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Comparison of oral chronic graft-versus-host disease characteristics between patients with malignant and non-malignant hematopoietic disorders

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Abstract

Objectives To characterize and compare the clinical manifestations of oral chronic graft-versus-host disease (cGVHD) in patients with malignant hematopoietic disorders versus those with non-malignant hematopoietic disorders, and to analyze associated risk factors.

Materials and methods Detailed examinations of the oral cavity were conducted in patients with malignant hematopoietic disorders ($n=52$) and non-malignant hematopoietic disorders ($n=56$) who developed oral cGVHD following allogeneic hematopoietic stem cell transplantation (allo-HSCT). The severity of oral cGVHD was scored, and logistic regression analysis was employed to identify risk factors for oral cGVHD ($n=261$).

Results The incidence of oral cGVHD in patients with malignant hematopoietic disorders was significantly higher compared to those with non-malignant hematopoietic disorders (51.49% vs 35.00%, $P=0.01$). Additionally, a significantly greater proportion of patients with malignant hematopoietic disorders had an oral lesion score exceeding 5 compared to patients with non-malignant hematopoietic disorders (17/52 vs 7/56, $P<0.0001$). The median time from transplantation to the onset of oral cGVHD was earlier in patients with malignant hematopoietic disorders than in patients with non-malignant hematopoietic disorders (6 months vs 7 months, $P=0.001$). Furthermore, female donors to male recipients [OR = 1.926, 95% CI (1.07, 3.442), $P=0.027$] emerged as an independent risk factor for oral cGVHD.

Conclusion Compared to patients with non-malignant hematopoietic disorders, those with malignant hematopoietic disorders exhibit a higher incidence of complications following allo-HSCT. Additionally, patients with malignant hematopoietic disorders experience a more rapid disease onset and are at a greater risk of developing severe oral cGVHD. Furthermore, female donors to male recipients represents a significant risk factor for oral cGVHD but not associated with diagnoses with benign and malignant blood disorders.

Clinical relevance This study elucidates the distinct characteristics of oral cGVHD in patients with malignant hematopoietic disorders and non-malignant hematopoietic disorders, providing valuable insights for developing more precise and personalized clinical treatment strategies for these patients.

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Keywords Malignant and non-malignant hematopoietic disorders, Allogeneic hematopoietic stem cell transplantation, Oral chronic graft-versus-host disease, Clinical characteristics, Risk factors

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents a significant therapeutic modality for both malignant hematopoietic disorders, such as leukemia, and non-malignant hematopoietic disorders, including thalassemia major (TM). In China, the incidence of leukemia is approximately 2.76 per 100,000 individuals, making it the most prevalent malignant disorder of the hematopoietic system. Thalassemia (TH), the most common single gene inherited disease globally, is particularly prevalent in countries within the Association of Southeast Asian Nations (ASEAN) and along the Belt and Road Initiative. Guangxi province, located in southern China, is one of the regions with a high incidence of TH [1]. Advances in transplantation techniques have significantly improved transplant success rates and extended patient survival [2, 3]. Nevertheless, chronic graft-versus-host disease (cGVHD) remains a major and severe complication following transplantation. Given that Guangxi is a region with a high incidence of thalassemia, cGVHD is also more prevalent in this area. The oral cavity is the most commonly affected organ in cGVHD cases, often being the earliest or sole site of onset, followed by the skin [4]. Previous studies have reported the prevalence of oral cGVHD in patients with cGVHD to range from 45 to 83% [5–8].

The clinical manifestations of oral cGVHD have been extensively documented in numerous studies. Lichenoid lesions in the oral mucosa serve as a diagnostic hallmark for oral cGVHD [9]. Other manifestations include oral ulcers, pseudomembranes, mucosal erythema, patchy hyperkeratosis, diffuse or dense flat white spots, lingual papillary atrophy, mucous cysts, and limited mouth opening [10]. In addition, involvement of the salivary glands often results in xerostomia, leading to increased tooth demineralization, severe dental caries, and recurrent secondary infections with Candida albicans. Oral mucosal ulcers cause significant pain, which adversely affects daily eating, nutritional intake, communication, and maintenance of oral hygiene. Dysesthesia, such as impaired taste and smell, along with xerostomia, can induce anxiety and mood disturbances, severely impacting patients' quality of life [11, 12]. Oral cGVHD is a potentially malignant disorder that may progress to oral squamous cell carcinoma (OSCC) if left uncontrolled over the long term, posing a threat to patient survival [13–16].

However, patients with malignant hematopoietic disorders and non-malignant hematopoietic disorders exhibit distinct differences in age, occupation, and other sociological characteristics. One study demonstrated no significant differences in the cumulative incidence of cGVHD among children with malignant diseases who underwent umbilical cord hematopoietic stem cell transplantation but did not address the incidence or clinical features of oral cGVHD [17]. Consequently, whether there are differences in oral cGVHD between these two groups remains unclear, and few studies have specifically focused on this issue. A comparative analysis and summary of the clinical characteristics of oral cGVHD in two groups could facilitate the development of more personalized management strategies for patients with oral cGVHD. Additionally, the incidence of cGVHD is influenced by factors such as age, sex, primary disease diagnosis, donor type, human leukocyte antigen (HLA) disparities, acute graft-versus-host disease (aGVHD) history, and conditioning regimen type [18–20]. However, risk factors for cGVHD vary across different tissues and organs, and the specific risk factors for oral cGVHD remain poorly understood. Clarifying the clinical characteristics and risk factors of oral cGVHD is crucial for effectively preventing this condition and improving patients' quality of life and long-term prognosis [21].

Therefore, this study retrospectively analyzed the clinical data of 261 patients with hematopoietic disorders who underwent allo-HSCT, aiming to characterize the cohorts of patients with malignant hematopoietic disorders and non-malignant hematopoietic disorders after allo-HSCT in terms of clinical findings, and to identify risk factors of oral cGVHD, in order to provide a reference for developing more accurate and personalized clinical treatment strategies for patients with oral cGVHD.

Materials and methods

Study objects

Patients diagnosed with hematopoietic disorders who underwent allo-HSCT at the Department of Hematopathology, First Affiliated Hospital of Guangxi Medical University, and subsequently received treatment at the Department of Periodontics and Oral Medicine, Hospital of Stomatology, Guangxi Medical University, between January 2012 and December 2022 were included in this study. The exclusion criteria were as follows: 1) Patients who experienced graft failure following the initial HSCT, died within 100 days post-HSCT, or had a recurrence of the original disease; 2) Patients with pre-existing oral lichenoid lesions or those caused by other factors prior to

allo-HSCT; 3) Patients with incomplete medical records or clinical examination data. This study was approved by the Ethics Committee of the Affiliated Stomatology Hospital of Guangxi Medical University (Approval Number: 2024055).

Data collection

Demographic information of patients, including age, sex, and diagnosis, was systematically collected. Data pertaining to HSCT, such as stem cell source, blood type compatibility, the gender combination of female donors and male recipients, donor sources, conditioning regimens, the use of anti-thymocyte globulin (ATG), graft-versus-host disease (GVHD) prophylaxis measures, and history of acute GVHD (aGVHD), were meticulously documented.

Conditioning regimens

Pre-transplantation conditioning regimens for the research subjects included the following agents, used either individually or in combination: Cytarabine (Ara-C), antithymocyte globulin (ATG), Busulfan (Bu), Lomustine (CCNU), Cyclophosphamide (Cy), total body irradiation (TBI), Fludarabine (Flu), Idarubicin (IDA), and Etoposide (VP16). And these regimens can be categorized into the following groups: myeloablative conditioning (MAC), nonmyeloablative conditioning (NMAC), reduced-intensity conditioning (RIC), MAC combined with ATG, NMAC combined with ATG, and RIC combined with ATG.

GVHD prophylaxis

Prophylactic regimens include cyclosporin A (CsA) in combination with mycophenolate mofetil (MMF) and methotrexate (MTX), or tacrolimus (FK506) in conjunction with MMF and MTX.

Oral examinations

Two oral mucosa specialists, with an inter-rater reliability Kappa value exceeding 0.9, conducted comprehensive examinations and documented the patients' oral health status. They also performed diagnoses and scoring of oral cGVHD in accordance with the 2014 National Institutes of Health (NIH) criteria (Table 1) [9] at the Department of Periodontics and Oral Medicine, Hospital of Stomatology, Guangxi Medical University.

Statistical analysis

SPSS 22.0 statistical software was used for data analysis. Student t test was used to compare the transplantation age and oral cGVHD scores between malignant hematopoietic disorders and non-malignant hematopoietic disorders populations, and Chi-square test was used to compare the incidence of oral cGVHD between patients with malignant hematopoietic disorders and non-malignant hematopoietic disorders. Rank sum test was used to compare the median time from transplantation to oral cGVHD onsets between patients with malignant hematopoietic disorders and non-malignant hematopoietic disorders. And logistic regression was used to analyze the risk factors of oral cGVHD.

Results

Demographic characteristics and clinical data of the study objects

A total of 261 patients who underwent allo-HSCT were included in this study. Among them, 101 patients were diagnosed with malignant hematopoietic disorders, primarily leukemia, while 160 patients were diagnosed with non-malignant hematopoietic disorders, mainly TM. The cohort comprised 162 males and 109 females, with a mean age of 17.44 ± 13.78 years (range: 2.33–59.20 years). The median follow-up duration post-transplantation was 840 days (range: 138–5110 days). Detailed clinical data, including stem cell sources, donor sources, HLA matching, conditioning regimens, GVHD prophylaxis strategies, female donor to male recipient status, and history of aGVHD, are summarized in Table 2.

Table 1 Scoring criteria of oral manifestations among oral cGVHD patients

Mucosal change	No evidence of cGVHD	Score	Mild	Score	Moderate	Score	Severe	Score
Erythema	None	0	Mild erythema or moderate erythema (< 25%)	1	Moderate (≥ 25%) or severe erythema (< 25%)	2	Severe erythema (≥ 25%)	3
Lichenoid	None	0	Hyperkeratotic changes (< 25%)	1	Hyperkeratotic changes (25%–50%)	2	Hyperkeratotic changes (> 50%)	3
Ulcers	None	0	None	0	Ulcers involving (≤ 20%)	3	Severe ulcers (> 20%)	6
Mucoceles	None	0	1–5 mucoceles	1	5–10 mucoceles	2	Over 10 mucoceles	3

Table 2 Demographic and clinical characteristics of the 261 enrolled patients

		Patients with oral cGVHD (*n* = 108)	Patients with non-oral cGVHD (*n* = 153)
Sex	Male, n (%)	71(65.74)	91(60.67)
	Female, n (%)	37(34.26)	62(39.33)
Age when allo-HSCT (mean ± SD, range, in yrs)		20.00 ± 14.85 (2.33–59.20)	15.22 ± 12.56 (3.00–53.00)
Age ≤ 18 n (%)		58 (53.70)	108 (70.59)
Age ≥ 18, n (%)		50 (46.30)	45 (29.41)
Diagnoses	Thalassemia major, Aplastic Anemia/Myelodysplastic Syndromes/Acute Myeloid Leukemia/Acute Lymphoblastic Leukemia/Acute Undifferentiated Leukemia, Lymphocytic Leukemia/Multiple Myeloma/Acute Monocytic Leukemia/Chronic Granulocytic Monocytic Leukemia/Chronic Myeloid Leukemia/T-cell Lymphoblastic Lymphoma	54/2/1/24/17/1/1/1/3/1/5/1	101/3/1/30/9/0/0/2/3/0/4/0
Stem cell source, n (%)	BMT + PBSCT	56 (51.85)	82 (53.59)
	PBSCT	43 (37.96)	56 (36.60)
	UCBT + BMT/UCTB + BMT + PBSCT/ UCTB + PBSCT	8 (7.40)	15 (9.80)
	BMT	1 (0.90)	1 (0.65)
Donor source, n (%)	Sibling donors	79 (73.15)	104 (67.97)
	Matched unrelated donors	23 (21.30)	34 (22.22)
	Mismatched unrelated donors	2 (1.85)	4 (2.61)
	Haploidentical donors	4 (3.70)	11 (7.19)
Blood type-match, n (%)	Yes	50 (46.30)	87 (56.86)
	No	58 (53.70)	66 (43.14)
Female donors to male recipients, n (%)	Yes	35 (32.41)	31 (20.26)
	No	73 (67.59)	122 (79.74)
Conditioning regimens, n (%)	MAC	18 (16.67)	15 (9.80)
	RIC	2 (1.85)	4 (2.61)
	NMAC	11 (10.19)	10 (6.54)
	MAC + ATG	2 (1.85)	7 (4.58)
	RIC + ATG	61 (56.48)	97 (63.40)
	NMAC + ATG	8 (7.41)	13 (8.50)
	TBI	6 (5.56)	7 (4.58)
GVHD prophylaxis, n (%)	FK-506 + MMF + MTX	35 (32.41)	51 (33.33)
	CsA + MMF + MTX	73 (67.59)	102 (66.67)
History of aGVHD, n (%)	None	85 (78.70)	129 (84.31)
	I–II	15 (13.89)	18 (11.76)
	III–IV	8 (7.41)	6 (3.92)
Presence of cGVHD in other sites, n(%)	Skin	43 (39.81)	15 (9.80)
	Eyes	17 (15.74)	1 (0.65)
	Liver	25 (23.14)	7 (4.58)
	Gastrointestinal tract	16 (14.8)	4 (2.61)
	Lung	9 (8.33)	2 (1.31)
	Nail	4 (3.70)	1 (0.65)
	Arthrosis	3 (2.78)	2 (1.31)

BMT Bone marrow hematopoietic stem cell transplantation, *PBSCT* Peripheral blood stem cell transplantation, *UCBT* Umbilical cord blood stem cell transplantation, *HLA* histocompatibility antibody, *MAC* Myeloablative conditioning, *NMAC* Nonmyeloablative conditioning, *RIC* Reduced-intensity conditioning, *TBI* Total body irradiation, *ATG* Human thymocyte globulin, FK-506 tacrolimus, *CsA* Cyclosporin A, *MMF* Mycophenolate mofetil, *MTX* Methotrexate, *aGVHD* Acute chronic graft-versus-host disease

The baseline characteristics of patients in the malignant disorder cohort and the non-malignant disorder cohort

Significant disparities were observed between patients in the malignant disease cohort and non-malignant disease cohort regarding transplantation age, stem cell source, and conditioning regimen. No significant differences were noted in other characteristics (Table 3).

Clinical characterization of patients with oral cGVHD

Among the 261 patients, 108 were diagnosed with oral cGVHD, while 153 did not develop this condition during follow-up, resulting in an overall oral cGVHD incidence rate of 41.37%. All 108 patients with oral cGVHD exhibited reticular white striated lesions on the oral mucosa. The most common clinical manifestations included oral mucosal ulcers and erosions, followed by xerostomia, pseudomembranes, and erythematous lesions. Other observed symptoms comprised oral mucosal blisters, atrophy of the tongue papillae, chapped lips, mucoceles, and limited mouth opening. The affected areas of the oral mucosa included the buccal mucosa, tongue, lip, palate, gingiva, floor of the mouth, and oral commissures. The buccal mucosa was the most frequently affected site, followed by the tongue, lip, and palatal mucosa. Over 84.6% of patients experienced involvement of more than two oral regions simultaneously. During follow-up, one patient was diagnosed with papillary epithelioma, and two patients developed secondary OSCC. These cases have been previously reported [13, 14]. All three patients had

Table 3 The baseline characteristics of patients in the malignant disorder cohort and the non-malignant disorder cohort

Characteristic		Malignant diseases cohort ($n=101$)	Non-malignant diseases cohort ($n=160$)	*P*-value
Sex	Male, n (%)	61(60.40)	101(63.13)	0.658
	Female, n (%)	40 (39.60)	59 (36.87)	
Age when allo-HSCT (mean ± SD, range, in yrs)		31.64 ± 10.58 (9.40–59.20)	8.48 ± 5.058 (2.33–42.50)	0.000
Stem cell Source, n (%)	BMT + PBSCT	48 (47.52)	90 (56.25)	0.013
	PBSCT	50 (49.50)	48 (30.00)	
	UCBT + BMT/ UCBT + BMT + PBSCT/ UCTB + PBSCT	2 (1.98)	21 (13.13)	
	BMT	1 (0.99)	1 (0.625)	
Donor Source, n (%)	Sibling donors	74 (73.27)	109 (68.13)	0.377
	Matched unrelated donors	21 (20.79)	36 (22.50)	
	Mismatched unrelated donors	1 (0.99)	5 (3.12)	
	Haploidentical donors	5 (7.13)	10 (6.25))	
Blood type-match, n (%)	Yes	58 (57.43)	79 (49.34)	0.205
	No	43 (42.57)	81(50.63)	
Female donors to male recipients, n (%)	Yes	30 (29.70)	36 (22.50)	0.192
	No	71 (70.30)	124 (77.50)	
Conditioning regimens n (%)	MAC	33 (32.67)	0 (0)	0.000
	RIC	2 (1.98)	4 (2.50)	
	NMAC	21 (20.79)	0 (0)	
	MAC + ATG	8 (7.92)	1 (0.62)	
	RIC + ATG	11 (10.89)	147 (91.88)	
	NMAC + ATG	18 (17.82)	3 (1.88)	
	TBI	8 (5.00)	5 (3.13)	
GVHD prophylaxis n (%)	FK-506 + MMF + MTX	41 (40.59)	58 (36.25)	0.481
	CsA + MMF + MTX	60 (59.41)	102 (63.75)	
History of aGVHD n (%)	None	79 (78.22)	135 (84.38)	0.423
	I–II	16 (15.84)	17 (10.62)	
	III–IV	6 (5.94)	8 (5.00)	

BMT Bone marrow hematopoietic stem cell transplantation, *PBSCT* Peripheral blood stem cell transplantation, *UCBT* Umbilical cord blood stem cell transplantation, *HLA* Histocompatibility antibody, *MAC* Myeloablative conditioning, *NMAC* Nonmyeloablative conditioning, *RIC* Reduced-intensity conditioning, *TBI* Total body irradiation, *ATG* human thymocyte globulin, FK-506:tacrolimus, *CsA* Cyclosporin A, *MMF* Mycophenolate mofetil, *MTX* Methotrexate, *GVHD* graft-versus-host disease, *aGVHD* acute chronic graft-versus-host disease

a history of leukemia prior to allo-HSCT, were over 30 years old at the time of transplantation, and had oral cGVHD for more than 24 months. According to the NIH-modified Oral Mucosa Rating Scale (OMRS), the oral characterization scores for patients with oral cGVHD were predominantly distributed between 2 and 6 points, with a mean score of 3.82 ± 1.89 (range: 1–9 points). The median time from transplantation to the onset of oral cGVHD was 6 months (range: 3–28 months).

Among the 108 patients with oral cGVHD, 52 patients had been diagnosed with malignant hematopoietic disorders prior to allo-HSCT, while 56 patients were diagnosed with non-malignant hematopoietic disorders. The incidence of oral cGVHD was significantly higher in patients with malignant hematopoietic disorders compared to those with non-malignant hematopoietic disorders (51.49% vs 35.00%, $P=0.01$). However, pseudomembranous lesions of the oral mucosa were more frequently observed in patients with non-malignant hematopoietic disorders (13/52 vs 26/56, $P=0.027$). Regarding the affected sites within the oral cavity, no significant differences were noted between the two groups. In terms of the mean OMRS, there was no overall significant difference between patients with malignant hematopoietic disorders and those with non-malignant hematopoietic disorders. Nevertheless, a significantly higher proportion of patients with malignant hematopoietic disorders exhibited an oral lesion score greater than 5 compared to those with non-malignant hematopoietic disorders (17/52 vs 7/56, $P<0.0001$). The median time from transplantation to the onset of oral cGVHD was earlier in patients with malignant hematopoietic disorders compared to those with non-malignant hematopoietic disorders (6 months vs 7 months, $P=0.001$). These findings are summarized in Table 4. Additionally, the typical clinical manifestations of oral cGVHD in patients with TM are illustrated in Fig. 1.

Involvement of other cGVHD target organs in oral cGVHD patients

Oral cGVHD may occur in isolation or concurrently with cGVHD affecting other organs and tissues. Among the 108 patients diagnosed with oral cGVHD, 26 exhibited involvements limited to the oral cavity, while the remaining cases also affected additional target organs and tissues. The most frequent co-occurrence was with cutaneous cGVHD, followed by ocular and hepatic cGVHD. In terms of organ involvement, more than two target organs were commonly affected. Furthermore, the incidence of pulmonary cGVHD was significantly higher in patients with malignant hematopoietic disorders compared to those with non-malignant hematopoietic disorders. No significant differences were observed in the involvement of other target organs between patients with malignant hematopoietic disorders and those with non-malignant hematopoietic disorders (Table 4).

The risk factors of oral cGVHD

Univariate analysis was performed to analyze sex, age at transplantation, hematologic diagnosis (malignant or non-malignant), donor sources, HLA-match, blood type-match, female donors to male recipients or not, stem cell sources, donor sources, GVHD prevention, using ATG or not and history of aGVHD. The results showed that age at transplantation, malignant hematologic diagnosis and female donors to male recipients had statistically significant impact on oral cGVHD, while there were no statistically significant differences in other factors. Furthermore, the results of logistic regression analysis showed that only female donors to male recipients [OR = 1.926, 95% CI (1.078, 3.442), $P=0.027$] is the independent risk factor of oral cGVHD. Malignant hematopoietic disorder does not independently serve as a risk factor for the development of oral cGVHD (Table 5).

Discussion

Oral cGVHD is a heterogeneous disorder that affects both the oral mucosa and salivary glands, significantly impacting patients' quality of life and, in severe cases, posing a substantial threat to their survival. This study constitutes the inaugural in-depth analysis and comparison of the clinical features of oral GVHD in patients with malignant and non-malignant hematopoietic disorders following allo-HSCT in Guangxi, China. Our findings provide valuable clinical insights for developing personalized management strategies for patients with oral cGVHD resulting from diverse hematopoietic disorders.

In this study, oral cGVHD manifestations were diverse and predominantly characterized by lichenoid lesions. Besides the typical lichenoid changes, the most prevalent oral features included ulcerative erosion (68.57%), followed by xerostomia (37.14%), pseudomembranous lesions (35.24%), and erythematous lesions (18.1%). Additionally, other manifestations observed were mucosal blisters (13.33%), lingual and papillary atrophy (8.57%), oral hyperkeratosis (7.62%), cheilitis (7.62%), superficial mucous cysts (7.62%), and trismus (4.76%). The buccal mucosa was the most frequently affected site and exhibited the most severe lesions, followed by the tongue mucosa. These clinical features of oral cGVHD are consistent with those reported in previous studies [22–24].

The incidence rates of cGVHD among thalassemia patients vary across different populations: 21.67% in the

Table 4 Clinical manifestations and characteristics of patients with oral cGVHD ($n = 108$)

		Total	Malignant hematopoietic disorders ($n = 52$)	Non-malignant hematopoietic disorders ($n = 56$)	*P*-value
oral cGVHD rate		41.37% (108/261)	51.49% (52/101)	35.00% (56/160)	0.01
Oral manifestations of cGVHD (n, %)	White reticular stripe lesion	108 (100)	52	56	
	Ulcer/ erosion	76 (70.37)	35 (67.31)	41 (73.21)	0.533
	Dry mouth	40 (37.03)	24 (46.15)	16 (28.57)	0.074
	Pseudomembrane	39 (36.11)	13 (25.00)	26 (46.43)	0.027
	Erythematous lesions	20 (18.5)	8 (15.38)	12 (21.43)	0.466
	Blister	15 (13.83)	4 (7.69)	11 (19.64)	0.096
	Mucocele	10 (11.11)	4 (7.69)	6 (10.71)	0.058
	Lingual papillary atrophy	10 (9.26)	4 (7.69)	6 (10.71)	0.058
	Chapped mouth and lip	9 (8.33)	3 (5.77)	6 (10.71)	0.492
	Limitation of mouth opening	6 (5.55)	4 (7.69)	2 (3.57)	0.425
Affected sites(n, %)	Buccal	95 (87.96)	47 (90.38)	48 (85.71)	0.560
	Tongue	77 (71.30)	37 (71.15)	40 (71.43)	1.00
	Lip	43 (39.81)	20 (38.46)	23 (41.07)	0.843
	Palate	39 (36.11)	21 (40.38)	18 (32.14)	0.551
	Gingiva	20 (18.52)	9 (17.31)	11 (19.64)	0.808
	Floor of mouth	4 (3.70)	2 (3.85)	2 (3.57)	1.00
	Corner of the mouth	8 (7.40)	3 (5.77)	5 (8.93)	0.718
Secondary oral tumor	Papillary epithelioma	1(0.93)	1(1.92)	0	
	OSCC	2(1.85)	2(3.85)	0	
NIH-modified OMRS (n, %)	1	12 (11.11)	8 (15.38)	4 (7.14)	
	2	22 (20.37)	10 (19.23)	12 (21.43)	
	3	15 (14.81)	7 (13.46)	8 (14.29)	
	4	16 (14.81)	5 (9.62)	11 (19.64)	
	5	19 (17.59)	5 (9.62)	14 (25.00)	
	6	19 (17.59)	13 (25.00)	6 (10.71)	
	7	2 (1.85)	1 (1.92)	1 (1.79)	
	8	2 (1.85)	2 (3.85)	0	
	9	1 (0.93)	1 (1.92)	0	
	Mean ± SD	3.82 ± 1.89	4.19 ± 2.07	3.63 ± 1.48	0.604
	≤ 5		35 (67.31)	49 (87.50)	< 0.0001
	> 5		17 (32.69)	7 (12.50)	
Median number of months from transplant to enrollment (Median, range)		6 (3–28)	6 (3–24)	7(3–28)	0.001
Involved organs (n, %)	Oral	108	52	56	
	Skin	43 (39.81)	21 (40.38)	22 (39.29)	1.00
	Eyes	17 (15.74)	11 (21.15)	6 (10.71)	0.187
	Liver	25 (23.14)	13 (25.00)	12 (21.43)	0.820
	Gastrointestinal tract	16 (14.8)	6 (11.54)	10 (17.86)	0.423
	Lung	9 (8.33)	8 (19.23)	1 (1.79)	0.014
	Nail	4 (3.70)	2 (3.85)	2 (3.57)	1.00
	Arthrosis	3 (2.78)	1 (1.92)	2 (3.57)	1.00

OSCC Oral squamous cell carcinoma, *OMRS* NIH-modified Oral Mucosa Rating Scale

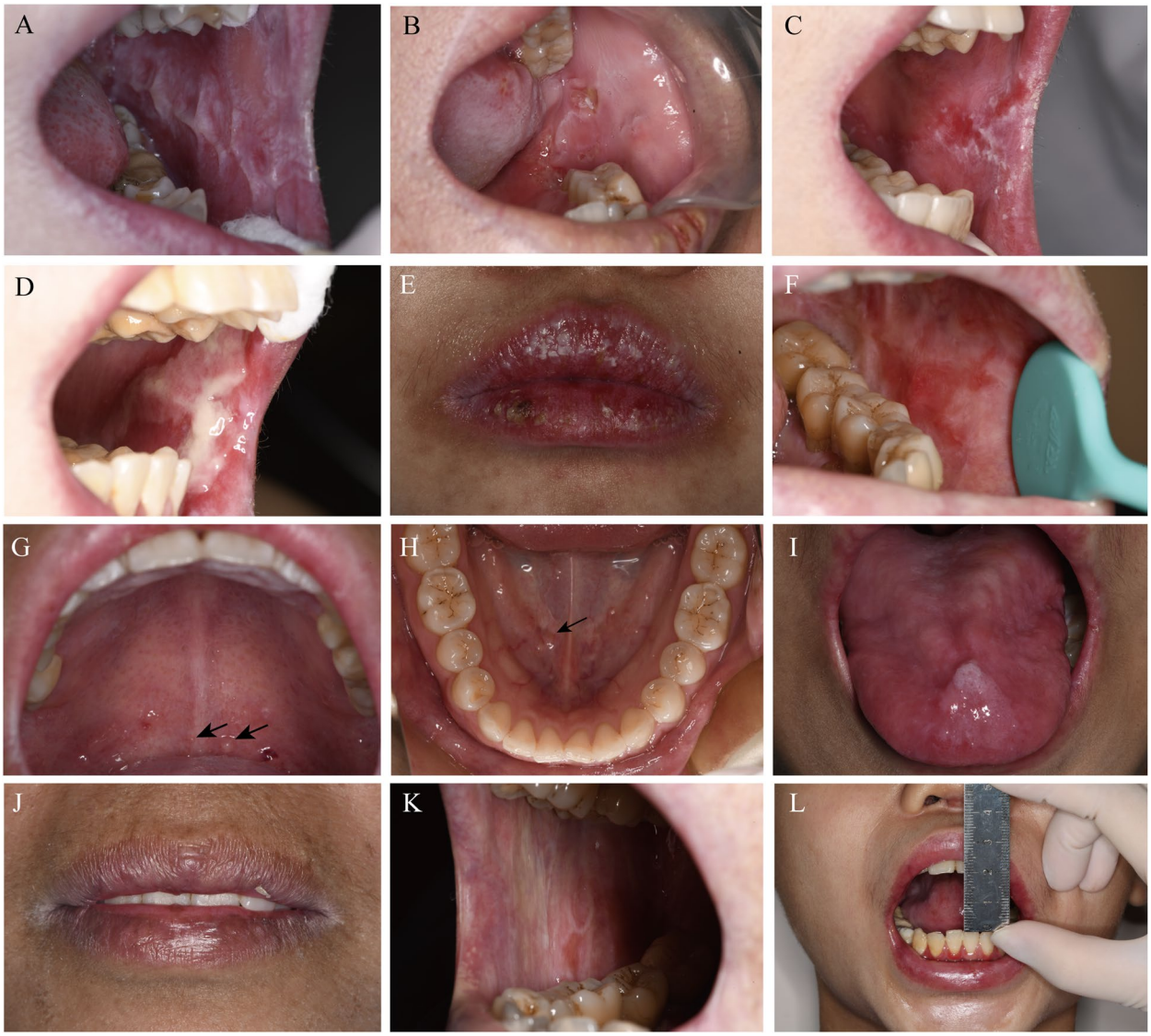

Fig. 1 Clinical manifestations of oral cGVHD in patients following allo-HSCT. **A** White reticulated striated lesion on the buccal mucosa of the oral cavity; **B**: Ulceration on the buccal mucosa; **C**: Erosion on the buccal mucosa; **D**: Grayish yellow pseudomembrane on the buccal mucosa; **E**: White pseudomembrane on the upper lip mucosa; **F**: Erythematous lesions on the buccal mucosa. **G** Blisters on the palate (black arrows); **H**: Mucous cysts on the floor of the mouth (black arrow); **I**: Lingual papillary atrophy **J**: Xerostomia and chapped corner of the mouth. **K** Submucosal fibrosis on the buccal mucosa; **L**: limitation of mouth opening

Thai population [25], 28% in the Egyptian population [26], and 8.3% in the Turkish population [27]. To date, there has been no reported data on the incidence rate of oral cGVHD in patients with non-malignant hematopoietic disorders. This study represents the first comprehensive analysis of the incidence and clinical characteristics of oral cGVHD in patients with non-malignant hematopoietic disorders. Our findings indicate that the prevalence of oral cGVHD in patients with non-malignant hematopoietic disorders was 41.37%, which is significantly lower than the 51.49% observed in patients with malignant hematopoietic disorders, while being higher than the 35.00% prevalence in patients with non-malignant hematopoietic disorders. The onset time of oral cGVHD in patients with non-malignant hematopoietic disorders was significantly later compared to patients with malignant hematopoietic disorders, potentially due to earlier discontinuation of anti-rejection drugs in patients with non-malignant hematopoietic disorders. In terms of average oral cGVHD scores, no significant difference was found between the two groups; however, patients with malignant hematopoietic disorders

Table 5 Analysis of risk factors of oral cGVHD ($n=261$)

	t/X2	*P*-value for single factor analysis	P-value for single logistic regression analysis	OR	95% CI of OR	
					lower limit	upper limit
Sex	1.055	0.304				
Age at transplantation	−3.073	0.002	0.062	1.031	0.998	1.065
Age ≤ 18 verse age ≥ 18	7.78	0.005	0.903	1.082	0.305	3.840
Hematologic diagnosis (malignant or non-malignant)	6.937	0.008	0.858	0.910	0.326	2.543
Female donors to male recipients	4.944	0.026	0.027	1.926	1.078	3.442
HLA-match	1.525	0.217				
Blood type-match	2.834	0.092				
Using ATG or not	2.040	0.153				
History of aGVHD	1.903	0.386				
GVHD prophylaxis	0.025	0.875				
Stem cell sources	0.322	0.606				
Donor Source	0.099	0.754				

ATG human thymocyte globulin, *OR* Odd ratio, *CI* Confidence interval

exhibited a wider distribution of scores and a higher proportion of severe cases (more than 5 points). These results suggest that oral cGVHD in patients with malignant hematopoietic disorders tend to have a faster onset and a higher likelihood of severe manifestations. Conversely, oral mucosal pseudomembranes were more prevalent in patients with non-malignant hematopoietic disorders. Additionally, we observed poorer oral hygiene in non-malignant hematopoietic disorders patients compared to patients with malignant hematopoietic disorders, possibly because most of patients with malignant hematopoietic disorders are younger minors for whom maintaining oral hygiene is more challenging. This may lead to a more complex oral microbial composition and a higher risk of infection and exudation when oral mucosal lesions occur. The presence of oral mucosal pseudomembranes can affect the efficacy of local treatments, indicating that dentists should pay closer attention to and enhance oral hygiene management measures for these patients.

Additionally, among the 108 patients with oral cGVHD, 26 (24.07%) patients exhibited localized cGVHD affecting only the oral cavity. In patients with multi-organ cGVHD, the most frequently affected sites associated with the oral cavity were the skin and eyes, in that order. The oral cavity may be one of the earliest organs involved in cGVHD [28], potentially indicating a correlation with cGVHD in other organs. Jeppesen et al. demonstrated a significant correlation between oral cGVHD scores and progressive damage to the eyes and skin [29, 30]. From an embryological perspective, the oral cavity, eyes, skin, nails, and genitals all originate from the ectoderm, suggesting potential similarities in pathogenesis. Therefore, patients with oral cGVHD should be vigilant for the development of skin and eye cGVHD. Previous studies have shown that histological changes in the lips, oral mucosa, and salivary glands, along with clinical manifestations of oral mucosal lesions, can serve as indicators of systemic cGVHD [31], This implies that optimizing the clinical management of oral cGVHD may positively impact the prevention and treatment of cGVHD in other organs. In our study, patients with malignant hematopoietic disorders had a higher likelihood of developing pulmonary cGVHD post-transplantation compared to those with non-malignant hematopoietic disorders.

For oral cGVHD, studies have demonstrated that malignant hematopoietic disorders, a history of aGVHD, total body irradiation (TBI), peripheral blood stem cell transplantation (PBSCT) [32], and female donors to male recipients were risk factors of oral cGVHD [33, 34]. In our study, logistic regression analysis revealed that only female donors to male recipients was an independent risk factor for oral cGVHD. Female donors to male recipients may increase the risk of cGVHD because the immune system of female donors can recognize H-Y and non-maternal genetic antigens specific to male recipients, thereby inducing an immune response [35]. No significant association was found between the history of aGVHD and the incidence of oral cGVHD. Regarding the tissue involvement of aGVHD, studies have shown that aGVHD rarely affects oral tissues [5, 36]. Mechanistically, there is no clear correlation between aGVHD and the pathogenesis of cGVHD, indicating that cGVHD is not a continuation or transformation of aGVHD [18]. Gabriel suggested that whether aGVHD could become an independent risk factor for cGVHD might be related

to patients receiving different myeloablative regimens [37]. Regarding donor sources, prior studies have demonstrated that patients undergoing PBSCT experienced lower rates of graft rejection and exhibited higher overall survival and disease-free survival rates compared to those who received bone marrow transplantation (BMT). However, the incidence of cGVHD was elevated in recipients who underwent PBSCT [38–40]. However, in this study, no correlation was found between donor source and the incidence of oral cGVHD. These discrepancies may be influenced by differences in population and transplantation techniques. Besides HSCT-related factors, Picardi found that poor oral hygiene and inadequate oral care may be local risk factors for oral lesions caused by cGVHD [41]. The oral cavity serves as a natural bacterial carrier environment, suggesting that microbial imbalance may also be a risk factor for oral cGVHD. Existing studies have shown that professional oral treatment reduced the incidence of oral mucositis, and preoperative oral preventive measures could shorten the time required for mucositis improvement in patients with oral cGVHD [42–44]. Managing the overall oral health status of patients before, during, and after transplantation positively impacts the prevention and treatment of oral cGVHD. In our study, we observed that the prevalence of oral cGVHD following allo-HSCT was higher among patients with malignant hematopoietic disorders compared to those with non-malignant hematopoietic disorders. However, neither benign nor malignant hematopoietic disorders were identified as independent risk factors for oral cGVHD. Instead, female donors to male recipients emerged as an independent risk factor for oral cGVHD. This suggests that the observed difference in prevalence is not attributable to the type of hematologic disease but may be influenced by the varying proportions of female-to-male transplants between the two groups.

Secondary tumors represent a significant late complication associated with long-term cGVHD and immunosuppression. The two most common solid tumors are cutaneous and OSCC [45]. In 2020, the World Health Organization (WHO) classified oral cGVHD as a potential precursor to oral malignancy [46]. The severity of oral cGVHD is correlated with an increased risk of secondary oral cancer, particularly when the duration of oral cGVHD exceeds 15 months, which is considered an independent risk factor due to target tissue damage and prolonged immunosuppressive therapy [47–49]. Study has shown that the tongue is the most frequent site of secondary oral tumors following allo-HSCT, accounting for 28.24% of cases, followed by the buccal mucosa (10.64%) and lip (5.56%) [50]. In this study, three patients with oral cGVHD who developed secondary oral tumors had leukemia as their primary disease, were over 30 years old at the time of transplantation, and experienced oral cGVHD for more than 24 months. The tongue was the predominant site of involvement, consistent with previous reports. Given the rising incidence of OSCC in patients with cGVHD, the NIH recommends annual oral examinations for patients surviving more than a year post-allo-HSCT [51–54]. Consequently, patients with oral cGVHD should undergo more frequent evaluations and extended follow-up periods, especially those with a disease course exceeding one year or a history of malignant hematopoietic disorders before allo-HSCT. Enhancing dentists' awareness of the association between oral cGVHD and OSCC can facilitate early diagnosis, improve clinical management, and enhance patient survival and quality of life.

Conclusion

In summary, we have systematically compared and analyzed the clinical characteristics of oral cGVHD following allo-HSCT in patients with both malignant and non-malignant hematopoietic disorders. Our findings indicate that the clinical manifestations of oral cGVHD differ significantly between these two patient populations. Specifically, patients with malignant hematopoietic disorders exhibit a higher incidence rate, more rapid onset, and greater likelihood of developing severe oral cGVHD post-transplantation. Conversely, oral mucosal pseudomembranes are more frequently observed in patients with non-malignant hematopoietic disorders. Additionally, female donors to male recipients represent a significant risk factor for oral cGVHD. This association is not observed in patients diagnosed with benign or malignant blood disorders. However, it is also important to note that oral cGVHD has the potential to undergo malignant transformation, particularly in patients with malignant hematopoietic disorders.

Abbreviations

Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
aGVHD	Acute graft-versus-host disease
cGVHD	Chronic Graft-versus-host Disease
OMRS	Oral Mucosa Rating Scale
OPMDs	Oral potential malignant disorders;
β-TM	β-Thalassemia Major
AA	Aplastic Anemia
MDS	Myelodysplastic Syndrome
AML	Acute Myelocytic Leukemia
ALL	Acute Lymphoblastic Leukemia
AUL	Acute uncategorized leukemia
LMCL	Lymphomatocytic leukemia
RRMM	Multiple myeloma
AMML	Acute monocytic leukemia
CMML	Chronic granular monocytic leukemia
CML	Chronic Myelocytic Leukemia
T-LBL	T lymphoblastoma
BMT	Bone marrow hematopoietic stem cell transplantation
PBSCT	Peripheral Blood Stem Cell Transplantation

UCBT	Umbilical Cord Blood Stem Cell Transplantation
HLA	Histocompatibility antibody
ATG	Human thymocyte globulin
FK506	Tacrolimus
CsA	Cyclosporin A
aGVHD	Acute chronic graft-versus-host disease

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Consent to publish declaration
A written consent for publication was obtained from the patient to publish all clinical details and any accompanying images. And the authors all agreed to publish this work.

Authors' contributions
Qiaozhi Jiang, Guocheng Mei and Renchuan Tao contributed to conception and design, data analysis and interpretation, and drafted and critically revised the manuscript. Xiangzhi Yong and Zhenmin Liu contributed to data analysis, interpretation, and critically revised the manuscript. Yuxi Zhou, Tiantian Wu, Yan Peng, Xinyu Chen, Jiaqi Huang and Zhongming Zhang contributed to data collection and analysis. Qiaozhi Jiang and Renchuan Tao contribute to fund acquirement.

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Data availability
The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
This study received approval from the Ethics Committee of the Affiliated Stomatology Hospital of Guangxi Medical University (Approval Number: 2024055). Written informed consent was obtained from all participants for the publication of this study, including all associated data and accompanying images.

Consent for publication
A written consent for publication was obtained from patients to publish all clinical details and any accompanying images.

Competing interests
The authors declare no competing interests.

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References

1. Kremastinos DT, Farmakis D, Aessopos A, Hahalis G, Hamodraka E, Tsiapras D, Keren A. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circ Heart Fail. 2010;3(3):451–8.
2. Chang YJ, Wu DP, Lai YR, Liu QF, Sun YQ, Hu J, Hu Y, Zhou JF, Li J, Wang SQ, et al. Antithymocyte globulin for matched sibling donor transplantation in patients with hematologic malignancies: a multicenter, open-label. J Clin Oncol. 2020;38(29):3367–76.
3. Zhai L, Liu Y, Huo R, Pan Z, Bin J, Li Z, Tang Q, Fan J. Quality of life in patients with β-thalassemia major: short-term and long-term effects after haematopoietic stem cell transplantation. Curr Stem Cell Res Ther. 2021;16(8):924–30.
4. Treister NS, Cook EF Jr, Antin J, Lee SJ, Soiffer R, Woo SB. Clinical evaluation of oral chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2008;14(1):110–5.
5. Imanguli MM, Alevizos I, Brown R, Pavletic SZ, Atkinson JC. Oral graft-versus-host disease. Oral Dis. 2008;14(5):396–412.
6. Mays JW, Fassil H, Edwards DA, Pavletic SZ, Bassim CW. Oral chronic graft-versus-host disease: current pathogenesis, therapy, and research. Oral Dis. 2013;19(4):327–46.
7. Noce CW, Gomes A, Copello A, Barbosa RD, Sant'anna S, Moreira MC, Correa ME, Maiolino A, Torres SR. Oral involvement of chronic graft-versus-host disease in hematopoietic stem cell transplant recipients. Gen Dent. 2011;59(6):458–62 quiz 463–454.
8. Fassil H, Bassim CW, Mays J, Edwards D, Baird K, Steinberg SM, Williams KM, Cowen EW, Mitchell SA, Hakim FT, et al. Oral chronic graft-vs.-host disease characterization using the NIH scale. J Dent Res. 2012;91(7 Suppl):45S-51S.
9. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transpl. 2015;21(3):389-401 e381.
10. Baumrin E, Loren AW, Falk SJ, Mays JW, Cowen EW. Chronic graft-versus-host disease. Part I: Epidemiology, pathogenesis, and clinical manifestations. J Am Acad Dermatol. 2024;90(1):1–16.
11. DePalo J, Chai X, Lee SJ, Cutler CS, Treister N. Assessing the relationship between oral chronic graft-versus-host disease and global measures of quality of life. Oral Oncol. 2015;51(10):944–9.
12. Boor M, Raber-Durlacher JE, Hazenberg MD, Rozema FR, Laheij A. Taste and smell disturbances in patients with chronic oral graft vs. host disease: an observational study. Front Oral Health. 2022;3:934607.
13. Liu Z, Peng Y, Yong X, Mei G, Yang Y, Yi C, Tao R. A case report of secondary oral squamous cell carcinoma after allogeneic hematopoietic stem cell transplantation. Oral Oncol. 2020;109:104629.
14. Wu T, Liu Z, Yong X, Mei G, Jiang Q, Fang M, Li P, Zhang Z, Tao R. P16-positive secondary tongue squamous cell carcinoma following allogeneic hematopoietic stem cell transplantation: a case report and literature review. Oral Oncol. 2021;121:105399.
15. Janowiak-Majeranowska A, Osowski J, Mikaszewski B, Majeranowski A. Secondary oral cancer after systemic treatment of hematological malignancies and oral GVHD: a systematic review. Cancers. 2022;14(9):2175.
16. Bar O, Elad S, Avni B, Abu-Tair J, Zaharia B, Hanut A, Zadik Y. Oral verruciform xanthoma in chronic graft-versus-host disease patients. Support Care Cancer. 2021;29(1):79–84.
17. Tang X, Fang J, Yu J, Li Z, Chen J, Sun X, Zhu Y, Hu S, Qin M, Tang Y et al. Clinical outcomes of unrelated cord blood transplantation in children with malignant and non-malignant diseases: multicenter experience in China. Pediatr Transpl. 2018;22(1):10.1111/petr.13090.
18. Flowers ME, Inamoto Y, Carpenter PA, Lee SJ, Kiem HP, Petersdorf EW, Pereira SE, Nash RA, Mielcarek M, Fero ML, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood. 2011;117(11):3214–9.
19. Grube M, Holler E, Weber D, Holler B, Herr W, Wolff D. Risk factors and outcome of chronic graft-versus-host disease after allogeneic stem cell transplantation-results from a single-center observational study. Biol Blood Marrow Transplant. 2016;22(10):1781–91.
20. Inamoto Y, Storer BE, Petersdorf EW, Nelson JL, Lee SJ, Carpenter PA, Sandmaier BM, Hansen JA, Martin PJ, Flowers ME. Incidence, risk factors, and outcomes of sclerosis in patients with chronic graft-versus-host disease. Blood. 2013;121(25):5098–103.

21. Stolze J, Boor M, Hazenberg MD, Brand HS, Raber-Durlacher JE, Laheij A. Oral health-related quality of life of patients with oral chronic graft-versus-host disease. Support Care Cancer. 2021;29(11):6353–60.
22. Scaraficci AC, Fernandes PM, Abreu Alves F, Filho JS, Jaguar GC. Oral manifestations of graft-versus-host disease in patients submitted to allogeneic hematopoietic stem cell transplantation: the experience of a Brazilian Cancer Center. Support Care Cancer. 2022;30(1):567–73.
23. Tanem KE, Wilberg P, Diep PP, Ruud E, Skaare AB, Brinch L, Herlofson BB. Oral chronic GVHD after allogeneic stem cell transplantation without total body irradiation performed at a young age. Support Care Cancer. 2022;30(5):4121–8.
24. Pengpis N, Prueksrisakul T, Chanswangphuwana C. Clinical characteristics of oral chronic graft-versus-host disease according to the National Institutes of Health (USA) consensus criteria. Med Oral Patol Oral Cir Bucal. 2014;2023:e167–73.
25. Lertkovit O, Anurathapan U, Hongeng S, Thokanit NS, Pakakasama S. Chronic graft-versus-host disease in children and adolescents with thalassemia after hematopoietic stem cell transplantation. Int J Hematol. 2021;113(4):556–65.
26. Mahmoud HK, Elhaddad AM, Fahmy OA, Samra MA, Abdelfattah RM, El-Nahass YH, Fathy GM, Abdelhady MS. Allogeneic hematopoietic stem cell transplantation for non-malignant hematological disorders. J Adv Res. 2015;6(3):449–58.
27. Yesilipek MA, Uygun V, Kupesiz A, Karasu G, Ozturk G, Ertem M, Şaşmaz İ, Daloğlu H, Güler E, Hazar V, et al. Thalassemia-free and graft-versus-host-free survival: outcomes of hematopoietic stem cell transplantation for thalassemia major. Turkish experience. Bone Marrow Transplant. 2022;57(5):760–7.
28. Bassim CW, Fassil H, Mays JW, Edwards D, Baird K, Steinberg SM, Cowen EW, Naik H, Datiles M, Stratton P, Gress RE, et al. Oral disease profiles in chronic graft versus host disease. J Dent Res. 2015;94(4):547–54.
29. Jeppesen H, Gjærde LK, Lindegaard J, Julian HO, Heegaard S, Sengeløv H. Ocular chronic graft-versus-host disease and its relation to other organ manifestations and outcomes after allogeneic hematopoietic cell transplantation. Transplant Cell Ther. 2022;28(12):833.e1–7.
30. Hamilton BK, Storer BE, Wood WA, Pidala JA, Cutler CS, Martin PJ, Chen G, Flowers ME, Lee SJ. Disability related to chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2020;26(4):772–7.
31. Resende RG, de Fátima C-S, Arão TC, Brito JA, Bittencourt H, Gomez RS, Abreu MH. Oral cGVHD screening tests in the diagnosis of systemic chronic graft-versus-host disease. Clin Oral Investig. 2012;16(2):565–70.
32. Hull KM, Kerridge I, Schifter M. Long-term oral complications of allogeneic haematopoietic SCT. Bone Marrow Transplant. 2012;47(2):265–70.
33. da Fonseca MA, Hong C. An overview of chronic oral graft-vs-host disease following pediatric hematopoietic stem cell transplantation. Pediatr Dent. 2008;30(2):98–104.
34. Piccin A, Tagnin M, Vecchiato C, Al-Khaffaf A, Beqiri L, Kaiser C, Agreiter I, Negri G, Kob M, Di Pierro A, et al. Graft-versus-host disease (GvHD) of the tongue and of the oral cavity: a large retrospective study. Int J Hematol. 2018;108(6):615–21.
35. Goulmy E. Human minor histocompatibility antigens: new concepts for marrow transplantation and adoptive immunotherapy. Immunol Rev. 1997;157:125–40.
36. Ion D, Stevenson K, Woo SB, Ho VT, Soiffer R, Antin JH, Treister NS. Characterization of oral involvement in acute graft-versus-host disease. Biol Blood Marrow Transplant. 2014;20(11):1717–21.
37. Aram G, Simon JAP, Remberger M, Caballero-Velazquez T, Martino R, Pinana JL, Ringden O, Esquirol A, Lopez-Corral L, Garcia I, et al. Reduced intensity conditioning increases risk of severe cGVHD: identification of risk factors for cGVHD in a multicenter setting. Medical oncology (Northwood, London, England). 2018;35(6):79.
38. Savani BN, Labopin M, Blaise D, Niederwieser D, Ciceri F, Ganser A, Arnold R, Afanasyev B, Vigouroux S, Milpied N, et al. Peripheral blood stem cell graft compared to bone marrow after reduced intensity conditioning regimens for acute leukemia: a report from the ALWP of the EBMT. Haematologica. 2016;101(2):256–62.
39. Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, Cutler CS, Westervelt P, Woolfrey A, Couban S, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med. 2012;367(16):1487–96.
40. Jo T, Arai Y, Kondo T, Mizuno S, Hirabayashi S, Inamoto Y, Doki N, Fukuda T, Ozawa Y, Katayama Y, et al. Advantages of peripheral blood stem cells from unrelated donors versus bone marrow transplants in outcomes of adult acute myeloid leukemia patients. Cytotherapy. 2022;24(10):1013–25.
41. Picardi A, Miranda M, Liciani F, Paterno G, Arcese W. Bollero P. Identification of oral risk factors for chronic graft versus host disease in haematological patients who underwent allogeneic haematopoietic stem cell transplantation. Oral Implantol (Rome). 2017;10(4):390–7.
42. Kashiwazaki H, Matsushita T, Sugita J, Shigematsu A, Kasashi K, Yamazaki Y, Kanehira T, Yamamoto S, Kondo T, Endo T, et al. Professional oral health care reduces oral mucositis and febrile neutropenia in patients treated with allogeneic bone marrow transplantation. Support Care Cancer. 2012;20(2):367–73.
43. Haverman TM, Raber-Durlacher JE, Raghoebar II, Rademacher WMH, Rozema FR, Hazenberg MD, Epstein JB, Treister NS. Oral chronic graft-versus-host disease: What the general dental practitioner needs to know. J Am Dent Assoc. 2020;151(11):846–56.
44. Santos PS, Coracin FL, Barros JC, Dulley FL, Nunes FD, Magalhaes MG. Impact of oral care prior to HSCT on the severity and clinical outcomes of oral mucositis. Clin Transplant. 2011;25(2):325–8.
45. Treister N, Duncan C, Cutler C, Lehmann L. How we treat oral chronic graft-versus-host disease. Blood. 2012;120(17):3407–18.
46. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, Gonzalez-Moles MA, Kerr AR, Lodi G, Mello FW, Monteiro L, Ogden GR, et al. Oral potentially malignant disorders: a consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. Oral Dis. 2021;27(8):1862–80.
47. Chaulagain CP, Sprague KA, Pilichowska M, Cowan J, Klein AK, Kaul E, Miller KB. Clinicopathologic characteristics of secondary squamous cell carcinoma of head and neck in survivors of allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Bone Marrow Transplant. 2019;54(4):560–6.
48. Santarone S, Natale A, Angelini S, Papalinetti G, Vaddinelli D, Di Bartolomeo A, Di Bartolomeo P. Secondary oral cancer following hematopoietic cell transplantation. Bone Marrow Transplant. 2021;56(5):1038–46.
49. Inamoto Y, Shah NN, Savani BN, Shaw BE, Abraham AA, Ahmed IA, Akpek G, Atsuta Y, Baker KS, Basak GW, et al. Secondary solid cancer screening following hematopoietic cell transplantation. Bone Marrow Transplant. 2015;50(8):1013–23.
50. Janowiak-Majeranowska A, Osowski J, Mikaszewski B, Majeranowski A. Secondary Oral Cancer after Systemic Treatment of Hematological Malignancies and Oral GVHD: A Systematic Review. Cancers (Basel). 2022;14(9):2175.
51. Atsuta Y, Suzuki R, Yamashita T, Fukuda T, Miyamura K, Taniguchi S, Iida H, Uchida T, Ikegame K, Takahashi S, et al. Continuing increased risk of oral/esophageal cancer after allogeneic hematopoietic stem cell transplantation in adults in association with chronic graft-versus-host disease. Ann Oncol. 2014;25(2):435–41.
52. Dean D, Sroussi H. Oral Chronic Graft-Versus-Host Disease. Front Oral Health. 2022;3: 903154.
53. Majhail NS, Brazauskas R, Rizzo JD, Sobecks RM, Wang Z, Horowitz MM, Bolwell B, Wingard JR, Socie G. Secondary solid cancers after allogeneic hematopoietic cell transplantation using busulfan-cyclophosphamide conditioning. Blood. 2011;117(1):316–22.
54. Elad S, Zadik Y, Zeevi I, Miyazaki A, de Figueiredo MA, Or R. Oral cancer in patients after hematopoietic stem-cell transplantation: long-term follow-up suggests an increased risk for recurrence. Transplantation. 2010;90(11):1243–4.

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