiated Research Program: BF, MR, GS. GS reports participating in an advisory board meeting for Hema Biologics in 2022 regarding blood factor products. CB reports grant funding from Alexion/Astra Zeneca Rare Disease.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2023.12.031.

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