主論文

Title

Development and internal validation of a clinical prediction model for acute Adjacent Vertebral fracture after vertebral Augmentation: the AVA score

Abstract

Aims

To develop and internally validate a preoperative clinical prediction model for acute Adjacent Vertebral fracture (AVF) after vertebral Augmentation to support preoperative decision-making, named AVA score.

Patients and Methods

In this prognostic study, a multicentre, retrospective single-level vertebral augmentation cohort of 377 patients from six hospitals in Japan was used to derive an AVF prediction model. Backward stepwise selection ($p<0.05$) was used to select preoperative clinical and imaging predictors for acute AVF after vertebral augmentation for up to 1 month, from 14 candidates. We assigned a score to each selected variable based on the regression coefficient and developed a scoring system named AVA score. We evaluated sensitivity and specificity for each cut-off, area under the curve (AUC), and calibration as diagnostic performance. Internal validation was conducted using bootstrapping to correct the optimism.

Results

Of the 377 patients used for model derivation, 58 (15%) had an acute AVF postoperatively. The following preoperative measures on multivariable analysis were summarised in the five-point AVA score: intravertebral instability (≥5 mm), focal kyphosis (≥10°), duration of symptoms (≥30 days), intravertebral cleft, and previous history of vertebral fracture. Internal validation showed a mean optimism of 0.019 with a corrected AUC of 0.77. A cut-off of ≤1 point was chosen to classify low-risk of AVF, for which only 4 of 137 subjects (3%) had AVF with 92.5%

sensitivity and 45.6% specificity. A cut-off of ≥4 points was chosen to classify high-risk of AVF, for which 22 of 38 (58%) had AVF with 41.5% sensitivity and 94.5% specificity.

Conclusion

In this study, the AVA score was deemed to be a simple preoperative method for the identification of patients at low- and high-risk for postoperative acute AVF. This model could be applied to individual patients and aid decision-making before vertebral augmentation.

Main text

Introduction

Vertebral compression fracture (VCF) is the most common fracture type worldwide.[1] The age-standardised incidence of morphometric VCF was reported as 10.7/1000 person-years in women and 5.7/1000 person-years in men in Europeans over 50 years of age.[2] VCF causes not only acute motion-induced pain but also spinal kyphosis and instability, causing chronic low back pain, neurological symptoms, and various health-related problems.[3, 4] Approximately one-third of people over 50 years of age are affected by osteoporosis,[5] and the number of VCFs that develop in the context of osteoporosis is expected to increase in the future, making it a serious social problem.

Although limited to refractory cases with severe ongoing pain after a recent unhealed fracture, vertebral augmentation is widely used as a minimally invasive and fast-acting treatment option.[6–8] However, there is concern regarding the association of vertebral augmentation with early postoperative adjacent vertebral fractures (AVF),[9, 10] with an incidence rate of approximately 20%[6]. There has been considerable interest in predicting the occurrence of AVF, as identification of high-risk patients can lead to reconsideration of vertebral augmentation, and identifying low-risk patients can lead to more positive adaptation.

Various predictors of AVF have been reported and a clinical prediction model (CPM) using "Cement leakage" and "Pre-existing fractures" to predict AVF at 2 years postoperatively[11] and another CPM using "Thoracic/thoracolumbar spine", "Old fracture presence", "Wedge angle before surgery", and "Correction" to predict AVF 6 months postoperatively[12] have been developed. However, they include intra-operative and post-operative information as predictors and cannot be used for clinical decision-making before vertebral augmentation. Recently, another CPM that predicts AVF within 2 months using preoperative information has been reported.[13] However, the precision of this CPM is inadequate due to the limited number of subjects (65 subjects at a single institution) and methodological ambiguities in variable selection and scoring.

Accordingly, we analysed data from a retrospective multicentre cohort to develop and internally validate a CPM (presented as a scoring system) for predicting the incidence of acute Adjacent Vertebral fracture after vertebral Augmentation using only preoperative information.

Patients and Methods

The derivation and internal validation of the clinical prediction model was obtained from a multicentre cohort across the six private hospitals in Japan. Each hospital has a department of spine surgery with a certified surgeon and routinely treats VCFs. This study was conducted in accordance with the World Medical Association's Declaration of Helsinki. After approval from the research ethics board of the primary research institution, approval from each local institutional research ethics board or the director of the respective sites was obtained. The informed consent was disclosed as an opt-out consent process in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines.[14]

Study populations used to develop a prediction model

We retrospectively collected data from consecutive patients with a VCF who underwent a single level vertebral augmentation (vertebroplasty or balloon kyphoplasty [BKP]) between April 2012 and June 2018. The exclusion criteria were as follows: previous vertebral fractures or fixation surgery on both adjacent vertebrae, fracture of the ankylosing spine, and the use of materials other than polymethylmethacrylate. Data were extracted from electronic medical records and picture archiving and communication systems by the principal researcher, YH, and co-investigators at each hospital.

Outcome measures

The primary outcome was the occurrence of AVF up to 1 month postoperatively. We included asymptomatic morphometric fractures. The AVF was defined based on the diagnosis independently made by YH using all available imaging information. The diagnosis was compared with information extracted from electronic medical records. If discrepancies arose between the imaging diagnosis and the medical records, the final decision was made by consensus between YH and the hospital co-investigator.

Predictor variables

As we intend for the model to be used preoperatively, we only considered predictors that would be available preoperatively. We first identified predictors of AVF obtained from keynote papers, which were readily available at the first assessment. Then, a panel of experts consisting of two neurosurgical supervisors (YH, SK) and two orthopaedic supervisors (MN, TS) was consulted to add factors that were considered clinically important. Consequently, fourteen variables (age,[15-17] female sex, bone density,[15,16] steroid use,[18] smoking habit,[19] fracture of the thoracolumbar junction,[12, 19] previous history of vertebral fracture,[12, 20] longer duration of symptoms,[21] low vertebral height,[22] large focal kyphosis,[23] intravertebral instability, intravertebral cleft,[24] preoperative treatment for osteoporosis, and endplate fracture) were selected as candidate predictors. Of these fourteen variables, large focal kyphosis and intravertebral instability were incorporated into the final model as fixed predictors after the expert panel meeting. Bone density was included as the young adult mean (YAM). The thoracolumbar junction was defined as T11 to L1. The vertebral height was defined as the anterior height of the vertebral body in a loaded X-ray lateral image taken in the standing or sitting position. Intravertebral instability was defined as the gap between vertebral height during loading and unloading.[25] Intravertebral cleft was defined as the observation of gas in the vertebral body on computed tomography (CT) imaging. Patients who started osteoporosis treatment within 2 weeks before vertebral augmentation were classified as not having had osteoporosis treatment. Endplate fracture was defined as a clear break in the

continuity of the endplate on CT imaging.

Prioritising the clinical usability with minimum burden on physicians, we dichotomised each continuous variable using cut-off values determined to be suitable with reference to previous studies at the expert panel meeting (age ≥80 years,[16] YAM ≤60 %, longer duration of symptoms ≥30 days, low vertebral height ≤15 mm, large focal kyphosis ≥10°, and intravertebral instability ≥5 mm).

Statistical analysis

We described the baseline characteristics of the patients according to the presence or absence of AVF. Categorical variables are presented as frequency (percentage) and continuous variables as median (interquartile range). Fisher's exact test was used to calculate the p-value as an index of the difference in characteristics between those with and without AVF. We derived and internally validated the scoring system, named the AVA score, via the steps described subsequently. We did not employ any imputation methods and performed complete-case analysis. All statistical analyses were performed using Stata version 15.1 (StataCorp LLC, College Station, TX, USA).

Selection of predictors

We applied backward stepwise selection using logistic regression to determine the predictors that would comprise the scoring system, from 14 candidates identified to be clinically important; a significance level of <0.05 (two-sided p-value) was selected for removal from the model.

Development of the scoring system

To ensure usability in clinical practice, we used the regression coefficients for each selected factor calculated from the mentioned prediction model to construct the scoring system.[26] Each regression coefficient was divided by the smallest one and rounded to the nearest integer to determine the weighting score for each variable to complete the AVA score.[27] The AVA score is expressed as an

individual's integer value by adding up the score assigned to each dichotomous variable, if present.

Evaluation of predictive performance

We also evaluated the performance of the AVA score. To estimate the ability to discriminate between patients with and without AVF up to 1 month postoperatively, we calculated the area undetr the curve (AUC) for the logistic regression model predicting AVF using only the AVA score. Furthermore, we presented predictive performance (sensitivity, specificity, and positive and negative likelihood ratios) stratified for each threshold of the AVA score. To assess calibration, we compared the observed proportion of AVF with the predicted risks. Accordingly, we tested the calibration using the Hosmer and Lemeshow goodness of fit test.

Internal validation

As an internal validation, we corrected the optimism of the AUC caused by overfitting to the original data using the bootstrap validation approach.[28, 29]

Results

Description of study cohort

A total of 505 subjects were potentially eligible for this study, of which 99 were excluded. Of the remaining 406 study subjects, 377 (93%) with no missing AVF judgements were included in the model derivation (Fig. 1). All 406 study subjects underwent BKP. Of the 377 patients, the median age was 81 years, 77% were female, VCF occurred at the thoracolumbar junction (T11-L1) in 66%, the median duration of symptoms was 16 days, and 15% had AVF (Table 1). Missing load X-rays were found in 31 out of 406 study subjects.

Model derivation

Table 1 also shows the characteristics and distribution of the candidate predictor variables by the occurrence of AVF for up to 1 month. The characteristics of subjects with and without AVF generally differed. Univariable analysis suggested that the following nine variables (including the two fixed variables); female sex, steroid use, previous history of vertebral fracture, longer duration of symptoms, low vertebral height, large focal kyphosis, intravertebral instability, intravertebral cleft, and preoperative treatment for osteoporosis were potentially relevant. Table 2 presents the five predictor variables retained by backward stepwise selection and those multivariable regression coefficients and weighted score. Important predictors of AVF were intravertebral instability ≥5 mm (regression coefficient 0.86, 95% confidence interval [CI] 0.18–1.53), focal kyphosis ≥10° (1.07, 95% CI 0.35–1.78), duration of symptoms ≥30 days (1.16, 95% CI 0.49–1.83), intravertebral cleft (1.15, 95% CI 0.48–1.83), and previous history of vertebral fracture (0.85, 95% CI 0.11–1.60). The scores for each predictor rounded to an integer were all 1, completing the five-point AVA score.

Model performance and internal validation

The AUC of the AVA score for AVF was 0.79 (95% CI 0.72–0.85). The prognostic performance of the prediction model at each threshold is shown in Table 3. Using a score cut-off of ≤1 yielded a sensitivity of 92.5% (95% CI 81.8–97.9), a specificity of 45.6% (95% CI 39.7–51.5), and a negative likelihood ratio of 0.17 (95% CI 0.06–0.43). Using a score cut-off of ≥4 yielded a sensitivity of 41.5% (95% CI 28.1–55.9), a specificity of 94.5% (95% CI: 91.3–96.8), and a positive likelihood ratio of 7.6 (95% CI 4.3–13.4). Specifically, only 4 of 137 subjects (3%) in whom the clinical prediction model estimated a 3% probability of AVF (score ≤1) actually developed AVF, whereas 22 of 38 (58%) of the subjects in whom the model estimated a 57% probability of AVF (score ≥4) actually developed AVF (Supplemental Table 1). Overall, the predicted probability of AVF agreed with the observed AVF (Figure 2). The adequate calibration was further supported by the Hosmer-Lemeshow p-value of 0.18. In the bootstrap internal

validation, the optimism of the AUC was calculated as 0.019 (95% CI 0.014–0.023), and subsequently, the optimism-corrected AUC for AVF was 0.77.

Discussion

We developed and internally validated a simple CPM for AVF using data from a retrospective, multicentre cohort that can be used by physicians prior to vertebral augmentation. AVF up to 1 month after vertebral augmentation can be predicted by the five-point AVA score calculated based on the preoperative predictors of intravertebral instability (≥5 mm), focal kyphosis (≥10°), duration of symptoms (≥30 days), intravertebral cleft, and previous history of vertebral fracture. This model can discriminate between patients who will develop acute AVF postoperatively and those who will not and show adequate calibration.

Implication for clinical practice

The AVA score is expected to quantify the risk of acute AVF after vertebral augmentation, allowing the identification of low-and high-risk groups of AVF prior to the procedure. Explicitly, a score ≤1 implies an extremely low risk of AVF (estimated probability 3%, negative likelihood 0.17), and a score ≥4 suggests a high risk of AVF (estimated probability 57%, positive likelihood 7.6). Prediction of AVF that may contribute to poor postoperative outcomes will be valuable to both clinicians and patients as it provides decision-making support with regard to vertebral augmentation and manages expectations concerning potential treatment options.

Comparison with existing literature

The performance of the AVA score can be compared to the c-statistic of other published models. The prognostic model for predicting AVF 2 years after vertebroplasty had an AUC of 0.72 in the validation cohort.[11] The other prognostic model for predicting AVF 6 months after BKP had an AUC of 0.87 in the test cohort (calculated from published data).[12] These models use intraoperative

214 factors (i.e., cement leakage) and postoperative factors (i.e., correction). While the use of
215 intraoperative and postoperative factors could improve diagnostic performance, it makes their use
216 preoperatively impossible. We believe that the performance of the AVA score was reasonable, as
217 indicated by an optimism-corrected AUC of 0.77 with preoperative information only.

218 Several studies have reported that intradiscal cement leakage seems to be an important
219 predictor of postoperative AVFs.[16, 30–33] However, it cannot be incorporated into a predictive model
220 used in the preoperative decision-making phase. Therefore, we used two preoperative measures,
221 “longer duration of symptoms” and “endplate fracture”, as alternative indicators for model
222 derivation. This is because endplate fractures are definitely associated with intradiscal cement
223 leakage, and we hypothesised that the longer the duration of symptoms, the worse the endplate
224 and intervertebral disc destruction. Postoperative correction[34, 35] has also been reported to be a
225 relevant predictor of AVF. Accordingly, we employed the preoperative indicator “intravertebral
226 instability” as an alternative indicator for model derivation. We believe that the bone cement
227 should be filled at low pressure into a pre-existing cavity and that the amount of cement and
228 degree of correction could not be arbitrarily manipulated. Moreover, we hypothesised that
229 intravertebral instability objectively demonstrates the intravertebral cavity. Subsequently,
230 although "endplate fracture" was not adopted in the final model, "longer duration of symptoms"
231 and "intravertebral instability" were selected as essential predictors.
232
233 ***Strengths and limitations***
234 The strengths of our study include the simplicity of the AVA score containing only five items with
235 a score of one point each. We believe that the simplicity will facilitate its use in clinical practice.
236 Another strength is the focus on patients in private emergency hospitals, where most of the
237 vertebral fractures are actually treated, rather than in advanced medical institutions, such as
238 university hospitals. This study population reflects normal clinical practice and enhances
239 generalisability. In addition, all six participating hospitals are accepting patients 24 hours a day,

7 days a week; thus, selection bias is expected to be low. Furthermore, we focused on acute AVFs only. Most cases of AVF after vertebral augmentation have been reported to occur soon after the procedure.[9, 36] Hence, acute AVF is likely to be strongly associated with vertebral augmentation. Finally, we used robust statistical techniques in the model derivation and internal validation, considering many of the required quality items for clinical prediction models, which increases our confidence in the study results.

Nonetheless, this study has limitations. First, as this was a model development study using a single dataset, only internal validation was available. Before applying the AVA score in clinical practice, an external validation is required to assess its utility. Second, two of the items that make up the model (large focal kyphosis and intravertebral instability) were absent in some subjects. This was due to standing or sitting X-rays that were not taken, probably due to intolerable pain. However, the percentage of missing measurements was small (7.6%), suggesting that the radiography itself is not unacceptable. Finally, BKP was performed on all of the study subjects because vertebral augmentation generally refers to BKP in the Japanese insurance system. Accordingly, it is unclear whether the results of the present study can be generalised to simple vertebroplasty. The fact that the subjects of the study were all Japanese also affects the generalisability.

In conclusion, we were able to identify five key preoperative measures that adequately predicted AVF up to 1 month after vertebral augmentation. It is plausible that the AVA score, when applied to individual patients, may be helpful for decision-making with regard to vertebral augmentation. Further research is warranted to independently evaluate the validity and clinical utility of this prediction model.

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374 **Tables**

375 Table 1. Characteristics of the patients.

	Total n=377	With missing	AVF n=58 (15)	No AVF n=319 (85)	p-value
Age (Years)	81 (76-85)	0	82 (77-86)	80 (76-85)	
≥80	213 (56)		37 (64)	176 (55)	0.25
Female	289 (77)	0	49 (84)	240 (75)	0.18
YAM (%)	64 (56-73)	41	62 (56-74)	65 (57-73)	
≤60	128 (38)		23 (43)	105 (37)	0.44
Steroid use	14 (4)	0	5 (9)	9 (3)	0.05
Smoking habit	17 (6)	77	1 (2)	16 (6)	0.49
Thoracolumbar junction	247 (66)	0	36 (62)	211 (66)	0.55
Previous history of vertebral fracture	232 (62)	0	42 (72)	190 (60)	0.08
Duration of symptom (days)	16 (10-29)	3	25.5 (17-48)	15 (10-25.5)	
≥30	104 (28)		28 (49)	76 (24)	<0.001
Vertebral height (mm)	16 (13-20)	29	11 (9-18)	17 (14-20)	
≤15	136 (39)		35 (65)	101 (34)	<0.001
Focal kyphosis (°)	8 (2-15)	29	12 (8-19)	7 (2-14)	
≥10	149 (43)		36 (67)	113 (38)	<0.001
Intravertebral instability (mm)	4 (2-6)	29	6 (2-7)	4 (2-6)	
≥5	115 (33)		30 (56)	85 (29)	<0.001
Intravertebral cleft	114 (30)	0	33 (57)	81 (25)	<0.001
Preoperative treatment for osteoporosis	134 (36)	1	28 (48)	106 (33)	0.04
Endplate fracture	57 (15)	0	11 (19)	46 (14)	0.42

Data are presented as number (%) and median (interquartile range). AVF, adjacent vertebral fracture; YAM, young adult mean of bone mineral density.

376

377 Table 2. AVA score for acute adjacent vertebral fracture after vertebral augmentation.

	Regression coefficient[a]	95% CI	p-value	Score
Intravertebral instability, ≥5 (mm)	0.86	(0.18-1.53)	0.01	1
Focal kyphosis, ≥10 (°)	1.07	(0.35-1.78)	0.004	1
Duration of symptom, ≥30 (days)	1.16	(0.49-1.83)	0.001	1
Intravertebral cleft	1.15	(0.48-1.83)	0.001	1
Previous history of vertebral fracture	0.85	(0.11-1.60)	0.03	1

CI, confidence interval.

[a]Estimated from a logistic regression.

378

379 Table 3. The performance of AVA score to discriminate acute adjacent vertebral fracture after
380 vertebral augmentation at each score cut-off.
381

Score cut-off	Sensitivity	Specificity	LR (+)	LR (-)
1	98.1	11.3	1.1	0.17
2	92.5	45.6	1.7	0.17
3	66.0	74.0	2.5	0.46
4	41.5	94.5	7.6	0.62
5	15.1	99.7	44.1	0.85

LR, likelihood ratio

382

Figure Captions

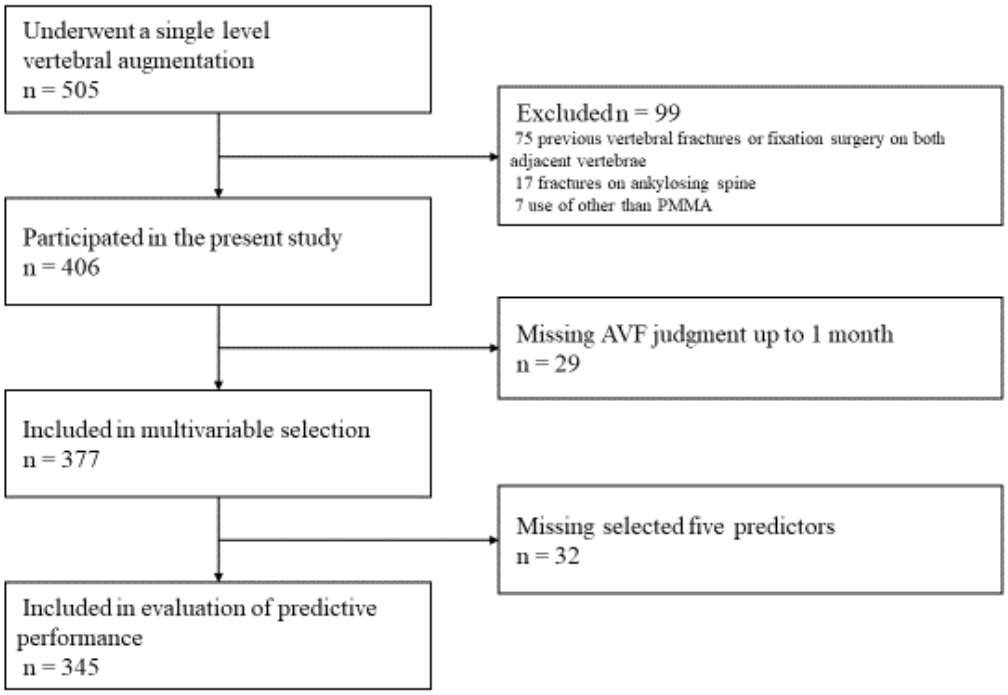
Fig.1 Flowchart of derivation populations.

AVF, adjacent vertebral fracture.

Fig.2 AVF occurrence expected by AVA score and actual value.

AVF, adjacent vertebral fracture.

389 **Figures**



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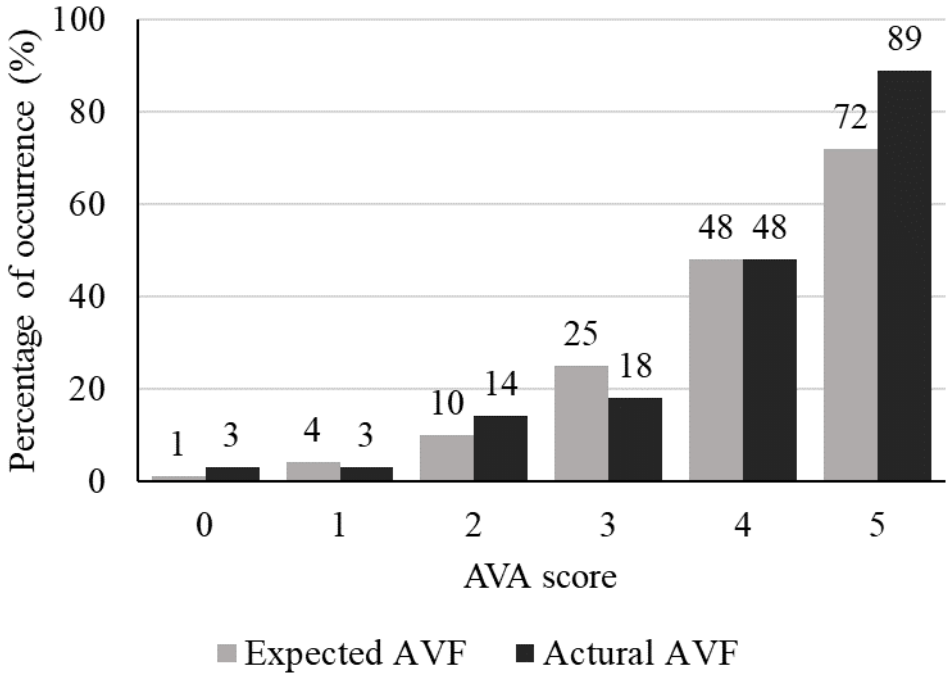
391 **Fig. 1**



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393 **Fig. 2**

394