Incidence of graft-versus-host-disease in Germany

Scheid, Christof; Kudernatsch, Robert; Eckart, Marie; Libutzki, Berit; Feig, Chiara; Mahlich, Joerg

Published in:
Journal of Public Health

DOI:
10.1007/s10389-022-01736-w

Publication date:
2023

Journal of Public Health (2023) 31:1609–1620
https://doi.org/10.1007/s10389-022-01736-w

ORIGINAL ARTICLE

Incidence of graft-versus-host-disease in Germany: evidence from health care claims data

Christof Scheid[1] · Robert Kudernatsch[2] · Marie Eckart[2] · Berit Libutzki[3,4] · Chiara Feig[3] · Jörg Mahlich[5,6]

Received: 21 February 2022 / Accepted: 18 July 2022 / Published online: 8 August 2022

Abstract

Objective Graft-versus-host disease (GvHD) can occur as an immunological response after an allogeneic hematopoietic cell transplantation (allo-HCT). Due to the rarity of the disease, German epidemiological data are scarce. Moreover, not all cases of GvHD are properly documented in daily practice. Against this background, this study aims at providing new estimates on the incidence of GvHD in Germany.

Methods Based on a large German claims database, a retrospective longitudinal analysis was conducted over a 6-year period. Patients were selected that received allo-HCT between 2014 and 2015. Follow up period was 3 years. To adjust the incidence for undocumented cases, steroid prescriptions after an allo-HCT was used as an approximation. Based on both documented and undocumented GvHD patients, incidence rates were calculated for the population of the German statutory health insurance (SHI).

Results Among 4,395,540 eligible database enrollees 3,737,317 were continuously insured. Among them we identified 297 patients who received an allo-HCT between 2014 and 2015. Depending on the extrapolation method, this corresponds to a yearly incidence of 2415–2840 for the SHI population. Of the 297 patients, 134 (i.e., 45.1%) developed a documented GvHD within three years after the transplantation which translates into a yearly incidence of 1125—1300 GvHD patients. Based on the medication regimens, we identified 83 additional patients with an suspected GvHD without a documented diagnosis. Extrapolated to the German SHI population, our estimates suggest that the annual incidence of GvHD, including undocumented cases, could be as high as 1822—2105, which is higher than previously reported.

Conclusion More patients may be affected by GvHD in Germany than reported. Appropriate adjustments need to be made when utilizing administrative data.

Keywords Graft vs host disease · Epidemiology · Germany · Database analysis · Claims data

✉ Jörg Mahlich
Joerg.mahlich@gmail.com

[1] Department I of Internal Medicine, Center for Integrated Oncology (CIO), University Hospital Cologne, Kerpener Str. 62, 50937 Cologne, Germany

[2] Janssen-Cilag GmbH, Johnson & Johnson Platz 1, 41470 Neuss, Germany

[3] HGC Healthcare Consultants GmbH, Graf-Adolf-Platz 15, 40213 Düsseldorf, Germany

[4] Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[5] Miltenyi Biomedicine, Friedrich-Ebert-Straße 68, 51429 Bergisch Gladbach, Germany

[6] DICE, Heinrich-Heine-University Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is an increasingly used curative modality for hematological malignancies (Harris et al. 2013). Graft-versus-host-disease (GvHD) is a common complication after allo-HCT and is associated with a mortality rate of 50% (Barton-Burke et al. 2008). GvHD can be subdivided into acute GvHD (aGvHD) and chronic GvHD (cGvHD). aGvHD usually manifests within 100 days following allo HCT but may also occur later ("late-onset") (Zeiser et al. 2019). It primarily affects the skin (rash/dermatitis), liver (hepatitis/jaundice), and gastrointestinal tract (abdominal pain/diarrhea) (Jacobsohn et al. 2007). aGvHD is staged (I–IV) and graded (0–4) by the extent of organ involvement (Zeiser et al. 2019). In comparison, the onset of cGvHD normally begins ≥ 100 days after

allo-HCT either de novo or following an aGvHD (Toubai et al. 2008). It can be divided into mild, moderate, and severe forms (Wolff et al. 2019) and has a wide range of clinical manifestations, including the skin, mucosa, muscles/joints, gastrointestinal tract, and lungs (Flowers and Martin 2015).

Although yearly transplant activities are accessible through the German registry for stem cell transplants (DRST) (DRST 2018), data on incidence of graft-versus-host-disease (GvHD) is limited. The current German consensus guideline on GvHD estimates that the risk of developing cGvHD after allo-HCT is around 50%, while it is between 30–60% for aGvHD (Wolff et al. 2019; Zeiser et al. 2019). The individual risk for aGvHD depends on several patient, donor, and transplant-related factors (Ferrara et al. 2009; Jamil and Mineishi 2015; Zeiser and Blazar 2017). The incidence of cGvHD is rising due to the increase in age, the increasing use of unrelated donors, of dose-reduced conditioning, and the use of blood stem cells (Lee et al. 2003). According to the consensus guidelines on aGvHD and cGvHD, immunosuppressive corticosteroid treatment plays an important role as first-line therapy. In mild cases, topical corticosteroids may be used. The combination of corticosteroids with other immunosuppressive agents should be considered to reduce the long term use of corticosteroids (Wolff et al. 2010; Martin et al. 2012; Mielcarek et al. 2015). In moderate or severe cases, systemic glucocorticoids are typically needed. For preventive measures, a combination of calcineurin inhibitors (CNI) and other immunosuppressants given from the time of transplantation is recommended. Corticosteroids are generally not considered appropriate for prophylaxis of GVHD (Wolff et al. 2019).

Although GvHD is a frequent immunological complication after an allo-HCT, the number of transplants is relatively small, making GvHD a rare disease with limited data on epidemiology. Moreover, in Germany coding in clinical practice is dominated by the main disease and related procedures, and therefore accurate coding of GvHD may be surrounded by uncertainties. Hence, it can be assumed that there are undocumented cases, and that the actual burden of disease for GvHD is higher than reported.

Based on claims data of the German statutory health insurance (SHI) system, the objective of this study was to evaluate the incidence of GvHD for both aGvHD and cGvHD after an initial allo-HCT considering both documented and potentially undocumented cases.

Methods

Data source and sample size

This retrospective longitudinal study was based on an anonymized database (Institute for Applied Health Research Berlin GmbH, InGef) from the German SHI claims data system. The German SHI was established in 1883 by chancellor Bismarck and was the first social health insurance system in the world (Busse et al. 2017). Currently, it covers around 88% of the German population. The InGef database provides information on ~4.9 million member-records from over 53 nationwide sick funds and resembles the overall German population in terms of morbidity, mortality, hospitalization, and drug usage (Andersohn and Walker 2016). The database has been used for health care research covering various indications (Kossack et al. 2018; Gothe et al. 2022; Sewerin et al. 2021, 2022; Mahlich et al. 2021). This analysis was conducted over a six-year period (2013–2018). The analysis was in line with the German guidelines of the "Good Practice of Secondary Data Analysis" (Swart et al. 2015). Moreover, we applied the items of the STROSA-checklist (STandardized Reporting Of Secondary data Analyses) (Swart and Schmitt 2014).

Ethical approval, data protection, and data availability

The analysis did not involve any decisions regarding interventions or the omission of interventions. Moreover, all individual patient data are anonymized in the research database to comply with German data protection regulations. Patient numbers below five were not reported. Accordingly, institutional review board/ethical approval and informed consent of the individuals were not required.

To conduct this study, the authors had access to the aggregated, anonymized healthcare data as per pre-defined study protocol. Due to the sensitivity of the data and data protection regulations, the analysis datasets of the current study will not be shared or stored at a public repository. Analysis datasets can be assessed upon request at the Institute for Applied Health Research Berlin (InGef), if required.

Patient selection for documented and undocumented cases

According to the German modification of the International Classification of Procedures in Medicine (ICPM), the index was defined as the first day of hospitalization with Operation and Procedure classification System (OPS) coding, of transfusion of peripheral hematopoietic stem cells (8–805.2—8–805.5 OPS codes) or transplantation of hematopoietic stem cells from the bone marrow (5–411.2—5–411.5 OPS codes) in 2014–2015 (two years pooled). Only continuously insured patients were included in the analysis to avoid loss to follow-up. Patients with initial allo-HCT were identified as having no record of transplantation and no documentation of GvHD diagnosis 365 days (baseline) before index. Those patients were individually observed over three years for

development of GvHD after allo-HCT and were identified using the International Statistical Classification of Diseases, 10th revision, German Modification (ICD-10-GM) of T86* (failure and rejection of transplanted organs and tissues) as at least one confirmed outpatient or inpatient (main or secondary) diagnosis, see Table 1. Steroid prescription is not a requirement to count as documented case (based on ICD-10). Since patients can develop both aGvHD and cGvHD, patients with documentation of both diseases were assigned into both subgroups (including initial documented diagnoses and diagnoses documented in the follow-up period).

As corticosteroids are typically used for initial treatment of GvHD according to German guidelines and other literature (Flowers and Martin 2015), the epidemiology of GvHD beyond documentation of the diagnosis (estimated number) was based on the outpatient medication use of topical and/or systemic corticosteroids. The division into topical and systemic corticosteroids was made using the anatomical therapeutic chemical classification (ATC), listed in Table 2. To distinguish between undocumented acute and chronic patients, the time to first corticosteroid prescription after allo-HCT was calculated and patients were differentiated according to time to steroid prescription (first prescription < 100 days after allo-HCT or first prescription ≥ 100 days after allo-HCT). The former category likely corresponds with an aGvHD and the latter with cGvHD as this distinction in timing post-transplant (< 100 days versus ≥ 100) has been suggested based on the current German guideline on GvHD rather than clinical manifestation, which is not accessible in the claims database used.

To account for a progressive onset of cGvHD after documented de novo aGvHD, both the time of first corticosteroid prescription and the length of corticosteroid prescription were examined. Patients with only documented aGvHD diagnosis who initially received first prescription of corticosteroids either (1) ≥ 100 days after allo-HCT or (2) < 100 days after allo-HCT and continued prescriptions for > 6 months, were subsequently assigned to the cGvHD group. Patients with only documented cGvHD were analyzed for prescriptions < 100 days after allo-HCT to be additionally assigned to the aGvHD group.

Three patient groups with allo-HCT were analyzed to determine estimated number by identifying additional patients with potentially undocumented GvHD cases:

(1) Patients with initial documented unspecific GvHD coding (T86.00 and/or T86.09 ICD-10-GM),

Table 1 Identification of patients with GvHD diagnosis based on the German modified International Statistical Classification of Diseases, 10th revision (ICD-10-GM)

	ICD-10-GM classification according to the German Institute for Medical Documentation and Information (DIMDI)
T86.–	Failure and rejection of transplanted organs and tissues
T86.00	Hematopoietic stem cell transplant failure
T86.01	Acute GvHD, grades I and II
T86.02	Acute GvHD, grades III and IV
T86.05	Chronic GvHD, mild
T86.06[1]	Chronic GvHD, moderate
T86.07[2]	Chronic GvHD, severe
T86.09	GvHD, unspecified

[1]T86.06: T86.03 ICD-10 code before 2016

[2]T86.07: T86.04 ICD-10 code before 2016

Table 2 Topical and systemic corticosteroids for outpatient treatment of GvHD

	Corticosteroids	
	Prescriptions based on anatomical therapeutic chemical (ATC) level in the outpatient setting and according to DIMDI	
Systemic corticosteroids	Betamethasone Cortisone Dexamethasone Hydrocortisone Methylprednisolone Prednisolone Prednisone Triamcinolone	H02 Corticosteroids for systemic use, pure
Topical corticosteroids	Betamethasone Budesonid Cortisone Dexamethasone Hydrocortisone Methylprednisolone Prednisolone Prednisone Triamcinolone	A01C Corticosteroids for oral local treatment A07EA Corticosteroids with local effects D07 Corticosteroids, dermatological preparations R01AD Corticosteroid S01 Ophthalmics S03 Ophthalmological and otological preparations

(2) Patients with initial documented specific acute (T86.01-T86.02 ICD-10-GM) or chronic (T86.05-T86.07 ICD-10-GM) GvHD coding, and
(3) Patients without GvHD documentation, see Table 3.

Hence, undocumented cases were searched for in these three groups via steroid prescription pattern.

Our basic assumption is that patients do not receive steroids in the outpatient setting for reasons other than GvHD. However, in some cases, corticosteroids may potentially be used as part of a therapy for relapse of the malignant disease. To correct for this potential bias in the estimated GvHD rate, patients with at least one prescription of a defined relapse medication (Table 4) within 6 months after first prescription of predefined corticosteroids were excluded from the estimated number. This applied to only one patient. This small correction factor highlights that GvHD case identification by using steroid prescription patterns is a sound approach. Based on the described patient selection (Table 3), the aim was to determine epidemiologic data and subsequently provide an epidemiological range from the minimum (documented patient counts with GvHD) to the maximum (sum of documented patients counts and estimated number of GvHD). We extrapolated our results to the entire German SHI population. For this, two factors were calculated based on the mean number of the German SHI population of 71,490,069 (2014–2018) and the number of insured persons in the database (lower range; 4,318,401), which is age- and gender-adjusted, versus the number of continuously insured persons in the database (upper range; 3,887,554) (Table 5). The number of insured persons in Germany was extracted from the KM6 statistics of the Federal Ministry of Health (Bundesministerium für Gesundheit 2022).

Table 3 Criteria for assigning patients after allo-HCT into the estimated number of undocumented cases

			Patient selection for estimated number
Assign to:			Interim steps for identifying potential undocumented GvHD patients after allo-HCT
GvHD (total)		Undocumented GvHD	Number of patients without any documented GvHD diagnosis in FU total[2] and started first steroid prescription either < 100 days or ≥ 100 days
Acute GvHD	(1)	Undocumented GvHD	Number of patients without any documented GvHD diagnosis in FU total and started first steroid prescription < 100 days
	(2)	Unspecific GvHD Dx[1] (T86.00 + T86.09)	Number of patients only documented with unspecific GvHD (no specific acute GvHD diagnosis coded in FU total). Out of these, the number of patients started first steroid prescription < 100 days
	(3)	Chronic GvHD Dx (T86.05–T86.07)[2]	Number of patients with documented chronic GvHD and without documented acute GvHD Dx in FU total. Out of these, the number of patients started first prescription < 100 days
Chronic GvHD	(4)	Undocumented GvHD Dx	Number of patients without any documented GvHD diagnosis in FU total and started first steroid prescription ≥ 100 days
	(5)	Undocumented GvHD Dx	Out of (1), patients with steroid use after > 100 days and for longer than 6 months
	(6)	Unspecific GvHD Dx (T86.00 + T86.09)	Number of patients only documented with unspecific GvHD (no specific chronic GvHD diagnosis coded in FU total). Out of these, the number of patients started first steroid prescription ≥ 100 days
	(7)	Unspecific GvHD Dx (T86.00 + T86.01)	Number of patients only documented with unspecific GvHD (no specific chronic GvHD diagnosis coded in FU total). Out of these, the number of patients started first steroid prescription < 100 days and continued steroid prescriptions longer than 6 months (after 100 days)
	(8)	Acute GvHD Dx (T86.01–T86.02)	Number of patients with documented acute GvHD and without documented chronic GvHD Dx in FU total. Out of these, the number of patients started first prescription ≥ 100 days
	(9)	Acute GvHD Dx (T86.01–T86.02)	Number of patients only documented with acute GvHD (no specific chronic GvHD diagnosis coded in FU total). Out of these, the number of patients started first steroid prescription < 100 days and continued steroid prescriptions longer than 6 months (after 100 days)

[1]Dx = coded/documented ICD-10-GM diagnosis; [2]FU total refers to the follow-up period of three years

[2]T86.06: T86.03 ICD-10 code before 2016; T86.07: T86.04 ICD-10 code before 2016

Table 4 Examination of relapse medication (for relapse) to correct the estimated number of GvHD

	Relapse medication (recurrence)		
	Prescriptions based on both anatomical therapeutic chemical (ATC) level in the outpatient setting and operation and procedure classification system (OPS) level in the inpatient setting according to DIMDI		
Relapse medication		ATC	OPS
	Carfilzomib	L01XX45	6–008.9
	Daratumumab	L01XC24	6–009.a
	Lenalidomide	L04AX04	6–003.g
	Elotuzumab	L01XC23	6–009.d
	Panobinostat	L01XX42	6–009.2
	Ixazomib	L01XX50	6–00a.9
	Melphalan	L01AA03	./
	Pomalidomide	L04AX06	6–007.a
	Doxorubicin	L01DB01	6–001.b or 6–002.8
	Vincristine	L01CA02	./
	Etoposide	L01CB01	./
	Cytarabine (Ara-C)	L01BC01	6–002.a
	Cisplatin	L01XA01	./
	Daunorubicin	L01DB02	./
	Blinatumomab	L01XC19	6–008.7
	Gemcitabine	L01BC05	6–001.1
	Vinblastine	L01CA01	./
	Vinorelbine	L01CA04	./
	Bleomycin	L01DC01	./
	Procarbazin	L01XB01	./
	Carmustin	L01AD01	6–003.3
	Vindesin	L01CA03	./
	Carboplatin	L01XA02	./
	Ifosfamid	L01AA06	./
	Asparaginase	L01XX02	6–003.n or 6–003.p or 6–003.r

Statistical analysis and outcomes

Descriptive statistics were used to analyze patient characteristics and summarized in a patient flow. Time in months from allo-HCT until first documented GvHD diagnosis (acute and chronic) was examined. Additionally, time in months from allo-HCT until first prescription of predefined topical and/or systemic corticosteroids for both documented and undocumented GvHD patients was analyzed. The outcome parameters, namely time-to-GvHD-diagnosis and time-to-steroid prescriptions based on Kaplan–Meier estimator, were evaluated to verify the comparability of documented and undocumented patients. For the time-to-steroid prescription analyses, logrank tests (pairwise) were performed between the group of documented and undocumented GvHD patients to show that there is no difference between the cohorts in the probability of an event (prescription of steroid). The aim was to confirm comparability between the two patient cohorts and to show that the estimation of undocumented GvHD cases and correction mechanism is reasonable. Calculation of probabilities was performed per month for the total observation of three years.

Results

Patient flow and characteristics of allo-HCT patients

Out of 4,395,540 insured persons in 2014–2015, 297 patients with initial allo-HCT were identified in the database, which corresponds to 2451–2840 patients extrapolated to the German SHI population per year (Fig. 1). This annual incidence of allo-HCT is comparable to the number of cases registered in the DRST (2996 in 2014 and 3052 in 2015) (Beelen and Mytilieneos 2015, 2016). Gender distribution showed a higher share of male patients (64%). Patients were on average 50.6 years old (SD 16.7), which is comparable to the median age of 50.09 estimated for Germany according to the DRST (Beelen and Mytilieneos 2019).

Documented GvHD diagnosis

Out of the 297 patients receiving an allo-HCT, 134 patients (i.e., 45%) developed GvHD (T86* ICD-10-GM) after allo-HCT within the follow-up period of 3 years (2016–2018). Among those, most patients (40%, n = 120) developed initial GvHD within the first year. The initial

Table 5 Epidemiological ranges of GvHD population (including documented cases and estimated number) and extrapolation to the German population

	Epidemiological ranges (incidence)				
	GvHD within 3 years of follow-up after allo-HCT				
	Documented GvHD coding[1] *Lower range* [†] *(extrapolation per year)*	Documented unspecific GvHD coding and steroid Rx[2]	Documented specific GvHD coding and steroid Rx[3]	Undocumented GvHD and steroid Rx[4]	*Upper range* [†] *(extrapolation per year)*
GvHD total	*134*[5] *(1125—1300)*	./	./	83	*217 (1822 – 2105)*
Acute GvHD	*90 (756–873)*	9	14	60	*173 (1452- 1678)*
Chronic GvHD	*71 (596–689)*	10 (4 + 6)	27 (21 + 6)	57 (23 + 34)	*165 (1385 –1601)*

[1]Patients with documented acute and/or chronic GvHD based on ICD-10-GM as well as patients with documented unspecific GvHD coding and later in FU total specific acute or chronic GvHD coding

[2]Patients with documented unspecific GvHD coding and started first steroid prescription either < 100 days or ≥ 100 days after allo-HCT. And patients continuing with steroid prescription after > 100 days and for longer than 6 months

[3]Patients with documented acute or chronic GvHD coding and estimated undocumented acute or chronic GvHD based on corticosteroids

[2,3] is only included when considering aGvHD and cGvHD separately

[4]Patients with no coding of GvHD (none) and started first steroid prescription either < 100 days or ≥ 100 days after allo-HCT

[5] Number of GvHD total excludes double count of patients with aGvHD and cGvHD

[†]For the extrapolation of patients with allo-HCT two factors are calculated based on the mean number of German members of the statutory health insurance of 71,490,069 (2014–2018) and the number of insured persons in the database (lower range; n = 4,395,540) versus the number of continuously insured persons in the database (upper range; n = 3,737,317). Factors range from 16.79 (71,490,069/4,395,540) to 19.40 (71,490,069/3,737,317)

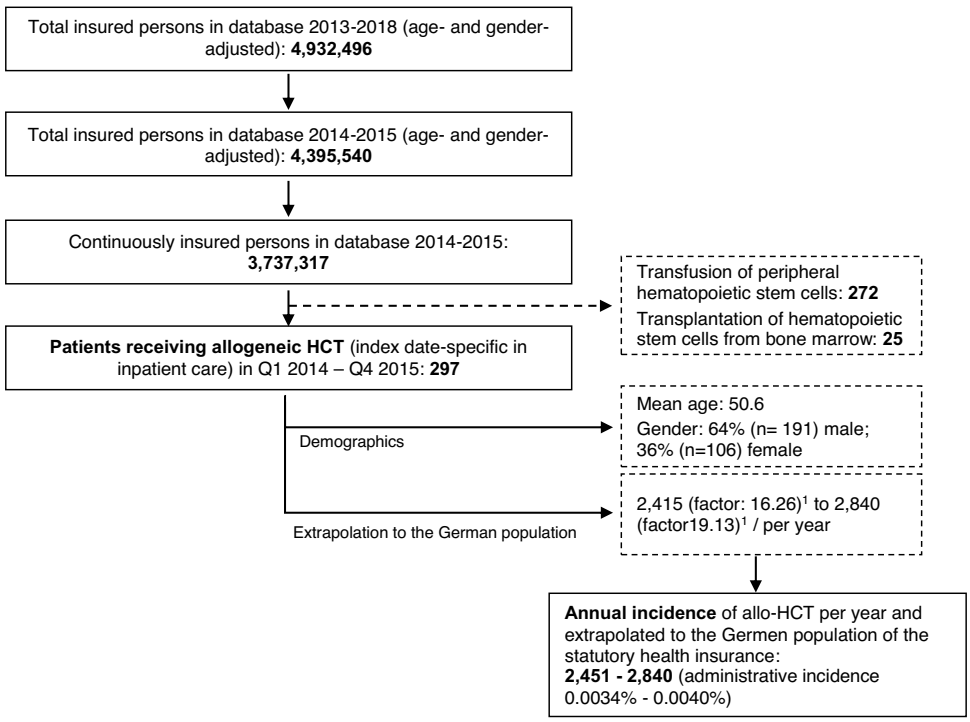

Fig. 1 Flow chart of study population with initial allo-HCT and extrapolated to the German population

diagnosis was documented 6.9 months (median) after allo-HCT (≥ 100 days) for cGvHD, and 1.8 months (median) after allo-HCT (< 100 days) for aGvHD.

Documented GvHD diagnosis was considered as the lower boundary of the epidemiological range, meaning that all patients with a respective diagnosis independent of a previous other GvHD diagnosis were considered. Out of the 134 patients with GvHD (total), 90 patients developed aGvHD (n = 78 with initial aGvHD, n = 8 with aGvHD after or simultaneously to cGvHD and n = 4 with aGvHD after unspecific GvHD diagnosis). In total, 71 patients with cGvHD in follow-up were identified (n = 30 with initial cGvHD, n = 34 with cGvHD after or simultaneously to aGvHD and n = 7 with cGvHD after unspecific GvHD diagnosis).

Undocumented GvHD diagnosis (estimated number)

Among the unspecific GvHD coded patient group (Table 3), nine patients were assigned to the aGvHD type and ten to the cGvHD type. Of those ten patients, six patients initiated steroids ≥ 100 days after an allo-HCT, and four started steroid treatment < 100 days after an allo-HCT and continued for more than 6 months. Fourteen patients with only documented cGvHD diagnosis were identified by prescriptions < 100 days after allo-HCT to be additionally assigned to the aGvHD group. Twenty-one patients with only documented aGvHD diagnosis who still received corticosteroids after ≥ 100 days after allo-HCT and continued prescriptions for > 6 months were subsequently assigned to the cGvHD group. In addition, six patients with only documented aGvHD diagnosis received their first prescription ≥ 100 days after an allo-HCT and therefore were also assigned to cGvHD.

Eighty-four patients without documented GvHD diagnosis received at least one prescription of topical and/or systemic corticosteroids (Table 2) within the 3-year follow-up. One patient was excluded due to relapse medication (Table 4); thus, 83 patients were assigned to the estimated number (28% after allo-HCT) that showed no documented GvHD coding.

Out of these 83 patients, 72% (n = 60) received their first prescription < 100 days after an allo-HCT, and hence were assigned to aGvHD; 28% (n = 23) received their first prescription ≥ 100 days after an allo-HCT, and hence were assigned to cGvHD. Of those 60 aGvHD patients that received their first prescription < 100 days after allo-HCT, 34 patients continued treatment with corticosteroids and had at least one prescription after 100 days for longer than 6 months and were therefore assigned to cGvHD as well.

Epidemiological ranges

Epidemiological ranges including extrapolation to the German population were computed, see Table 5. Documented GvHD diagnoses were used as the lower range. The sum of documented GvHD patient counts and estimated number resulted in the upper range. Considering both documented (GvHD total n = 134; excluding double count of patients with aGvHD and cGvHD) and undocumented (n = 83) patients, the share of patients developing GvHD after allo-HCT within three follow-up years was at 73%.

Patient characteristics

The share of male patients is comparable between documented GvHD at 60% (n = 81 out of 134) and undocumented GvHD at 69% (n = 57 out of 83) (Table 6). Regarding aGvHD type, the share of male patients is 13% higher for the estimated number (70%) compared to the documented aGvHD patients (57%), whereas the share of chronic male patients is only 4% higher for the estimated number (62%) compared to documented patients (58%). This male predominance aligns with the literature (Beelen and Mytilieneos 2019). Age stratification (< 12 years vs. ≥ 12 to < 18 years vs. ≥ 18 years) reveals that the majority of GvHD patients (n = 202; 93%) were 18 years or older (≥ 18 years). Among those patients being 18 years or older, 62% (n = 126 out of 202) were documented and 38% (n = 76 out of 202) were undocumented. Only 7% (n = 15) of the GvHD patients (total) were younger than 18 years, with a mean age for GvHD patients (total) of 50.7 years (SD 16.4). Overall, patient characteristics are comparable between documented GvHD patients and the estimated number.

Comparability between documented and undocumented cases

Kaplan–Meier curves were plotted, showing the time-to-steroid prescription and time-to-diagnosis-documentation of aGvHD (Fig. 2). Over the first two months of follow-up, the prescription patterns for documented and undocumented aGvHD patients were nearly identical. The median time to diagnosis was 1.8 months showing that most patients with documented aGvHD were diagnosed within 100 days after allo-HCT.

Figure 3 shows the time-to-steroid prescription and time-to-diagnosis-documentation of cGvHD. Time-to-steroid prescription patterns after 6 months are comparable for the documented (23%) and undocumented (28%) cGvHD patient groups. Over 3 years of follow-up, Fig. 3 illustrates that the documented cGvHD patient group is not completely congruent with its estimated number, particularly in comparison to the acute type.

Table 6 Characteristics of patients with GvHD (including documented cases and estimated number) differentiated between acute and chronic subgroup

Characteristics of patients with GvHD			
GvHD (total)	Documented GvHD	Estimated number of GvHD	Total
Number of patients, n (database)	134	83	217
Age (SD)	50.9 (16.4)	50.4 (16.7)	50.7 (16.4)
N < 12 years	< 5	< 5	7 (3%)
N ≥ 12 to < 18 years	< 5	< 5	8 (4%)
N ≥ 18 years	126 (94%)	76 (92%)	202 (93%)
Gender, n (%)			
Male	81 (60%)	57 (69%)	138 (64%)
Female	53 (40%)	26 (31%)	79 (36%)
Acute GvHD	Documented acute GvHD	Estimated number of acute GvHD	Total
Number of patients, n (database)	90	83	173
Age (SD)	51.4 (17.2)	50.0 (15.2)	50.8 (16.2)
N < 12 years	< 5	< 5	< 5
N ≥ 12 to < 18 years	< 5	< 5	8 (5%)
N ≥ 18 years	83 (92%)	78 (94%)	161 (93%)
Gender, n (%)			
Male	51 (57%)	58 (70%)	109 (63%)
Female	39 (43%)	25 (30%)	64 (37%)
Chronic GvHD	Documented chronic GvHD	Estimated number of chronic GvHD	Total
Number of patients, n (database)	71	94	165
Age (SD)	52.6 (13.3)	50.2 (16.5)	51.2 (15.2)
N < 12 years	0	< 5	< 5
N ≥ 12 to < 18 years	< 5	< 5	< 5
N ≥ 18 years	69 (97%)	88 (94%)	157 (95%)
Gender, n (%)			
Male	41 (58%)	58 (62%)	99 (60%)
Female	30 (42%)	36 (38%)	66 (40%)

Discussion

With this study following a comprehensive explorative analysis of claims data, we are able to present real-world-evidence for GvHD after allo-HCT in Germany. This retrospective longitudinal study provides insights into the epidemiology and related burden of disease of patients with GvHD who are difficult to access and have not been previously investigated by German health claims data. This method can be used as a best-practice example to collect epidemiological data on rare diseases with a potentially high number of undocumented cases. With regard to the lack of data on the incidence of GvHD and subgroups in Germany, these first insights into patient numbers are especially valuable.

The current consensus guideline on GvHD estimates that the risk of developing GvHD after allo-HCT is 50% for cGvHD and 30–60% for aGvHD (Wolff et al. 2019; Zeiser et al. 2019). This study reveals that by considering documented cGvHD patients only, the share of patients developing cGvHD within three follow-up years after allo-HCT is only 24% (n = 71 out of 297). However, by adding the undocumented cases, the share of patients developing cGvHD after allo-HCT increases to 56% (n = 165 out of 297), which is even higher than previously described. When it comes to the extrapolated incidence, older studies reported 500 new patients per year for Germany (Wolff et al. 2011), which is even slightly lower than the annual number of documented cases in our analysis (596–689). Including the potentially undocumented patients results in an estimated incidence of 1385—1601, which would be more than three times that previously reported. One explanation is that increasing incidence rates for cGVHD are observed all across Europe, which can be attributed to increasing patient age and the increasing use of mismatched donors (Arai et al. 2015).

Similarly, this study identifies that only 30% (n = 90 out of 297) of documented patients developed aGvHD after allo-HCT; however, considering the estimated number, this study identifies a share of 58%, which is at the upper end of previous estimations.

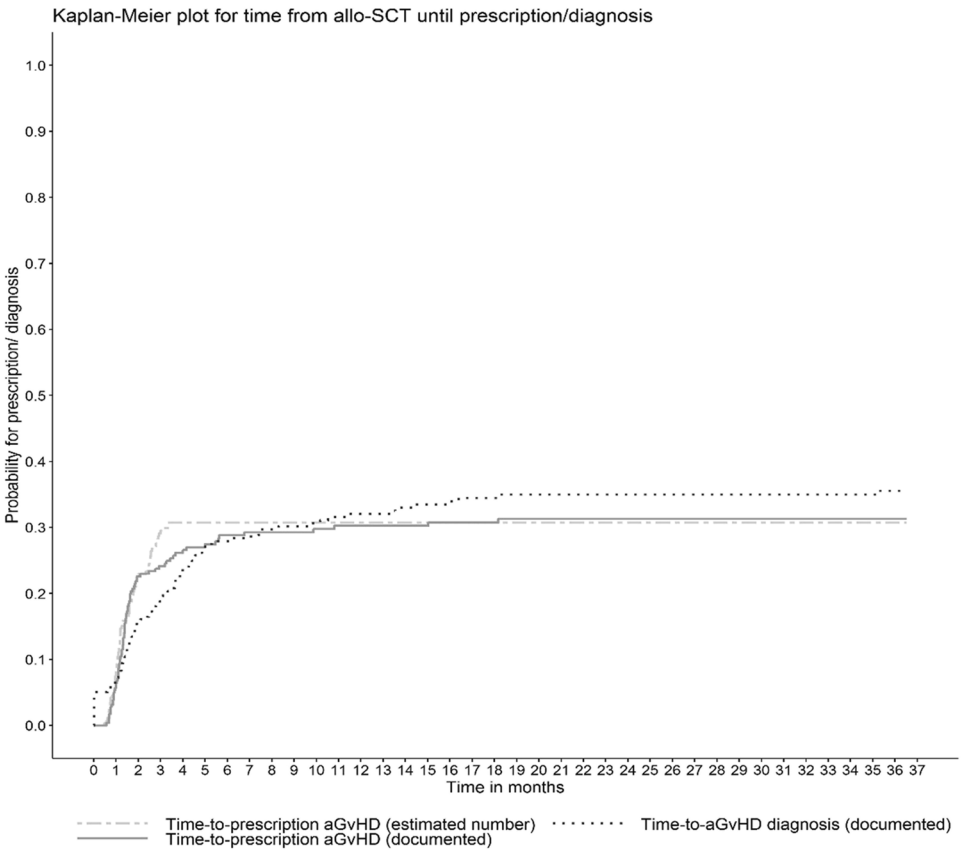

Fig. 2 Kaplan–Meier plot for probability in months from allo-HCT until steroid prescription for both documented and undocumented acute GvHD patients, and until documentation of acute GvHD diagnosis

This research has shown that more patients are presumably affected than documented and therefore their resource use is not visible among the GvHD patient collective. The high number of estimated but not documented cases warrants more detailed analyses within these cohorts. Large scale studies including documented and undocumented cases are needed to assess the specific characteristics and needs of all patients suffering from GvHD after allo-HCT. The high estimated incidence of GvHD after allo-HCT, as shown in this study, underlines the necessity for improving interventions for both prevention and treatment of GvHD and related post-transplant immune dysfunction. This is underlined by a high burden of disease and mortality rate of GvHD patients (Goerner et al. 2002).

SHI claims data is primarily designed to allocate resources in the healthcare system and the accuracy of the obtained information depends on coding practices (Konrad et al. 2019). Hence, only documented patients are observed, which can lead to an underestimation of the administrative incidence. This is why this methodological approach was used to identify potentially undocumented cases.

Kaplan–Meier plots showing the probability of prescription of corticosteroids among documented and undocumented patients cohorts suggests the comparability of the aGvHD type, whereas the prescription patterns for the cGvHD cohorts were less indicative. Such findings hint at a poor documentation of (late onset) cGvHD diagnosis without steroid prescription after 100 days of allo-HCT.

According to guidelines of aGvHD and cGvHD, treatment with corticosteroids plays an important role as first-line therapy. However, inpatient prescriptions were not accessible in the analysis due to diagnosis-related group (DRG) lump sums. For instance, six patients were identified with only documented aGvHD diagnosis who received their first prescription ≥ 100 days after an allo-HCT. Therefore, those patients were assigned to the cGvHD group. However, those six patients might imply a late onset of aGvHD or they received first prescription of corticosteroid in the inpatient sector, which would not be visible in the database. Due to this limitation of German SHI claims data, patients who received steroids in the inpatient sector and were not documented based on ICD-10-GM coding could not be identified as GvHD cases. Moreover, disease severity was not visible in the dataset for undocumented cases (estimated number based on steroid prescription). A differentiation may be of interest for further studies based on datasets, which include the specific information.

The key assumption to allow capture of undocumented GvHD cases is that every GvHD event can be identified by use of corticosteroids. This may potentially have led to

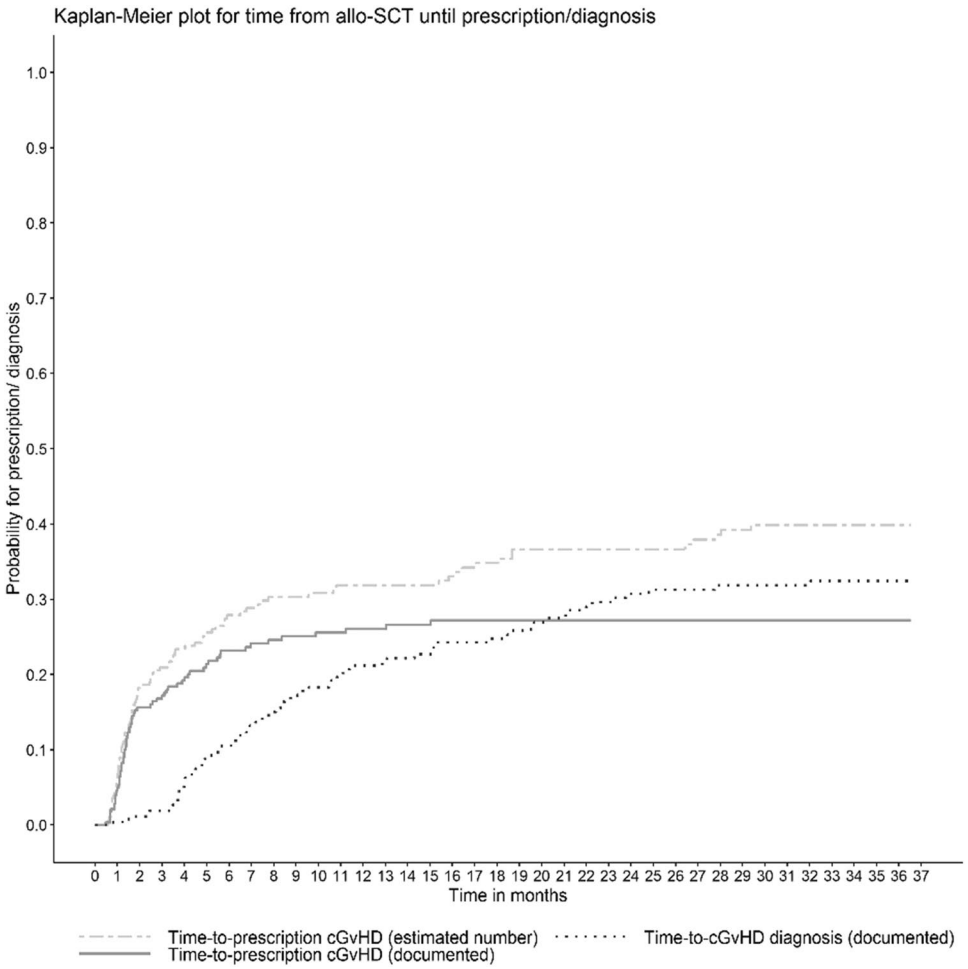

Fig. 3 Kaplan–Meier plot for probability in months from allo-HCT until steroid prescription for both documented and undocumented chronic GvHD patients, and until documentation of chronic GvHD diagnosis.

an overestimation of GvHD cases; however, the analysis focuses on outpatient steroid prescriptions. In the outpatient setting it is very unlikely that a patient receives a prescription of steroids for reasons other than GvHD (e.g., transfusion premedication). Another assumption in our study is that corticosteroids are not considered for prophylactic use, as typically a combination of a CNI such as Cyclosporin A or Tacrolimus with methotrexate or mycophenolate Mofetil (MMF) are used as prophylactic therapy (Zeiser et al. 2019).

Moreover, three factors may have influenced the estimation of GvHD cases, which should be considered for further studies analyzing steroid prescriptions and assess those as a possible correction factor. First, the distinction in timing post-transplant (< 100 days versus ≥ 100) for developing aGvHD or cGvHD has been made based on the current German guideline on GvHD rather than clinical manifestation, which is not accessible in the claims database used. Second, corticosteroids may have been prescribed for adverse reactions other than GvHD, such as auto-immune diseases or patients may have received for a short time corticosteroids for unspecific reasons (diarrhea, nausea). Third, patients living at distant sites (distant to the transplant center) may have received a preemptive or anticipatory prescription to be taken in case of GVHD.

Apart from premedication for infusion/transfusion and relapse medications for the underlying disease, which may require combination with a corticosteroid, any event, which triggers the use of corticosteroids, can be considered a GvHD event after allo-HCT.

In conclusion, to account for the complexity of GvHD and to take coding practices in a real-world setting into consideration, one must rely on surrogate parameters for assessing clinical manifestation or medication intake in addition to identifying patients solely based on disease documentation.

Author contributions All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. CS, RK, ME, CF, BL, and JM were involved in the study design, the statistical analysis plan, and the interpretation of the results. BL drafted and CS and JM edited the manuscript. All authors read and approved the final version of the manuscript.

Funding This study was funded by Janssen-Cilag GmbH and conducted by HGC Healthcare Consultants GmbH and the Institute for Applied Health Research Berlin GmbH (InGef) in line with the study protocol.

Data availability Due to the sensitivity of the data and data protection regulations, the analysis datasets of the current study will not be shared or stored at a public repository. Analysis datasets can be assessed upon reasonable request at the Institute for Applied Health Research Berlin (InGef).

Declarations

Ethics approval and informed consent All individual patient data are anonymized in the research database to comply with German data protection regulations. Patient numbers below five were not reported. Accordingly, institutional review board/ethical approval and informed consent of the individuals were not required.

Consent for publication Not applicable as only aggregate data are reported.

Competing Interests RK, JM, and ME were employees of Janssen-Cilag GmbH during conducting of this study. JM holds stocks from JNJ. BL and CF were employees of HGC during conducting of the study, a consulting company that received funding from Janssen-Cilag to conduct the study in collaboration with the Institute for Applied Health Research Berlin GmbH (InGef) in line with the study protocol. CS is employed at the University Hospital Cologne and received honoraria from Janssen-Cilag. All authors have no other relevant affiliations or financial involvement with any other organization or entity with a financial interest in the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Andersohn F, Walker J (2016) Characteristics and external validity of the German Health Risk Institute (HRI) Database. Pharmacoepidemiol Drug Saf 25(1):106–109

Arai S, Arora M, Wang T et al (2015) Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant 21:266–274

Barton-Burke M, Dwinell DM, Kafkas L et al (2008) Graft-versus-host disease: a complex long-term side effect of hematopoietic stem cell transplant. Oncology (Williston Park). 2008;22(11 Suppl Nurse Ed):31–45

Beelen D, Mytilieneos J (2015) Jahresbericht 2014 - DRST Deutsches Register für Stammzelltransplantationen. Available from: http://www.drst.de/drst/download/jb2014.pdf

Beelen D, Mytilieneos J (2016) Jahresbericht 2015 - DRST Deutsches Register für Stammzelltransplantationen. Available from: http://www.drst.de/drst/download/jb2015.pdf

Beelen D, Mytilieneos J (2019) Jahresbericht 2018 - DRST Deutsches Register für Stammzelltransplantationen [Internet]. Available from: http://www.drst.de/drst/download/jb2018.pdf

Bundesministerium für Gesundheit. Mitglieder und Versicherte der Gesetzlichen Krankenversicherung (GKV), Berlin 2022; available at: https://www.bundesgesundheitsministerium.de/themen/krankenversicherung/zahlen-und-fakten-zur-krankenversicherung/mitglieder-und-versicherte.html

Busse R, Blümel M, Knieps F, Bärnighausen T (2017) Statutory health insurance in Germany: a health system shaped by 135 years of solidarity, self-governance, and competition. Lancet 390(10097):882–897

DRST - Deutsches Register für Stammzelltransplantation [Internet]. 2018 [cited 2020 Aug 18]. Available from: http://www.drst.de/drst/index.html

Ferrara JLM, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet 373(9674):1550–1561

Harris AC, Ferrara JLM, Levine JE (2013) Advances in predicting acute GVHD. Br J Haematol 160(3):288–302

Flowers MED, Martin PJ (2015) How we treat chronic graft-versus-host disease. Blood 125(4):606–15

Jacobsohn DA, Vogelsang GB (2007) Acute graft versus host disease. Orphanet J Rare Dis 2:35

Goerner M, Gooley T, Flowers MED et al (2002) Morbidity and mortality of chronic GVHD after hematopoietic stem cell transplantation from HLA-identical siblings for patients with aplastic or refractory anemias. Biol Blood Marrow Transplant 8(1):47–56

Gothe H, Brinkmann C, Schmedt N et al (2022) Is there an unmet medical need for palliative care services in Germany? Incidence, prevalence, and 1-year all-cause mortality of palliative care sensitive conditions: real-world evidence based on German claims data. J Public Health 30:711–720

Jamil MO, Mineishi S (2015) State-of-the-art acute and chronic GVHD treatment. Int J Hematol 101(5):452–466

Konrad R, Zhang W, Bjarndóttir M, Proaño R (2019) Key considerations when using health insurance claims data in advanced data analyses: an experience report. Health Systems 9(4):317–325

Kossack N, Schindler C, Weinhold I et al (2018) German claims data analysis to assess impact of different intraocular lenses on posterior capsule opacification and related healthcare costs. J Public Health 26:81–90

Lee SJ, Vogelsang G, Flowers MED (2003) Chronic graft-versus-host disease. Biol Blood Marrow Transplant 9(4):215–233

Mahlich J, May M, Feig C et al (2021) Persistence with biologic therapy and associated costs of patients with inflammatory bowel disease: a German retrospective claims data analysis. Crohn's & Colitis 360 3(2):otab011

Martin PJ, Rizzo JD, Wingard JR et al (2012) First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant 18(8):1150–1163

Mielcarek M, Furlong T, Storer BE et al (2015) Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. Haematologica 100(6):842–848

Sewerin P, Borchert K, Meise D et al (2021) Real world treatment persistence with biologic disease modifying antirheumatic drugs among German patients with psoriatic arthritis - a retrospective database study. Rheumatol Ther 8(1):483–497

Sewerin P, Borchert K, Meise D et al (2022) Health resource utilization and associated healthcare costs of biologic disease modifying antirheumatic drugs in German patients with psoriatic arthritis. Arthritis Care Res. https://doi.org/10.1002/acr.24598

Swart E, Gothe H, Geyer S, Jaunzeme J, Maier B, Grobe T, Ihle P (2015) Good practice of secondary data analysis (GPS): guidelines and recommendations. Gesundheitswesen 77(2):120–126

Swart E, Schmitt J (2014) STandardized Reporting Of Secondary data Analyses (STROSA) - Vorschlag für ein Berichtsformat für Sekundärdatenanalysen. Z Für Evidenz Fortbild Qual Im Gesundheitswesen 108(8–9):511–516

Toubai T, Sun Y, Reddy P (2008) GVHD pathophysiology: is acute different from chronic? Best Pract Res Clin Haematol 21(2):101–117

Wolff D, Bertz H, Greinix H et al (2011) The treatment of chronic graft-versus-host disease. Dtsch Arztebl Int 108(43):732–740
Wolff D, Gerbitz A, Ayuk F et al (2010) Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. Biol Blood Marrow Transplant 16(12):1611–1628
Wolff D, Zeiser R, Scheid C et al (2019) Graft-versus-host Erkrankung, chronisch. Onkopedia. 2019 [cited 2020 Aug 17]. Available from: https://www.onkopedia.com/de/onkopedia/guidelines/graft-versus-host-erkrankung-chronisch
Zeiser R, Blazar BR (2017) Acute graft-versus-host disease - biologic process, prevention, and therapy. N Engl J Med 377(22):2167–2179
Zeiser R, Wolff D, Scheid C et al (2019) Graft-versus-Host Erkrankung, akut . Onkopedia [cited 2020 Aug 17]. Available from: https://www.onkopedia.com/de/onkopedia/guidelines/graft-versus-host-erkrankung-akut