Aus dem
Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE)
Institut der Ludwig-Maximilians-Universität München

Analyse von Sekundär- und Primärdaten aus der Routineversorgung zur Beantwortung von versorgungsrelevanten Fragestellungen zur Optimierung der Versorgung von Patienten mit angeborenen oder erworbenen Gerinnungsstörungen

Dissertation
zum Erwerb des Doktorgrades der Humanbiologie
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

vorgelegt von
Vanessa Margarethe Sibylle Kratzer

aus
München

Jahr
2024

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Analyse von Sekundär- und Primärdaten aus der Routineversorgung zur Beantwortung von versorgungsrelevanten Fragestellungen zur Optimierung der Versorgung von Patienten mit angeborenen oder erworbenen Gerinnungsstörungen

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München, 11.09.2024	Vanessa Kratzer
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Inhaltsverzeichnis

Abkürzungsverzeichnis

Faktor V…… Gerinnungsfaktor V

FVIII……Gerinnungsfaktor VIII

FXIII……Gerinnungsfaktor XIII

GDNG……..Gesetz zur Nutzung von Gesundheitsdaten

HA……Hämophilie A

KHEntgG…….Krankenhausentgeltgesetz

NiB……Nichtinterventionelle Beobachtungstudie

RWD……...Real World Data

STROBE…….Strenghtening the Reporting of Observational Studies in Epidemiology

STROSA…… …….Standardisierte Berichtsroutine für Sekundärdatenanalysen

TK…….....Thrombozythenkonzentrat

Gender-Disclaimer

Im folgenden Text werden die Patienten der Hämophilie A nicht gegendert, da diese Krankheit primär Männer betrifft und die hier gezeigten Auswertungen mit einer rein männlichen Kohorte durchgeführt wurden.

Publikationsliste

Publikationen der kumulativen Dissertation

V. Kratzer, V. Rölz, C. Bidlingmaier, R. Klamroth, J. Behringer, A. Schramm, U. Mansmann, K. Berger **Can German health insurance claims data fill information gaps in rare chronic diseases: Use case of haemophilia A Hämostaseologie.** Hamostaseologie. 2024 Jul 1. doi: 10.1055/a-2276-4871. Epub ahead of print. PMID: 38950623.

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V. Kratzer, K. Berger, H. Eichler, M. Ganslmeier, K. Holstein, R. Klamroth, W. Mondorf, C. Pfrepper, U. Scholz, A. Tiede, S. Halimeh. **Burden of mild hemophilia A in Germany.** Jahrestagung der Gesellschaft für Thrombose und Hämostaseforschung (GTH) 2022

V. Kratzer, H. Eichler, M. Ganslmeier, S. Halimeh, K. Holstein, R. Klamroth, W. Mondorf, C. Pfrepper, U. Scholz, A. Tiede, K. Berger. **Impact of moderate/severe Haemophilia A on German patients' daily activities** World Federation of Haemophilia (WFH) 2022

Ihr Beitrag zu den Veröffentlichungen

1.1 Beitrag zu Paper I

Bei dieser Arbeit war es meine Aufgabe, unter Anleitung meiner Betreuerin den Analyseplan zu entwerfen, und diesen mit klinischen Experten und Vertretern der AOK Bayern zu besprechen und anschließend zu finalisieren. Für den Datentransfer zur Auswertung von Sozialdaten § 75 SGB X wurde eine genaue Datenerfassung definiert. Diese Aufgabe habe ich in Zusammenarbeit mit den Coautoren übernommen. Die Datenaufbereitung der übermittelten Rohdaten und deren Auswertung lag ebenfalls in meiner Verantwortung. Die Interpretation der Datenanalysen wurde gemeinsam mit den Coautoren diskutiert. Ein Vorentwurf des Manuskripts wurde von mir verfasst. Dieser Entwurf wurde den Coautoren zur Begutachtung zugesandt und deren Kommentare in das Manuskript integriert. Zusätzlich habe ich die Einarbeitung der Revieweranmerkungen des Journals übernommen.

1.2 Beitrag zu Paper II

Für diese Publikation war ich an der Datenerhebung beteiligt. Darüber hinaus war ich unter der Aufsicht und Anleitung meiner Hauptbetreuerin an der Datenverarbeitung, der Durchführung der Analyse und der Gestaltung der Abbildungen beteiligt. Gemeinsam mit dem Autorenteam entwarf ich den Analyseplan und war für die Auswertung der gesammelten Daten verantwortlich. Darüber hinaus war ich an der Interpretation der Daten und am Entwurf des Manuskripts beteiligt. Zusammen mit den anderen Autoren war ich für die kritische Durchsicht und Überarbeitung des Manuskripts zuständig.

2. Einleitung

„Versorgungsforschung untersucht, beschreibt, erklärt und evaluiert die Kranken- und Gesundheitsversorgung und ihre Rahmenbedingungen unter Alltagsbedingungen, so dass auf dieser Grundlage neue Versorgungskonzepte entwickelt werden können“ [1]. Von Outcomeforschung, epidemiologischer Forschung, gesundheitsökonomischen Analysen, Lebensqualitätsmessungen bis hin zu Patient:innenpräferenzen deckt die Versorgungforschung [2] ein breites Themenspektrum ab. Auf Basis von Primär- und Sekundärdaten aus der Routineversorgung wird in der Versorgungsforschung Evidenz generiert, um unter anderem nachstehende Fragen zu beantworten: Wie lassen sich Behandlungspfade, Patient flows und Ressourcenverbäuche anhand von Routinedaten beschreiben? Wie ist die Versorgungsqualität im Versorgungsalltag? Gibt es regionale Unterschiede in der Versorgungsqualität? Wie viele und welche Patient:innen erhalten bestimmte Therapien? Entspricht die Routineversorgung der Patient:innen den Leitlinien?

Insbesondere im Kontext der Versorgung von Patient:innen mit erblichen und erworbenen Gerinnungsstörungen ist die Beantwortung versorgungsrelevanter Fragestellungen anhand von Daten aus der Routineversorgung von großer Bedeutung für die Sicherstellung einer bedarfsgerechten, qualitätsgesicherten, nachhaltigen, aber auch ökonomischen Versorgung.

Die angeborene Hämophilie, ist ein Beispiel für eine erbliche Gerinnungsstörung. Die Hämophilie A ist mit einer Inzidenz von 1 von 5.000 männlichen Geburten eine seltene Erkrankung [3]. Die Therapie der Hämophilie ist kostenintensiv. Frühere Analysen zeigen Gesamtkosten von 319.024 € pro Patienten pro Jahr in Deutschland für schwere Hämophilie (A+B) [4]. Für Erwachsene mit schwerer Hämophilie und Inhibitoren wurden Kosten zwischen 287.500 € (6 Monate, „low-responder“) und 17.253.000 € (36 Monate, „high-responder“) für die Immuntoleranztherapie geschätzt [5]. Angesichts steigender Kosten im deutschen Gesundheitswesen wird die Beantwortung der Frage nach dem Wert und Zusatznutzen neuer, kostenintensiver Therapien für die Kostenträger immer wichtiger [6]. Daher ist es bei einer kostenintensiven Therapie wie der der Hämophilie A von großem Interesse, Faktoren wie z.B. Ressourcenverbräuche und Kosten der Komorbiditäten zu identifizieren [7]. Für Deutschland liegen derzeit keine aktuellen, sektorübergreifende Informationen basierend auf Sekundärdaten, zu Ressourcenverbrauch, Kosten, Schweregrad, Alter oder Komorbiditäten bei Patienten mit Hämophilie-A mit und ohne Inhibitoren vor.

Bei malignen hämatologischen Patient:innen mit Thrombozytopenie, einer erworbenen Gerinnungsstörung, werden zur Behandlung Thrombozytenkonzentrate (TK) eingesetzt. Da Thrombozytenkonzentrate eine knappe Ressource darstellen, weil Blutprodukte bislang nicht synthetische hergestellt werden können und TKs ausgewählte Spender:innen benötigen [8], ist eine optimale Nutzung dieser Ressource erforderlich. Transparenz über Thrombozytenkonzentratverbrauch, Transfusionsintervalle, Patien:innenmerkmale und den Grad der Übereinstimmung der Leitlinien mit dem Versorgungsalltag ist notwendig, um die optimale Nutzung dieser knappen Ressource zu verbessern. Bislang wurde in Deutschland nicht untersucht, welche Daten in der Routineversorgung üblicherweise erhoben werden und welche Informationen für eine evidenzbasierte Diskussion über die TK Versorgung und den optimalen Blutproduktgebrauch relevant sind.

Die Analyse von Daten aus dem Versorgungsalltag kann dazu beitragen, die Transparenz der Versorgungsrealität zu erhöhen. Hierbei können beispielsweise Behandlungsmuster sowie die Transfusionsintervalle und Leitlinienadhärenz von Thrombozytenkonzentraten erfasst werden, um die Evidenz für wissenschaftliche und klinische Diskussionen, Empfehlungen zum optimalen Einsatz von Thrombozytenkonzentraten und das Transfusionsmanagement in Deutschland zu verbessern.

2.1 Angeborene und erworbene Gerinnungsstörungen

Die Hämostase ist ein lebensnotwendiger Prozess, der zur Stillung einer Blutung führt. Der Körper produziert 14 verschiedene plasmatische Gerinnungsfaktoren, die für die Blutgerinnung verantwortlich [9] sind. Eine verstärke Blutgerinnung kann zu Thrombosen, intravasalen Blutgerinnungen, führen. Eine unzureichende Blutgerinnung wird durch Defekte oder einen Mangel an Blutbestandteilen wie Blutgerinnungsproteinen und/oder Blutplättchen verursacht. Bei Störungen der Hämostase wird zwischen hereditären und erworbenen Blutgerinnungsstörungen unterschieden.

Hereditäre Gerinnungsstörungen

Hereditäre Gerinnungsstörungen, wie der angeborene FXIII-Mangel, der mit einer Prävalenz von 1 : 2–3 Millionen Personen [10] auftritt oder der Faktor V-Mangel mit einer geschätzten Prävalenz von 1: 1 Millionen [11] sind seltene Erkrankungen. Eine hereditäre Gerinnungsstörung ist die „Bluterkrankheit“, die Hämophilie. Die Hämophilie A kommt weltweit bei rund einem von 5.000 männlichen Neugeborenen vor [12]. Hämophilie ist eine seltene vererbte X-chromosomale Blutgerinnungsstörung. Bei der Hämophilie A (HA) führt eine Mutation im FVIII-Gen, das für den Gerinnungsfaktor VIII (FVIII) kodiert, zu einer unzureichenden Blutgerinnung. Abhängig von der Restaktivität des Gerinnungsfaktors werden verschiedene Grade der Hämophilie unterschieden: schwer (<1%), mittelschwer (1% bis ≤5%) und leicht (>5% bis 40%) [13]. In Deutschland sind etwa 6.000 bis 7.000 Patienten von Hämophilie betroffen, von denen etwa 3.000 bis 4.000 eine dauerhafte Behandlung benötigen [14, 15].

Die Therapie der Hämophilie A wird zu 90% durch die Substitution von FVIII bestimmt. Bei der Substitutionstherapie mit Faktorkonzentraten handelt es sich um eine lebenslange und sehr kostenintensive Therapie. Da die Therapie patientenindividuelle Anpassungen erfordert, können die Therapiekosten von Patient zu Patient stark variieren. In Deutschland wird die wirtschaftliche Belastung durch die direkten Kosten für schwere Hämophilie A auf das 79-fache der durchschnittlichen Pro-Kopf-Gesundheitsausgaben geschätzt [16]. Neue Hämophilietherapien, wie bispezifische monoklonale Antikörper oder Gentherapien [17, 18], sind erst seit kurzer Zeit zur Behandlung zu Verfügung oder stehen kurz vor der Zulassung davor [19]. Diese werfen Fragen nach dem Wert innovativer Behandlungen im Vergleich zu Standardbehandlungen für Entscheidungen über die Ressourcenallokation im Gesundheitswesen auf [20]. Umfassende Informationen über Ressourcenverbräuche, Behandlungspfade und Kosten aus der Routineversorgung sind hier eine

notwendige Grundlage für evidenzbasierte Entscheidungsfindung. Dasselbe gilt für die Entwicklung und Diskussion zukünftiger Erstattungsmodelle.

Erworbene Gerinnungsstörungen

Bei erworbenen Gerinnungsstörungen variiert die Prävalenz und Inzidenz in Abhängigkeit von der Grunderkrankung und der zugrundeliegenden Population: So liegt die Inzidenz von Erkrankungen mit begleitender Thrombozytopenie beim myelodysplatischen Syndrom bei 3-4 pro 100.000/Jahr, bei akuten Leukämien bei 1,5-3,5 pro 100.000/Jahr und bei der aplastischen Anämie bei 0,2-0,5 pro 100.000/Jahr [21]. Patient:innen mit hämatologischen Neoplasien, stellen dabei eine besonders gefährdete Gruppe dar. Dies ist darauf zurückzuführen, dass bei ihnen sowohl die Grunderkrankung als auch die Therapie mit einer Thrombozytopenie assoziiert sind. Im Jahr 2019 erkrankten über 12.000 Menschen an einer Leukämie [22]. Im Laufe Ihres Lebens erkrankt in Deutschland jede 99. Frau und jeder 75. Mann an Leukämie [23]. Die demografische Entwicklung in den kommenden Jahrzehnten wird die Häufigkeit von Krebserkrankungen weiter ansteigen lassen: So wird ein Anstieg der Inzidenz um 55% zwischen 2007 und 2050 erwartet [24]. Bei hämato-onkologischen Patient:innen sind Thrombozytentransfusionen unerlässlich zur Vorbeugung und Behandlung von Blutungen und Thrombozytopenien [25]. Thrombozytenkonzentrate sind jedoch eine knappe und wertvolle Ressource, sie können bislang nicht künstlich hergestellt werden und man ist auf die Spendebereitschaft Gesunder angewiesen [8]. Die Haltbarkeit der Transfusionen beträgt nur 4 bzw. 5 Tage [26, 27]. Der demographische Wandel wird einen Rückgang der Spenderzahlen und damit eine negative Beeinflussung des Angebots an zellulären Blutprodukten mit sich bringen [28-30]. Diese Entwicklungen, von steigendem Bedarf bei abnehmenden Spenderzahlen, könnten zu Engpässen in der Versorgung mit Blutprodukten und steigenden Preisen führen. Aus diesem Grund ist ein optimaler Einsatz von Thrombozytenkonzentraten erforderlich. Über die aktuelle Transfusionspraxis, die Outcomes sowie der leitliniengerechten Thrombozytentransfusion in der klinischen Routineversorgung ist in Deutschland wenig bekannt.

2.2 Real World Data (Sekundär- und Primärdaten) für die Versorgungsforschung

Real World Data sind Daten über den Gesundheitszustand von Patient:innen oder die Erbringung von Gesundheitsleistungen, die routinemäßig erhoben werden und nicht aus klinischen Studien stammen. Real World Data können sowohl Primär- als auch Sekundärdaten sein.

Primärdaten

Bei Primärdaten handelt es sich um Daten, die für einen bestimmten Zweck beziehungsweise für eine Studie erhoben wurden. Sie können durch verschiedene Methoden erhoben werden wie beispielsweise Umfragen, Beobachtungsstudien und Interviews.

Die Erhebung von Primärdaten, z.B.: im Rahmen einer klinischen nichtinterventionellen Beobachtungstudie (NiB), enthält beispielsweise Informationen wie Diagnosen, Symptome, Behandlungsverläufe und Interventionen. Die Verwendung solcher Primärdaten ermöglicht eine detaillierte Untersuchung individueller Krankheitsverläufe. Die Vorteile der Erhebung von Primärdaten in NiBs,

die aus der Routineversorgung stammen, sind vielfältig. NiB-Daten weisen eine hohe externe Validität auf und lassen Rückschlüsse auf den tatsächlichen Verlauf der Behandlung zu. Zusätzlich sind die Daten im Vergleich zu beispielsweise Krankenkassendaten granulärer. So können für Patient:innen Laborwerte, Medikation und Eingriffe im Zusammenhang erfasst und analysiert werden. Diese Vorteile sind jedoch mit einem hohen Zeit- und Ressourcenaufwand für die Dokumentation verbunden. Das Fehlen von Daten aus anderen Einrichtungen des Gesundheitswesens, z. B. aus der ambulanten Versorgung, der Rehabilitation und zu den Outcomes nach der Entlassung, kann die Aussagekraft der Daten einschränken, da nur Teilbereiche der Gesundheitsversorgung abgebildet werden können.

Um eine qualitativ hochwertige Berichterstattung über Beobachtungsstudien zu gewährleisten, wurden für Beobachtungsstudien eine Leitlinie -STROBE (STrenghtening the Reporting of OBservational Studies in Epidemiology) erstellt [31].

Sekundärdaten

Sekundärdaten sind bereits existierende Daten, die für einen anderen Zweck als für die Forschung erhoben wurden, wie beispielsweise klinische Dokumentationen (z. B. elektronische Krankenakten), Abrechnungsdaten von Krankenkassen, Krankenhausabrechnungen (z.B. § 21 Datensatz nach § 21 Abs. 4 und Abs. 5 KHEntgG), Daten aus Ämtern oder Registern, Daten von Biobanken und Daten aus Gesundheitsapplikationen [32].

Sekundärdatenanalysen, z.B. basierend auf Krankenkassenabrechnungsdaten, nehmen an Bedeutung zu [33, 34]. Krankenkassenabrechnungsdaten entstehen im Zusammenhang mit der Abrechnung von Leistungen zwischen Krankenkassen und den Leistungserbringern (Ärzten, Krankenhäusern, Apotheke) [35]. Sie enthalten Informationen über die abgerechneten erbrachten medizinischen Leistungen und die Medikation sowie deren Kosten, Diagnosen, Versicherteninformationen (Alter, Geschlecht) und Informationen über die Leistungserbringer (Fachrichtung, ambulant oder stationär).

Die Analyse von anonymisierten Krankenkassendaten bietet zahlreiche Vorteile. Ein Vorteil ist die große und sektorenübergreifende Datenbasis. Diese Daten liefern Hinweise, z.B. über die Diagnose von Krankheiten und die Inanspruchnahme von ambulanten und stationären Gesundheitsleistungen. Dadurch werden große und umfassende Studien mit vielen Teilnehmenden ermöglicht, die z.B. für die Erforschung seltener Erkrankungen oder ungewöhnlicher Krankheitsverläufe notwendig, aber ansonsten sehr aufwändig und teuer sind. Darüber hinaus können Patient:innengruppen, die ansonsten nicht einwilligungsfähig wären (Behinderte, Kinder etc.), in Sekundärdaten-Studien eingeschlossen werden [36]. Zusätzlich können Krankenkassendaten über lange Zeiträume hinweg analysiert werden. Das bietet die Möglichkeit Trends, Veränderungen und Muster in der Versorgung sowie der Gesundheit der Bevölkerung im Laufe der Zeit zu erkennen und zu untersuchen.

Allerdings gibt es auch Hürden bei der Nutzung von Sekundärdaten. Dazu gehört die fehlende Detailtiefe und Kontextinformationen, da z.B. Abrechnungen aus dem ambulanten Sektor von Krankenkassen nur quartalsmäßig erhoben werden sowie Kodierungsungenauigkeiten oder z.B.

Schweregrade der Hämophilie nicht durch ICD-Codes abgebildet werden. Es bedarf daher geeigneter Methoden zur Datenanalyse und Interpretation sowie einer sorgfältigen Überprüfung der Datenqualität, um aussagekräftige Ergebnisse aus Sekundärdaten zu erzielen.

Zur Vereinheitlichung der Qualität von wissenschaftlichen Sekundärdatenanalysen und deren Berichterstattung wurde die Leitlinie STROSA (STandardisierte BerichtsROutine für SekundärdatenAnalysen) entwickelt. Die Einhaltung dieser Richtlinien ermöglicht es Dritten, Studien fundiert zu beurteilen und wirkt einer Verzerrung durch die selektive Veröffentlichung von Ergebnissen entgegen [37].

Im Gegensatz zu den strengen Auswahlkriterien in klinischen Studien spiegeln Real World Data die tatsächliche Praxis und Behandlungsumgebung wider. Bei der Nutzung dieser Daten sind methodische Herausforderungen zu bewältigen und die beschriebenen Einschränkungen zu beachten [38]. Diese hängen von der Datenquelle ab, z.B. mangelnde Granularität der Daten oder Ungenauigkeiten bei der Datenerfassung. Dennoch sind sie ein wertvolles Instrument zur Verbesserung des Verständnisses von Gesundheitszuständen und der Patient:innenversorgung in der realen Welt [36]. Aus Sekundärdaten können besonders für seltene Erkrankungen beispielsweise historische Kontrollgruppen erstellt werden, deren Ergebnisse einen Wirksamkeitsvergleich zwischen innovativen Arzneimitteln/Therapien und der aktuellen Standardversorgung darstellen können [39, 40].

Um in Deutschland die Nutzbarkeit von Gesundheitsdaten zu erleichtern, wurde das Gesetz zur Nutzung von Gesundheitsdaten (GDNG) auf den Weg gebracht. Das im Dezember 2023 vom Deutschen Bundestag verabschiedete GDNG zielt darauf ab, unter anderem auch die in der elektronischen Patient:innenakte (Gesetz zur Beschleunigung der Digitalisierung des Gesundheitswesens-DigiG) erhobenen Gesundheitsdaten künftig besser für die Forschung nutzen zu können. Eine zentrale Datenzugangs- und Koordinierungsstelle soll pseudonymisierte Gesundheitsdaten aus verschiedenen Datenquellen miteinander verknüpfen können und bürokratische Barrieren abbauen. Sollte dies gelingen, könnten RWD schneller und umfassender analysiert und einige der derzeitigen Einschränkungen überwunden werden. Dennoch bleibt das Verständnis der Datenstrukturen und des Kontextes der verschiedenen Quellen unerlässlich für die Generierung und Interpretation aussagekräftiger Ergebnisse.

2.3 Zielsetzung und Fragestellungen

Ziel der vorliegenden Dissertation ist es, einen Beitrag zur Evidenzgenerierung für die Beantwortung von versorgungsrelevanten Fragestellungen zu leisten, die als Grundlage für Entscheidungen in der gesundheitlichen Versorgung dienen können. Das Spektrum der Fragestellungen und methodischen Ansätze zur Beantwortung versorgungsrelevanter Fragen wird anhand von Beispielen aus der Versorgung von Patient:innen mit hereditären und erworbenen Gerinnungsstörungen illustriert. Dabei sollen folgende versorgungsrelevante Fragestellungen beantwortet werden:

Paper I:

- Wie lässt sich die Kohorte von Patienten mit dokumentierter ICD-10-GM D.66 (Hereditärer Faktor-VIII-Mangel) in Bezug auf Demographie und Komorbiditäten anhand der Abrechnungsdaten der AOK Bayern beschreiben?
- Wie oft treten klinische Outcomes, insbesondere Gelenkerkrankungen und kardiovaskuläre Erkrankungen, in der Hämophilie-Kohorte auf?
- Wie hoch ist, differenziert nach ambulantem und stationärem Sektor, der Ressourcenverbrauch für die Hämophilie A und Ihre Komorbiditäten?
- Wie hoch sind die Gesamtkosten pro Jahr in Abhängigkeit von Alter und Schweregrad?
- Wie hoch sind die Kosten der Medikation der Hämophilie A stratifiziert nach Alter und Schweregrad?
- Stellt die Granularität der Informationen in deutschen Krankenkassendaten eine geeignete Datenquelle dar, um Ressourcenverbräuche und Kosten seltener Erkrankungen zu analysieren?

Paper II:

- Welche Patient:innen (Kohortengröße, Demographie, klinische Charakteristika) erhalten wie viele Thrombozytenkonzentrate in der hämato-onkologischen Abteilung eines Universitätsklinikums in einem Zeitraum von 3 Monaten?
- Können aus den Transfusionsintervallen Transfusions- bzw. Behandlungsmuster abgeleitet werden?
- Werden Thrombozytentransfusionen leitliniengerecht nach *Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten, Gesamtnovelle 2020* [41] transfundiert?
- Werden alle notwendigen Variablen in der Routineversorgung erfasst, so dass wiederkehrende Analysen zur Bedarfs- und Qualitätsmessung genutzt werden können?

3. Zusammenfassung

Zu Behandlungspfaden, Leitlinienadhärenz, Ressourcenverbräuchen und Kosten in der Routineversorgung (stationär und ambulant) von Patient:innen mit hämostaseologischen Erkrankungen im Versorgungsalltag besteht nur eine begrenzte Transparenz. Als Informationsquelle für die Analyse der Routineversorgung werden zunehmend Real World Data diskutiert. In den Veröffentlichungen im Rahmen der vorgelegten Dissertation werden verschiedene Real World Data Quellen genutzt, um versorgungsrelevante Fragestellungen im Kontext der Versorgung von Patienten mit hämostaseologischen Erkrankungen zu beantworten. Das eine Mal anhand einer erblichen, seltenen Erkrankung (Hämophilie A) mit kostenintensiver Therapie, das andere Mal anhand einer häufigen Erkrankung (Thrombozytopenie) bei hämatologischen malignen Erkrankungen, bei der die supportive Therapie (Thrombozytenkonzentrate) eine knappe Ressource darstellt.

Im ersten Teil der Dissertation wurde untersucht, wie die Analyse von Real World Data aus Krankenkassenabrechnungsdaten in Deutschland zur Generierung von Evidenz in Bezug auf Ressoucenverbräuche, Kosten und Behandlungsmustern bei seltenen Erkrankungen am Beispiel der Hämophilia A beitragen können, da es hierzu erst wenige Informationen gibt. Die Hämophilie A ist eine seltene Blutgerinnungsstörung, deren Behandlung mit sehr hohen, lebenslangen Kosten verbunden ist. Kostenintensive Therapien sind erst in jüngster Zeit auf den Markt gekommen oder stehen kurz vor der Markteinführung, so dass Informationen über Ressorcenverbäuche und Kosten für die Findung neuer Erstattungsmodelle von großer Bedeutung sind. Die retrospektive Analyse von pseudonymisierten Abrechnungsdaten der „AOK Bayern – Die Gesundheitskasse“ lieferte Informationen zur Bestimmung von Ressourcenverbrauch und Kosten. Patienten mit ICD-10-GM-Code D66 und HA-Medikation wurden in die deskriptiven Analysen einbezogen. Die Schweregrade wurden anhand des dokumentierten HA-Medikationsverbrauchs eingeteilt. Für den Zeitraum von 3 Jahren (2017-2019) wurden insgesamt 257 Patienten identifiziert: leichte HA, 104 Patienten (Durchschnittsalter 40,0 Jahre; SD 22,9); mittelschwere HA, 17 Patienten (51,2 Jahre; SD 24,5); schwere HA, 128 Patienten (34,2 Jahre; SD 18,5). Es waren 8 Patienten in der Kategorie mit Inhibitoren (37,8 Jahre; SD 29,6). Eine Psychotherapie wurde bei 28,8% (leicht) bis 32,8% (schwer) der Patienten kodiert. Eine Gelenkerkrankung wurde bei 46,2% (leicht) bis 61,7% (schwer) der Patienten dokumentiert. Die durchschnittlichen direkten Kosten/Patient/Jahr lagen bei Patienten mit leichter Hämophilie A bei dem 1,34-fachen, bei Patienten mit mittelschwerer Hämophilie A bei dem 11-fachen, bei Patienten mit schwerer Hämophilie A bei dem 81-fachen und bei Patienten mit Hemmkörperhämophilie bei dem 223-fachen der durchschnittlichen Jahresausgaben pro Versicherten der „AOK Bayern – Die Gesundheitskasse“ (2019). Die durchschnittlichen jährlichen stationären Kosten pro Patient für Patienten mit leichter HA betrugen 4.715 € (SD 8.939), für Patienten mit mittelschwerer HA 4.292 € (SD 3.970), bei Patienten mit schwerer HA lagen die mittleren jährlichen stationären Kosten pro Patient bei 2.317 € (SD 2.521) und für Patienten mit Hemmkörpern bei 3.642 € (SD 3.600). Es ist zu beachten, dass diese stationären Kosten keine Zusatzentgelte für HA-Medikamente enthalten, da sie nicht im Datensatz enthalten waren. Die Kosten für HA-Medikamente machten bei Patienten (Inhibitor-Mittelschwer) über 90% und bei Patienten mit leichter HA 46,1% der durchschnittlichen jährlichen direkten Kos-

ten aus. Die Notwendigkeit einer individualisierten Behandlung wird durch die große Kostenspanne deutlich. Die Analyse zeigt auch, dass die Krankheitslast der Patienten (dokumentierte Depressionen, Psychotherapie, Behandlungen) in allen Schweregradgruppen möglicherweise unterschätzt wird. Leichte und mittelschwere HA-Patienten verbrauchen Ressourcen wie Psychotherapie, Antidepressiva, Schmerztherapie vergleichbar mit schweren HA Patienten. Ebenfalls werden Gelenkerkrankungen bei Patienten mit leichter Hämophilie A unterschätzt. Die Analyse von deutschen Krankenkassendaten liefert Informationen über Ressourcenverbrauch und Kosten, die als Basisinformationen eine wichtige Quelle für die Verbesserung der Evidenz als Grundlage für nachfolgende Wertermittlungen für neue Therapien im Vergleich zur Standardtherapie sein können. Die Limitationen der Datenanalyse waren der Mangel an differenzierten ICD-Codes für die Schweregradklassifikation der Hämophilie A sowie fehlende Informationen zu Zusatzentgelten der stationären Kosten.

Im zweiten Teil der Dissertation wurden die Thrombozytenkonzentrattransfusionen bei hämatoonkologischen Patient:innen in der klinischen Routineversorgung anhand von Primärdaten analysiert. Transfusionen von Thrombozytenkonzentraten sind eine wichtige supportive Therapie, insbesondere bei Krebspatient:innenen, die nach einer zytotoxischen Chemotherapie eine Thrombozytopenie entwickeln. In Deutschland ist wenig über die Transfusionspraxis und die Outcomes von Thrombozytentransfusionen in der klinischen Routineversorgung von Patient:innen mit einer malignen Erkrankung bekannt. Durch eine prospektive monozentrische Beobachtungsstudie in der Abteilung Hämatologie/Onkologie des Ludwig-Maximilians-Universität Klinikums Großhadern wurde untersucht, ob Daten, die in der stationären Routineversorgung von Krebspatient:innen erhoben werden, die Informationen zur Anzahl der Transfusionen pro Patient:in, welche Patient:innen die meisten Thrombozytenkonzentrate erhalten, Transfusionsintervalle und Leidlinienadhärenz, enthalten. Anschließend wurde aus der Literatur und den für diese Studie gesammelten Daten ein Blue Print mit allen Datenpunkten erstellt, die für die Messung der Qualität, die Effizienz und das Management von Thrombozytenkonzentrattransfusionen wesentlich sind. Dieser Blue Print kann als Grundlage für digitale Datenerfassungssysteme dienen, die in Zukunft umfassende Analysen ermöglichen und wiederkehrende Aufgaben und Analysen drastisch vereinfachen sollen. Im Beobachtungszeitraum von 3 Monaten (März-Mai 2015) erhielten 94 Patient:innen insgesamt 942 Thrombozytenkonzentrate. Das Durchschnittsalter (±SD) betrug 54,6 Jahre (±13,9), 68% der Patient:innen waren männlich. Die Ergebnisse zeigen, dass die Anzahl und Intervalle der Transfusionen der Thrombozytenkonzentrate heterogen war. Eine kleine Gruppe von Patient:innen (n=12) erhielt 41,6% aller Thrombozytentransfusion. Die häufigste Grunderkrankung (n=82; 87,2%) von Patient:innen, die Thrombozytenkonzentrate erhielten, waren an bösartigen Neubildungen des lymphatischen und hämatopoetischen Gewebes erkrankt. Über 80% der Thrombozytentransfusionen wurden leitliniengerecht transfundiert, 174 (18.47%) Thrombozytenkonzentrate wurden bei einem Thrombozytenwert über dem Schwellenwert von 10 G/L transfundiert, ohne dokumentierten Risikofaktor [41]. Da nicht alle relevanten Daten routinemäßig erhoben werden, um z.B.: Outcomes wie Blutungen oder Krankheitsstadien wie Refraktärität zu bestimmten, könnte das in dieser Studie erarbeitete Modell einer Datenliste, die alle für

wissenschaftliche Analysen notwendigen Variablen beinhaltet, als Blue Print für zukünftige softwaregestützte Datenerhebungssysteme dienen. Die Digitalisierung des Gesundheitswesens, wie die Einführung der elektronischen Patient:innenakte oder klinische Dokumentationssoftware, könnte zukünftig zu einer strukturierteren Datenerfassung führen und die Möglichkeit schaffen, verschiedene Datenquellen miteinander zu verknüpfen, um eine optimale Nutzung der Thrombozytenkonzentrate und ein optimales Transfusionsmanagement zu gewährleisten.

Die hier durchgeführten Analysen demonstrieren die bestehenden Möglichkeiten von Primär- und Sekundärdatenanalysen zur Beantwortung von versorgungsrelevanten Fragestellungen zur Optimierung der Versorgung von Patienten mit Gerinnungsstörungen. Die Analyse von Sekundärdaten kann insbesondere bei seltenen Erkrankungen, wie z. B. der Hämophilie A, wichtige Informationen liefern. Dazu gehören Ressourcenverbrauch, Kosten und klinische Outcomes, wie das Auftreten von Komorbiditäten oder die Anzahl stationärer Aufenthalte, die für die Bewertung innovativer Therapien wichtig sind. Die Analyse von Primärdaten aus der hämato-onkologischen Abteilung eines Universitätsklinikums schafft Transparenz hinsichtlich des Einsatzes von Thrombozytenkonzentraten. Regelmäßig durchgeführte Analysen zur Bedarfs- und Qualitätsmessungen generieren fortlaufend wichtige Informationen für die Diskussion über den optimalen Einsatz von Thrombozytenkonzentraten.

Bei der Interpretation der Daten ist es jedoch wichtig, die Limitationen der jeweiligen Datenquelle, wie beispielsweise Datenqualität (z.B.: Vollständigkeit, Vollzähligkeit, hinreichende ICD-Codierung) und Granularität, zu berücksichtigen. Aufgrund bestehender Limitationen ist es wichtig, Möglichkeiten des Datenlinkage verschiedener Datenquellen aus dem Versorgungsalltag zu erprrioben, um versorgungsrelevante Fragestellungen bestmöglich beantworten zu können.

4. Abstract (English):

In routine care (inpatient and outpatient) of patients with hemostaseological disorders, there is often limited transparency about treatment patterns, guideline adherence, resource use, and costs. Real World Data are increasingly being discussed as a source of information for the analysis of routine medical care. The range of applications of Real World Data as shown in this dissertation by the example of coagulation disorders. One the one hand, a hereditary, rare disease (hemophilia A) with cost-intensive therapy, on the other hand using a common disease (thrombocytopenia) in hematological malignancies where supportive therapy (platelet concentrates) is however a scarce resource.

The first part of the dissertation examined how the analysis of real-world data from health insurance billing data in Germany can contribute to the generation of evidence regarding resource consumption, costs and treatment patterns for rare diseases using the example of haemophilia A, as there is little information available. Haemophilia A is a rare blood clotting disorder whose treatment is associated with very high, lifelong costs. Cost-intensive therapies have only recently come onto the market or are about to be launched, so that information on resource consumption and costs is of great importance for finding new reimbursement models. Retrospective analysis of anonymized claims data from "AOK Bayern - Die Gesundheitskasse" provided information to determine resource use and costs. Patients with ICD-10-GM-Code D66 and HA medication were included in the descriptive analyses. Severity levels were categorised based on HA medication consumption. For the 3-year period (2017-2019), a total of 257 patients were identified: mild HA, 104 patients (mean age 40.0 years; SD 22.9); moderate HA, 17 patients (51.2 years; SD 24.5); severe HA, 128 patients (34.2 years; SD 18.5). There were 8 patients in the category with inhibitors (37.8 years; SD 29.6). Psychotherapy was coded in 28.8% (mild) to 32.8% (severe) of patients. Joint disease was documented in 46.2% (mild) to 61.7% (severe) of patients. The average direct costs/patient/year were 1.34-fold for patients with mild hemophilia A, 11-fold for patients with moderate HA, 81-fold for patients with severe hemophilia A, and 223-fold for patients with inhibitory hemophilia of the average annual expenditure per insured person of “AOK Bayern – Die Gesundheitskasse” (2019). The mean annual inpatient cost per patient was €4,715 (SD 8,939) for patients with mild HA, €4,292 (SD 3,970) for patients with moderate HA, €2,317 (SD 2,521) for patients with severe HA, and €3,642 (SD 3,600) for patients with inhibitors. It should be noted that these inpatient costs do not include additional fees ('Zusatzentgelte') for HA medication, as they were not included in the dataset. The cost of HA medication for over 90% of the average annual direct costs for patients (inhibitor-moderate) and 46.1% for patients with mild HA. The wide range of costs highlights the need for individualised treatment. The analysis also shows that patient burden (documented depression, psychotherapy, and treatments) is underestimated in all severity groups. Mild and moderate HA patients consume resources such as psychotherapy, antidepressants, and pain therapy comparable to severe HA patients. Documented joint disease is also underestimated in patients with mild haemophilia A. The analysis of German health insurance data provides information on resource consumption and costs, which can be an important source for improving evidence as a basis for subsequent value judgements for new therapies compared to standard therapy. The limitations of the data analysis were the lack of differentiated ICD codes for the severity classification of haemophilia A and the lack of information on additional charges for inpatient costs.

In the second part of the dissertation, platelet transfusions in haemato-oncological patients in routine clinical care were analyzed using primary data. Transfusions of platelet concentrates (PC) are an important supportive therapy, especially in cancer patients who develop thrombocytopenia

after cytotoxic chemotherapy. In Germany, little is known about current transfusion practice and outcomes of platelet transfusions in routine clinical care of patients. A prospective monocentric observational study in the Department of Haematology/Oncology at the Ludwig-Maximilians-Universität Klinikum Großhadern investigated whether data collected in the routine inpatient care of cancer patients contain information on the number of transfusions per patient, which patients receive the most PCs, transfusion intervals and bleeding line adherence. A blue print was then created from the literature and the data collected for this study with all the data points that are essential for measuring the quality, efficiency and management of platelet transfusions. This blue print can serve as the basis for digital data collection systems that will enable comprehensive analyses in the future and drastically simplify recurring tasks and analyses. The results show that the distribution of platelet concentrate was not uniform among patients. During the observation period of 3 months (March-May 2015), 94 patients received a total of 942 platelet concentrates. The average age (±SD) was 54.6 years (±13.9), 68% of the patients were male. The results show that the number and intervals of platelet transfusions were heterogeneous. A small subgroup of patients (n=12) received 41.6% of all platelet transfusions. The most common underlying disease (n=82; 87.2%) was malignant neoplasm of lymphoid and hematopoietic tissue. Over 80% of platelet transfusions were transfused according to guidelines, 174 (18.47%) platelet transfusions were transfused with a platelet count above the threshold of 10 G/L, without a documented risk factor [41]. Since not all relevant data is routinely collected, e.g. to determine outcomes such as bleeding or disease stages such as refractoriness, the model of a data list developed in this study, which includes all variables necessary for scientific analyses, could serve as a blue print for future software-supported data collection systems. The digitalisation of the healthcare system, such as the introduction of electronic patient records or clinical documentation software, could lead to more structured data collection in the future and create the possibility of linking different data sources to ensure optimal use of platelet concentrates and transfusion management.

The analyses carried out here demonstrate the existing possibilities of primary and secondary data analyses for answering care-relevant questions to optimize the care of patients with coagulation disorders. The analysis of data from routine care can also provide fundamental information for rare diseases, such as haemophilia A. This includes resource consumption, costs and clinical outcomes such as the occurrence of comorbidities or the number of inpatient stays, which are important for the evaluation of innovative therapies. The analysis of primary data from the haemato-oncology department of a university hospital can increase the transparency of routine transfusion patterns and contribute to the optimal use of scarce resources such as platelet concentrates. Regular analyses of demand and quality measurements continuously generate important information for the discussion on the optimal use of platelet concentrates.

When interpreting the data, however, it is important to consider the limitations of the respective data source, such as data quality (e.g: comprehensiveness, completeness, sufficient ICD coding) and granularity. Due to existing limitations, it is important to explore the possibilities of data linkage of different data sources from routine care in order to best answer care-related questions.

5. Paper I

Can German health insurance claims data fill information gaps in rare chronic diseases: Use case of haemophilia A

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Hämostaseologie (ISSN 0720-9355)

akzeptiert am 20.02.2024

Journal impact factor 3.21

Rank by Journal Impact Factor: Hematology 39/79 (53.8%)

Can German health insurance claims data fill information gaps in rare chronic diseases: Use case of haemophilia A

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Article type: Original Article

Keywords: Haemophilia A, Claims data, Health economics, Rare disease

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Abstract

Claims data are increasingly discussed to evaluate health care for rare diseases (resource consumption, outcomes and costs). Using haemophilia A (HA) as a use case, this analysis aimed to generate evidence for the aforementioned information using German statutory health insurance (SHI) claims data.

Claims data (2017 to 2019) from the German SHI "AOK Bayern - Die Gesundheitskasse" were used. Patients (pts) with ICD-10-GM codes D66 and HA medication were included in descriptive analyses. Severity levels were categorized according to HA medication consumption.

In total, 257 pts were identified: mild HA, 104 pts (mean age 40.0 years; SD 22.9); moderate HA, 17 pts, (51.2 years ;SD 24.5); severe HA, 128 pts, (34.2 years;SD 18.5). There were 8 pts categorized with inhibitors (37.8 years; SD 29.6). Psychotherapy was reported among 28.8% (mild)-32.8% (severe) of pts. Joint disease was documented for 46.2% (mild)-61.7% (severe) of pts. Mean direct costs/patient/year were 1.34x for mild, 11x for moderate, 81x higher for severe HA patients and 223x higher for inhibitor pts than the mean annual expenditure per AOK Bayern insurant (2019).

German SHI data provide comprehensive information. The patient burden in HA is significant with respect to joint disease and psychological stress regardless of the HA severity level. The cost of HA care for patients is high. Large cost ranges suggest that the individual situation of a patient must be considered when interpreting costs. The main limitation of SHI data analysis for haemophilia A was the lack of granularity of ICD Codes.

Zusammenfassung

Abrechnungsdaten werden zunehmend diskutiert, um die Gesundheitsversorgung bei seltenen Erkrankungen (Ressourcenverbrauch, Outcomes und Kosten) zu evaluieren. Ziel dieser Analyse war es, am Beispiel der Hämophilie A (HA) anhand von Abrechnungsdaten der gesetzlichen Krankenversicherung (GKV) Evidenz für die oben genannten Informationen zu generieren.

Verwendet wurden Abrechnungsdaten (2017 bis 2019) der AOK Bayern - Die Gesundheitskasse. In die deskriptiven Analysen wurden Patienten mit den ICD-10-GM-Codes D66 und/oder D68.31 und HA-Medikation eingeschlossen. Die Schweregrade wurden nach der Einnahme von HA-Medikation klassifiziert.

Insgesamt wurden 257 Patienten identifiziert: leichte HA, 104 Patienten (Durchschnittsalter 40,0 Jahre; SD 22,9); mittelschwere HA, 17 Patienten (51,2 Jahre; SD 24,5); schwere HA, 128 Patienten (34,2 Jahre; SD 18,5). Es gab 8 Patienten, die mit Inhibitoren kategorisiert wurden (37,8 Jahre; SD 29,6). Eine Psychotherapie wurde bei 28,8% (leicht) bis 32,8% (schwer) der Patienten dokumentiert. Eine Gelenkerkrankung wurde bei 46,2% (leicht) bis 61,7% (schwer) der Patienten dokumentiert. Die durchschnittlichen direkten Kosten/Patient/Jahr lagen bei Patienten mit leichter HA um das 1,34-fache, bei Patienten mit mittelschwerer HA um das 11-fache, bei Patienten mit schwerer HA um das 81-fache und bei Patienten mit Inhibitoren um das 223-fache über den durchschnittlichen jährlichen Ausgaben pro Versicherten der AOK Bayern (2019).

Die deutschen GKV-Daten liefern umfassende Informationen. Die Belastung der Patienten durch HA ist unabhängig vom Schweregrad der HA im Hinblick auf Gelenkerkrankungen und psychische Belastung erheblich. Die Kosten der HA-Versorgung für die Patienten sind hoch. Große Kostenspannen legen nahe, dass bei der Interpretation der Kosten die individuelle Situation des Patienten berücksichtigt werden muss. Die größte Einschränkung bei der Analyse der GKV-Daten für Hämophilie A war die fehlende Granularität der ICD-Codes.

Introduction

Rare diseases affect approximately 263-446 million people worldwide [1]. Gene therapy and other new technologies have become available and offer great promise in treating rare diseases. To evaluate whether these new therapies are advantageous (in terms of treatment patterns, outcomes in relation to costs) compared to established standard therapies, information for the innovative treatment and the current standard therapy is needed. Haemophilia A disease is a suitable use case for a rare chronic disease with high treatment costs. FVIII replacement therapy [2] has been the standard of care for many years. Since 2017, a series of innovative therapies, such as gene therapies, bispecific antibodies, and substances with prolonged half-lives, have been licenced or are nearly ready for market launch [3].

Congenital haemophilia A is a rare hereditary X-linked blood clotting disorder. A mutation in the FVIII gene coding for coagulation factor VIII (FVIII) results in impaired haemostasis [4]. Depending on the residual activity of the clotting factor, which is determined by the respective mutation, different degrees of haemophilia are distinguished: severe (<1%), moderate (1% to ≤5%), and mild (>5% to 40%)[5]. In Germany, approximately 6,000 to 7,000 patients are affected by haemophilia, of whom approximately 3,000 to 4,000 require permanent treatment [6, 7]. The main clinical symptom is recurrent joint bleeding, particularly in the ankle, knee and elbow joints, which can lead to long-term joint damage and even complete loss of function and disability.

Treatment of haemophilia A is 90% dependent on factor VIII replacement. As the therapy has to be adapted to the individual patient, the costs of therapy can vary greatly, ranging from €46,879 to nearly €281,274 (US study, exchange rate 07.03.2023) annually, depending on disease severity [8]. Costs also depend on therapy regimens, as prophylaxis costs are approximately four times higher than those of on-demand therapy [9]. In Germany, the economic burden of direct costs for severe HA is estimated to be 79 times higher than the mean per capita health expenditure [10]. The increasing costs for innovative therapies such as

bispecific monoclonal antibodies or gene therapies [11, 12] raise questions about the value of innovative treatments compared to standard treatments for decisions on health care resource allocation. Basic updated information for treatment patterns, outcomes, costs of HA and HA-specific comorbidities stratified by age and severity is a necessary basis for value assessment of innovative therapies. To describe these aspects fully, cross-sectoral information on the care-associated resource consumption, outcomes, and costs of as many patients as possible is needed. For many other diseases, secondary data have already been increasingly used to meet the information needs mentioned above. A major advantage of secondary data is the chance to obtain access data from larger populations more quickly compared to prospective observational studies. Especially in the case of a rare disease such as haemophilia A, observational studies are time-consuming, and the logistical effort for these studies is huge. Secondary data sources such as registries cannot be used, as the national German register of haemophilia patients does not contain comorbidity variables such as joint and cardiovascular disease [13]. Clinical medical records include only inpatient health services, and the dataset of the Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigung, KV) solely covers outpatient services. Only the claims data from the health insurance funds contain cross-sectoral information on inpatient and outpatient care of a patient.

For Germany, there is currently no updated evidence on treatment pathways, resource use and costs, severity, age, or comorbidities for patients with haemophilia A inhibitors. The aim of the analysis is to generate this evidence using statutory health insurance claims data and to investigate whether this data source contains all necessary information for additional evidence on the use case of haemophilia A beyond clinical trials of rare diseases.

Methods

Study Design

A retrospective analysis of anonymisedclaims data from the statutory health insurance "AOK Bayern - Die Gesundheitskasse" [14] was performed. The observation period was from 2017 to 2019. An application (including guarantee of confidentiality Art.32 EU-DSGVO) in accordance with § 75 Transmission of Social Data for Research was submitted, and approval was obtained from the highest state authority (Bavarian State Ministry for Health and Care). The analysis of the SHI claims data was in accordance with the guidelines standardized reporting of secondary data analyses (STROSA)[15].

Study cohort

Inclusion criteria were male of any age, ≥350 days per year with AOK Bayern and a confirmed ICD-10-GM diagnosis of D66 (hereditary factor VIII deficiency). The inclusion criterion was as follows: patients who received HA-specific medication, including at least one prescription of HA medication (FVIII concentrates, bypassing agents, emicizumab, desmopressin or tranexamic acid) between 2017 and 2019.

Severity level and inhibitory antibodies

As there is no ICD coding for different degrees of haemophilia severity, the severity of haemophilia was estimated using the highest annual consumption of HA-specific medication during the study period. The following thresholds were based on data from the German Haemophilia Registry and expert knowledge:

- Severe: ≥90,000 IU/year of FVIII concentrates or at least one prescription of emicizumab between March and December 2019
- Moderate: ≥40,000 to <90,000 IU/year of FVIII concentrates
- Mild: <40,000 IU/year of FVIII concentrates or at least one prescription of desmopressin/tranexamic acid without FVIII use

Categorisation of Severe HA and additionally having one of the following criteria was defined

to indicate the presence of inhibitory antibodies:

- Administration/prescription of bypassing agents
- At least one prescription of emicizumab between February 2018 and February 2019
- Additional ICD-10-GM D68.31 (Haemorrhagic disorder due to factor VIII antibodies)

Treatment patterns

Treatment patterns were determined by inpatient visits, hospital length of stay (LOS), hospital emergency admissions, outpatient physician visits, diagnostic procedures (laboratory tests and ultrasound), joint surgeries (arthroscopic and arthroplastic surgery), pain therapy, psychotherapy, outpatient physiotherapy, and the quantity of administered/prescribed medication for HA and comorbidities (HIV/HBV/HCV medication, analgesics, antidepressants).

Resource consumption and costs:

Resource consumption and direct costs in the inpatient and outpatient medical sectors were determined based on the number of medical services if HA or HA-related ICD-GM-10 codes, such as bleedings, HIV, HBV, HCV, depression, joint diseases, or cardiovascular diseases, were used. Medical services with no link to the diagnoses were excluded.

- Resource consumption:

  Resource consumption considered the following categories: inpatient visits, hospital length of stay, hospital emergency admissions, outpatient physician visits, diagnostic procedures (laboratory tests and ultrasound), joint surgeries (arthroscopic and arthroplastic surgery), pain therapy, psychotherapy, outpatient physiotherapy, and the quantity of administered/prescribed medication for HA and comorbidities. Inpatient and outpatient medical services were merged in the analysis.

- Direct Costs:

  Direct costs could be identified for the following categories: costs for inpatient medical

care and costs for outpatient medical care (medication, total outpatient physician visits per treatment case, diagnostics, joint surgeries, psychotherapy, pain therapy, and physiotherapy). Inpatient costs per inpatient visit, including all services provided except additional fees, could be calculated using G-DRG data by multiplying the basic DRG value by the relative weight. The costs of physician medical services per treatment case were included based on the accounting data from AOK Bayern. For subgroups, costs such as diagnostic procedures, joint surgeries, pain therapy and psychotherapy were calculated on the basis of reimbursement rates of the EBM catalogue for the relevant calendar quarter. The costs of outpatient medication prescriptions were determined using the mean price per defined daily doses (DDD) for SHIs in Germany. Outpatient physiotherapy costs were calculated on the basis of the mean cost per treatment unit of the "AOK-Bundesverband" in the calendar year the service was provided.

Statistical Analysis

Descriptive data analysis was used. The mean, standard deviation (SD), median, minimum and maximum were calculated for subgroups stratified by severity and age groups.

Statistical analyses were performed using R version 4.1.3 statistical software.

Results

Detailed tables on resource consumption, costs and inhibitors stratified by age and severity can be found in the appendix.

Patient characteristics

Between 2017 and 2019, for 752 male patients, a diagnosis of D66 or D68.31 was documented. One patient was excluded due to missing year of birth. Because of missing HA medication, 494 patients were excluded. The final patient cohort consisted of 257 patients.

Table 1 shows the baseline characteristics of the study population. Of the study cohort, 57 (22.2%) patients were children ≤18 years, 105 (40.9%) were adults ≥19 to ≤44 years and 95 (37.0%) ≥45 years. Severity categorized by FVIII consumption showed 104 (40.5%) patients with mild HA, 17 (6.6%) with moderate HA and 128 (49.8%) with severe HA. There were 8 inhibitor patients (3%). Bleeding was documented in 18 patients (7.0%) during the study period. The most common documented comorbidities were joint disease (n=142, 55.3%) and depression (n=56, 21.8%). Cardiovascular disease were documented for 10 (3.9%) patients.

Table 1. Baseline characteristics of the study population

	Mild (N=104)	Moderate (N=17)	Severe (N=128)	Inhibitor (N=8)	Total (N=257)
Mean-Age years (SD)	40.0 (22.9)	51.2 (24.5)	34.2 (18.5)	37.8 (29.6)	37.8 (21.5)
Age groups, n (%)					
Children ≥ 0 to ≤ 18 years	25 (24.0)	<5	27 (21.1)	<5	57 (22.2)
Adults ≥ 19 to ≤ 44 years	35 (33.7)	<5	65 (50.8)	<5	105 (40.9)
Adults ≥ 45 years	44 (42.3)	12 (70.6)	36 (28.1)	<5	95 (37.0)
Bleedings					
n (%)	<5	<5	12 (9.4)	0 (0.0)	18 (7.0)
Mean (SD)	NA	NA	1.1 (1.6)	NA	0.87 (1.3)
Median [Min; Max]	NA	NA	0.33 [0.33, 5.7]	NA	0.33 [0.33; 5.7]
HIV, n (%)	<5	<5	17 (13.3)	<5	20 (7.8)
HBV, n (%)	10 (9.6)	<5	34 (26.6)	<5	50 (19.5)
HCV, n (%)	<5	<5	12 (9.4)	<5	15 (5.8)
Depression, n (%)	28 (26.9)	3 (17.6)	23 (18.0)	<5	56 (21.8)
Joint disease, n (%)	48 (46.2)	9 (52.9)	79 (61.7)	6 (75.0)	142 (55.3)
- Haemophilic arthropathy	7 (6.7)	<5	35 (27.3)	<5	47 (18.3)
- Osteoarthritis	31 (29.8)	6 (35.3)	51 (39.8)	<5	92 (35.8)
- Joint arthroplasty	10 (9.6)	2 (11.8)	14 (10.9)	<5	28 (10.9)
- Other joint disease	28 (26.9)	5 (29.4)	49 (38.3)	<5	85 (33.1)
Cardiovascular disease, n (%)	5 (4.8)	<5	<5	<5	10 (3.9)
Care level, n (%)	13 (12.5)	<5	10 (7.8)	<5	28 (10.9)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, Min, minimum; Max, maximum; n, number; SD, standard deviation. Results are not given for n<5 for data protection reasons

Resource consumption

A total of 113 (44.0%) patients had an inpatient visit during the analysed period. The mean length of hospital stays ranged from 4.0days in severe patients to 9.7 days in inhibitor patients (see Table 2). Outpatient visits were documented for 251 (97.7%) patients with a mean of 10 visits/year for mild HA, 18 visits/year for moderate HA, 13 visits/year for severe HA and 19 visits/year for inhibitory HA. Ultrasound diagnostics were billed for 46 (17.9%) patients, and laboratory diagnostics were performed on 129 (50.2%) patients. Overall, 77 (30.0%) received outpatient physiotherapy. Psychotherapy was prescribed 81 (31.5%) patients. Of these 30 had mild haemophilia, 6 had moderate haemophilia, 42 had severe haemophilia, and less than 5 had inhibitory haemophilia. The age structure regardless of the severity level shows that 13 (21.0%) patients who received psychotherapy were 18 years or younger, 31 (38.3%) were between 19-44 and 37 (45.7%) were 45 years and older (see Appendix).

Table 2. Total mean resource consumption and medical services per year stratified by severity level

	Mild (N=104)	Moderate (N=17)	Severe (N=128)	Inhibitor (N=8)
Factor replacement therapy (IU)				
n (%)	69 (66.3)	17 (100.0)	128 (100.0)	8 (100.0)
Mean (SD)	3,572 (4,740)	32,113 (14,671)	220,481 (115,589)	1,325,729 (1,337,429)
Median	1.667	26,667	199,833	878,377
[Min; Max]	[167;26,667]	[13,333; 56,000]	[35,000; 531,667]	[350,595; 4,353,355]
Emicizumab (DDD)				
n (%)	0 (0.0)	0 (0.0)	<5	7 (87.5)
Mean (SD)	NA	NA	NA	120 (106)
Median [Min, Max]	NA	NA	NA	80 [28; 332]
Antidepressants (DDD)				
n (%)	15 (14.4)	<5	12 (9.4)	0 (0.0)
Mean (SD)	133 (205)	NA	195 (191)	NA
Median [Min, Max]	27 [2.7; 610]	NA	123 [2.2; 502]	NA
Analgesics (DDD)				
n (%)	77 (74.0)	12 (70.6)	90 (70.3)	8 (100.0)
Mean (SD)	58 (142)	206 (347)	92 (201)	183 (310)
Median [Min; Max]	16 [0.56; 1,007]	28 [7.2; 1,159]	23 [1.1; 1,687]	54 [6.2; 934]
Hospital Length of Stay (LOS) days				
n (%)	41 (39.4)	11 (64.7)	48 (37.5)	5 (62.5)
Mean (SD)	8.7 (14)	8.4 (7.9)	4.0 (5.3)	9.7 (11)
Median [Min; Max]	2.3 [0.33; 73]	5.0 [0.33; 24]	1.7 [0.33; 23]	4.7 [0.67; 26]
Hospital emergency admissions				
n (%)	28 (26.9)	8 (47.1)	26 (20.3)	<5
Mean (SD)	0.52 (0.31)	1.1 (0.85)	0.60 (0.38)	NA
Median [Min; Max]	0.33 [0.33; 1.3]	0.67 [0.33; 2.7]	0.50 [0.33; 1.7]	NA
Outpatient physician visits				
n (%)	101 (97.1)	17 (100.0)	125 (97.7)	8 (100.0)
Mean (SD)	10 (13)	18 (23)	13 (12)	19 (9.3)
Median [Min; Max]	5.3 [0.33; 78]	13 [0.33; 98]	8.7 [0.33; 62]	20 [7.7; 35]
Joint surgeries				

n (%)	6 (5.8)	<5	9 (7.0)	0 (0.0)
Mean (SD)	0.39 (0.14)	NA	0.37 (0.11)	NA
Median [Min; Max]	0.33 [0.33; 0.67]	NA	0.33 [0.33; 0.67]	NA
Psychotherapy				
n (%)	30 (28.8)	6 (35.3)	42 (32.8)	<5
Mean (SD)	5.2 (15)	3.1 (3.2)	2.7 (4.0)	NA
Median [Min; Max]	0.67 [0.33; 79]	1.8 [0.33; 7.5]	0.67 [0.33; 18]	NA
Physiotherapy				
n (%)	20 (19.2)	<5	48 (37.5)	6 (75.0)
Mean (SD)	7.6 (15)	NA	30 (64)	38 (33)
Median [Min; Max]	2.3 [0.33; 58]	NA	7.8 [0.67: 377]	24 [2.0; 81]

n = total number during study period of 3 years; Mean and Median = per year; Results are not given for n<5 for data protection reasons; Min= minimum; Max= maximum; SD=standard deviation; DDD= defined daily dose; IU= International unit; Hospital Length of Stay (LOS)

Direct costs

The total mean annual costs per severe HA categorised patient were 264,666 € (SD 141,302; median: 238,311) (see Figure 1 and Table 3). In children with severe HA, the mean annual cost per patient was 210,267 € (SD 88,801), the mean annual cost per adult (19 to ≤ 44 years) patient with severe HA was 292,925 € (SD 152,276), and in adults (≥ 45 years) with severe HA, it was 254,440 € (SD 142,537). In patients with moderate HA, the mean annual total costs were 36,122 € (SD 24,891), with the most expensive age group being adults (19 to ≤ 44 years) with 50,724€ (SD 29,386). Mild HA patients' mean annual total costs were 4.371€ (SD 7.514), whereas adults (≥ 45 years) were the most expensive with 5,123€ (SD 8,906). HA medication costs accounted for 99.7% in severe HA patients, 90.5% in moderate HA patients and 46.1% in mild HA patients. Inpatient mean annual costs were 4,715€ (SD 8,939) in mild HA patients, 4,292€ (SD 3,970) in moderate HA patients, 2,317€ (SD 2,521) in severe HA patients.

Table 3. Mean direct costs (€) per year of inpatient and outpatient medical care a stratified by severity levels

	Mild (N=104)	Moderate (N=17)	Severe (N=128)	Inhibitor (N=8)
Total costs				
n (%)	104 (100.0)	17 (100.0)	128 (100.0)	8 (100.0)
Mean (SD)	4,371 (7,514)	36,122 (24,891)	264,666 (141,302)	725,441 (697,275)
Median	1,534	34,884	238,311	578,301
[Min; Max]	[23; 54,651]	[6,083; 76,493]	[2,258; 657,647]	[49,021; 2,107,897]
Inpatient Costs*				
n (%)	42 (40.4)	11 (64.7)	50 (39.1)	5 (62.5)
Mean (SD)	4,715 (8,939)	4,292 (3,970)	2,317 (2,521)	3,642 (3,600)
Median	1,958	2,830	1,244	3,710
[Min; Max]	[244; 52,916]	[654;13,447]	[363; 11,827]	[475; 9,386]
Outpatient costs:				
Medication for HA				
n (%)	84 (80.8)	16 (94.1)	127 (99.2)	8 (100.0)
Mean (SD)	2,284 (4,948)	32,029 (24,187)	263,874 (139,733)	720,274 (697,962)
Median	127 [1.6;30,029]	31,849 [31;71,338]	239,657	574,802
[Min; Max]			[22,286; 651,803]	[46,036; 2,107,134]
Medication for HIV, HBV, HCV, antidepressants, analgesics				
n (%)	78 (75.0)	14 (82.4)	96 (75.0)	8 (100.0)
Mean (SD)	225 (1,180)	3,073 (5,584)	1,692 (4,068)	1,639 (3,785)
Median	17 [0.95;10,149]	38 [4.8;14,962]	31 [0.93; 20,173]	58 [9.0; 10,910]
[Min; Max]				
Patient physician visits				
n (%)	102 (98.1)	17 (100.0)	126 (98.4)	8 (100.0)
Mean (SD)	430 (798)	657 (981)	433 (446)	639 (408)
Median	266 [11;7,486]	377 [9.3;4,143]	262 [10; 2,731]	548 [197; 1,468]
[Min; Max]				

n = total number during study period of 3 years; Mean and Median = per year; Min= minimum; Max= maximum; SD=standard deviation * Additional fees (Zusatzentgelte) are not included. Aggregated information on additional costs for the analysed patients is as follows: 12 times >€50,000EUR and 13 times >€ 100,000EUR has been charged."

Inhibitor Patients:

Bypassing FVIII medication mean (n=<5) consumption was 574,417 IU/year (SD 715,548), and bypassing FVIIa mean (n=8) consumption was 901,333 IU/year (SD 1,346,377). The mean total costs were 725,441 €/patient/year (SD 697,275) (see Figure 1). HA medication covered

99.3% (720,274 € [SD 697,962]) of mean annual total costs. The mean inpatient costs were 3,642 €/patient/year (SD 3,600), and the mean outpatient medical services were 639 €/patient/year (SD 408). HA medication covered 99.3% of the mean annual direct costs per patient.

Discussion

In this study, basic evidence was generated on treatment patterns in routine care and the cost of haemophilia A patients from the SHI perspective by using data from Bavarian statutory health insurance. To date, there is only limited current information on haemophilia A inpatient and outpatient treatment patterns, resource consumption, costs and outcomes. HA medication covered 46.1-99.7% of the mean annual direct costs per patient. Depression was documented for 21.8% of patients, and over 30% of HA patients received psychotherapy. Joint disease was documented for 55.3% of patients, and 10 (3.9%) had documented cardiovascular disease.

The number of HA patients with joint diseases in this cohort was higher than in the adult male German population, with a lifetime prevalence for osteoarthritis of 18.1% [16]. Of the 10 patients with CVD, 8 were aged 45 years and older. Therefore, the dataset contained 8.4% of older HA patients with documented CVD, which is less than the German adult male population of similar age (12.3%) [17].

According to this analysis, the mean HA-related direct costs per patient were 1.34 times higher for mild HA, 11 times higher for moderate HA, 81 times higher for severe HA and even 223 times higher for inhibitor patients than the mean annual expenditure per insurant for health care (3,256.45 €) by the AOK Bayern in 2019 [14]. The total HA-specific cost per year was the highest for inhibitory patients 725,441€; (SD 697,275), followed by patients with severe HA, with a mean annual total cost of 246,666 € (SD 141,302). Total costs for patients with moderate haemophilia A were 36,122 € (SD 24,891) and 4,371 € (SD 7,514) in mild HA patients per year. For mild and moderate HA, LOSs were longer than those for severe and inhibitor patients. One reason for this might be the age distribution in the severity groups.-Mild and moderate patients had the highest proportion of patients over 45 years and the highest mean age. The mean annual inpatient costs per patient based on OPS Codes for patients with mild HA were €4,715 (SD 8,939), which was comparable to the costs for patients with moderate HA at €4,292 (SD 3,970). For patient with severe HA, the mean annual per patient inpatient costs based on

the OPS Codes was 2,317€ (SD 2,521). It should be noted that these inpatient costs do not include additional fees ('Zusatzentgelte') for HA medication, as they were not included in the dataset. Based on the AOK side communicated aggregated information, additional fees of about € 1,9 Mio were charged for the underling cohort. 12 times >€50,000 and 13 times >€100,000. It is assumed that most of these additional fees were charged in the context for major procedures in patients with severe hemophilia. Haemophilia-associated outpatient visits and therefore, costs did not differ substantially between severity levels. Yet especially the higher inpatient costs for mild and moderate HA patients as well as the high number of outpatient visits suggest that probably also for services without HA association corresponding ICD Codes where coded and thus appear in the results presented here.

Data on the cost of haemophilia in Germany are scarce. One study analysed haemophilia A and B across all severities and showed mean costs of €194,000[18], whereas another study analysed patients with severe haemophilia A and B and showed mean costs of €319,000 per year per patient[10]. US studies show a wide range of costs. From a median cost per year of €306,530 (exchange rate 06.03.2023) for patients with inhibitors and €92,523 for haemophilia A patients without inhibitors [19] to €383,658 to €519,048 per patient mean total annual health care costs for haemophilia A on FVIII prophylaxis [20]. In Portugal, the yearly cost per patient without inhibitors is €39,654, and it is €302,189 per patient with inhibitors[21]. This overview of the international range of costs shows that costs vary greatly with haemophilia subtype, severity level, inhibitors and the costs for factor concentrates. The data analysis presented here shows updated evidence on treatment pathways, resource use and costs, severity, age, comorbidities and patients with haemophilia A inhibitors, for which there were scarce data for Germany. The HA costs shown here fit well into the overall international cost range. Differences in health care systems and medication costs, especially in FVIII unit costs and dosing regimens, must be taken into account in international comparisons. The following aspects must be taken into consideration for the interpretation of haemophilia-specific outpatient and medication costs

based on the German SHI claims database. The presented drug treatment costs might be slightly overestimated, as SHIs negotiate pharmacy and manufacturer discounts that are not included in the dataset.

With a market share of approximately 40% for AOK-Bayern, this group does represent a large part of the Bavarian population [22]. However, it is unclear whether the results can be extrapolated to the whole population with statutory health insurance due to the given sociostructural characteristics of AOK-Bayern insurances[23]. As the dataset was primarily generated for the purpose of billing, some information is not appropriately documented for epidemiological analyses. The first reading of the SHI data, just using ICD D66 as the filter, resulted in a far too large number of patients and a male/female distribution of almost 50/50, which does not correspond to the biology of haemophilia A. In addition, approximately 500 patients were excluded because they did not receive any HA-specific medication during the observation period of 3 years. It cannot be ruled out that the exclusion criteria may have excluded a number of mild patients who have not needed medication in 3 years. However, referring to the mean factor consumption of the Paul-Ehrlich-Institute, there should not be many patients with haemophilia A who have not received any medication in 3 years. These patient identification problems might be caused by coding deficits. However, these problems can be managed with appropriate expert knowledge of the clinical picture of the target disease and its typical treatment pathways. Therefore, in this study, only patients with a confirmed D.66 and at least one haemophilia A medication prescription were included in the analysis. Medical services were only included in the analysis if they were associated with a diagnosis of HA or an HA-associated comorbidity (indicated by corresponding ICD Codes) to approximate HA costs as closely as possible. The main issue while analysing SHI data for haemophilia A was the lack of severity level classification, as there is currently no differentiated ICD coding of haemophilia A severity levels. As the phenotype and disease burden of haemophilia are strongly related to severity, this is a major limitation. One way to establish an approximate classification

is to assess severity levels according to annual FVIII consumption, as done in this analysis.

This SHI data analysis showed signals such as the increased psychological stress of haemophilia patients. Depression was diagnosed in 21.8% (n=56) of patients, which is considerably higher than the 12-year prevalence in the general male population of 6.1% [24]. Previous studies assessing anxiety and depression using questionnaires reported 38-54% of haemophilia patients with these diseases [25]. It is also interesting to note that on average, even patients with mild and moderate haemophilia (categorised by factor VIII consumption) suffer more frequently from depression than the average nonhaemophilic population in Germany. This data analysis suggests that mild and moderate haemophilia patients do not consume large amounts of FVIII but require other resources and medications to a similar extent as severe haemophilia patients. Further studies have already confirmed that even patients with mild and moderate HA have more limitations in QoL and physical and psychosocial impacts than the general population [26, 27]. To generate more comprehensive evidence additional studies should be carried out on the aforementioned points. German statutory health insurance claims data are a source of information for generating signals and answering a variety of health care related questions. However, it is also important to carefully consider the specifics associated with claims data as described in the method and discussion section. The completion of claims data by more granular clinical data would be crucial to increase the strength of evidence based on claims data and their interpretation. It is also important to note that SHIs vary in the number of their insured patient population and the demographics of their insured individuals, including social status. Therefore, analyses based on data from multiple SHI funds would be the best approach for comprehensive evidence generation, especially when large data sets are needed to analyse even rarer diseases than haemophilia A. However, due to access hurdles e.g. to administrative and regulatory time consuming processes the analyses of data from multiple SHIs is challenging. The need to combine information from different sources, are addressed by decision-makers and health policymakers through the Gesundheitsdatennutzungsgesetz (GDNG), which was signed in

December 2023.The main objective of the law is to facilitate the use of health data. Based on this law the Health Research Data Center “Forschungsdatenzentrum Gesundheit (FDZ)” at the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) is being further developed. It is intended that the FDZ will be able to link pseudonymized health data from different data sources. Nonetheless, understanding the data structures and context of data from different sources remains a prerequisite for generating and interpreting reliable evidence.

Conclusion

Data analyses of SHI data as shown here on the use case haemophilia A provide information on resource consumption and costs. This information can be used as baseline information for subsequent value assessments. Further signals, such as patient burden and psychological stress in mild/moderate and severe haemophilia A patients and the significant number of joint diseases in mild haemophilia patients, are underestimated. These signals should be investigated in subsequent studies. The limitations in severity coding in ICD-10-GM are fundamental in haemophilia A research based on real-world data. The introduction of individual codes for severity levels would improve the analyses considerably. As outcomes (e.g., bleedings) are rarely recorded or the association with haemophilia is not clear, more precise statements, data linkage (e.g. FDZ) or further studies (e.g., surveys) are needed.

Declarations

Ethics approval and consent to participate:

Cooperation Agreement to comply with the provisions of Regulation (EU) 2016/679 (General Data Protection Regulation - "DSGVO") and that data is only used to the extent permitted by data protection law (78 SGB X).

Consent for publication

Not applicable

Availability of data and materials

Data are not publicly available but were made available to the authors via §75 SGB X proposal.

Competing interests

U. Mansmann, K. Berger, V. Kratzer, V. Rölz. A. Schramm, J.Behringer has no relevant financial or nonfinancial interests to disclose. C. Bidlingmaier received Honoraria research grants or advisory boards: Bayer, Biotest, CSL Behring, NovoNordisk, Pfizer, Roche/Chugai, Sanofi, SOBI, Takeda. C. Bidlingmaier is Co-principal Investigator of the German Pediatric Hemophilia research database which is or was supported with research grants by most companies in the field of hemophilia. R. Klamroth received Honoraria, research grants or advisory boards: Bayer, BioMarin, Biotest, CSL Behring, Grifols, NovoNordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI, Takeda.

Funding

Research grants were received from ROCHE Pharma AG and Rudolf-Marx-Stiftung. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data

collection and analysis were performed by Vanessa Kratzer, Verena Rölz. The first draft of the manuscript was written by Vanessa Kratzer, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Figures

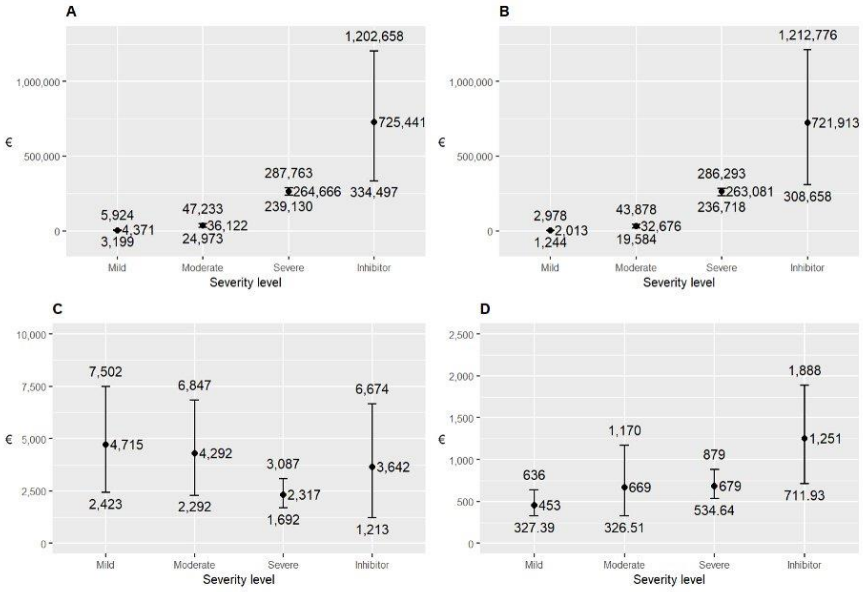

Figure 1: Mean direct (A) total costs, (B) medication costs, (C) inpatient costs and (D) outpatient costs (mean, 95% confidence interval) in €/patient/year for 2017 to 2019 stratified by severity level based on HA-specific medication. N(Mild)= 104; N(Moderate)= 17; N(Severe)= 128 ; N(Inhibitor)= 8

Appendix

Appendix 1 Total mean resource consumption, medical services per year, mean direct costs (€) per year of inpatient and outpatient medical care stratified by severity levels and age

	Mild				Moderate				Severe				Inhibitor*
	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Children ≥ 0 to ≤ 18 years	Adults ≥ 19 to ≤ 44 years	Adults ≥ 45 years	Total	Total
	(N=25)	(N=35)	(N=44)	(N=104)	(N=3)	(N=2)	(N=12)	(N=17)	(N=27)	(N=65)	(N=36)	(N=128)	(N=8)
Factor replacement therapy (IU)													
n (%)	12 (48.0)	22 (62.9)	<5	69 (66.3)	<5	<5	12 (100.0)	17 (100.0)	27 (100.0)	65 (100.0)	36 (100.0)	128 (100.0)	8 (100.0)
Mean (SD)	6,153 (8,228)	3,742 (4,273)	NA	3,572 (4,740)	NA	NA	31,292 (15,095)	32,113 (14,671)	174,526 (75,061)	247,679 (127,235)	205,840 (107,097)	220,481 (115,589)	1,325,729 (1,337,429)
Median [Min, Max]	3,583 [167, 26,667]	2,417 [167, 19,000]	NA	1,667 [167, 26,667]	NA	NA	26,083 [13,333, 56,000]	26,667 [13,333, 56,000]	166,000 [45,167, 371,667]	238,000 [55,000, 516,667]	196,042 [35,000, 531,667]	199,833 [35,000, 531,667]	878,377 [350,595, 4,353,355]
Emicizumab (DDD)													
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<5	0 (0.0)	<5	<5	7 (87.5)
Mean (SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	120 (106)
Median [Min, Max]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	80 [28, 332]
Desmopressin (DDD)													
n (%)	<5	NA	<5	10 (9.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)
Mean (SD)	NA	NA	NA	4.7 (2.3)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Median [Min, Max]	NA	<5	NA	4.2 [1.7, 8.3]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tranexamic acid(DDD)													
n (%)	17 (68.0)	18 (51.4)	15 (34.1)	50 (48.1)	0 (0.0)	0 (0.0)	5 (41.7)	5 (29.4)	9 (33.3)	17 (26.2)	8 (22.2)	34 (26.6)	<5
Mean (SD)	4.7 (3.8)	5.3 (3.1)	5.1 (6.0)	5.1 (4.3)	NA	NA	7.0 (5.9)	7.0 (5.9)	4.8 (3.5)	5.9 (6.3)	7.2 (5.8)	5.9 (5.5)	NA
Median [Min, Max]	4.2 [0.83, 12]	4.6 [0.83, 13]	4.2 [0.42, 25]	4.2 [0.42, 25]	NA	NA	4.2 [1.7, 17]	4.2 [1.7, 17]	4.2 [0.83, 13]	4.2 [0.42, 27]	5.0 [1.7, 17]	4.2 [0.42, 27]	NA

HIV/HBV/HVC medication (DDD)													
n (%)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	<5	13 (36.1)	16 (12.5)	<5
Mean (SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	320 (195)	329 (175)	NA
Median [Min, Max]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	370 [28, 660]	370 [28, 660]	NA
Antidepressants (DDD)													
n (%)	0 (0.0)	6 (17.1)	9 (20.5)	15 (14.4)	0 (0.0)	<5	<5	<5	0 (0.0)	8 (12.3)	<5	12 (9.4)	0 (0.0)
Mean (SD)	NA	50 (84)	188 (246)	133 (205)	NA	NA	NA	NA	NA	136 (162)	NA	195 (191)	NA
Median [Min, Max]	NA	19 [6.0, 222]	74 [2.7, 610]	27 [2.7, 610]	NA	NA	NA	NA	NA	75 [2.2, 467]	NA	123 [2.2, 502]	NA
Analgesics (DDD)													
n (%)	16 (64.0)	25 (71.4)	36 (81.8)	77 (74.0)	<5	0 (0.0)	11 (91.7)	12 (70.6)	22 (81.5)	39 (60.0)	29 (80.6)	90 (70.3)	8 (100.0)
Mean (SD)	9.0 (7.4)	21 (29)	105 (197)	58 (142)	NA	NA	223 (359)	206 (347)	9.9 (8.0)	112 (276)	128 (134)	92 (201)	183 (310)
Median [Min, Max]	4.8 [1.7, 24]	11 [0.56, 130]	33 [1.7, 1,007]	16 [0.56, 1,007]	22 [22, 22]	NA	29 [7.2, 1,159]	28 [7.2, 1,159]	5.8 [2.2, 27]	19 [1.1, 1,687]	75 [2.2, 404]	23 [1.1, 1,687]	54 [6.2, 934]
Inpatient visits													
n (%)	6 (24.0)	11 (31.4)	26 (59.1)	43 (41.3)	<5	<5	8 (66.7)	11 (64.7)	13 (48.1)	23 (35.4)	18 (50.0)	54 (42.2)	5 (62.5)
Mean (SD)	0.39 (0.14)	0.52 (0.35)	0.87 (0.58)	0.71 (0.52)	NA	NA	1.6 (1.2)	1.3 (1.1)	0.79 (0.50)	0.70 (0.44)	0.72 (0.74)	0.73 (0.56)	1.3 (1.6)
Median [Min, Max]	0.33 [0.33, 0.67]	0.33 [0.33, 1.3]	0.67 [0.33, 2.3]	0.67 [0.33, 2.3]	NA	NA	1.2 [0.33, 3.7]	0.67 [0.33, 3.7]	0.67 [0.33, 1.7]	0.67 [0.33, 2.0]	0.33 [0.33, 3.3]	0.67 [0.33, 3.3]	0.67 [0.33, 4.0]
Hospital Length of Stay													
n (%)	6 (24.0)	10 (28.6)	25 (56.8)	41 (39.4)	<5	<5	8 (66.7)	11 (64.7)	13 (48.1)	20 (30.8)	15 (41.7)	48 (37.5)	5 (62.5)
Mean (SD)	1.1 (0.62)	9.7 (23)	10 (11)	8.7 (14)	NA	NA	10 (8.4)	8.4 (7.9)	4.6 (6.4)	2.5 (2.1)	5.3 (7.1)	4.0 (5.3)	9.7 (11)
Median [Min, Max]	1.0 [0.33, 2.0]	1.7 [0.33, 73]	6.3 [0.67, 43]	2.3 [0.33, 73]	NA	NA	7.2 [3.3, 24]	5.0 [0.33, 24]	1.3 [0.67, 21]	1.8 [0.67, 9.3]	1.7 [0.33, 23]	1.7 [0.33, 23]	4.7 [0.67, 26]
Hospital emergency admissions													
n (%)	<5	<5	20 (45.5)	28 (26.9)	<5	0 (0.0)	6 (50.0)	8 (47.1)	9 (33.3)	9 (13.8)	8 (22.2)	26 (20.3)	<5
Mean (SD)	NA	NA	0.58 (0.34)	0.52 (0.31)	NA	NA	1.3 (0.90)	1.1 (0.85)	0.70 (0.42)	0.56 (0.24)	0.54 (0.47)	0.60 (0.38)	NA
Median [Min, Max]	NA	NA	0.33 [0.33, 1.3]	0.33 [0.33, 1.3]	NA	NA	1.0 [0.33, 2.7]	0.67 [0.33, 2.7]	0.67 [0.33, 1.7]	0.67 [0.33, 1.0]	0.33 [0.33, 1.7]	0.50 [0.33, 1.7]	NA
Outpatient physician visit													

n (%)	24 (96.0)	34 (97.1)	43 (97.7)	101 (97.1)	<5	<5	12 (100.0)	17 (100.0)	27 (100.0)	63 (96.9)	35 (97.2)	125 (97.7)	8 (100.0)
Mean (SD)	6.1 (8.1)	8.0 (14)	14 (12)	10 (13)	NA	NA	24 (26)	18 (23)	11 (8.3)	11 (11)	18 (15)	13 (12)	19 (9.3)
Median [Min, Max]	4.7 [0.67, 41]	3.3 [0.33, 78]	9.7 [0.33, 62]	5.3 [0.33, 78]	NA	NA	16 [0.33, 98]	13 [0.33, 98]	8.0 [1.3, 33]	8.3 [0.33, 48]	16 [1.0, 62]	8.7 [0.33, 62]	20 [7.7, 35]
Ultrasound diagnostics													
n (%)	<5	<5	12 (27.3)	17 (16.3)	<5	0 (0.0)	5 (41.7)	6 (35.3)	<5	13 (20.0)	<5	20 (15.6)	<5
Mean (SD)	NA	NA	0.89 (1.0)	0.78 (0.87)	NA	NA	0.80 (0.65)	0.72 (0.61)	NA	0.46 (0.22)	NA	0.52 (0.40)	NA
Median [Min, Max]	NA	NA	0.67 [0.33, 4.0]	0.67 [0.33, 4.0]	NA	NA	0.33 [0.33, 1.7]	0.33 [0.33, 1.7]	NA	0.33 [0.33, 1.0]	NA	0.33 [0.33, 2.0]	NA
Laboratory analyses													
n (%)	14 (56.0)	15 (42.9)	31 (70.5)	60 (57.7)	<5	<5	6 (50.0)	8 (47.1)	14 (51.9)	28 (43.1)	16 (44.4)	58 (45.3)	<5
Mean (SD)	3.6 (2.7)	3.6 (5.3)	4.3 (5.4)	4.0 (4.8)	NA	NA	6.6 (8.4)	6.4 (7.2)	5.5 (7.8)	4.1 (4.0)	9.6 (8.6)	5.9 (6.8)	NA
Median [Min, Max]	3.3 [0.67, 9.7]	2.0 [0.33, 21]	1.7 [0.33, 23]	2.2 [0.33, 23]	NA	NA	3.3 [0.33, 23]	3.8 [0.33, 23]	1.7 [0.33, 26]	3.0 [0.33, 12]	7.8 [0.33, 33]	4.2 [0.33, 33]	NA
Joint surgeries													
n (%)	0 (0.0)	<5	5 (11.4)	6 (5.8)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	5 (7.7)	<5	9 (7.0)	0 (0.0)
Mean (SD)	NA	NA	0.40 (0.15)	0.39 (0.14)	NA	NA	NA	NA	NA	0.40 (0.15)	NA	0.37 (0.11)	NA
Median [Min, Max]	NA	NA	0.33 [0.33, 0.67]	0.33 [0.33, 0.67]	NA	NA	NA	NA	NA	0.33 [0.33, 0.67]	NA	0.33 [0.33, 0.67]	NA
Psychotherapy													
n (%)	7 (28.0)	6 (17.1)	17 (38.6)	30 (28.8)	0 (0.0)	<5	5 (41.7)	6 (35.3)	5 (18.5)	23 (35.4)	14 (38.9)	42 (32.8)	<5
Mean (SD)	0.48 (0.18)	17 (31)	2.9 (4.6)	5.2 (15)	NA	NA	3.6 (3.3)	3.1 (3.2)	1.3 (1.9)	2.3 (3.1)	3.8 (5.6)	2.7 (4.0)	NA
Median [Min, Max]	0.33 [0.33, 0.67]	1.3 [0.33, 79]	1.0 [0.33, 19]	0.67 [0.33, 79]	NA	NA	2.7 [0.33, 7.5]	1.8 [0.33, 7.5]	0.67 [0.33, 4.7]	0.67 [0.33, 11]	1.0 [0.33, 18]	0.67 [0.33, 18]	NA
Pain therapy													
n (%)	0 (0.0)	<5	6 (13.6)	7 (6.7)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	<5	<5	6 (4.7)	0 (0.0)
Mean (SD)	NA	NA	1.1 (0.78)	2.1 (2.7)	NA	NA	NA	NA	NA	NA	NA	3.7 (5.3)	NA
Median [Min, Max]	NA	NA	1.0 [0.33, 2.3]	1.0 [0.33, 8.0]	NA	NA	NA	NA	NA	NA	NA	1.0 [0.33, 14]	NA
Outpatient physiotherapy													
n (%)	<5	5 (14.3)	14 (31.8)	20 (19.2)	0 (0.0)	<5	<5	<5	5 (18.5)	23 (35.4)	20 (55.6)	48 (37.5)	6 (75.0)
Mean (SD)	NA	3.1 (2.7)	9.7 (18)	7.6 (15)	NA	NA	NA	NA	12 (9.8)	16 (27)	51 (93)	30 (64)	38 (33)
Median [Min, Max]	NA	2.7 [0.67, 7.0]	2.3 [0.67, 58]	2.3 [0.33, 58]	NA	NA	NA	NA	10 [4.0, 29]	4.0 [0.67, 87]	19 [2.0, 377]	7.8 [0.67,	24 [2.0, 81]

												377]	
Total costs													
n (%)	25 (100.0)	35 (100.0)	44 (100.0)	104 (100.0)	<5	<5	12 (100.0)	17 (100.0)	27 (100.0)	65 (100.0)	36 (100.0)	128 (100.0)	8 (100.0)
Mean (SD)	3,567 (7,409)	3,999 (5,535)	5,123 (8,906)	4,371 (7,514)	NA	NA	35,039 (27,428)	36,122 (24,891)	210,267 (88,801)	292,925 (152,276)	254,440 (142,537)	264,666 (141,302)	725,441 (697,275)
Median [Min, Max]	282 [39, 31,165]	1,203 [27, 20,790]	2,803 [23, 54,651]	1,534 [23, 54,651]	NA	NA	28,781 [6,083, 76,493]	34,884 [6,083, 76,493]	198,717 [91,337, 432,145]	286,629 [61,515, 652,110]	238,623 [2,258, 657,647]	238,311 [2,258, 657,647]	578,301 [49,021, 2,107,897]
Inpatient medical care													
n (%)	6 (24.0)	10 (28.6)	26 (59.1)	42 (40.4)	<5	<5	8 (66.7)	11 (64.7)	13 (48.1)	21 (32.3)	16 (44.4)	50 (39.1)	5 (62.5)
Mean (SD)	978 (485)	3,207 (5,543)	6,157 (10,654)	4,715 (8,939)	NA	NA	5,473 (4,069)	4,292 (3,970)	2,617 (3,473)	1,891 (1,462)	2,633 (2,796)	2,317 (2,521)	3,642 (3,600)
Median [Min, Max]	1,007 [383, 1,542]	865 [269, 18,104]	2,495 [244, 52,916]	1,958 [244, 52,916]	NA	NA	4,252 [1,570, 13,447]	2,830 [654, 13,447]	1,187 [530, 11,827]	1,274 [629, 6,704]	1,499 [363, 10,046]	1,244 [363, 11,827]	3,710 [475, 9,386]
HA medication													
n (%)	25 (100.0)	31 (88.6)	28 (63.6)	84 (80.8)	<5	<5	11 (91.7)	16 (94.1)	27 (100.0)	65 (100.0)	35 (97.2)	127 (99.2)	8 (100.0)
Mean (SD)	3,079 (7,227)	2,899 (4,707)	891 (1,091)	2,284 (4,948)	NA	NA	29,382 (26,162)	32,029 (24,187)	208,621 (87,493)	291,318 (151,748)	255,529 (138,645)	263,874 (139,733)	720,274 (697,962)
Median [Min, Max]	32 [6.3, 30,029]	692 [6.3, 20,111]	680 [1.6, 4,069]	127 [1.6, 30,029]	NA	NA	14,323 [31, 61,873]	31,849 [31, 71,338]	197,511 [90,329, 423,189]	286,246 [61,482, 651,803]	242,452 [22,286, 651,791]	239,657 [22,286, 651,803]	574,802 [46,036, 2,107,134]
Medication for HIV, HBV, HCV, antidepressants, analgesics													
n (%)	16 (64.0)	25 (71.4)	37 (84.1)	78 (75.0)	<5	<5	12 (100.0)	14 (82.4)	22 (81.5)	41 (63.1)	33 (91.7)	96 (75.0)	8 (100.0)
Mean (SD)	7.9 (6.5)	27 (55)	454 (1,696)	225 (1,180)	NA	NA	3,584 (5,904)	3,073 (5,584)	8.9 (6.9)	772 (2,408)	3,958 (5,793)	1,692 (4,068)	1,639 (3,785)
Median [Min, Max]	4.9 [0.98, 19]	12 [1.4, 282]	46 [0.95, 10,149]	17 [0.95, 10,149]	NA	NA	69 [4.8, 14,962]	38 [4.8, 14,962]	8.5 [1.5, 26]	34 [0.93, 10,829]	237 [2.0, 20,173]	31 [0.93, 20,173]	58 [9.0, 10,910]
Outpatient physician visits, total													
n (%)	25 (100.0)	34 (97.1)	43 (97.7)	102 (98.1)	<5	<5	12 (100.0)	17 (100.0)	27 (100.0)	64 (98.5)	35 (97.2)	126 (98.4)	8 (100.0)
Mean (SD)	248 (380)	500 (1,272)	480 (387)	430 (798)	NA	NA	857 (1,111)	657 (981)	329 (244)	373 (406)	624 (572)	433 (446)	639 (408)
Median [Min, Max]	142 [11,	199 [13,	417 [17,	266 [11, 7,486]	NA	NA	507 [9.3,	377 [9.3,	254 [31,	238 [10,	473 [32,	262 [10,	548 [197,

	1,909]	7,486]	1,794]				4,143]	4,143]	1,193]	1,985]	2,731]	2,731]	1,468]
Outpatient diagnostic procedures (ultrasound, laboratory analyses)													
n (%)	14 (56.0)	19 (54.3)	32 (72.7)	65 (62.5)	<5	<5	9 (75.0)	11 (64.7)	16 (59.3)	34 (52.3)	17 (47.2)	67 (52.3)	5 (62.5)
Mean (SD)	122 (208)	102 (175)	70 (157)	91 (173)	NA	NA	144 (255)	134 (231)	107 (165)	133 (210)	275 (241)	163 (216)	80 (167)
Median [Min, Max]	77 [0.40, 824]	45 [1.8, 583]	9.1 [0.20, 680]	25 [0.20, 824]	NA	NA	14 [2.8, 714]	29 [2.8, 714]	31 [2.8, 573]	39 [0.20, 721]	213 [0.40, 756]	51 [0.20, 756]	2.8 [0.20, 378]
Outpatient joint surgeries													
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Median [Min, Max]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outpatient pain therapy													
n (%)	0 (0.0)	<5	5 (11.4)	6 (5.8)	0 (0.0)	0 (0.0)	<5	<5	0 (0.0)	<5	<5	<5	0 (0.0)
Mean (SD)	NA	NA	24 (22)	50 (67)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Median [Min, Max]	NA	NA	19 [3.9, 61]	21 [3.9, 181]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outpatient psychotherapy													
n (%)	7 (28.0)	6 (17.1)	17 (38.6)	30 (28.8)	0 (0.0)	<5	5 (41.7)	6 (35.3)	5 (18.5)	23 (35.4)	14 (38.9)	42 (32.8)	<5
Mean (SD)	3.9 (2.2)	1,371 (2,849)	86 (232)	324 (1,309)	NA	NA	36 (44)	31 (41)	17 (30)	63 (161)	122 (295)	78 (207)	NA
Median [Min, Max]	5.4 [0.99, 6.3]	38 [5.4, 7,130]	16 [5.3, 981]	11 [0.99, 7,130]	NA	NA	12 [5.3, 109]	11 [5.3, 109]	5.5 [1.0, 71]	11 [5.3, 779]	16 [5.3, 1,102]	11 [1.0, 1,102]	NA
Outpatient physiotherapy													
n (%)	<5	5 (14.3)	14 (31.8)	20 (19.2)	0 (0.0)	<5	<5	<5	5 (18.5)	23 (35.4)	20 (55.6)	48 (37.5)	6 (75.0)
Mean (SD)	NA	69 (65)	209 (379)	164 (323)	NA	NA	NA	NA	268 (200)	350 (569)	1,088 (1,986)	649 (1,375)	816 (694)
Median [Min, Max]	NA	57 [13, 169]	53 [13, 1,223]	53 [6.4, 1,223]	NA	NA	NA	NA	233 [96, 606]	82 [13, 1,872]	404 [43, 8,115]	174 [13, 8,115]	529 [43, 1,718]

*Inhibitor patients are only indicated in total, since the group sizes are <5 and therefore may not be indicated for data protection reasons.

6. Paper II

Transparency on Platelet Transfusion in Routine Cancer Care: The Key for Optimal Blood Usage?

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Oncology Research and Treatment (ISSN 2296-5270)

(2022) 45 (6): 336–343.

DOI: 10.1159/000522659

Journal impact factor: 2.4

Rank by Journal Impact Factor: Oncology 195/ 242 (21.8%)

Oncology Research and Treatment

Research Article

Oncol Res Treat 2022;45:336–342
DOI: 10.1159/000522659

Received: September 28, 2021
Accepted: February 14, 2022
Published online: February 16, 2022

Transparency on Platelet Transfusion in Routine Cancer Care: The Key for Optimal Blood Usage?

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Keywords
Pathogen-inactivated platelets · Apheresis platelets · Haematology/Oncology patients · Platelet transfusion

Abstract

Introduction: In Germany, up to 75% of platelet concentrates (PCs) are administered to haematological and oncological patients. Only limited transparency exists on the characteristics of haematological/oncological patients receiving PC transfusions, treatment patterns, and guideline adherence in daily clinical routine care. This information would be key for managing platelet supply and optimal platelet usage strategies. This study aimed to analyse data from clinical routine transfusions to fill the aforementioned information gaps and to create an inventory as a blueprint for electronic data capturing systems that allow simplified, recurring analyses. ***Methods:*** Prospective open-label, single-centre, observational study in a German tertiary teaching haematological/oncological setting. All inpatients who received any transfusion of PCs (pathogen-inactivated or conventional) in routine use over a period of 3 months (March 2015–May 2015) were consecutively included. Except for age (≥18 years), no exclusion criteria were applied. For guideline adherence, the *Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives* – amended edition 2020 were used. An inventory blueprint was created through a narrative literature review and the data collected in this study. ***Results:*** Ninety-four patients received 942 PCs. The mean (±SD) age was 54.6 (±13.9) years, 68% were male and 86% were diagnosed with a haematological disease. Thirteen patients received 42% of all transfused PCs. The mean ± SD number of transfused PC per patient was 10.81 ± 9.24. Five (0.5% per transfusion) minor adverse events were documented. Approximately 19% of PCs were not administered according to existing guidelines. The mean transfusion interval was 1.71 ± 1.1 days, and the mean increment was 12.62 ± 14.7 G/L. The inventory showed which platelet transfusion-specific data should be documented for answering questions in terms of quality, effectiveness, and management of PC transfusions. ***Conclusions:*** Platelet transfusions in a haematological/oncological setting are highly individual in terms of the total number of transfusions and transfusion intervals. The majority of all PC transfusions were given to only a small group of patients. Continuous, structured real-world data collection/evaluation and benchmarking with data from more centres seems essential in determining specific needs in this vulnerable patient group, assessing the quality of transfusion practices, determining effectiveness, and anticipating future demand for platelets and a sustainable blood supply. So far, not all relevant data are collected routinely. The advancing digitalization of health systems offers opportunities to collect and link data and thus make them more accessible and evaluable.

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Introduction

Haemato-oncological patients are a vulnerable patient group overall and especially with respect to platelet transfusion. Platelet transfusions are essential to prevent and treat bleeding in thrombocytopenic, immunosuppressed patients. The risk of bleeding not only depends on the platelet count but also on the underlying disease, recent haemorrhage, and complications such as sepsis, uraemia, anaemia, necrosis in tumour tissue, and defects in coagulation function [1]. Given these factors and prophylactic transfusion therapy, this patient group receives approximately 75% of all transfused platelet concentrates (PCs) in Germany [2]. PCs are a scarce, valuable resource, as their provision depends on donations. Demographic developments will cause a decrease of blood donors, which could lead to bottlenecks in the supply of blood products in the future [3–5]. Consequently, the appropriate use of PCs for the right patient at the right time is indispensable.

Although PC transfusions are part of clinical routine, certain points need to be discussed. A discussion is ongoing about the different PC types (apheresis vs. pool, plasma-suspended vs. additive solution-suspended, ABO-matched transfusions, pathogen-inactivated [PI] vs. non-inactivated PCs) and their impact on safety, effectiveness, and costs. Clinical discussions on PC transfusion practice (e.g., platelet thresholds, prophylactic vs. therapeutic transfusion; diagnosis and handling of PC refractoriness) are also continuing [6–8]. A possible solution to some of these dialogues could be PI platelets, which have a longer shelf life and fewer transfusion reactions [9, 10]. However, ethics, cost, and feasibility due to the absence of a homogeneous patient population [11] are challenges for randomized studies in this area. Real-world data and advancing digitalization could be an opportunity to improve the quality of evidence [12] in transfusion medicine.

Basic updated information for the abovementioned discussions are patient demographics, clinical characteristics, number of transfusions per patient, transfusion intervals, and guideline adherences. So far, no German study has investigated the data generally collected in routine care and the relevant information for evidence-based discussions on PC supply, optimal blood usage, and health economic considerations. Therefore, this prospective, single-centre observational study evaluated whether data documented in routine inpatient cancer care will provide information to fill the aforementioned information gaps, including PI platelets in mixed transfusion as an example. Based on these real-world data, guideline adherence of PC transfusion was also evaluated. Subsequently, we further sought to create an inventory of essential information as a blueprint for the creation of electronic data collection systems for future comprehensive analyses, which will make it possible to drastically simplify recurring tasks and analyses.

Table 1. Patient characteristics

	All patients (n = 94)
Sex, *n* (%)	
Female	30 (31.9)
Male	64 (68.1)
Age, years, mean (range, SD)	54.6 (22–90, 13.9)
HSCT, *n* (%)	
Allogenic	27 (28.7)
Autologous	15 (16)
Solid tumours, *n* (%)	5 (5.3)
Hematologic malignancies, *n* (%)	82 (87.2)
AML	32 (34)
ALL	12 (12.8)
Lymphoma	21 (22.3)
Indolent lymphoma	16 (17.1)
Mature T/NK cell L	2 (2.1)
Hodgkin-lymphoma	1 (1.1)
Other lymphoma	2 (2.1)
Monocytic leukemia	2 (2.1)
Multiple myeloma	12 (12.8)
MDS	2 (2.1)
OMF	1 (1.1)
Others, *n* (%)	7 (7.4)

HSCT, haematopoietic stem-cell transplantation; AML, acute myelogenous leukaemia; ALL, acute lymphoblastic leukaemia; MDS, myelodysplastic syndrome; OMF, osteomyelofibrosis.

Materials and Methods

Study Design and Patients

This prospective, non-interventional, single-centre observational study included consecutive haematology/oncology inpatients who received at least one transfusion of PCs in routine clinical care in a German teaching hospital in Munich. The study followed a naturalistic design, and routine clinical platelet transfusion was documented consecutively for all patients over a period of 3 months (March 2015–May 2015). Patients younger than 18 years old were excluded. Except for age, no exclusion criteria were applied.

PC Transfusion

All PCs transfused in this study were derived from apheresis collection. For transfusion, either conventional (CONV) platelet products or PI products (INTERCEPT® Cerus, Concord, CA, USA) were used on a routine clinical basis. Only PCs of blood groups O and A were used. CONV platelet components were obtained from the Department of Transfusion Medicine, Cell Therapeutics and Haemostaseology of the Ludwig-Maximilians-Universität Hospital of Munich. Exclusively single-donor apheresis platelets were produced according to standard operating procedures and applied after 30 Gy of gamma irradiation. Intercept-treated PI apheresis concentrates were obtained from Haema AG, Leipzig, Germany.

Treatment

The indication for platelet transfusions during the observational period was determined by the patient's treating physician. Physicians had no influence on the PC type. The type of PC provided was randomly assigned by the Department of Transfusion Medicine.

Table 2. List of patients and characteristics of the 75% percentile of total number of transfusions per patient

Patient	Age	Gender (f/m)	Disease	Death (Y/N)	Total PC number	SCT N/auto/allo
1	57	m	ALL	N	44	Allo
2	35	m	AML	N	38	Allo
3	58	m	ALL	Y	36	N
4	49	m	ALL	N	36	Allo
5	22	m	Hepatocellular carcinoma	Y	34	Auto
6	47	f	Indolent lymphoma	Y	33	Allo
7	54	f	Monocyte leukaemia	N	33	Allo
8	45	m	MDS	Y	30	Allo
9	45	f	AML	Y	28	Allo
10	65	m	AML	Y	28	N
11	61	m	Indolent lymphoma	Y	26	Auto
12	32	m	ALL	N	26	Allo

ALL, acute lymphoblastic leukaemia; AML, acute myelogenous leukaemia; MDS, myelodysplastic syndrome.

Adverse Events

Following each transfusion of platelet components, patients were monitored (symptoms, severity, and causality) for adverse events (AEs). The investigator recorded any AEs with an onset within 24 h following the start of the transfusion.

Guideline Adherence

Guideline adherence was evaluated using the *Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives* – amended edition 2020 and the risk factors for bleeding complications of the German Medical Association (Bundesärztekammer [BÄK]). Transfusions with a platelet count of more than 10 G/L (Group C patients with acute platelet dysfunction due to chemotherapy include patients with thrombocytopenia in the context of disease or therapy without concomitant risk of bleeding) [13] before PC transfusion. No documentation of at least one of the risk factors for bleeding complications of the BÄK was considered not guideline adherent.

Data Collection

The Blood Centre records and patient medical records served as data sources. All PC transfusion-related treatment patterns, outcomes, and AEs, as well as intervals between transfusions, were recorded. Data were captured electronically on an electronic case report form in the electronic data capture system and in SPSS. Patient confidentiality was protected using coded patient identification numbers assigned by the electronic data capture system. The data were analysed by descriptive statistical methods.

Inventory

For the inventory of data collection for recurring analyses, a list of all relevant variables to quality, effectiveness, and management of PC transfusion was derived from the literature and the real-world data collected for this study.

Results

Patients

During the observation period, 94 patients received at least one platelet transfusion. The population was predominantly male (68.1% vs. 31.9%). The mean age was 54.6 years (22–90 years). The largest subpopulation with respect to primary diagnosis suffered from haematopoietic and lymphatic malignant neoplasms (82 patients; 87.2%). Forty-two patients underwent haematopoietic stem-cell transplantation (SCT) during the observation period, of which 27 received allogeneic SCT and 15 autologous SCT (see Table 1).

Platelet Transfusion

The analysis included 942 platelet transfusions, of which 476 (50.5%) were CONV PCs, and 466 (49.5%) were PI PCs. The mean ± SD number of transfused PC per patient was 10.81 ± 9.24 (median, 8; range, 1–44) PCs during the study period. The results show that the distribution of PCs among patients was not uniform. Fifty-five patients received between 1 and 7 transfusions during the observation period and a total of 178 transfusions or 18.9% of the total number of transfusions. Eighteen patients received 8–15 PCs (total, 209 PCs; 22.2%), whereas 9 patients received 16–23 (163 PCs; 17.3%). A small subgroup of 12 patients received more than 23 PCs each (see Table 2). In total, this subgroup received 392 PCs or 41.6% of all transfused PCs (see Fig. 1). Figure 2 shows the transfusion patterns are highly individual in terms of the number of PCs and transfusion intervals but no repetitive pattern for any patient group. The inventory (see Table 3) shows which PC transfusion-specific data need to be collected routinely for scientific evaluations. Of the total of 942 PCs transfused, 174 (18.47%) were not transfused according to the guidelines. This means that 18.47% of the PC transfusions were given at a platelet value above 10 G/L, and no risk factors (according to BÄK) were documented.

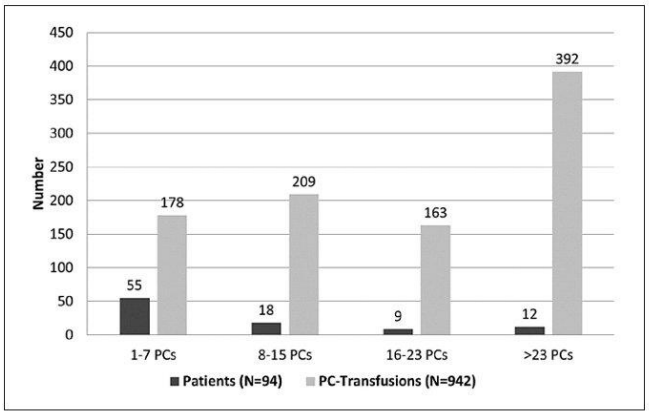

Fig. 1. Distribution of PC transfusions among patients. Patients (dark grey) were grouped according to the total number of PCs transfused during the observation period. The total number of PCs transfused to the respective group (light grey).

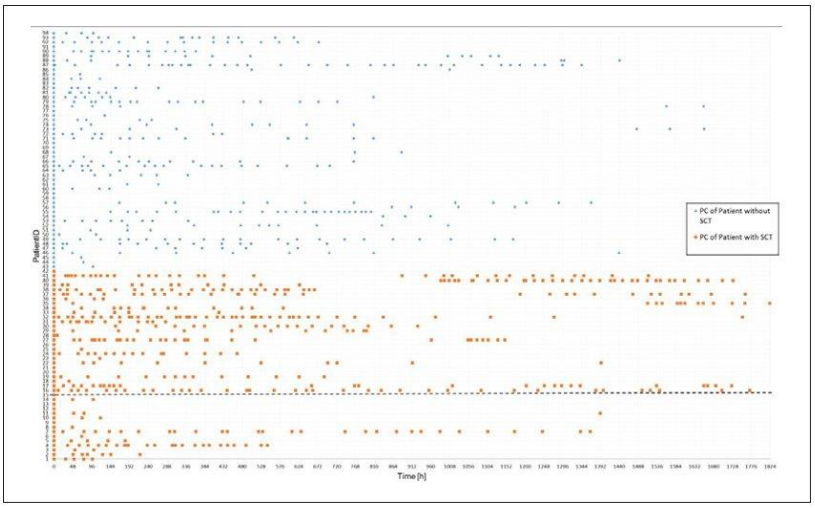

Fig. 2. Transfusion intervals in hours for each patient. Each dot indicates a platelet transfusion. PC transfusions of patients who did not receive SCT (blue) and PC of patients who received SCT (orange). The dashed black line divides the SCT group into patients who received autologous or allogeneic SCTs. Patients 1–15 underwent autologous SCT, whereas patients 16–42 received allogeneic SCT.

Interval/Increment/AEs

The mean ± SD transfusion interval was 1.65 ± 1.1 days, PI PC transfusion interval was 1.64 ± 1.1 days, and CONV PC was 1.65 ± 1.2 days. The mean increment was 12,624 ± 14.7 G/L. CONV platelet increment was 14.01 ± 15.8 G/L, and PI PCs showed an increment of 11.2 ± 13.3 G/L. Five (0.5% per transfusion and per patient) minor AEs were documented.

Bleeding

Bleeding that required PC transfusion was documented for 3 patients (76 PCs). In 2 patients (50 PCs), bleeding was documented before and after PC transfusion, whereas bleeding occurred before PC transfusion in the third patient (26 PCs).

Table 3. Inventory blueprint

Patient characteristics	
Illness	ICD CODE_____
Gender	Female ☐ Male ☐
Height	_____cm
Weight	_____kg
Surgeries	Yes☐ No☐ NA☐
Comorbidities (mucositis)	Yes☐ No☐ NA☐
Platelet levels before transf.	____G/L
Treatment	
SCT	Yes☐ if so: Allo☐ Auto ☐ No☐ NA☐
Chemo	Yes☐ No☐ NA☐
Medical history	
Previous reactions on PC	Yes☐ if so, which:_____ No☐ NA☐
Pregnancies	Yes☐ No☐ NA☐
Transfusion specific	
Time and date of transfusion	Time:__:__ Date_____
Platelets level 1 h after transfusion	____G/L
Platelets level 24 h after transfusion	____G/L
PC type	_____ (e.g., Apheresis, PI, etc.)
Age of PC	____days
PC dose	_____$\times 10^9$
Antibody screening	Yes☐ No☐ NA☐
Refractoriness documented	Yes☐ No☐ NA☐
Fever shortly after transfer	Yes☐:____°C No☐ NA☐
Risk factors*	
Clinical signs of haemorrhage	Yes☐ No☐ NA☐
Fever above 38°C	Yes☐:____°C No☐ NA☐
Infections	Yes☐ No☐ NA☐
Complications (graft-versus-host disease [GvHD])	Yes☐ No☐ NA☐
Leukocytosis	Yes☐ No☐ NA☐
Plasmatic (pro-haemorrhagic) coagulopathy	Yes☐ No☐ NA☐
Steep platelet count drop	Yes☐ No☐ NA☐
Pre-existing areas of necrosis	Yes☐ No☐ NA☐
Transfusion reaction	Yes☐ if so, which:_____ No☐ NA☐

* According to Table 2.5.1.4 of *Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives* – amended edition 2020 ("risk factors for the occurrence of bleeding complications in thrombocytopenia").

Discussion/Conclusion

This paper describes the transfusion patterns observed in this study. A total of 942 PCs were transfused to 94 patients over a period of 3 months, and 82% of patients suffered from a haematological malignancy. A previous retrospective study in this centre has shown almost the same number of transfused platelets, a comparable number of patients and demographic, and clinical characteristics within a 3-month period [14]. The data are also in line with other German studies [15, 16], but information on real-life transfusion patterns has not yet been established for Germany. A small number of patients received 42% of all PCs. Most patients who underwent transfusion received an allogeneic SCT, which matched the higher number of PC for patients with allogeneic SCT in the literature [17]. Furthermore, the data show that transfusion in this vulnerable patient group is highly individual due to the heterogeneity of the patient's clinical characteristics and subsequent needs.

Safety

Platelet transfusion is safe, and only a limited number of non-severe transfusion reactions have been documented. Available studies showed similar percentages per transfusion and per patient AEs [18]. However, the distribution of PC in the patient population showed that some patients get particularly many PCs. Due to the high number of transfusions, these patients have a higher risk of infection from contaminated PCs. One way to further reduce this risk for such a vulnerable group is to use PI PCs [19]. Our results showed no evidence of intolerability in the mixed administration of PI and CONV PCs. However, this was not the primary research question of our study; thus, a more detailed investigation may be needed.

Effectiveness

As our data demonstrate, the absolute count increment measurement and the transfusion intervals of the PI PC compared with the CONV PC differ only minimally. Similar results were also reported in other European studies [16, 20]. Many studies show that PI PCs provide benefits to patients through an extended shelf life [9], which, unfortunately, is not yet approved in Germany. Fewer AEs, including allergic transfusion reactions, naturally improved safety against transfusion-transmitted infections, especially bacterial, and viral infections. However, from a societal perspective and taking into account the globalization of infectious diseases, the saving of donors, a longer shelf life, and a more stable supply of blood products are important considerations [21].

Guideline Adherence

The increasing complexity and number of treatment options in oncological and haematological diseases and supportive therapy demand for easy-to-apply and high-quality guidelines [22]. In order to support the treating physicians in the indication for a transfusion and for the economic use of PCs, evidence-based guidelines, such as the *Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives* – amended edition 2020, have been established [13]. In pursuing the goal of platelet conservation, the guidelines must be adopted in everyday clinical practice. In this study, more than 80% of the transfusions were adherent to the guidelines. Still, 175 PCs were not given according to the guidelines and without documented reasons. A similar study was carried out in the same haematology/oncology ward in 2012. During these 3 months in 2012, 81% of nearly 1,000 PC transfusions were guidelines-compliant. Non-adherence to guidelines can have multiple reasons, like time shortage, ignorance, experience, lack of applicability, and confusing guidelines design [23]. The fact that the results of non-adherent PC transfusions did not change in a period of 3 years should invite a closer examination of the reasons for non-adherence in order to maximize conserved use in PC administration.

Data Collection

The sparse data on bleeding suggest that a structured data collection in daily clinical transfusion routine using the stated inventory, for example, is needed. This inventory could serve as a blueprint for digital clinical software applications. In the future, patient data and variables, such as correct count increment or a steep drop in thrombocytes, could be calculated automatically. Such structured data collection will help clarify the highly individual transfusion events observed in this study. Such data would increase transparency and thereby the possibility of routine scientific data analysis, which enables evidence-based decisions on blood management, routine evaluations, and benchmarking both internally and between hospitals.

This study has shown that a small number of patients received most PC transfusions in a haematology/oncology department of a tertiary centre. The PC transfusion process is highly individual. Furthermore, our study highlights the challenges of platelet transfusion practice in clinical care, such as heterogeneity in the patient population. A guideline adherence of 80% indicates room for improvement. Since not all relevant data were collected routinely, the inventory created in this study, which contained all variables needed for scientific evaluations, could serve as a blueprint for future software-based data collection systems. Digitalization of the healthcare system and of electronic patient records could lead to a more structured data collection and create the possibility of linking to different data resources to address the aforementioned issues and for optimal use and transfusion management.

Statement of Ethics

This non-interventional observational survey was conducted in accordance with the applicable European regulations governing clinical investigations of medical devices (Council Directive 93/42/EEC, EN ISO 14155:2011) and the ICH Guideline for Good Clinical Practice E6 (CPMP/ICH/135/95). The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Medical Department Ludwig-Maximilians-University Munich (reference number: 034-15 MUC-HV00093). Written informed consent was obtained from participants to participate in the study.

Conflict of Interest Statement

K. Berger receives fees for participation in advisory boards from Cerus Corporation. H. Ostermann receives fees for talks and participation in advisory boards from Cerus Corporation. R. Henschler, V. Kratzer, C. Rieger, and G. Wittmann declare no conflicts of interests.

Funding Sources

This study was sponsored by research grants from Cerus™ Europe B.V., MH Amersfoort, The Netherlands and the Rudolf Marx-Stiftung, Ludwig-Maximilians-University, Munich.

Author Contributions

Karin Berger has been involved in the development of the conceptional study design and protocol development, ethical review submission, data collection, data analyses, and writing the draft as well the final version of the manuscript. Reinhard Henschler has been involved in designing the study, interpretation of the results. He contributed to the final version of the publication. Vanessa Kratzer has been involved in data collection, data analyses, drafting, and writing

up the final version of the publication. Christina Rieger supported as a clinician on the ward data collection in routine clinical care and contributed to the final version of the publication. Georg Wittmann has been involved in the design the study, interpretation of the results, and contributed to the final version of the publication. Helmut Ostermann has been the medical advisor of the study. He conceived and designed the study, critically reviewed the results, and contributed to the draft and final version of the publication.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from Karin Berger.

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Danksagung

Ich möchte mich an dieser Stelle bei allen bedanken, die mich während meiner Dissertation unterstützt haben.

Zunächst möchte ich mich bei meiner Betreuerin/Mentorin PD Karin Berger-Thürmel bedanken. Sie hat mich während des gesamten Prozesses kontinuierlich angeleitet, unterstützt und ermutigt. Ihre fachliche Expertise und ihre motivierenden Worte haben mich durch die Höhen und Tiefen dieser Dissertation begleitet.

Für die wertvollen Anregungen und die konstruktive Kritik meiner Mitbetreuer, Professor Helmut Ostermann und Professor Ulrich Mansmann, möchte ich mich ebenfalls herzlich bedanken.

Nicht zuletzt gilt meinem Verlobten Alessandro Colonna sowie meinen Eltern und engen Freunden ein ganz besonderer Dank für ihre stets liebevolle Unterstützung.