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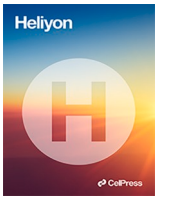

Research article

Influence of periodontal status on patients undergoing hematopoietic stem cell transplantation: A retrospective analysis☆

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ABSTRACT

Objective: This retrospective analysis aimed to evaluate the prevalence of periodontitis in patients undergoing hematopoietic stem cell transplantation, and investigate the effects of various periodontal statuses and risk factors on oral infection incidence.
Study design: Medical records of patients pre– and post–hematopoietic stem cell transplantation from June 2019 to October 2021were reviewed. The study examined the effort of different periodontal statuses on oral complications and infections in patients during transplantation.
Results: Of 549 transplant patients studied, 363 had periodontitis. Patients with or without periodontitis showed significant differences in mean age, male proportion, and mucositis incidence during transplantation ($P < 0.05$). Bacteremia rates were slightly higher in patients with periodontitis, but not significant. Male proportion, age, and hospitalization duration significantly increased with advancing periodontitis stages. Only two patients experienced periodontal complications, that were effectively managed and did not interfere in the grafting process.
Conclusion: Periodontitis is prevalent in patients with hematopoietic diseases. Despite its association with oral mucositis, the occurrence of periodontal infection remains low and controllable.

Clinical relevance

Although periodontitis may heighten the incidence of oral mucositis in individuals undergoing hematopoietic stem cell transplantation, it appears not to increase the risk of infection, a rare and manageable issue in patients with untreated periodontitis.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) stands as a pivotal treatment for various diseases, including leukemia, aplastic anemia, myelodysplastic syndrome, multiple myeloma, lymphoma, and autoimmune diseases [1]. However, the chemotherapeutic regimens cause serious side effects, including myelosuppression and immunosuppression. These make patients more susceptible to severe infections, such as life–threatening septicemia [2]. The reason for this is neutropenia and mucosal injury caused by the side effects of preconditioning and cytotoxic drugs like high–dose cyclophosphamide and/or cytarabine, along with post–transplant methotrexate (MTX). As a result, the oral mucosa is damaged frequently, making the oral cavity a crucial entry point for systemic infections [3]. Therefore, it is recommended that individuals undergoing HSCT should have a dental examination and any oral

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infection should be eradicated before the conditioning regimen begins. Most scholars believe that it is necessary to evaluate the oral health status of patients and provide appropriate interventions before HSCT [1,4,5]. Periodontal disease is not only the most common oral disease in general population but also HSCT recipients. Periodontal disease may increase the risk infection during transplantation or chemotherapy and therefore, requires more attention. Studies have shown that periodontal diseases can cause local and systemic complications during myelosuppression [2]. This study aimed to retrospectively analyze the periodontal status of patients prior to hematopoietic stem cell transplantation and to evaluate the impact of periodontal status on infection and complications during transplantation. To facilitate the dental intervention, an appropriate protocol is necessary for HSCT patients with periodontal disease.

2. Materials and methods

This study involved a retrospective review of electronic medical records (dental examination records and Inpatient medical record) from patients before and after hematopoietic stem cell transplantation conducted at the Department of Stomatology, Peking University People's Hospital (Beijing, China) between June 2019 and October 2021. Data encompassing patient general information (sex, age, and blood disease type), baseline oral examination status, imaging data, HSCT type (autologous or allogeneic), and presence of bacteremia during transplantation were collected.

Inclusion criteria comprised.

1. Patients aged >18 years old were included in the study.
2. Patients were diagnosed with various blood disorders such as Acute myeloid leukemia, Acute lymphocytic leukemia, Myelodysplastic syndrome, Multiple myeloma, lymphoma, and Aplastic anemia.
3. Patients who received Hematopoietic stem cell transplantation before March 2022, and have complete dental and Inpatient medical records.

Exclusion criteria comprised.

1. Patients who have not received transplant treatment before March 2022.
2. Patients with non–hematological diseases;
3. Patients whose medical records were incomplete.

Table 1
The general information between the periodontitis and non-periodontitis group.

	periodontitis group		Non-periodontitis group		P
Number of patients (N, %)	363	66.12 %	186	33.88 %	
Male (N, %)	229	63.09 %	91	48.92 %	0.0014[a]
Female (N, %)	134	36.91 %	95	50.08 %	
Age(mean ± SD, years) (range)	43.31 ± 12.47 (19–69)		36.82 ± 12.48 (19–64)		0.00[a]
Visited a dentist at least one time within a year (N, %)	71	19.6 %	39	21.0 %	0.6964
Had periodontal symptoms when hematologic disease was diagnosed (N, %)	18	5.0 %	12	6.5 %	0.4663
Had oral symptoms during chemotherapy (N,%)	126	34.7 %	77	41.4 %	0.1245
Type of transplantation (N, %)					
autologous	47	12.95 %	13	6.99 %	0.0342[a]
allogeneic	316	87.05 %	173	93.01 %	
Primary hematologic disease (N, %)					
Acute myeloid leukemia	126	34.71 %	62	33.33 %	
Acute lymphocytic leukemia	81	22.31 %	50	26.88 %	
MM	37	10.19 %	10	5.38 %	
MDS	49	13.50 %	28	15.05 %	
aplastic anemia	19	5.23 %	6	3.23 %	
lymphoma	21	5.79 %	17	9.14 %	
others	30	8.26 %	13	6.99 %	
time interval 1(mean ± SD, day)[1]	29.01 ± 29.18		35.43 ± 44.98		0.6321
hospitalization days 2(mean ± SD, day)	31.95 ± 15.74		36.61 ± 20.54		0.0309[a]
Days of fever during transplantation (mean ± SD, day)	2.17 ± 2.17		2.31 ± 2.51		0.9958
Acute GVHD (N, %)	229	63.09 %	109	58.60 %	0.3067
Mucositis during transplantation (N, %)	100	27.55 %	32	17.20 %	0.0073[a]
periodontal infection during transplantation(N)	2		0		
Bacteremia during transplantation (N,%)	29	8.00 %	12	6.45 %	0.5166

1.Time interval refers to the number of days from oral examination to hospitalization for HSCT.
2. Hospitalization days were defined as the number of days from the first day of hospitalization to discharge during HSCT.
3. MM: multiple myeloma.
MDS: aplastic anemia, myelodysplastic syndrome.
GVHD: Graft-Versus-Host Disease.
[a] $P < 0.05$.

4. Patients aged <18 years old.

Participants were categorized into the periodontitis group and non–periodontitis groups based on four periodontal indices, probing depth (PD), clinical attachment loss (CAL), bleeding on probing, and radiographic bone loss (RBL). Using the 2018 periodontitis staging standard [6], those with periodontitis were further divided into stages I, II, III, and IV. In stage I, the heaviest site of the adjacent CAL was 1–2 mm, RBL was less than 15 % in the coronal third, and maximum PD was < 4 mm. In stage II, the heaviest site of the adjacent CAL ranged 3–4 mm, RBL at the coronal third was 15–33 %, and the maximum PD was < 5 mm. The primary type of bone resorption was horizontal resorption during stages I and II, and no tooth loss was attributed to periodontitis. For statistical purposes, patients in stages III and IV were combined because of the small patient numbers. In stages III and IV, the heaviest site of the adjacent CAL is > 5 mm, and the RBL is extended to the middle or apical third of the root. Statistical analysis was conducted using SPSS software (version 25.0 for Windows, SPSS Inc). The normality of the data was checked using a histogram and Kolmogorov-Smirnov Lillefors tests. $P > 0.05$ indicates the data follows a normal distribution. Categorical variables were assessed using the chi–square test or Fisher's exact test, whereas continuous variables were evaluated using Student's t–test, Mann–Whitney test, or Kruskal–Wallis. $P < 0.05$ indicated a noteworthy difference between the results of various groups. The IRB of our hospital granted a writing exemption as this retrospective.

3. Result

In this study, patients were included: 363 with periodontitis and 186 without. General information and disease conditions are detailed in Table 1. Among patients with periodontitis, male proportion, mean age, auto–transplantation proportion, and mucositis incidence were significantly higher than in those without periodontitis. Although the rate of bacteremia in patients with periodontitis was slightly higher, the difference was not significant. Table 2 illustrates a comparison of different stages of periodontitis. As the periodontitis stages increased, a notable increase in male proportion, mean age, the time interval between oral examination and hospitalization for HSCT, and hospitalization duration was observed.

None of the patients underwent nonsurgical periodontal treatment, such as scaling or deep cleaning. Within the III–IV periodontitis group, nine individuals required tooth extraction due to severe periodontitis. Two patients underwent rinsing and extraction of their teeth after eliminating the periodontal abscess. Interestingly, no significant differences were observed in the time interval between oral examination and hospitalization for HSCT ($P = 0.978$), hospitalization days ($P = 0.402$), days of fever ($P = 0.719$), and mucositis ($P = 0.685$) between patients with and without tooth extraction.

During transplantation, only two male patients with stage II periodontitis experienced periodontal complications, having received no prior periodontal treatments. Fortunately, both cases were effectively resolved through medical treatment and had no adverse on the transplantation process (Table 3).

WBC: White blood cells.

Table 2
The general information and disease conditions between different periodontitis stages.

	Stage I		StageII		Stage III-IV		P
Number of patients (N,%)	189	52.07 %	117	32.23 %	57	15.70 %	
male (N,%)	106	56.08 %	74	63.25 %	49	85.96 %	0.0002[a]
female (N,%)	83	43.92 %	43	36.75 %	8	14.04 %	
Age(mean ± SD, years) (range)	39.80 ± 12.23		46.21 ± 11.51		48.98 ± 11.71		0.00[a]
Type of transplantation(N,%)							
autologous	20	10.58 %	18	15.38 %	9	15.79 %	0.3747
allogeneic	169	89.42 %	99	84.62 %	48	84.21 %	
Primary hematologic disease(N,%)							
Acute myeloid leukemia	76	40.21 %	39	33.33 %	11	19.30 %	
Acute lymphocytic leukemia	48	25.40 %	22	18.80 %	11	19.30 %	
MM	16	8.47 %	12	10.26 %	9	15.79 %	
MDS	21	11.11 %	13	11.11 %	15	26.32 %	
aplastic anemia	6	3.17 %	7	5.98 %	6	10.53 %	
lymphoma	10	5.29 %	10	8.55 %	1	1.75 %	
others	12	6.35 %	14	11.97 %	4	7.02 %	
time interval 1(mean ± SD, day)	26.61 ± 27.20		28.10 ± 25.54		39.55 ± 39.32		0.0415[a]
hospitalization days 2(mean ± SD, day)	31.20 ± 15.10		32.06 ± 17.16		34.37 ± 14.78		0.0492[a]
Days of fever during transplantation (mean ± SD, day)	2.31 ± 2.2		1.96 ± 2.12		2.40 ± 2.22		0.2157
Mucositis during transplantation (N,%)	53	28.04 %	32	27.35 %	15	26.32 %	0.9662
odontogenic infection during transplantation(N)	0		2		0		

[a] $P < 0.05$.

Table 3
Periodontal complications of the two patients.

	Patient oncologic characteristics	Odongenic complication	treatment	outcome
A	acute myeloid leukemia, Allogeneic HSCT +5 days WBC = 0.0 x 10^9/L	gingival swelling and pain in the right lower molar	iodine glycerin, ultraviolet radiation, recombinant human interleukin-11 were applied to the oral cavity, IV Meropenem and IV Vancomycin Hydrochloride	symptom resolution at HSCT +15 days
B	acute myeloid leukemia, Allogeneic HSCT +5 days WBC = 0.0 x 10^9/L	periodontal abscess of left lower molar	iodine glycerin, ultraviolet radiation was applied to the oral cavity IV piperacillin sodium/tazobactam sodium and IV Amikacin	symptom resolution at HSCT +10 days

HSCT: Hematopoietic stem cell transplant.

4. Discussion

Periodontal disease encompasses a range of conditions affecting supportive periodontal tissues, such as gums, periodontal ligament, alveolar bone, and cementum. It compasses gingivitis and periodontitis. Both gingivitis and mild to moderate periodontitis are prevalent in the general population and tend to increase with age. The prevalence of adult periodontitis is very high in the Chinese mainland and the periodontal condition is associated with patient age and smoking status [7]. Research suggests a potential elevation in the prevalence of gingivitis and periodontitis among patients with hematologic malignancies [8,9]. However, studies also indicate that although the proportion of periodontitis might be slightly higher in patients with hematologic diseases than in the general population, no statistically significant difference exists [10]. In our study, periodontitis prevalence stood at 66.1 %, and notably, the mean age of patients without periodontitis was significantly lower than that of patients with periodontitis, aligning with trends observed in the general population in China.

Periodontitis is commonly classified as mild, moderate, or severe based on criteria such as alveolar bone loss, tooth mobility, and PD. The prevalence of severe periodontitis in the general population of Western countries is approximately 10 %−15 % [11]. In China, 62 % of adults have periodontitis: 12 % with mild, 40 % with moderate, and 10 % with severe diseases [12]. A study involving 91 patients undergoing HSCT showed that 11 (12 %) experienced moderate to severe horizontal bone loss [13]. Similar proportions of mild, moderate, and severe periodontitis having been observed in patients undergoing HSCT compared with those in the healthy population [3,14].

To the best of our knowledge, this is the first study to employ a periodontitis staging system to assess the severity of periodontitis in patients undergoing bone marrow transplantation. Phases I–IV of periodontitis correspond with mild, moderate, and severe periodontitis, respectively [6]. In our study, the proportion of patients with severe periodontitis undergoing HSCT was mirrored that of healthy individuals previously reported. A greater number of patients exhibited mild periodontitis than moderate periodontitis, which differs from the pattern observed in the general Chinese population [12]. This difference might be attributed to the younger mean age of patients undergoing HSCT in this study (19–69 years) than that of the general population (35–47 years), and the prevalence and severity of periodontitis increases significantly with age. Notably, in our study, patients with mild periodontitis were significantly younger than those with moderate or severe cases. As observed in the broader population [7], the proportion of women with periodontitis decreased with a lower ratio than that of men at each stage.

Bacteremia and systemic inflammation stemming from periodontal infections could elevate the risk of systemic diseases, including infective endocarditis, other cardiovascular diseases, stroke, premature delivery with low birth weight, and diabetes mellitus [15]. The impact of periodontitis on bacteremia risk in patients post-HSCT remains uncertain. Some researchers posit that periodontitis might increase the risk of bacteremia during transplantation, potentially leading to septicemia [16]. Therefore, the recommendation is for the extraction of teeth with a poor periodontal prognosis. Grabers et al.' also proposed an association between periodontal disease, untreated periapical abscesses, and an increased risk of streptococcaemia in the neutropenic phase post-transplantation [17]. Moreover, studies highlight a higher incidence of bacteremia caused by streptococcal species among transplant recipients who did not receive basic periodontal treatment [18]. Similarly, a prospective study indicated a higher bacteremia incidence among patients with gingivitis/periodontitis than healthy individuals [19]. However, conflicting results exist. Some studies found no correlation between severe periodontal disease and bacteremia [16]. Although patients with bacteremia exhibited poorer periodontal status than those without, the difference lacked statistical significance [20]. Importantly, a microbiological study of bacteremia using PCR confirmed that although Streptococcus was detected in oral samples from most of the 10 patients undergoing HSCT with periodontitis, no bacteria were found in the peripheral blood of any patient. Effective oral treatment, such as nonsurgical periodontal treatment has been suggested to prevent oral bacteria-related bacteremia in HSCT recipients [3].

Our findings revealed a slightly higher incidence of bacteremia in patients with periodontitis than that in those without during transplantation, yet this discrepancy did not reach statistical significance. Notably, the severity of periodontitis significantly impacted the waiting time before transplantation and the duration of the procedure. The time interval for mild periodontitis before transplantation was significantly shorter than that for severe periodontitis. Furthermore, the transplantation duration was significantly shorter than that for severe periodontitis. Transplantation in patients with severe periodontitis has been hypothesized to be delayed due to tooth extraction or other dental treatments. Patients with periodontitis may experience an elevated rate of mucositis or an increased susceptibility to additional infectious complications, potentially resulting in extended transplantation durations. The reliability of our study is bolstered by its larger patient sample compared with previous research efforts.

Two types of oral infections occur during myelosuppression after HSCT: odontogenic and nonodontogenic infections. Non-odontogenic infections mainly stem from oral mucositis (OM), the primary nonhematological complication of HSCT [21]. OM lesions primarily manifest on non-keratinized mucosal surfaces such as the ventral and lateral areas of the tongue, floor of the mouth, soft palate, buccal mucosa, and medial lip epithelium [22]. Their severity can vary from mucosal atrophy, swelling, and mild erythema to severe oral ulcers [22]. Previous studies have reported OM prevalence ranging 41%–100 % [2,3,13,19,23–25]. To date, consensus lacks on whether periodontal status affects OM incidence. Several studies indicate that gingivitis, periodontitis, and oral hygiene status have no bearing on OM incidence and severity [24,26]. Conversely, one study found a positive correlation between gingival index, plaque index, and OM incidence [25]. Similarly, another study indicated that patients with gingivitis or periodontal disease were more susceptible to OM [20]. Certain researchers argue that pre-transplantation periodontal treatment can mitigate gingival inflammation and significantly improve periodontal health status, potentially reducing OM incidence and severity [2]. Our results also confirm a significantly higher OM incidence in patients with periodontitis than in those without; however, no significant difference emerged in OM incidence among different periodontitis stages. Notably, periodontitis substantially heightens the likelihood of OM.

We conducted a study analyzing patients with hematological malignancies who initially presented with gingival bleeding or other oral symptoms. No significant difference was observed in the prevalence of periodontitis between the two groups and patients without oral symptoms. Moreover, our funding indicated that periodontitis did not impact the incidence of mucositis in patients with hematological malignancies.

Previous literature rarely reported on periodontal infections during transplantation. In our study, only two patients developed periodontal infections. Symptoms emerged on the 5th day following stem cell infusion(HSCT+5), coinciding with patient neutropenic phase and severe immunosuppression, with WBC and NE < 0.2*109/L. This finding aligns with previous studies. For instance, one study documented only one patient with periodontitis and gingival swelling who was severely immunosuppressed, exhibiting an extremely low neutrophil counts. The infection was gradually resolved after antibiotic treatment [27]. Another study showecasd two out of 37 patients developing periodontal abscesses during hematologic chemotherapy and transplantation. Similarly, two patients had extremely low WBC counts ($<$0.4*109/L), and their infections were managed effectively by antibiotics [28]. These findings suggest that the although incidence of periodontal infections is rare in patients undergoing HSCT, they can occur during periods of neutropenia or severe immunosuppression. Fortunately, their infections seem controllable with escalating antibiotic therapy.

Previous treatments for periodontal disease in BMT or patients undergoing HSCT typically involve the extraction of teeth with periodontal abscesses, PD $>$ 8 mm, or severe mobility, rather than providing comprehensive therapy. The teeth can be saved aforementioned symptoms. Therefore, thorough cleaning and oral hygiene instructions must be given [13,28,29]. Treatment can lead to improved periodontal status, markedly reducing periodontal inflammation, OM incidence and severity, as well as the occurrence of both oral and systemic infections [2,29]. In our study, nine patients underwent tooth extraction because of periodontitis before transplantation. None of the patients developed acute periodontal infections or complications during transplantation. However, the proportion of patients who received periodontal treatment in our study was lower than that reported previously. One possible reason could be that dental examinations typically occur near the beginning of the transplantation, providing limited time for oral therapy. However, the patient's overall health and willingness to receive oral treatment should be considered.

We aim to identify optimal periodontal treatment strategies for patients undergoing HSCT. Our recommendation does not lean towards comprehensive or radical periodontal treatment. Instead, we advise tooth extraction, periodontal scaling, and root based on patient's overall health, pre-transplant schedule, and periodontal status. We propose a personalized treatment plan.

1. Remove acute periodontal abscess (evidenced by gingival swelling, palpable pain, sinus tract suppuration), degree III looseness, or PD $>$ 8 mm.
2. Consider periodontal scaling or deep cleaning before transplantation, accounting for patient coagulation and scheduling.
3. Ensure completion of dental treatments $<$2 weeks before conditioning.
4. Offer comprehensive oral hygiene instructions covering tooth brushing techniques, mouthwash usage, and gap cleaning methods.
5. Maintain comprehensive dental care in the transplant facility and regular follow-ups with dentists during transplantation.

To the best of the knowledge, this is the first study to analyze periodontitis prevalence in Chinese patients undergoing HSCT. It explores the impact of different periodontal statuses and risk factors on oral infection incidence, with a significantly larger case pool than most similar studies. However, our study has limitations stemming from its retrospective nature and occasional inaccuracies in oral documentation by hematologists. Furthermore, statistical bias might exist due to a small subset of patients with periodontal infection undergoing dental treatment. Prospective studies are required to validate these results.

In conclusion, periodontitis is prevalent in patients undergoing HSCT, mirroring its occurrence in the general Chinese popular. Periodontitis slightly increases of bacteremia incidence and significantly raises OM risk. However, periodontal infection risk is relatively low and manageable. The various periodontitis stages following the extraction of symptomatic teeth did not affect the incidence of periodontal complications during transplantation. Our findings will assist hematologists in estimating and controlling the patients' oral examination. Meanwhile, dentists can quickly and accurately evaluate patients' conditions, leading to efficient treatments. This will save medical resources and patients' treatment costs.

Ethics declarations

This study was reviewed and approved by the Ethics Committee of Peking University People's Hospital, with the approval number: IRB (2023PHE037-001). Informed consent was not required for this study because we collected previous case data, and the process of

analysis was anonymous.

Data availability statement

The data used and analyzed during the current study is available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Xuan Gao: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization, Data curation. **Shengnan Zhao:** Writing – review & editing, Writing – original draft, Validation, Investigation, Data curation, Conceptualization. **Shuting Wang:** Methodology, Investigation, Data curation, Writing – review & editing. **Yang Sun:** Investigation, Conceptualization. **Chengzhi Gao:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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