Delayed Socket Healing After Dental Extraction in Patients Undergoing Myelosuppressive Chemotherapy for Hematological Malignancy: Incidence and Risk Factors

Akashi, Masaya ; Kishimoto, Megumi ; Kusumoto, Junya ; Yakushijin, Kimikazu ; Matsuoka, Hiroshi ; Komori, Takahide

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Delayed socket healing after dental extraction in patients undergoing myelosuppressive chemotherapy for hematological malignancy: Incidence and risk factors

Masaya Akashi DDS PhD*†[1], Megumi Kishimoto DDS‡[1], Junya Kusumoto DDS‡[1], Kimikazu Yakushijin MD PhD§[2], Hiroshi Matsuoka MD PhD‖[2], Takahide Komori DDS PhD¶[1]

† Assistant Professor, ‡ Graduate fellow, § Lecturer, ‖ Associate Professor, ¶ Professor and Chairman

[1]Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

[2]Department of Medical Oncology/Hematology, Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

*Correspondence to:

Masaya Akashi DDS PhD

Department of Oral and Maxillofacial Surgery

Kobe University Graduate School of Medicine

7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan

Tel.: +81-78-382-6213; Fax: +81-78-382-6229

E-mail: akashim@med.kobe-u.ac.jp

Abstract

Purpose: The purpose of this study was to measure the frequency and identify factors associated with delayed socket healing after dental extraction in patients undergoing myelosuppressive chemotherapy for hematological malignancy.

Materials and Methods: This prospective cohort study focused on delayed healing after extraction in patients with hematological malignancy. Sockets with delayed healing were defined as those with intense pain and bone exposure 1 week postoperatively. Patients with and without delayed socket healing were compared using the Fisher's exact test and the Mann–Whitney U-test with some variables. Receiver operating characteristics curve analysis was conducted to define cutoff values for delayed healing.

Results: One hundred ninety-four dental extractions in 93 patients with a median age of 64 years (range, 20–85 years) were analyzed. The incidence of delayed socket healing was 7.5 % (7 of 93 patients). There was no postoperative bleeding. Older age, type of hematological malignancy (acute leukemia), shorter time between dental extraction and initiation of chemotherapy, low platelet count or hemoglobin level, requirement for red cell concentrate or platelet transfusion, and absorbable hemostatic agent use were significantly associated with the occurrence of delayed socket healing. Platelet and hemoglobin cutoffs were $4.6\times10^4/\mu L$ and 7.7 g/dL, respectively.

Conclusions: Although dental extraction can be safely performed in patients undergoing myelosuppressive chemotherapy for hematological malignancy, oral surgeons should understand the potential risk for delayed socket healing. When considering dental extraction, patients with hematological malignancy and low hemoglobin or platelets should be informed about the possibility of delayed socket healing.

[246/300 words]

Introduction

Myelosuppressive chemotherapy for hematological malignancy places patients in an immunocompromised condition. The development of infection during chemotherapy for hematological malignancy can be life-threatening. The oral cavity is a port of bacterial entry for systemic infections.[1] Although elimination of odontogenic foci is recommended before initiation of chemotherapy,[2] complete elimination is sometimes impossible because of time limitations.[3] Another problematic issue is the lack of criteria for deciding appropriate dental management prior to myelosuppressive chemotherapy.[4] Some studies have established dental intervention protocols for patients with hematological malignancy, including indications and contraindications for dental extraction.[5,6] For example, avoidance of invasive procedures, even periodontal probing, has been recommended during chemotherapy that induces neutropenia.[2]

Sequelae and complications such as bleeding, pain, and infection after dental extraction in patients with hematological malignancy are of great concern for oral and maxillofacial surgeons.[1] Raut et al.[1] evaluated 69 dental extractions in 388 patients with hematological malignancy and reported a resulting complication rate of 13 % (9/69 teeth). These complications included delayed medical treatment for hematological malignancy, bleeding, and platelet transfusion. In another study by Fillmore et al.[7] that included 200 dental extractions in 68 patients with hematological disease and concomitant thrombocytopenia (platelet count of $10\times10^4/\mu L$ or less at the time of consultation or extraction), 7.4 % of patients (5/68) had postoperative bleeding that was significantly associated with lower platelet levels; the rate of postoperative infection in that study was 2.9 % (2/68 patients).

Delayed healing, related chiefly to localized osteitis or infection at the surgical site, is the most frequent complication after dental extraction, affecting 10 % of patients who undergo removal of third molars [8]. Localized osteitis is also known as dry socket, alveolar osteitis, necrotic socket, and fibrinolytic alveolitis.[9] The most common risk factors for developing dry socket include patient age,

history of previous infection, and difficulty of dental extraction.[10] Immunocompromised state as well as smoking and use of oral contraceptives are additional risk factors associated with true alveolar osteitis.[9]

In addition to prophylactic dental extraction prior to chemotherapy, removal of infected teeth after initiation of chemotherapy is sometimes necessary to treat acute inflammation and pain. In patients with myelosuppression, delayed socket healing can occur after dental extraction, with problematic symptoms of dry socket, such as putrid odor and intense pain that radiates to the ear and neck.[11] The purpose of this study was to identify the incidence and risk factors for delayed socket healing after dental extraction in patients undergoing myelosuppressive chemotherapy for hematological malignancy. The investigators hypothesize that the myelosuppressive state caused by chemotherapy affects socket healing. The specific aim of the study was to determine the cutoff values of hematological parameters for prediction of delayed socket healing.

Materials and methods

STUDY DESIGN

To address the research purpose, the investigators designed and implemented a prospective cohort study focusing on delayed socket healing after dental extraction in patients with hematological malignancy. The study population was composed of hematological malignancy patients presenting for evaluation of dental condition and oral management in the Department of Oral and Maxillofacial Surgery of Kobe University Hospital between October 2012 and October 2016. The inclusion criteria were confirmed cases of patients with hematological malignancy who were introduced to our department. Patients were excluded if they were younger than 20 years or did not receive chemotherapy. The ethics committee of Kobe University approved this study. Written informed consent was obtained from all participants.

DENTAL INTERVENTION PROTOCOL

Hematologists generally referred patients to our department for pre-therapeutic assessment of dental condition and provided information about diagnosis, regimen and schedule of chemotherapy, and myelosuppression grade of chemotherapy, details of which have been described in our previous reports.[2,6,12] This grading system stratifies chemotherapy regimens for hematological malignancy into four grades according to the severity of myelosuppression, as follows:

Grade A (mild myelosuppression): Oral chemotherapeutic agents and infusions performed for outpatients (e.g., rituximab alone for malignant lymphoma).

Grade B (moderate myelosuppression): The representative regimens were consolidation for leukemia, or CHOP for malignant lymphoma, among others.

Grade C (severe myelosuppression): The representative regimens were remission induction for acute leukemia, among others.

Grade D (severe myelosuppression and persistent immunodeficiency): Myeloablative or reduced-intensity conditioning for hematopoietic stem cell transplantation.

At the first visit, the attending doctors assessed dental condition with medical inquiries, intraoral examination, and panoramic radiographs in all patients. The attending dental hygienist provided oral hygiene instruction to maintain a plaque index < 20 %. According to our established dental intervention protocol for patients with hematological malignancy,[6] caries, residual roots, and ill-fitting prostheses were conservatively treated. Teeth with marginal periodontitis and probing depth greater than 8 mm, severe mobility, or severe inflammation; teeth with apical periodontitis and periapical radiolucency greater than 5 mm on dental x-ray image or symptoms such as pain; and partially erupted teeth with ongoing or past history of symptoms were removed. All dental extractions were performed under local anesthesia with prophylactic antibiotic administration.[6] Although our goal was to complete all dental interventions according to our protocol, there were patients in whom elimination of odontogenic foci (i.e., removal of teeth with severe marginal periodontitis) could not be completed because the

progressive state of their disease required immediate initiation of chemotherapy. For patients who did not finish all dental interventions, conservative treatments were performed, such as professional mechanical tooth cleaning[13] and local irrigation to prevent acute infection of untreated odontogenic foci during chemotherapy.

POTENTIAL PREDICTOR VARIABLE

We reviewed the following preoperative patient parameters as the predictor variables: age, sex, type of hematological malignancy, smoking history, presence of diabetes mellitus, *de novo* status, myelosuppression grade of chemotherapy, timing of dental extraction, time interval between dental extraction and scheduled initiation of chemotherapy, administration of granulocyte colony-stimulating factor, and transfusion of red cell concentrate (RCC) or platelets. To determine the cutoff values of hematological parameters for prediction of delayed socket healing in patients undergoing chemotherapy for hematological malignancy, results of blood exam just before dental extraction were assessed. In patients who received transfusions, results of blood exam before transfusion were used for evaluation. Indications for transfusion were hemoglobin below 7 g/dL for RCC transfusion and platelets below $5\times10^4/\mu L$ for platelet transfusion. It is noteworthy that although RCC was transfused for anemia caused by hematological malignancy and myelosuppressive chemotherapy, platelets were transfused for the purpose of dental extraction.

Excessive trauma and surgical difficulty can result in delayed healing and the development of alveolar osteitis following dental extraction.[9] Therefore, tooth extraction procedures were divided into two groups according to the necessity for bone removal. The use of an absorbable hemostatic agent, mandibular wisdom tooth extraction, and the number of extracted teeth were also evaluated as surgical factors. Oxidized regenerated cellulose (ORC) was the only absorbable hemostatic agent used in this study.

OUTCOME VARIABLE

The primary outcome of this study was delayed socket healing in patients undergoing myelosuppressive chemotherapy. Blum et al.[9] reported that alveolar osteitis typically begins 1 to 3 days after dental extraction and that onset is within a week in 95 % to 100 % of all cases. The duration of alveolar osteitis varies to some degree, depending on the severity of the disease, but usually ranges from 5 to 10 days.[9] Cardoso et al.[11] described exposure of the alveolar osseous walls in dry socket with total or partial clot loss, accompanied by continuous, intense, and frequently radiating pain that is not relieved by analgesics. In the present study, all patients who underwent dental extraction were followed up 1 week postoperatively. Extraction sockets with persistent intense pain caused by conditions similar to dry socket or bone exposure 1 week after dental extraction were defined as sockets with "delayed healing." Sockets with delayed healing completely lacked granulation tissue within the socket (Fig. 1). In contrast, "normal healing" was defined as extraction sockets without symptoms, including pain, and with sufficient colonization of granulation tissue 1 week after dental extraction.[14] Follow-up was continued for patients with delayed socket healing; the postoperative course was recorded in the medical charts.

STATISTICAL ANALYSIS

Statistical analyses were performed with R software (R Development Core Team, 2011). The primary endpoint of this study was identification of the incidence and risk factors of delayed socket healing in patients undergoing myelosuppressive chemotherapy. Socket healing was compared between patient groups with Fisher's exact test for discrete variables and the nonparametric Mann–Whitney U-test (two-tailed) for continuous variables. A value of $p < 0.05$ was considered to indicate statistical significance. The secondary endpoint of this study was determination of cutoff values of hematological parameters for the prediction of delayed socket healing in patients undergoing chemotherapy for hematological malignancy. Receiver operating characteristics (ROC) curve analysis was conducted to

define cutoff values for the prediction of delayed healing according to the area under the curve (AUC). The AUC describes how well the predictive model discriminates cases with from without delayed socket healing. The AUC ranges from 0.5 to 1.0, where 0.5 is used as the reference and 1.0 indicates perfect prediction.

Results

During the evaluation period, 104 consecutive adult patients (63 men and 41 women) with a median age of 61 years (range, 20–85 years) presented. Among all 104 patients, 93 (89 %; 52 men and 41 women) with a median age of 64 years (range, 20–85 years) underwent dental extraction. Although most patients underwent prophylactic dental extraction before the initiation of chemotherapy, according to the dental intervention protocol mentioned above, some patients underwent dental extraction after the initiation of scheduled chemotherapy because of intense tooth pain requiring opioid administration. The chemotherapy myelosuppression grades of patients who underwent dental extraction were B (67.7 %), C (11.8 %), A (10.8 %), and D (9.7 %).

Before dental extraction, six patients (6.5 %) received platelet transfusion and five (5.4 %) received RCC. Patients who underwent platelet transfusion had a median hemoglobin of 7.2 g/dL (range, 6.5–10.5 g/dL) and a median platelet count of 3.2×10^4/μL (range, 2.0–5.8×10^4/μL). Patients who received RCC transfusion had a median hemoglobin of 7.0 g/dL (range, 6.5–7.5 g/dL) and a median platelet count of 5.1×10^4/μL (range, 2.0–9.2×10^4/μL). None of the patients had postoperative bleeding after dental extraction.

A total of 194 teeth were extracted in 93 patients; delayed healing occurred in 17 sockets (8.8 %). Seven patients had delayed socket healing, for an overall incidence of 7.5 % (7/93 patients). Although five patients with delayed socket healing achieved epithelization 3 to 6 weeks after dental extraction, the remaining two patients required 1 to 2 years after dental extraction for complete epithelization.

Therefore, the incidence of long-term sequelae such as osteonecrosis-like lesions in this study was 2.2 % (2/93 patients). There was no interruption or delay of chemotherapy for hematological malignancy in any patient because of complications of dental extraction.

The results of the Fisher's exact test for discrete variables and the Mann–Whitney U-test for continuous variables showed that older age ($P = .023$), acute leukemia ($P = .024$), shorter time between dental extraction and initiation of chemotherapy ($P = .021$), use of absorbable hemostatic agent ($P = .017$), lower platelet count ($P < .001$) or hemoglobin ($P = .001$), and preoperative transfusion of platelets ($P < .001$) or RCC ($P = .044$) were significantly associated with delayed socket healing (Table 1).

The ROC curves of hematological parameters to predict delayed socket healing are shown in Figure 2. Cutoffs were 4.6×10^4/μL for platelets (AUC 0.96) and 7.7 g/dL for hemoglobin (AUC 0.86). The ROC curve of patient age showed that the cutoff to predict delayed socket healing was 62 years (AUC 0.758). The ROC curve of the interval between dental extraction and the initiation of chemotherapy showed that the cutoff was 0 days (AUC 0.763), indicating that the incidence of delayed socket healing was significantly higher among patients who underwent dental extraction after initiation of chemotherapy than among those who completed extraction before initiation of chemotherapy. The summary of ROC curves is shown in Table 2.

Discussion

The purpose of this study was to identify the incidence and risk factors for delayed socket healing after dental extraction in patients undergoing myelosuppressive chemotherapy for hematological malignancy. The authors hypothesize that the myelosuppressive state caused by chemotherapy affects socket healing. The specific aim was to determine hematological cutoff values for prediction of delayed socket healing. This study showed that the incidence of delayed socket healing was 7.5 %. Older age, type of

hematological malignancy (acute leukemia), shorter time between dental extraction and initiation of chemotherapy, low hemoglobin or platelet count, requirement of preoperative transfusion of platelets or RCC, and use of absorbable hemostatic agent were associated with an increased risk of delayed socket healing. Platelets below $4.6\times10^4/\mu L$ and hemoglobin below 7.7 g/dL were cutoffs for prediction of delayed socket healing.

Before chemotherapy for hematological malignancy, dental evaluation with elimination of odontogenic foci is recommended.[15] However, *de novo* hematological malignancy patients are often already immunocompromised because of untreated cancer. Moreover, patients occasionally experience intractable pain caused by odontogenic foci after the initiation of myelosuppressive chemotherapy. Dental oncologists must decide whether to eliminate causative odontogenic foci with consideration of patients' myelosuppressed state.

A few studies have investigated complications after dental extraction in patients with hematological malignancy.[1,7,16] Raut et al.[1] reported that the incidence of bleeding requiring platelet transfusion after dental extraction in patients with hematological malignancy was 2.2 % (2/93 patients). One patient in that study received a platelet transfusion before dental extraction; there were no postoperative infections. Yamagata et al.[16] evaluated dental status between 3 and 492 days before the initiation of hematopoietic stem cell transplantation; in that study, seven symptomatic impacted third molars were extracted in six patients without complications. Fillmore et al.[7] reported a high incidence of bleeding among patients with platelet counts of $2\times10^4/\mu L$ or lower, and therefore defined "very low" platelets as below this threshold. Patients with myeloid leukemia in that study had the lowest mean platelet count ($3.25\times10^4/\mu L$) of all patient diagnoses, because thrombocytes are of myeloid lineage.[7] Henderson et al.[17] advocated for preoperative platelet transfusion to achieve a platelet count of $5\times10^4/\mu L$ for minor surgery or $10\times10^4/\mu L$ for more invasive surgery. Most researchers seem to agree that preoperative transfusion is reasonable to achieve platelet counts of $5\times10^4/\mu L$ for procedures with

minimal bleeding risk.[7] However, the recent guideline for platelet transfusion from the American Association of Blood Banks makes a weak recommendation for prophylactic platelet transfusion only for major elective nonneuraxial surgery in patients with a platelet count less than $5\times10^4/\mu L$ [18]; dental extraction is categorized as minor surgery.[19] Another guideline states that although prophylactic platelet transfusion before dental extraction is not required, transfusion aiming to achieve a count above $1\times10^4/\mu L$ may be reasonable.[20] In the present study, no postoperative bleeding occurred after dental extraction, probably because platelet transfusion was performed in patients with counts below $5\times10^4/\mu L$.

This study selected delayed socket healing after dental extraction as the primary endpoint, because the authors hypothesized that myelosuppression caused by malignancy and chemotherapy might influence socket healing after dental extraction. Low platelet count was the most significant risk factor for delayed socket healing after dental extraction in this study. This finding is similar to the results of Fillmore et al.,[7] who found that low platelet count was significantly associated with surgical site infections. Platelet-derived growth factor and endothelial growth factor have pivotal roles in the natural healing of extraction sockets.[21, 22] It is well known that platelet-rich plasma improves soft-tissue healing of extraction sockets and decreases the incidence of alveolar osteitis and postoperative pain.[22, 23] Platelets themselves contain alpha granules that upon degranulation release cytokines that stimulate cell migration and enhance cellular-level events to expedite wound healing.[24] It is also known that platelet-rich fibrin allows the slow release of cytokines, contributing to the formation and stabilization of blood clots after dental extraction.[25] Platelet quantity and quality are critical because some patients' immune systems sequester and destroy platelets shortly after platelet administration.[7] Fillmore et al.[7] noted little to no improvement in platelet levels after transfusion and recommended that platelets should be transfused in the immediate preoperative phase or intraoperatively to maximize circulating platelets available for hemostasis at the time of surgery. The results of the present study indicate that platelet transfusion is adequate for hemostasis after dental extraction but may not guarantee sufficient socket

healing after extraction in patients with thrombocytopenia. Low hemoglobin was also significantly associated with delayed socket healing in this study. It is well-known that anemia affects wound healing[26] and that hemoglobin decline correlates with deterioration and progression of wounds.[27] Hemoglobin is an essential oxygen transporter to wounds[28] and probably has an important role in socket healing after dental extraction.

The timing of dental extraction was associated with the occurrence of delayed socket healing. Raut et al.[1] divided dental extractions into four periods: before, during, and after chemotherapy, and between cycles. Most patients in that study underwent dental extraction during chemotherapy. Shimada et al.[29] reported that the incidence of surgical site infection in patients who underwent dental extraction before chemotherapy was 3.6 % (1/28 patients); the median time between dental extraction and chemotherapy initiation in that study was 13 days (range, 0–66 days). Although potential sources of infection in the oral cavity should ideally be identified and eliminated before the first chemotherapy cycle, occasionally dental extraction cannot be performed because of a tight chemotherapy schedule.[29] Although it is difficult to decide whether teeth causing inflammation and pain should be removed after scheduled initiation of chemotherapy, there is often no alternative treatment for unrestorable teeth in patients with severe symptoms such as intense pain requiring opioid administration. When deciding to undergo dental extraction after initiation of chemotherapy, patients need to be fully informed about the possibility of delayed socket healing resulting in persistent pain and the risk of secondary osteomyelitis.

There was no significant difference in absolute neutrophil count (ANC) between patients with normal versus delayed healing. In the study of Fillmore et al.,[30] which included 116 neutropenic patients who underwent dental extraction (no patient had an ANC above 1,500/μL), the incidence of complications was 8.6 % (10/116 patients) and all complications were minor, such as delayed healing, surgical site infection, and prolonged postoperative pain. Notably, Fillmore's study reported that delayed healing was not associated with ANC, similar to the results of this study. Because low ANC was

associated with prolonged postoperative pain, it was recommended that careful attention be paid to pain control in patients with profound neutropenia.[30]

Interestingly, the use of an absorbable hemostatic agent was associated with delayed socket healing in this study. The effect of absorbable hemostatic agents on wound healing remains controversial. A previous study in rats concluded that ORC, gelatin sponge, and collagen sponge neither impaired nor promoted soft-tissue wound healing.[31] In contrast, another study found that ORC impeded early bone healing in rabbits, where it caused an increased inflammatory response and impaired osseous regeneration with ongoing residual material in a rabbit tibial defect.[32] We conclude that absorbable hemostatic agents should be used only when continuous bleeding from the bony surface of the extraction socket is present.

There were some limitations in this study. This study had a small sample size and only seven patients had delayed socket healing; therefore, multivariate logistic regression analysis was not conducted. However, this study revealed that the incidence of delayed socket healing after dental extraction in patients who underwent myelosuppressive chemotherapy for hematological malignancy was 7.5 %, an incidence higher than that reported for young, healthy, and nonsmoking male patients (1–4 %).[33] There was no postoperative bleeding in this study. Although dental extraction can be safely performed in patients undergoing myelosuppressive chemotherapy for hematological malignancy, oral surgeons should know the following risk factors for delayed socket healing: older age, type of hematological malignancy (acute leukemia), shorter time between dental extraction and initiation of chemotherapy, low platelet count or hemoglobin, requirement of preoperative transfusion of platelets or RCC, and use of an absorbable hemostatic agent. When deciding to undergo dental extraction, patients with hematological malignancy and low platelets or hemoglobin (specifically, platelets $\leq 4.6\times10^4/\mu L$ or hemoglobin ≤ 7.7 g/dL) need to be informed about the possibility of delayed socket healing. In the future, a large multicenter study should be conducted to be amendable to extrapolation.

Conflict of interests

We have no conflict of interests.

Ethics statement/confirmation that permission of patients was given

The institutional review board for clinical research at Kobe University Hospital approved the consent procedure and the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Figure Legends

FIGURE 1. Representative image of delayed socket healing. This photo was taken 10 days after dental extraction. The socket lacks granulation tissue and there is bone exposure and redness of the surrounding mucosa. The patient had intense pain similar to dry socket.

FIGURE 2. Receiver operating characteristics curves to identify cutoff values of hematological parameters for the prediction of delayed socket healing after dental extraction in patients undergoing myelosuppressive chemotherapy. *A*, The platelet count cutoff is 4600/μL. *B*, The hemoglobin cutoff is 7.7 g/dL. *C*, The age cutoff is 62 years. *D*, The cutoff for the interval between dental extraction and initiation of chemotherapy is 0 days.

Table 1 Predictors of delayed socket healing following dental extraction

Variable	Delayed socket healing		*P* Value
	with (n = 7)	without (n = 86)	
Preoperative factors			
Age (years)	69 (62–76)	62 (20–85)	.023[c]
Sex (male)	4 (57.1)	48 (55.8)	1[d]
Diabetes mellitus	1 (14.3)	8 (9.3)	.522[d]
Smoking	4 (57.1)	45 (52.3)	1[d]
Type of hematological malignancy			.024[d]
Acute leukemia	5 (71.4)	23 (26.7)	
Others	2 (28.6)	63 (73.3)	
Myelosuppression grade of chemotherapy[a]			.442[d]
A (mild)	0	10 (11.6)	
B (moderate)	5 (71.4)	58 (67.4)	
C (severe)	2 (28.6)	9 (10.5)	
D (myeloablative)	0	9 (10.5)	
De novo patients	5 (71.4)	61 (70.9)	1[d]
Time between dental extraction and initiation of chemotherapy (days)[b]	−2 (−6–23)	8 (−4–57)	.021[c]
Hematological parameters			
Hemoglobin (g/dL)	7.4 (6.5–10.5)	10.1 (6.7–15)	.001[c]
Platelet count (10^4/μL)	4.0 (2–12.4)	19.9 (5–67.5)	<.001[c]
White blood cell count (/μL)	4300 (570–14200)	4950 (1100–34800)	.471[c]
Absolute neutrophil count (/μL)	2520 (90–4430)	3125 (90–21576)	.103[c]
Albumin (g/dL)	3.5 (2.3–4)	3.6 (1.4–4.9)	.173[c]
Transfusion before extraction			
Platelets	4 (57.1)	2 (2.3)	<.001[d]
Red cell concentrate	2 (28.6)	3 (34.9)	.044[d]
Granulocyte colony-stimulating factor administration	1 (14.3)	4 (4.7)	.320[d]
Surgical factors			
Number of teeth extracted at once	3 (1–4)	2 (1–7)	.304[c]
Mandibular wisdom tooth extraction	0	15 (17.4)	.593[d]
Bone removal for extraction	1 (14.3)	14 (16.3)	1[d]
Absorbable hemostatic agent use	6 (85.7)	32 (37.2)	.017[d]

Data are reported as median (range) or number (percentage) of study participants.

[a]Details are described in the text.

[b]Positive values indicate days before initiation of chemotherapy; negative values indicate days after initiation of chemotherapy.

[c]Mann–Whitney U test

[d]Fisher's exact test

1 **Table 2** Summary of receiver operating characteristics curves

Variable	Cutoffs	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Platelet count (10^4/μL)	4.6	85.7	100	0.958 (0.876-1)
Hemoglobin (g/dL)	7.7	85.7	86	0.862 (0.718-1)
Age, y	62	100	47.7	0.758 (0.62-0.896)
Time between dental extraction and initiation of chemotherapy (days)[b]	0	71.4	93	0.763 (0.482-1)

2 Abbereviations: AUC, area under the curve; CI, confidence interval.

Figure

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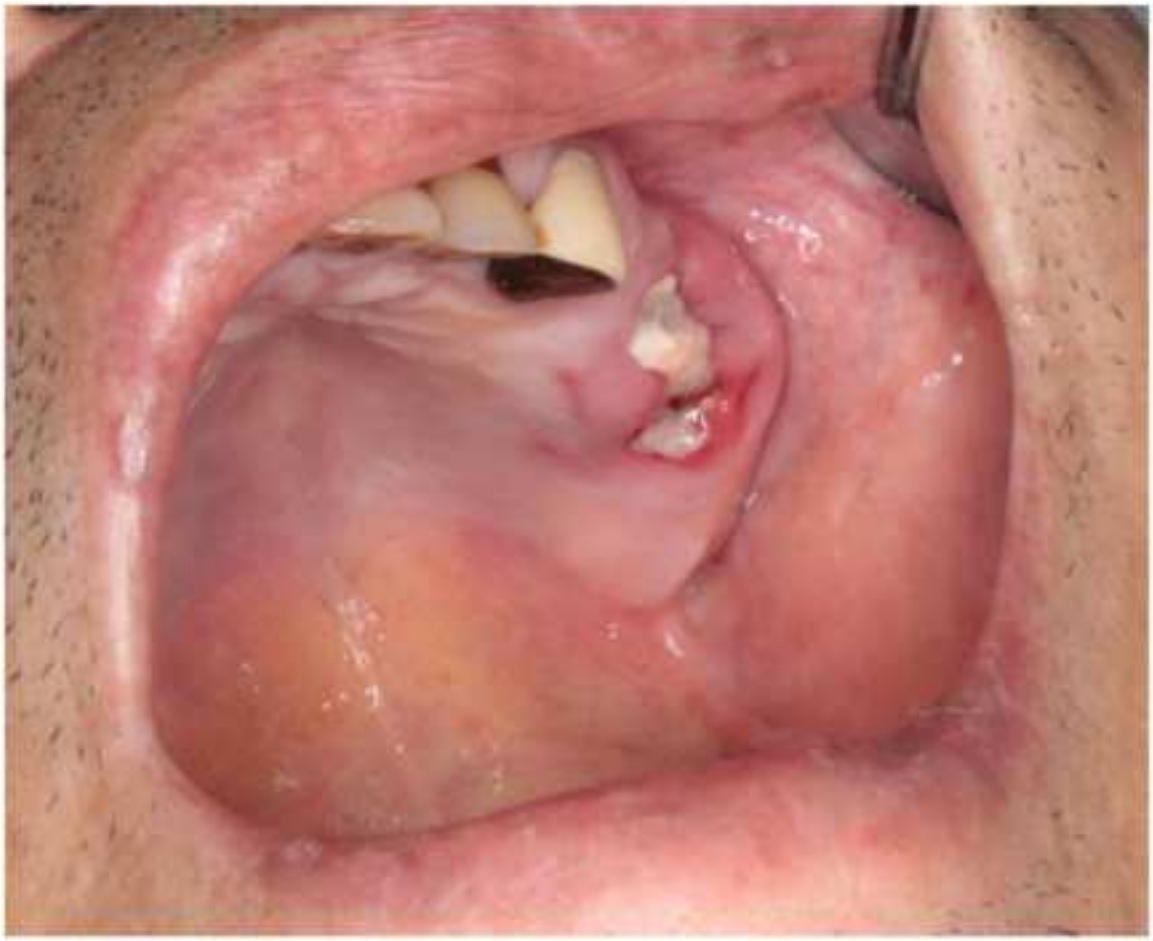

Figure 1

Figure
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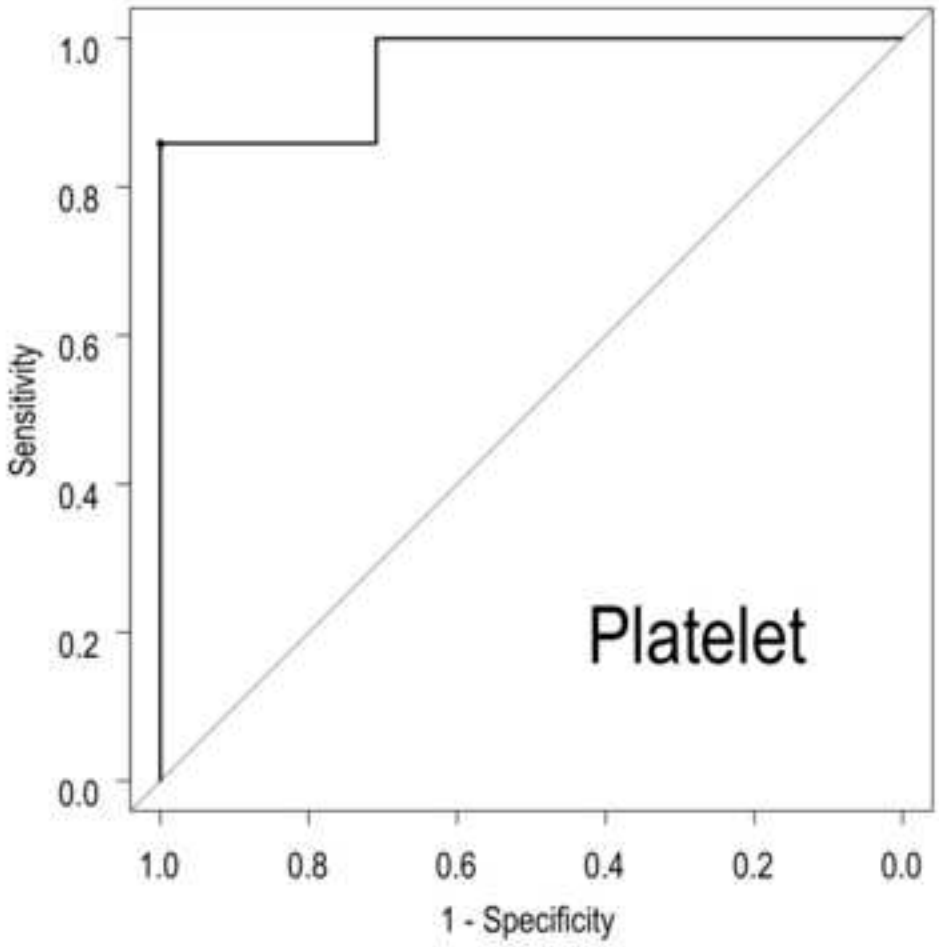

Figure 2

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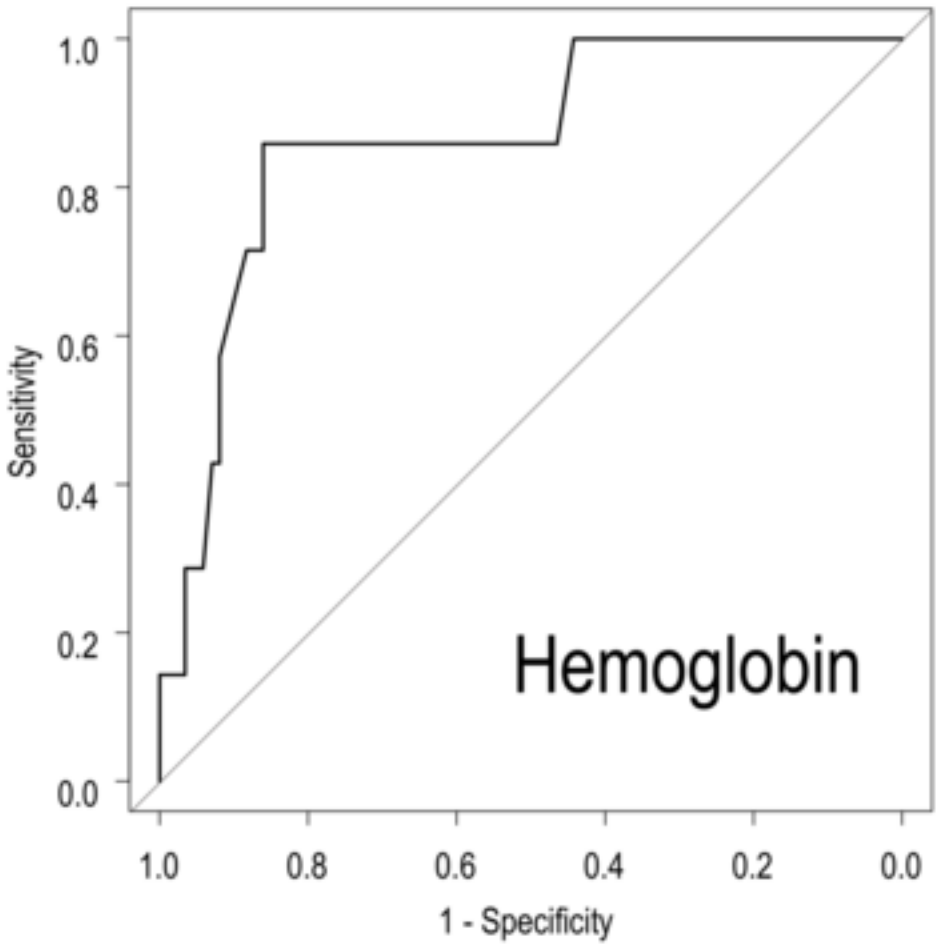

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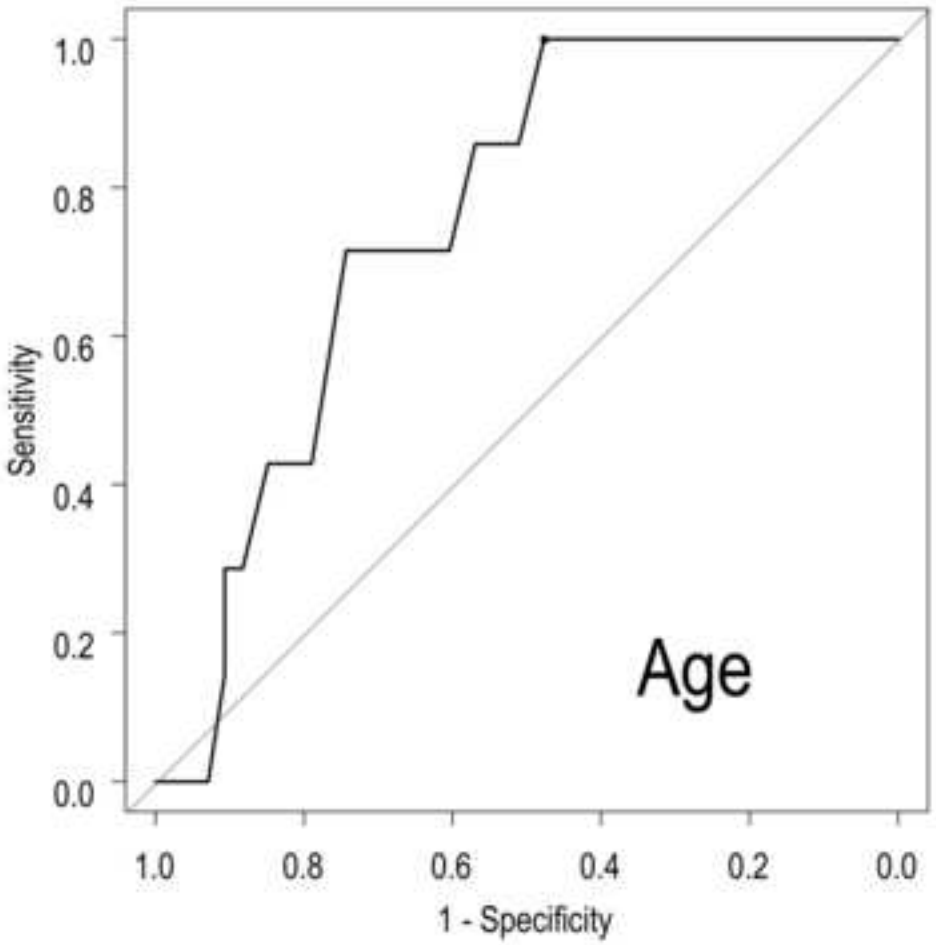

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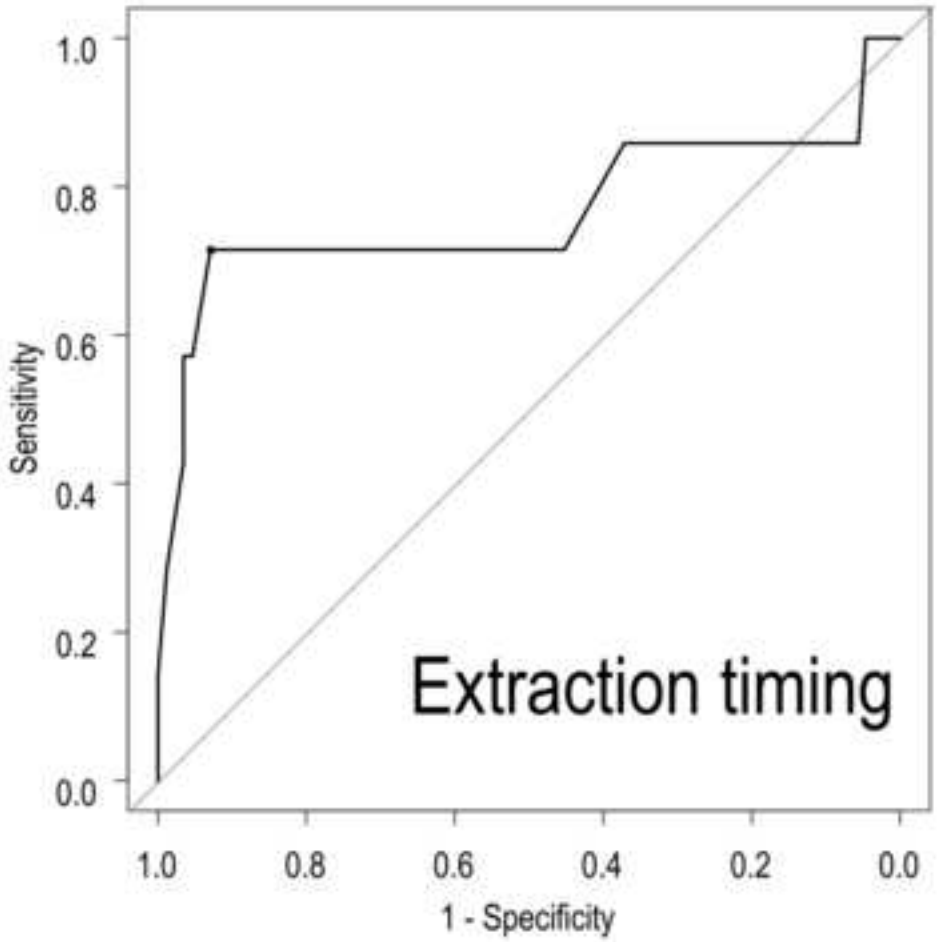

Figure 2