



# Feasibility of Non-window Three-Dimensional-Printed Porous Titanium Cage in Posterior Lumbar Interbody Fusion: A Pilot Trial

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**Background:** The commercially available design of a three-dimensional (3D)-printed titanium (3D-Ti) cage can be divided into two types according to the presence of a window: a cage with a window that allows filling of bone graft materials and a non-window cage for stand-alone use. This prospective observational case series study aimed to explore the clinical feasibility of using a non-window type 3D-Ti cage in cases of combined window and non-window cage implantation. Furthermore, we evaluated the bone in growth patterns of non-window cages and their correlation with published fusion grading systems.

**Methods:** A total of 31 consecutive patients who underwent single-level posterior lumbar interbody fusion surgery were included. Two 3D-Ti cages with different designs were inserted: a non-window cage on the left side and a window cage on the right side. Radiographic fusion was defined by the segmental angle between flexion and extension radiographs (F-E angle) and cage bridging bone (CBB) scores on computed tomography. The association between the F-E angle and osteointegration scoring system including the surface osteointegration ratio (SOR) score was analyzed.

**Results:** Radiographic fusion was achieved in 27 of 31 patients (87%) at 12 months postoperatively. Among the non-window cages, 23 of 31 (74.2%) had fair SOR scores, while 19 of 31 (61.3%) window cages had fair intra-cage CBB scores. The higher the SOR score was, the smaller the flexion-extension angle (SOR 0 vs. SOR 1:  $6.30^\circ \pm 2.43^\circ$  vs.  $1.95^\circ \pm 0.99^\circ$ ,  $p < 0.001$ ; SOR 0 vs. SOR 2:  $6.03^\circ \pm 2.43^\circ$  vs.  $0.99^\circ \pm 0.74^\circ$ ,  $p < 0.001$ ).

**Conclusions:** The clinical feasibility of using a non-window 3D-Ti cage during lumbar interbody fusion might be acceptable. Furthermore, a newly suggested fusion criterion for the use of the non-window cage, the SOR score, showed a significant association with the published fusion grading systems, demonstrating its feasibility in determining interbody fusion in lumbar spinal surgery.

**Keywords:** Titanium, Printing, Lumbar surgery, Spinal fusion, Ossteointegration

Lumbar interbody fusion has become one of the most commonly performed procedures for degenerative disease of the lumbar spine,<sup>1)</sup> showing favorable clinical outcomes. To achieve desirable results, solid fusion of the operated segment is crucial.<sup>2)</sup> Since Hacker et al.<sup>3)</sup> successfully reported using an interbody cage, various materials and designs for interbody cages have been introduced, including stainless steel, polyetheretherketone (PEEK), titanium alloy, and carbon fibers, to provide early mechanical stability and a fusion bed for the operated segments.

Received December 30, 2022; Revised April 25, 2023;

Accepted April 28, 2023

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Among these materials, PEEK and titanium are the most widely used materials. PEEK has a similar elastic modulus to the vertebral body, which could decrease the stress-shielding effect on the operated segment.<sup>4)</sup> However, its poor biocompatibility inhibits bone growth on the cage surface.<sup>5,6)</sup> In contrast, titanium alloy has superior biocompatibility, promotes osteoblast migration, and results in bone formation on the surface.<sup>7,8)</sup> Still, its high elastic modulus compared with the vertebral body remains a concern.<sup>9,10)</sup>

Recently, three-dimensional (3D) printers have allowed the generation of a porous structured titanium cage, which minimizes the disadvantages of titanium alloy including its high elastic modulus and metal artifact on computed tomography (CT) and magnetic resonance imaging while maintaining its biocompatibility.<sup>11)</sup> The commercially available design of a 3D-printed titanium (3D-Ti) cage can be divided into two types according to the presence of a window: a cage with a window that allows filling of bone graft materials and a non-window cage for stand-alone use. In the case of a window cage, the grafted material in the cage void can induce new bone bridging, which is not possible with non-window cages.

To our knowledge, no studies have prospectively evaluated the bone ingrowth patterns between 3D-Ti window and non-window cages. We hypothesized that 3D-Ti cages with and without a window will provide equally favorable radiographic outcomes. Therefore, we aimed to evaluate the clinical feasibility of using a 3D-Ti non-window cage in a case series involving combined implantation of window and non-window cages before conducting a randomized trial and to evaluate the radiographic fusion patterns of non-window cages and their correlation with published fusion grading systems.

## METHODS

### Study Design and Participants

This study was a prospective case series conducted at three institutes and was approved by each Institutional Review Board (No. 2305-001-19468). A total of 31 consecutive patients, who signed informed consents and planned to undergo single-level posterior lumbar interbody fusion (PLIF) surgery for degenerative lumbar disease between July 2018 and January 2020, were included. The inclusion criteria were as follows: (1) patients aged  $\geq 18$  years and  $\leq 85$  years and (2) patients with available stress radiographs and multiaxial reconstructed CT scans obtained 12 months postoperatively. Patients with medical conditions that could inhibit the fusion process, including malnour-

ishment, infection, and other metabolic diseases, were excluded.

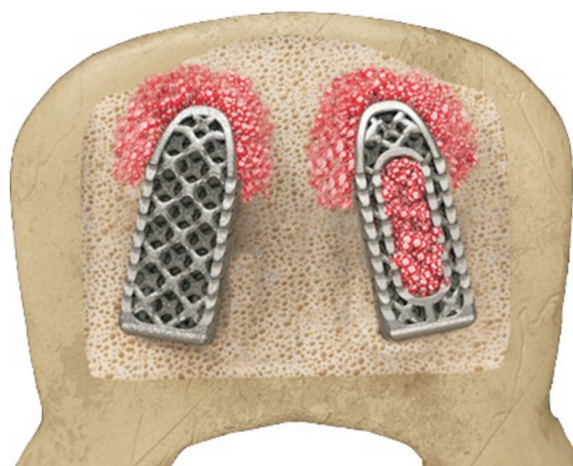
### Surgical Procedure

Three spine surgeons from three different institutions (KSS, DGC, and JJY) performed PLIF with identical procedures. After disc preparation, an equal amount of 6 mL of extra-cage bone graft, consisting of a half-mixed combination of local autologous bone from laminectomy and allograft, was used to fill the anterior intervertebral space bilaterally. Subsequently, 3D-Ti cages (Genoss, Suwon, Korea) with different designs were inserted: a non-window cage was used on the left side, and a window cage filled with local autobone was used on the right side (Fig. 1).

### Determination of Fusion Criteria and Radiologic Evaluation

Radiographic fusion was defined on both stress radiographs and CT 12 months postoperatively according to the agreement of two spine surgeons (DWH and CWJ). Fusion in stress radiographs was defined when the following criteria were fulfilled: (1) no cage subsidence more than 3 mm and (2) less than  $3^\circ$  difference in the segmental angle between flexion and extension radiographs (F-E angle) at 12 months postoperatively.<sup>12,13)</sup>

On multiaxial reconstructed CT, we used the following scoring system, which was previously reported,<sup>12)</sup> to investigate the bridging bone patterns with the two different titanium cages. For the window cage, we used the



**Fig. 1.** Illustration of the surgical method using bilateral interbody three-dimensional-printed titanium cages with different graft compositions and bone graft. Prior to the cages being inserted, an equal amount of 6 mL of bone graft material, consisting of a half-mixed combination of autologous local bone and allograft chip bone, was placed in the anterior intervertebral space bilaterally.

intra-cage bridging bone (InCBB) score and extra-cage bridging bone score. This system evaluates the new bone formation pattern intra- and extra-cage and assigns 0 to 2 points according to the degree of completion of bone bridging (grade 0: no bridging; grade 1: incomplete bridging or bridging at the superior or inferior endplate with a clear radiolucent line; grade 2: complete bridging). The higher the sum of these scores was, the more firm and stable fusion was achieved in the segment.<sup>12)</sup>

For the non-window cage, we developed a surface osteointegration ratio (SOR) score that evaluates the osteointegration ratio between the cage's surface and the endplates on sagittal CT images. When a translucent line was visible between the cage and the endplate in more than 50% of the sagittal images, zero points were assigned. When more than 50% of the endplate was integrated with the cage without a translucent line, 1 point was assigned. The scores for the upper and lower endplates were summed for a maximum score of 2 (Fig. 2).

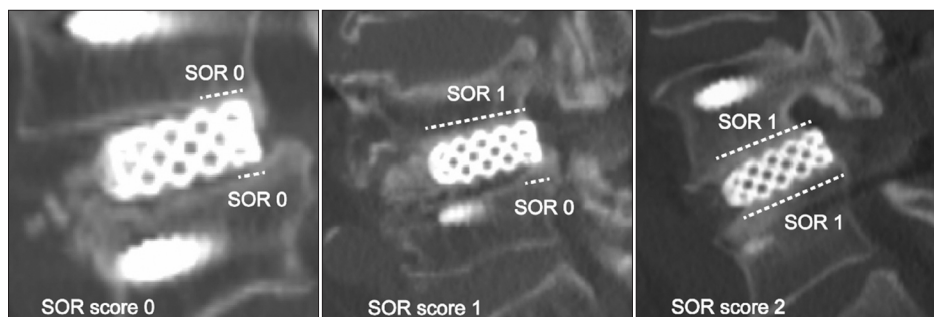
### Clinical Outcome Measurement

The clinical outcomes were evaluated using patient-reported outcome (PRO) measures including the leg pain numeric rating scale (NRS), the 12-item short form survey (SF-12), the Oswestry Disability Index (ODI), and the EuroQoL-5 dimension (EQ-5D). The ODI<sup>14)</sup> is a self-administered questionnaire that measures "back-specific function" on a 9-item scale with six response categories each. The EQ-5D is a five-dimensional health state classification; the five dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. An EQ-5D "health state" is defined by selecting one level from each dimension. The EQ-5D preference-based measure

can be regarded as a continuous outcome scored on a 0 to 1.00 scale, with 1.00 indicating "full health" and 0 representing death. These data were collected preoperatively and reassessed at 3, 6, and 12 months postoperatively. In 12 domains, the SF-12<sup>15)</sup> evaluates a patient's physical, social, and mental health. It consists of two components including physical and mental parts that summarize a patient's health status. The population mean for the SF-12 scale is 50, with a standard deviation of 10. A higher score indicates a healthier condition.

### Statistical Analysis

In calculating the sample size, the primary endpoint of this study was the proportion of endplate-cage surface osteointegration in the fusion group and the anticipated proportion of osteointegration in the fusion group at 12 months postoperatively was 90%. With a two-sided 95% confidence interval of 12%, 25 fusion segments were needed. Assuming a fusion rate with the 3D-Ti cage of 90%,<sup>16)</sup> a total of 28 patients were needed. Considering a dropout rate of 10%, we enrolled 32 patients in this study. G\*Power software version 3.1.9.7 (Düsseldorf, Germany) was used to calculate the sample size. The continuous variables between the fusion and non-fusion groups were analyzed using independent *t*-tests. Differences in the F-E angle according to the SOR score were compared using analysis of variance. Simple linear regression analysis was performed to evaluate the correlation between the CBB and SOR scores. In addition, a subgroup analysis was performed within the fusion group to compare the bone formation patterns between the window and non-window cage sides. All statistical analyses were performed using IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA).



**Fig. 2.** Newly introduced radiographic osteointegration evaluation system for the non-window type cage. The surface osteointegration ratio (SOR) score assesses the level of osteointegration and translucency between the cage surface and each upper and lower endplate. One point is assigned to each endplate when more than 50% of the endplate is integrated with the cage without translucency, for a maximum score of 2. The left image shows a SOR score of 0 point, as osteointegration is less than 50% on both the upper and lower endplates. The middle image shows a SOR score of 1 point, as osteointegration is 50% or more on the upper endplate but less than 50% on the lower endplate. The right image shows a SOR score of 2 points, as osteointegration is 50% or more on both the upper and lower endplates.

## RESULTS

### Patient Characteristics and Surgical Outcomes

A total of 31 patients with a mean age of  $74.2 \pm 6.9$  years were enrolled in the study. Baseline demographic parameters and the PRO results were compared according to the fulfillment of fusion criteria (Table 1). Fusion criteria were fulfilled in 27 of 31 patients (87%) at 12 months postoperatively. Age, sex, operation level, and cage height were not significantly different between the fusion and non-fusion groups (Table 1). All PRO measures including the ODI, leg pain NRS, SF-12, and EQ-5D scores were improved at 12 months postoperatively compared with preoperative values, and there were no significant differences between the fusion and non-fusion groups (Table 1).

### F-E Angle and SOR Score with the Non-window Cage

The F-E angle in the group with SOR scores of 1 and 2 was significantly lower than that in the group with an SOR score of 0; in contrast, there was no significant difference in the F-E angle between the group with an SOR score of 1 and the group with an SOR score of 2 (SOR 0 vs. SOR 1:  $6.30^\circ \pm 2.43^\circ$  vs.  $1.95^\circ \pm 0.99^\circ$ ,  $p < 0.001$ ; SOR 0 vs. SOR 2:  $6.03^\circ \pm 2.43^\circ$  vs.  $0.99^\circ \pm 0.74^\circ$ ,  $p < 0.001$ ; SOR 1 vs. SOR 2:  $1.95^\circ \pm 0.99^\circ$  vs.  $1.80^\circ \pm 2.07^\circ$ ,  $p = 0.248$ ) (Fig. 3).

### Correlation of Bridging Bone Scoring System and SOR Score System

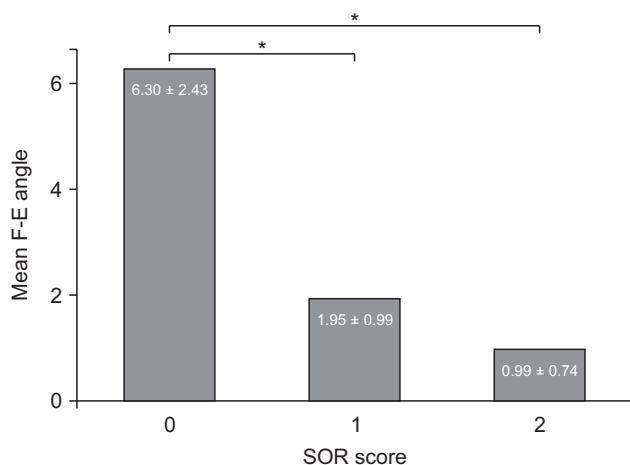
The correlation between the CBB and SOR scores was evaluated using simple linear regression analysis. The regression analysis showed that the SOR score was statistically significantly positively correlated with the bridging bone scoring systems ( $R^2 = 0.356$ ,  $p < 0.001$ ) (Table 2).

**Table 1.** Descriptive Analysis of Clinical Characteristics in the Present Study

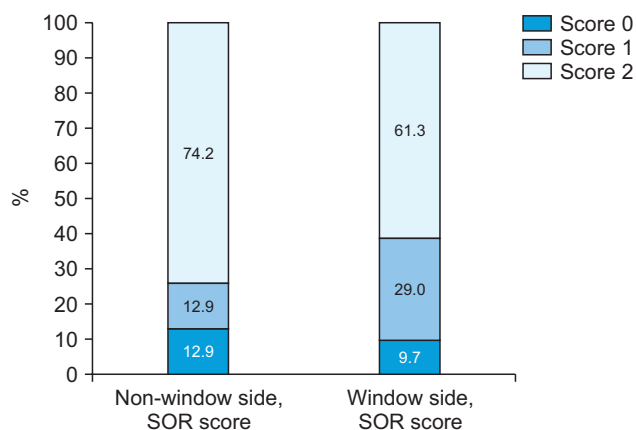
Variable	Fused	Non-fused	Total	p-value
Number of patients	27 (87)	4 (13)	31	-
Age (yr)	$73.8 \pm 6.9$	$77.2 \pm 6.3$	$74.2 \pm 6.9$	0.353
Female sex	20 (74)	2 (5)	22 (71)	0.689
Operation level				0.431
L2–3	1 (3.7)	0	1 (3.2)	
L4–5	11 (40.7)	3 (75.0)	14 (45.2)	
L5–S1	15 (55.6)	1 (25.0)	16 (51.6)	
Cage height (mm)	$9.3 \pm 0.6$	$9.0 \pm 0.8$	$9.3 \pm 0.6$	0.341
ODI				
Preoperative	$0.505 \pm 0.159$	$0.565 \pm 0.174$	$0.512 \pm 0.159$	0.554
Postoperative 12 mo	$0.149 \pm 0.112$	$0.198 \pm 0.149$	$0.155 \pm 0.156$	0.568
NRS				
Preoperative	$7.8 \pm 1.3$	$8.0 \pm 1.6$	$7.8 \pm 1.3$	0.840
Postoperative 12 mo	$1.8 \pm 1.4$	$3.3 \pm 2.2$	$2.0 \pm 1.6$	0.289
SF-12				
Preoperative	$33.0 \pm 10.8$	$24.0 \pm 3.9$	$31.9 \pm 10.6$	0.112
Postoperative 12 mo	$42.1 \pm 8.1$	$41.0 \pm 10.5$	$42.0 \pm 8.3$	0.800
EQ-5D				
Preoperative	$0.420 \pm 0.219$	$0.432 \pm 0.126$	$0.422 \pm 0.208$	0.876
Postoperative 12 mo	$0.808 \pm 0.124$	$0.722 \pm 0.257$	$0.797 \pm 0.144$	0.555

Values are presented as number (%) or mean  $\pm$  standard deviation.

ODI: Oswestry Disability Index, NRS: numeric rating scale, SF-12: 12-item short form survey, EQ-5D: EuroQoL-5 dimension.



**Fig. 3.** Association between the flexion-extension (F-E) angle and surface osteointegration ratio (SOR) score. The F-E angle in the group with SOR scores of 1 and 2 was significantly lower than that in the group with an SOR score of 0. Values are presented as mean  $\pm$  standard deviation. \* $p < 0.05$ .



**Fig. 4.** Comparison of the intra-cage new bone formation ratio of the two types of cages. Among non-window cages, 23 out of 31 cages (74.2%) showed fair surface osteointegration ratio (SOR) scores, while among the window cages, 19 of 31 cages (61.3%) showed fair intra-cage bridging bone scores, indicating fair new bone formation in the void.

**Table 2.** Univariate Regression Analysis for Osteointegration Scoring Systems of the Communicating Bridging Bone Score

Univariate regression analysis for bridging bone score			
	$\beta$ (95% confidence interval)	$R^2$	$p$ -value
SOR score	2.407 (1.806–3.001)	0.356	$< 0.001$

SOR: surface osteointegration ratio.

### Intra-cage Osteointegration Patterns of Two Types of Cages

The cages that scored 2 points in the InCBB score, SOR score, or had a positive CB sign were classified into the fair intra-cage bone formation group. Among non-window cages, 23 out of 31 (74.2%) cages showed fair SOR scores (Fig. 4). On the other hand, among window cages, 19 out of 31 (61.3%) cages showed fair InCBB scores, indicating fair new bone formation in the void (Fig. 4).

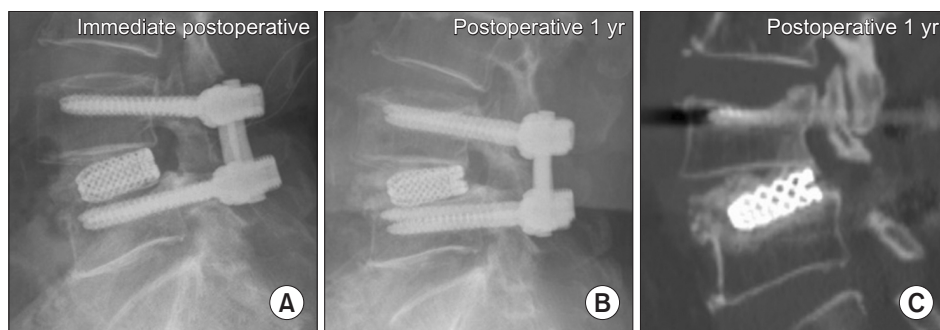
## DISCUSSION

The present study demonstrated that patients who underwent PLIF with a non-window 3D-Ti cage without bone graft material on one side showed favorable radiologic and clinical outcomes. Furthermore, the osteointegration scoring system that evaluates bone growth around the 3D-Ti cage, the SOR, showed favorable agreement with the known published radiographic fusion criteria.<sup>12)</sup>

The overall fusion rate in the present study was 87.1%, which is consistent with the findings of previ-

ous studies,<sup>17,18)</sup> reporting a fusion rate of 80%–86% at 1 year postoperatively. Furthermore, the results from CT scans confirmed that even without bone graft materials, sufficient endplate-cage intersurface bone ingrowth was achieved on the non-window cage side. Arts et al.<sup>19)</sup> reported that a 3D-Ti cage accelerated the fusion process in the early postoperative period even without a bone graft or biomaterial compared with a PEEK cage in cervical fusion surgery. This result is in accordance with the present study, which demonstrated a consistent surface osteointegration score compared with the window-type cage side with a favorable interbody fusion rate.

Titanium alloy is a biocompatible material that can promote bone growth and has been used for decades in the orthopedic and spinal surgery fields.<sup>20)</sup> The elastic modulus of earlier titanium alloy cages was much stronger than that of bone.<sup>21)</sup> Therefore, cage subsidence has been reported due to a stress-shielding effect in the fusion segment.<sup>22)</sup> By comparison, a 3D-Ti cage decreases the elastic modulus, which prevents the stress-shielding effect.<sup>23)</sup> However, it remains controversial whether the void structure within the cage for bone graft materials affects the structural stability of a 3D-printed cage. For this reason, a non-window type cage has been used, but in this case, there is controversy regarding whether bone graft material should be placed in the cage because it may be detrimental for interbody fusion. However, from the present study, we confirmed that sufficient bone growth in the endplate-cage intersurface could be achieved on the non-window cage side. These results suggest that favorable interbody fusion can be achieved even with a non-window titanium

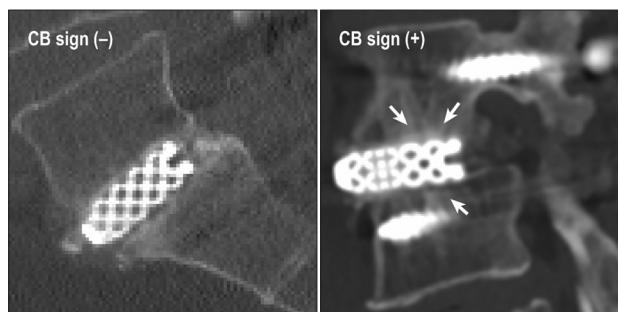


**Fig. 5.** Representative case for cage subsidence. (A) A 64-year-old male patient who underwent L4–5 posterior lumbar interbody fusion surgery. (B, C) Cage subsidence was confirmed 1 year postoperatively on simple radiographs and multi-axial computed tomography scans.

cage alone without bone graft material while providing sufficient structural stability.

The ideal interbody cage must be rigid enough to maintain stability but preferably have a similar Young's modulus to that of bone to prevent subsidence and stress-shielding.<sup>24)</sup> Titanium alloy cages have excellent biocompatibility and mechanical stability.<sup>7,8)</sup> Still, due to the difference in the elastic modulus between titanium and cortical bone, a higher cage subsidence rate than with a PEEK cage remains a concern.<sup>9,10)</sup> Several factors are reportedly associated with cage subsidence following interbody fusion including poor endplate bone quality, narrow and tall cage, and endplate injury during disc preparation.<sup>25-31)</sup> Therefore, careful disc preparation to avoid endplate injury, especially during the use of a 3D-Ti cage, is a crucial factor for preventing cage subsidence (Fig. 5).

The feasibility of using fusion criteria to assess bridging bone is a concern that remains in spinal surgery using a titanium cage. The Bridwell interbody fusion grading system is the most well-known tool used to evaluate fusion rates in spinal surgery; still, due to metal artifacts associated with titanium alloy, concerns about the feasibility of its use remain.<sup>32)</sup> Recently, our team suggested a scoring system<sup>12)</sup> that evaluates intra-cage and extra-cage osteogenesis patterns on CT scans and reported its usefulness in determining interbody fusion in lumbar fusion surgery. In the present study, we have presented the SOR score as a novel grading system to evaluate the endplate-cage intersurface osteointegration (Fig. 2). The results demonstrated that the SOR score was significantly correlated with the bridging bone score and with the F-E angle on dynamic radiographs (Table 2 and Fig. 3). In this context, the SOR scoring system with the 3D-Ti cage seems to be clinically useful for determining segment fusion in lumbar spinal surgery. In addition, previous research by Segi et al.<sup>33)</sup> reported that patients with a positive trabecular remodeling sign had lower rates of instrument failure and pseudoarthrosis. In our study, the communicating bridging sign, which indicates trabecular remodeling, (Fig.



**Fig. 6.** The communicating bridging (CB) sign on sagittal computed tomography images (white arrows) is considered positive when newly generated bone passes through the internal structure of the cage itself with trabecular remodeling signal.

6) was also observed in patients who achieved firm fusion. Considering this, we believe that the communication bridging sign could be a clinical determinant for evaluating fusion in non-window 3D-Ti cages.

On the comparison of the intra-cage new bone formation ratio of the two types of cages, 23 cases (74.2%) with the non-window cage had fair SOR scores, while only 19 cases (61.3%) with the window cage side had fair InCBB scores (Fig. 4). Although direct comparison of the two types of cages in the current study design is difficult, these results could demonstrate that the non-window type cage can achieve sufficient surface osteointegration similar to the window type cage. Furthermore, these results support the clinical applicability of the SOR scoring system for evaluating fusion with the non-window 3D-Ti cage.

This study has several limitations. First, the study population was limited in size, and the follow-up duration was relatively short. While we elucidated the sample size calculation process in the Materials and Methods section, we acknowledge that a cohort of 31 cases may not provide sufficient statistical power. However, we believe that this pilot study, which aims to assess the feasibility of non-window cages rather than directly comparing window and non-window cages on a 1 : 1 basis, can have clinical

significance with the current design. Second, in the current study design, a direct comparison of two cages is difficult because the two types of cages were inserted in the same segment, potentially influencing each other's cage-endplate fusion. This is because if the cage-endplate fusion is first achieved on one side cage, the motion on the other side is reduced and the fusion process can be facilitated, which can bias the accurate evaluation. However, it should be considered that this study was a preliminary study to evaluate the clinical feasibility of using a 3D-Ti non-window type cage before performing a randomized trial. Despite these limitations, our study has some strengths in that the intra-cage bone formation patterns of the window and non-window type 3D-Ti cages were descriptively compared. A further randomized prospective study involving an objective comparative analysis with the window cage is being conducted.

In conclusion, the present study demonstrated that the clinical feasibility of using a non-window 3D-Ti cage for lumbar interbody fusion might be acceptable. Furthermore, the osteointegration tendency of the cage indicated

that a 3D non-window cage itself could act as fusion bed without any bone graft materials in the cage void. Furthermore, a newly suggested fusion criterion for non-window cages, the SOR score, showed a significant association with the bridging bone score and F-E angle on dynamic radiographs, demonstrating its feasibility in determining interbody fusion in lumbar spinal surgery.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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