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Quick risk assessment profile (qRAP) is a prediction model for post-traumatic venous thromboembolism

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ABSTRACT

Objective: The Risk Assessment Profile (RAP) score is used as a tool of risk prediction in post-traumatic venous thromboembolism (VTE), but this scoring system is complicated to use in clinical settings due to its many variables. The objective of this study was to validate the utility of the RAP model and to develop a simpler risk prediction model for post-traumatic VTE.

Methods: We conducted an observational study at two emergency and critical care centres in Japan between 2013 and 2016. Consecutive adult trauma patients who survived for 24 h or more after admission to the hospital were enroled. One prediction model (quick RAP model) was created with 6 variables based on clinical utility, experience, and thrombogenic mechanism from 17 variables in the conventional RAP model. We calculated diagnostic performance with 95% confidence interval (95% CI) by exact method.

Results: We identified and analysed 859 patients. Twenty-six patients (3.0%) had VTE (17 with deep venous thrombosis alone, 2 with pulmonary embolism alone, and 7 with both). In the external validation, the RAP model had a sensitivity of 100% (95% CI, 86.8–100%) and specificity of 37.9% (95% CI, 34.6–41.3%). In contrast, the qRAP model had a sensitivity of 96.2% (95% CI, 80.4–99.9%) and specificity of 56.2% (95% CI, 52.7–59.6%). In the internal validation, receiver-operating characteristic curve analysis showed that the two models had similar area under the curve values that were not significantly different (0.832 and 0.800, respectively; RAP vs qRAP, p = 0.477).

Conclusions: We developed a practical, modified predictive model for VTE, the qRAP model, which appeared only slightly less accurate than the conventional RAP model and had the advantage of being simpler to use to predict VTE. In our dataset, the conventional RAP model was also evaluated as useful for the prediction of post-traumatic VTE.

Introduction

Since it was reported that trauma patients are at risk for the development of venous thromboembolism (VTE) because of hypercoagulability, immobilisation, and venous injury, many researchers have studied the prevention of VTE [1–4]. The incidence of deep vein thrombosis (DVT) varies from 5 to 63% depending on patient risk factors, modality of prophylaxis, and methods of detection [5,6].

A number of independent risk factors have been reported [7], but it is difficult to estimate risk because trauma patients have different backgrounds, types, and severities of injury. Greenfield et al. compiled the Risk Assessment Profile (RAP) for thromboembolism using the modified Delphi technique and divided the assessment into four categories: underlying conditions, iatrogenic factors, injury-related factors, and age [8] (Supplementary Table S1). In their study, patients with a RAP score of 5 or more were at high risk for the development of VTE. A cost analysis of the risk/benefit ratio for VTE revealed that prophylaxis was beneficial in this high-risk group [9].

However, this scoring system is complicated to use in clinical settings due to its many variables. The objective of the present study was to validate the utility of the RAP model and to develop a simpler risk prediction model for post-traumatic VTE.

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Patients and methods

Study population

This study was conducted at two emergency and critical care centres (Osaka University Graduate School of Medicine and the National Center for Global Health and Medicine) in Japan. Each year, approximately 250 and 350 trauma patients are admitted to each critical care centre, respectively. The data of the trauma patients were collected retrospectively between January 2013 and March 2014 and prospectively between April 2014 and March 2016. Consecutive adult patients defined as those 18 years or older who survived for 24 h or more after admission to the hospital were enroled. Patients were excluded if they had a known hypercoagulable state (anti-thrombin III deficiency, protein C or S deficiency, or anti-phospholipid-protein antibodies), if they were pregnant, or if they had previously undergone therapy with heparin, warfarin, or low-molecular-weight heparin. Information on the patients' age, sex, past medical history, body mass index, diagnosis, Glasgow Coma Scale (GCS), transfusions, Injury Severity Score (ISS) [10,11], Abbreviated Injury Scale (AIS) [12], surgery, central femoral line, laboratory data, prophylaxis of thrombosis, length of hospital stay, and outcome were collected. Once the inclusion criteria were met, a RAP score was calculated within 24 h of admission. We defined complex lower extremity fracture as containing one of the following: (1) comminution fracture, (2) severe soft tissue injury, (3) loss of bone due to trauma, (4) disruption of the articular surface, (5) multiple fractures at several levels in a single bone, or (6) associated joint dislocation. We included all pelvic fractures (without distinction between stable and unstable type). According to our hospital protocol based on the American College of Chest Physicians guidelines [13], the risk of VTE was stratified within 24 h of hospitalisation. At 24 h after admission, patients who required respirator management or bed rest due to trauma were treated as high-risk patients. Moderate- to high-risk patients received lower extremity duplex ultrasound (LEDU) once weekly in the ICU. In addition, LEDU or a contrast CT scan was performed each time clinical symptoms (lower extremity pain or swelling) or abnormalities in blood tests (FDP or D-dimer) were observed. Surveillance LEDU was performed from the groin to the ankle. DVT was defined as thrombosis in a non-superficial vein as detected by LEDU or CT. Pulmonary embolism was defined as thrombosis in a pulmonary artery as detected by CT. When DVT was suspected by LEDU, the overall diagnosis of VTE was finally confirmed by CT with intravenous contrast to rule out pulmonary embolism and to evaluate proximal progression of the DVT. Moderate-risk patients received mechanical VTE prophylaxis (elastic stockings or intermittent pneumatic compression), whereas high-risk patients received pharmacologic and mechanical VTE prophylaxis (intermittent pneumatic compression) unless contraindicated. Pharmacologic therapy was started as soon as possible at 24 h of injury after first confirming no progression of anemia. Standard pharmacologic prophylaxis during the study period was 10,000 U of unfractionated heparin administered as a continuous intravenous infusion per day and adjusted to the reference value upper limit of the activated partial thromboplastin time. Pharmacologic therapy was discontinued when the patients could get out of bed.

Statistical analyses and model development

Summary statistics are presented as the mean (with standard deviation [SD]) and median (with interquartile range [IQR]) as appropriate. The clinical variables were assessed by univariate analysis, including the χ^2 test or Fisher's exact test for categorical data and the unpaired *t*-test or Mann-Whitney U test for continuous data. The threshold for significance was $p < 0.05$.

We did not use a variable selection technique because traditional methods used for selecting variables, such as forward and backward selection or stepwise regression, tend to lack reproducibilities of clinical findings, resulting in models that predict outcomes in the current dataset well but become unreliable in other datasets. Therefore, in the new prediction model reported here, all variables were selected on the basis of clinical utility, experience, and thrombogenic mechanism. We compared two models: the conventional RAP model with 17 variables and the quick RAP (qRAP) model, with only 6 variables (Fig. 1). When generating the new model, we considered the six variables as dichotomous variables.

The models were validated by analysis of sensitivity and specificity, and 95% confidence interval (95% CI) for the percentages were calculated by using exact methods (primary outcome). The performance of each model was assessed with receiver-operating characteristic (ROC) curve analysis as a secondary analysis. The comparison of the area under the curves (AUCs) was tested with the bootstrap method in consideration of the fact that both AUCs were calculated from the same data [14].

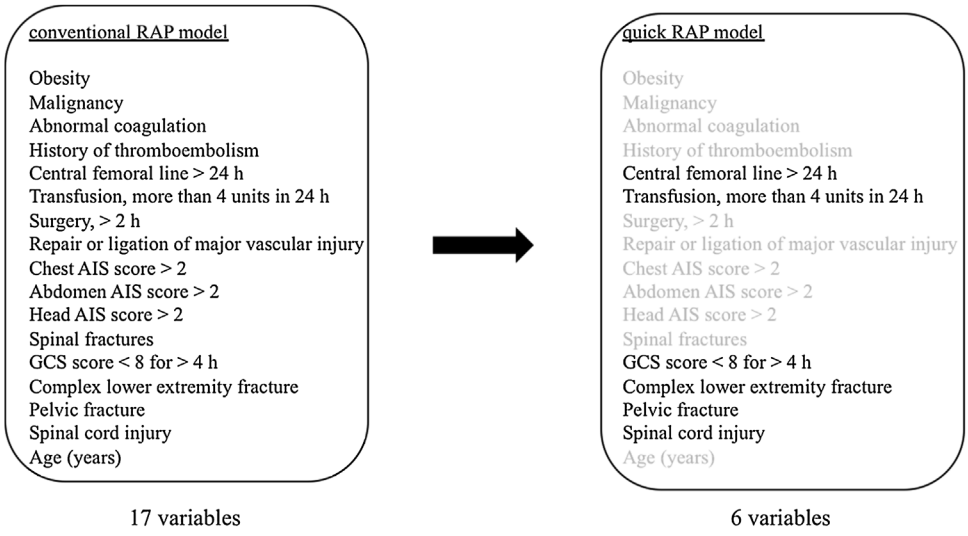

Fig. 1. The variables of each prediction model. *RAP* Risk Assessment Profile, *AIS* Abbreviated Injury Scale, *GCS* Glasgow Coma Scale.

Statistical analysis was conducted with JMP statistical software (version 11.1.1 for Windows; SAS Institute Inc., Cary, NC) and R software (version 3.3.1; R Development Core Team, Vienna, Austria).

This study was approved by the ethics committees of Osaka University and the National Center for Global Health and Medicine.

Results

Patient characteristics

There were 1020 trauma patients who required hospitalisation during the study periods. Of these patients, 859 (median ISS: 9, IQR: 4–16) were included in the analysis (Fig. 2), and 26 patients (3.0%) had VTE (17 with deep venous thrombosis alone, 2 with pulmonary embolism alone, and 7 with both).

There was no significant difference in age and sex between the VTE and non-VTE groups. However, the VTE group had a tendency for higher ISS and longer length of stay (LOS) than the non-VTE group (Table 1).

Distribution of items in the RAP and qRAP models

The distribution of items in the RAP and qRAP models in the VTE/non-VTE groups is shown in Fig. 3. All patients with VTE in our study had a RAP score of 5 or more (Fig. 3-A), which was consistent with a previous report defining the high-risk group as having a RAP score of 5 or more points [9]. The distribution of positive items for qRAP is shown in Fig. 3-B. We defined qRAP positive as indicating that a patient had at least one of the six variables, whereas qRAP negative indicated that a patient had none of the variables. Accordingly, one VTE patient was included as qRAP negative.

Sensitivity and specificity of the RAP and qRAP models

Statistical analysis showed that the sensitivity of the RAP score (≥ 5) was 100% (95% CI, 86.8–100%), the specificity was 37.9% (95% CI, 34.6–41.3%), and the VTE group had a significantly higher RAP score than the non-VTE group (9.0 vs 6.3, $p < 0.001$). In contrast, the sensitivity of the qRAP was 96.2% (95% CI, 80.4–99.9%), and the specificity was 56.2% (95% CI, 52.7–59.6%) (Table 2).

ROC curve analysis

The ROC curves for the outcome of VTE in the two models showed that the RAP model had an AUC value of 0.832 (95% CI, 0.755 to 0.898) whereas that of the qRAP model was 0.800 (95% CI, 0.729 to 0.863) (Fig. 4). There was no significant difference in the AUCs between the two models ($p = 0.477$).

Discussion

This study validated the conventional RAP model through the use of our dataset and showed that this model had high sensitivity and predictive performance for the development of VTE (sensitivity: 100%, specificity: 37.9%). We compiled the qRAP model as a new prediction model that was reduced to 6 variables: central femoral line, transfusion, GCS score, complex lower extremity fracture, pelvic fracture, and spinal cord injury. We then found that ROC analysis indicated no significant difference by removing variables from the conventional model.

The conventional RAP model was compiled by using the modified Delphi technique and included a number of variables related to trauma. In the validation of the RAP model, Gearhart et al. reported a sensitivity of 100% and specificity of 39% at the cut-off point of 5 [9]. In contrast, Hegsted et al. reported a sensitivity of 82% and specificity of 57% [15], and Zander et al. reported a sensitivity of 83% and specificity of 37%, with an area under the ROC curve (AUROC) of 0.66 [16]. The sensitivity and specificity in our study were consistent with the values in these previous studies.

The RAP model has clinical limitations because it includes the AIS codes. The model was designed with the intent to stratify patients shortly after admission to guide in subsequent VTE surveillance and prophylaxis. Ideally, this would be completed within the first 24–48 hours as encouraged by the surgical care improvement project [8]. However, at most institutions, the AIS score is not calculated until after discharge. As such, AIS values are not clinically useful as variables in a model that must be applied shortly after admission. In addition, AIS coding requires specialised training. Therefore, we considered whether we could create a model that excluded the AIS coding.

Another clinical limitation of the RAP model is its many variables, so we compiled the qRAP model with only 6 variables. All variables in the qRAP model were selected on the basis of clinical utility, experience, and thrombogenic mechanism. VTE has traditionally been attributed to venous stasis, endothelial injury, and hypercoagulability, as defined by Virchow's triad [17]. In this respect, it makes sense that the RAP model and qRAP model include all components of the triad. Rogers et al. developed a prediction model of VTE, the Trauma Embolic Scoring System (TESS) [18]. TESS included five variables, age, ISS, obesity, ventilator days, and lower extremity fracture, and had the best prediction for those patients with a score of more than 6 (sensitivity, 81.6%; specificity, 84%; AUROC, 0.89). After that, Zander et al. validated the

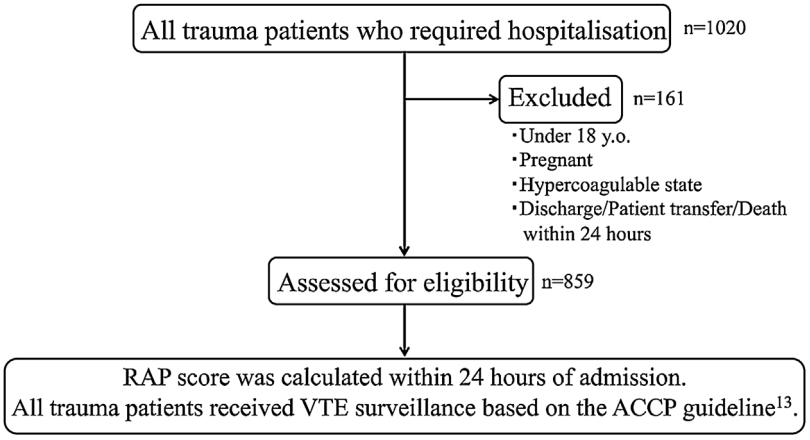

Fig. 2. Patient enrolment. *RAP* Risk Assessment Profile, *VTE* venous thromboembolism, *ACCP* American College of Chest Physicians.

Table 1
Clinical and demographic data of the study population (n = 859).

Variables	VTE (n = 26)	Non-VTE (n = 833)	p Value
Age, mean (SD), y	61.1 (22.3)	57.9 (22.6)	0.48
Sex (male), n (%)	15 (58)	532 (64)	0.52
ISS, median (IQR)	13.5 (9-25.5)	9 (4-16)	< 0.01
LOS, days, median (IQR)	35 (18-59)	9 (4-22)	< 0.01
Time to event, days, median (IQR)	7.5 (6-12)	–	–
Obesity, n (%)	6 (23)	192 (23)	1.00
Malignancy, n (%)	1 (4)	41 (5)	1.00*
Abnormal coagulation, n (%)	0 (0)	4 (0.5)	1.00*
History of thromboembolism, n (%)	0 (0)	8 (1)	1.00*
Central femoral line > 24 h, n (%)	0 (0)	17 (2)	0.43*
Transfusion of more than 4 units in 24 h, n (%)	5 (19)	71 (9)	0.07*
Surgery > 2 h, n (%)	1 (4)	63 (8)	0.71*
Repair or ligation of major vascular injury, n (%)	0 (0)	2 (0.2)	1.00*
Chest AIS score > 2, n (%)	9 (35)	138 (17)	0.03*
Abdomen AIS score > 2, n (%)	2 (8)	37 (4)	0.33*
Head AIS score > 2, n (%)	4 (15)	164 (20)	0.59
Spinal fractures, n (%)	2 (8)	140 (17)	0.29*
GCS score < 8 for > 4 h, n (%)	4 (15)	69 (8)	0.27*
Complex lower extremity fracture, n (%)	13 (50)	138 (17)	< 0.01*
Pelvic fracture, n (%)	7 (27)	75 (9)	< 0.01*
Spinal cord injury, n (%)	3 (12)	103 (12)	1.00*

Data are mean (SD) or median (IQR). *VTE* venous thromboembolism; *SD* standard deviation; *IQR* interquartile range; *ISS* Injury Severity Score; *LOS* length of stay; *AIS* Abbreviated Injury Scale; *GCS* Glasgow Coma Scale.
Asterisks indicate the p-value for Fisher's exact test.

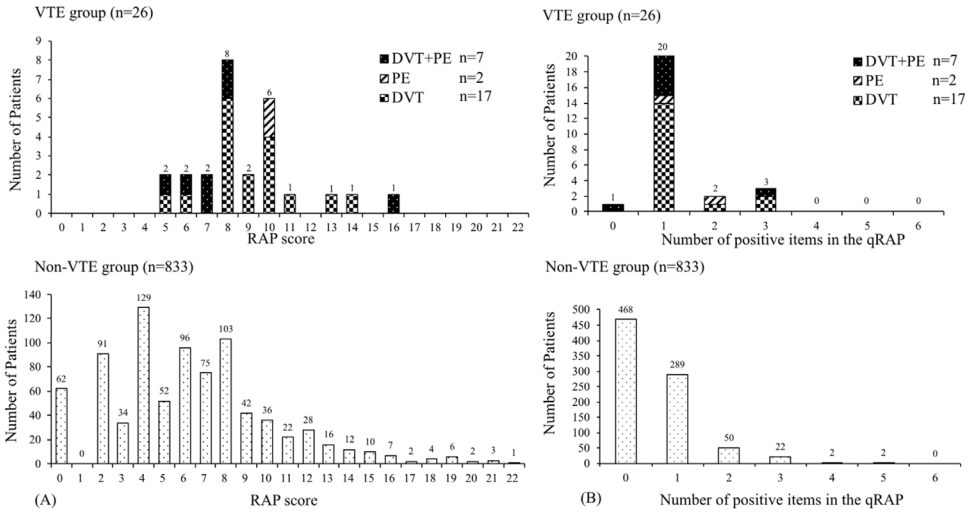

Fig. 3. (A) Distribution of the Risk Assessment Profile (RAP) scores in the venous thromboembolism (VTE) and non-VTE groups. The horizontal axis of this graph is the RAP score, and the vertical axis is patient number. All patients with VTE were contained in the high-risk group. (B) The distribution of positive items for quick RAP in the venous thromboembolism (VTE) and non-VTE groups. The horizontal axis of this graph indicates the number of positive items in the qRAP and the vertical axis is patient number. *DVT* deep vein thrombosis, *PE* pulmonary embolism.

Table 2
Sensitivity, specificity, and predictive values of the RAP and qRAP models for VTE/Non-VTE.

	Sensitivity (95% CI) n/N	Specificity (95% CI) n/N	PPV (95% CI) n/N	NPV (95% CI) n/N
RAP (≥ 5)	1.00 (0.87-1.00) 26/26	0.38 (0.35-0.41) 316/833	0.05 (0.03-0.07) 26/543	1.00 (0.99-1.00) 316/316
qRAP	0.96 (0.80-1.00) 25/26	0.56 (0.52-0.60) 468/833	0.06 (0.04-0.09) 25/390	1.00 (0.99-1.00) 468/469

RAP Risk Assessment Profile; *qRAP* quick Risk Assessment Profile; *VTE* venous thromboembolism; *CI* confidence interval; *PPV* positive predictive value; *NPV* negative predictive value.

TESS and found that it had a sensitivity of 49% and specificity of 72%, with an AUROC of 0.66. They explained these findings as the failure of TESS to include variables related to hypercoagulability; rather, TESS included variables related to venous stasis (age, obesity, ventilator days) and endothelial injury (lower extremity fracture) [15].

Interestingly, univariable analysis showed patients with a chest AIS score > 2 to have a tendency for VTE in the present study.

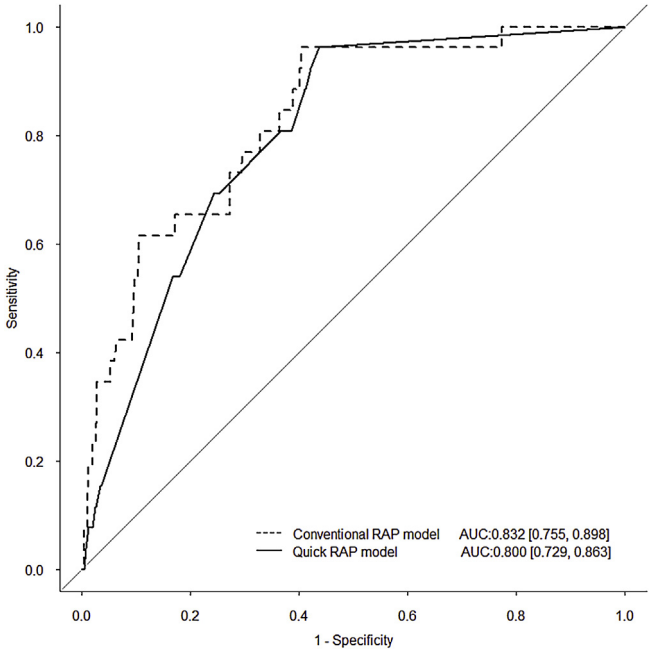

Fig. 4. Receiver operating characteristic curves for the two models in predicting venous thromboembolism. *RAP* Risk Assessment Profile, *AUC* area under the curve.

Knudson et al. reported that the patients with severe chest injury had a 42% increased likelihood of pulmonary embolism (odds ratio [OR], 1.42; CI, 1.30–1.55) with little risk of DVT (OR, 1.07; CI, 1.01–1.12) [19]. They explained by using the Trauma Square model that severe chest injury caused inflammation and led to hypercoagulability. Recent studies have proposed that inflammation should be included as a fourth component of Virchow's triad [20]. Thus, including objective evaluations of inflammation in a model may improve risk stratification.

Moreover, including trauma severity in the model may also improve its performance; for example, unstable pelvic fracture and stable pelvic fracture have the same risk in the conventional RAP model and the qRAP model. In future research, we will evaluate whether distinguishing trauma severity improves prediction performance.

Limitations of our study include the retrospective period and the usual limitations inherent to this type of analysis. The number of events in this study was small. The absence of a statistically significant difference does not directly indicate that using qRAP is no different from using the conventional RAP model. The small number of events may be the reason for the lack of a statistically significant difference. Another potential limitation of our new prediction model is the lack of external validation. In addition, routine surveillance by LEDU was insufficient in the prospective period, and therefore, the incidence of asymptomatic DVT may be underestimated.

In conclusion, we developed a practical, modified predictive model for VTE, the qRAP model (with the number of variables reduced to 6), which appeared to be only slightly less accurate than the conventional RAP model and had the advantage of being simpler to use in the prediction of VTE. Furthermore, we confirmed that the conventional RAP model was useful for the prediction of post-traumatic VTE.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.injury.2019.06.020.

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