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ORIGINAL ARTICLE

Major central nervous system complications after allogeneic stem cell transplantation: A large retrospective study on 888 consecutive adult patients

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Abstract

Objectives: Major complications affecting the central nervous system (CNS) present a challenge after allogeneic stem cell transplantation (allo-SCT).

Methods: Incidence, risk factors, and outcome were retrospectively analyzed in 888 patients in a monocentric study.

Results: Cumulative incidence (CI) of major CNS complications at 1 year was 14.8% (95%CI 12.3%-17.2%). Median follow-up is 11 months. CNS complications were documented in 132 patients: in 36 cases, classified metabolic; 26, drug-related neurotoxicity (14 attributed to cyclosporine A, 4 to antilymphocyte globulin); 11, cerebrovascular (ischemic n = 8, bleeding n = 3); 9, infections; 9, psychiatric; and 9, malignant. The cause of CNS symptoms remained unclear for 37 patients (28%). Multivariate analysis demonstrated an association of CNS complication with patient age ($P < .001$). The estimated OS of patients with any CNS complication was significantly lower than in patients without neurological complications ($P < .001$), and the CI of non-relapse mortality (NRM) was higher for patients with CNS complication ($P < .001$). A significant negative impact on survival can only be demonstrated for metabolic CNS complications and CNS infections (NRM, $P < .0001$ and $P = .0003$, respectively), and relapse ($P < .0001$).

Conclusion: CNS complications after allo-SCT are frequent events with a major contribution to morbidity and mortality. In particular, the situations of unclear neurological complications need to be clarified by intensive research.

KEYWORDS

allogeneic transplantation, central nervous system, complications

1 | INTRODUCTION

Allogeneic stem cell transplantation (allo-SCT) is a curative approach for high-risk hematological malignancies and non-malignant diseases. Despite continuous improvements in the prevention and clinical management of drug-related toxicity, graft-versus-host disease (GVHD), and opportunistic infections, the failure rate of allo-SCT is still a major issue. Relapse incidence depends on the underlying disease. Non-relapse mortality (NRM) occurs in approximately 20% of patients.[1] An accurate estimation of NRM incidence and severity is difficult because it depends on a large number of patient-related and treatment-related variables (age, comorbidity, pre-treatment, conditioning intensity, infectious epidemiology). NRM is caused by many different complications. In particular, central nervous system (CNS) complications after allo-SCT are regarded a frequent complication. The incidence of CNS complications has been calculated to be between 11% and 56%.[2-8] Among the possible mechanisms that cause CNS side effects and diseases after allo-SCT, the most common are drug toxicity (calcineurin inhibitors,[9] methotrexate, busulfan, other cytotoxic agents, irradiation, azoles), opportunistic infections,[10-15] impairment of metabolic homeostasis due to sepsis or organ failure, and CNS relapse of the underlying malignancy. There is a wide overlap between the clinical features of different CNS syndromes. Thus, in clinical practice, the differential diagnosis is difficult. The ensuing delay in clinical management may lead to a significant increase in mortality rate.

Here, a retrospective analysis of all major CNS complications affecting patients transplanted in one institution during a 5-year period was performed in order to evaluate the incidence of diverse categories of CNS diseases, to identify risk factors and to analyze the impact on the outcome of allo-SCT.

Novelty statement

1. New aspect of this work: The proportion of major CNS complications with unclear etiology is 28%.
2. Central finding of this work: Higher age is the main risk factor for the development of major CNS complications after allogeneic stem cell transplantation.
3. Specific clinical relevance of this work: Expectations of the course of specific major CNS complications are set into perspective.

2 | DATA COLLECTION AND STATISTICAL ANALYSIS

All major CNS complications occurring during post-transplant follow-up were reviewed through chart review. Major CNS complications were defined by neurological symptoms that required brain imaging with either CNS computer tomography (cCT) or CNS magnetic resonance imaging (cMRI) at least once, and/ or lumbar puncture (LP) at the discretion of the treating physician. According to respective clinical, radiological, and laboratory findings, CNS complications were classified into 7 different pathogenetic categories: *toxicity-related*, *metabolic* (defined as secondary to systemic sepsis, electrolyte disorder, renal or liver failure), *infectious*, *cerebrovascular*, *psychiatric*, *malignant* (defined as CNS relapse of the underlying disease), and *unclear*. Categorical variables were compared between groups using the Pearson χ^2 test. Continuous variables were compared between groups using the Mann-Whitney U test. Overall survival (OS) was estimated by the method of Kaplan and Meier survival using the *survminer* package in R, and compared by the log rank test. Cumulative incidences (CIs) of major CNS complications, of NRM, and of relapse were calculated with the *cmprsk* package in R.[16,17] Death due to any cause was considered a competing risk when estimating the CI of CNS complications. NRM and relapse were considered competing risks. Tests were carried out two-sided, and statistical significance was assumed when $P < .05$. Where indicated, statistical analysis was performed using R version 3.5.3 "Great Truth".[18] Else, SPSS Statistics was used (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0). Treatment of patients followed standard operating procedures that in parts have been published elsewhere.[19]

3 | PATIENTS

All 888 consecutive patients who received an allo-SCT at the Department of Stem Cell Transplantation of the University Medical Center Hamburg-Eppendorf between January 2014 and December 2018 were analyzed. Median follow-up was 11 months after transplant. Patients were at a median age of 58 (range 18-79) years. Transplantation was for high-risk hematological malignancies (n = 872, including 358 acute myeloid leukemias, 303 other myeloid neoplasia, 59 acute lymphoblastic leukemias, 78 lymphomas, and 74 plasma-cell disorders) and non-malignant diseases (n = 16, including 13 aplastic anemia, 1 autoimmune disease, and 2 rare inherited disorders). The majority of patients received a peripheral blood stem cell graft (n = 834, 93.9%). In 77.3% of cases, the donor was unrelated (n = 687), and in 4.2% of cases, the donor was haploidentical relative (n = 37). Conditioning regimens were classified according to the current definition into myeloablative (MAC, n = 500, 56.3%) and reduced-intensity (RIC, n = 388, 43.7%).[20] Total-body irradiation (TBI) was administered to 211 patients (23.8%). Acute GVHD (aGVHD) of any grade was experienced by 486 patients (54.7%), and the total incidence of chronic GVHD was 36% (cGVHD, n = 322). Patients and transplant characteristics are summarized in Table 1.

4 | RESULTS

Major CNS complications after allo-SCT occurred at a frequency of 14.9% (132/888). CI of major CNS complications at 1 year

TABLE 1 Patient and transplant characteristics and association with the incidence of CNS complications

Variable	All patients	Without CNS complication (%)	With CNS complication (%)	Statistical significance (*P*-values)
Patients	888	762 (85.81)	132 (14.19)	
Sex male	538	456 (84.76)	82 (15.24)	.696
Age median (range)	58 (17-79)	57 (17-77)	62 (19-79)	**.001**
Diagnosis				
AML	358	311 (86.87)	47 (13.13)	.229
ALL	59	49 (83.05)	10 (16.95)	
MDS, MPN	303	253 (83.50)	50 (16.50)	
Lymphoma (NHL/ HD)	78	62 (79.49)	16 (20.51)	
Plasma-cell neoplasia	74	65 (83.84)	9 (16.16)	
Non-malignant diseases	16	0	0	
CD34+ $\times 10^6$ cells (graft), Median (range)	7.1 (0.13-17.9)	7.1 (0.13-17.9)	6.8 (1.25-12.2)	0.684
Type of donor				
Unrelated	687	577 (81.07)	110 (18.93)	0.17
Related	201	179 (89.05)	22 (10.95)	
HLA matching				
Matched	851	734 (86.25)	117 (13.75)	.098
Haploidentical	37	28 (75.67)	9 (24.33)	
Patient CMV				
Positive	519	440 (84.78)	79 (15.22)	.342
Negative	367	315 (85.83)	52 (14.17)	
Donor CMV				
Positive	487	412 (84.60)	75 (15.40)	.621
Negative	401	344 (85.78)	57 (14.22)	
Stem cell source				
PBSC	834	710 (85.13)	124 (14.87)	.916
BM	54	46 (85.18)	8 (14.82)	
Conditioning intensity				
MAC	500	441 (88.20)	59 (11.80)	**.004**
RIC	388	315 (81.18)	73 (18.82)	
TBI	211	180 (85.31)	31 (14.69)	.936
IST (GVHD prophylaxis)				
ATG	680	579 (85.15)	101 (14.85)	0.986
MTX	6	5 (83.3)	1 (16.7)	.903
CSA	739	632 (85.52)	107 (14.48)	.323
MMF	778	656 (84.31)	122 (15.69)	.319
TAC	90	70 (78.8)	20 (22.2)	.160
mTOR inhibitor (EVE, SIR)	8	7 (87.5)	1 (12.5)	.888
Acute GVHD	486	406 (83.54)	80 (16.46)	.187
Chronic GVHD	322	280 (86.96)	42 (13.04)	.235

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, anti–T-lymphocyte globulin; BM, bone marrow; CSA, cyclosporine A; IST, immunosuppressive therapy; MAC, myeloablative conditioning; MDS, myelodysplasia; MMF, mycophenolic acid; MPN, myeloproliferative neoplasia; mTOR, mammalian target of rapamycin, EVE, everolimus, SIR, sirolimus; MTX, methotrexate; PBSC, peripheral blood stem cells; RIC, reduced-intensity conditioning; TAC, tacrolimus; TBI, total-body irradiation. Statistically significant values are displayed in bold numbers.

was 14.8% (95% CI 12.3%-17.2%), and at 2 years, 16.4% (95%CI 13.7%-19.1%). The onset of neurological symptoms occurred at a median time of 52 days after transplantation (range start of conditioning—1243 days after transplantation). Neurological complications mostly occurred in the first 100 days after transplantation (87/132, 66%). Most common neurological symptoms (Table 2) were cognitive impairment with confusion or delirium (n = 48), vigilance impairment (n = 26), cephalgia (n = 11), seizure (n = 16), aphasia/dysphasia (n = 13), motor impairment or muscular weakness (n = 18), ocular symptoms (anisocoria n = 2, diplopia n = 4), recurrent syncope (n = 8), depression (n = 3), and psychosis (n = 3). Mostly, more than one characterizing symptom or sign were observed. Diagnostic workup included at least one cCT (n = 87 patients), one cMRI (n = 79), and one LP (n = 55).

TABLE 2 Prevalent neurological symptoms/ signs

Prevalent symptoms/signs	Patients (n)
Cognitive impairment, disorientation, confusion	48
Vigilance impairment	26
Motor impairment, weakness	18
Seizure	16
Aphasia/dysphasia	13
Cephalgia	11
Dizziness	10
Syncope (relapsing)	8
Ocular symptoms, diplopia	4
Psychosis	3
Depression	3
Meningismus/neck stiffness	1

TABLE 3 Classification of CNS complications

Category	n (%)
Metabolic	36 (27.3)
Drug-related toxicity	26 (19.7)
Infectious	9 (6.8)
Hematological relapse	9 (6.8)
Cerebrovascular	11 (8.3)
Psychiatric	4 (3)
Unclear	37 (28)

4.1 | Categories of CNS complications

The final neurological diagnosis (Table 3) was classified as metabolic in 36 cases (27.3%). In 26 cases, the etiology was assumed to be drug-related (19.7%): Of them, 14 were attributed to cyclosporine A (CSA) toxicity, and 4 to antilymphocyte globulin. Eleven cases (8.3%) were classified as cerebrovascular events (ischemic n = 8, bleeding n = 3). Nine patients (6.8%) had an infectious CNS complication: 2 Epstein-Barr virus–related, 3 cytomegalovirus-related, 1 JC virus–related, 1 human herpesvirus 6–related, 1 septic embolism, and 1 CNS toxoplasmosis (Table 4). The clinical characteristics of the infectious complications are summarized in Table 5. Nine patients (6.8%) experienced a hematological relapse of the underlying disease because of which they had received allo-SCT. CNS relapses occurred in 4 patients affected by acute leukemia (3 AML and 1 ALL), two patients affected by myelodysplastic syndromes, two patients affected by non-Hodgkin lymphoma, and one patient affected by multiple myeloma. Eight out of these nine patients were in remission before transplant, whereas one patient with primary CNS diffuse large B-cell lymphoma had active disease at the time of allo-SCT. Despite the clinical, radiological, and laboratory investigations, for 37 patients (28.0%) the cause of CNS symptoms remained unclear.

4.2 | Risk factors

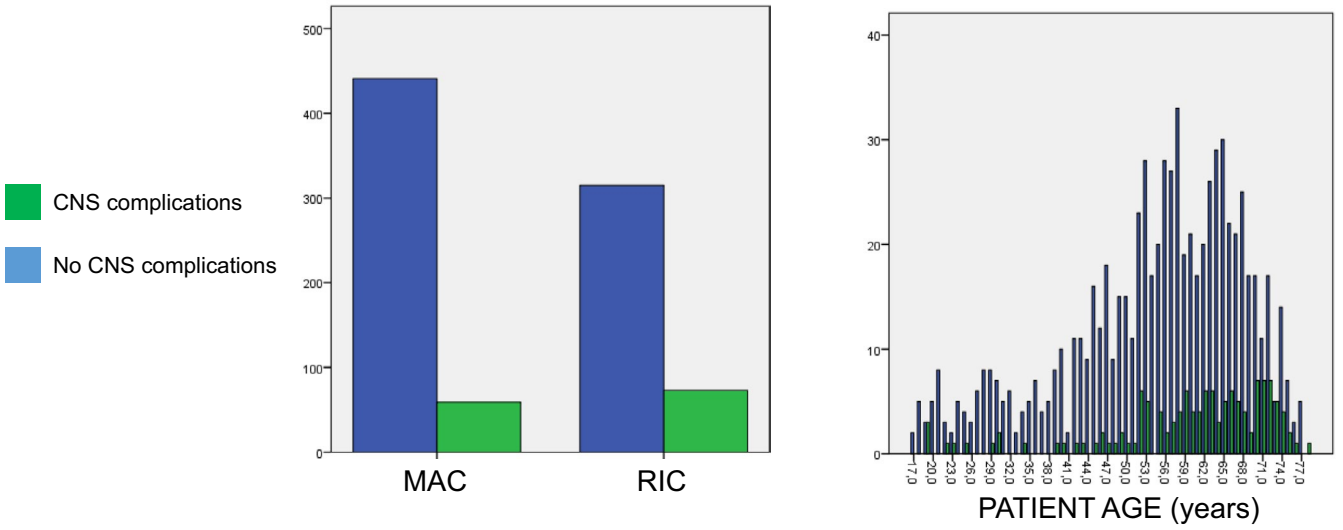
As shown in Table 1, the no statistically significant association was found between the occurrence of CNS complication and the type of transplant (related/unrelated and haploidentical/matched), type of diagnosis (AML, ALL, other myeloid, plasma cell disorder, lymphoma, non-malignant), the use of different immunosuppressive drugs (antilymphocyte globulin, CSA, tacrolimus, mycophenolic acid), patient and donor sex or age, patient and donor CMV serostatus, or number of transplanted CD34+ cells. Major CNS complications

TABLE 4 Results of cerebrospinal fluid examination in different categories of CNS complications

CSF investigation	Unclear	Metabolic	Toxicity	Relapse	Infectious
Patients with diagnostic LP, n (%)	14 (37.8)	13 (35.3)	11 (42.3)	8 (88.9)	8 (88.9)
Protein level n. elevated/ n. performed, median (range), mg/L	8/14 794 (416-2148)	4/13 479.5 (234-1701)	6/10 572 (286-1487)	8/8 980.5 (469-2406)	6/8 753 (435-1969)
Cell count n. elevated/ n. performed, median cells (range)/μL	11/14 54 (4-603)	8/13 14.5 (1-248)	3/10 5 (1-31)	6/8 39.5 (1-1096)	5/8 14.5 (0-36)
Cytomorphology abnormality (frequency)	Lymphocytic pleocytosis (4/9)	Lymphocytic pleocytosis (1/6)	Lymphocytic pleocytosis (1/10)	Presence of blasts (6/8)	Lymphocytic pleocytosis (1/4)
Flow cytometry n. abnormal/n. performed	0/3	0/1	0/5	3/4	0/2

TABLE 5 Infectious complications

Patient	Age	Diagnosis	Transplant	CNS complication clinical features	Imaging	Microbiology findings	Final neurological diagnosis	Outcome
#1	59	MDS	MUD	Vigilance impairment, motor hemisyndrome	(MRI) paraventricular and basal ganglia hyperintensity in FLAIR	EBV (4500 cp/mL in CSF)	EBV-encephalopathy	TRM
#2	56	MDS	MUD	Delirium	(MRI) Multifocal cortical/subcortical T2-hyperintense lesions	*Toxoplasma gondii* (qualitative PCR in CSF)	Toxoplasma encephalitis	TRM
#3	72	MDS	MUD	Vigilance impairment, disorientation	(MRI) No aberrant image	EBV (20 000 cp/mL in CSF)	EBV-encephalopathy	TRM
#4	65	AML	MUD	Dysphagia, dysarthria, tetraparesis	(MRI) Subcortical T2-hyperintense lesions with gadolinium-enhancement	JC virus (1000 cp/mL in CSF)	Progressive multifocal leukoencephalopathy (PML)	TRM
#5	39	MDS	MUD	Disorientation, psychosis	(MRI) Bilateral T2-hyperintensity of hippocampi and amygdala	HHV-6 (9000 cp/mL in CSF)	HHV6-related limbic encephalitis	Resolution
#6	46	NHL	MUD	Disorientation, confusion	(CT scan) No aberrant image	CMV (1000 cp/mL in CSF)	CMV encephalopathy	TRM
#7	40	AML	MUD	Muscular weakness, diffuse paresthesia	(MRI) Paraventricular T2-hyperintense lesions. (ENG/EMG) Demyelinating PNP	CMV primary infection (serology + PCR in blood)	CMV-triggered encephalitis/ polyneuropathy	Resolution
#8	71	MDS	MUD	Motor hemisyndrome, septic shock	(MRI) Multiple septic emboli	No pathogen isolation	Intracranial septic embolism	TRM
#9	61	PMF	MUD	Dysphagia, paraparesis, disorientation	(MRI) Multiple paraventricular T2-hyperintense lesions	CMV (3×10^7cp/mL in CSF)	CMV encephalopathy	TRM



Multivariate regression analysis

Variables	Sign.
MACRIC	,156
PATage	,001

FIGURE 1 Distribution of CNS complications among MAC/ RIC transplants and according to patient age

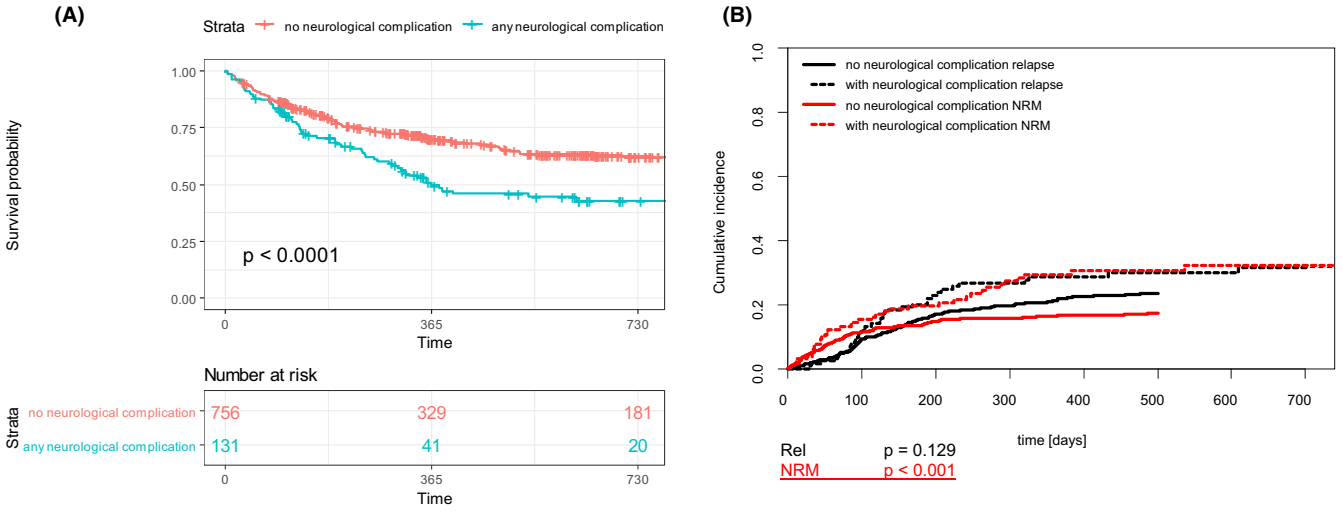


FIGURE 2 (A) Impact of CNS complications on overall survival. (B) Cumulative incidence of non-relapse mortality and relapse stratified according to the occurrence of CNS complications

after allo-SCT are significantly more frequent in older patients ($P < .001$). Age was considered as a continuous variable. As depicted in Figure 1, a significantly higher proportion of patients after RIC-based transplantation experienced CNS complications (RIC vs MAC; $P = .004$). The significance of the impact of conditioning intensity was lost when entered into a multivariate regression analysis with patient age ($P = .156$). Patients with an unclear CNS complication did not show a higher occurrence of acute or chronic GVHD (Pearson's χ^2, $P = .187$ and $P = .235$, respectively). No significant difference was found in the proportion of CNS complication categories in the early (<100 days) and late (>100 days) post-transplant phase. In particular, although metabolic neurological complications are more frequent in the early phase after allo-SCT (32% of CNS complications occurring before day 100% vs 17% of those occurring later), statistical significance was missed ($P = .07$).

4.3 | Impact of CNS complications on allo-SCT outcome

The estimated OS of patients with any CNS complication is significantly lower (49.7%, 95% CI 41.1%-60.1%, at 1 year) than that of

patients without neurological complications (70.2%, 95% CI 66.7%-73.8%, respectively, $P < .001$; Figure 2). CIs of relapse and of NRM between each group of CNS complications and the group without CNS complications were compared exploiting a competing risk model. The CI of relapse was higher for patients with CNS complications, but the difference did not reach statistical significance ($P = .129$), whereas the CI of NRM was significantly higher for patients with CNS complications. One-year NRM of patients with CNS complications vs without CNS complications was 29.4% (95% CI 21.1%-37.8%) and 16.7% (95%CI 13.9%-19.4%), respectively ($P < .001$). Metabolic CNS complications and CNS infections significantly increased the probability to experience NRM ($P < .0001$ and $P = .0003$, respectively). Patients in the neurotoxicity category, patients in the cerebrovascular category, and patients with unclear CNS symptoms neither showed a statistically significant CI of relapse nor NRM in comparison with the complication-free group. Finally, as expected, CNS relapse is strongly correlated with the probability of systemic disease relapse ($P < .0001$). The impact on NRM and relapse incidence of each CNS complication group is depicted in Figure 3.

5 | DISCUSSION

We confirmed that CNS complications are a common event after allo-SCT, reporting a frequency of 14.2%, in line with the current literature.[4-8] In one report from 1998, a significantly higher frequency of neurological complications was reported.[3] In this work, the setting was prospective and the authors included peripheral nervous system complications. Thus, this broader approach does not contradict our results as our analysis focused on major complications of the CNS, which were recorded retrospectively.

In our analysis, the most important risk factors statistically associated with the occurrence of CNS complications is patient age. In previous reports, the use of TBI in the conditioning regimen was associated with a higher risk of CNS complications.[6] The results presented here are unable to confirm this association. The cited study includes a large number of patients receiving high-dose TBI (12 Gy), whereas in our study population, the use of TBI >8 Gy is rare (14.6%). In univariate analysis, we modeled a positive effect of reduced-intensity compared to myeloablative conditioning on CNS complications; that is, complications were significantly higher in the RIC group. Multivariate regression did not confirm the independent impact of conditioning intensity ($P = .165$), most likely explained by the fact that RIC transplantation is mostly used for elderly patients. RIC is an independent risk factor in a recent publication by Sakellari et al[7] that also analyzed a very large monocentric cohort. In contrast to the data demonstrated here, age was not a risk factor in the work by Sakellari et al[7] In addition, the population they analyzed was fairly younger with a median age of 36 years versus 59 years in our analysis, which might explain the

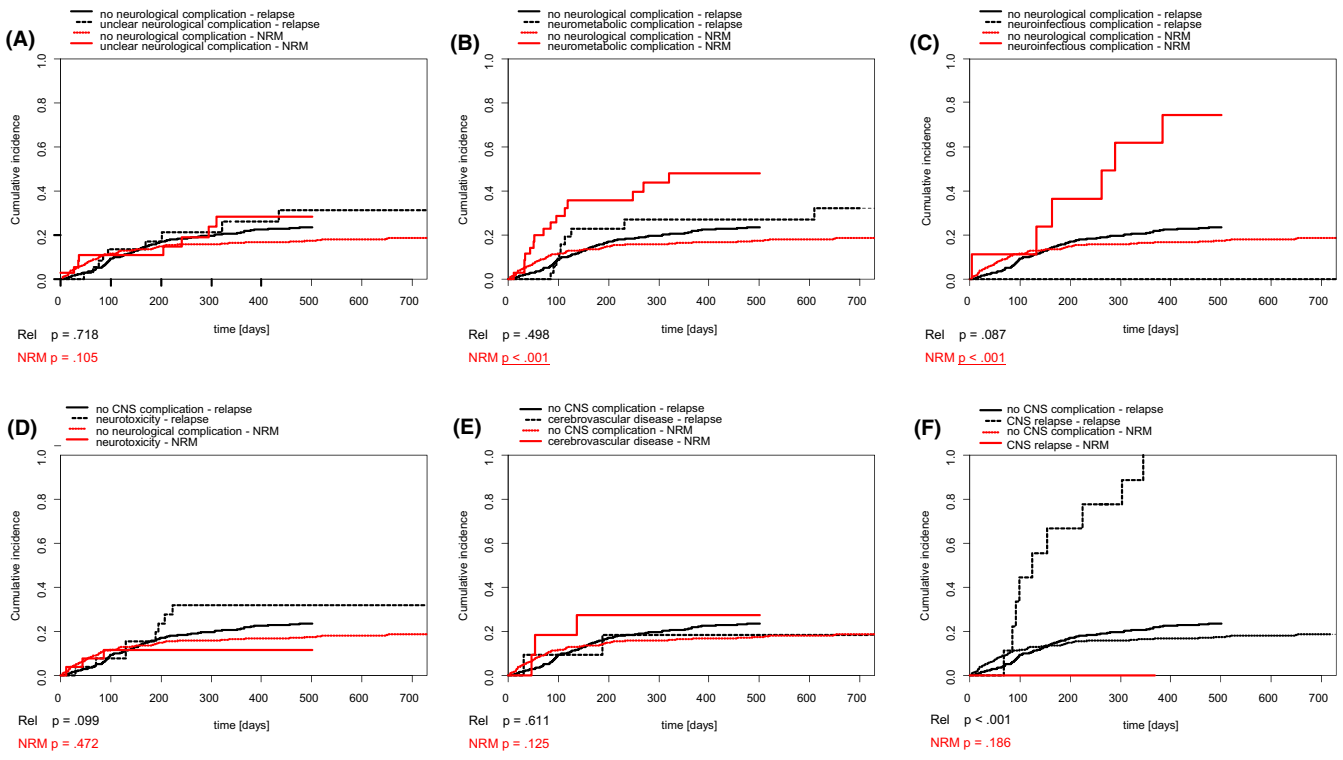


FIGURE 3 Cumulative incidence of non-relapse mortality and relapse in different groups of CNS complications in comparison with NRM and relapse of patients without CNS complications. (A) unclear CNS complications; (B) metabolic-related CNS complications; (C) infectious CNS complications; (D) drug toxicity; (E) cerebrovascular complications; (F) CNS relapse of hematological malignancy

contradictory findings.[7] Prospective data collection of cases taking into account performance status (Karnofsky/ECOG score) and comorbidity (Sorror score) of the patients is needed to eventually confirm the significance of these data.

Our data demonstrate that the diagnostic efficacy regarding complications of the CNS is still unsatisfactory in a considerable proportion of cases. For more than one-fourth of patients with CNS complications, a diagnosis that reflects the etiology of the CNS complications and transcends a merely descriptive denomination had not been established. The CI of relapse and NRM of this specific group of patients in comparison with the patients without neurological complications is not different. Clinical reports and preclinical evidence suggest that post-transplant neurological symptoms may be due to an alloimmune pathogenesis[21-23] but CNS-GVHD still is a controversial entity. In previous reports,[7,8] the occurrence of CNS-GVHD is related to systemic GVHD; in our study population, we could not document any association between the occurrence of unclear CNS complication and both aGVHD and cGVHD. Prospective accurate evaluation of the unclear CNS complications is needed to clarify the possible pathogenetic mechanism in order to improve the clinical management of these conditions.

The cited papers[1-7] exploring neurological complications after allo-SCT showed a strong impact on mortality. In the study presented here, we confirm a significantly increased CI of NRM for the patients experiencing CNS complications; in addition, we demonstrate that the excess mortality is mostly due to the metabolic and infectious complications, whereas the other categories of CNS complications, independently analyzed, had no significant impact on NRM.

Retrospective in nature, the results presented here might be an underestimation of neurological complications after allo-SCT. Late complications treated in different hospitals might evade the tightest scrutiny of documentation efforts. Additionally, neurological complications that are less severe and do not prompt the workup with imaging and LP cannot be respected in such an analysis. Those include hallucinations associated with triazole use. Through the large population screened, estimations are still reliable and provide a realistic view on the situation.

In conclusion, CNS complications of allo-SCT are a major cause of morbidity and mortality after allo-SCT, limiting the safety of the procedure in particular for elderly patients who are increasingly transplanted worldwide.[1] Early diagnostics and timely targeted treatment in the presence of CNS-related clinical manifestations may be required to improve clinical outcome of allo-SCT.

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CONFLICT OF INTEREST

The authors declare no conflict of interest with regard to this manuscript.

AUTHOR CONTRIBUTIONS

DM, MC, and NK designed the study. DM and MC wrote the manuscript. DM and MC performed statistical analysis. LB, AB, WB, TU, CW, FA, NF, JF, UG, SR, and CC contributed to primary data analysis (clinical assessment, microbiological assessment, neuroradiological assessment) and collection and were cardinal to treatment decisions.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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