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Hounsfield unit to serum pentosidine ratio predicts screw loosening after lumbar interbody fusion

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Abstract

Purpose This study aimed to identify whether the ratio of the vertebral Hounsfield unit to serum pentosidine (H/P ratio), which reflects bone density and quality, can predict screw loosening after spinal fusion surgery.

Methods A retrospective case-control study was conducted in 35 patients (mean age 71 ± 10.4 years, 18 men) who underwent spinal interbody fusion for lumbar spine disease between June 2020 and February 2022. Screw loosening was evaluated by computed tomography at 12 months postoperatively. Information was collected on patient background characteristics, including age, sex, body mass index, diagnosis, dialysis status, smoking history, diabetes, steroid use, and osteoporosis. Imaging parameters, the surgical method used, number of fixed intervertebral segments, intervertebral level (including L5/S1 or not), and the H/P ratio were also investigated. Risk factors associated with screw loosening and pseudarthrosis were examined in univariable and multivariable logistic regression analyses. A P-value of < 0.05 was considered statistically significant.

Results Screw loosening occurred in 14 of 35 patients (40%). Multivariate analysis revealed that the H/P ratio (odds ratio 0.09, confidence interval 0.02–0.53, $P = 0.007$) was a significant risk factor for screw loosening at 12 months postoperatively.

Conclusion This study demonstrates that the H/P ratio, which reflects both bone density and deterioration of bone quality in the vertebral body, may serve as a predictor of screw loosening at 12 months after lumbar spinal surgery.

Keywords Spinal fusion surgery, Screw loosening, Hounsfield unit, Pentosidine

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Introduction

Pedicle screw placement is a standard procedure in spine surgery [1–3]. Implant-related complications include screw loosening, which adversely affects the local mechanical environment and leads to several postoperative complications such as pain, fusion failure, and pseudo-articulation [4–7]. Osteoporosis is particularly common in elderly patients and is an important risk factor for screw loosening [4, 8]. Therefore, it is important to identify risk factors that predict postoperative loosening before surgery.

Spinal Hounsfield unit (HU) values on preoperative computed tomography (CT) are a simple indicator of the degree of osteoporosis [9–11] and are known to correlate with bone density [9, 10, 12, 13]. Recently, vertebral HU values have been reported to be a risk factor for screw loosening after spinal surgery [14–18]. According to the current definition of osteoporosis, bone volume, mineral density, and tissue material properties are important determinants of bone strength. Collagen is major constituent of bone. Collagen cross-linking plays an important role in bone strength [19–22]. An accumulation of non-enzymatic cross-linking such as advanced glycation end products (AGEs), which is induced by glycation or oxidation, has a negative effect on bone strength [19, 23–25]. An AGE, pentosidine, is a surrogate marker of whole accumulation of AGEs in bone [13]. The levels of plasma or urinary pentosidine shows significant positive correlation to the content of pentosidine in bone [26]. Bone strength is not only dependent on the bone mineral phase reflected as HU values, but also on pentosidine accumulation in bone. Therefore, we hypothesized that a combination of the HU value and serum pentosidine, an AGE that reflects deterioration in bone quality, could more accurately reflect vertebral bone strength. Therefore, the purpose of this study was to determine the contribution of bone density and bone quality, which define bone strength, to screw loosening after lumbar spine surgery and to examine whether the ratio of the vertebral HU value, which reflects bone density, to serum pentosidine, which reflects deterioration in bone quality, could be a predictor of screw loosening.

Methods

Patients who underwent spinal interbody fusion surgery at our university hospital between June 2020 and March 2022 were retrospectively reviewed. The study was carried out in accordance with principles laid down in the Declaration of Helsinki, and the study protocol was approved by the Jikei University School of Medicine Ethics Committee (30–115 [9136]). All patients provided written informed consent.

Preoperative data were collected, including demographics (age, sex, body mass index, and tobacco use),

clinical characteristics (diagnosis, hypertension, diabetes, osteoporosis, dialysis, and serum pentosidine), and surgical data (operative technique, number of intervertebral levels fused, and intervertebral lesion level [including L5/S1 or not]). Serum pentosidine was measured using the ELISA method (FUSHIMI Pharmaceutical Co Ltd., Kagawa, Japan.) [27]. The HU value was measured from the L4 vertebra downwards on preoperative lumbar CT scans [15]. Spinal surgery was performed for lumbar spinal canal stenosis, lumbar degenerative spondylolisthesis, or lumbar spondylolisthesis using transforaminal lumbar interbody fusion, posterior lumbar interbody fusion, or lateral lumbar interbody fusion, depending on the individual case. Notably, for lateral lumbar interbody fusion, two-stage surgery and simultaneous anterior–posterior fusion were included. Patients with multiple fusions involving four or more vertebrae and those for whom essential data, such as laboratory or CT findings, were missing were excluded from the study.

The ratio of the HU value to the serum pentosidine level (the H/P ratio) was calculated from the preoperative data for serum pentosidine, an indicator of deterioration of bone quality, and the HU value, an indicator of bone density [10, 28–30].

The primary outcome was the prevalence of screw loosening at 12 months postoperatively. In this study, screw loosening was defined as translucency of ≥ 1 mm around the pedicle screw on a CT scan of the lumbar spine obtained 12 months after surgery [4].

All statistical analyses were performed using GraphPad Prism (version 5; GraphPad Software Inc., La Jolla, CA) and Stata (version 14; StataCorp LLC, College Station, TX). Data are shown as the mean \pm standard deviation or as the number and percentage as appropriate. Univariable and multivariable logistic regression analyses were performed to investigate the association of preoperative factors with screw loosening. The optimal cut-off value was defined as the highest Youden index value obtained on a receiver-operating characteristic (ROC) curve. Briefly, the Youden index provides the optimal cut-off for a continuous variable by showing the score that offers the best trade-off between sensitivity and specificity. The area under the ROC curve was calculated to determine the discrimination ability of the logistic regression models. All tests were two-sided and a P -value of < 0.05 was considered statistically significant. The patients were divided into two groups based on the H/P ratio cut-off value, and preoperative factors were compared between the groups using the independent t -test and chi-squared test.

Results

Demographics

The cohort comprised 35 patients (18 men, 17 women). The mean age was 71 ± 10.4 years (49 to 90 years). Table 1

Table 1 Patient demographic, clinical, and surgical characteristics

Variable	n	%	H/P ratio cut-off value		P-value
			< 1482.6	> 1482.6	
Age, years (mean ± SD)	71 ± 10.4		72 ± 13.3	71 ± 7.0	0.97
Sex					0.09
Male, n (%)	18	51.4	11 (68.8%)	7 (36.8%)	
Female, n (%)	17	48.6	5 (31.3%)	12 (50.0%)	
BMI (mean ± SD)	22.2 ± 5.0		21.4 ± 2.8	23.1 ± 3.5	0.1
Tobacco smoking (yes)	5	14.3	1 (6.3%)	4 (21.1%)	0.35
Diagnosis					0.85
Lumbar spinal canal stenosis	16	45.7	7 (43.7%)	9 (47.4%)	
Lumbar degenerative spondylolisthesis	16	45.7	8 (50%)	8 (42.1%)	
Lumbar spondylolisthesis	3	8.6	1 (6.3%)	2 (10.5%)	
Hypertension (yes)	21	60	8 (50%)	13 (68.4%)	0.32
Diabetes (yes)	4	11.4	3 (18.8%)	1 (5.3%)	0.31
Osteoporosis (yes)	11	31.4	7 (43.8%)	4 (21.1%)	0.27
Dialysis (yes)	5	14.3	4 (25%)	0 (0%)	0.03
Surgical technique					0.32
TLIF	17	48.6	9 (56.3%)	8 (42.1%)	
PLIF	9	25.7	5 (31.3%)	4 (21.1%)	
LLIF	7	20	1 (6.2%)	6 (31.6%)	
TLIF + LLIF	2	5.7	1 (6.2%)	1 (5.2%)	
Intervertebral fusion level, n					0.16
1	26	74.3	11 (68.7%)	15 (79.0%)	
2	7	20	5 (31.3%)	2 (10.5%)	
3	2	5.7	0 (0%)	2 (10.5%)	
Lesion level (L5/S1 or not) (yes)	4	11.4	1 (6.3%)	3 (15.8%)	0.61
Serum pentosidine (mean ± SD)	0.071 ± 0.096		0.094 ± 0.12	0.052 ± 0.02	0.007
Hounsfield unit value (mean ± SD)	116.3 ± 53.8		76.0 ± 63.7	127.1 ± 39.3	0.12

BMI, body mass index; H/P ratio, Hounsfield/pentosidine ratio; LLIF, lateral lumbar interbody fusion; PLIF, posterior lumbar interbody fusion; SD, standard deviation; TLIF, transforaminal lumbar interbody fusion

summarizes the demographic, clinical, and surgery-related data for each patient. The prevalence of screw loosening was 40% (14/35 patients). The cut-off value for the H/P ratio calculated from the ROC curve was 1482.6. Patients were divided into two groups based on this cut-off value (Table 1). The prevalence of screw loosening was 68.8% (11/16 patients) when the H/P ratio was < 1482.6 and 15.8% (3/19 patients) when it was > 1482.6. There were significant between-group differences in dialysis status ($P=0.03$) and the serum pentosidine level ($P=0.007$) (Table 1). However, there was no significant difference in any of the other variables between the groups.

Risk factors related to screw loosening

Univariate analysis of demographic, clinical, and surgery-related data was performed to identify risk factors for screw loosening after spinal surgery (Table 2). The only significant risk factor identified was the H/P ratio (odds ratio [OR] 0.09, confidence interval [CI] 0.02–0.43, $P=0.003$). Next, multivariate analysis was performed using the H/P ratio, diabetes status (OR 5.45, CI 0.5–58.92, $P=0.13$), and dialysis status (OR 5.45, CI 0.5–58.92,

$P=0.13$), all of which had been found to have a P -value of < 0.2 in univariate analysis. In multivariate analysis, the H/P ratio (OR 0.09, CI 0.02–0.53, $P=0.007$) was the only factor that had a significant effect on the likelihood of screw loosening after lumbar spine surgery (Table 2).

Discussion

In this study, risk factors for screw loosening at 12 months after lumbar interbody fusion were analyzed using the demographic and preoperative data for 35 patients with lumbar spine disease. We found that the prevalence of screw loosening was 40% (Table 1), and multivariate analysis revealed that bone mineral density and the H/P ratio, which we developed as an indicator of bone fragility, were significant independent prognostic factors (Table 2).

Loosening of pedicle screws is a major complication of spine surgery and should be monitored for because it causes back pain and neurological symptoms and requires additional surgery [7]. Loosening of pedicle screws has been reported to occur in 0.8–27% of cases, with rates of higher than 50% in patients with osteoporosis [7, 31–33]. In this study, the screw loosening rate was

Table 2 Univariate and multivariate analysis of risk factors for screw loosening after spinal surgery

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (mean \pm SD)	0.97	0.91–1.04	0.39			
Sex	0.42	0.1–1.68	0.22			
BMI	0.95	0.77–1.17	0.61			
Tobacco	0.33	0.03–3.28	0.3			
Diagnosis			0.91			
LCS vs. LDS	1.3	0.32–1.18	0.72			
LCS vs. LS	0.83	0.06–11.28	0.89			
LDS vs. LS	0.64	0.05–8.62	0.74			
Hypertension	1.35	0.35–5.44	0.67			
Diabetes	5.45	0.5–58.92	0.13	3.79	0.22–65.24	0.36
Osteoporosis	1.39	0.33–5.9	0.66			
Dialysis	5.45	0.5–58.92	0.13	0.94	0.06–14.95	0.96
Surgical technique			0.28			
TLIF vs. PLIF	0.22	0.03–1.42	0.11			
TLIF vs. LLIF	0.26	0.04–1.7	0.16			
PLIF vs. LLIF	1.17	0.12–10.99	0.89			
TLIF vs. TLIF + LLIF	0.78	0.04–14.75	0.87			
PLIF vs. TLIF + LLIF	3.5	0.14–84.69	0.44			
LLIF vs. TLIF + LLIF	3	0.12–73.64	0.5			
Number of intervertebral fusion level			0.54			
1 vs. 2	2.52	0.46–13.8	0.29			
1 vs. 3	1.89	0.11–33.89	0.67			
2 vs. 3	0.75	0.03–17.51	0.86			
HU/Pent ratio	0.09	0.02–0.043	0.003	0.09	0.02–0.53	0.007

CI, confidence interval; H/P ratio, Hounsfield/pentosidine ratio; LCS, lumbar spinal canal stenosis; LDS, lumbar degenerative spondylolisthesis; LLIF, lateral lumbar interbody fusion; LS, lumbar spondylolisthesis; OR, odds ratio; PLIF, posterior lumbar interbody fusion; SD, standard deviation; TLIF, transforaminal lumbar interbody fusion

40%, which is relatively high. In contrast, in the report on complications after posterior fixation by Marie-Hardy et al., the prevalence was 9.6% when defined as screw pull-out and 40.4% when defined as a translucent band of > 1 mm around the screw on a radiograph [4], suggesting that the prevalence depends on the definition of loosening. Previously reported risk factors for screw loosening include low bone density and older age [6, 7, 32, 34]. In the present study, age was not a significant risk factor.

Bone fragility is an important component in screw loosening and is thought to be caused by deterioration of bone quality and loss of bone mineral density [35, 36]. Bone quality includes bone microstructure, accumulation of microfractures, bone metabolic turnover, and deterioration of bone collagen [37, 38]. Increased oxidative stress is known to be associated with accumulation of AGEs in bone, which results in deterioration of the bone matrix [37, 38]. Pentosidine is a surrogate marker for AGE levels overall [39]. High levels of pentosidine in blood and urine correlate positively with the AGE level in bone and are known to be a risk factor for bone fracture.

Shin et al. identified that the HU value in the L4 vertebra independently predicted postoperative screw loosening in the spine [15]. However, the HU value reflects bone

density only and does not consider the effect of deterioration of bone quality. Indeed, we have encountered patients with high bone density accompanied a high level of pentosidine, in whom screw loosening occurred. Therefore, we performed this retrospective study to test the hypothesis that the preoperative serum pentosidine level could predict screw loosening. Our univariate analysis of the serum pentosidine level and the HU value as explanatory variables identified that the HU value was a significant factor (OR 0.99, CI 0.97–1.00, $P=0.05$) but pentosidine was not (OR 6.3, CI 0.16–244.28, $P=0.29$). In multivariate analysis, only the HU value was a significant prognostic factor (OR 0.98, CI 0.97–1.00, $P=0.02$). This finding is consistent with previous reports [15]. Therefore, we developed the H/P ratio, which combines the two factors of bone strength and deterioration of bone quality. Only this ratio remained a significant prognostic factor in multivariate analysis (Table 2); the OR for the H/P ratio was lower than that for the HU value and was considered a stronger predictor of screw loosening. The cut-off value for the H/P ratio obtained from the ROC curve was found to be 1482.6. The patients were divided into two groups based on this cut-off value, and significant between-group differences in haemodialysis status

and pentosidine level were found (Table 1). Serum pentosidine was not significant in univariate analysis ($P=0.29$) when the HU value and pentosidine level were entered as explanatory variables. Therefore, we speculated that the difference in the H/P ratio was a significant factor in the characteristics of the groups.

This study had three main limitations. First, it had a retrospective cohort design and a small sample size, so the statistical power was low. In addition, a small sample size results in an inhomogeneous size for each diagnosis. Furthermore, the high prevalence of loosening may make logistic regression analysis unreliable. Other factors, such as the large number of variables and the lack of effect size analysis, may reduce statistical power and reliability. Second, the small sample size may have precluded selection of all potential risk factors for screw loosening. For example, factors such as screw, rod, cage size and material, and implant manufacturer were not examined. Furthermore, certain parameters related to spinal alignment have been reported to be risk factors for screw loosening [2], but in the present study, imaging parameters related to preoperative spinal alignment were not analyzed. Use of steroids has also been reported to be a risk factor for screw loosening [17] but was not included in the analysis. Third, the surgeries were not performed by the same surgeon, and the surgical technique used in each case was chosen by the individual operator. This should be taken into consideration when interpreting the findings of the study.

In conclusion, **in this retrospective study the H/P ratio was a stronger risk factor for screw loosening after spine surgery than the HU value alone.** This finding is attributed to the fact that the H/P ratio includes the serum pentosidine level, which reflects deterioration of bone quality, whereas the HU value reflects bone density alone. Further basic and clinical studies are expected to clarify the relationship between pentosidine and other factors related to deterioration of bone quality and screw loosening after spine surgery.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12891-024-08236-w>.

Supplementary Material 1

Acknowledgements

The manuscript received English-language editing from ThinkSCIENCE (Tokyo, Japan). This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author contributions

D.A. designed the study and drafted the article. T.K. and K.S. collected the data. D.A. and K.M. analysed the data. M.S. and A.S. supervised the project. All authors read and approved the contents of this study.

Funding

The authors received no funding for this research.

Data availability

The data generated during this study are available within the article. Datasets analyzed during the preparation of this study are included as electronic supplementary material.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The study protocol was approved by the Jikei University School of Medicine Ethics Committee (30–115 [9136]).

Informed consent

All patients provided written informed consent.

Received: 25 February 2024 / Accepted: 20 December 2024

Published online: 26 December 2024

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