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Development and Validation of Oral Bleeding Risk Scoring System (OBRS) for Predicting Post-tooth-extraction Bleeding in Patients Undergoing Treatment with Warfarin: A Single Centre Study

メタデータ	言語: English 出版者: 公開日: 2020-07-15 キーワード (Ja): キーワード (En): 作成者: FUKUZAWA, Satoshi, HOSHI, Keika, OKAMOTO, Toshihiro, ANDO, Tomohiro メールアドレス: 所属:
URL	http://hdl.handle.net/10470/00032472

TWMUJ 3: 1-10, 2019

Original

Development and Validation of Oral Bleeding Risk Scoring System (OBRS) for Predicting Post-tooth-extraction Bleeding in Patients Undergoing Treatment with Warfarin: A Single Centre Study

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(Accepted October 29, 2018)
(Advance Publication by J-STAGE February 7, 2019)

Introduction: This study aimed to develop an oral bleeding risk scoring system (OBRS) for predicting the post-tooth-extraction bleeding risk in patients medicated with warfarin.

Materials and Methods: We included a derivation cohort of 211 consecutive inpatients from April 1, 2013 to March 31, 2015 and a validation cohort of 63 consecutive inpatients from April 1, 2015 to March 31, 2016 who underwent tooth extraction at Tokyo Women's Medical University hospital. Post-tooth-extraction bleeding was observed in 29 (13.7%) cases in the derivation cohort. Using multivariate logistic analysis, three predictors (international normalized ratio of prothrombin time: PT-INR, drugs, incision) were selected for the final model.

Results: OBRS was derived as follows: PT-INR × 2+drugs+incision. Receiver operating characteristic curves provided area under the curve of 0.77 (95%CI, 0.67 to 0.85) for OBRS, 0.61 (95% CI, 0.50 to 0.71) for HAS-BLED score, and 0.69 (95% CI, 0.56 to 0.79) for PT-INR. The high-risk cut-off OBRS value was 5.08 points. Post-tooth-extraction bleeding was observed in 9 (14.2%) cases in the validation cohort. Sensitivity and specificity were 100% and 90.7%, respectively. The OBRS showed excellent performance with respect to predictor score.

Conculusions: The proposed OBRS showed good performance for predicting post-tooth extraction bleeding in patients undergoing warfarin treatment.

Key Words: tooth extraction, risk score, warfarin, bleeding

Introduction

Reducing the risk of oral bleeding in patients undergoing warfarin treatment is essential in clinical practice. However, an effective predictive scoring system has not been developed to date. Discontinued warfarin administration preoperatively reduces the risk of post-tooth-extraction bleeding; however, this approach is not feasible in clini-

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doi: 10.24488/twmuj.2018001
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Table 1 HAS-BLED score.

HAS-BLED bleeding risk score	Risk factor clinical characteristics
H: Hypertension	Uncontrolled, >160 mmHg systolic
A: Abnomal renal or liver function (1 point each)	A1: Presence of chronic dialysis, renal transplantation or serum creatinine ≥200 μmol/L
	A2: Chronic hepatic disease (e.g., cirrhosis), bilirubin >2 × upper limit of normal AST/ALT/ALP >3 × upper limit of normal
S: Stroke	Previous history
B: Bleeding	Bleeding history or predisposition
L: Labile INRs	Unstable/high INRs or poor time in therapeutic range (eg, <60%)
E: Elderly	>65 years
D: Drugs or alcohol (1 point each)	D1: Concomitant antiplatelet agents or NSAIDs
	D2: Alcohol excess

Alcohol excess, Criteria from the European Society of Cardiology 23 were used.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAIDs, non-steroidal anti-inflammatory drugs.

cal settings.

Wahl reported that among at least 2,673 patients whose warfarin dose was reduced or withdrawn for at least 2,775 visits to dental procedure, 22 patients developed embolic complications (0.8% of cessations), including 6 fatal events (0.2% of cessations).[1] Therefore, patients scheduled to undergo tooth extraction who have achieved target international normalized ratio of prothrombin time (PT-INR) should not stop the warfarin treatment.[2, 3]

According to the guidelines issued in the UK, patients undergoing warfarin therapy should not stop medication prior to tooth extraction if their PT-INR is stable. With respect to risk assessment, serious haemorrhagic complications of post-tooth-extraction bleeding are unlikely in patients with PT-INR values in the therapeutic range of 2.0-4.0.[4]

In Japan, the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction recommended a PT-INR of 3.0 as the maximum safety threshold for tooth extraction.[5] However, studies have indicated that some patients with controlled PT-INR of <3.0 developed post-tooth-extraction bleeding.[6-8]

The usefulness and accuracy of evaluation based solely on the PT-INR are limited; therefore, evaluating the interaction of warfarin and other relevant factors preoperatively is necessary. In this study, we proposed oral bleeding risk scoring system (OBRS) for predicting post-tooth-extraction bleeding risk in patients undergoing warfarin treatment, which would enable improved hospitalization management and postoperative haemostasis, and help prevent complications.

In the recent years, HAS-BLED score (**Table 1**) has been used as an index for evaluating bleeding risk in patients with atrial fibrillation (AF) undergoing anticoagulant therapy.[9] HAS-BLED score was developed based on evaluation of 3,978 patients in the Euro Heart Survey on AF, which aimed to assess the individual bleeding risk of patients with AF, and aid in making clinical decision regarding antithrombotic therapy in patients.[9] The score evaluates 9 items that potentially contribute to patients' overall potential bleeding risk, and subsequently, ranks patients according to their rate of risk of major bleeding episode in the following year.

Therefore, a scoring system that predicts patients' post-tooth-extraction bleeding risk is necessary. This study aimed to develop a novel and simple OBRS for predicting the post-tooth-extraction bleeding risk in patients under warfarin treatment.

Materials and Methods

1. Study design

The study was a retrospective cohort study. The Ethics Committee of Tokyo Women's Medical University, To-

Table 2 Baseline characteristics of the derivation and validation cohorts.

	Derivation cohort group (n=211)	Validation Cohort group (n=63)	p value *p<0.05
Patient			
Men, n (%)	112 (53)	32 (51)	0.74
Median age	72	71	0.39
Age>65 y, n (%)	154 (73)	52 (83)	<0.001*
Medical history			
Hypertension, n (%)	28 (13)	20 (32)	<0.001*
Chronic kidney disease, n (%)	21 (10)	4 (6)	0.39
Chronic liver disease, n (%)	0 (0)	0 (0)	
Stroke, n (%)	38 (18)	9 (11)	0.49
Bleeding history, n (%)	9 (4)	2 (3)	0.7
Drugs, n (%)	59 (28)	14 (22)	0.37
Labial INR, n (%)	11 (5)	1 (2)	0.24
PT-INR	2.01±0.99	2.01±0.42	0.99
HAS-BLED Score (points)	1.43±0.45	1.56±0.96	0.34
Local factor			
Incision, n (%)	54 (26)	23 (37)	0.09
Bone milling, n (%)	64 (30)	17 (27)	0.06
Number of extracted teeth (mean±SD)	2.3±2.11	1.63±1.26	0.03*

kyo, Japan, approved the study (approval code: 3909-R).

2. Study population and eligibility criteria

The study subjects included 274 consecutive Japanese inpatients (144 men and 130 women; average age: 68.9 years) at the Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University Hospital, who underwent tooth extraction between April 1, 2013 and March 31, 2016 while receiving a maintenance dose of warfarin. Of these patients, 211 cases were included in the derivation cohort (early phase: April 1, 2013 to March 31, 2015) and 63 cases in the validation cohort (late phase: April 1, 2015 to March 31, 2016) (**Table 2**).

In all cases, we performed inpatient tooth extraction while continuing orally administered warfarin; in addition, concomitant antiplatelet agents were continued at the maintenance dose. Exclusion criteria were: age of < 20 years old at time of hospital admission, presence of comorbid blood diseases, and PT-INR level of ≥3.5, as indicated by results of blood tests performed on the day prior to tooth extraction. Patients underwent follow-up examinations of oral wound healing for 2 weeks period after discharge. Doctors' and nurses' records obtained from the electronic medical records were registered along with the clinical data in a combined database. All patients who were hospitalized and underwent multiple tooth extractions during the study period, were included in the analysis.

3. HAS-BLED score

The acronym HAS-BLED stands for Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile international normalized ratio (INRs), Elderly and Drugs or alcohol. Patients with systolic blood pressure of 160 mmHg, at the time of arrival at the hospital, were categorized as having hypertension. Patients were categorized as having abnormal renal or liver function based on the following conditions: receiving haemodialysis or underwent kidney transplant; with a serum creatinine level ≥2.26 mg/dL in the most recent blood test; with chronic liver diseases, such as liver cirrhosis, and bilirubin levels at least two times the normal upper limit in most recent blood test; and with at least three times the normal upper limit of either alanine transaminase, aspartate aminotransferase, or alkaline phosphatase levels in most recent blood test. Patients were categorized as having a stroke or bleeding based on information obtained from medical interviews on hospital admission. Labile INRs indicated patients with unstable or high INRs or poor clotting time in the therapeutic range (time in therapeutic range <60% of recommended value). In this study, cases in which control of warfarin was necessary for

tooth extraction with high INR (PT-INR ≥3.5) by outpatient examination were defined as labile INRs. Patients who were ≥65 years of age at the time of tooth extraction were categorized as elderly. Patients with medical history of long-term administration of antiplatelet agents or non-steroidal anti-inflammatory drugs (NSAIDs) or patients with alcohol dependency were included in the drug and alcohol category. One point was allocated for each of these categories, with maximum possible score of 9 points.

4. Tooth extraction procedure

Each patient's primary physician was consulted preoperatively regarding his or her general medical status and history of use of anticoagulants. In patients presenting with acute symptoms, such as periodontal abscesses, apical periodontitis, or pericoronitis, around the tooth to be extracted, procedures such as incision and drainage were performed as necessary and antibiotics were prescribed for at least 3 days. The patients' meals were limited in amounts of vitamin K. During tooth extraction, electrocardiogram, blood pressure, pulse rate, and percutaneous oxygen saturation levels were monitored. For Local anaesthesia, 1.8-3.6 mL of 2.0% lidocaine containing 1/80,000 units of epinephrine (Ora Injection Dental Cartridge, Showa Yakuhin Kakou Co., Tokyo, Japan), was administered. Minimally invasive tooth extraction was performed. In cases with indication of multiple teeth to be extracted were spread over ≥1/3rd of total jaw area, all teeth were extracted in one procedure; and when teeth to be extracted were spread over ≥1/3rd of total jaw area, multiple teeth were usually extracted in one procedure if the procedure was expected to last ≤30 min. The procedure was conducted under consideration of patients' age and presence of any comorbid disease. After extraction, curettage of inflammatory granulation tissue around the wound border was performed, haemostatic gelatin sponge (Spongel, Astellas Pharma Inc., Tokyo, Japan) was inserted into the socket, and suturing was performed to reduce size of the wound border. The patient was requested to bite down on a piece of absorbent cotton for 20 min after completion of tooth extraction, in order to achieve pressure haemostasis. At 30 min after tooth extraction, the patient was examined to confirm cessation of bleeding. After extraction, patients were instructed to avoid strong or frequent gargling and to rest as much as possible. Post-extraction meals comprised gruel-like food. If patients experienced pain after tooth extraction, they were administered acetaminophen, 1500 mg/day.

5. Post-tooth-extraction bleeding

Post-tooth-extraction bleeding was defined that patients who underwent any medical haemostatic procedure were categorized as having bleeding. Haemostatic procedures performed under examining oral surgeons' decision are described below. In case of moderate-to-severe bleeding that was difficult to resolve using primary haemostasis alone, local dental anaesthetic containing 1/80,000 epinephrine, which has vasoconstrictive effects, was infiltrated at dose of 1.0-1.8 mL around the tooth extraction wound. Pressure was applied to the wound by instructing patients to bite down on a piece of gauze or absorbent cotton. Nevertheless, if insufficient control of bleeding was determined, injection of additional local haemostatic agent(s) or additional suturing of the wound was performed as necessary. For patients with repeated bleeding or prolonged exudative bleeding after undergoing haemostatic procedures, haemostatic splint was fabricated to cover the wound after lining with periodontal pack or denture-based tissue conditioner.

Patients who exhibited bleeding but in for who haemostatic procedures were deemed unnecessary were instructed to rest adequately and refrain from excessive gargling. Patients with mild bleeding and oozing, were requested to bite down for 20 min on a piece of gauze or absorbent cotton placed on the tooth extraction wound, to achieve pressure haemostasis. Regular follow-up examinations were performed by oral surgeons twice a week, and involved complete assessment of wound healing. Patients who did not require further treatment for post-tooth-extraction bleeding were categorized as "no bleeding group."

6. Risk factors

For determining risk factors, we analyzed data of both HAS-BLED score factors and local factors. Data collection and analysis included evaluation of local factors such as the number of teeth extracted in one procedure, gingival incision, and cutting the alveolar bone. An incision indicates that a gingival incision is made during

tooth extraction. Drug definition was 1 point by using antiplatelet drugs or using NSAIDs. Alcohol addiction was also defined as 1 point separately.

7. Statistical analysis

The subjects were divided into two groups: patients who experienced post-tooth-extraction bleeding (bleeding); and patients who did not, experience post-tooth-extraction bleeding (no bleeding); and patients' characteristics were compared between groups. Continuous variables were examined using Welch's t-test. Nominal variables were examined using Fisher's exact test. The significance level (p) was 0.05. Based on the results obtained, forced-entry multivariate logistic regression analysis was performed on significant factors. Bootstrap method was used to assess discrimination, in which 1,000 random samples were drawn with replacements from the original dataset.

Subsequently, parameter estimates from analysis were scored to create optimum OBRS formula. Receiver operating characteristic (ROC) curves were created to compare OBRS with each PT-INR and HAS-BLED to determine significant predictor of post-tooth-extraction bleeding. For statistical analysis, JMP Pro12 (SAS Institute Inc., Cary, NC, USA) and Statistical Package for the Social Sciences (SPSS) software version 22.0 (Chicago, IL, USA) were used.

Results

1. Study population

Thirty-eight patients (13.9% 38/274 cases) met the definition of bleeding cases. We included 28 cases (13.7% 29/211 cases) in the derivation cohort, and nine cases (14.3% 9/63 cases) in the validation cohort. Regarding the timing of the post-tooth-extraction bleedings, there were 28 cases within 24 hours after tooth extraction, 5 cases for 1 to 3 days, and 5 cases for 4 to 7 days. There were 8 cases of additional prescriptions of antibiotics and formulation of acetaminophen to pain with bleeding, but only 3 cases bleeding newly after prescription. Haemostasis with localized haemostatics procedure was performed in all patients with post-tooth-extraction bleedings, and there was no mortality from haemorrhage. Derivation cohort and Validation Cohort in the patient group showed a significant difference in age and hypertension in both groups, but no significant difference was found in other factors (**Table 2**). There was no alcoholism in this patient group. We defined drugs as either long-term administration of antiplatelet agents or NSAIDs.

2. Predictors for the post-tooth-extraction bleedings

We examined the association between the candidate predictors and the post-tooth-extraction bleedings in multivariable logistic regression. The association of post-tooth-extraction bleeding is shown **Table 3** in the derivation cohort. Drugs were adopted without adopting the HAS-BLED score because significant differences were found only in drugs by factor of HAS-BLED score. The final model predictors included PT-INR, drugs and incision (**Table 3**).

Logistic regression analysis showed that PT-INR, drugs, incision were independent variable for predicting tooth extraction bleeding (**Table 4**).

Using JMP, estimates for each item were as follows: PT-INR, 2.1; drugs, 1.1; and incision, 1.3. We performed model examination through bootstrap method. The comparison between the bootstrapped model and the simple logistic model showed a similar regression coefficient for each variable and no change beta coefficient (**Table 5**).

Estimate ratios were calculated using the lowest estimate (drugs) as reference: drugs (1.1/1.1=1), PT-INR (2.1/1.1=1.9), and incision (1.3/1.1=1.2). The ratio of the score was calculated from the odds ratio in the logistic regression analysis (**Table 5**).

The resulting formula (formula 1=PT-INR × 1.9 + drugs × 1 + incision × 1.2 was compared to a simplified formula (formula 2=PT-INR × 2 + drugs × 1 + incision × 1). AUC for formula 1 was 0.76 (95%CI, 0.66 to 0.84), and for formula 2, 0.77 (95% CI, 0.67 to 0.85), without significant difference (**Figure 1** shows ROC graph comparing the two formula). Therefore, formula 2 was selected for use in OBRS (**Table 6**).

Figure 2 shows ROC graph comparing OBRS with each HAS-BLED and PT-INR. AUC of OBRS was 0.77 (95% CI, 0.67 to 0.85), HAS-BLED, 0.61 (95% CI, 0.50 to 0.71), and PT-INR, 0.69 (95% CI, 0.56 to 0.79). AUC of OBRS was statistically significant compared to those

Table 3 Patient characteristics of the derivation cohort.

	Total patients (n=211)	Bleeding group (n=29)	No bleeding group (n=182)	p value *p<0.05
Patient				
Men, n (%)	112 (53)	20 (69)	92 (51)	0.07
Median age	72	68	72	0.39
Age>65 y, n (%)	154 (73)	21 (72)	133 (73)	0.94
Medical history				
Hypertension, n (%)	28 (13)	4 (14)	24 (13)	0.56
Chronic kidney disease, n (%)	21 (10)	5 (17)	16 (9)	0.14
Chronic liver disease, n (%)	0 (0)	0 (0)	0 (0)	
Stroke, n (%)	38 (18)	9 (31)	29 (16)	0.93
Bleeding history, n (%)	9 (4)	2 (7)	7 (4)	0.11
Drugs, n (%)	59 (28)	13 (45)	46 (25)	0.03*
Alcoholism, n (%)	0 (0)	0	0	
Labial INR, n (%)	11 (5)	3 (10)	8 (4)	0.18
PT-INR	2.01±0.99	2.31±0.56	1.96±0.41	0.001*
HAS-BLED Score (points)	1.43±0.45	1.79±1.08	1.38±0.96	0.04*
Local factor				
Incision, n (%)	54 (26)	12 (41)	42 (23)	0.04*
Bone milling, n (%)	64 (30)	16 (55)	48 (26)	0.16
Number of extracted teeth (mean±SD)	2.3±2.11	3±2.35	2.2±2.06	0.69

Table 4 Logistic regression model.

	Odds ratio	95% CI	Score points	p value
PT-INR	7.9	3.1-22.3	2	< 0.001*
Incision	3.7	1.5-9.5	1	0.0056*
Drugs	2.9	1.2-7.1	1	0.0196*

CI, confidence interval. *p<0.05

Table 5 Model comparison after bootstrapping.

	B	B 95% CI	Bootstrapped B	Bootstrapped B 95% CI
PT-INR	2.1	1.1 to 3.1	2.1	1.1 to 3.4
Incision	1.3	0.39 to 2.2	1.3	0.34 to 2.3
Drugs	1.1	0.17 to 2.0	1.1	0.20 to 2.0
Constant	-7.0	-10 to -5.0	-7.0	-10 to -5.0

CI, confidence interval; PT-INR, international normalized ratio of prothrombin time; B, beta coefficient.

AUC of PT-INR and HAS-BLED (**Figure 2**).

Thus, OBRS showed significantly improved ability to predict post-tooth-extraction bleeding compared with each PT-INR and HAS-BLED score.

Subsequently, OBRS values were set and compared to HAS-BLED score. ROC curve indicated cut-off value of 5.08 points.

3. Model performance

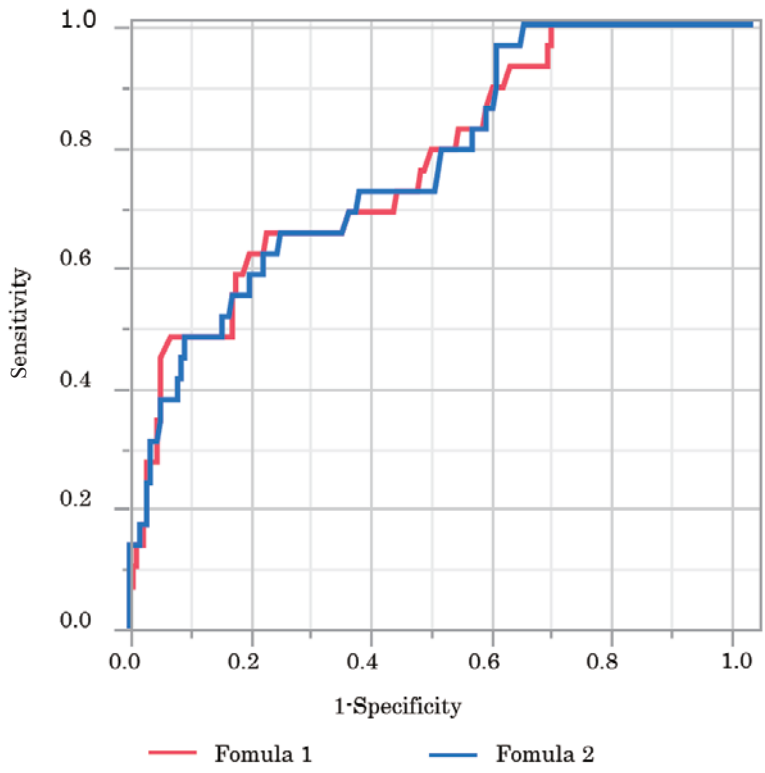
For temporal validation, we examined model performance in validation cohort, which included recently treated patients in the late phase (**Table 7**). Bleeding event at cut-off value of OBRS was examined. Sensitivity and specificity were 100% and 90.7%, respectively, for cut-off score of 5.08 points (**Figure 3**). OBRS had excellent performance in terms of predictor score.

Discussion

Reports indicated that incidence of post-tooth-extraction bleeding in patients with warfarin tranged between 0.6 and 22.8%.[1, 6, 7, 10] Our results indicated incidence rate of 13.9%.

Despite relatively high incidence rate of post-tooth-extraction bleeding since subjects of the present study were hospitalized, patients may have complained about trivial amounts of bleeding under this environment; hence, higher number of haemostatic procedures may have been performed, which may explain result of high incidence of bleeding.

It is not practical or advisable to discontinue use of warfarin in patients who are scheduled to undergo tooth extractions,[11] since such discontinuation could lead to systemic complications. Scoring systems such as HAS-



	AUC	95% CI
Formula 1	0.76	0.66-0.84
Formula 2	0.77	0.67-0.85

p=0.23

Figure 1 Receiver operating characteristic curve of formula 1 vs. formula 2.

Table 6 OBRS definition.

Element	Definition	Score points
PT-INR	PT-INR, international normalized ratio of prothrombin time	PT-INR value × 2 points
Drugs	Concomitant antiplatelet agents or NSAIDs	1 point
Incision	The surgeon needed an incision for tooth extraction	1 point

BLED, which were developed for use in patients with AF, are not accurate in predicting post-tooth-extraction bleeding, as they do not relate to local and specific factors. Kataoka et al reported that HAS-BLED score was not effective to predict risk of bleeding following tooth extraction.[12] We analysed the association of post-tooth-extraction bleeding with each item in the HAS-BLED score. Significant differences were found between bleeding and no bleeding groups with regard to PT-INR, drugs, incision, and HAS-BLED score (**Table 3**). Since HAS-BLED score includes both PT-INR and drugs, we included the two subcategories without including the overall HAS-BLED score in OBRS.

Care was taken to include specific local and dental factors in OBRS. We combined categories of PT-INR and drugs which were significant (for tooth extractions) items of HAS-BLED with local dental factors, such as incision. Although tooth extraction can involve several elements, such as necessity for lifting the mucoperiosteal flap or removing the alveolar bone, statistical analysis revealed incision and subsequent suturing had significant impact on risk of post-tooth-extraction bleeding in patients undergoing warfarin treatment. As part of developing OBRS, we evaluated the risk ratio, and determined the cut-off value of 5.08 points, which indicated that complicated exodontia requiring incisions in patients administered an-

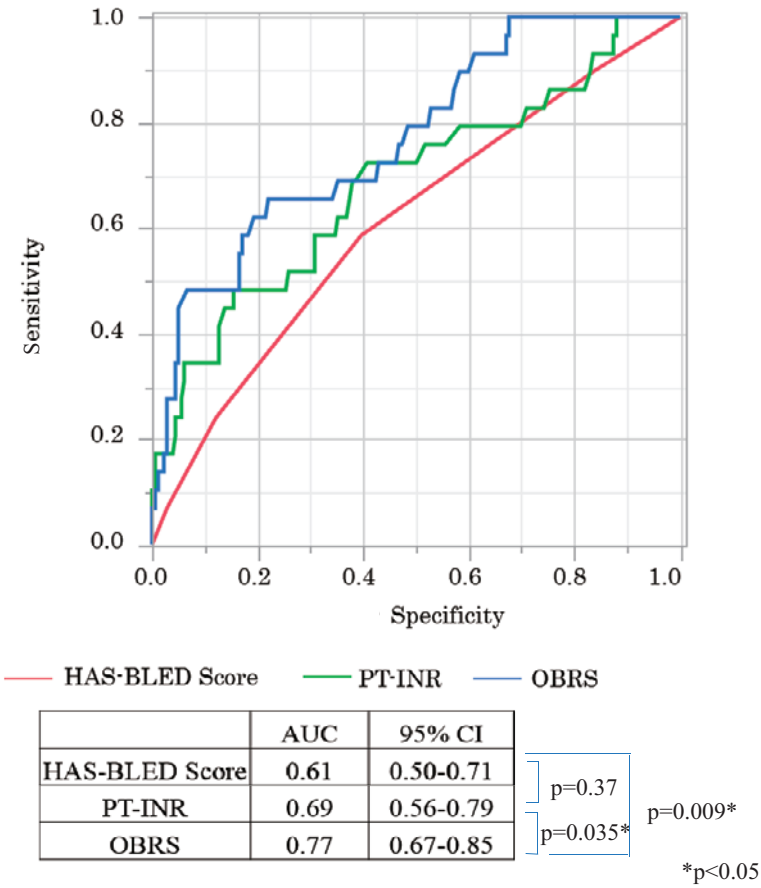
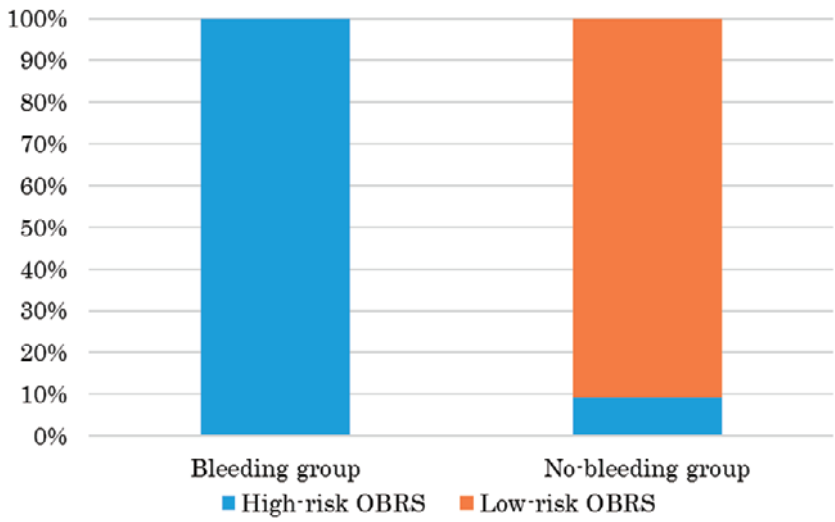


Figure 2 Receiver operating characteristic curve of HAS-BLED score vs. OBRS.
PT-INR, international normalized ratio of prothrombin time; OBRS, oral bleeding risk scoring system.

Table 7 Patient characteristics of the validation cohort.

	Total patients (n=63)	Bleeding group (n=9)	No bleeding group (n=56)	p value *p<0.05
Patient				
Men, n (%)	32 (51)	6 (67)	26 (46)	0.3
Median age	71	74	72	0.48
Age>65 y, n (%)	52 (83)	7 (78)	45 (80)	0.94
Medical history				
Hypertension, n (%)	20 (32)	4 (44)	16 (29)	0.3
Chronic kidney disease, n (%)	4 (6)	1 (11)	3 (5)	0.47
Chronic liver disease, n (%)	0 (0)	0 (0)	0 (0)	
Stroke, n (%)	9 (11)	0 (0)	9 (16)	0.34
Bleeding history, n (%)	2 (3)	1 (11)	1 (2)	0.27
Drugs, n (%)	14 (22)	2 (22)	12 (21)	1
Alcoholism, n (%)	0 (0)	0 (0)	0 (0)	
Labial INR, n (%)	1 (2)	0 (0)	1 (2)	0.57
PT-INR	2.01±0.42	2.51±0.28	1.93±0.38	0.001*
HAS-BLED Score (points)	1.56±0.96	1.67±1.12	1.54±0.95	0.004*
Local factor				
Incision, n (%)	23 (37)	8 (89)	15 (27)	0.04*
Bone milling, n (%)	17 (27)	6 (67)	11 (20)	0.01
Number of extracted teeth (mean±SD)	1.63±1.26	1.44±0.72	1.67±1.33	0.62



	Bleeding group	No-bleeding group
High-risk OBRS	9	5
Low-risk OBRS	0	49

Figure 3 Risk classification and outcome (OBRS).

tithrombotic agents can progress to high-risk procedure.

The effect of warfarin is greater in Japanese subjects; therefore, therapeutic range of warfarin is set lower in Japanese population than that in Western populations.[13] Since the study included Japanese subjects only, investigations of race-based differences should be conducted before extrapolating OBRS results to other patient groups. Moreover, large multicentre study is necessary.

In this study, it is likely that system setting would consider haemostasis measures for post-tooth-extraction bleeding as high expense group of OBRS; in contrast, few instances of post-tooth-extraction bleeding occurred among patients in low-risk group, indicating that these patients do not need to be treated at specialized medical institutions, even if undergoing treatment with warfarin. However, measuring PT-INR prior to tooth extraction is still essential.

To the best of our knowledge, this is the first study to develop new risk score for post-tooth-extraction bleedings. Since the study was a retrospective cohort study conducted at a single institution, large-scale prospective cohort studies, including out patients, are needed in future.

Conclusion

PT-INR value, drugs with antiplatelet effects, incision at the time of tooth extraction, and their interactions were identified as risk factors that predicted bleeding after tooth extraction in patients receiving warfarin therapy. We proposed novel bleeding risk evaluation method (OBRS) for predicting risk of post-tooth-extraction bleeding in patients undergoing warfarin therapy.

Acknowledgements

A part of this study has been presented at the 61st Congress of Japanese Society of Oral and Maxillofacial Surgery (November 25, 2016, Chiba).

Conflicts of Interest: The authors declare that they have no conflict of interest regarding this work.

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