Incidence, Risk Factors and Complications of Ocular Graft-Versus-Host Disease Following Hematopoietic Stem Cell Transplantation

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• PURPOSE: **The purpose of this research was to evaluate the incidence, risk factors, and complications of ocular graft-versus-host disease (GVHD) in a large single-center study.**

• DESIGN: **Retrospective observational case series.**

• METHODS: **This study included 283 patients who underwent hematopoietic stem cell transplantation (HSCT) between 2005 and 2020. Ocular GVHD was diagnosed according to International Chronic Ocular GVHD Consensus Group criteria. Potential risk factors for ocular GVHD were evaluated using the Cox proportional hazards model.**

• RESULTS: **The cumulative incidence of ocular GVHD was 19.7% at 1 year, 29.3% at 2 years, 40.7% at 3 years, 47.2% at 4 years, and 49.7% at 5 years. Ocular GVHD was significantly associated with recipient age (hazard ratio [HR]: 1.228; 95% confidence interval [CI]: 1.033–1.459; $P = .020$); female sex (HR: 1.797; 95% CI: 1.195–2.703; $P = .005$); peripheral blood stem cell use (PBSC) (HR: 2.079; 95% CI: 1.268–3.411; $P = .004$); and previous acute GVHD (HR: 1.276; 95% CI: 1.073–1.518; $P = .006$). Ocular complications after HSCT included cataract, corneal ulcer, corneal perforation, lacrimal obstruction, herpetic keratitis, and cytomegalovirus retinitis.**

• CONCLUSIONS: **Half of patients developed ocular GVHD in the 5 years following HSCT. Older age, female sex, use of PBSC, and acute GVHD disease were significant predictors of ocular GVHD. Hematologists and ophthalmologists should be aware of its vision threating complications.**

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Hematopoietic stem cell transplantation (HSCT) is the only definitive therapeutic strategy for a large group of hematological, autoimmune, and hereditary disorders.[1] Graft-versus-host disease (GVHD) continues to be a leading cause of morbidity and mortality after allogeneic HSCT, limiting its chances of success.[2] The condition is the result of a highly complex immune process, involving donor T-cell responses to host antigens and the dysregulation of pro-inflammatory cytokines followed by the development of immunity-mediated inflammation and fibrosis of target tissues and organs.[3]

In the past, the distinction of acute versus chronic GVHD was based on the time of its onset. Acute GVHD was defined as disease occurring in the first 100 days after transplantation, whereas GVHD occurring after 100 days was referred to as chronic.[4] However, this arbitrary distinction did not account for the differences in pathogenesis and clinical manifestations of the 2 forms. Thus, the US National Institutes of Health (NIH) consensus development project defined new criteria for the diagnosis, recommending that acute and chronic GVHD should be distinguished based on clinical manifestations.[5] Although acute GVHD is characterized by maculopapular erythematous rash, cholestatic hepatitis, and gastrointestinal symptoms, chronic GVHD is a pleiotropic multiorgan syndrome whose diagnosis requires at least 1 diagnostic manifestation or 1 distinctive manifestation confirmed by biopsy or other testing.[6]

Ocular GVHD is a frequent manifestation of chronic GVHD, occurring in 30%–60% of patients after HSCT.[7-9] Dry eye disease associated with fibrosis of lacrimal and meibomian glands, superficial punctate keratopathy, and conjunctival scarring represent the hallmark of the disease. In more severe cases, the disease may be complicated by corneal neovascularization, infectious keratitis, and sterile corneal perforation leading to melting and perforation.[9,10] Previously reported risk factors for ocular GVHD include acute GVHD,[8] diabetes mellitus,[11] and non-white ethnicity.[12] However, results of the available studies are inconsistent, and the incidence of other complications than dry eye disease remains largely undetermined.

The objective of the present study was to evaluate the incidence, risk factors, and complications of ocular GVHD. For this purpose, a retrospective study was conducted using

data involving 283 hematological patients who underwent allogeneic HSCT in a single Italian center.

MATERIALS AND METHODS

This single-center retrospective study included adult patients who received a first allogeneic HSCT between January 2005 and January 2020 at the Hematology Units of the S.Orsola-Malpighi University Hospital (Bologna, Italy) and underwent subsequent ocular surface examinations at the Ophthalmology Unit of the same hospital. Exclusion criteria included survival <100 days after transplantation; presence of other ocular surface disorders or any systemic disease potentially affecting the ocular surface at the time of HSCT; and missing ophthalmological data after HSCT. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee (Comitato Etico di Area Vasta Emilia Centro della Regione Emilia-Romagna).

The source of stem cells was bone marrow (BM), peripheral blood, or cord blood. All donors were matched related or matched unrelated donors. Human leukocyte antigen (HLA) compatibility was based on the best available typing results at the time of the analysis. The conditioning was myeloablative or reduced-intensity regimen based on patient age, previous treatments, comorbidities, and status of malignancy. All patients underwent GVHD prophylaxis using either cyclosporine and methotrexate or cyclosporine and mycophenolate mofetil. Demographic and hematological data, including age, sex, primary hematological disorder; type of donor and source of hematopoietic stem cells; intensity of conditioning; age and sex of donor; presence of sex; HLA and ABO type mismatch; and cytomegalovirus (CMV) donor positivity were recorded for each patient.

We defined standard-risk diseases as acute myeloid leukemia and acute lymphoblastic leukemia in first or

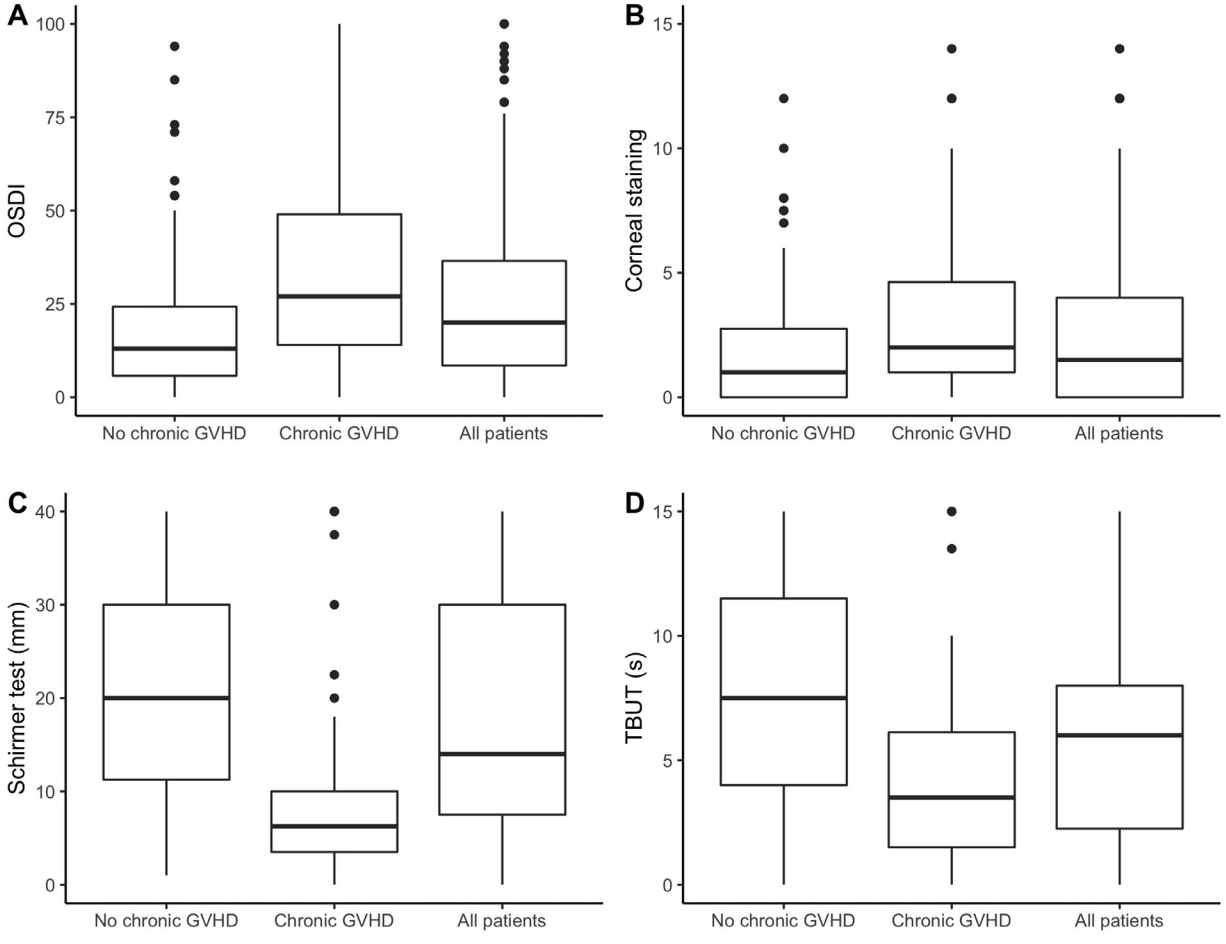

FIGURE 1. Boxplots of OSDI. .A. OSDI; .B. corneal staining; .C. Schirmer test; and .D. TBUT 5 years following allogeneic HSCT. All parameters are significantly different between patients with and without chronic GVHD.
GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; OSDI = ocular surface disease index; TBUT = tear break-up time.

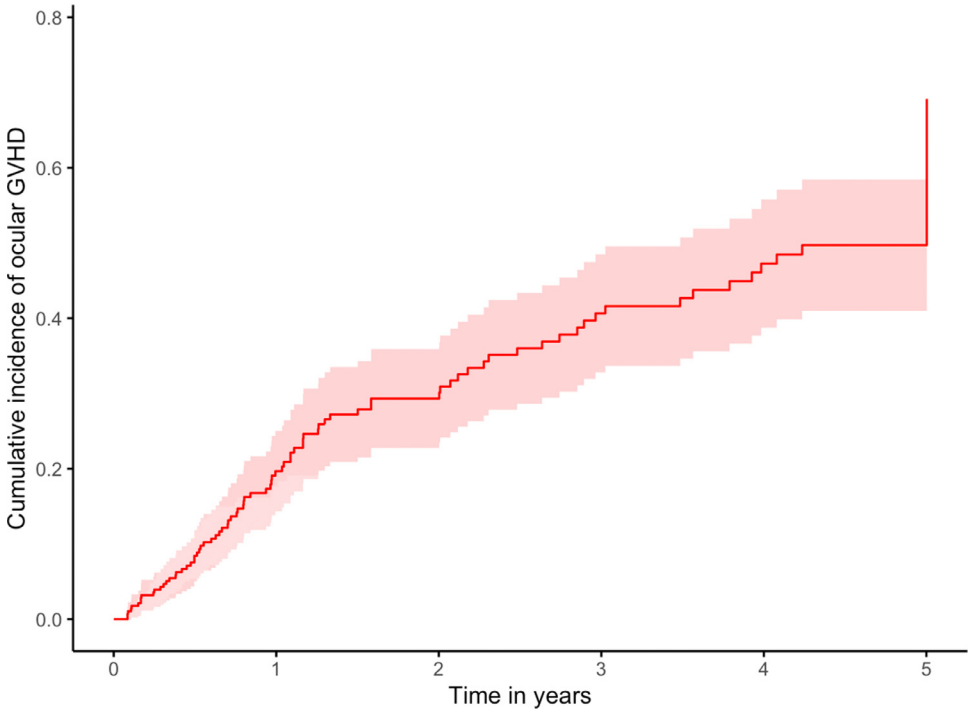

FIGURE 2. 5-year cumulative incidence curve of ocular GVHD following allogeneic HS
GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation.

second remission; chronic myeloid leukemia in the first or second chronic phase or in the accelerated phase; myelodysplastic syndrome with refractory anemia or refractory anemia with ringed sideroblasts; and aplastic anemia. All other conditions were defined as high risk. Grading of acute GVHD was performed in on a scale of 0–IV according to the Glucksberg classification system.[13] The severity of chronic GVHD was scored using 2014 NIH criteria, which uses a scale of 0–3 scale for each organ and a global score of mild, moderate, or severe.[6]

Ophthalmic examinations after HSCT were performed at months 3, 6, and 12, and every year thereafter. A subgroup of patients was also examined before HSCT 7 to 9 days before the beginning of the conditioning regimen. Subjective ocular discomfort symptoms were scored by using the Ocular Surface Disease Index (OSDI) validated questionnaire.[14] Subsequently, all patients underwent a comprehensive ocular surface examination including tear film break-up time (TBUT), corneal staining, and the Schirmer test. TBUT was evaluated after administration of 2 μL of 2% fluorescein dye and measurement of the time interval between the last complete blink and the first appearance of a dry spot or disruption in the tear film. Corneal staining was graded using the National Eye Institute score.[15] The Schirmer test was performed without anesthesia, using test strips kept in the temporal lower conjunctival sac for 5 minutes with closed eyes. Dry eye disease before HSCT was ascertained according to Tear Film and Ocular Surface Society Dry Eye Workshop II Criteria.[16]

The diagnosis of ocular GVHD was based on the International Consensus Criteria on Chronic Ocular GVHD Group, which assigns a scoring point of 0–3 to the Schirmer test, corneal fluorescein staining, and OSDI, and a scoring point of 0–2 to conjunctival injection.[17] However, these criteria were introduced only in 2013, and we did not routinely score conjunctival injection before then. Thus, modified criteria were used without conjunctival injection, and the aggregate was reduced by 1 score point, which was required for reaching the diagnosis: in the presence of systemic GVHD, a score $\geq$5 indicated ocular GVHD; in the absence of systemic GVHD, a score $\geq$7 indicated ocular GVHD. The number of complications were recorded.

The incidence of ocular GVHD was estimated on the basis of cumulative incidence curves, with death following HSCT as a competing risk.[18] The Cox proportional hazards model was used to evaluate the effect of confounding variables on the likelihood of developing ocular GVHD. The following variables evaluated for association included: patient and donor ages at transplantation; hematological diagnosis; donor type; source of HSCT; presence of donor-recipient sex mismatch and HLA mismatch; ABO mismatch; intensity of conditioning regimen (myeloablative vs. reduced intensity); total body irradiation; use of anti-T-lymphocyte globulin; acute GVHD grades 1–4; and donor CMV immunoglobulin G serostatus. Factors having

a P value <0.1 for association with ocular GVHD by univariate testing were added sequentially to a multivariate Cox regression model. Mann-Whitney U test was used to compare the ocular surface parameters in patients with and without systemic GVHD. Continuous variables are reported as mean ± SD, unless otherwise stated. All analyses were conducted using R version 4.0.0 software and RStudio version 1.2.5042 software (R Project, Vienna, Austria).

RESULTS

A total of 283 patients (162 male and 121 female subjects) were included in the study. Mean age at the time of transplant was 45.8 ± 12.2 years (range: 18–72 years). Baseline hematological characteristics are shown in Table 1. A pretransplantation baseline ophthalmic examination was available in 144 patients (50.9%). In those patients, mean OSDI before HSCT was 10.0 ± 11.3, corneal staining was 1.7 ± 2.3, the Schirmer test value was 20.3 ± 13.0 mm, and the TBUT was 8.6 ± 4.6 s.

Following HSCT, 101 patients (35.7%) developed acute GVHD, and 67 patients (23.7%) developed grades II–IV acute GVHD. Among the patients with acute GVHD, 16 of 101 (15.1%) had documented conjunctival involvement in the form of hyperemia, chemosis, or discharge. Conversely, 96 patients (33.9%) developed extraocular chronic GVHD involving the skin in 85 of them (30.0%); in the mouth in 66 (23.3%); the liver in 26 (9.2%); the lung in 37 (13.1%); the joints in 20 (7.1%); the gastrointestinal tract in 15 (5.3%); and the genitalia in 16 (5.7%). Five years following HSCT, mean OSDI was 25.6 ± 20.6, corneal staining was 2.4 ± 3.1, the Schirmer test value was 17.3 ± 12.7 mm, and TBUT was 6.5 ± 4.5 s. As shown in Figure 1, all ocular surface parameters turned out to be significantly worse in patients with systemic GVHD (all $P < .05$).

Figure 2 shows the cumulative incidence curve of ocular GVHD. The cumulative incidence of ocular GVHD was 19.7% at 1 year, 29.3% at 2 years, 40.7% at 3 years, 47.2% at 4 years, and 49.7% at 5 years. The median time from HSCT to the onset of ocular GVHD was 397 days. Among the patients with ocular GVHD, 77.1% had ocular GVHD in the context of systemic GVHD, whereas 22.9% had isolated ocular GVHD.

The factors examined for an association with ocular GVHD by univariate analysis are shown in Table 2. Recipient age and female sex were identified as significant risk factors for ocular GVHD (respectively, $P = .032$, $P = .024$). The use of peripheral blood stem cells (PBSC) was associated with an increased hazard of ocular GVHD ($P = .006$). Acute GVHD (grades I–IV) was a significant predictor of ocular GVHD ($P < .001$). The other factors showed no significant association with the hazard of ocular GVHD (always, $P > .05$).

TABLE 1. Baseline Hematological Characteristics of the Study Cohort

Characteristic	Value
Diagnosis	
ALL	50.0 (17.7)
AML	90.0 (31.8)
CLL	7.0 (2.5)
CML	22.0 (7.8)
HL	26.0 (9.2)
MDS	26.0 (9.2)
MM	20.0 (7.1)
NHL	26.0 (9.2)
Other	16.0 (5.7)
Disease risk	
Standard risk	157.0 (55.5)
High risk	126.0 (44.5)
Source of stem cells	
Bone marrow	87.0 (30.7)
Peripheral blood	182.0 (64.2)
Cord blood	14.0 (4.9)
Type of donor	
Matched unrelated donor	205.0 (72.4)
Matched related donor	78.0 (27.6)
Sex match	
Male-to-male (match)	117.0 (41.3)
Female-to-female (match)	38.0 (13.4)
Female-to-male	45.0 (15.9)
Male-to-female	83.0 (29.3)
HLA compatibility	
Matched	167.0 (59.0)
Mismatched (≥1 antigen)	116.0 (41.0)
ABO compatibility	
Matched	117.0 (41.3)
Mismatched	166.0 (58.7)
Type of conditioning	
Myeloablative	200.0 (70.7)
Reduced intensity	83.0 (29.3)
Total body irradiation	28.0 (9.9)
Anti T-lymphocyte globulin	224.0 (79.2)
Donor CMV positivity	134.0 (47.3)

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CMV = cytomegalovirus; HL = Hodgkin lymphoma; MM = multiple myeloma; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma.

As shown in Figure 3, A, the multivariate Cox model confirmed that the hazard of ocular GVHD was significantly increased in older recipients (hazard ratio [HR]: 1.228; 95% confidence interval [CI]: 1.033–1.459; $P = .020$), female recipients (HR: 1.797; 95% CI: 1.195–2.703; $P = .005$), PBSC (HR: 2.079; 95% CI: 1.268–3.411; $P = .004$), and previous acute GVHD (HR: 1.276; 95% CI: 1.073–1.518; $P = .006$).

TABLE 2. Univariate Cox Regression Analysis of Risk Factors for Ocular GVHD.

Factor	HR	95% CI	*P*
Recipient age (per decade)	1.242	1.043–1.478	.015[a]
Female recipient	1.588	1.063–2.371	.024[a]
Standard-risk disease	1.015	0.676–1.525	.943
Reduced intensity conditioning	1.077	0.674–1.722	.756
Total body irradiation	0.695	0.384–1.257	.229
Anti-T-lymphocyte globulin	1.395	0.849–2.293	.189
Peripheral blood stem cells	1.963	1.218–3.162	.006[a]
Matched unrelated donor	1.222	0.790–1.889	.368
Donor age	1.001	0.985–1.018	.899
Female-to-male match	0.961	0.455–2.033	.918
Male-to-female match	1.593	0.844–3.016	.151
HLA mismatch	1.372	0.893–2.109	.149
ABO type mismatch	1.189	0.789–1.793	.408
Donor CMV positivity	1.053	0.690–1.606	.811
Acute GVHD (grades I–IV)	1.334	1.124–1.583	<.001[a]
Pre-transplantation dry eye disease	1.837	1.060–3.184	.030[a]

CI = confidence interval; CMV = cytomegalovirus; GVHD = graft-versus-host disease; HR = hazard. ratio; HLA = human leukocyte antigen.
[a]$P < .05$.

TABLE 3. Number of Patients Who Developed Ocular Complications Following HSCT

Complications	Number (%)[a]
Cataract	28.0 (9.9)
Corneal ulcer	11.0 (3.9)
Lacrimal obstruction	8.0 (2.8)
Herpetic keratitis	3.0 (1.1)
Cytomegalovirus retinitis	3.0 (1.1)
Retinal detachment	2.0 (0.7)
Corneal perforation	2.0 (0.7)
Branch retinal vein occlusion	2.0 (0.7)
Anterior uveitis	2.0 (0.7)
Pseudophakic cystoid macular edema	2.0 (0.7)
Punctate inner choroidopathy	1.0 (0.4)
Endophthalmitis	1.0 (0.4)
Choroidal neovascularization	1.0 (0.4)

HSCT = hematopoietic stem cell transplantation.
[a]N = 283.

Among the 144 patients who underwent a pre-transplantation baseline ophthalmic examination, 52 patients (36.1%) had dry eye disease already, before HSCT. In univariate analysis, pre-transplantation dry eye disease was significantly associated with an increased hazard of developing ocular GVHD (HR: 1.837; 95% CI: 1.060–3.184; $P = .030$). However, incorporating pre-transplantation dry eye disease in the multivariate model, ocular GVHD was significantly associated with recipient age (HR: 1.452; 95% CI: 1.094–1.928; $P = .010$), female recipients (HR: 2.068; 95% CI: 1.145–3.736; $P = .016$), and previous acute GVHD (HR: 1.380; 95% CI: 1.056–1.805; $P = .019$) but not with pre-transplantation dry eye disease (HR: 1.357; 95% CI: 0.723–2.544; $P = .342$), and PBSC (HR: 1.756; 95% CI: 0.885–3.487; $P = .107$) (Figure 3, B).

The ocular complications observed in the study cohort during the follow-up are reported in Table 3. Cataract was the most common complication, occurring in 28 patients (9.9%). Of those patients, 13 (4.6%) had posterior subcapsular cataract. Mean age at the moment of diagnosis of cataract was 49.8 ± 10.2 years. All patients underwent cataract extraction using phacoemulsification. After surgery, 2 patients developed cystoid macular edema, while endophthalmitis occurred in another 1 patient.

Eleven patients (3.9%) developed corneal ulcer during the follow-up period (Figure 4, A). Despite medical treatment consisting in aggressive lubrications with tear substitutes, topical antibiotics and bandage contact lens, in 2 patients the stromal melting progressed to corneal perforation requiring tectonic penetrating keratoplasty (PK) (Figure 4, B). However, in 1 of those patients, the graft failed to re-epithelialize (Figure 4, C), and the perforation recurred. After multiple repeated PK procedures, each of which failed due to recurrence of corneal perforation, the eye developed phthisis bulbi. Another eye with corneal ulcer underwent Gundersen conjunctival flap (Figure 4, D) and subsequent staged PK due to descemetocele with impending perforation.

Eight patients (2.8%) developed lacrimal obstruction due to punctual/canalicular stenosis (6 patients) or nasolacrimal duct obstruction (2 patients). Dacryocystorhinos-

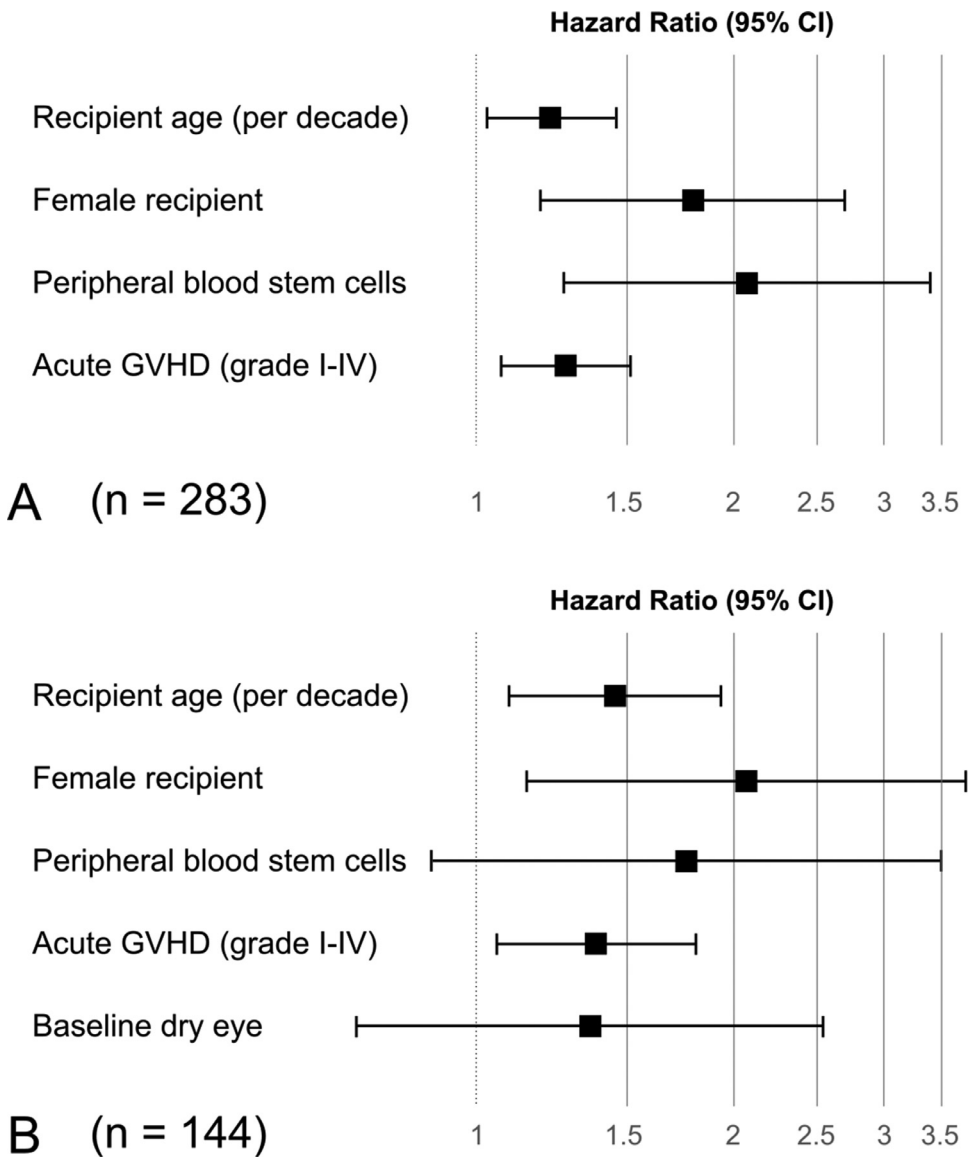

FIGURE 3. Forest plots show the impact of covariates included in the Cox proportional hazards model on the ocular GVHD incidence. Boxes represent the hazard ratios, and the horizontal bars extend from the lower limit to the upper limit of the 95% confidence interval. A. Model applied to all patients (n = 283). B. Model applied to the subgroup of patients who underwent a pre-transplant baseline ophthalmological examination (n = 144). GVHD = graft-versus-host disease.

tomy was performed in 1 patient (0.4%). Less common complications included herpetic keratitis (1.1%), CMV retinitis (1.1%), anterior uveitis (0.7%), retinal detachment (0.7%), branch retinal vein occlusion (0.7%), punctate inner choroidopathy (0.4%) and choroidal neovascularization (0.4%) (Table 3). Most of those infrequent complications occurred in unique patients, except for 3 cases: 1 patient who had both anterior uveitis and punctate inner choroidopathy in the same eye, a second patient who had corneal ulcer in 1 eye and retinal detachment in the fellow eye, and a third patient who had corneal perforation in 1 eye and branch retinal vein occlusion in the fellow eye.

DISCUSSION

The present study retrospectively analyzed the incidence of ocular GVHD in patients who underwent HSCT in the authors' institution. Half of the patients developed ocular GVHD at 5 years following transplantation. Recipient age, use of PBSC, and history of acute GVHD were significantly associated with ocular GVHD, in agreement with previous studies of systemic GVHD.[19-23] Moreover, female sex of recipients and pre-transplantation dry eye disease were significant predictors of ocular GVHD.

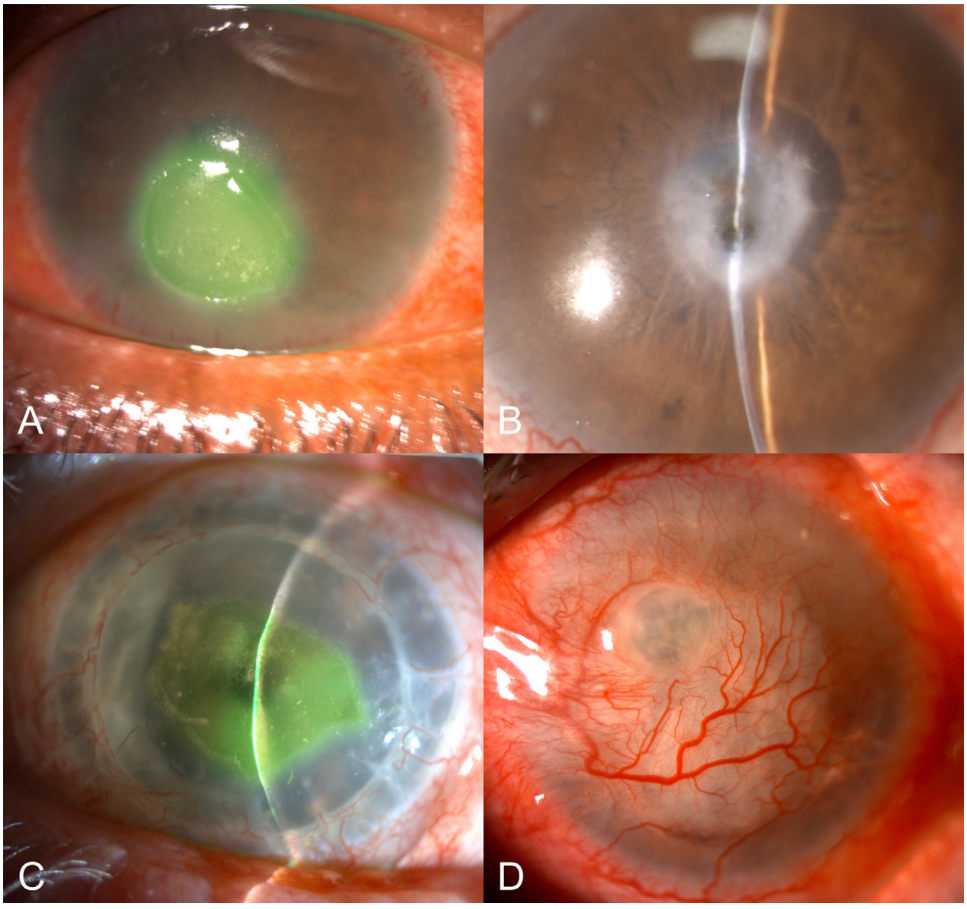

FIGURE 4. Representative images of patients with ocular complications following allogeneic HSCT. Inferior corneal ulcer staining with fluorescein. A. Sterile corneal perforation secondary to non-healing ulcer B. Persistent epithelial defect following tectonic keratoplasty due to corneal perforation. C. Gundersen conjunctival flap for descemetocele with impending perforation .D. HSCT = hematopoietic stem cell transplantation.

Ophthalmic complications that occurred in the study cohort included cataract, corneal ulcer, corneal perforation, lacrimal obstruction, herpetic keratitis, CMV retinitis, retinal detachment, branch retinal vein occlusion, anterior uveitis, cystoid macular edema, punctate inner choroidopathy, endophthalmitis, and choroidal neovascularization.

The incidence of ocular GVHD varies consistently across different studies, and this is partially due to the heterogeneity of diagnostic criteria.[24-28] The NIH criteria, which were developed for use by non-ophthalmologists,[5] rely on subjective findings to reach the diagnosis and are limited by ambiguity and absence of objective signs. Therefore, the International Chronic Ocular GVHD Consensus Group developed a new diagnostic system based on the Schirmer test results, the OSDI, corneal fluorescein staining, and conjunctival injection.[17] In the present study, the International Chronic Ocular GVHD Consensus Group criteria were used to reclassify patients who had undergone HSCT in the authors' institution. The cumulative incidence of ocular GVHD at 1, 2, 3, 4 and 5 years was, respectively, 20%, 29%, 41%, 47%, and 50%. Interestingly, 23% of patients developed isolated ocular GVHD with no systemic GVHD. Although this type of clinical presentation was rare in some studies,[27] other authors reported ocular GVHD in the absence of systemic GVHD in up to 38% of patients.[29]

Using the International Chronic Ocular GVHD Consensus Group criteria, Berchicchi and associates[28] reported an incidence of ocular GVHD of 41%, 48%, and 52% at, respectively, 6, 12, and 24 months. However, survival analysis was not performed, and the study did not account for subjects who were lost to follow-up or competing risks preventing the development of GVHD, such as mortality, following HSCT. Jeppesen and associates[30] performed a survival analysis and reported a cumulative incidence of 16% at 3 years and 18% at 5 years in patients treated with myeloablative conditioning, and of 28% at 3 years and 35% at 5 years in those treated with nonmyeloablative conditioning. However, the diagnosis of ocular GVHD was reached without using the OSDI score. Thus, it is difficult to compare the re-

sults of the present study with those of the above-mentioned ones.

Understanding the risk factors for systemic GVHD is important to improve its prevention and management. In this study, older patients had a higher risk of developing ocular GVHD. High recipient age was identified as a risk factor for chronic GVHD in numerous previous studies.[19-21] Moreover, previous reports showed that a female donor for a male recipient was a strong predictor of chronic GVHD.[19,22] In the present study, this sex combination was not associated with ocular GVHD, which conversely was more common in female recipients. The cause for this finding, reported herein for the first time, is unclear. Female patients may face a heightened risk of ocular GVHD due to the effects of sex on the prevalence of dry eye disease.[31]

Recently, the use of PBSC has greatly increased due to its advantages over BM including faster engraftment and ease of collection.[32] However, the use of PBSC is a recognized risk factor for developing chronic GVHD.[22,23,33] The association may be due to the higher number T cells and $CD34^+$ cells in PBSC than in BM grafts.[30] The present study confirms the fact that the PBSC graft is also a significant risk factor for ocular GVHD.

Several previous studies of chronic systemic GVHD reported that prior acute GVHD was the most powerful predictor of chronic GVHD.[20,21,33] In agreement with this, the present study observed a higher risk of developing ocular GVHD in patients with prior acute GVHD. Conversely, the authors did not identify an association between donor type, sex and age, disease stage, intensity of conditioning, administration of total body irradiation, use of anti T-lymphocyte globulin, ABO and HLA mismatch, CMV serostatus, and the risk of ocular GVHD.

Ocular surface epithelia undergo constant turnover and are susceptible to cytotoxicity from numerous chemotherapeutic agents and targeted therapies used before HSCT.[34] Previous studies demonstrated that dry eye disease is already present in a significant percentage of patients before transplantation.[35-37] In accordance with this, 36% of patients in the present cohort had dry eye disease before transplantation. Moreover, pre-existing dry eye was a significant risk factor for developing ocular GVHD in univariate analysis. However, the association was no longer significant after multivariate adjustment. This may be caused by the low statistical power of the model, which included only half of the patients who had available pre-HSCT data. Therefore, further research is still needed to clarify the relationship between ocular GVHD and pre-transplantation dry eye disease.

Cataract was the most common complication following HSCT, occurring in 10% of patients. It was diagnosed at a mean age of approximately 50 years, a considerably younger age than the mean age of patients undergoing cataract surgery in the general population.[38] This complication may result from chemotherapeutic toxicity, total body irradiation, and prolonged use of systemic corticosteroids, as reflected by the high incidence of posterior subcapsular cataract. Given special attention to the perioperative management of ocular surface disease, cataract surgery has generally a favorable outcome in patients with GVHD.[39] Nevertheless, the incidence of postoperative complications such as cystoid macular edema and endophthalmitis may be higher.

Corneal ulceration occurred in 4% of patients. This is slightly higher than in previous studies, which reported an incidence ranging from 1.6%–2.4%.[29,40] Although most cases were successfully managed with medical therapy, 2 eyes (0.7%) rapidly progressed to stromal melting and corneal perforation. The rapid stromal keratolysis might have been due to the action of proteolytic enzymes involved in the degradation of extracellular matrix, such as matrix metalloproteinases and neutrophil elastase, which are overexpressed in eyes with ocular GVHD.[41] This imposes the prompt recognition and early aggressive treatment of corneal ulcers occurring after HSCT. Although tectonic PK may be performed in case of perforation, it is characterized by an overall poor prognosis due to ocular surface inflammation and severe dryness.[42]

As previously reported,[43] 3% of patients developed lacrimal obstruction secondary to the chronic inflammation and cicatrizing changes of the ocular surface. Because the decreased lacrimal outflow in patients with dry eye disease may be beneficial, its surgical correction should be delayed. In contrast to corneal ulcer and lacrimal obstruction that are probably related to the immunity damage to the ocular surface, other complications observed in the study such as herpetic keratitis, CMV retinitis, retinal detachment, and endophthalmitis may be due to systemic immunosuppression rather than GVHD. Although these nonocular surface complications are rare, they may cause significant visual morbidity and reduce quality of life.[44] Thus, the ophthalmic screening following HSCT should include a comprehensive ophthalmic examination including dilated fundoscopy.

This study has some limitations that should be noted. First, due to the retrospective design, it may have been prone to misclassification error and bias. Therefore, prospective studies are still required to confirm the present results. Second, because conjunctival injection was not recorded before 2013, ocular GVHD was diagnosed using modified International Chronic Ocular GVHD Consensus Group criteria that did not include that parameter. Third, the study included patients who received HSCT over a long time period, and protocols for prophylaxis and treatment of GVHD have not been consistent over time, which may have influenced the results.

In conclusion, approximately half of the present patients developed ocular GVHD in the 5 years following HSCT. Older age, female sex, use of PBSC, acute GVHD, and dry eye disease before transplantation are associated with ocular GVHD development, and patients with those risk factors should be monitored more carefully. Early recognition and management of ocular GVHD are imperative to avoid its detrimental complications and prevent potential vision loss.

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