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ORIGINAL RESEARCH ARTICLE

Treatment Pathways and Health Outcomes of German Patients with Chronic Graft-Versus-Host Disease After Allogeneic Hematopoietic Cell Transplantation: A Retrospective Health Claims Data Analysis

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Abstract

Background Although chronic graft-versus-host-disease (cGvHD) is an important long-term complication after allogenic hematopoietic cell transplantation (allo-HCT) and is associated with increased healthcare resource utilization, real-world evidence is scarce.

Objectives The aim of the study was to evaluate survival of patients with cGvHD in Germany and to analyze hospitalization and treatment patterns.

Patients and Methods Based on a German claims database with 4.9 million enrollees, a retrospective longitudinal analysis covering a 6-year period between 2013 and 2018 was conducted. Patients with allo-HCT in 2014 or 2015 (index date) and no record of transplantation or documentation of GvHD 365 days prior to index were included. Patients who subsequently developed a cGVHD were compared with those who did not develop a cGVHD within 3 years after index date. cGVHD cases were identified based on documented International Classification of Diseases, Tenth Revision (ICD-10) diagnosis and treatment algorithms. Since the onset of cGvHD is defined at 100 days after allo-HCT, only those alive beyond day 100 were considered in the survival analysis. Patients who did not survive the first 100 days after allo-HCT were censored to prevent a selection bias due to early mortality within patients without GvHD. Survival rates were plotted using the Kaplan–Meier estimator. The number of hospitalizations and average lengths of stay as well as treatment patterns were descriptively examined.

Results Overall, 165 cGvHD patients were identified and compared with 43 patients without cGVHD. Short-term survival rates were better for patients with cGvHD; the 6-month survival probability was 95.8% for patients with cGVHD and 83.7% for patients without cGVHD. However, long-term survival was better in patients without GvHD; The 30-month survival probability was 65.5% for patients with cGVHD and 76.7% for patients without cGVHD. While overall 90% of cGvHD patients were hospitalized at least once, the share was only half for patients without GvHD (44%). 78.2% of patients with cGVHD received corticosteroids in combination with other predefined immunosuppressants.

Conclusion Findings from this study reveal a high disease burden associated with cGvHD. This underlines the high medical need for new interventional strategies to improve survival and morbidity after allo-HCT.

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Key Points

Chronic graft-versus-host disease (cGvHD) is a common complication after allogenic hematopoietic cell transplantation (allo-HCT), a treatment option for several blood cancers.

We find that in the first year after allo-HCT, survival was better for patients who developed a cGvHD, however after 12 months, survival was best in patients without GvHD.

Hospitalization rates were twice as high for patients with cGVHD than for those who did not develop a GvHD.

1 Introduction

Chronic graft-versus-host-disease (cGvHD) is a protracted reaction of the donor immune system against tissue of the recipient resulting from impaired tolerance mechanisms. cGvHD presents a major and potentially life-threatening complication after allogeneic hematopoietic cell transplantation (allo-HCT), an increasingly used curative modality for hematological malignancies (e.g. leukemia, lymphoproliferative diseases) [1]. According to current literature, approximately 50% of patients develop a cGvHD after allo-HCT [2], with a subsequent 10-year disease-specific survival of 51% [3]. While infections and acute GvHD mainly affect the early phase after transplantation and mainly cause transplant-associated early mortality, cGvHD is the most significant long-term complication. The onset of cGvHD is defined based on clinical features and typically occurs more than 100 days after allo-HCT and can be divided into three levels of severity: mild, moderate, and severe [4]. Generally, the clinical manifestations can vary, mostly affecting the skin, mucosa, muscles/joints, the gastrointestinal tract and the lung. While mild and moderate courses primarily decrease quality of life, severe forms can have a substantial negative impact on long-term survival [4]. Depending on the patient population, first-line therapy (topical or systemic corticosteroids, often combined with calcineurin inhibitors [CNIs] [5]) can achieve complete remission of cGvHD in approximately 20% (adults) to 50% (children) of cases [6]. If symptoms progress during the first 4 weeks of therapy or symptoms do not improve within 8–12 weeks, second-line therapy should be initiated [7, 8], including CNIs, extracorporeal photopheresis (ECP), and mammalian target of rapamycin (mTOR) inhibitors [6].

Although cGvHD is the most relevant long-term complication after allo-HCT [1] and is associated with greater healthcare utilization, reported real-world data (RWD) on survival, hospitalization, and treatment patterns in Germany are scarce.

The objective of this study was to gain real-world evidence (RWE) based on statutory health insurance (SHI) claims data on the German care situation by assessing the survival of patients developing cGvHD after allo-HCT in comparison with transplanted patients without any GvHD. In addition, we analyzed resource use in terms of hospitalization and prescribed medication.

2 Materials and Methods

2.1 Data Source and Sample Size

This study was based on an anonymized German SHI claims database (Institute for Applied Health Research Berlin GmbH [InGef]), providing information on approximately 4.9 million member records from over 53 nationwide German SHIs. The representative sample was age and sex adjusted to the German population, and has a good overall accordance in terms of morbidity, mortality, hospitalization, and drug use [9]. The database was extensively used in German health services research [10–12]. The analysis spans the years from 2013 to 2018.

2.2 Study Design and Patient Selection

Included patients were pooled in 2014–2015, with index 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 to 8-805.5 OPS codes) or transplantation of hematopoietic stem cells from the bone marrow (5-411.2 to 5-411.5 OPS codes) according to the German modification of the International Classification of Procedures in Medicine (ICPM). Only patients without record of transplantation or documentation of GvHD 365 days prior to index were included. Patients were individually observed for 3 years after index, whether they developed a documented cGvHD, using the International Classification of Diseases, Tenth Revision, German Modification (ICD-10-GM) of T86.05 (mild), T86.06/T86.03 (moderate), or T86.07/T86.04 (severe) as at least one confirmed outpatient or inpatient (main or secondary) diagnosis. Additionally, patients with no specific cGvHD but acute (T86.01, T86.02), unspecific (T86.00, T86.09) GvHD, or no GvHD documentation but prescriptions of corticosteroids, were identified. Based on the first corticosteroid prescription ≥100 days after allo-HCT or <100 days after allo-HCT but continued prescriptions for >6 months

were assigned as estimated cGvHD cases. Although current definitions of cGvHd are independent from the time point after transplant, the vast majority of cGVHD cases occur >100 days after allo-HCT. Therefore we used this time point to separate aGvHD from cGvHD. Patients without GvHD were defined as patients with neither diagnosis (excluding all coding of ICD-10 T86) nor prescription of corticosteroids within 3 years of follow-up after index. The methodological approach and the validation of the estimation has been outlined elsewhere [13].

Due to the varying impact on the quality of life and survival caused by heterogenic disease patterns, different levels of severity of cGvHD were included. In total, seven patient groups were established in this study and were analyzed for 3 years: documented cGvHD patients (divided into mild cGvHD, moderate cGvHD, and severe cGvHD), estimated cGvHD, and total cGvHD, representing the sum of documented and estimated cGvHD cases. The last group comprised patients without GvHD (neither documented nor estimated based on corticosteroid prescriptions).

2.3 Statistical Analysis and Outcomes

Descriptive statistics were used to analyze hospitalizations, including length of stay (LOS) and cumulated days, as well as treatment utilization (medication and interventions). To ensure individual data privacy, quantities smaller than five (< 5) were not displayed.

Survival rates were plotted using the Kaplan–Meier estimator to evaluate the time until death for all seven groups. Since the onset of cGvHD is defined at 100 days after allo-HCT, all patients not surviving until day 100 were censored [14], accounting for early relapses and preventing selection bias due to early mortality within patients without GvHD. Due to potential death during the initial hospitalization at the allo-HCT, outpatient corticosteroid prescription cannot be identified and therefore estimation of cGvHD based on prescription patterns is not possible for these patients. As a result, only patients alive 100 days after transplantation were included in this analysis, censoring previously deceased patients. Log-rank tests were conducted between documented and estimated cGvHD cases, including the different levels of severity. All Kaplan–Meier curves were calculated per day. Calculation of probabilities was performed per month (30 days each) for the total observation period of 3 years, considering the longest available follow-up period.

Different parameters for inpatient resource utilization were examined, namely the share of patients hospitalized at least once, mean number of hospitalizations per patient with at least one hospitalization, average LOS per admission, and the cumulated days in hospital per patient. An admission or discharge diagnosis of GvHD (main or secondary) was not necessary for inclusion. Moreover, the initial hospitalization at index necessary for the transplantation was not included in this analysis as an inpatient visit. All figures regarding hospitalizations were adjusted to the time insured.

Prescriptions of predefined medication according to treatment guidelines were analyzed for both documented and estimated cGvHD cases, but not by level of severity. Since systemic corticosteroids are the standard first-line therapy for a more severe course of disease, the analysis focused on therapies combined with systemic corticosteroids. A first evaluation step showed that neither a therapy with only one defined medication or intervention nor predefined treatment pathways were used for treating cGvHD. Patients with combination therapy needed at least one prescription of systemic corticosteroid and at least one prescription of defined medication or intervention (Table 1) within one-quarter during the first year of follow-up. Topical corticosteroids and medications were included as a possible combination and clustered as one group (topical therapies). The five most prescribed systemic corticosteroids were examined as well as the 15 most combined treatments. Moreover, the number of combined therapies per patient group was evaluated. Since defined medications are specifically selected for treatment of cGvHD, treatment utilization was not analyzed for patients without GvHD.

This analysis was conducted following the 11 guidelines of the 'Good Practice of Secondary Data Analysis' (GPS) [9]. Moreover, the STROSA (STandardized Reporting Of Secondary data Analyses) checklist items were reviewed and applied [15, 16].

Table 1 Patient groups selected in this study based on ICD-10-GM coding (documented cGvHD) and corticosteroid prescriptions (estimated number)

Patient group	*N*
Total cGvHD	165
Documented cGvHD (T86.05–T86.07)	71
Documented mild cGvHD (T86.05)	9
Documented moderate cGvHD (T86.06/86.03)	25
Documented severe cGvHD (T86.07/T86.04)	37
cGvHD estimated number[a]	94
Without any GvHD[b]	80

cGvHD chronic graft-versus-host disease, *ICD-10-GM* Classification of Diseases, Tenth Revision, German Modification, *allo-HCT* allogenic hematopoietic cell transplantation, *aGvHD* acute graft-versus-host disease

[a]No identification of cGvHD based on ICD-10-GM; estimation based on systemic or topical corticosteroid prescriptions after allo-HCT (previous aGvHD or unspecific GvHD coding possible)

[b]Patients with previous allo-HCT, but no identification of any GvHD based on neither ICD-10-GM coding nor corticosteroid prescriptions

3 Results

The database contained 4,932,496 patients between 2013 and 2018, of whom 3,727,317 were continuously insured and selected for further analysis. Of this sample, 297 patients received an allo-HCT between January 2014 and December 2015. Mean age was 50.6 years, 64% were female, and 36% were male. Of the 297 patients with allo-HCT, 165 developed a cGvHD within 3 years and were considered for our analysis; 71 of the 165 patients with cGvHD were identified by a documented ICD-10 diagnosis, and 94 by the treatment algorithm (estimated number). Among the remining 132 patients who did not develop a cGvHD, 52 could only be identified as acute graft-versus-host disease (aGvHD) patients due to documented ICD-10 diagnosis or treatment algorithm, but not identified as cGvHD patients. The remaining 80 patients could not be allocated to neither aGvHD nor cGvHD and were therefore identified as patients without GvHD (see Table 2 for details of the study population).

3.1 Survival After Allogeneic Hematopoietic Cell Transplantation

Two Kaplan–Meier curves were plotted comparing the survival probability of documented, estimated cGvHD cases and patients without developing GvHD. Since 46.3% ($n = 37$) of patients without GvHD died within 100 days, 43 patients were at risk in this patient group. No censoring was needed for the patient groups with cGvHD since all patients were alive 100 days after allo-HCT, resulting in 165 total cGvHD patients (71 documented and 94 estimated) at risk 100 days after allo-HCT.

Figure 1 shows the survival rate of the total cGvHD group (including both documented and estimated cGvHD cases) compared with the documented cases, estimated cases, and patients without GvHD.

At 12 months, survival of the total cGvHD group was at 82.4% ($n = 136$), while the rate for documented cGvHD patients was 78.9% ($n = 56$) and 85.1% ($n = 80$) for patients with estimated cGvHD. Survival of patients with no GvHD was 81.4% ($n = 35$) at 12 months. The survival curve showed two phases: before 12 months, survival appeared to be superior for patients with cGvHD, however in the longer term, survival was best in patients without GvHD. The 6-month survival probability was 95.8% for patients with cGvHD and 83.7% for patients without cGvHD. On the other hand, the 30-month survival probability was 65.5% for patients with cGvHD and 76.7% for patients without cGvHD. A pairwise log-rank p-value test revealed a significant difference in survival between documented and estimated cGvHD cases ($p = 0.048$). To assess whether this was due to different cGvHD severity, the analysis was repeated dividing documented patients by level of severity.

Figure 2 illustrates the survival probabilities of documented cGvHD patients by severity compared with estimated cGvHD and patients without GvHD. Inferior survival was confined to those patients with severe cGvHD compared with patients with mild to moderate cGvHD, estimated cGvHD, or no GvHD ($p = 0.023$).

3.2 Hospitalization

Figure 3 displays overall inpatient utilization for all seven patient groups within 3 years of follow-up. Overall, 90% ($n = 149$) of the total cGvHD population was hospitalized at least once. The share of hospitalized patients was highest for severe patients at 97% ($n = 36$), followed by moderate at 92% ($n = 23$) and mild cases at 89% ($n = 8$). The share of hospitalizations for estimated cases was comparable with the mild form at 87% ($n = 82$). The hospitalization rate for the documented cGvHD group, independent of severity, was 94% ($n = 67$). The lowest share was seen for the group without GvHD, where less than half were hospitalized at least once (44%; $n = 35$) (Fig. 3a).

Analyzing the number of hospitalizations during total follow-up per resource user, patients with documented cGvHD had an average of 4.7 inpatient episodes, compared with 4.4 in patients with estimated cGvHD and 3.8 in patients with no GvHD. Regarding cGvHD severity, inpatient episodes averaged at 3.3 for mild GvHD, 4.2 for moderate GvHD, and 6.2 for severe GvHD (Fig. 3b).

Comparing the LOS per admission, patients with severe cGvHD stayed in hospital for an average of 22.1 days compared with 19.5 days for moderate cases and 13.1 days for mild cases. Time per admission was lowest for estimated patients with GvHD (11.5 days), while patients without GvHD spent, on average, 12.4 days in hospital (Fig. 3c).

Analyzing cumulated days in hospital per patient during the total follow-up showed the high disease burden of severe cGvHD. These patients were hospitalized, on average, 111.4 days during 3 years of follow-up. While patients with moderate cGvHD spent, on average, 79.5 days in hospital, the average time was 44.4 days for patients with mild cGvHD. Estimated cases and patients without GvHD showed an average of 42 and 53.6 days in hospital, respectively (Fig. 3d).

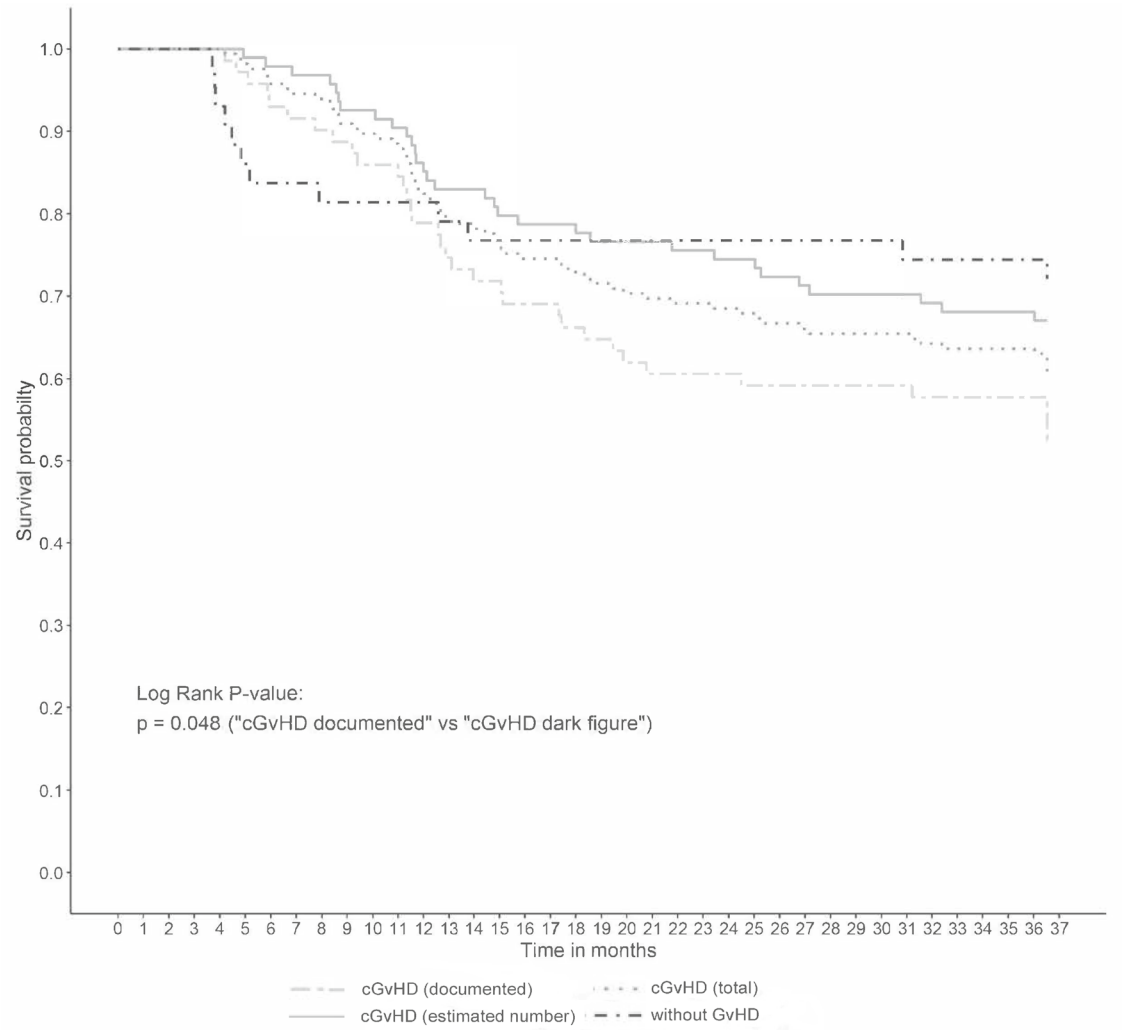
3.3 Treatment Patterns

Treatment patterns were evaluated by comparing the number of cGvHD patients (both documented and estimated) receiving (1) corticosteroids as monotherapy (systemic or topical); (2) systemic corticosteroids combined with other defined systemic or topical therapy; (3) other defined systemic or topical therapy without corticosteroids; and (4) no defined

Table 2 Systemic corticosteroids and included topical and systemic therapies analyzed for combination

		Included therapies	
		Prescriptions based on both ATC (outpatient) and German OPS (inpatient) according to the German DIMDI and interventions according to the doctor's fee scale "Einheitlicher Bewertungsmaßstab" (EBM)	
Systemic corticosteroids		Betamethasone Cortisone Dexamethasone Hydrocortisone Methylprednisolone Prednisolone Prednisone Triamcinolone	H02 corticosteroids for systemic use, pure
Systemic therapies	Systemic medications	Tacrolimus* Cyclosporin Sirolimus (mTOR inhibitor)* Everolimus (mTOR inhibitor)* Mycophenolate mofetil (MMF) Methotrexate Hydroxychloroquine Clofazimine Pentostatine Rituximab* Imatinib* Tocilizumab* Abatacept* Thalidomide Interleukin 2* Cyclophosphamide Ruxolitinib* Ibrutinib* Bortezomib* Azathioprine Retinoids Alemtuzumab* Etanercept* Antithymozyten globulin	L04A Immunosuppressants L01X Other antineoplastic agents L01X Protein kinase inhibitors P01BA Aminoquinolines J04BA Drugs for treatment of lepra L03AC Interleukins D05BB Retinoids for treatment of psoriasis
	Systemic interventions	PUVA UVA/UVB Extracorporeal photopheresis (ECP) Thoraco-abdominal irradiation (TAI)	EBM: 30431, OPS: 8-560.1 EBM: 30430, OPS: 8-560.3 OPS: 8-824 OPS: 8-523.4
Topical therapies	Topical corticosteroids	Betamethasone Budesonide 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
	Topical medications	Saliva substitutions Salicylates, combinations Quinine and derivatives Ursodeoxycholic acid (UDCA) Estriol Tacrolimus Pimecrolimus* Cyclosporin Sirolimus Retinoids	A01AD Other agents for local oral treatment M09AA Quinine and derivatives A05AA Bile acids and derivatives G03C Estrogens D11A Other dermatological preparations S01XA Other ophthalmologicals D10AD Retinoids for topical use in acne D10BA Retinoids for treatment of acne

ATC Anatomical Therapeutic Chemical, *OPS* Operation and Procedures Classification System, *DIMDI* Institute of Medical Documentation and Information, *mTOR* mammalian target of rapamycin, *PUVA* psoralen plus ultraviolet-A, *UVA* ultraviolet A, *UVB* ultraviolet B, *OPS basis



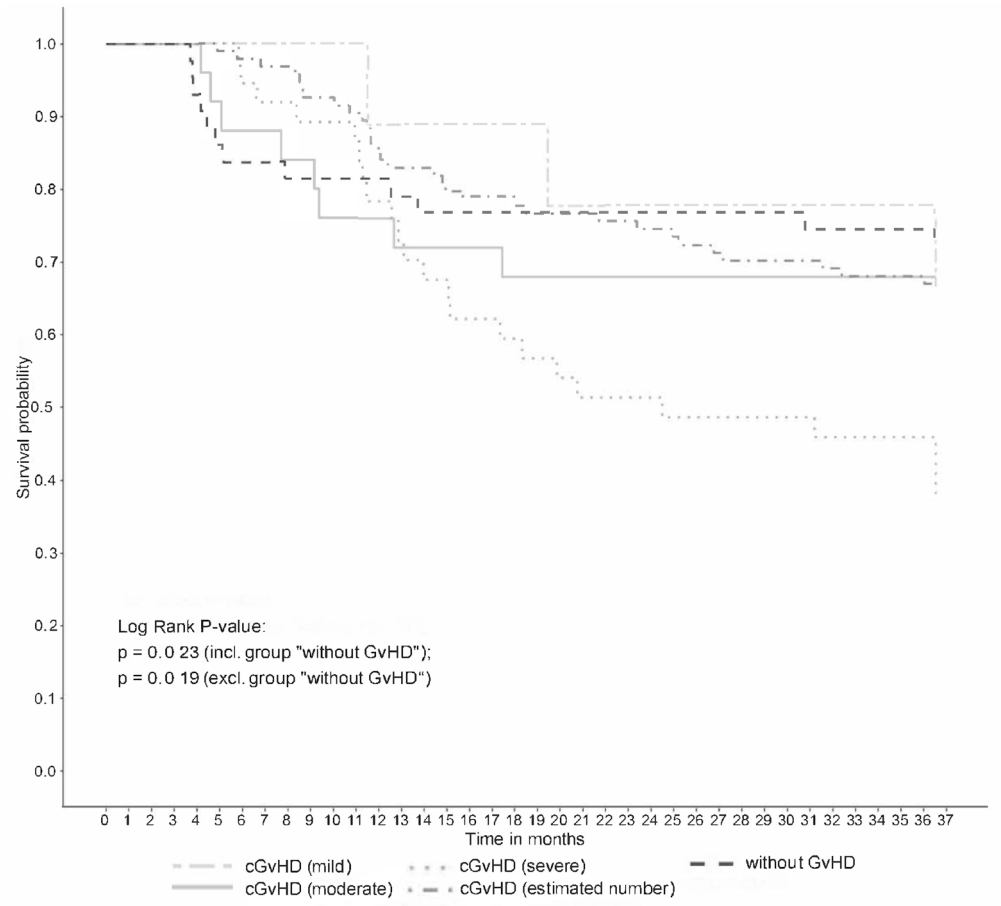
	Survival probability					
	6 months	12 months	18 months	24 months	30 months	36 months
estimated number cGvHD (n at risk = 94)	n.a.[1]	85.1%	77.7%	n.a.	n.a.	n.a.
documented cGvHD (n at risk = 71)	93.0%	78.9%	66.2%	n.a.	n.a.	n.a.
Total cGvHD (n at risk = 165)	95.8%	82.4%	72.7%	68.5%	65.5%	n.a.
Without GvHD (n at risk = 43)	83.7%	n.a.	n.a.	76.7%	76.7%	n.a.

[1]events n= <5 due to data protection, probability cannot be stated.

Fig. 1 Kaplan–Meier plot for the time from allo-HCT until death for cGvHD, differentiated by documented, estimated number, total, and without GvHD. *allo-HCT* allogeneic hematopoietic cell transplantation, *cGvHD* chronic graft-versus-host disease

systemic or topical therapy. As most patients were assigned to group (2), further analyses focused exclusively on these patients.

Overall, 129 of 165 total cGvHD patients (78.2%) were included, while 85.9% of documented (61 of 71 patients) and 72.3% of estimated cGvHD cases (68 of 94 patients) met the inclusion criteria.



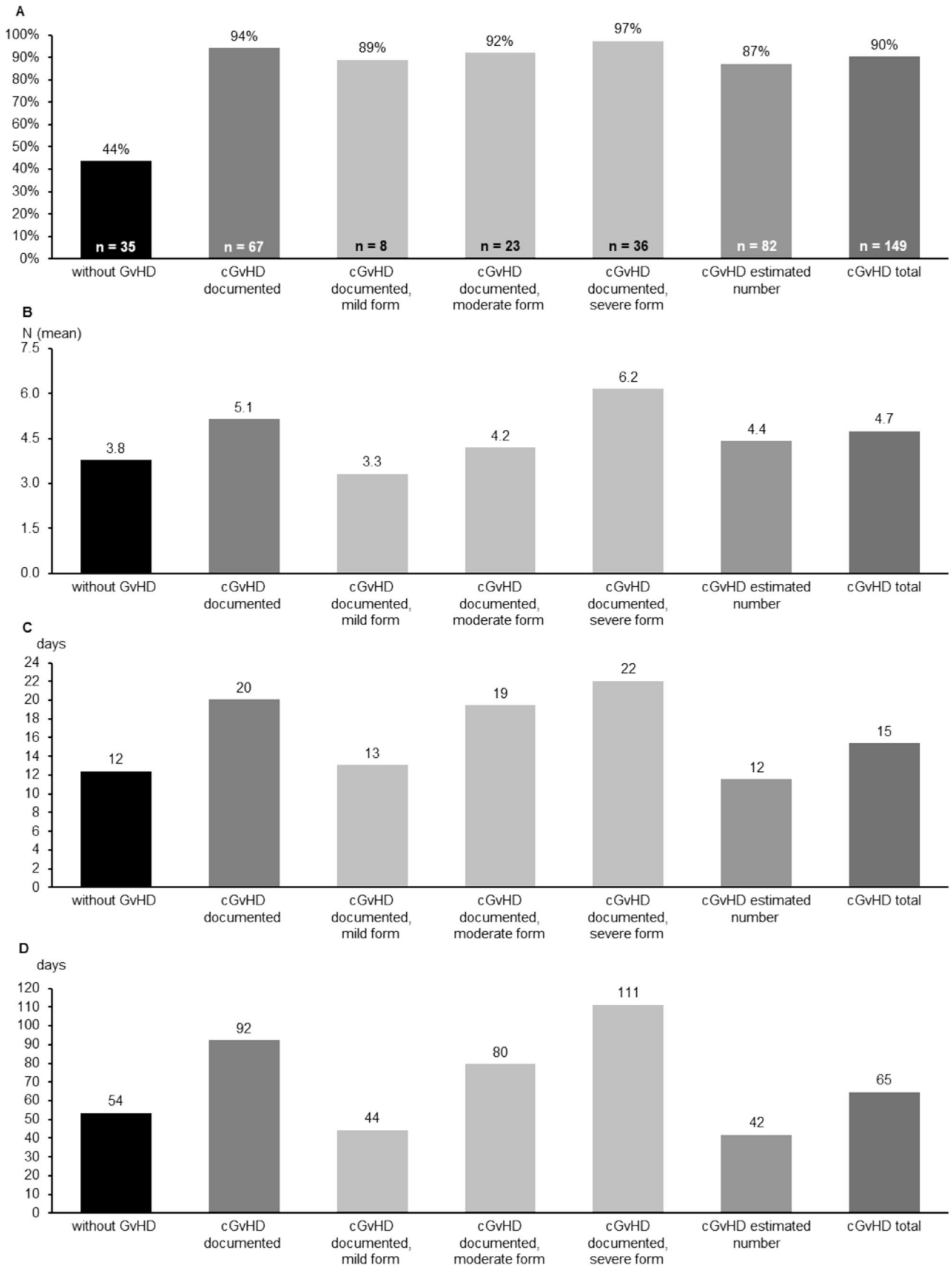
	Survival probability					
	6 months	12 months	18 months	24 months	30 months	36 months
estimated number cGvHD (n at risk = 94)	n.a.[1]	85.1%	77.7%	n.a.	n.a.	n.a.
Documented mild cGvHD (n at risk = 9)	100.0%	n.a.	88.9%	n.a.	77.8%	77.8%
Documented moderate cGvHD (n at risk = 25)	n.a.	n.a.	n.a.	68.0%	68.0%	68.0%
Documented severe cGvHD (n at risk = 37)	n.a.	78.4%	59.5%	n.a.	n.a.	n.a.
Without GvHD (n at risk = 43)	83.7%	n.a.	n.a.	76.7%	76.7%	n.a.

[1]events n= <5 due to data protection, probability cannot be stated.

Fig. 2 Kaplan–Meier plot for the time from allo-HCT until death for cGvHD, differentiated by level of severity, estimated number, and without GvHD. *allo-HCT* allogeneic hematopoietic cell transplantation, *GVHD* graft-versus-host disease, *cGvHD* chronic graft-versus-host disease

The average number of prescriptions per patient (including systemic corticosteroids) was comparable for documented (3.44 prescriptions) and estimated cGvHD (3.14); thus, prescriptions averaged at 3.29 for the total cGvHD group. Figure 4a illustrates the number of therapies used in combination per group. While 33% ($n = 20$) of documented patients had three additional therapies combined with systemic corticosteroids, 31% ($n = 19$) had two additional therapies. On the other hand, estimated cases mostly combined two additional therapies (40%, $n = 27$) followed by 31% ($n = 21$) with three additional therapies.

The most combined systemic corticosteroid for the total cGvHD group was prednisolone at 71% ($n = 92$), followed by prednisone at 39% ($n = 50$) and methylprednisolone at


A
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70%
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10%
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94%
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92%
97%
87%
90%
n = 35
n = 67
n = 8
n = 23
n = 36
n = 82
n = 149
without GvHD
cGvHD documented
cGvHD documented, mild form
cGvHD documented, moderate form
cGvHD documented, severe form
cGvHD estimated number
cGvHD total
B
N (mean)
7.5
6.0
4.5
3.0
1.5
0.0
3.8
5.1
3.3
4.2
6.2
4.4
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C
days
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111
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65

◂**Fig. 3** Hospitalization rates and lengths of stay. **a** Share of patients hospitalized within 3 years of follow-up. **b** Mean number of hospitalizations per patient with at least one hospitalization (resource user) within 3 years of follow-up. **c** Average time (in days) of length of stay per admission. **d** Cumulated time (in days) in hospital per patient within 3 years of follow-up. *GVHD* graft-versus-host disease, *cGVHD* chronic graft-versus-host disease

19% ($n = 25$). Dexamethasone and hydrocortisone were each prescribed for 7% ($n = 9$) of patients. The distribution was comparable for the documented and estimated groups, showing the same ranking of prescription frequencies (Fig. 4b).

Comparing therapies combined with systemic corticosteroids revealed comparable results for the documented and estimated groups (Fig. 4c). For documented patients, the most combined therapy was ursodeoxycholic acid (UDCA), prescribed for 70% of patients ($n = 43$), followed by cyclosporine A and topical corticosteroids, both at 67% ($n = 41$). For estimated cases, cyclosporine A was the most used combination at 63% ($n = 43$), followed by UDCA at 53% ($n = 36$) and topical corticosteroids at 50% ($n = 34$).

Consequently, these three medications were the most frequently used combinations for the total cGvHD group as well, with 65% ($n = 84$) receiving cyclosporine A, 61% ($n = 79$) receiving UDCA, and 58% ($n = 75$) receiving topical corticosteroids. Other frequently prescribed therapies were mycophenolate mofetil (MMF) at 44% ($n = 57$), tacrolimus at 29% ($n = 37$), and rituximab at 15% ($n = 19$). ECP was only performed among documented cGvHD patients (15%; $n = 9$).

4 Discussion

cGvHD is the major long-term complication in patients having received allo-HCT; however, there are only limited data from prospective clinical studies or retrospective registry analyses. Using a different approach through the analysis of a claims database, this retrospective longitudinal study sought to provide RWE on hospitalization, treatment patterns, and outcomes for cGvHD patients. To account for potential underreporting of cGvHD, a category of patients not documented as cGvHD but estimated to have cGvHD based on previously defined criteria was included [13].

Findings from this study regarding survival probability after allo-HCT suggest an overall high impact of cGvHD, regardless whether documented or undocumented. While severe cGvHD cases showed the lowest long-term survival, survival probabilities for moderate, mild, or estimated cGvHD as well as for patients without GvHD were comparable. The cause of death was not evaluated, leaving the possibility for patients to die due to relapse rather than cGvHD. An American study by Goerner et al. [17] showed comparable survival probabilities for the total cGvHD group. Investigating 113 patients with cGvHD affecting multiple organs for 27 years, survival rates after 3 years were at approximately 70%.

However, the trend for lower mortality for mild cGvHD compared with patients without GvHD could indicate a protective effect of mild cGvHD (graft-versus-leukemia effect), as described in other studies [1]. A previous study from 2014 identified cGvHD as a positive impact factor for relapse prevention in patients with allo-HCT after chronic myeloid leukemia [18].

Regarding survival for the group without GvHD, potential sources of bias need to be addressed. Patients without GvHD dying before day 100 could not be at risk to develop cGvHD at a later timepoint, therefore without correction this would result in more long-term survivors in the patient group with cGvHD. Therefore, only those alive beyond day 100 were considered in the survival analysis to address this early mortality, which revealed a negative survival effect of severe cGvHD. Meanwhile comparable survival rates were found for moderate, mild, and estimated cGvHD as well as patients without GvHD.

Besides survival, hospitalization was used as a surrogate marker for disease burden of cGvHD. While most patients with cGvHD were hospitalized at least once within 3 years, the number of hospitalizations and the LOS varied with cGvHD severity.

While mildly affected patients only showed half as many hospitalizations and, on average, nine fewer days per admission than severe cases, the resource use was still high. Even for mild cases, the cumulated time in hospital within 3 years was nearly 1½ months (44.4 days), not including initial hospitalization for transplantation. Findings regarding the inpatient utilization for cGvHD are in line with another study analyzing cGvHD based on RWD from 2019 [19]. That study by Bachier et al. was based on US claims data and focused on the evaluation of epidemiology, treatment, resource utilization and underlying costs. They identified an average of 2.8 inpatient visits per patient, which was lower than the 4.7 visits for the total cGvHD group in this study. However, this study included 3 years of follow-up, while the US analysis only included 1 year. In addition, access to inpatient health care may also differ between US and Germany due to different reimbursement systems. A recent claims database study by Yu et al. [20] found hospitalization rates for corticosteroid-resistant cGvHD patients to be twice as high compared with patients who did not develop a cGvHD after allo-HCT, which is in line with our results.

The comparable number of prescribed therapies per patient and the similar use of the individual medications indicate a high comparability of estimated and documented cGvHD cases. Moreover, the heterogeneity of therapies per patient within 1 year indicate a high variety of treatment approaches not strictly oriented at predefined pathways.

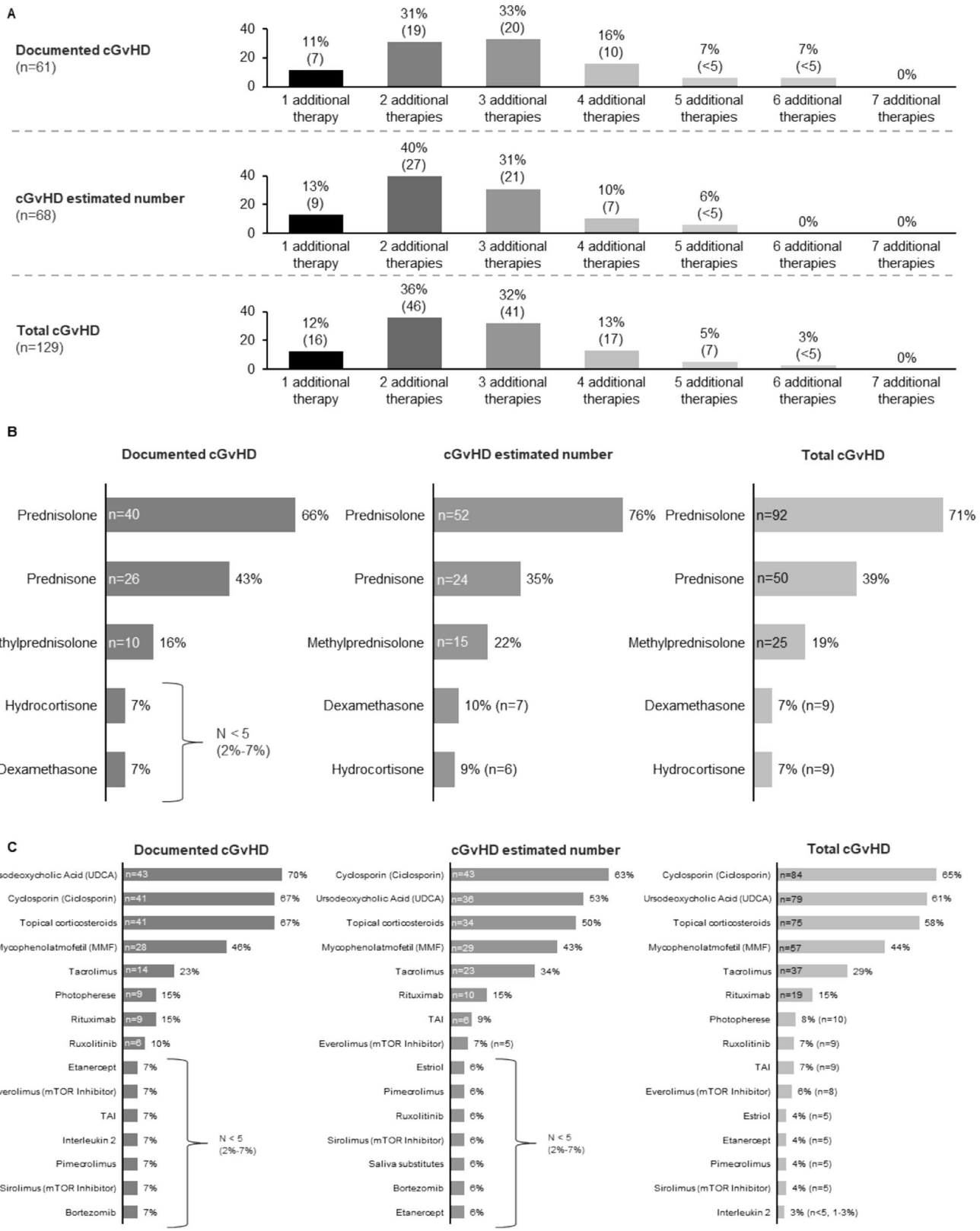

Fig. 4 Treatment dynamics and drug utilization in cGvHD patients differentiated by documented, estimated number, and total. **a** Number of additional therapies combined with systemic corticosteroids. **b** Ranking of systemic corticosteroids. **c** Ranking of additional therapies combined with systemic corticosteroids. *cGvHD* chronic graft-versus-host disease, *mTOR* mammalian target of rapamycin, *TAI* thoraco-abdominal irradiation

An analysis of second-line treatment patterns by Wolff and Lawitschka [8] also concluded that strict second-line pathways for cGvHD are not applicable but need to rely on 'trial-and-error-systems'. The authors also identified the relevant treatment options mentioned, such as CNIs, rituximab, ECP, or MMF. Again, findings from Bachier et al. [19] showed comparable results. Overall, 25 unique therapeutic agents were identified as treatment options for cGvHD and over 80% of patients with documented cGvHD received systemic corticosteroids. Thus, corticosteroids appear to be the only uniform standard approach to tackle cGvHD to date, resulting in an urgent need for additional standardized approaches. In fact, several prospective randomized studies on cGvHD are being conducted that will hopefully change the treatment landscape soon.

Besides patients with documented cGvHD, we found a high number of patients with estimated but undocumented cGvHD. These patients received, on average, three or more medications related to cGvHD within 1 year. 87% of patients were hospitalized at least once and, on average, 4.4 times within 3 years, representing a greater resource utilization compared with patients without GvHD. Since 56.9% of the total included cGvHD patients were estimated cases, findings regarding survival, hospitalization, and treatment utilization reveal an extensive use of resources and an overall high burden associated with estimated cGvHD in Germany. This underlines the high medical need for new interventional strategies to improve survival and quality of life in patients after allo-HCT. Those strategies should also encompass hospital care financing because current hospital revenues stemming from the standard rating benchmark catalog (EBM) seem to be insufficient for providing guideline-oriented medical care for allo-HCT survivors [21].

Several limitations of this study must be addressed. Administrative data such as claims data in general are not designed for research purposes and contain only a very limited set of medical parameters. Due to the lack of relevant clinical variables, we did not make an attempt to explain survival by a multivariable model. A common problem in any database analysis is the coding quality as disease codes do not always reflect clinical reality [22]. We tackled this issue by identifying cGvHD patients not only by their documented diagnosis but also by the medical treatment, specifically by use of corticosteroids. However, some uncertainties about patient selection in this study remain.

5 Conclusions

Consistent with previous studies, we found survival outcomes after allogeneic hematopoietic cell transplantation were best in patients with mild cGVHD, possibly due to the graft-versus-leukemia effect. However, overall mortality was still high and there is a strong medical need for new therapy options such as innovative cell and gene therapies.

Declarations

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Conflict of interest/competing interest Marie Eckart is an employee of Janssen-Cilag. Jörg Mahlich and Robert Kudernatsch were employed at Janssen-Cilag during the conduct of this study and may hold stocks from JNJ. Vincent Straub, Berit Libutzki, and Chiara Feig are employees of HGC, a consulting company that received funding from Janssen-Cilag to conduct this study in collaboration with the Institute for Applied Health Research Berlin GmbH (InGef) in line with the study protocol. Christof Scheid 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.

Ethics approval The analysis did not involve any decisions regarding interventions or the omission of interventions. 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 to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Analysis datasets will not be shared or stored at a public repository, and can be assessed upon reasonable request at the Institute for Applied Health Research Berlin (InGef).

Code availability Available upon reasonable request at the Institute for Applied Health Research Berlin (InGef).

Author contributions CS, RK, CF, ME, VC, BL, and JM were involved in the study design, statistical analysis plan, and interpretation of the results. VS drafted the manuscript, and CS and JM edited the manuscript. All authors read and approved the final version of the manuscript.

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