Predicting the course of hematopoietic neoplasm through oral bacterial examination

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Abstract

Many medical institutions have recently conducted studies on the relationship between patients with hematopoietic neoplasms and oral cavity. Statistical analysis of the bacterial populations was performed in this study to identify how oral microflora and health conditions (e.g., dental caries and periodontal diseases) affect the prognosis of patients with hematopoietic neoplasms. Patients undergoing inpatient treatment from January to December 2020 at the Department of Hematology at Showa University, Japan, who required perioperative oral management were included in the study. The oral health of the patients was examined at the initial dental visit, and oral bacterial samples were collected from the tongue, buccal mucosa, and palate of 47 patients who consented to participate after receiving an explanation about the study. Statistical analyses performed after dividing the subjects into two groups following the treatment course showed that *Stenotrophomonas maltophilia* and *Gemella sanguinis* were significantly more common in the poor-course group. However, no significant difference in bacterial examination results was noted among the four groups (myeloid neoplasm chemotherapy, myeloid neoplasm hematopoietic stem cell transplantation (HSCT), lymphoid neoplasm chemotherapy, and lymphoid neoplasm HSCT groups) classified based on disease and treatment method. The detection rate of bacteria potentially causing infectious diseases at the initial dental examination tended to be higher in this study in the poor-course group. The findings of the current study suggest that early detection of pathogenic bacteria after commencing hematology treatment could predict the poor-course that may lead to mortality or severe infections.

Key words : hematopoietic neoplasms, oral bacterium, perioperative oral management, *Stenotrophonomas maltophilia*

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Introduction

Perioperative oral management performed as a part of medical-dental collaboration is effective in preventing loose teeth from falling out intraoperatively. The process is also helpful in preventing postoperative aspiration pneumonia and oral mucositis during chemotherapy in patients scheduled for surgery or chemotherapy[1,2]. Patients with cancer and hematopoietic neoplasms may experience adverse oral events (e.g., oral mucositis and dysgeusia) during chemotherapy and other treatments[3]. Oral bacteria, (e.g., periodontopathogenic bacteria) may enter the bloodstream of patients undergoing hematopoietic stem cell transplantation

(HSCT) through the oral mucosa or periodontitis, causing septic shock, and severe infections[4, 5]. Additionally, oral candidiasis and herpes labialis may increase during leukopenia following chemotherapy or HSCT[6]. Patients are recommended to undergo dental examinations and receive the necessary dental treatment early to avoid the delay in treating primary diseases caused by bacterial infections of oral origin and adverse oral events[7, 8]. Furthermore, good oral hygiene reduces oral mucositis severity and may also lower the risk for septic shock caused by oral bacteria[9, 10].

Showa University Hospital receives requests for dental examinations from the Department of Hematology. After obtaining patients' consent, an oral assessment was conducted and perioperative oral management for those scheduled to receive chemotherapy or HSCT was continuously implemented. Patients who cannot undergo oral cleaning in the outpatient setting or who are hospitalized in an aseptic room were visited for cleaning. When eliminating an infection by tooth extraction, symptoms were checked, blood test data monitored (e.g., neutrophil and platelet counts), and the attending physician is consulted before administering dental treatment[11]. Patients were also encouraged to continue dental checkups with their local or family dentist after hospital discharge.

Many medical institutions have conducted studies on the relationship between hematopoietic neoplasm and oral cavity[4, 5, 7]. According to a study, 41% of sepsis cases in patients with a bone marrow transplant are caused by α-*Streptococcus* sp., which are oral bacteria[5]. Another study has reported that *Staphylococcus epidermidis* and *Streptococcus oralis* from the oral cavity are detected in blood cultures and may cause bacteremia; this finding is similar to immunocompromised patients with central venous catheters[9]. The Department of Hematology at the hospital of the current study found that anaerobic bacteria, *Candida*, and *Enterococcus* are involved in causing oral mucosal diseases in patients undergoing HSCT[12].

The effective methods of perioperative oral management were explored in this study to identify how oral microflora and the environment affect the prognosis of perioperative patients with hematological diseases. Whether oral bacteria isolated in the early stages of treatment in patients with poor courses (e.g., septic shock or death) would affect the course of subsequent hematologic treatment was also investigated. Patients were urged to undergo dental

examination early after the start of chemotherapy, in cooperation with the Department of Hematology, to examine oral health and collect oral bacterial samples from the patients. Furthermore, all patients were divided into two groups according to symptoms course and four groups according to disease and treatment method for comparison.

Materials and methods

The subjects of this study were patients requiring perioperative oral management who underwent dental examination at the Department of Dentistry and Oral Surgery from the Department of Hematology of the hospital of this study between January and December 2020. Additionally, oral bacteria were collected from 47 patients who were admitted to the Department of Hematology, scheduled for chemotherapy or HSCT, and consented to participate after receiving an explanation about the study.

Oral bacterial samples were collected from the tongue, buccal mucosa, and palate. Dentures, if any, were removed before collecting oral bacterial samples. BD BBL CultureSwab™ Plus (Becton, Dickinson, and Co., Ltd., Tokyo, Japan) was used to determine the species and quantify the bacteria, and BML, Inc. (Tokyo, Japan) performed the analysis. Sterile swabs of specimen collection were cultured anaerobically and analyzed using VITEK MS (Sysmex bioMérieux Co, Ltd., Tokyo, Japan) to identify the anaerobic bacteria[12, 13]. The sterile swabs were diluted in 1-mL sterile water and anaerobically cultured on a blood agar medium at 37°C for 3–5 days. Bacterial collection, culture on blood agar medium, and bacterial analysis were performed by the first author to ensure procedure consistency. Referring to the method used by Osakabe *et al.*[12], the oral mucosa was evaluated using NCI-CTCAE v.5.0, WHO scale, and ROAG, and intraoral photographs were taken during collection. The following information was obtained from the medical records: diagnosis, sex, dental formula, periodontal pocket examination results, panoramic X-ray findings, blood test results, blood culture results, the number of days to a dental examination, and the number of days from sample collection to chemotherapy. The poor-course group included patients with cases of mortality, including mortality due to the primary disease by the end of April 2021; infection (e.g., pneumonia during bacterial collection); and septic shock, including suspicious cases after bacterial collection. Other patients who were discharged from the hospital, temporarily

returned home, or moved to the next treatment stage were defined as the good-course group. Statistical analysis was performed using the chi-square test for sex and Mann-Whitney *U*-test for all other variables to compare these two groups. The Kruskal-Wallis test was used for comparison among the four groups of myeloid and lymphoid neoplasms divided into chemotherapy and transplantation (myeloid neoplasm chemotherapy, myeloid neoplasm HSCT, lymphoid neoplasm chemotherapy, and lymphoid neoplasm HSCT groups). Patients, who did not undergo HSCT, regardless of treatment progress, were defined as the chemotherapy group. Statistical analysis was performed using IBM SPSS v.23 (IBM Japan, Ltd., Tokyo, Japan) at a significance level of $P<0.05$.

This study was conducted after approval by the Ethics Committee on Research Involving Human Subjects, Showa University School of Medicine (approval no.: 2908).

Results

Figure 1 presents the flow diagram of the study. Of the enrolled patients, 27 were men, and 20 were women. Of these, 32 (68.1%) and 15 (31.9%) were in the good-course and poor-course groups, respectively. Although two patients were suspected of having septic shock, the blood cultures were negative and the diagnosis was not confirmed. Figure 2 shows the age groups and sex of the study subjects. The age range was 24–90 years old (mean, 60.9±17.2 years old), and the highest number of subjects were in their 70s.

Moreover, 15 (31.9%) and 32 (68.1%) patients had myeloid and lymphoid neoplasms, respectively.

The target diseases included malignant lymphoma (21 subjects), acute and chronic myeloid leukemia (nine subjects), multiple myeloma (seven subjects), myelodysplastic syndrome (six subjects), and acute and chronic lymphocytic leukemia (four subjects). For disease treatment, three (6.4%), 12 (25.5%), 19 (40.4%), and 13 (27.7%) patients were in the myeloid neoplasm chemotherapy (Mn-C), myeloid neoplasm HSCT (Mn-HSCT), lymphoid neoplasm chemotherapy (Ln-C), and lymphoid neoplasm HSCT (Ln-HSCT) groups, respectively. Eight of the patients in the poor-course group were scheduled for or had undergone HSCT.

1) Examination in good and poor-course groups

Table 1 shows the comparison between the good- and poor-course groups. The reference values for blood tests were based on the Guidelines for Clinical Laboratory Testing 2018 of the Japanese Society of Laboratory Medicine. The number of treated teeth was significantly higher in the poor-course group in the dentistry-related items ($P=0.02$) compared with the good-course group. In addition, 12 and five denture users were noted in the good- and poor-course groups, respectively. Additionally, platelets ($P=0.01$) and neutrophils ($P=0.04$) were significantly decreased in the laboratory parameters. In addition, no significant differences were observed between patients who underwent a dental examination before and after treatment initiation.

Table 2 presents the results of oral bacteria detected in samples obtained from each collection site. A comparison was made based on the bacteria that were commonly found in the overall poor-course
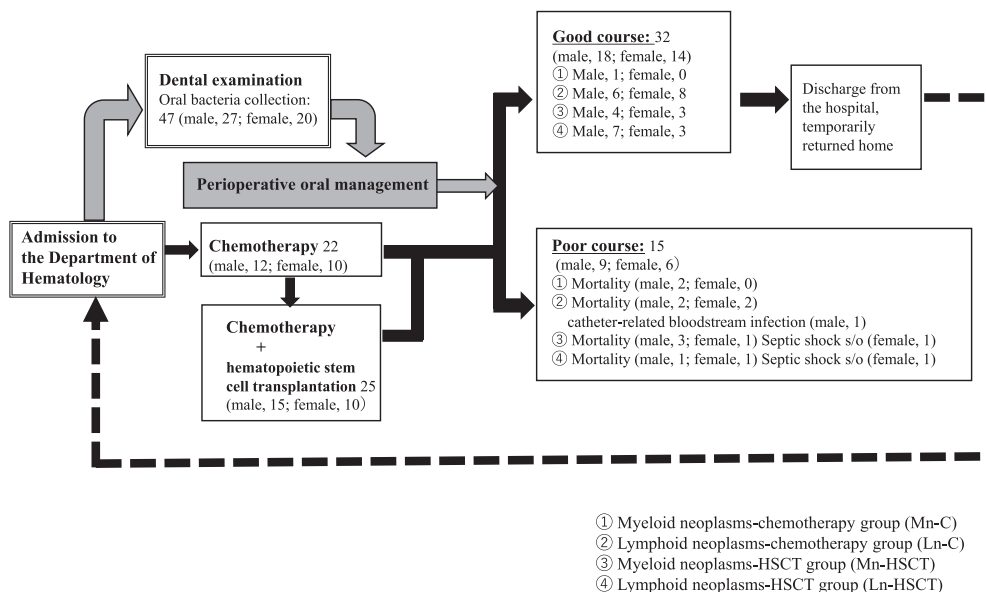

① Myeloid neoplasms-chemotherapy group (Mn-C)
② Lymphoid neoplasms-chemotherapy group (Ln-C)
③ Myeloid neoplasms-HSCT group (Mn-HSCT)
④ Lymphoid neoplasms-HSCT group (Ln-HSCT)

Fig. 1. Process and breakdown of this study

(Number of subjects) $N = 47$

Male: Mean age is 61.7 ± 16.0 years old
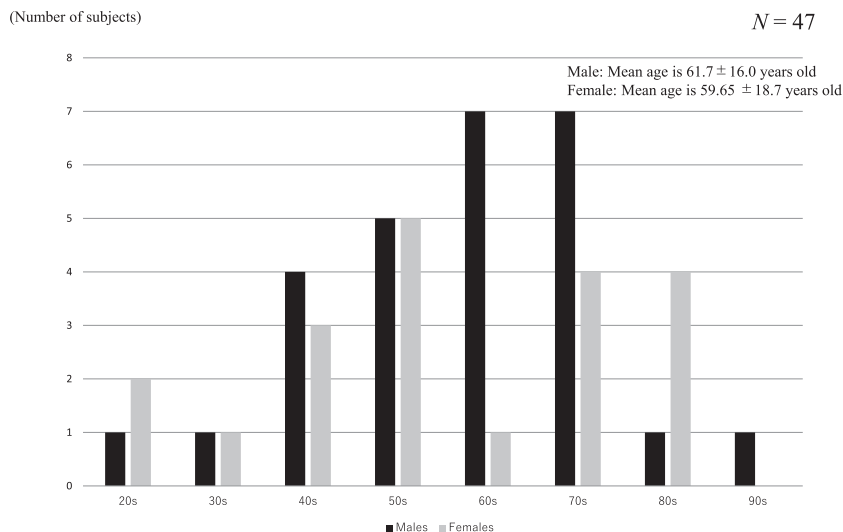Female: Mean age is 59.65 ± 18.7 years old

Fig. 2. Graph by age group and gender

Table 1. Comparison between the good and poor course groups

			Reference value	Good course group ($n = 32$)	Poor course group ($n = 15$)	*P* value
Medical record information	Gender	Male		18	9	0.20
		Female		14	6	0.20
	Age			58.3 (17.4)	66.4 (15.5)	0.13
	Number of days from bacterial collection to chemotherapy			−7.2 (15.9)	−8.2 (12.7)	0.60
	Number of days to initial dental examination			10.4 (14.5)	10.5 (11.1)	0.34
Dentistry-related	Number of remaining teeth			24.3 (9.2)	24.2 (6.6)	0.43
	Number of teeth with dental caries			1.3 (1.4)	0.9 (1.2)	0.41
	Number of root canal treated teeth			3.0 (2.7)	4.4 (2.2)	0.06
	Number of treated teeth			9.1 (5.4)	13.3 (5.5)	0.02*
	Number of teeth with periodontal pockets of ≧ 4 mm			1.6 (2.2)	2.2 (4.4)	0.64
	Number of loose teeth			0.9 (2.2)	1.2 (1.5)	0.12
Test results	BMI	(kg/m²)	18.5−25.0	22.4 (3.5)	21.1 (2.8)	0.22
	Alb	(g/dl)	4.1−5.1	3.6 (0.5)	3.5 (0.5)	0.40
	CRP	(mg/dl)	≦ 0.14	1.74 (3.44)	1.50 (2.12)	0.85
	WBC	(10^3/μl)	3.3−8.6	7.1 (7.7)	9.4 (19.2)	0.16
	Platelets	(10^4/μl)	15.8−34.8	17.8 (9.7)	8.7 (8.9)	0.01*
	Neutrophils	(10^3/μl)		5.7 (7.0)	3.3 (5.1)	0.04*

Gender : Chi-square test ; others : Mann-Whitney *U*-test* indicates *P* < 0.05.
The values indicate the mean, and the figures in parentheses indicate the standard deviation.

group. Bacteria were classified into oral streptococci, periodontopathogenic bacteria, and pathogenic bacteria according to their types and characteristics[9, 14-23]. Furthermore, Table 2 presents the bacteria detected in the good- or poor-course group. *α -Streptococcus* sp. was the most frequently detected bacteria on the tongue, buccal mucosa, and palate in the good- and poor-course groups. Among the top seven bacteria, *Stenotrophomonas maltophilia*, coagulase-negative *Staphylococcus* (CNS) sp., *Staphylococcus epidermidis*,

Haemophilus parainfluenzae, *Enterobacter* sp., *Gemella sanguinis*, and *Streptococcus gordonii* were detected in the poor-course group.

A significant difference was observed for *S. maltophilia* in the tongue, buccal mucosa, and palate when the oral bacteria in the two groups were compared. In the buccal mucosa, a significant difference was observed for *G. sanguinis*. However, no significant differences in oral *streptococci* and periodontopathogenic bacteria were noted. Moreover, no significant difference was noted between the two groups in the evaluation of the oral mucosa using NCI-CTCAE v.5.0, WHO scale, and ROAG at the initial examination.

2) Examination by disease classification

Table 3 shows the result of the comparison among the four groups (myeloid neoplasm chemotherapy, myeloid neoplasm HSCT, lymphoid neoplasm chemotherapy, and lymphoid neoplasm HSCT groups). A significant difference was noted in the number of existing teeth when the dentistry-related items were compared among the four groups. In the Mn-C, Mn-HSCT, Ln-C, and Ln-HSCT groups, one, four, 11, and one were denture users, respectively. Significant differences were observed in age, the number of existing teeth, platelets, and neutrophils in other items. Furthermore, a difference was observed among the groups shown in Table 3. It indicated that age, platelets, and neutrophils in the Ln-C group were $P \leq 0.04$ compared with the Mn-HSCT group, age in the Ln-C group was $P \leq 0.03$ compared with the Ln-HSCT group, and platelets in the Ln-C group was $P = 0.03$ compared with the Mn-C group. Statistical analysis was performed for pathogenic bacteria items that demonstrated differences among the four groups, but no significant differences were observed (Table 4).

Furthermore, no significant difference was observed among the four groups in terms of poor outcomes and evaluation scores on NCI-CTCAE v.5.0, WHO scale, and ROAG during the initial examination.

Discussion

1) Plan for this study

The factors that affect the treatment course in patients with hematopoietic neoplasms during the initial dental examination were examined in this study. However, the number of patients who developed septic shock was lower compared with the previous study[24]. On the day after the onset, oral bacteria were recollected from only one patient who developed septic shock to compare the results with blood culture and oral bacteria at the initial dental examination.

No significant differences in the number of days from oral bacterial collection to chemotherapy and the first dental visit in the two- and four-group comparisons because the protocol was based on close collaboration. This result shows that the time between chemotherapy and dental examination and the number of days between hospitalization and the first dental examination was almost similar for the patients included in the study.

Furthermore, no significant differences were observed in the number of teeth with dental caries, root canal-treated teeth, teeth with ≥ 4-mm periodontal pockets, and loose teeth between the two and four groups in terms of oral health. These results signify the absence of significant differences in the oral streptococci and periodontopathogenic bacteria in patients included in this study.

2) Characteristics of the poor-course group

Neutrophils ($P = 0.04$) and platelets ($P = 0.01$) were significantly lower in the poor-course group than in the good-course group. This result suggests that infections caused by oral bacteria and bleeding during tooth extraction warrant careful attention[6, 11, 25]. Additionally, intraoral findings revealed that the number of treated teeth was significantly higher ($P = 0.02$) in the poor-course group. Moreover, the mean age of the subjects in the poor-course group was higher than that in the good-course group, which may have increased the number of treated teeth.

The oral bacterial results showed a significant difference in *S. maltophilia* ($P \leq 0.01$), and three of the four patients in whom this bacterium was detected from the tongue and buccal mucosa samples died. Of the four patients, two had malignant lymphoma (one relapsed), one had multiple myeloma, and one had acute myeloid leukemia. Additionally, three patients were in the first chemotherapy cycle (in the case of relapse, the first cycle was at the hospital of this study after treatment at another hospital) and one was in the fourth cycle. Furthermore, two patients were scheduled for HSCT and four patients developed septic shock, bacterial pneumonia, and catheter-related bloodstream infections. This bacterium is drug-resistant and can be fatal to patients with pneumonia and bacteremia[16, 17]. Notably, many patients with hematopoietic neoplasms have decreased neutrophil

Table 2. Good vs. poor course groups and comparing the number of detected cases and detection rate

			Good course group (n = 32)	Poor course group (n = 15)	P value
Oral streptococci	α-*Streptococcus* sp.	Tongue	31 (96.9%)	14 (93.3%)	0.58
		Buccal Mucosa	30 (93.8%)	14 (93.3%)	0.96
		Palate	30 (93.8%)	14 (93.3%)	0.96
	γ-*Streptococcus* sp.	Tongue	28 (87.5%)	13 (86.7%)	0.94
		Buccal Mucosa	27 (84.4%)	13 (86.7%)	0.84
		Palate	26 (81.3%)	11 (73.3%)	0.54
	Streptcoccus mitis/oralis	Tongue	7 (21.9%)	4 (26.7%)	0.72
		Buccal Mucosa	9 (28.1%)	5 (33.3%)	0.72
		Palate	10 (31.3%)	3 (20.0%)	0.43
	Streptcoccus parasanguinis	Tongue	14 (43.8%)	4 (26.7%)	0.27
		Buccal Mucosa	6 (18.8%)	3 (20.0%)	0.92
		Palate	11 (34.4%)	4 (26.7%)	0.60
	Streptcoccus gordonii	Tongue	2 (6.3%)	1 (6.7%)	0.96
		Buccal Mucosa	5 (15.6%)	3 (20.0%)	0.71
		Palate	3 (9.4%)	0 (0.0%)	0.23
Periodontopathogenic	*Prevotella* sp.	Tongue	11 (34.4%)	8 (53.3%)	0.22
		Buccal Mucosa	9 (28.1%)	2 (13.3%)	0.27
		Palate	9 (28.1%)	6 (40.0%)	0.42
	Prevotella melaninogenica	Tongue	3 (9.4%)	1 (6.7%)	0.76
		Buccal Mucosa	**10 (31.3%)**	2 (13.3%)	0.19
		Palate	11 (34.4%)	1 (6.7%)	0.05
	Fusobacterium nucleatum	Tongue	9 (28.1%)	4 (26.7%)	0.92
		Buccal Mucosa	11 (34.4%)	3 (20.0%)	0.32
		Palate	10 (31.3%)	4 (26.7%)	0.75
Pathogenic bacteria	*Stenotrophomonas maltophilia*	Tongue	0 (0.0%)	4 (26.7%)	0.00*
		Buccal Mucosa	0 (0.0%)	4 (26.7%)	0.00*
		Palate	0 (0.0%)	3 (20.0%)	0.01*
	Staphylococcus epidermidis	Tongue	2 (6.3%)	3 (20.0%)	0.16
		Buccal Mucosa	4 (12.5%)	2 (13.3%)	0.94
		Palate	2 (6.3%)	2 (13.3%)	0.42
	Neisseria sp.	Tongue	16 (50.0%)	3 (20.0%)	0.05
		Buccal Mucosa	14 (43.8%)	3 (20.0%)	0.12
		Palate	13 (40.6%)	2 (13.3%)	0.06
	Coagulase-negative Staphylococcus (CNS)	Tongue	5 (15.6%)	3 (20.0%)	0.71
		Buccal Mucosa	3 (9.4%)	2 (13.3%)	0.69
		Palate	3 (9.4%)	3 (20.0%)	0.31
	Enterobacter sp.	Tongue	4 (12.5%)	2 (13.3%)	0.94
		Buccal Mucosa	3 (9.4%)	2 (13.3%)	0.69
		Palate	3 (9.4%)	2 (13.3%)	0.69
	Candida sp.	Tongue	4 (12.5%)	2 (13.3%)	0.94
		Buccal Mucosa	5 (15.6%)	2 (13.3%)	0.84
		Palate	2 (6.3%)	1 (6.7%)	0.96
	Haemophilus parainfluenzae	Tongue	1 (3.1%)	3 (20.0%)	0.06
		Buccal Mucosa	3 (9.4%)	3 (20.0%)	0.31
		Palate	0 (0.0%)	1 (6.7%)	0.14
	Gemella sanguinis	Tongue	**4 (12.5%)**	0 (0.0%)	0.16
		Buccal Mucosa	0 (0.0%)	2 (13.3%)	0.04*
		Palate	3 (9.4%)	3 (20.0%)	0.31

Mann-Whitney *U*-test　*indicates *P* < 0.05. The figures in parentheses indicate the detection rate.
In boldface　Higher detection in the good course group
　　　　　　　　Higher detection in the poor course group

Table 3. Comparison by disease and treatment method

		Reference value	Mn-C (*n* = 3)	Ln-C (*n* = 19)	Mn-HSCT (*n* = 12)	Ln-HSCT (*n* = 13)
Medical record information	Gender — Male		3	9	7	8
	Gender — Female		0	10	5	5
	Age		69.0 (19.3)	70.3 (16.0) * †	53.8 (14.6)	51.6 (11.9)
	Number of days from bacterial collection to chemotherapy		−8.3 (8.0)	−4.0 (10.0)	−11.9 (22.3)	−8.3 (12.3)
	Number of days to initial dental examination		10.0 (5.9)	7.3 (8.8)	15.8 (20.7)	9.4 (9.5)
	Poor outcomes		2	5	5	3
Dentistry-related	Number of remaining teeth		23.3 (6.6)	18.9 (10.4) †	27.8 (3.0)	28.8 (3.1)
	Number of teeth with dental caries		1.3 (1.9)	1.1 (1.4)	1.3 (1.2)	1.2 (1.3)
	Number of root canal treated teeth		5.0 (3.6)	3.3 (2.4)	4.3 (3.0)	2.3 (1.7)
	Number of treated teeth		11.7 (5.2)	8.2 (5.4)	13.8 (5.7)	10.5 (5.0)
	Number of teeth with periodontal pockets of ≧ 4 mm		0.0	0.7 (1.1)	3.3 (4.7)	2.2 (2.5)
	Number of loose teeth		1.0 (1.0)	0.8 (1.5)	0.7 (1.5)	1.5 (2.8)
Test results	BMI (kg/m^2)	18.5–25.0	21.6 (1.7)	22.1 (3.8)	21.4 (2.7)	22.3 (3.4)
	Alb (g/dl)	4.1–5.1	3.6 (0.2)	3.4 (0.7)	3.7 (0.4)	3.6 (0.3)
	CRP (mg/dl)	≦ 0.14	3.27 (1.49)	1.72 (4.24)	1.79 (2.05)	1.16 (1.71)
	WBC (10^3/μl)	3.3–8.6	26.6 (35.9)	7.8 (6.0)	4.3 (6.7)	7.3 (9.7)
	Platelets (10^4/μl)	15.8–34.8	2.5 (1.9)	19.8 (8.8) * ‡	9.4 (7.8)	16.7 (10.9)
	Neutrophils (10^3/μl)		0.7 (0.7)	6.3 (6.2)	3.2 (5.5) *	5.1 (7.7)

Kruskal-Wallis test
The values indicate the mean, and those in parentheses indicate the standard deviation.
*$P <$ 0.05, significant difference in the Mn-HSCT
†$P <$ 0.05, significant difference in the Ln-HSCT group
‡$P <$ 0.05, significant difference in the Mn-C group

counts and immunodeficiency, requiring careful attention to infection and pneumonia[18]. Moreover, an oral bacterial examination was conducted after septic shock onset in one patient. *S. maltophilia* and *Acinetobacter baumannii* were detected in both the first and second collections. The latter causes opportunistic infections and septicemia, and is a drug-resistant bacterium similar to *S. maltophilia*[26]. Furthermore, methicillin-resistant *Staphylococcus aureus* was detected in blood cultures and oral bacterial collection after septic shock onset. This bacterium is also associated with high morbidity and mortality and has contributed to septic shock development[27]. The poor-course was thought to be predicted during dental examination when these organisms were detected because these bacteria can cause fatal infections. Additionally, *G. sanguinis*, which showed a significant difference in the buccal mucosa, is involved in systemic infections (e.g., infective endocarditis)[20, 21].

Enterobacter sp. and CNS, which were detected in the poor-course group, have been identified in blood cultures of patients diagnosed with sepsis[16]. *S. epidermidis* and *S. gordonii* also pose a risk for infection[9, 20, 22]. No cases of septic shock caused by *Streptococcus* sp. or other oral bacteria were noted in this study. Similarly, some studies have concluded that sepsis of oral origin did not occur and that treatment could be postponed in chronic dental infection cases[28]. Moreover, no difference in the number of days until the initial dental examination was found in the current study, suggesting that both groups received intervention at an appropriate time.

3) Characteristics based on disease treatment classification

No significant difference in oral streptococci and periodontopathogenic bacteria were noted when the two groups were compared, indicating that pathogenic bacteria influenced the disease course. When the four groups were compared according to

Table 4. Comparison by disease and treatment method (pathogenic bacteria compare the number of detected cases and detection rate)

		Mn-C (n = 3)	Ln-C (n = 19)	Mn-HSCT (n = 12)	Ln-HSCT (n = 13)	P value
Stenotrophomonas maltophilia	Tongue	0 (0.0%)	2 (10.5%)	1 (8.3%)	1 (7.7%)	0.94
	Buccal mucosa	0 (0.0%)	2 (10.5%)	1 (8.3%)	1 (7.7%)	0.94
	Palate	0 (0.0%)	1 (5.3%)	1 (8.3%)	1 (7.7%)	0.95
Staphylococcus epidermidis	Tongue	1 (33.3%)	2 (10.5%)	1 (8.3%)	1 (7.7%)	0.62
	Buccal mucosa	1 (33.3%)	3 (15.8%)	0 (0.0%)	2 (14.3%)	0.38
	Palate	0 (0.0%)	2 (10.5%)	1 (8.3%)	1 (7.7%)	0.94
Neisseria sp.	Tongue	1 (33.3%)	10 (52.6%)	4 (33.3%)	4 (30.8%)	0.58
	Buccal mucosa	2 (66.7%)	10 (52.6%)	3 (25.0%)	2 (15.4%)	0.09
	Palate	1 (33.3%)	8 (42.1%)	3 (25.0%)	3 (23.1%)	0.66
Coagulase-negative Staphylococcus (NCS)	Tongue	1 (33.3%)	3 (15.8%)	1 (8.3%)	3 (23.1%)	0.68
	Buccal mucosa	1 (33.3%)	2 (10.5%)	1 (8.3%)	1 (7.7%)	0.62
	Palate	1 (33.3%)	3 (15.8%)	2 (16.7%)	0 (0.0%)	0.35
Enterobacter sp.	Tongue	0 (0.0%)	3 (15.8%)	2 (16.7%)	1 (7.7%)	0.79
	Buccal mucosa	0 (0.0%)	4 (21.1%)	0 (0.0%)	1 (7.7%)	0.26
	Palate	0 (0.0%)	4 (21.1%)	0 (0.0%)	1 (7.7%)	0.26
Candida sp.	Tongue	1 (33.3%)	2 (10.5%)	1 (8.3%)	2 (15.4%)	0.69
	Buccal mucosa	1 (33.3%)	2 (10.5%)	2 (16.7%)	2 (15.4%)	0.78
	Palate	0 (0.0%)	1 (5.3%)	1 (8.3%)	1 (7.7%)	0.95
Haemophilus parainfluenzae	Tongue	0 (0.0%)	2 (10.5%)	1 (8.3%)	1 (7.7%)	0.94
	Buccal mucosa	0 (0.0%)	1 (5.3%)	3 (25.0%)	2 (15.4%)	0.39
	Palate	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0.41
Gemella sanguinis	Tongue	0 (0.0%)	1 (5.3%)	1 (8.3%)	2 (15.4%)	0.73
	Buccal mucosa	1 (33.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0.07
	Palate	1 (33.3%)	4 (21.1%)	1 (8.3%)	0 (0.0%)	0.23

Kruskal-Wallis test
The figures in parentheses indicate the detection rate.

disease treatment, only the pathogenic bacteria were statistically analyzed, and no significant difference was noted among the four groups. Additionally, a significant difference in patient age was noted, but this observation was considered to be based on HSCT indication[29]. The results showed a significant difference in the number of existing teeth, with the Ln-C group having the lowest value (18.9±10.4). The number of existing teeth was 18.8±11.3 and 19.2± 7.2 in the good- and poor-course groups, respectively, without difference depending on the course. The mean age of patients in the Ln-C group was the highest among the four groups, which may be because patients in this group also had significantly fewer existing teeth than those in the other groups. Similar to the comparison between the two groups, significant differences were noted in platelets and neutrophils. Promoting perioperative oral management while focusing careful attention to the test results is necessary regardless of disease type or treatment status[11].

4) Future prospects
This study established that detecting bacteria that can cause sepsis and infection tended to be higher in the poor-course group than in the good-course group during the initial dental examination. Although only one patient went into septic shock, these results suggest that the detection of these bacteria during initial dental examination indicates a fatal disease course in the future.

Drug-resistant bacteria, *S. maltophilia* and *Acinetobacter* sp., were detected in patients with septic shock during the initial dental examination before septic shock onset. *S. maltophilia* was also detected in patients with bacterial pneumonia during the initial dental examination. A decrease in leukocyte count is observed in association with chemotherapy or HSCT in patients with hematopoietic neoplasms[4]. As aforementioned, the possibility of a poor-course can be predicted during the dental examination when these bacteria are detected. Additionally, frequent interventions have the advantage of facilitating the

detection of oral changes (e.g., the onset of mucositis and oral candidiasis) during treatment.

Eliminating the infection source at an early stage and various bacterial examinations are required to improve the accuracy of treatment course predictions in patients with hematological diseases. In this study, the bacteria were tested at BML, Inc. and identified using VITEK MS. However, in both procedures, many anaerobic bacteria died between bacterial collection and culture, which may not be reflected in the results. Thus, further investigation is warranted although no characteristic bacteria were detected on the tongue, buccal mucosa, or palate. The detection of anaerobic and drug-resistant bacteria was possible in this study; however, using a next-generation sequencer[30] for bacterial examination to more precisely identify the bacteria may lead to a better treatment course.

During the sample collection period of this study, the spread of COVID-19 resulted in hospital-wide restrictions on admissions. Collecting bacterial samples from the planned number of patients was challenging because of the decrease in dental interventions for hospitalized patients. Increasing the number of patients is aimed in future studies.

Patients scheduled for chemotherapy or HSCT may have a period when their immunity is greatly compromised as treatment progresses. Therefore, these patients need to be carefully observed for bacteria that are not considered problematic in healthy adults. During the perioperative oral management of diseases other than hematopoietic neoplasms, few opportunities to collect oral bacteria were noted unless symptoms of oral candidiasis exist. However, the results of this study suggest that obtaining oral bacterial results during the initial dental examination will help prevent infections. Continuing the collaboration with the Department of Hematology to provide dental intervention from the early treatment stage is important although no significant difference in the number of days from admission to dental examination was noted in the good- and poor-course groups.

The risk of infection from oral bacteria is decreasing due to screening by dentists at the beginning of treatment of primary diseases. Therefore, perioperative oral management with close medical-dental collaboration should be effective in improving the treatment of primary diseases.

This study examined the effects of perioperative oral management on oral health conditions and prognosis after commencing treatment in patients with hematopoietic neoplasms. Upon comparing the oral bacteria between the good- and poor-course groups, no significant differences were noted in oral streptococci and periodontopathogenic bacteria. However, the pathogenic bacteria, *S. maltophilia* and *G. sanguinis*, were detected significantly more often in the poor-course group. The patients in this group also had lower neutrophil counts and were more likely to develop opportunistic infections due to deterioration in their general condition. Thus, the oral bacterial examination may help predict infection development during early dental intervention after the start of treatment in patients with hematopoietic neoplasms.

Conflict of interest disclosure

The authors have no conflict of interest to declare.

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