Oral health of patients with severe haematological malignancies and disorders before and after haematopoietic stem cell transplantation

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2 ABSTRACT

Introduction and objectives: Potentially lethal haematological disorders and malignancies – such as myelodysplastic syndromes, acute and chronic leukaemias, severe aplastic anaemias and lymphomas – represent a heterogeneous group of diseases characterised by alterations in the proliferation and function of blood cells. It was reported decades ago that patients with acute leukaemia (AL) have signs of specific leukaemia-related oral lesions, such as petechias, gingival bleeding, and gingival swelling. Previous studies have also concluded that general dental treatment needs to be high among haematological cancer patients at the time of diagnosis and before cancer treatments, but the data are sparse. Thus, there is a need to gather contemporary information on the state of oral health of these patients.

Poor oral health is considered a risk factor for several diseases, including specific cancers, but the associations between oral health and severe haematological malignancies and disorders are unclear. The existing knowledge is based on a limited number of studies and the results are contradictory.

Treatments of these disorders and malignancies are often intensive and may include chemotherapy, radiation therapy, and haematopoietic stem cell transplantation (HSCT). Thus, the elimination of possible oral foci has been suggested in oral health protocols for such patients. As well as the disorders and malignancies themselves, their treatments are known to affect oral health. As HSCT procedures and success rates have increased, a growing number of patients have experienced serious short- and long-term side effects and comorbidities. Due to the toxic effects of chemotherapies, total body irradiation, and immunosuppression, HSCT recipients are at risk of oral side effects during and after HSCT. Side effects of the therapy in the oral cavity are common and approximately 80% of patients are affected by comorbidities such as mucositis, hyposalivation, and graft versus host disease (GvHD).

The purpose of this thesis was to investigate the oral health parameters of adult patients with severe haematological malignancy or disorder before HSCT and the progression of the oral health parameters post-HSCT. The results were compared with controls of normal population. Additionally, the associations between oral health parameters and hyposalivation with survival were investigated.

Methods: A group of 572 adult patients referred for dental examination to University Center for Dental Medicine Basel from Hematological Department of University Hospital

Basel between 2008 and 2018 was included in the sub-studies of this thesis. From 2008 to 2016, the data collection was retrospective, and for 2018 prospective. A dental examination conducted included the following: decayed, missing, and filled teeth (DMFT) index; calculation of number of teeth; stimulated salivary flow rate (SSFR); presence of periodontitis; presence of acute infections; panoramic radiographs and if needed, additional radiographs. After HSCT, the presence of oral GvHD was additionally examined. In the longitudinal part of the study, the patients were examined six, 12, and 24 months post-HSCT. The changes in SSFR and influence of SSFR on other oral health parameters and on six-month survival were examined.

The control group consisted of 289 adults recruited from the Swiss Bone Marrow Donor Registry of the Blood Transfusion Service SRC Basel, Switzerland. Oral examination was performed for the controls in University Center for Dental Medicine Basel, in a process similar to that previously described – with the exception that radiographs were not taken and, instead, a clinical periodontal status was performed.

In the first sub-study (8.1), the final study population included 143 allogeneic HSCT recipients matched with controls by age and sex. In the second sub-study (8.2), a total of 149 patients who had got their haematological diagnosis not more than six months ago were included and compared with a control group of 154 subjects of same mean age. For the longitudinal part of the study (8.3), 269 allogeneic HSCT recipients were included.

Results: In the first sub-study (8.1), the mean SSFR and mean DMFT index and number of caries lesions were observed to be poorer among HSCT recipients than controls (all p-values < 0.05). Acute symptomatic infections were observed in nine HSCT recipients (6.3%) and none of the controls. The number of teeth was lower among the HSCT recipients, but no statistically significant difference was observed. Statistically significant differences in the measures of current or previous periodontitis were not observed.

In the second sub-study (8.2), where patients with newly diagnosed severe haematological malignancy or disorder were compared with controls, the mean SSFR of the patients was significantly lower than the mean SSFR of the controls ($p < 0.005$). Additionally, the number of caries lesions was significantly higher in the patient group than in the control group ($p < 0.005$). There were fewer teeth and a higher DMFT index in the patient group compared to the control group, but the differences were not statistically significant. Acute symptomatic infections were observed in eight (5.4%) patients and in none of the controls ($p < 0.01$).

In the third longitudinal study (8.3), 40 HSCT recipients (14.8%) died within six months after HSCT. Among the deceased recipients, hyposalivation and caries were more common pre-HSCT than in recipients who survived more than six months ($p < 0.05$). HSCT recipients with hyposalivation pre-HSCT had a higher risk of death (HR: 1.90, 95% CI: 1.00-3.60; $p = 0.044$) within six months post-HSCT compared to recipients without hyposalivation. Additionally, hyposalivation pre-HSCT was associated with a higher DMFT index score ($p < 0.05$) and a lower number of teeth ($p < 0.005$) 24 months post-HSCT in comparison to those without hyposalivation.

Conclusions and clinical relevance: Patients with severe haematological disease demonstrated a high prevalence of oral disorders at the time of diagnosis and at the time of pre-HSCT. Hyposalivation and caries were associated with a lower rate of survival in HSCT recipients. In addition, hyposalivation predisposed patients to deterioration of oral health post-HSCT. These findings support the recommendations for early dental examination at the time of diagnosis. Efficient preventive strategies are important to maintain the oral health of these patients.

3 ABBREVIATIONS

aGvHD - Acute graft versus host disease

AL - Acute leukaemia

ALL - Acute lymphoblastic leukaemia

AML - Acute myeloid leukaemia

ASCO - American Society of Clinical Oncology

cGvHD - Chronic graft versus host disease

CLL - Chronic lymphocytic leukaemia

CML - Chronic myeloid leukaemia

CTC - Common toxicity criteria

DMFT index - Decayed, missing, filled, teeth index

GvHD - Graft versus host disease

HSCT - Haematopoietic stem cell transplantation

HSV - Herpes simplex virus

ISOO - International Society of Oral Oncology

MASCC - Multinational Association of Supportive Care in Cancer

MDS - Myelodysplastic syndrome

MM - Multiple myeloma

MPN - Myeloproliferative neoplasm

NCI - National Cancer Institute

NIH - National Institute of Health

OHM - Department of Oral Health & Medicine

Pre-HSCT - Before haematopoietic stem cell transplantation

Post-HSCT - After haematopoietic stem cell transplantation

RAL - Radiological attachment loss

RIC - Reduced intensity conditioning

SAA - Severe aplastic anaemia

SSFR - Stimulated salivary flow rate

TBI – Total body irradiation

UZB - University Center for Dental Medicine Basel

WHO - World Health Organisation

4 INTRODUCTION – REVIEW OF THE LITERATURE

In recent years, the associations between oral health and common noncommunicable diseases have been studied extensively, with many found to be important [1-3]. However, the relationship between oral health and haematological malignancies and disorders, as well as the influence of oral health on treatment outcomes for these malignancies and disorders, remains contested. This thesis provides more detailed evidence on the oral health of patients with severe haematological malignancies and disorders.

Recent scientific reports show that oral health and diseases have an impact on general health [1, 2]. Oral diseases and neglect in oral health care can lead to acute and even life-threatening general infections, such as septicaemia [3]. Oral diseases are widespread, common, and cumulative in nature, and they have been observed to have various influences on general health. Oral diseases and many non-communicable diseases have same risk factors, but there is also substantial evidence of an association between oral health and pathogenesis, for example, in diabetes and cardiovascular disease [1, 4]. Recent studies of chronic oral infections, such as periodontitis, have shown that this persistent low-grade oral inflammation is associated with several malignancies and with overall cancer mortality [5, 6]. To date, there is no conclusive evidence that poor oral health is a risk factor for haematological disorders or malignancies [6, 7].

Several studies have found that the oral health status of patients with haematological malignancies prior to cancer treatments may correlate with comorbidities, such as mucositis, during and after cancer treatments [8-10]. It has also been suggested that cancer treatments can cause oral side-effects via direct toxicity, and that cancer patients are more likely to develop oral health problems during and after their treatments [11, 12].

The data on the oral health of patients with severe haematological malignancies and disorders before and after haematopoietic stem cell transplantation (HSCT) are scarce. Moreover, the quality of the data in terms of number of participants, methodologies used, and data analyses reported are partially imprecise. Hence, this thesis provides novel evidence that offers an insight into oral problems in adult patients with haematological malignancies and disorders, before and after HSCT.

4.1 Short introduction to severe haematological malignancies and disorders and their treatments

Severe haematological disorders and malignancies – such as leukaemias, lymphomas, and severe anaemias – can frequently affect all blood cell lineages causing neutropenia, thrombocytopenia, and anaemia [13-16]. Although the reasons for most haematological disorders and malignancies remain unknown, some risk factors have been identified. These include exposure to benzene and previous radio-chemotherapeutic cancer treatments [13-17].

4.1.1 Haematological diagnoses

This subsection details the most common haematological diagnoses relevant to this thesis. These diagnoses can be sub-grouped according to many different criteria, such as risk level and genotype, but these are not addressed in detail here.

Myelodysplastic syndrome (MDS) is one of the most common haematological malignancies and it consists of a heterogeneous group of diseases characterized by dysplasia and cytopenia in myeloid cell lineages. Such patients have an increased risk of developing acute myeloid leukaemia (AML). Intensive chemotherapy followed by allogeneic HSCT is the only curative treatment. Incidences of MDS are highest among older people (> 70 years) [14, 16].

AML is the most commonly diagnosed acute leukemic malignancy in adults. AML is characterised by proliferation in differentiation of myeloid cell lines (e.g., neutrophils, erythrocytes, and platelets). Although AML can occur at any time, the incidence increases with age, and it is usually diagnosed among older adults. Chemotherapy possibly combined with HSCT is considered as therapy [13, 16].

In myeloproliferative neoplasms (MPN), there is an observable increase in the production of red or white blood cells, or platelets, produced by bone marrow. Myelofibrosis, polycythaemia vera, and essential thrombocytopenia are MPNs. Chronic myeloid leukaemias (CML) are also type of MPN, usually diagnosed among older patients (average of 60 years). First-line treatment for CML is done with tyrosine kinase inhibitors, but if there is primary resistance against tyrosine kinase inhibitors or no response, allogeneic HSCT is provided for eligible patients [16].

Acute lymphoblastic leukaemia (ALL) affects the lymphoid line of blood cells, causing insufficient maturation in lymphocytes (T- and B-cells, natural killer cells). It is more common among children than adults. Chemotherapy and, if needed, total body irradiation (TBI) are used as first-line treatment. High-risk ALL patients are treated with allogeneic HSCT [16].

In chronic lymphocytic leukaemia (CLL), non-functioning B-cells accumulate in various tissues and organs, such as bone marrow and spleen. It is the most frequent leukaemia among adults, and its onset is usually at older age. Its progression is slow. For low-risk patients without symptoms, the preferred treatment is regular monitoring of their condition. Patients with symptoms and higher risk factor are treated with chemotherapy and autologous HSCT, though the only curative treatment is allogeneic HSCT [16].

Lymphomas are malignancies affecting the lymphoid system. They are divided into Hodgkin's lymphomas and non-Hodgkin's lymphomas. Hodgkin's lymphomas have two peaks in prevalence, among young adults (15-35 years) and older adults (> 50 years). Hodgkin's lymphoma is characterised by special Reed-Sternberg giant cells, and the first affected areas of this disease are usually the upper body lymph nodes (e.g., neck, armpits). Non-Hodgkin's lymphomas are more common than Hodgkin's lymphomas and several subgroups can be classified. Preferred therapy depends on the aggressiveness of the malignancy and the number of sites affected. Chemotherapy, radiotherapy, and HSCT are used for treatment [15, 16].

Multiple myeloma (MM) is a malignancy affecting plasma cells, the antibody producing white blood cells. It can be treated but there is no curative care for the condition. Bone lesions are often part of MM; and thus, bone-modifying agents are administered as medication to prevent bone fractures. High-dose chemotherapy and autologous HSCT are used for eligible patients. Relapse is usual and life-long cancer medications are needed [16].

Severe aplastic anaemia (SAA) is a disease caused by bone marrow failure. In SAA, there is a failure in the production of new blood cells, causing fatigue, elevated risk of bleeding, and increased risk of infections. It can occur at any age. The disease is treated with allogeneic HSCT, blood transfusions, or immunosuppressive therapy [16].

4.1.2 Treatments

The treatments for severe haematological malignancies and disorders are often intensive, including chemotherapies, irradiation, and HSCT [16, 18-21].

Chemotherapy is a systemic treatment, in use for more than 100 years. Chemotherapeutic agents cause inhibition of cell mitosis and block extracellular signalling of cells. Today, multiple different chemotherapeutic agents are used for treatments of haematological malignancies. Patients of HSCT often get various chemotherapy schemas and multiple cycles, depending on the diagnosis, stage of malignancy or disorder, and the condition and age of patient. Typical chemotherapeutic agents used for haematological malignancies are anthracyclines, cytosine arabinosides, asparaginases, cyclophosphamides, methotrexate, and vincristines [16].

The first – and, if needed, second – cycle of chemotherapy is called ‘induction therapy’. This aims to eliminate malignant cells and to enable haematological recovery. The therapy before HSCT may be myeloablative, meaning complete aplasia: hypo-cellular marrow without erythropoiesis, megakaryopoiesis, and myelopoiesis, or given with reduced intensity in certain cases where high dose chemotherapy is not tolerated. When recovery is achieved, the next cycle of treatment begins – this ‘consolidation therapy’ is given to maintain the state of remission. It is important to keep in mind that, during aplasia, patients are at high risk for infections. Chemotherapies causing bone marrow aplasia are not merely toxic for the haematopoietic system, also mucositis and skin toxicity are often reported as side effects [16, 21].

4.1.3 Haematopoietic stem cell transplantation

In the 1950s, HSCT was found to be a curative treatment for some end-stage acute leukaemia (AL) patients [20]. In recent decades, improved treatment procedures have led to a decrease in mortality and morbidity rates, an increase in success rates, and an extension of patients’ life expectancy [21, 22]. Nevertheless, a remarkable number of patients die after HSCT. The main reasons for death are relapse (30%), graft versus host disease (GvHD) (25%) and infection (10%) [23].

The number of treated patients has increased. In 2017, there were more than 40,000 HSCT treatments in Europe [24]. Moreover, the use of HSCT is no longer limited to severe haematological malignancies and disorders, but it is also used for certain autoimmune disorders and solid tumours [25] Therefore, a growing number of patients are suffering from short- and long-term comorbidities after treatment. These patients need supportive care, sometimes for the rest of their lives [22].

The HSCT treatment aims to re-establish haematopoietic functions, meaning full recovery of haematological and immunologic systems, which should result in normal physical functioning [20, 21]. Stem cells are collected either from a donor (allogeneic HSCT) or from the patient herself (autologous HSCT) [16, 18, 21]. Factors affecting HSCT outcome are the patient's age and stage of diagnosis and, in allogeneic HSCT, the histological compatibility of donor and recipient. As the treatment itself might be life-threatening and several complications are common, the patients should be chosen carefully, and a risk-benefit ratio should always be estimated [16, 18, 21]. The main indications for HSCT are listed in Table 1.

Table 1. Main indications for HSCT [25]

	Autologous HSCT	**Allogeneic HSCT**
Myeloid malignancies	AML	AML MDS MPN CML
Lymphoid malignancies	Plasma cell disorders Hodgkin's lymphoma Non-Hodgkin's lymphoma	ALL CLL Non-Hodgkin lymphoma
Non-malignant disorders	Autoimmune disorder	SAA Thalassemia Other anaemias Primary immune deficiency
Solid neoplasms	Neuroblastoma Germ cell tumour Soft tissue sarcoma Ewing sarcoma	
Acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), haematopoietic stem cell transplantation (HSCT), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), severe aplastic anaemia (SAA)		

The HSCT treatment is given after a conditioning regimen in which different chemotherapeutic agents are used to eradicate the recipient's own haematopoietic stem cells, suppressing the immune system before transplantation of haematopoietic multipotent stem cells. The patient continues to be aplastic until the transplanted cells have cleaved and proliferated [21].

In some schemas, haematological cancer patients (HSCT recipients) receive TBI as part of their treatment. Irradiation is a well-known, quantity-bound treatment, which can have both reversible and irreversible impacts on various organs and tissues [26-28].

In contrast to autologous HSCT, in allogeneic HSCT, the period of aplasia is longer and more severe. Thus, the patients undergoing allogeneic HSCT are at higher risk of secondary infections and susceptible to allogeneic transplantation-specific complications, such as GvHD. To avoid severe side effects and to enable allogeneic HSCT for older people and those with suboptimal conditions, reduced intensity conditioning (RIC) is used [21, 25]. The disadvantage of RIC is the greater risk of relapse and reoccurrence of the haematological malignancy [25].

Table 2. Common supportive medications used during and after HSCT

Medication group	**Medication**	**Used for**
Immunosupressives	Cyclosporine, tacrolimus	Required to GvHD prevention and treatment by calcineurin inhibition affecting T-cell proliferation
	Systemic corticosteroids; methylprednisolone and prednisone	Required to GvHD prevention and treatment by suppression numerous immune pathways
	Mycophenolate mofetil and pentostatin	Required to treatment of steroid-refractory GvHD by immunosuppression of T-cell proliferation
Infection prophylaxis	Antibiotics (amoxicillin), Antivirals (valacyclovir, aciclovir), Antifungals (fluconazole)	Required for bacterial, viral and fungal infection prophylaxis
Bone modifying agents	Pamidronate, zoledronate, denosumab	Multiple myeloma patients for bone fracture prevention
Drugs for acid related disorders	Pantoprazole, proton pump inhibitor	Gastric ulcer and reflux prevention by reduction of gastric acid secretion
Other possible necessary medications	Pain killers, sleep medications, anti-depressants	
Graft versus host disease (GvHD)		

The HSCT treatment is followed by engraftment. Engraftment is defined as a stage in which neutrophil counts are above 0.5×10^9 /l for a period of three days. Platelet engraftment occurs when platelet counts are above 20×10^9/l without previous platelet

transfusions in the previous five days. Immunological recovery takes usually 3-6 months and for some parts even several years to gain full recovery [29].

After HSCT, patients usually need a wide range of different medications, some for extended periods of time [30-33]. The most commonly provided medications are listed in Table 2. It is well known that several medications can reduce salivary flow and that polypharmacy increases the risks of hyposalivation, a condition that may lead for further oral comorbidities [34, 35] Haematological cancer treatments are known to cause acute and long-term oral side effects and, as evidence shows, the side effects of these treatments often worsen the patient's quality of life [36-39].

4.2 Oral health at the time of haematological diagnosis and pre-HSCT

4.2.1 Oral leukemic-related manifestations at the time of haematological diagnosis

In the 1960s, Roath et al. and Lynch et al. found that patients with AL had specific AL-related oral lesions [40, 41]. In later research, depending on the study design and the timing of oral examination (in relation to the onset of haematological malignancy or disorder), between 4.0% and more than 50% of patients with AL were found to have signs of specific leukaemia related oral lesions [42]. The most commonly described oral lesions were petechias, gingival bleeding, ulcerations, and gingival hyperplasia and swelling. Lynch et al. report that oral lesions are more often found among patients diagnosed with advanced disease [41]. As haematological malignancies and disorders are today diagnosed in the early stages of the disease, oral signs are seldom the first sign leading to diagnosis. However, in a recent study, more than 30% of the patients with a new diagnosis of AL had oral mucosal signs related to leukaemia [42]. Differential diagnosis of oral manifestations of leukaemia is challenging, and determination of their association with haematological malignancies might be difficult.

4.2.2 Common oral health

Acute oral mucosal changes are not the only oral diseases or disorders that haematological patients have at the time of diagnosis. Recent studies suggest that AL patients often have poor oral health and are in urgent need of dental treatment at the

time of diagnosis [42, 43]. One study found that more than 40% of 263 AL patients needed oral treatment. At the time of diagnosis, they were exhibiting oral symptoms such as visible caries, dental pain, and teeth mobility [42]. Another recent study found a high prevalence of caries and periodontitis in a group of 39 patients with newly diagnosed AL before they received cancer treatments. The study found that the patients had significantly more caries and missing teeth than seen in healthy controls [43]. Another study reported that, in 24 leukaemia patients, the salivary flow rate was statistically significantly lower before the initiation of treatments than among healthy controls [44].

Few previous studies have investigated the oral health status of patients pre-HSCT in the last two decades. These studies are listed in Table 3. Several of these conclude that 90% and more of the patients were in need of some dental treatment, and one study found that 97.4% of patients had at least one potential dental infection foci [9, 45, 46]. Caries prevalence has been observed to vary between 32% [46] and 67% [47]. Different degrees of periodontitis have been observed ranging from just 0.6% of patients [48] to 67% [45]. The prevalence of oral infections was reported to be 6.4% in a study of autologous HSCT recipients and patients receiving high-dose chemotherapy [49]. According to the study results, the need for oral or dental treatment varies depending on the study setting and the descriptives of the patients. The treatments given by dental professionals were often oral hygiene information, scaling, filling, or extractions [9, 45, 47, 50-52].

At the time of HSCT, some patients had already received treatments for their underlying disease, with some having been treated for several years. These previous therapies could have affected their oral health, particularly their salivary flow rate, if chemotherapies and TBI had been used. Studies on the effect of chemotherapies on salivary flow rate in HSCT recipients are inconsistent and sparse [39]. These effects, together with the stressful period of undergoing treatments causing fatigue, could have led to deterioration of oral health pre-HSCT [53]. However, as described previously, patients with newly diagnosed AL had worse oral health parameters than healthy control subjects prior to any cancer treatments and a notable need for dental and oral treatment [42, 43].

Table 3. Previous studies about oral health of patents pre-HSCT

Author	Year	Subject n	HSCT type	Mean age	Dental treatment need % (n)	Decayed teeth % (n)	Periodontal disease % (n)	Other parameters	% (n), or other if mentioned
Pattni et al	2000	26	allo	38				Number of teeth mean	26
								Neglible to mild bone loss	61 (14 (of 23))
Graber et al	2001	42	allo	38		67 (31)		Extraction needed	47 (20)
								Mean periodontal bone loss	13 mm
Akintoye et al	2003	77	allo	38	86(66)		18.2 (14)	Extractions needed	42 (32)
Melkos et al	2003	58	auto & allo	40		52 (30)	35 (20)	Periapically infected teeth	33 (19)
								Retained roots	22 (13)
Elad et all	2003	46	auto & allo	38		50 (23)	37 (10(from 27))	Gingivitis	15 (7)
								Calculus deposits	54 (25)
								Residual roots	6.5 (3)
								Mucosal pathology	6.5 (3)
Yamagata et al	2006	41	auto	41	93 (38)	64 (26)	59 (24)	Apical periodontitis	46 (19)
								Pulpitis	5 (2)
Durey et al	2009	94	auto & allo	49		53 (46)	43 (38)	Gingivitis	52 (45)
								Calculus	61 (54)
								Failing restorations	16 (14)
								Periapical pathology	21 (18)
								Edentulous	6.3 (6)
Fernandes et al	2013	48	auto	50	98		29 (14)	Number of teeth mean	24
								DMFT mean	13
								BOP	17
								Visible plaque (% of sites)	45
Ertas et al	2014	36	allo	32	94 (34)	8		Gingivitis	80
Mawardi et al	2014	405	na	53				Need for dental restoration	46
								Need for dental extraction	21
								Need for endodontic therapy	5
Tinoco-Araujo et al	2015	100	auto & allo	range 4-78		34 (34)		DMFT mean	14
Schuurhuis et al	2016	63	auto	51				Number of teeth mean	25
								Acute infection	6 (4)
								Current oral complaintment	22 (14)
								Chronic oral infection	73 (46)
								Healthy periodontium	5 (3)
Sultan et al	2017	91	allo	48		38 (34)		Periodontal bone loss severe	12 (11)
								Periodontal bone loss mild	88 (80)
								Calculus mild/insignificant	91 (83)
								Calculus moderate severe	9 (8)
								Periapical pathology requiring ex or endodontic therapy	11 (10)

HSCT - Haematological stem cell transplantation, auto - autologous HSCT, allo - allogeneic HSCT, DMFT - Decayed Missing Filled Teeth index, BOP - bleed on Probing % sites, ex - extraction

4.3 Oral health during and after HSCT

Oral side effects occur frequently during intensive treatments of haematological malignancies and disorders. A study of 79 haematological patients revealed that almost half had some therapy-related oral comorbidities [54]. Evidence also suggests that patients' previous oral health problems, such as periodontitis, can also have an impact on the severity of other treatment related side effects, including mucositis [10, 47].

4.3.1 Oral infection foci

The oral source as foci of systemic infection was recognised in the 19th century research [55]. Contemporary understanding holds that there are different ways in which oral diseases act as source of systemic infection [3]. Acute infections, which spread from oral and dental tissues (e.g., decayed teeth causing abscesses and even septicaemia) are well understood [3, 55]. In recent decades, it has been observed that persistent low-grade inflammation, such as chronic gingivitis or periodontitis, may increase the likelihood of developing systemic disorders and that these oral inflammations are associated with increased cancer incidences and cancer mortality [2, 5, 6, 56, 57]. Low-grade inflammation is defined as chronic production of inflammatory factors, such as slightly increased inflammation marker C-reactive protein [58].

Researchers have assumed that during neutropenia and immunosuppression, oral microbes can cause both acute local odontogenous and systemic infections among patients undergoing high-dose chemotherapies and HSCT [59, 60]. However, the results of previous studies among HSCT patients about potential oral foci causing infections during and after chemotherapies and HSCT are inconsistent. It has been estimated that oral screenings and treatments conducted on patients before HSCT would reduce systemic infections by a third. Pre-HSCT elimination of obvious dental foci could theoretically prevent one in 500 deaths [61]. Additionally, oral screening and dental foci elimination would also reduce overall medical care costs by preventing cases of post-HSCT comorbidity, such as bacteraemia [52].

Various acute and chronic oral diseases and disorders have been listed as possible oral foci of infection. These include advanced caries, leaking fillings, moderate or advanced

gingivitis and periodontitis, root canal infection and periapical periodontitis, impacted teeth with pericoronitis, and mucosal ulcerative lesions [21, 45, 62-65].

In the 1980s and up to the beginning of the 1990s, several studies suggested that oral infections can cause fever and that dental foci can act as a source of systemic infections in patients undergoing HSCT [60, 66-69]. Recent studies have not fully confirmed this, although some cases have been observed. One study compared patients who received complete, invasive dental treatment before chemotherapy with patients who had no dental treatment. A significant difference was observed between the groups. Patients with complete, invasive dental protocol had significantly fewer oral and systemic infectious complications [65]. In addition, in a study of 18 allogeneic HSCT patients, those who had gingivitis or periodontitis had higher risk for bacteraemia, compared with patients without periodontal disease [70]. In contrast, another recent study compared patients whose dental treatment needs had been compromised with patients whose dental treatment needs had been fulfilled and found no difference in bacteraemia risk during and after HSCT [71].

Due to time limitations and poor overall health condition of haematological patients, dental practitioners cannot always conduct recommended procedures to eliminate oral infections [50, 51, 71]. In healthy individuals, wound healing after tooth extraction takes approximately two weeks. In haematologically compromised patients, wound healing may be prolonged and/or substantially impaired. Risk of complications, such as bleeding and secondary infections, is evident; and such complications can postpone the cancer treatments [50, 59]. Dental procedures themselves often cause bacteraemia, for which proper antimicrobial prophylaxis is needed. Furthermore, invasive dental procedures are not the only factors, daily routines and basic oral care – such as tooth brushing and, in people with periodontitis, even chewing – are likely to cause bacteraemia [72-74].

However, advanced periodontal disease diagnosed by radiographs was not identified as a risk factor for septicaemia or mortality in 77 HSCT recipients. Septicaemia-associated blood cultures were found in 64% of the patients, but no association between bone loss and periodontal or oral origin blood cultures was observed [75]. Furthermore, in a study of 58 allogeneic HSCT recipients, no significant correlations were found between dental foci and systemic infections, mucositis, and survival rate post-HSCT [76]. A preliminary study of 38 patients who received intensive chemotherapy (and minimal pre-treatment dental procedures) concluded that chronic oral foci could be left untreated. This was because, during chemotherapy, dental problems did not usually progress to an acute stage [64]. In another study of 48 autologous HSCT recipients, bacteraemia was more

common among patients with higher frequency of oral disorders, though the difference was not statistically significant [9]. In a study of patients receiving intensive chemotherapy or autologous HSCT, it was found that chronic asymptomatic oral foci do not appear to create additional risks during cancer therapies [49]. Similarly, a study of 166 HSCT recipients compared patients who received limited and intensive dental care, respectively, and found no difference in septicaemia incidences [10]. A recent study found no association between oral foci and survival or severe infection complications within six months post-HSCT [77]. As contemporary treatment protocols recommend, all patients receive antimicrobial prophylaxis during and after HSCT for infection prophylaxis. As expected, the use of antibiotics also prevents infections of oral origin. Thus, the common practice of administering antibiotics can lead to study biases, as prophylactic anti-infective medication also prevents oral infections. If this study bias is not taken into account, it can lead to underestimation of the risk of oral origin foci and systemic infection.

4.3.2 Fungal infections

After HSCT, patients are at high risk of developing secondary infections. Invasive and systemic fungal infections are a considerable cause of morbidity and even mortality [32, 33]. Patients are also susceptible to oral local candida infections. Although candida species are considered commensals of the normal oral flora and their relative proportion is limited in healthy individuals, they can act as an opportunistic pathogen, when provided with sustainable environmental condition and nutrients from the host [78]. Changes in oral microbiome may occur in patients who receive prophylactic antibiotics and immunosuppression after HSCT. Thus, after HSCT, candida species can gain pre-dominance and cause infection [32, 78]. Patients also often have reduced salivary flow rates during and after HSCT. This, along with the possible reduction of oral hygiene, can act as risk factors for candida infection [67, 78-80]. In patients treated with topical corticosteroids for oral chronic GVHD post-HSCT, the risk of oral candidiasis further increases [78]. In a review of patients receiving cancer therapy, the oral colonisation of fungal species during and after chemotherapy treatments was over 70%, and oral candidiasis was observed in 38% of cases. Today, the post-HSCT routine involves the provision of prophylactic anti-fungal medication to patients to avoid fungal infections and the use of them reduced the amount of infections remarkably [32, 33].

Oral candidiasis can have various symptoms, or it can be asymptomatic. Pseudomembranous and erythematous candidiasis are the most frequently observed forms associated with cancer treatments. Superficial whitish pseudo-membranes can be detected in the labial and buccal mucosa, on hard and soft palate, and on the tongue. The white surface membrane can be removed easily by gentle rubbing. Underneath the whitish membrane, the mucosa is erythematous. Patients report experiencing burning sensation and taste disturbances. Loss of filiform papillae can also be observed. Systemic antifungal medications, which are administered to the patients, prevent oral manifestations of candida [32, 78].

Good oral hygiene should be maintained for effective prevention of oral candidiasis. Special care should be taken of patients with dentures. The denture should be decontaminated with the same anti-microbial agent as the oral cavity to prevent re-contamination by the microbial flora [63].

4.3.3 Viral infections

It is understood that HSCT recipients are at high risk of viral infection during the neutropenic phases, because antiviral lymphocyte functions are reduced. The viral infection can be exogenous, most often respiratory viruses or an endogenous re-activation of a herpes virus, adenovirus, or hepatitis. The most common oral viral infections are re-activated forms of the herpes simplex virus (HSV) HSV-1 and HSV-2, as the majority of adult population are latent carriers of the virus. Symptoms include pain in the mouth, which is most severe in the beginning of infection, followed by burning and itching sensations. Oral vesicles occur on buccal mucosal membranes and often also extra orally on the lips. These lesions usually suggest a re-activation of a virus, whereas intraoral lesions combined with systemic symptoms are an indication of a primary infection. The vesicles develop into ulcers. Lesions are typically completely healed within 8-10 days [81]. The HSV infections were found to be more frequent among cancer patients if oral ulcerations, caused for example by mucositis, were present compared to in patients without oral ulcerations [82].

An anti-viral prophylactic medication (e.g., valacyclovir or aciclovir) is routinely provided to HSCT patients to prevent oral herpetic infections [83]. Varicella zoster is another member of the HSV family often re-activated among HSCT recipients [84]. If the re-activation of the virus occurs in the facial area, this can affect the trigeminal nerve and cause long-term comorbidities, such as neuralgia [85]. In addition, one study of 49

allogeneic HSCT recipients found that positive DNA samples of Epstein Barr virus were a significant predictor of ulceration of keratinized mucosa [86].

4.4 Mucositis

Oral mucositis is a toxic reaction to chemotherapies and irradiation to the mucosa. The whole alimentary tract can be affected, causing severe pain and dysfunction resulting in diarrhoea. Due to the loss of mucosal barrier functions, severe, even lethal effects can occur. The scope of this thesis is oral health, thus oral mucositis is addressed here in more depth.

Oral mucositis occurs in 75-100% of patients who receive high-dose conditioning chemotherapy before HSCT. It occurs to a lesser extent when conventional chemotherapy is used [27, 87]. Depending on the grade of oral mucositis, it can cause erythema, mild to severe pain, and ulcerations, which might act as sites for secondary infection and cause nutritional impairment [27]. In a study of HSCT patients, 42% reported oral mucositis, more precisely mouth soreness, as the most debilitating comorbidity caused by the treatments [88]. Oral mucositis in patients undergoing HSCT is linked with worse clinical outcomes. Patients with severe oral mucositis stayed in hospital for prolonged periods, compared to patients without mucositis or mild mucositis [89, 90].

Mucositis has different grading systems. In most, the measured elements are symptoms, clinical signs of the disease and the impact that mucositis has on general functioning of the patient. Widely used grading scales for clinical and research purposes are provided by the World Health Organization (WHO) and the National Cancer Institute (NCI) – the common toxicity criteria (CTC) [91, 92]. According to WHO, the grading scale begins at grade 0 (no signs) and ends with grade 4 (alimentation not possible). The grade 1 category includes erythema or soreness. Grade 2 includes erythema and ulcerations but with an ability to eat solid foods. Grade 3 classification indicates ulcers and a requirement for a liquid diet. The classification system issued by NCI-CTC starts from grade 1, mucositis with asymptomatic or mild symptoms, and continues to grade 4 mucositis, which has life-threatening consequences for which urgent interventions are needed. At the end of the spectrum is grade 5, which indicates death.

Several procedures are recommended for prevention and reduction of mucositis symptoms. Recommendations for prevention and treatment of oral mucositis include cryotherapy (placing ice in the mouth during chemotherapy delivery), low-level laser therapy, good oral hygiene, rinsing mucosal membranes with saline or sodium bicarbonate mouthwash, and pain medications when needed [27]. In a recent preliminary study, it was reported that treatment with hyperbaric oxygen could reduce the prevalence of mucositis [93].

Poor oral health of patients before therapy is associated with mucositis and severe intraoral pathology during neutropenic phases [10, 47, 94]. Patients with periodontitis and gingivitis had statistically higher rates of mucositis, when compared to those without periodontal diseases [9, 94]. The presence of periodontitis-related bacteria, such as *Porhyromonas gingivalis,* was associated with ulcerative mucositis [8]. Evidence suggests that professional dental cleaning and scaling pre-HSCT could reduce the prevalence and grade of mucositis [95]. It is also advisable that patients receive information about the importance of oral hygiene during the therapies, as this may reduce the severity and duration of oral mucositis [10, 27, 94-96].

Chlorhexidine rinsing is often provided to reduce the bacterial load during neutropenia, especially if oral hygiene cannot be maintained at an optimal stage. As chlorhexidine can be toxic to mucous membranes, its use to prevent mucositis is not recommended and should be avoided if mucositis appears [27, 63]. Use of chlorhexidine can also lead to minor reversible comorbidities, such as taste disturbances and colouring of teeth and mucosal surfaces.

4.5 Salivary flow rate changes during and after therapy and their consequences

Saliva has many important roles in the oral cavity (Table 4). It is a protective lubricant, which maintains a healthy environment for hard and soft tissues of the oral cavity; it has a dominant role in enamel and dentin remineralisation; it regulates the oral microbiome; and it is essential for the ability to speak, sleep, and eat comfortably [35, 97-99]. In case of hyposalivation, the cleaning, remineralisation, and protective effects of saliva are affected due to a lack and changes in the composition of saliva. One evident and well-known risk of prolonged hyposalivation is an elevated risk of caries [97]. The functions and components of saliva are listed in Table 4.

Hyposalivation (e.g., insufficient salivary flow) is defined in most of the guidelines as 0.7ml/min or under that of stimulated salivary flow rate (SSFR) and 0.1ml/min or under when unstimulated [34]. Hyposalivation can lead to acute and long-term comorbidities such as caries, periodontitis, and oral candidasis [34, 35]. On the other hand, xerostomia (a subjective sensation of oral dryness) is a symptom which is not dependent on salivary flow rates, but is instead probably due to changes in the consistence and quantity of the saliva [35]. Xerostomia may appear even when the salivary flow rate stays above the diagnostic limit for hyposalivation [34].

Table 4. Functions and components of saliva

Function	Components	Effect
Lubrication	Total fluidity and salivary flow rate	Enables swallowing and speaking
Buffer capacity	Bicarbonate, Phosphate	Neutralisation of acids
Remineralisation	Fluoride, phosphate, Calcium	Enamel surface remineralisation
Protective coating	Mucins	Formation of protective pellicle on tooth surface
Antibacterial activity	Lysozyme, Lactoferrin, Lactoperoxidase, Secretory Immunoglobulin A	Bacteria cell wall degradation, inhibition of biofilm formation, microbial agglutination
Digestive functions	Amylase enzyme, Proteases	Chemical digestion by breaking starch

Salivary flow rate decreases due to cytotoxic effects of chemotherapies and HSCT on salivary glands [100-102]. However, the reasons for and mechanisms of hyposalivation caused by chemotherapy are still not fully understood. It seems that some patients may temporarily suffer from hyposalivation during and following cancer chemotherapy, while others do not. It is likely that there are several different mechanisms that determine how different regiments and HSCT affect salivary glands [39]. An even greater decrease in salivary flow rates has been observed in cases where patients received TBI [103]. It is assumed that this is associated with the direct toxicity of irradiation and its effect on salivary glands. However, HSCT-related reduction in salivary flow rate is mostly reversible, although it can take anything from several months to a year before normal rates of salivary flow is observed in recuperating patients [102, 103]. A study of 228 allogeneic HSCT recipients revealed that hyposalivation (SSFR ≤ 0.7ml/min) can often be detected before HSCT, with 40% of patients suffering from it. Six months after treatment, 51% of recovering HSCT patients had hyposalivation, and 31% a year later.

There was a continuing improvement, as two years after HSCT only 21% of patients suffered from hyposalivation [103]. However, some patients recovering from HSCT had reduced salivary flow rates and xerostomia years after completing their HSCT treatment [37, 103, 104]. Thus, hyposalivation is often, but not always, reversible. It is also noted that, in a small study of 24 leukemic patients, the salivary flow rates were statistically significantly lower before the initiation of any cancer treatments than among the healthy controls [44].

As well as the amount of saliva, its composition can also change during cancer therapies. Salivary changes can occur immediately after HSCT [102]. There is the possibility of an inflammatory response in which levels of secretory immunoglobulin A are decreased and levels of proinflammatory cytokines and salivary albumin are increased. Some studies discovered measurable changes in saliva composition of HSCT recipients half a year after treatment. The antimicrobial defence mechanisms of saliva had changed due to an increase in the levels of secretory protease inhibitors and lactoferrin [102, 105]. There is also evidence that the buffer capacity of saliva decreases after chemotherapy and HSCT, leading to a shift to more virulent and cariogenic composition of microbiome composition in the oral cavity [100, 106, 107].

Hyposalivation and xerostomia have been identified as the most important contributors to the worsening of the quality of life after cancer therapies [37, 38, 108]. The effects of dry mouth include impaired taste, sleeping problems, and speaking difficulties – dysfunctions which affect both physical and mental wellbeing of the patient [35, 36, 97]. Another unwanted side effect that can impair the patient's quality of life is the direct toxicity of chemotherapies and irradiation of oral mucosal membranes. Radiation can harm taste and olfactory receptors and cause taste disturbances. Chemotherapy-related taste disturbances, including bitter taste sensations, are usually short-term and reversible, but changes that have lasted for months and even years have been reported [36, 104, 109].

When treating patients who experience dry mouth and hyposalivation, the main goal is to ease their symptoms and prevent comorbidities. The patient should be advised about the importance of adequate hydration and recommended to take small sips of water as often as needed. Most available moisturising agents provide only short-term relief to dry mouth, but they can be administered if patients gain temporary relief when using them. Sugar-free candies and chewing gums can also be used to stimulate salivary flow. To prevent caries, topical fluorides (rinses, toothpaste, gels) should be used as part of daily oral hygiene routine. Unnecessary food intake, such as excessive snacking, should be

restricted to minimise acid attacks and demineralisation of teeth. However, adequate calorie intake should be ensured and patients' overall situation taken into account [35].

4.6 Common chronic oral infections after HSCT

There is insufficient knowledge of the chronic oral infections, periodontitis and caries, with which HSCT recipients commonly suffer. Only a small number of studies with short follow-up times have investigated the prevalence and incidence rates of periodontitis, and the number of decayed, missing, and filled teeth (DMFT index) on patients recuperating from HSCT treatment [46, 94, 110, 111]. In most cases, chronic oral infections progress slowly. Oral microbiome composition and level of oral hygiene has a remarkable impact on their development [34, 35, 99].

In a study of 36 HSCT recipients, the patients were examined first before HSCT treatments and a second time six months after their treatment. A statistically significant increase was seen in the DMFT index scores [46]. A questionnaire-based study conducted with patients who had received HSCT between one and more than 10 years ago found that self-reported incidences of oral comorbidities were high. Caries was reported by 36.7% of the study participants and gum disease only by 16% [110]. Improvements in periodontal health three and six months after HSCT were reported in two studies of 36 and 29 patients, respectively, who had followed an intense oral care programme and received anti-infective treatment pre-HSCT. There was a notable reduction in gingival inflammation [94, 111].

4.7 Long-term oral comorbidities after chemotherapies and HSCT

4.7.1 Graft versus host disease (GvHD)

GvHD is a complication caused by allogeneic HSCT. GvHD is a complex alloimmune inflammatory reaction in which donor B- and T-cells, in conjunction with certain other donor cells, become activated, causing damage to host tissues and becoming a significant cause of morbidity and mortality after HSCT [112-114]. The disease is divided in two types: acute GvHD (aGvHD) and chronic GvHD (cGvHD) [115, 116].

Acute GvHD affects the skin, gastrointestinal tract, and liver and can cause numerous comorbidities such as skin rash, nausea, severe pain, bleeding, vomiting, and diarrhoea

[114, 116, 117]. It typically appears shortly (within 100 days) after HSCT, but later manifestation is possible.

In contrast to aGvHD, cGvHD usually occurs later and the symptoms are different. While cGvHD can be an extension of aGvHD, it can also occur without previous signs [115, 117]. The organs affected by cGvHD are mouth, eyes, skin, genitalia, oesophagus, lungs and muscles and fascia, and the condition can be restricted to one organ or be widespread [116]. Chronic GvHD occurs in approximately 40-70% of allogeneic HSCT recipients, and incidences have been increasing in recent decades [112, 118-120].

The diagnostic criteria for oral cGvHD, according to the National Institutes of Health (NIH), includes the typical lichenoid changes of oral mucosa, which occur most often in the buccal mucosa and on the tongue, though other intraoral surfaces and the lips may be affected. Ulcerations and erythema can be associated with the disease, but these are not considered diagnostic signs by themselves, nor are isolated hyperkeratotic leukoplakic plaques [121]. Typical symptoms associated with oral cGvHD are xerostomia and hyposalivation [101, 120]. Decreased range of motion in the jaw can be a sign of diffuse sclerosis of submucosa. In GvHD diagnosis, a scale of 0-3 (ranging from *no involvement* to *severe impairment*) is used for each organ. Clinical diagnosis using NIH guidelines might be challenging and other additional symptoms should be recorded [116, 122]. Furthermore, other undefined and clinically cGvHD-related manifestations or atypical signs and symptoms may appear [116, 121].

There is evidence that cGvHD can cause late changes in salivary flow rates and confound saliva functions [101, 123-125]. Although it has been suggested that hyposalivation is associated with cGvHD, not all studies confirm the correlation between mucosal changes and reduced salivary flow rates [102]. One study concludes that although severe cGvHD is associated with oral dryness [37], while another [126] demonstrated no significant changes in salivary flow rates at onset of cGvHD. Therefore, it has been proposed that changes in salivary gland functions may be a separate manifestation of cGvHD that differs from mucosal cGvHD findings [122, 125].

Few studies and case reports describe patients with oral cGvHD who develop rampant caries. Factors predisposing patients to cGvHD-related caries are reduced salivary flow rate, modified composition of saliva, changes in the oral microbiome, restricted ability to open one's mouth, and pain in the mouth (with the latter two potentially leading to reduced oral hygiene). Patients experiencing these symptoms are at high risk of developing caries. According to case descriptions, the development of deep caries is

rapid, several teeth are seriously affected, and occurrences of cervical and root caries are typically observed [124, 127, 128]. Carious teeth are prone to fractures and the sharp edges of fractured teeth may cause irritation on mucosal surfaces, thus provoking the appearance of mucosal lesions [127].

Local therapy aims to relieve symptoms in the oral cavity and maintain mucosal integrity. It is primarily used if oral cGvHD is resistant to systemic treatment or when the oral cavity is the only site affected. Commonly used medications are steroids, such as budesonide and dexamethasone, and calcineurin inhibitor tacrolimus [129, 130]. The knowledge and effectiveness of the local therapy remains limited [130]. Maintaining good oral hygiene is important for preventing secondary infections, including local dental infections, such as periodontitis and caries [112]. The general recommendation is that patients are frequently invited to oral examinations, as this will help to detect possible early signs of cGvHD-related oral comorbidities.

4.7.2 Other long-term comorbidities

Guidelines for oral care regarding HSCT patients mention that orofacial pain, especially tooth sensitivity, is a possible comorbidity that may occur after HSCT [63]. Orofacial pain is described as pain with a musculoskeletal, sinogenic, neural, or dental origin in the frontal part of the head, including the oral cavity [131]. There are no specific studies with HSCT patients on the prevalence and grade of tooth sensitivity during and immediately after HSCT. A questionnaire-based study with a group of 48 patients five years after HSCT and a healthy control group found no difference in tooth sensitivity between the groups [104]. The assumption of higher risk for tooth sensitivity is likely to be based on clinical implications or extrapolations from studies of head and neck cancer patients. However, several studies have been conducted among patients with head and neck cancer, and a third of these continued to experience orofacial pain, including tooth sensitivity, six months after completing cancer therapies. It must be noted that the invasive treatments and high-dose local irradiation treatment of solid tumours differ strongly from HSCT treatment procedures [132]. In addition, neurotoxicity, which can cause orofacial pain, most often jaw pain, is a side effect of chemotherapies and is suffered by other cancer patients [12, 28, 133]. Reversible pulpitis-like pain caused by neurotoxicity of high-dose chemotherapy to the mandibular nerve has also been observed [11]. However, no studies have specifically shown the relationship between antineoplastic medicaments and their impact on tooth sensitivity [134].

In previous studies of HSCT recipients, a high risk of solid secondary malignant neoplasms, including oral squamous cell carcinoma, has been observed. The risk for secondary cancer development increases with time. Follow-up examinations five years after HSCT revealed that the risk of secondary malignancy development had increased from 1.2% to 1.6%; and 15 years after treatment, the risk had increased from 3.8% to 14.9%. It has been observed that the risk of secondary malignancy development was higher if TBI was applied [135]. Another study concluded that that the risk of secondary oral cancer was more than 10 times higher after HSCT than in the normal population [136].

In MM patients, bone-modifying agents, such as bisphosphonates and human monoclonal antibodies (denosumab), are frequently used for medication. A severe side effect of these medications is osteonecrosis of the jaw [31]. Medication-related osteonecrosis of the jaw is a potentially serious intra oral or extra oral bone fistula, with exposed bone. Medication-related osteonecrosis is diagnosed in patients without previous radiation to the jaw region and if fistula does not heal within eight weeks. It may occur in the maxilla or the mandible, but mandible is more often affected. Medication-related osteonecrosis has been diagnosed in between 1% and 9% of the patients using bone-modifying agents for their advanced cancer. To reduce the risk of osteonecrosis, preventive oral care assessment should be provided prior to medication (bisphosphonates, denosumab). Knowledge about prevention and treatment of medical-related osteonecrosis remains limited [137].

4.8 Contemporary oral health protocols pre-HSCT

Several guidelines and protocols have been published about the oral healthcare of HSCT patients [21, 27, 45, 61-65, 138]. The existing protocols for managing oral diseases and associated infectious complications in HSCT recipients are commonly based on extrapolations from a few clinical studies and on clinical experiences of other oncological diseases, such as head and neck cancer and other solid organ transplantations [139]. Dental therapy provided before chemotherapies and HSCT varies between different institutions worldwide, from minimal invasive care to radical dental treatment [63, 140]. However, according to previous studies, not all HSCT recipients are provided with oral examinations. Oral health protocols might not be included in all

healthcare centres, or they might be skipped due to time limitations owing to the urgent need for cancer treatments and weakened overall health condition [51, 62, 141].

In general, oral care guidelines recommend that a clinical oral examination is conducted and radiographs taken if needed. Acute infections should be eliminated. The oral examination should be done as early as possible to provide the necessary dental and oral treatments before commencing the HSCT therapy [62].

A series of guidelines are published by the Multinational Association of Supportive Care in Cancer (MASCC), the International Society of Oral Oncology (ISOO), and the American Society of Clinical Oncology (ASCO) for clinicians to help with pre- and post-cancer treatments, preventive interventions, and supportive care. They include a position paper on basic oral care for HSCT patients, reviews about oral care management of mucositis, reviews of studies made on medications and other supplements used for mucositis treatments, and a clinical guideline for medication-related osteonecrosis of the jaw [27, 63, 137, 138].

The most radical guidelines for oral healthcare recommend that all possible foci be eliminated before cancer treatments. This is similar to the oral treatment guidelines for head and neck cancer patients, who receive local irradiation of the oral area [63]. Some treatment protocols advise that oral treatments should be tailored to individual needs, according to the toxicity of given regimen and the risk level of oral and infectious complications [62]. The cancer treatment may need to be started as soon as possible. Thus, lack of time, low thrombocyte counts, severe neutropenia, and general health-related issues are factors that can prohibit invasive oral treatment prior to cancer treatment. Oral function should be maintained whenever possible, especially when tooth extractions are considered. The ability of the patient to eat comfortably with the remaining teeth and dentures after HSCT should be a concern [63]. Sharp and fractured teeth should be removed, and ill-fitting dentures and orthodontic appliances avoided, as this can prevent mucosal irritation and reduce the risk of bleeding and infection during HSCT [62].

Almost all oral care protocols suggest maintaining proper and intensive oral hygiene before, during, and after HSCT, including rinsing frequently with bland solutions such as saline, disinfection of dentures, use of soft toothbrushes, and use of toothpaste with fluoride. Patients should also be informed before HSCT about possible comorbidities, for instance mucositis and reduction of salivary flow.

Regular oral examinations are recommended after completing HSCT. This ensures that late comorbidities (e.g., caries) are treated accordingly and preventive measures are taken as early as possible. In the case of reduced salivary flow rates, additional use of fluoride supplements is recommended. Where there is limited mouth opening ability due to cGvHD affecting musculoskeletal tissues, physiotherapy should be considered [63].

5 AIMS OF THE STUDY

As the number of HSCT procedures and their success rates have increased, a growing number of patients have experienced short- and long-term side effects and comorbidities. There is thus a need for a better understanding of the general prognosis of HSCT-related oral side effects and how they affect patients' oral status and well-being. However, recent knowledge of the oral health of HSCT patients at the time of diagnosis and pre-HSCT, compared to that of the normal population, remains sparse.

This thesis aims to investigate the oral health of adult patients who are newly diagnosed (<6 months) with severe haematological malignancy or disorders, and patients who are receiving HSCT treatment, both pre- and post-HSCT. In particular, the research examines the prevalence and aetiology of oral diseases and disorders and the dental treatment needs of patients with severe haematological malignancy or disorders, compared with controls of the normal population. Additionally, the progression of oral diseases and disorders and their associations with overall treatment outcome and oral comorbidity are examined regularly for up to two years.

5.1 Specific objectives

The first sub-study (8.1) describes the oral health of adult HSCT recipients (pre-HSCT), compared with an age- and sex-matched control group. The oral health parameters assessed include radiological attachment loss (RAL) indicating periodontal health status, caries prevalence, number of teeth, prevalence of acute infections, SSFR and DMFT index.

The second sub-study (8.2) considers the state of oral health of adult patients with severe haematological malignancy or disease, whose diagnosis was not older than six months. These patients were compared with age-matched controls. An additional aim of the study was to compare oral health parameters within the patient group according to different diagnoses and treatment-related factors, including medications and chemotherapies.

The third sub-study (8.3) evaluated changes in the abovementioned oral health parameters pre-HSCT, compared with oral health status at 6, 12, and 24 months post-HSCT. The association between survival after six months of HSCT and oral health pre-

HSCT was analysed. The SSFR was collected at every appointment and changes were assessed over the observation period of 24 months. The association of pre-HSCT SSFR with GvHD post-HSCT was analysed. Finally, the study aimed to determine whether salivary screening was a useful tool for predicting post-HSCT comorbidity.

6 HYPOTHESES

Based on previous studies and clinical observations, the following hypotheses are proposed:

- At the time of diagnosis and pre-HSCT, patients have an enhanced need for dental treatment.
- At the time of diagnosis and pre-HSCT, patients have worse oral health than control subjects without severe haematological malignancy or disorders.
- Post-HSCT, patients are at a very high risk of oral infection, particularly caries.
- Poor oral health parameters can predispose patients to mortality after HSCT.
- Salivary measurement of patients pre-HSCT is a potential predictive tool for detecting oral comorbidities during and after HSCT.

7 PATIENTS AND METHODS

7.1 Ethical declaration

This research project was conducted in line with the World Medical Association Declaration of Helsinki principles of good clinical practice and local legally applicable requirements.

The studies were approved by the Ethics Committee Basel (EKBB) Ethikkommission Nordwest- und Zentralschweiz (EKNZ), Switzerland. This includes both the retrospective part of this study (Ref.Nr. EK: 311/10) and the prospective part (EKNZ:2017-02268), as well as the control group study (Ref.Nr. EK:357/08) and the use of haematological data from the medical records (Ref.Nr. EK:117/05).

7.2 Patients

The study was carried out in the University Center for Dental Medicine Basel (UZB) Department of Oral Health & Medicine (OHM) in collaboration with the Department of Haematology, University Hospital of Basel, Switzerland. Approximately 100 patients undergoing annual HSCT in the University Hospital Basel were examined in the UZB for their oral health. Included in the study were all adult (> 18 years) HSCT recipients who received an oral examination.

This thesis comprises three observational studies – starting retrospectively with patients who received HSCT and got oral examination pre-HSCT in UZB between 2008 and 2016 (n = 475). For 2018 onwards, the study design was prospective (n = 97).

7.3 Study design and measurements

All subjects included in the retrospective part of this study have undergone thorough oral examinations by an experienced dentist pre-HSCT and at 3, 6, 12, 24, 60 months post-HSCT in the Department of Oral Health & Medicine, UZB (former School of Dental Medicine, Department of Preventive Dentistry and Oral Microbiology, University of

Basel). For the prospective part, oral examinations were conducted similarly by the author of the thesis in Department of Oral Health & Medicine.

All the clinical parameters of oral health needed for this study (including DMFT index score, salivary flow measurements, caries incidence, number of teeth, presence of acute or chronic oral foci, and presence of oral GvHD) were collected during these clinical examinations.

A panoramic dental x-ray was taken from all pre-HSCT patients. In addition, intraoral x-rays were taken when required and x-rays of the patients were re-examined by a radiologist when necessary. Chronic infectious dental foci were noted. The findings included apical periodontitis in the x-rays, RAL > 3mm, non-vital teeth with deep caries, root remnants, and partially erupted wisdom teeth with chronic pericoronitis. Acute oral infections were diagnosed when fistulas, symptomatic periapical processes, symptomatic deep caries, acute pericoronitis, wounds/ulcers, or acute periodontal abscesses were observed.

The SSFR of the patients was measured at every appointment. Stimulation was achieved by asking the patient to chew a neutral paraffin gum continuously for six minutes. After one minute, the patient's whole saliva secreted over five minutes was collected and converted to mL/min. Measurements under 0.7mL/min were considered hyposalivation [97].

Relevant data from medical records (stem cell source, use of TBI, conditioning chemotherapy used, other diagnoses, anti-infective and prophylactic and other medications used, the presence of acute and chronic GvHD, infectious complications, remission vs. recurrence of the disease, survival, and cause of death of non-survivors) were collected and examined.

The control group consisted of 258 generally healthy Swiss volunteers (107 male and 151 female, mean age of 43.5 years, age range 21-58 years) from the Swiss Bone Marrow Donor Registry. A thorough oral and periodontal examination of the control subjects was conducted by the third supervisor of this thesis in a previous study [142].

8 PUBLICATIONS

This thesis is based on the listed publications.

8.1 Common oral diseases in allogeneic HSCT-recipients pre-HSCT

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ORIGINAL ARTICLE

WILEY Haematology

Common oral diseases in allogeneic haematopoietic stem cell transplantation (HSCT) recipients pre-HSCT

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Abstract

Objectives: The purpose of this study was to compare the prevalence of common oral diseases between allogeneic haematopoietic stem cell transplantation (HSCT) recipients and healthy controls.

Materials and methods: A total of 143 adult allogeneic HSCT recipients who were treated for haematological malignancies between 2008 and 2016 were included in the study. The HSCT recipients were age and sex matched with healthy controls. A dental examination was performed on the HSCT recipients prior to HSCT. Differences in stimulated saliva flow rate (SSFR), decayed, missing and filled teeth (DMFT) index, number of teeth, number of caries lesions, and measures of current or previous periodontitis (radiological attachment loss >3 mm or probing pocket depth ≥4 mm) between HSCT recipients and controls were examined.

Results: Stimulated saliva flow rate, DMFT index and the number of caries lesions were poorer in the HSCT recipients pre-HSCT compared to controls (all *P*-values <0.05). No statistically significant differences in the measures of current or previous periodontitis were observed.

Conclusions: Stimulated saliva flow rate was low and caries was common in HSCT recipients prior to HSCT. Efficient preventive strategies are important in order to maintain the oral health of these patients.

KEYWORDS
caries, DMFT, haematology, periodontitis, stem cell transplantation

1 | INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is a treatment used for patients with life-threatening diseases and disorders of the haematopoietic system. HSCT was found to be a curative treatment for some end-stage acute leukaemia patients over 60 years ago. The number of HSCTs increased in recent years, and the milestone of 1 million HSCTs was reached in 2012.[1-3]

Allogeneic HSCT involves an intensive conditioning regimen, that includes high-dose chemotherapy or reduced intensity therapy and, possibly, total body irritation (TBI). The aim of this regimen is the eradication of haematopoietic stem cells and immune system suppression. Haematopoietic multipotent stem cells are collected from a donor, and the cells are infused to re-establish haematopoietic functions.[1,3,4] Subsequent to improvements made in the transplantation procedures in terms of human leucocyte antigen-matching, the control of graft vs host reactions and the control of infectious complications, the number of long-term survivors has been constantly increasing.[5] Nevertheless, allogeneic HSCT remains associated with considerable acute and long-term comorbidities that also affect oral health.[6-8]

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Several studies investigated the associations of poor oral health with various systemic diseases and cancer development.[9-12] Poor oral health, especially periodontitis, may be associated with certain cancers in different tissues, including those of the mouth, pancreas, colorectum and lungs.[9,11,12] Studies also suggested a relationship between periodontitis and overall cancer mortality.[13,14] The evidence of associations between oral diseases and haematological malignancies is very limited. One study observed that, periodontitis was associated with non-Hodgkin's lymphoma.[15] Another study found an association between periodontitis and haematological cancers in men.[14]

Similar to the studies on the associations between oral diseases and haematological malignancies, descriptive studies focused on the oral health of patients with disorders of the haematopoietic system and/or upcoming HSCT are also scarce. The vast majority of studies on HSCT recipients have focused on post-HSCT symptoms related to GvHD, mucositis and hyposalivation. We have also participated in these studies and showed that HSCT recipients suffer from hyposalivation, especially 6 months after transplantation, and even years post-HSCT.[6,7,16] Hyposalivation is a known risk factor for oral diseases and may predispose patients to caries in particular.[17] In line with this assumption, there is evidence suggesting poor oral health and high dental treatment needs of HSCT recipients pre-HSCT.[18-20] Another very recent study, with a limited number of subjects, observed that patients with newly diagnosed acute leukaemia already have poorer oral health, in terms of caries and periodontitis, prior to any treatments compared with healthy controls.[21]

The current study examined the oral health of allogeneic HSCT recipients pre-HSCT. The hypothesis was that allogeneic HSCT recipients have poorer oral health than healthy controls prior to transplantation.

2 | PATIENTS AND METHODS

The Ethikkommision Nordwest- und Zentralschweiz (EKNZ), Switzerland approved this study (Ref. Nr EKNZ:311-10) which was performed in accordance with the Declaration of Helsinki.

Adult allogeneic HSCT recipients who were treated in the Department of Hematology, University Hospital Basel, Switzerland, for haematological malignancies between 2008 and 2016, with complete medical and oral health status, were initially included in this prospective cross-sectional study. The study excluded patients whose medical or dental status was not complete or who could not be sex and age matched with a healthy control (Figure 1). The HSCT recipients included in this study may have received anticancer therapies using standard chemotherapy schemas even years before proceeding to HSCT and had received conditioning chemotherapy with or without TBI, as previously described.[6]

The healthy control group was recruited from the Swiss Bone Marrow Donor Registry of The Blood Transfusion Service SRC Basel, Switzerland.[22] The final study groups were formed via blinded matching of the HSCT recipients with controls by age and sex.

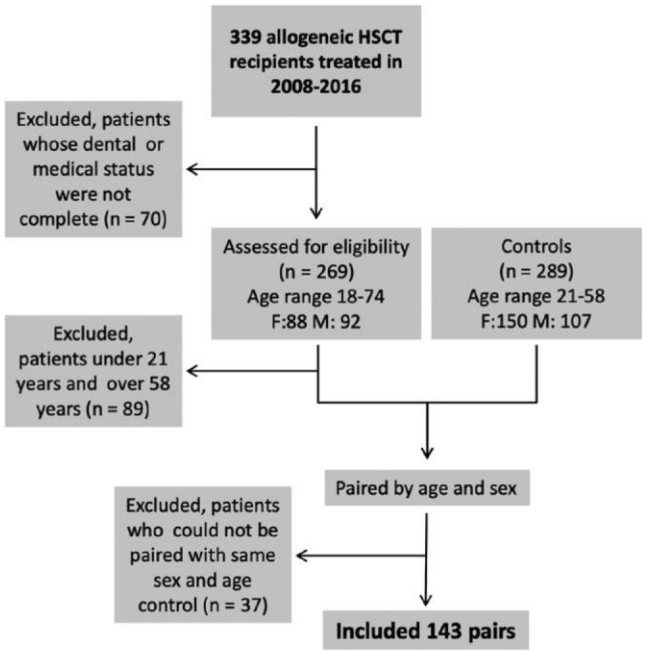

FIGURE 1 Flow diagram showing patient selection for the study

The dental examinations of the patients were carried out by experienced dental practitioners in the Department of Preventive Dentistry and Oral Microbiology, School of Dental Medicine, University of Basel, immediately prior to HSCT (most often a few days prior). A thorough clinical oral examination included a panoramic radiograph and decayed, missing and filled teeth (DMFT) index calculation according to the WHO.[23] Acute oral infections were diagnosed if (a) fistula, (b) symptomatic periapical process, (c) symptomatic deep caries, (d) wound/ulcer or (e) acute periodontal abscess were observed.

Stimulated saliva flow rate (SSFR) was measured at the beginning of the dental examination and before any clinical assessments. SSFR was collected by chewing a neutral paraffin wax. An individually packed, commercially available, neutral piece of paraffin wax (0.9 g/wax; Orion Diagnostica, Espoo, Finland) was chewed for 1 minute while swallowing saliva. Chewing was continued for 5 minutes, and generated saliva was collected. SSFR measurements of ≤0.7 mL/min were defined as hyposalivation and <0.3 mL/min as severe hyposalivation.[17] All relevant medical data, including diagnosis and conditioning-related information, were collected from medical records.

To avoid bacteraemia and to shorten the time needed to perform dental examinations of the severely ill HSCT recipients, ongoing or treated periodontitis was assessed from panoramic radiographs. Periodontitis was determined according to Pepelassi and Diamanti-Kipioti, to be present if radiological attachment loss (RAL), for example, the distance between the cementoenamel junction (CEJ) and the alveolar bone crest was observed to be >3 mm.[24]

The oral health of the healthy control group was similarly examined by the same dental practitioners. Panoramic radiographs were not taken of the healthy control group, but a detailed periodontal

TABLE 1 Descriptives of the study subjects

	Allogeneic HSCT recipients (143)
Age	
Mean; range(y)	44.8 (21-58)
Sex	
Female	73
Male	70
Diagnosis (n; %)	
AML	49 (34.3)
MDS	10 (7.0)
ALL	29 (20.3)
CML	5 (3.5)
CLL	8 (5.6)
PCD	10 (7.0)
MPN	8 (5.6)
MH	3 (2.1)
NHL	18 (12.6)
Other	3 (2.1)
Karnofsky	
Mean; range	92.4 (40-100)
Ablative conditioning (n; %)	
Yes	122 (85.3)
No	21 (19.0)
TBI (n; %)	
Yes	61 (42.7)
No	77 (53.8)
n.app	5 (3.5)

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; MDS, myelodysplastic syndrome; MH, Hodgkin's lymphoma; MPN, myeloproliferative neoplasm; NHL, non-Hodgking's lymphoma; PCD, plasma cell dyscrasia.

examination, including pocket depth measurements, was conducted. Periodontitis was diagnosed to be present if either ≥2 interproximal sites with clinical attachment loss (CAL) ≥3 mm and ≥2 interproximal sites with probing depth (PD) ≥4 mm or ≥1 interproximal site with PD ≥5 mm were observed.[25]

2.1 | Statistics

The means and standard deviation of the oral health parameters, including SSFR, DMFT index, number of teeth, number of caries lesions and the frequency of periodontitis, were calculated and compared between allogeneic HSCT recipients and controls. The Pearson Chi-square, *t* test and Mann-Whitney *U* test were used to determine statistical significance. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS software, version 23.

3 | RESULTS

3.1 | Study population

A total of 143 of the 339 adult allogeneic HSCT recipients were ultimately included in this study after age- and sex-matching with healthy controls (Figure 1). The mean age of both study groups (HSCT recipients and controls) was 44.8 years (21-58), with 70 male and 73 female subjects per group. Ninety-one (63.6%) of the HSCT recipients had been diagnosed with their haematological malignancy within 1 year, 40 (28.0%) recipients were diagnosed within 1-5 years, and 12 (8.4%) recipients were diagnosed more than 5 years before the pre-HSCT dental check-up. The descriptive statistics and diagnoses of the HSCT recipients are presented in Table 1.

3.2 | Stimulated salivary flow rates

The pre-HSCT SSFRs (n = 120) of the HSCT recipients were significantly lower (mean: 1.1 ± 0.7 mL/min) compared to the SSFRs of the healthy controls (1.4 ± 0.7 mL/min; $P = 0.0015$).

3.3 | Cariological status

The number of caries lesions was significantly higher in HSCT recipients pre-HSCT (mean ± SD: 0.9 ± 1.6) compared to controls (mean ± SD: 0.4 ± 1.0; $P = 0.002$). Similarly, the DMFT index was significantly higher compared with controls ($P = 0.016$). No statistically significant difference in the number of teeth was observed (Table 2).

3.4 | Periodontitis

Periodontitis was present in 53.8% of HSCT recipients and 49.0% of controls. The difference was not statistically significant. The mean RAL of the HSCT recipients was 4.8 mm ± SD: 2.8 mm.

3.5 | Acute infections

Acute symptomatic infections were observed in nine HSCT recipients (6.3%) and none of the controls. One patient had a fistula, two patients had a symptomatic periapical process, four patients had symptomatic caries and two patients had other acute infections.

4 | DISCUSSION

The present study examined the oral health of HSCT recipients pre-HSCT compared with a healthy age- and sex-matched control group. Oral health parameters, including SSFR, DMFT index and number of caries lesions, were statistically significantly poorer in HSCT recipients compared to the controls in the present study.

TABLE 2 Comparisons of DMFT index, number of teeth, number of caries lesions, and presence of periodontitis between HSCT recipients and controls

	Mean (±SD)	Yes (%)	No (%)	*P*-value
Allogeneic HSCT recipients				
DMFT index	16.8 (7.2)			0.016
Number of teeth	26.2 (5.7)			0.222
Number of caries lesion	0.9 (1.6)			0.002
Periodontitis (n; %)		77 (53.8)	66 (46.2)	0.408
Controls				
DMFT index	14.7 (6.5)			
Number of teeth	27.8 (2.5)			
Number of caries lesion	0.4 (1.0)			
Periodontitis (n; %)		70 (49.0)	73 (51.0)	

Previous studies focusing on oral diseases of HSCT recipients pre-HSCT are sparse, and the results are somewhat inconsistent. Similar to our results, a high prevalence of oral diseases was observed in a study by Durey et al (2009), as 93.6% of 94 subjects had some oral disease or a need for dental treatment pre-HSCT and in a study by Elad et al (2003), the prevalence of decayed teeth was 50% and need for scaling and oral hygiene instruction was 47.8% in 46 subjects pre-HSCT.[18,20] However, another study reported no differences in caries parameters of HSCT recipients pre-HSCT compared with a randomly selected registry-based population consisting of a similarly aged group.[26] Busjan et al[21] found that 39 patients with newly diagnosed acute leukaemia already had poorer oral health, including caries and periodontitis, prior to any treatments compared with a healthy control group. These intriguing findings suggest that the preceding therapies do not completely explain the poor oral health of HSCT recipients.

One third (36.4%) of the HSCT recipients in our study were diagnosed with their haematological malignancies over 1 year before the pre-HSCT dental check-up. Therefore, the likelihood that the preceding anticancer therapies also affected oral health is high among these recipients. HSCT recipients commonly receive intensive conditioning chemotherapy, with or without TBI, prior to HSCT.[4] Chemotherapy and the conditioning elicit oral morbidity, particularly hyposalivation.[6-8,17,27] The present study is also consistent with, and further confirms, our previous results, in which SSFR was lower pre-HSCT compared to a control group.[6,7,16] Saliva protects against oral diseases, and the hyposalivation observed in this study may markedly contribute to oral comorbidities.[17]

We did not have information on the dental treatment history of the HSCT recipients prior to our examination. Therefore, the patients may have had dental care, more than usual, between their initial diagnosis and HSCT. This treatment could explain the difference in DMFT index. However, and contrary to this assumption, the number of caries was higher in the HSCT recipients compared to the controls. One limitation of this study is that information on preceding dental treatments was not available. Further studies are needed, particularly to investigate whether hyposalivation is already more common in patients with haematological disorders at the time of diagnosis.

Poor oral health, especially periodontitis and tooth loss, was linked to several systemic diseases, cancers and increased mortality.[9-12,15] However, there is little evidence suggesting poor oral health as a risk factor for haematological malignancies.[14,15] The influence of periodontitis and other oral infections on treatment outcomes and oral and systemic morbidity in haematological malignancies was suggested already decades ago.[28-32] However, some studies of particular chronic oral infections found not association with severe systemic complications post-HSCT.[33,34] Therefore, the effects of periodontitis and poor oral health on treatment outcomes and oral comorbidity post-HSCT are not clear and warrant further study. However, periodontal diseases are, at least, common in HSCT recipients.[18,19,35] Our results on periodontitis are consistent with previous studies, as in the current study, a high prevalence of periodontitis, in terms of RAL >3 mm, was observed in 53.8% of these HSCT recipients.[18,19,35] Periodontitis was slightly more prevalent in HSCT recipients compared with the controls, but the result was not statistically significant. Owing to different measurement methods for the presence of periodontitis between HSCT recipients and controls, comparison must be treated with caution. Our examinations could not include all of the necessary oral parameters to assess periodontal and gingival diseases and oral hygiene due to the often poor health conditions, immunosuppression and time limitations. Periodontitis in HSCT recipients was determined via measuring radiological attachment loss from panoramic radiographs, and periodontitis in the controls was determined via measuring clinical attachment loss and probing pocket depth. According to the recommendation by Pepelassi and Diamanti-Kipioti, the bone level in panoramic radiographs was considered to be normal if the distance between CEJ and AC was up to 3 mm. Therefore, alveolar bone was considered lost, indicating periodontitis, if the CEJ-AC distance was >3 mm.[24] This RAL-based method was used for HSCT recipients, as in our previous study, to avoid bacteraemia and to keep the dental visits short, because these visits occurred just prior to transplantation.[26] This method may cause inaccuracies in the diagnosis of periodontitis, and it is possible

that early signs of periodontal disease and gingivitis were not noticed.[24,36] Furthermore, information on the activity of periodontal disease or past treatment of periodontitis could not be obtained with this method. This limitation should be considered a weakness of the methodology, but this method was chosen to avoid harming the HSCT recipients.

The HSCT recipients were compared with a healthy control group that was recruited from the Swiss Bone Marrow Donor Registry. Bone marrow donors are often relatives of HSCT recipients, and the controls were age- and sex-matched with the recipients to enhance the comparability even further. In the limits of this study, oral health habits or lifestyle-related confounders were not available and could not be adjusted for in this study. However, the prevalence of smoking was somewhat lower among HSCT recipients compared with the controls (36% vs 41%). Due to the narrow age distribution (26-58 years) and female prevalence in the controls, the oldest HSCT recipients were excluded from the study (Figure 1). Younger subjects generally have fewer medications and other illnesses, and this removes some of the most relevant confounders and makes the study groups highly comparable. Further studies, with longitudinal follow-up, on the associations of biochemical, social and behavioural factors with oral health in HSCT recipients are warranted.

In conclusion, oral examinations pre-HSCT showed a high prevalence of oral disorders in HSCT recipients. These findings support the recommendations for an early dental check-up prior to HSCT to eliminate acute infection foci, prepare HSCT recipients, and, if possible, investigate the effects of oral disorders on post-HSCT complications.[29,37]

CONFLICT OF INTEREST

The authors state no conflict of interest.

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8.2 Oral disorders in patients with newly diagnosed haematological diseases

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ORIGINAL ARTICLE

Oral disorders in patients with newly diagnosed haematological diseases

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Abstract

Objective This study aimed to examine saliva flow rates and prevalence of dental and periodontal diseases of patients with newly diagnosed severe haematological diseases and compare these findings with age-matched controls of normal population.

Methods A total of 149 patients diagnosed with haematological diseases aimed to be treated with haematological stem cell transplantation between 2008 and 2018 and 154 controls were included in the study. A dental examination was performed for patients within a maximum of 6 months after diagnosis. Differences were compared in terms of the stimulated salivary flow rate (SSFR); decayed, missing and filled teeth (DMFT) index; number of teeth; caries prevalence; presence of periodontitis and acute infections.

Results The mean SSFR of the patient group was significantly lower (1.1 ml/min ± 0.7 ml/min) than the mean SSFR of the controls (1.3 ml/min ± 0.5 ml/min; $p = 0.004$). The number of caries lesions was significantly higher in the patient group (mean ± SD, 1.1 ± 1.9) than in the control group (mean ± SD, 0.4 ± 1.2; $p < 0.001$). There were fewer teeth and a higher DMFT index in the patient group compared to the control group, but the differences were not significant. Acute symptomatic infections were observed in eight (5.4%) patients and in none of the controls ($p < 0.01$).

Conclusions and clinical relevance Oral examinations in patients with newly diagnosed severe haematological disease demonstrated a higher prevalence of caries, acute infections and lower mean SSFR compared with the controls. These findings support the recommendations for early dental examination at the time of diagnosis.

Keywords Haematology · Caries · DMFT index · Hyposalivation

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Introduction

Potentially lethal haematological disorders and malignancies represent a heterogeneous group of diseases characterised by alterations in the proliferation and function of blood cells [1–3]. Treatments of these diseases, such as leukaemia, lymphoma and severe aplastic anaemia, are often intensive and may include chemotherapy, total body irradiation and haematopoietic stem cell transplantation (HSCT) [4–6]. Not only the diseases, but also their treatments are known to affect oral health [6–10].

During the past decade, knowledge of the association between oral health and systemic health has grown. Poor oral health has been associated with various systemic diseases and cancers as well as with cancer mortality [11, 12]. To date, there has been little evidence for the consideration of poor oral health as a risk factor for haematological diseases [13].

Several known risk factors, such as exposure to benzene and some genetic disorders, account for only a small number of observed haematological diseases [1–3, 14]. Those known risk factors are mostly different from those of dental diseases, excluding some common general factors, like smoking, ageing and occasionally sex [1, 3, 13, 15, 16].

Previous studies have confirmed that prior to HSCT, the need for dental treatment is evident. HSCT recipients suffer from chronic and acute dental diseases, such as caries and periodontitis [8, 17, 18]. However, the majority of these patients have received cancer therapies, some of them even for several years [4, 19, 20]. These therapies are known to have short- and long-term influences, including mucositis and hyposalivation, on oral health [6–9]. Hyposalivation is a well-known risk factor for common oral diseases such as caries, periodontitis and candida infections [21]. Hence, it is likely that oral health prior to HSCT is affected by previous therapies.

Nonetheless, recent studies have also suggested that patients with newly diagnosed acute leukaemia suffer from poor oral health before the administration of any cancer therapies. Clinical signs of oral diseases, including visible caries, dental pain or tooth mobility, were observed in 44% of patients with newly diagnosed acute leukaemia [22]. Another study [23] reported a greater prevalence of caries and periodontitis in patients with acute leukaemia before any cancer treatment compared with controls. Thus, these results suggest that previous therapies cannot comprehensively explain poor oral health before HSCT, as poor oral health, at least among subjects with acute leukaemia, is evident at the time of diagnosis.

The objective of this study was to compare oral health parameters in patients with newly diagnosed severe haematological diseases planned to be treated with HSCT with age-matched controls. More specifically, the differences in the prevalence of caries, periodontitis and acute oral infections as well as the stimulated salivary flow rate (SSFR) between patients and controls were evaluated. Additional aim of the study was to compare oral health parameters within the patient group according to different diagnoses and treatment-related factors including medications and chemotherapies.

Materials and methods

Adult patients (≥ 18 years old) with haematological diseases planned to be treated with HSCT and who were diagnosed less than 6 months before and treated in the Department of Hematology, University Hospital Basel, Switzerland (see diagnoses Table 1.). Patients with complete medical and oral health status were initially included in this cross-sectional study. Data were collected for patients treated between 2008 and 2018. The exclusion criteria were age greater than 65 years, incomplete dental or medical status and edentulous patients.

Table 1 Descriptive characteristics of the study subjects

	Patients ($n = 149$)	Controls ($n = 156$)
Age mean (range)	48.2 (19–64)	48.1 (25–57)
Sex *n* (%)		
Female	68 (45.6)	83 (53.9)
Male	81 (54.4)	71 (46.1)
Smoking *n* (%)		
Yes	66 (44.3)	72 (46.2)
No	73 (49.0)	82 (52.6)
N. app	10 (6.7)	2 (1.3)
Diagnosis *n* (%)		
AML	20 (13.4)	
MDS	15 (10.1)	
ALL	68 (45.6)	
PCD	22 (14.8)	
Other	24 (16.1)	
Number of chemotherapies *n* (%)		
None	31 (20.8)	
1	25 (16.8)	
2 or more	91 (61.1)	
N. app	2 (1.3)	
Comorbidity index mean (± SD)	2.57 (1.0)	
Other diagnoses *n* (%)		
Yes	98 (65.8)	
No	51 (34.2)	
How many drugs together *n* (%)		
None	32 (21.5)	
1–2	31 (20.8)	
3 or more	78 (52.3)	
N. app	8 (5.4)	
Range	0-13	
SSFR *n* (%)		
Hyposalivation < 0.3 ml/min	7 (4.8)	2 (1.3)
Hyposalivation 0.3–0.7 ml/min	36 (24.5)	34 (22.1)
Normal SSFR > 0.7 ml/min	104 (70.7)	118 (76.6)

AML acute myeloid leukaemia, *MDS* Myelodysplastic syndrome, *ALL* acute lymphoblastic leukaemia, PCD plasma cell dyscrasia, Others (chronic myeloid leukaemia, chronic lymphocytic leukaemia, bone marrow failure, myeloproliferative neoplasm, non-Hodgkin-lymphoma), *SSFR* stimulated salivary flow rate

A control group of individuals from the normal Swiss population were recruited from the Swiss Bone Marrow Donor Registry of The Blood Transfusion Service SRC Basel, Switzerland, as previously described [24]. Thus, the controls were stem cell donors, often relatives of the HSCT-recipients,

and there were no exclusion criteria according to demographics or health.

Dental examinations were carried out in the Department of Oral Health and Medicine (previously: Department of Preventive Dentistry and Oral Microbiology), School of Dental Medicine, University of Basel. The dental examinations were performed 1 to 3 days after hospital admission. The clinical and radiological oral examinations revealed the following parameters: the decayed, missing and filled teeth (DMFT) index according to the WHO [25], the SSFR, acute oral infections and radiological attachment loss (RAL).

The SSFR was measured at the beginning of the dental examination and before any clinical assessments. The SSFR was collected by the spitting method after mechanical stimulation by chewing a neutral standardised paraffin wax, similar to our previous studies [7, 26]. SSFR measurements of ≤ 0.7 mL/min were defined as hyposalivation [21]. Acute oral infections were diagnosed if fistulas, symptomatic periapical processes, symptomatic deep caries, wounds/ulcers or acute periodontal abscesses were observed.

To avoid bacteraemia in severely ill individuals, often pancytopenia patients, periodontitis was assessed from panoramic radiographs as a measure of cumulative periodontal disease [27]. Periodontitis was determined as described in previous studies to be present if RAL (the distance between the cementoenamel junction and the alveolar bone crest) was > 3 mm [26, 28].

The oral health of the control group was similarly examined by the same dentists. A complete clinical periodontal examination was performed, but panoramic radiographs were not taken to avoid unnecessary x-ray exposure.

Data including haematological diagnosis, other diagnoses and regular medications at the time of hospitalisation as well as the number of previous or current chemotherapy regimens were collected from medical records (see Table 1). Other diagnoses were grouped according to the International Classification of Diseases (ICD-10) [29]. The Charlson age-adjusted comorbidity index score was calculated for patients [30].

Regular medications were grouped according to the 1st level classification of the Anatomical Therapeutic Chemical (ATC) classification system of the WHO [31]. Additionally, the 2nd level classification of the ATC was used to make subgroups of the medications that likely had an effect on the SSFR and that were the most commonly used in these patients, including antibacterials, antivirals, antimycotics, analgesics, antipsychotics and medications for diabetes [32]. Groups with only five or fewer recordings were combined as "other".

Statistical analysis

The mean age of the required control group was significantly lower than the age of the primary study group. To avoid the bias of differing ages, the oldest patients (age greater than 65 years) were excluded in order to approximate the mean of ages.

The mean, median and standard deviation of the oral health parameters, including the SSFR, DMFT index, number of teeth, number of caries lesions, frequency of acute infections and presence of periodontitis, were calculated and compared between the patients and age-matched controls. Additionally, the oral health parameters were compared between the patients with and without a certain haematological diagnosis or different medications.

Descriptive univariate analyses were performed separately according to sex. The odds ratio was calculated for caries prevalence. Pearson chi-square, t test, and Mann-Whitney U tests were used to determine statistical significance. One-way analysis of covariance (ANCOVA) and non-parametric Krusal-Walli H tests were conducted to adjust for the effects of confounding factors including age, sex, smoking, number of chemotherapies, age-adjusted comorbidity range, number or type (according to the ATC classification) of regular medications, effects of other diagnoses (yes/no) according to ICD-10 classifications and number of days after diagnosis on the SSFR and cariological status, respectively. p values < 0.05 were considered statistically significant. Statistical analyses were performed with SPSS version 24 (IBM Corporation, Amonk, IL, USA).

Results

Study population

A total of 149 patients and 154 controls were included in the study. The mean age of both study groups (patients and controls) was 48 years. All of the patients had been diagnosed with their haematological diseases within 6 months before the dental examination (mean 102 days, range 2–182 days). Fifty-one (34.2%) patients had no other diagnoses. The descriptive statistics of the patients and controls are presented in Table 1.

Stimulated salivary flow rates in patients vs controls

The mean SSFR of the patients was significantly lower (1.1 ml/min ± 0.7 ml/min) than the mean SSFR of the controls (1.3 ml/min ± 0.5 ml/min; $p = 0.004$). The difference in the mean SSFR remained highly significant when adjusted for age and sex ($p < 0.005$). In the patient group, 29.3% suffered from hyposalivation (SSFR ≤ 0.7 ml/min), and 22.7% of the control group suffered from hyposalivation; however, the difference was not statistically significant ($p = 0.197$).

Stimulated salivary flow rates and co-variables between patient groups

The effects of smoking, number of chemotherapies, age-adjusted comorbidity range, number or type (according to the ATC classification) of regular medications, effects of other diagnoses (yes/no) according to ICD-10 classifications and number of days after diagnosis on the SSFR were not statistically significant (all p values > 0.05).

Cariological status in patients vs controls

The number of caries lesions was significantly higher in the patient group (mean 1.1 ± SD 1.9) than in the control group (mean ± SD 0.4 ± 1.2; $p < 0.001$). Additionally, when analysed separately by sex (female patients vs female controls; male patients vs male controls), the number of caries lesions was significantly higher in both patient groups than in both control groups (mean ± SD 1.19 ± 2.02 vs 0.33 ± 0.9, $p = 0.002$; 1.10 ± 1.81 vs 0.59 ± 1.41 $p = 0.01$, respectively). The odds ratio of caries prevalence was 2.73 ($p < 0.001$, CI 95% 1.66–4.5) for patients compared with controls.

The DMFT index was higher in the patient group than in the control group, but the difference was not statistically significant. The number of teeth was lower in the patient group than in the control group, but the difference was not statistically significant (Table 2).

Cariological status and co-variables between patient groups

Analysis of the patients showed the caries prevalence to be significantly higher in patients who had other additional diagnoses than in patients without other diagnoses ($p = 0.037$). Effects of smoking, number of chemotherapies, age-adjusted comorbidity range, number or type (according to the ATC classification) of regular medications and number of days after diagnosis on the on caries prevalence were not statistically significant (all p values > 0.05).

Periodontitis in patients vs controls

Periodontitis was present in 58.4% of the patients and 60.8% of the controls. The difference was not statistically significant. The mean RAL of the patients was 4.6 mm ± SD 2.1 mm.

Acute infections in patients vs controls

Acute symptomatic infections were observed in eight (5.4%) patients and in none of the controls, and the difference was statistically significant ($p = 0.003$). Three patients had a fistula, two patients had ulcerations, one patient had an acute periodontal lesion and two patients had other acute infections.

Discussion

The current study examined oral health of adult patients with newly diagnosed severe haematological diseases and compared the findings with those of age-matched controls of normal population. Patients had higher prevalence of caries and lower stimulated salivary flow rate (SSFR) and more acute dental infections than controls.

The effects of haematological cancer therapies on the salivary flow rate in HSCT patients after HSCT and patients who have received irradiation are well known, as shown in our and other previous studies [33–35]. Hyposalivation has been reported to be particularly prevalent 6-month post-HSCT with gradual improvement within 2 years [34]. The current study is partly in line these previous findings as SSFR was observed to be statistically significantly lower already pre-HSCT among patients with newly diagnosed haematological disease compared with the controls. However, there was no statistically significant difference in the prevalence of hyposalivation (SSFR < 0.07 ml/min) between patients and controls. One previous study has focused on salivary flow rate of 24 patients with newly diagnosed acute leukaemia. In that study, lower salivary flow rate of the patients was observed already before the initiation of chemotherapies compared with healthy controls [36]. In keeping with that study, the current study

Table 2 Comparisons of the DMFT index, number of teeth, number of caries lesions and presence of periodontitis between patients and controls

	Mean (± SD)				p value
	Patients		Controls		
DMFT index	17.4 (7.7)		16.5 (6.5)		0.243
Number of teeth	26.3 (5.4)		27.4 (2.4)		0.359
Number of caries lesions	1.14 (1.9)		0.44 (1.2)		< 0.001
	Yes (%)	No (%)	Yes (%)	No (%)	
Periodontitis n (%)	87 (58.4)	62 (41.6)	93 (60.4)	60 (39.0)	0.380
Acute infections n (%)	8 (5.4)	140 (94.0)	154 (100)	0 (0)	0.003

could not reveal any difference in the SSFR between patients with or without chemotherapy (116 patients, yes; 31 patients, no), and the SSFR of the patients remained statistically significantly lower among patients with or without chemotherapy compared with the controls. Thus, within the limitations of this study, the effect of chemotherapy on saliva flow rate remains unclear and warrants further studies. Similarly, a review article concludes that studies of the effects of chemotherapy on saliva flow rate are sparse and contradictory, and consistent conclusions of the effects can not be drawn [37].

The effect of the number of medications on SSFR was also examined in this study. Polypharmacy and some types of medications, such as analgesics and antipsychotics, have been previously stated as risk factors for hyposalivation [21, 32, 38, 39]. However, and in line with our own previous study, no association of the number of medications or the type of medication with the SSFR could be observed [35]. Thus, the reason of low SSFR among patients with newly diagnosed haematological disease remains partly unclear. Stress is known to reduce salivary flow rate and as these haematological disorders and malignancies are both mentally and physiologically stressful, this could explain reduced SSFR at least partly [40].

Previous studies of oral diseases among adults with severe newly diagnosed haematological disorder or malignancy are limited. Two previous recent studies on patients with acute leukaemia observed high needs of oral health care at the time of diagnosis [22, 23]. In line with the study by Busjan et al. [23], also in this study, the caries prevalence of the patients was significantly higher compared with the controls. Patients also had more missing teeth than controls; however, unlike in the study by Busjan et al., this difference did not reach statistical significance [23]. In addition to the two recent previous studies, our study also included patients with other diagnoses than acute leukaemia (see Table 1). However, the different haematological diagnoses did not have an effect on the studied oral health parameters. Therefore, according to this study, patients with severe haematological diagnoses should be considered at risk of caries, acute infections and low SSFR already shortly after the diagnosis.

In the current study, the only statistically significant confounding factor for high caries prevalence was the "other medical diagnoses" subgroup. This result may be explained by the fact that patients with other diagnoses were significantly older (mean 50 years) than patients with no other diagnoses (mean 44 years) and that oral health decreases and the DMFT index increases with ageing [41]. A weakness of this study is that the confounding factors of caries particularly including, sugar intake, oral health habits, nor plaque scores could not be studied, and the reason for the high caries prevalence remains unclear and thus needs further investigation. Poor oral health has been associated with low socioeconomic status and various systemic diseases and cancers as well as with cancer mortality [11, 12, 15]. However, there is virtually no evidence that poor oral health is a risk factor for severe haematological disorders or malignancies. In one study, an association of periodontitis with lymphoma in men was reported [13]. Within the limits of this study, an association of oral diseases, particularly caries, with haematological diseases is intriguing, but it must be noted that information concerning previous dental treatments, socioeconomic status and behavioural aspects of the patients were not available; hence, the effects of these potential confounders could not be taken into account. Furthermore, this study compared the prevalence of oral diseases between patients and controls and even though caries was observed to be more prevalent among the patients, associations of oral diseases with haematological diseases can not be determined with this study design.

In contrast to the results reported by Busjan et al. [23], no difference in the prevalence of periodontitis could be found between newly diagnosed patients and controls. However, the presence of periodontitis was determined with different methods between the patients and controls. The periodontitis in patients was determined with indirect assessment of the cumulative effects of periodontitis in panoramic radiographs. This method was selected to avoid bacteraemia in patients with very low neutrophil and thrombocyte counts and to keep the dentist visit as short as possible. However, the activity or the early stages of the disease cannot be evaluated from the x-ray [42–44]. Thus, this method may underestimate the presence of early stages of periodontitis and thus, the result must be treated with caution.

The comparability of the patients and the controls should be considered critically. The controls who were registered to the Swiss Bone Marrow Donor Registry were age matched and often relatives of the patients with severe haematological disorder or malignancy, and thus, the comparability could be considered good. The controls were not matched according to sex, and the distribution was not completely same, but the difference between these groups was not statistically significant. However, it is possible that people who registered might be more health conscious than the average population and thus have better oral health parameters, which could lead to skewed data and could make the differences more pronounced.

In conclusion, oral examinations in patients with newly diagnosed severe haematological disease demonstrated a high prevalence of oral disorders. These findings support the recommendations for early dental examination at the

time of diagnosis so that patients can be given the necessary oral and dental treatments and information concerning oral health and cancer treatments.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was conducted in accordance with the Declaration of Helsinki and was approved by the regional ethics committee (Ethikkommision Nordwest- und Zentralschweiz (EKNZ), Switzerland: EKNZ: 311-10 and EKNZ: 2017–02268).

Informed consent Informed consent was obtained from all the patients participating in 2018 (EKNZ: 2017-02268), the former data was collected retrospectively and formal consent was not required (EKNZ: 311-10).

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8.3 Common oral diseases, hyposalivation and survival post-HSCT, a longitudinal study

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Common oral diseases, hyposalivation and survival post-HSCT, a longitudinal study

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Abstract

Objectives: Haematopoietic stem cell transplantation (HSCT) recipients are at risk of side effects within the oral cavity. The purpose of this study was to examine progression of common oral diseases and hyposalivation and their associations with survival in allogeneic HSCT recipients.

Methods: Two hundred and sixty nine adult HSCT recipients treated with HSCT between 2008 and 2016 were included in this study. The associations of caries, decayed, missing, filled teeth (DMFT) index, radiological attachment loss and stimulated salivary flow rate with 6-month survival and the progression of the oral disorders within 2 years were examined.

Results: Forty HSCT recipients (14.8%) deceased within 6 months post-HSCT. Among the deceased recipients, hyposalivation and caries were more common pre-HSCT than in recipients who survived over 6 months ($P < 0.05$). HSCT recipients with hyposalivation pre-HSCT had higher risk of death (HR: 1.90, 95% CI:1.00-3.60; $P = 0.044$) within 6 months post-HSCT compared with recipients without hyposalivation. Hyposalivation pre-HSCT was associated with a higher DMFT index score ($P < 0.05$) and a smaller number of teeth ($P < 0.005$) 24 months post-HSCT in comparison with those without hyposalivation.

Conclusions: Hyposalivation and caries were associated with a lower rate of survival in HSCT recipients. Additionally, hyposalivation predisposed to deterioration of oral health post-HSCT.

KEYWORDS

dental caries, dmf index, graft vs host disease, haematology, hyposalivation, stem cell transplantation

1 | INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is a treatment used for patients with life-threatening diseases and disorders of the haematopoietic system. In HSCT, haematopoietic multipotent stem cells are collected either from a donor (allogeneic-HSCT) or the patient him/herself (autologous-HSCT). Before transplantation, intense conditioning regimen including high-dose chemotherapy and for some indications, total body irradiation (TBI) is used to eradicate patients' own haematopoietic stem cells.[1-3] Subsequent to improvements of the transplantation procedures, the number of long-term survivors has increased and the

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prevalence of life-threatening complications has decreased over the years.[3-7] However, less severe side effects are still common and can affect nearly all organs.[3,4,7] HSCT recipients are predisposed to infectious diseases, and the quality of life can be reduced throughout the lifetime.[4,7-10] Thus, prevention and treatment of these comorbidities are of increasing clinical importance and essential for supportive care.

Side effects and disorders of the oral cavity are common and can be found in approximately 80% of the HSCT recipients. Of these, hyposalivation is particularly frequent and may be one of the fundamental factors in the pathogenesis of oral disorders post-HSCT.[8-14] Over time, hyposalivation and changes in salivary composition and oral biofilms almost inevitably cause dental caries, periodontitis and mucosal infections.[13-16] Additionally, hyposalivation and xerostomia (subjective sensation of dry mouth) can lead to oral discomfort, may affect the patient's ability to eat and cause increased need of supportive cancer care.[8,13,14,16,17] Hyposalivation is associated with oral GvHD and mucositis and could thus even be associated with survival.[12,18-22] Among HSCT recipients, this has not been studied, but hyposalivation and associated saliva alterations have been observed to co-exist with aspiration pneumonia as well as frailty and death among elderly.[23-26]

Reasons for hyposalivation in HSCT recipients are likely multifactorial. The conditioning regimen before HSCT can potentially affect salivary glands, particularly if TBI is used.[3,27] Additionally, salivary glands are commonly affected by Graft vs Host Disease (GvHD). In GvHD, the infiltrating T- lymphocytes cause cytotoxicity in the salivary glands and reduce the secretion of saliva.[19-22] Furthermore, HSCT recipients often need a broad range of medications, most of which might reduce saliva secretion.[13] However, in our previous study, use of medications could not explain hyposalivation in HSCT recipients.[27,28]

Several current guidelines support dental screening and elimination of potential oral foci before HSCT as the HSCT treatment includes strong immunosuppression predisposing recipients to severe infection complications.[3,9,11,29] It has been estimated that 1.8 of every 1000 deaths could be prevented with dental treatment before HSCT.[30] However, the recommendations are somewhat inconsistent and based on a limited number of studies, some of which have shown that chronic oral foci including deep caries are not associated neither with survival nor infection complications.[31,32] Nonetheless, several studies have confirmed relationship between periodontal bacteria and oral mucositis and that the treatment of periodontitis can reduce oral comorbidities, in terms of mucositis post-HSCT, and thus, enhance healing of the recipients.[33,34]

Only a few studies exist on the oral health of adult subjects pre- and post-HSCT. These studies suggest hyposalivation to be common and oral health to deteriorate after the HSCT.[8,12,15,27,35,36] Additionally, there are no studies on the effects of hyposalivation or the most common oral infections caries and periodontitis on survival post-HSCT. Thus, in this study, the prevalence, consequences and progression of caries and periodontitis, as well as hyposalivation were examined in a considerably large number of allogeneic HSCT recipients pre- and up to 24 months post-HSCT.

2 | PATIENTS AND METHODS

This retrospective observational longitudinal study was performed according to the Declaration of Helsinki and was approved by ethics committee (Ethikkommision Nordwest- und Zentralschweiz (EKNZ), Switzerland: EKNZ: 311-10).

Adult allogeneic HSCT recipients who were treated for haematological malignancies in the Department of Hematology, University Hospital Basel, Switzerland, between 2008 and 2016 with complete medical and oral health status were included. HSCT recipients whose Stimulated salivary flow rate (SSFR) was not measured, panoramic radiography was not taken pre-HSCT or who were edentulous were excluded. Before oral examination, most HSCT recipients had received conditioning chemotherapy either with or without TBI as previously described.[28,37] Diagnosis, conditioning-related information, survival as well as the presence and grade of acute GvHD (aGvHD) according to the modified Glucksberg criteria by Przepiorka et al (1995) (symptoms starting <100 days post-HSCT) and presence and grade of chronic GvHD (cGvHD) according to Filipovich et al (2005) were collected from the medical records.[38-40]

Clinical and radiological oral and dental examinations were carried out by experienced dentists in the Department of Oral Health & Medicine (previous Department of Preventive Dentistry and Oral Microbiology), University Center for Dental Medicine Basel, University of Basel. The first oral examination took place prior to HSCT following the normal routine protocol of the clinic always including a panoramic radiograph, SSFR measurements and clinical diagnostics and post-HSCT also observation of oral manifestations of GvHD (yes/no). All HSCT recipients participated in a prospective oral disease prevention programme. Oral hygiene instruction was provided, daily use of fluoride containing mouth rinses and toothpaste as well as saliva substitutes and chlorhexidine-containing mouth rinse were recommended for HSCT recipients in aplasia.[11] Follow-up examinations were performed 6, 12 and 24 months post-HSCT.

Stimulated salivary flow rate measurement was conducted at each appointment as described in our previous studies.[28,41] SSFR ≤ 0.7 mL/min was defined as hyposalivation, and SSFR ≤ 0.3 mL/min as severe hyposalivation.[13] Oral and dental examination, including decayed, missing, filled teeth (DMFT) index according to WHO, was performed.[42] Current or already treated periodontitis was assessed from panoramic radiographs. Periodontitis was determined to be present if radiological attachment loss (RAL), for example the distance between the cementoenamel junction and the alveolar bone crest, was observed to be >3 mm.[43]

2.1 | Statistics

Mean, median and standard deviation of the oral health parameters including SSFR, DMFT index, number of teeth, number of caries lesions and the frequency of periodontitis were calculated and put in relation to SSFR (hyposalivation vs normal SSFR). Descriptive univariate analyses were done by sex (male vs female)

TABLE 1 Descriptives of the study subjects (269)

Age, mean (range)	50.6 (19-74)
Sex n (%)	
Female	127 (47.2)
Male	142 (52.8)
Diagnosis n (%)	
AML	89 (33.1)
MDS	28 (10.4)
ALL	37 (13.8)
CML	9 (3.3)
CLL	16 (5.9)
PCD	28 (10.4)
BMF	7 (2.6)
MPN	21 (7.8)
MH	3 (1.1)
NHL	27 (10.0)
Other	4 (1.5)
Karnofsky, mean (range)	91.1 (40-100)
Ablative conditioning n (%)	
Yes	218 (81.0)
No	51 (19.0)
TBI n (%)	
Yes	110 (40.9)
No	150 (55.8)
n.app	9 (3.3)

Abbreviations: ALL, Acute Lymphoblastic Leukaemia; AML, Acute Myeloid Leukaemia; BMF, Bone Marrow Failure; CLL, Chronic Lymphocytic Leukaemia; CML, Chronic Myeloid Leukaemia; MDS, Myelodysplastic Syndrome; MH, Hodgkin's Lymphoma; MPN, Myeloproliferative Neoplasm; NHL, Non-Hodgkin's-Lymphoma; PCD, Plasma Cell Dyscrasia; TBI, Total Body Irradiation.

and by survival status (survived vs deceased). ANOVA was used to determine the association of SSFR with presence and grade of cGvHD and univariate analyses to determine the association of SSFR with presence of oral manifestations of GvHD. Pearson Chi-square, *t* test and Mann-Whitney *U* test were used to determine statistical significance. *P*-value of < 0.05 was considered as statistically significant. For the survival analysis, Cox proportional hazards regression models were used to analyse the 6-month survival of HSCT recipients with and without hyposalivation pre-HSCT. Statistical analyses were performed with IBM SPSS software, version 23 (IBM Corporation, Amonk).

3 | RESULTS

3.1 | Study population

A total of 269 adult allogeneic HSCT recipients (m/f: 142/127; age mean: 50.6 years; range 19-74 years) were included. Excluded were 73 allogeneic HSCT recipients whose dental or medical data were not complete. 155 (57.6%) recipients had received the diagnosis within 1 year of the pre-HSCT dental examination, 69 (25.7%) recipients between one to 5 years and 45 (16.7%) more than 5 years prior to HSCT. Descriptive data and diagnoses are presented in Table 1. In the follow-up examinations 140, 106 and 49 individuals participated at 6, 12 and 24 months post-HSCT, respectively. During the study period, 101 HSCT recipients were deceased.

The mean SSFR in all HSCT recipients pre-HSCT was 1.13 (± 0.72) mL/min. In 15 (5.6%) HSCT recipients pre-HSCT, the SSFR was <0.3 mL/min, 76 (28.3%) 0.3-0.7 mL/min and >0.7 mL/min in 178 (66.2%). The mean DMFT index score was 18.9 (±7.7), mean number of teeth 24.7 (± 6.7), mean number of caries lesions 1.0 (± 2.2) and the prevalence of periodontitis (RAL > 3 mm) 65.1%.

3.2 | Associations of SSFR and oral disorders with survival post-HSCT

Forty HSCT recipients (14.8%) deceased during the first 6 months post-HSCT. There was no statistically significant difference in age (mean age 49.5 years vs 50.8 years) or sex (male 52.5% vs female 52.8%) between the deceased and the survivors after 6 months post-HSCT. Hyposalivation (SSFR ≤ 0.7 mL/min) pre-HSCT was more common among the deceased compared with the survivors (47.5% vs 31.4%; $P = 0.048$). Also, caries incidence was higher among the deceased compared with the survivors within 6 months post-HSCT (mean 2.0 ± 3.0 vs 0.88 ± 2.0; $P = 0.044$). There were no statistically significant differences in mean DMFT index, the number of teeth or the presence of periodontitis (RAL > 3 mm) between the deceased and the survivors within 6 months post-HSCT (Table 2).

In the survival analysis, HSCT recipients who had hyposalivation (SSFR ≤ 0.7 mL/min) pre-HSCT had a higher risk of death 6 months post-HSCT. The age- and sex-adjusted hazard ratio of dying within 6 months post-HSCT was almost twice as high in the hyposalivation group, HR: 1.90 (95% CI: 1.00-3.60; $P = 0.044$), compared with the reference group which consisted of HSCT recipients without hyposalivation pre-HSCT.

3.3 | Stimulated saliva flow rates and associations of hyposalivation with DMFT index, caries, number of teeth and GVHD post-HSCT

Stimulated salivary flow rate 6 months post-HSCT was lower (mean: 0.93 ± 0.6 mL/min) compared with SSFR pre-HSCT (1.13 ± 0.73 mL/min; $P = 0.009$). However, after a year the SSFR returned to the initial level (1.13 ± 0.63 mL/min) and 2 years post-HSCT above the initial level (1.27 ± 0.75 mL/min).

There was no statistically significant difference in mean DMFT index between HSCT recipients with hyposalivation pre-HSCT and recipients with normal SSFR pre-HSCT or 6 and 12 months post-HSCT. 24 months post-HSCT, the mean DMFT index in HSCT recipients with hyposalivation pre-HSCT was higher compared with HSCT recipients with normal SSFR (23.55 ± 5.61 vs 17.95 ± 7.07; $P = 0.02$; Table 3). The results on the number of teeth were in line with those

TABLE 2 Comparison of survival and pre-HSCT oral health parameters

	Survival ≤ 6 mo (40)	Survival > 6 mo (229)	*P*-value
SSFR mL/min mean (±SD)	0.98 (0.7)	1.15 (0.7)	
SSFR ≤ 0.7 mL/min (n; %)	19 (47.5)	72 (31.4)	0.048
Number of caries mean (±SD)	2.0 (3.0)	0.9 (2.0)	0.044
Number of teeth mean (±SD)	24.1 (6.5)	24.8 (6.8)	
DMFT index mean (±SD)	18.5 (8.7)	18.9 (7.5)	
RAL> 3 mm (%)	22 (55.0)	153 (66.8)	

Abbreviations: DMFT index, Decayed Missing Filled Teeth index; RAL, Radiological Attachment Loss; SSFR, Simulated Salivary Flow Rate.

on DMFT index, as 24 months post-HSCT, the HSCT recipients with hyposalivation had a lower number of teeth compared with HSCT recipients with normal SSFR (mean 20.7 ± 7.6 vs 27.0 ± 4.9; $P = 0.001$).

Caries was consistently more prevalent pre-HSCT and 6, 12 and 24 months post-HSCT in HSCT recipients with hyposalivation but the differences were not statistically significant, except for caries prevalence pre-HSCT (mean caries in HSCT recipients with hyposalivation vs normal SSFR pre-HSCT: 1.45 ± 2.4 vs 0.84 ± 2.0; $P = 0.04$, respectively).

There was no statistically significant difference in aGvHD (no vs yes and/or according to grade I-IV) post-HSCT between HSCT recipients with hyposalivation pre-HSCT and recipients with normal SSFR pre-HSCT. Additionally, hyposalivation pre-HSCT was not associated with cGvHD (mild, moderate or severe cGvHD). However, mean SSFR of patients suffering from severe cGvHD was lower when compared to the patients with limited or no cGvHD post-HSCT but the differences were not statistically significant. The mean SSFR of patients with severe cGvHD did not return to the initial level 24 months post-HSCT rather stayed at the same level as 1 year post-HSCT (1.04 mL/min). Six months post-HSCT, the presence of oral manifestation of GvHD was noted in 64 (23.6%) and 12 months post-HSCT in 44 (16.2%) HSCT recipients. Hyposalivation post-HSCT (6 and 12 months) was not statistically significantly associated with the presence of oral manifestation of GvHD.

4 | DISCUSSION

The present study examined oral health and changes in oral health parameters during a 2-year follow-up in a large number of HSCT recipients. The novel findings of this study were that hyposalivation and caries were associated with an increased risk of death within 6 months post-HSCT. Age, sex, conditioning type and intensity were not associated with survival. The age- and sex-adjusted hazard ratio (HR) of dying within 6 months post-HSCT was almost twice as high in the hyposalivation group when compared to the group consisting of HSCT recipients without hyposalivation pre-HSCT. These results are in line with previous studies, showing associations between hyposalivation, frailty and mortality. However, these studies were performed among older people with a different medical background. [23-25] Nonetheless, some of the HSCT-recipients also suffer from similar clinical appearance of cachexia and frailty as elderly who commonly suffer from hyposalivation.[24] The possible use of SSFR as a predictor for higher risk of death needs further investigation.

Decreased SSFR rates were common already pre-HSCT. Before the transplantation, 15 (5.6%) HSCT recipients had very low SSFR (<0.3 mL/min), 76 (28.3%) 0.3-0.7 mL/min and 178 (66.2%) >0.7 mL/min. After the transplantation, the SSFR was observed to reduce further, being clearly lower 6 months post-HSCT compared with SSFR pre-HSCT. After that, a gradual improvement of SSFR was observed and 12 months post-HSCT, SSFR was at the level of pre-HSCT values and even slightly higher 24 months post-HSCT (Table 3). This commonly observed hyposalivation and gradual improvement of SSFR over time after HSCT is in line with previous studies and further supports the findings which have shown cytotoxic effects of chemotherapy and irradiation to damage salivary glands. Apocrine functions then regenerate gradually during years.[16,17,19,27,28] However, in this study the SSFR of HSCT recipients with severe cGVHD did not return back to the initial level within the 24 months. This situation is also observed in previous studies, in which malfunctions of salivary

TABLE 3 Oral health parameters compared with SSFR

Oral examination time point	SSFR mL/min (±SD) all	N (SSFR ≤0.7 mL/min/>0.7 mL/min)	Number of caries lesions (±SD)		
			SSFR ≤0.7 mL/min	SSFR >0.7 mL/min	*P*-value
Pre-HSCT	1.1 (0.7)	91/178	1.5 (2.4)	0.8 (2.0)	0.04
6 mo post-HSCT	0.9 (0.6)	42/98	2.3 (3.6)	1.6 (2.8)	0.56
12 mo post-HSCT	1.1 (0.6)	32/74	1.8 (3.1)	1.3 (2.2)	0.22
24 mo post-HSCT	1.3 (0.8)	11/38	2.6 (3.5)	0.7 (1.1)	0.13

Abbreviations: DMFT index, Decayed Missing Filled Teeth index; SSFR, Stimulated Salivary Flow Rate.

glands have been reported in patients with cGvHD.[19-21] Nonetheless, this study also suggests that the higher risk of death in the HSCT recipients with hyposalivation may actually explain some of this improvement observed, as hyposalivation (SSFR ≤ 0.7 mL/min) pre-HSCT was significantly more common among the deceased, compared with the survivors. Thus, the former studies may exaggerate the regeneration potential of salivary tissues.[16,17,27,28] Nonetheless, in our previous study, hyposalivation and persisting sicca symptoms were observed to be relatively common several years post-HSCT.[8]

Hyposalivation was not associated with acute or chronic GvHD or oral manifestation of GvHD. In some of the previous studies, cGvHD has been found to affect salivary glands and lead to salivary dysfunction after the onset of GvHD.[20,21,44] However, within the limits of this study, hyposalivation pre-HSCT seems not to have a causative role in the pathogenesis of any form of GvHD. Supporting this assumption, also in a study by Boer et al (2015), no statistically significant differences in salivary flow rates could be found in HSCT recipients at the time of oral GVHD onset.[15] Thus, further prospective clinical studies are necessary to clarify this issue.

In the current study, DMFT index was used to determine past and present cariological infections in HSCT recipients. An earlier study with only 36 HSCT recipients has reported a statistically significant increase in DMFT index score already 6 months post-HSCT.[35] Our study cannot thoroughly confirm this previous finding. Likewise, a couple of studies with a 100-day follow-up did not notice any changes in DMFT index or an increase in new dental caries lesions in this short follow-up period.[15,36] However, in this study, hyposalivation was observed to be associated with progression towards a higher DMFT index score. 24 months post-HSCT, the DMFT index score was statistically significantly higher in HSCT recipients with hyposalivation, compared with the HSCT recipients with normal SSFR. The results on the number of teeth were in line with those on DMFT index. 24 months post-HSCT, HSCT recipients with hyposalivation had a significantly lower number of teeth compared with HSCT recipients with normal SSFR. These findings support our hypotheses and many previous studies where hyposalivation has been observed as a risk factor for oral diseases that may eventually lead to tooth loss and expensive oral rehabilitation. Additionally, caries prevalence was observed to be consistently higher in HSCT recipients with hyposalivation at all study time points, but the results were not statistically significant, except for HSCT recipients with hyposalivation pre-HSCT. However, it must be noted that our results may underestimate the cariological problems in HSCT recipients post-HSCT. All the HSCT recipients in the study were referred to a prospective oral disease prevention programme including oral healthcare instruction, as these preventive measures are expected to prevent caries and reduce the effects of hyposalivation.[9,11,13,14]

Ongoing or treated periodontitis in HSCT recipients was determined by measuring RAL from panoramic radiographs. With this method, the prevalence of current or treated periodontitis in this study population was 65%. There is recent evidence on the association of periodontitis with overall cancer mortality.[45] However, previous results of studies of periodontitis' associations with serious infectious complications, like septicaemia, in adults with leukaemia are contradictory.[46,47] In our study, the prevalence of periodontitis pre-HSCT in HSCT recipients who deceased within 6 months post-HSCT was slightly higher in comparison with survivors, but the difference was not statistically significant. It should be noted that the method of determining the presence of periodontitis is inaccurate and can lead to underestimation of the effect of periodontitis on post-HSCT comorbidity and survival, and these results must be observed with caution. This RAL based manner, used also in our previous study, was used to keep the dental visits as short as possible and to avoid bacteraemia and infectious complications prior to the HSCT.[41]

Some of the HSCT recipients have received therapies for their underlying diseases already for years, which could have influenced the oral health pre-HSCT. However, when divided into groups according to time from diagnosis (under 1 year, 1-5 years, over 5 years), there were no statistically significant differences between these groups in the oral health parameters (results not shown). However, a study by Busjan et al (2017) with a limited number of patients with newly diagnosed acute leukaemia had poorer oral health parameters already prior to any treatments when compared with healthy controls.[48] Based on the current and previous studies the diagnosis and preceding therapies cannot completely explain the poor oral health but warrant further studies.

In this study, a considerable loss in the study population was observed. 269 HSCT recipients were included in the study pre-HSCT. However, only 158 HSCT recipients were examined 6 months post-HSCT, 116 participated 1 year post-HSCT and only 57 HSCT recipients 2 years post-HSCT. 101 HSCT recipients deceased during the observation period. Thus, mortality explains only a part of the loss in HSCT recipients. HSCT recipients are referred to University Hospital Basel for HSCT from different centres located at some distance. Many HSCT recipients had difficulties to travel to Basel and

Number of teeth (±SD)			DMFT index (±SD)		
SSFR ≤0.7 mL/min	SSFR >0.7 mL/min	*P*-value	SSFR ≤0.7 mL/min	SSFR >0.7 mL/min	*P*-value
23.9 (7.4)	25.2 (6.4)	0.26	19.0 (7.6)	18.8 (7.8)	0.81
23.9 (8.0)	26.1 (5.2)	0.17	19.4 (7.5)	18.6 (7.6)	0.55
24.3 (7.7)	25.5 (5.8)	0.71	18.2 (8.1)	18.9 (6.9)	0.67
20.7 (7.6)	27.0 (4.9)	0.001	23.5 (5.6)	17.9 (7.1)	0.02

had a dentist in their home district, so follow-up was not done in our department. The loss in the study population may cause bias in the results, but the authors feel that this does not skew the primary outcomes.

In conclusion, hyposalivation and caries were associated with a lower rate of survival within 6 months post-HSCT. Further studies are needed to confirm this finding. Additionally, hyposalivation pre-HSCT was associated with an increased DMFT score and a lower number of teeth 2 years post-HSCT. The use of SSFR measurement as a cheap and easy predictor for higher risk of oral comorbidity can be recommended.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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9 DISCUSSION AND CONCLUSIONS

9.1.1 Dental treatment needs in general

The studies revealed that oral treatment needs were high and approximately 80% of patients had either caries or RAL > 3mm or both. This is in accordance with the findings of previous studies, which have shown that more than 90% of patients have some oral disease or need for dental treatment before HSCT [9, 45, 50]. Furthermore, in another study, approximately 50% of the 86 HSCT recipients had decayed teeth and needed oral hygiene instruction [51]. However, it is not possible to make a precise comparison between studies, as many parameters differ (e.g., the categories for oral disease and disorder, outcome variables, and the non-homogenous patient groups). The scarcity and heterogeneity of studies about common oral diseases among HSCT recipients has been noted in previous reviews, guidelines, and a report about caries and periodontitis in cancer survivors [63, 102, 143]. For example, the mean age of the participants in the different studies listed in Table 3 is notably varied (mean range 32-53 years). It is well-known that oral health reduces with age, and the oral health of younger study participants was better than that of older adults.

It can be assumed that previous cancer therapies may have weakened the oral health of some patients prior to HSCT, as, in the preceding years, they may have received different therapies (e.g., several chemotherapy cycles and medications). While the results of studies on the influence of chemotherapies on salivary flow rates in cancer patients are contradictory and limited, as stated in a recent review article [39], this thesis shows that patients with newly diagnosed haematological disease had worse values for oral health parameters when compared to controls, supporting the data from two other recent studies [42, 43]. Thus, previous cancer therapies cannot – at least not entirely – explain poor oral health before HSCT.

9.1.2 Hyposalivation and its secondary consequences

A novel finding of the second sub-study (8.2), with its remarkable number of patients, SSFR was observed to be lower in patients with newly diagnosed haematological malignancy or disease than in controls. Similar results have been observed in a small study of 24 patients conducted in the 1990s [44]. In the first sub-study (8.1), the mean SSFR was significantly lower in the patient group when compared to controls. In the longitudinal study (8.3), hyposalivation was common and 34% of the patients in the

longitudinal study (8.3) had SSFR ≤0.7ml/min. Likewise, the high prevalence of hyposalivation before HSCT was supported by a study of 228 allogeneic HSCT recipients [103]. Previous studies have observed that SSFR decreases after HSCT and returns back to pre-HSCT levels one year post-HSCT [102, 103].

No associations were observed with diagnosis, medications used, number of chemotherapies, or number of days from diagnosis with SSFR; and the reasons for the lower SSFR remain unclear and needs further investigation. The effect of chemotherapy to salivary flow rates has been assessed in previous studies but, as shown in a review article, the effect remains unclear and the results are contradictory [39]. The psychological effects of stress, anxiety, and depression are commonly experienced by HSCT recipients before and during the transplantation process [53]. These factors might have an influence on SSFR and should be considered a possible cause of salivary flow reduction.

As some of the HSCT recipients suffer from reduced salivary flow rate even decades after HSCT [103], they should be provided with intensive preventive care and regular oral examinations. A study of patients with palliative cancer care showed that oral comorbidities were common, but the information about oral adverse effects of cancer therapies was insufficient and only 30% had received instructions and information on the importance of oral hygiene during and after therapies [141].

9.1.3 Caries and DMFT

The WHO supports the diagnosis of caries lesions in epidemiological studies if the surface of teeth is softened or a cavity is present. Early stages of caries are thus not recommended for inclusion.

The prevalence of cavitated lesions or lesions with soft surface in this thesis varied from 33% to 44%, falling into the lower range of the findings from other studies (see Table 3). In addition, in the second sub-study (8.2), caries was more common among patients with newly diagnosed haematological disorder or malignancy and before HSCT than among the controls. Previous such comparisons of haematological adult patients and controls are very sparse. However, the results are supported by a study in which 39 newly diagnosed AL patients had significantly more caries and fewer teeth than the healthy control group [43].

In some studies (Table 3), the very high (up to 67% [47]) prevalence of caries or the difference between compiled caries and required fillings raises the question of whether early stage decays were also included. Occasionally, the studies separately categorised carious teeth and required fillings [45, 50, 51]. Indeed, fillings may be needed due to reasons other than caries, such as a chipped tooth or lost filling, which indicates previous caries or disorders other than active caries, such as erosion and trauma. However, the guidelines followed for clinical oral diagnoses in those studies were often not described. The reason for higher caries prevalence at the time of diagnosis warrants further study.

The patients in this thesis received chemotherapy as part of HSCT. The prevalence of caries in cancer survivors was reported to be the highest for those who received chemotherapy, followed by those who underwent irradiation or a combination of the two [143]. The difference in caries prevalence could be due to the patient group receiving only radiation also consisting often of patients with head and neck cancer. The treatment protocols for eliminating possible oral foci before cancer treatment are more aggressive for patients with head and neck cancer, leading to higher DMFT due to missing teeth; but if oral foci elimination and intensive preventive approaches succeed, this leads to a decreased incidence of caries.

Longitudinal studies about common oral diseases among HSCT recipients are very sparse and follow-up times have been short, comprising only months. In contrast, at the 24-month follow-up in the third sub-study (8.3) of this thesis, it was observed that the DMFT index score was statistically significantly higher in HSCT recipients with hyposalivation than in those with normal SSFR. In the studies of this thesis, DMFT index was used to determine past and present cariological infections in HSCT recipients, and the incidences of new caries were also calculated. An earlier study of 36 HSCT recipients reported a statistically significant increase in DMFT index score at six months post-HSCT [46]. The third sub-study (8.3) did not confirm the previous findings, as no significant difference in DMFT index was found six months after HSCT. Likewise, two studies with a 100-day follow-up found no changes in DMFT index or increase in new dental caries lesions in this short time period [126, 144]. The findings of the third sub-study (8.3) support the hypothesis that salivary measurements could be used as a potential predictive tool to detect oral comorbidities during and after HSCT. As hyposalivation was associated with increased DMFT index, it could be viewed as a risk factor for deterioration of oral health, eventually leading to tooth loss and expensive oral rehabilitation after HSCT. Additionally, although the observed caries prevalence was consistently higher in HSCT recipients with hyposalivation at all study time points, the

results were not statistically significant, except for HSCT recipients with hyposalivation pre-HSCT. However, the results may be underestimating the cariological problems in HSCT recipients post-HSCT, as all the patients were assigned to guidance and intensive prospective oral disease prevention programmes recommending use of extra fluoride and oral healthcare instructions during and after HSCT. Nevertheless, the oral health parameters worsened among HSCT recipients with hyposalivation, while these preventive measures are expected to prevent caries and reduce the effects of hyposalivation [63, 97, 140, 145].

9.1.4 Periodontitis

According to WHO, almost 50% of adult population has at least some signs of periodontitis and almost all have signs of gingivitis [4]. The prevalence of periodontitis among both patients and controls in the studies of this thesis is in line with WHO data. Periodontal disease causing low-grade inflammation has been found to be associated with specific types of cancer (e.g., oral, oesophageal, and gastric) [6]. The survival of cancer patients with periodontitis was decreased [5]. Among patients with haematological cancer, the data on periodontitis prevalence are sparse, and consistent associations between increased risk of haematological malignancies and periodontitis have not been found [6]. Plaque accumulation causes periodontal inflammation such as bleeding and attachment loss in the normal population. It was hypothesised in a previous study of leukemic patients that poor periodontal parameters and bleeding could be correlated with haematological parameters, though no statistically significant results were found. As among the healthy population, an association was found between plaque accumulation and poor periodontal parameters [146]. In one cohort study (n = 48 375), a significant increase in bone loss was found (measured by radiographs) in non-Hodgkin's lymphoma patients, but other types of haematological cancer had no significant association with bone loss [147]. Furthermore, the same group later updated the study and found periodontal disease to be a risk factor for non-Hodgkin's lymphomas [7]. In this thesis, there was no statistically significant variance in prevalence of periodontitis (RAL > 3mm) for different haematological diagnoses, and a higher periodontitis prevalence was not found among patients with non-Hodgkin's lymphoma when compared to controls or other haematological malignancies. Thus, this thesis does not support previous findings based on similar diagnostics methods. However, this could be due to the smaller patient population in this study. Moreover, periodontal diagnosis in this thesis was based on radiographs, which can underestimate the early stages of

periodontal disease and do not provide as accurate data as when combined with clinical diagnostics. However, both cancers and periodontitis have many common and different confounding factors, which make analysis of the associations challenging.

Several studies have investigated the association of periodontal health before HSCT with mucositis [8-10]. Professional dental care and instructions for intensive oral hygiene were associated with shorter and less severe grade of mucositis [10, 27, 94-96]. Mucositis can be life threatening, lengthen hospital stays, and cause discomfort for the patient. As the prevalence of periodontal problems is high, as shown in the studies of this thesis and elsewhere, recommendations should be followed for early oral examination and necessary periodontal interventions. Furthermore, positive outcomes for periodontal health after HSCT due to intensive preventive approaches and guidance for patients have been reported [9, 94].

It should be noted that the results of some previous studies may be unreliable. The very low prevalence of periodontitis (0.6% and 16% [48, 110]) is far from that in the general adult population, according to WHO [4]. Thus, the study showing an association between periodontitis and infection complications during HSCT must be treated with caution, despite its sample size being large [48]. In the third sub-study (8.3) of this thesis, an association was not seen between periodontitis prevalence and survival at six months, and there was no difference in periodontitis prevalence between patient and normal populations.

9.1.5 Oral GvHD

In the third longitudinal study (8.3), hyposalivation was not associated with acute or chronic GvHD or oral manifestation of GvHD. However, cGvHD has been found to affect salivary glands and lead to salivary dysfunction after the onset of GvHD [101, 148, 149]. Thus, it has been hypothesised that salivary gland involvement could be a separate manifestation of GvHD with or without oral mucosal signs, despite their anatomical proximity [122, 125]. In future studies, oral mucosal and salivary gland GvHD involvement should be investigated independently to clarify this issue. As the prevalence of hyposalivation was high before HSCT and the cytotoxic effects of chemotherapy and irradiation causing damage of salivary glands, involvement of GvHD is certainly not the only reason for reduced salivary flow rates. However, in this study, the SSFR of HSCT recipients with severe cGvHD did not return to the initial level within the 24 months. This

is in line with findings of previous studies, where malfunctions of salivary glands were reported in patients with cGvHD [101, 148, 150].

9.1.6 Oral health and survival

The age- and sex-adjusted hazard ratio (HR) of dying within six months post-HSCT was almost twice as high in the hyposalivation group when compared to the group consisting of HSCT recipients without hyposalivation pre-HSCT. Previous studies have found associations between hyposalivation, frailty, and mortality. However, these studies were performed among older people with different medical backgrounds [151-153]. It could be assumed that patients with longer history of cancer treatment have decreased SSFR. However, surprisingly, the SSFR was also significantly lower among patients with newly diagnosed haematological disorders or malignancy. The use of SSFR as a predictor of survival needs further research.

Caries was more common pre-HSCT in deceased patients than among recipients who survived more than six months ($p < 0.05$). High caries prevalence is related to low socio-economic status and there is some evidence that low socio-economic status could have a negative impact on HSCT outcomes [4, 154]. Caries is also associated with poor life-style habits, which could indicate poor overall health behaviours and delayed seeking of treatment for symptoms of the haematological malignancy and disorder. This could lead to delayed diagnosis and disease progression, thus worsening the prognosis. High caries prevalence could also be associated with poor oral health habits. Lack of regular tooth and oral cleaning could cause a shift to a more pathogenetic oral environment. Previous studies have found that good oral hygiene reduces the severity of mucositis and shortens its length. In the case of inadequate oral hygiene, these patients might have increased risk of mucositis, which can be lethal itself, and ulcerations caused by it can act as ports of infection [10, 47, 94]. The information about the socio-behavioural status and oral health habits of the patients in the studies of this thesis was not available, which could have verified this issue. Therefore, the reason for the lower survival rate among patients with higher caries prevalence could not be clarified.

A recent cohort study found associations between periodontitis and overall cancer mortality [5]. In the third sub-study (8.3), periodontitis was somewhat higher pre-HSCT in patients who were deceased within six months after HSCT than among survivors, though the difference did not reach statistical significance. The method used in this thesis to determine the presence of periodontitis from radiographs could be considered somewhat

inaccurate and could lead to underestimation of the effect of periodontitis on post-HSCT comorbidity and survival. Thus, these results must be observed with caution.

9.1.7 Acute oral infections

Studies in the 1980s and 1990s found that infections of oral origin were common during HSCT [60, 66, 68, 69]. However, oral health has significantly improved in Western Europe and the oral health of the average HSCT patient can be assumed to have improved since the 1980s [4]. Even more important for the increased success of HSCT are the improvements achieved in HSCT procedures in recent decades, leading to increased survival rates [23]. In the first and second sub-studies (8.1 and 8.2), symptomatic acute oral infections were found among 5.4-6.3% patients pre-HSCT and in none of the controls. The results are in the same range of those of a study among autologous HSCT recipients and patients who received high-dose chemotherapy, as 6.4% had acute infections before therapy began [49]. This supports the guidelines for early as possible oral examination to treat and eliminate these obvious infection foci before HSCT.

In a prospective study of 86 patients with haematological malignancy, it was found that patients with incomplete dental interventions had statistically significantly more frequent inflammatory complications during chemotherapy. A positive oral origin blood culture was found in one patient, but without any oral signs. In no cases was chemotherapy interrupted or postponed due to odontogenic infection [65]. It must be noted that the patients, who still had possibly untreated oral foci could not be treated because chemotherapy took priority, due to the stage of the haematological cancer, which might itself cause higher risk for complications. However, in contrast, another recent study found no difference in risk of bacteraemia during and after HSCT among patients with compromised dental status and among those whose dental treatment needs were met [71]. Additionally, non-symptomatic chronic oral infections could be left untreated, as they probably do not cause infections during HSCT [49, 77]. There are many reasons why the spread of oral infections to systemic infection is today significantly less common than in the 1980s; for example, oral health in general has improved in recent decades, and patients are provided with prophylactic anti-microbial medications. Infections as a cause of death among HSCT recipients have significantly decreased [23]. In the third sub-study (8.3), the reason for death was in most cases marked as HSCT-related or due to the progression of the haematological disease. Infections of oral origin were not

compiled, and similar results were found in a recent study where oral infections were not associated with infectious complications [77].

9.2 Clinical relevance of the studies and summary

The results of this thesis could be used to assess the oral health of HSCT recipients. The importance of improving treatment protocols to offer good, supportive care to patients with severe haematological malignancies and disorders has been shown. The high prevalence of common oral diseases and disorders before and after HSCT among these patients has been observed, which supports the guidelines for oral care interventions among patients before and after HSCT.

The oral health of patients with a newly diagnosed haematological malignancy and disease and patients with upcoming HSCT was investigated, and their respective dental treatment needs were found to be substantial. Caries, acute infections, and DMFT index were high, when compared with control groups. The longitudinal changes of oral health parameters were also assessed and patients with hyposalivation can be considered at an elevated risk of further oral health problems (higher caries prevalence, elevated DMFT index, and reduced number of teeth). Hyposalivation and caries were also associated with lower survival rate.

Based on these results, it is recommended that oral health be examined at the time of diagnosis, as the patients are strongly in need of oral and dental treatment.

The novel findings for reduced salivary flow rates in patients before HSCT, compared to the controls, and their possible association with survival will raise new questions for future research. The importance of saliva should not be underestimated and patients with reduced SSFR should be informed of the necessary preventive approaches to maintain oral function before HSCT. The use of SSFR measurement as a cost-effective and easy predictor of higher risk of oral comorbidity is recommended.

9.3 Limitations

The heterogeneity of the study population can be considered as a limitation of this study. The diagnoses varied, and ALL was the most common, though several others were included (e.g., chronic leukaemia, MDS, and SAA). However, to diminish this bias in the

third sub-study (8.3), patients' oral health parameters were compared according to their diagnoses and no statistically significant differences were found. It may be that more precise results could be achieved by working with larger patient groups, with analyses conducted separately for each diagnosis.

In the longitudinal study, there was a notable loss of patients. Mortality explains only a part of this loss, as 101 HSCT recipients died during the 24-month study period. The greater involvement of the patients in the follow-up and larger study groups could strengthen this analysis, as mentioned above. Additionally, as the longitudinal data collection was retrospective, when missing follow-up was noted, patients could not be called in for examinations as the relevant timepoints had passed.

Moreover, the information about the patients' socio-behavioural status, oral hygiene habits, and regularity of dentist visits before the first intervention in the UZB OHM clinic was unknown.

In general, the patients should have been sent to the oral examination; but the examinations could not be done if the general health status of the patient did not allow her to be transported to the dental clinic. This might have excluded some of those with worse general health conditions at the time of diagnosis or pre-HSCT. This is, however, a minor proportion of the patients and probably did not cause bias to the results.

The patients were often neutropenic and anaemic; thus, the diagnosis of present or previous periodontitis was based on radiographs and RAL. This method can lead to inaccuracies in the diagnosis of periodontitis, preventing determination of the activity of the disease. Early signs of periodontal disease and gingivitis cannot be recorded using this method. This limitation could be considered a weakness of the methodology.

9.4 Implications for future research

It remains unclear why worse oral health was observed among patients with newly diagnosed severe haematological disorder or malignancy, compared with controls, and further studies are thus needed. The socio-behavioural aspect and history of dental treatments and habits could help to identify possible reasons for this difference or reveal confounders.

Further longitudinal studies are needed to gather evidence-based data on tooth sensitivity. This is commonly mentioned in the guidelines, but as yet, no studies have sought evidence from HSCT patients.

The use of saliva as a predictor of survival warrants further investigation. Medications, age, or other analysed factors do not reveal the reason for lower SSFR in the deceased patients, and additional investigations are needed to clarify the issue. The impact of periodontal disease or gingivitis on survival should be studied using a more accurate diagnostic method. The role of acute and chronic oral infections in patient death should be explored using large, contemporary data sets.

10 CONTRIBUTION TO THE PhD PROJECT

I contributed to the conception and design of this thesis, with the help of my supervisors. In particular, I wrote the research proposal.

I have participated in the collection of the medical and dental data from the medical records for the retrospective data.

I prepared the ethical approval for the ethics committee for the prospective data collection. Additionally, I recruited the patients for the prospective part and collected all the medical and dental data that were used. I was also responsible for the processing and matching of the data.

I participated in data analysis and interpretation. For the first publication, I assisted in the statistical analyses. For the second publication my responsibilities were increased, and I conducted statistical analyses – partly on my own and together with the supervisors. Finally, for the third publication, I planned and contributed the statistical analyses, working primarily alone, with some help from a statistician.

I carried out the literature research and background reading for the manuscripts and thesis. I drafted all the manuscripts. Furthermore, I was the corresponding author and completed the submission procedure for all three publications.

I also made poster presentations and presented our results in two congresses.

11 CURRICULUM VITAE

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