

## CLINICAL ARTICLE

# Does Preoperative Modic Changes Influence the Short-term Fusion Rate of Single Level Transforaminal Lumbar Interbody Fusion?—a Matched-pair Case Control Study

Yang Xiao, MM , Peng Xiu, MD, Xi Yang, MD , Liang Wang, MD, Tao Li, MD, Quan Gong, MD, Limin Liu, MD, Yueming Song, MD 

*Department of Orthopaedic, Orthopaedic Research Institute, West China Hospital, Sichuan University, Chengdu, China*

**Objective:** At present, the influence of Modic changes (MCs) on postoperative fusion rate of lumbar interbody fusion (LIF) is mainly focused on the medium- and long-term fusion rate, while the short-term fusion rate has not been reported. The aim of this study was to compare the short-term fusion rate of lumbar degenerative disease patients with and without MCs after single level transforaminal lumbar interbody fusion (TLIF).

**Methods:** In this retrospective and matched-pair case control study, we included 100 patients who underwent TLIF from January 2017 to January 2020 and had at least two follow-up visits over a two-year period. Fifty patients with MCs (MCs group) were matched with 50 patients without MCs (non MCs group) for age, sex, surgical level, diagnosis, operative time, and intraoperative blood loss. We collected the X-ray and computed tomography (CT) data of patients from 3 months to 2 years after the operation to assess bony fusion and the cage union ratio. According to the type of cage, the MCs group was further divided into the nano-hydroxyapatite/polyamide 66 (n-HA/PA66) group and polyetheretherketone (PEEK) group, and the fusion performance between the two groups was compared. Finally, age, sex, body mass index (BMI), smoking and cage type were included in the logistic regression model for risk factor analysis.

**Results:** The bony fusion rates in the MCs group at 3 months, 6 months, 1 year and 2 years after surgery were significantly lower than those in the non MCs group ( $P < 0.05$ ) (23.8% vs 62.5%, 52.6% vs 78.9%, 61.1% vs 83.3%, 74.0% vs 90.0%). The average coronal cage union ratios of the upper and lower endplates in the MCs group were significantly lower than those in the non MCs group ( $54.3\% \pm 17.5\%$  vs  $75.0\% \pm 17.2\%$ ,  $P < 0.05$ ;  $73.3\% \pm 12.0\%$  vs  $84.9\% \pm 8.0\%$ ,  $P < 0.05$ ). Similarly, analogous results were obtained by comparing the MCs and non MCs groups' three-dimensional CT sagittal plane images ( $62.5\% \pm 16.5\%$  vs  $76.1\% \pm 12.4\%$ ,  $P < 0.05$ ;  $67.0\% \pm 13.9\%$  vs  $79.8\% \pm 11.5\%$ ,  $P < 0.05$ ).

**Conclusion:** Short-term fusion rates were lower in the MCs group than in the non MCs group. The coronal and sagittal cage union ratio in the MCs group was lower than that in the non MCs group. The fusion performance of n-HA/PA66 and PEEK cages in the MCs group was comparable.

**Key words:** Lumbar degenerative disease; Modic changes; Nano-hydroxyapatite/polyamide 66; Polyetheretherketone; Transforaminal lumbar interbody fusion

## Introduction

Modic changes (MCs) are vertebral body marrow changes adjacent to the endplates visible on magnetic

resonance imaging (MRI) that are characterized by abnormal signals from the endplate and bone beneath the endplate on MRI.<sup>1,2</sup> MCs were discovered and reported by Michael

**Address for correspondence** Xi Yang, MD, Department of Orthopaedic, Orthopaedic Research Institute, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China. Email: [formosa88@163.com](mailto:formosa88@163.com)

Yang Xiao and Peng Xiu contribute equally and should be co-first author.

Received 29 January 2023; accepted 21 May 2023

Orthopaedic Surgery 2023;15:2309-2317 • DOI: 10.1111/os.13795

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

T. Modic in 1988.<sup>1,2</sup> While MCs are more common in middle-aged and elderly patients with spinal degeneration, it can also be seen in young people who take glucocorticoids for a long time and have a long history of poor posture. MCs are divided into three types: type I, bone marrow edema and inflammation, decreased signal on T1-weighted imaging (T1WI) and increased signal on T2-weighted imaging (T2WI); type II, marrow ischemia, conversion of normal red hemopoietic bone marrow into yellow fatty marrow, increased signal on T1WI, and unchanged or slightly increased signal on T2WI; and type III, subchondral bone sclerosis, decreased signal on T1WI and T2WI.<sup>3</sup> The overall reported prevalence of MCs is 5.8%, varying from 18% to 62% in patients with low back pain, with type II MCs being the most common type.<sup>4,5</sup>

Patients with lumbar degenerative diseases (LDDs) requiring lumbar interbody fusion (LIF) have a higher rate of MCs. The inflammatory environment of the intervertebral space in patients with MCs may influence osteogenesis and ultimately bone fusion; many cytokines, including IL-6, IL-8, and TNF- $\alpha$ , are produced, all of which can inhibit osteogenesis or promote bone resorption to varying degrees,<sup>6,7</sup> and may ultimately affect bone fusion.

Kim *et al.*<sup>8</sup> and Kwon *et al.*<sup>9</sup> found that the fusion rate was lower in patients with MCs than in those without MCs. Erinc *et al.*<sup>10</sup> confirmed that there was no significant difference in the fusion rate after posterior lumbar interbody fusion (PLIF) between patients with MCs and those without MCs. However, all the above studies took the last follow-up as the observation point, and the average follow-up time was more than 30 months; thus, the short-term fusion rate and the dynamic process of fusion were not examined. Due to the inflammatory environment in the intervertebral space and endplate sclerosis, we suspect that the short-term fusion rate is different from normal in patients with MCs. Cage migration and screw loosening are associated with a lack of early postoperative fusion of implanted bone, which will not only lead to prolonged recovery, but may also cause corresponding clinical symptoms.<sup>11-13</sup> Therefore, it is necessary to explore the short-term fusion rate in patients with and without MCs.

Cages are essential devices for LIF. Such cages support the vertebrae and maintain the intervertebral space height after removal of the intervertebral disc. There are many kinds of cages, such as those made of polyetheretherketone (PEEK), nano-hydroxyapatite/polyamide 66 (n-HA/PA66), titanium alloys, bioglass, and bioceramics. As a bioactive cage material, n-HA/PA66 has achieved satisfactory results, but its effect in patients with MCs is still unknown. In addition, different from other studies, the cage union ratio was selected as an index in this study to evaluate fusion in LDD patients with and without MCs in detail. The cage union ratio is the percentage of fused bone between the vertebral endplate and the local bone placed in the cage with respect to the transverse diameter of the cage.<sup>14,15</sup> Therefore, the aim of this study is: (i) to explore the influence of MCs on the short-term fusion rate after

transforaminal lumbar interbody fusion (TLIF) surgery; and (ii) to further compare the fusion performance of n-HA/PA66 and PEEK cages.

## Methods

### Study Design

This was a retrospective matched-pair study. We collected 954 patients diagnosed with LDD with or without MCs at our hospital from January 2017 to January 2020 who underwent TLIF with cage implantation. In total, 136 patients were enrolled according to the inclusion/exclusion criteria (66 had MCs and 70 had no MCs). To eliminate selective bias, we performed 1:1 matching according to age, sex, surgical level, diagnosis, operative time and intraoperative blood loss. Finally, 100 patients were recruited for the study, including 50 for the MCs group and 50 for the non MCs group (Fig. 1). According to the type of cage, the MCs group was further divided into the n-HA/PA66 group and the PEEK group, and the fusion performance in the two groups was compared. Finally, age, sex, body mass index (BMI), smoking and cage type were included in a logistic regression model for risk factor analysis.

### Inclusion/Exclusion Criteria

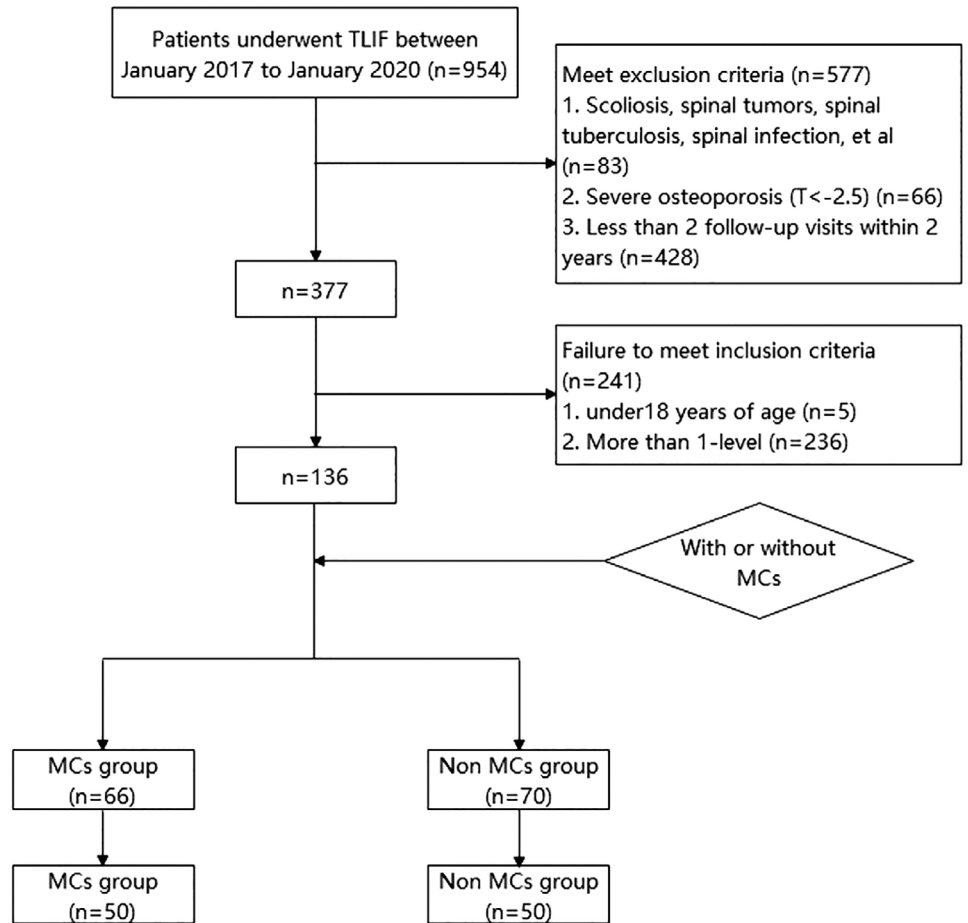
The inclusion criteria were as follows: (i) age of at least 18 years; (ii) diagnosis of lumbar spondylolisthesis, lumbar spinal stenosis, lumbar disc herniation or recurrent lumbar disc herniation; and (iii) treatment with single-level TLIF between January 2017 and January 2020 with n-HA/PA66 or PEEK cage implantation in the decompressed space. The exclusion criteria were as follows: (i) diagnosis of lumbar degenerative scoliosis, spinal tumors, spinal tuberculosis or spinal infection; (ii) severe osteoporosis ( $T < -2.5$ ); or (iii) fewer than 2 follow ups within 2 years after surgery.

### Ethics Review

The research was conducted according to the principles of the Declaration of Helsinki. The ethics committee of West China Hospital (No. 2019-654) approved the study. All patients signed written informed consent forms.

### Operative Technique

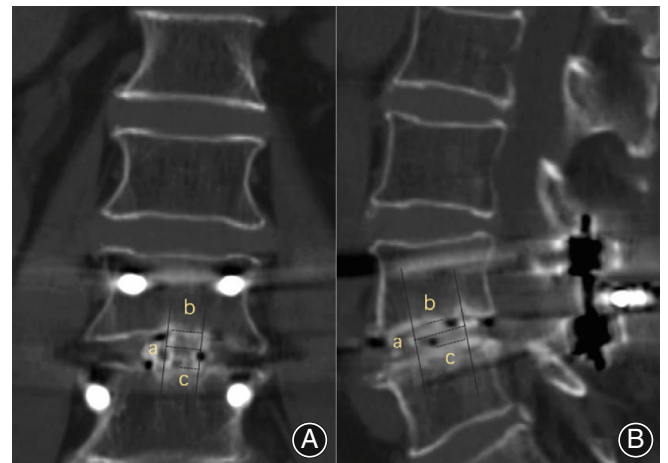
All patients were operated on by one of four senior spine surgeons after general anesthesia was included. The patients were not randomized to the type of cage; the decision to use an n-HA/PA66 or PEEK cages was made by the surgeon. After pedicle screw positioning, TLIF was performed as described by Gum *et al.*<sup>16</sup> Fragments of bone were acquired by removing cartilage and fibrous tissue from excised bone, which was then morselized. After filling the cage with bone fragments, superfluous bone was implanted into the anterior and contralateral disc space, and then the cage was implanted into the interbody space. Finally, the spine screw-rod system was reinforced longitudinally again, and correct positioning of the cage was confirmed under fluoroscopy.

**FILTERING CATABASE****FILTERING COMPLETE****GROUP****MATCHED GROUP**

**Fig. 1** The flow diagram of including patients in this study.

**Imaging Analysis**

The presence of MCs was determined by magnetic resonance imaging (MRI). X-ray and three-dimensional computed tomography (CT) examinations were performed pre-operation, postoperation, and 3 months, 6 months, 1 year and 2 years after surgery. Fusion and subsidence were evaluated by X-ray and three-dimensional CT examinations of the lumbar spine. The fusion grade was assessed according to the Brantigan and Steffee criteria, as follows: grade I, obvious radiographic pseudarthrosis; grade II, probable radiographic pseudarthrosis; grade III, uncertain radiographic status; grade IV, probable radiographic fusion; and grade V, radiographic fusion.<sup>17</sup> Grades  $\geq$ IV were considered to indicate fusion, and grades  $<$ IV were considered to indicate nonfusion. In addition, the cage union ratio was measured by three-dimensional CT of the lumbar spine to evaluate the fusion of the cage with the upper and lower endplates (Fig. 2). We also randomly selected 48 patients to evaluate the reliability of the imaging measurements. This assessment was carried out by two orthopedic surgeons (Y. X. and P. X.) to evaluate intra-observer reliability. One of the doctors (Y. X.) took



**Fig. 2** (A) Coronal cage union ratio, percentage of coronal union cage length. Upper,  $b/a \times 100\%$ ; lower,  $c/a \times 100\%$ . (B) Sagittal cage union ratio, percentage of sagittal union cage length. Upper,  $b/a \times 100\%$ ; lower,  $c/a \times 100\%$ .

radiological measurements and then retook them 1 week later to evaluate inter-observer reliability. The intraclass coefficients (ICCs) of the intra-observer and inter-observer reliability were 0.896 and 0.924, respectively.

### Statistical Analysis

All data were analyzed using SPSS 26.0 software (SPSS, Inc., Chicago, IL, USA). Continuous data are presented as the mean  $\pm$  standard deviation and were analyzed by using independent Student's *t* tests. Categorical data were compared by using Pearson's chi-square test, Yate's continuity correction or Fisher's exact test. Studies have confirmed that BMI and smoking are risk factors for bone fusion.<sup>18–21</sup> Therefore, we constructed a binary logistic regression model to exclude the interference of age, gender and cage type and verify the previous conclusions. A *P* value less than 0.05 was considered to indicate a significant difference.

### Follow-up and Outcome Measurement

The aim of this study was to explore the effect of MCs on the short-term fusion rate. We defined short-term as 2 years after surgery and accounted for the dynamic changes in

fusion. Therefore, imaging data (mainly X-rays and three dimensional CT) were obtained 3 months, 6 months, 1 year and 2 years after surgery. Fusion grades were evaluated by X-ray and three dimensional CT using Brantigan and Steffee criteria and fusion rates were calculated for each group. Moreover, five consecutive 3D thin-slice reconstruction CT images of the lumbar spine were selected to calculate the cage union ratio, and then the average was calculated.

## Results

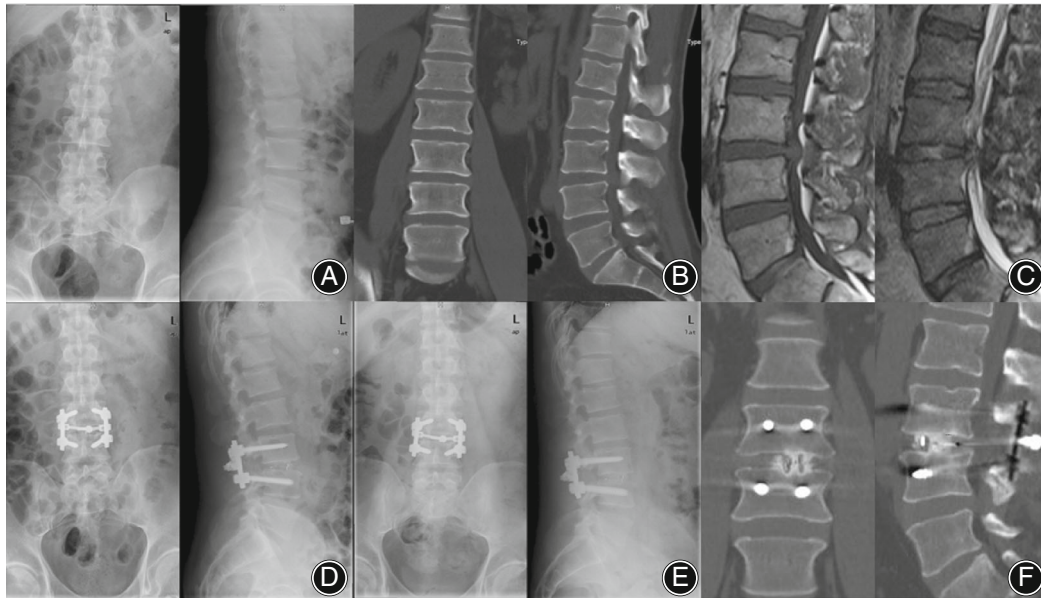
### Patient Demographics

A total of 100 patients were enrolled in this study, including 39 males and 61 females with an average age of 54.4 years (range 29–77 years). The surgical level was L3-L4 in nine patients, L4-L5 in 51 patients, and L5-S1 in 40 patients. Of the 100 patients, 49 were diagnosed with lumbar spondylolisthesis, 31 with lumbar spinal stenosis, 17 with lumbar disc herniation, and three with recurrent lumbar disc herniation. According to the presence or absence of MCs, 100 patients were divided into two groups: MCs group, including 50 patients with MCs; and non MCs group, including 50 patients without MCs (Figs. 3



**Fig. 3** A 56-year-old female patient underwent transforaminal lumbar interbody fusion with a polyetheretherketone (PEEK) cage due to L4-L5 lumbar disc herniation. MRI of patient suggested L4-L5 modic change (Type II). Preoperative lumbar radiographs (A–C). The postoperative radiographs (D). The final follow-up radiographs at 2 years after surgery showed that autogenous bone granules within the cage achieved satisfactory bony fusion (E, F). Of note, the surface of the PEEK cage fits closely with the bone tissue and is well integrated with both the upper and lower endplates. (Cage union ratio at the upper endplate: coronal = 57.5%, sagittal = 48.9%; at the lower endplate: coronal = 67.9%, sagittal = 76.2%).





**Fig. 4** A 40-year-old male patient underwent transforaminal lumbar interbody fusion with a polyetheretherketone (PEEK) cage due to L3-L4 lumbar disc herniation. Preoperative lumbar radiographs (A–C). The postoperative radiographs (D). The final follow-up radiographs at 1 year after surgery showed that autogenous bone granules within the cage achieved satisfactory bony fusion (E, F). Of note, the surface of the PEEK cage fits closely with the bone tissue and is well integrated with both the upper and lower endplates. (Cage union ratio at the upper endplate: coronal = 66.7%, sagittal = 76.9%; at the lower endplate: coronal = 79.9%, sagittal = 79.0%).

**TABLE 1** Demographic and baseline characteristics of the patients

Parameters	MCs Group (n = 50)	Non MCs Group (n = 50)	t/ $\chi^2$	P
Age (years)	54.5 ± 9.6	54.3 ± 10.3	−0.080	0.936
Sex (n)			0.042	0.838
Male	20	19		
Female	30	31		
Surgical level (n)			2.038	0.362
L3-L4	3	6		
L4-L5	24	27		
L5-S1	23	17		
Diagnosis (n)			4.711	0.184
Lumbar spondylolisthesis	29	20		
Lumbar spinal stenosis	11	20		
Lumbar disc herniation	8	9		
Recurrent lumbar disc herniation	2	1		
Operative time (min)	199.9 ± 13.6	195.9 ± 10.3	−1.650	0.102
Intraoperative blood loss (mL)	308 ± 72.4	300 ± 93.1	−0.480	0.633

**TABLE 2** Comparison of bony fusion rate at different follow-up times between two groups

Follow-up time	MCs Group (%)	Non MCs Group (%)	t/ $\chi^2$	P
3 months	23.8	62.5	12.536	0.000*
6 months	52.6	78.9	5.846	0.016*
1 year	61.1	83.3	4.431	0.035*
2 years	74.0	90.0	4.336	0.037*

\* Mean that statistical significance between two groups ( $P < 0.05$ ).

and 4). There was no significant difference in age, sex, surgical level, diagnosis, operative time or intraoperative blood loss between the two groups ( $P > 0.05$ ) (Table 1).

#### Bony Fusion in the Two Groups

The bony fusion rates in the MCs group at 3 months, 6 months, 1 year and 2 years after the operation were 23.8%, 52.6%, 61.1% and 74.0%, respectively. The bony fusion rates in the non MCs group at the same follow-up times were 62.5%, 78.9%, 83.3% and 90.0%, respectively. The bony

**TABLE 3 Comparison of cage union ratio at the final follow-up between two groups**

Parameters	MCs group*	Non MCs group*	t/X <sup>2</sup>	P
Coronal (%)				
Upper endplate	54.3 ± 17.5	75.0 ± 17.2	2.525	0.020 <sup>†</sup>
Lower endplate	73.3 ± 12.0	84.9 ± 8.0	2.675	0.014 <sup>†</sup>
Sagittal (%)				
Upper endplate	62.5 ± 16.5	76.1 ± 12.4	2.155	0.042 <sup>†</sup>
Lower endplate	67.0 ± 13.9	79.8 ± 11.5	2.266	0.033 <sup>†</sup>

\* All values are expressed as the mean ± standard deviation (SD).; <sup>†</sup> Mean that statistical significance between two groups ( $P < 0.05$ ).

**TABLE 4 Comparison of bony fusion rate between n-HA/PA66 and PEEK cage**

Follow-up time	n-HA/PA66 (%)	PEEK (%)	t/X <sup>2</sup>	P
3 months	15.0	46.7	0.838	0.360
6 months	52.6	52.6	0.000	1.000
1 year	65.0	56.2	0.286	0.593
2 years	76.0	72.0	0.104	0.747

fusion rate in the MCs group were significantly lower than those in the non MCs group ( $P < 0.05$ ) (Table 2).

### Cage Union Ratio in the Two Groups

The average coronal cage union ratios for the upper and lower endplates were significantly lower in MCs group than in non MCs group ( $54.3\% \pm 17.5\%$  vs  $75.0\% \pm 17.2\%$ ,  $P < 0.05$ ;  $73.3\% \pm 12.0\%$  vs  $84.9\% \pm 8.0\%$ ,  $P < 0.05$ ), as evaluated on the coronal plane using three-dimensional CT. Similarly, analogous results were obtained by comparing the MCs and non MCs groups' three-dimensional CT sagittal plane images ( $62.5\% \pm 16.5\%$  vs  $76.1\% \pm 12.4\%$ ,  $P < 0.05$ ;  $67.0\% \pm 13.9\%$  vs  $79.8\% \pm 11.5\%$ ,  $P < 0.05$ ) (Table 3).

**TABLE 5 Complications between the two groups**

Complications	MCs Group	Non MCs Group
Perioperatively		
CSF* leakage	1	0
Wound infection	0	1
Nerve root injury	0	0
Endplate injury	2	0
Implanted-related		
Screw loosening	0	0
Screw broken	0	1
Cage subsidence	5	3
Cage retropulsion/migration	0	1
Total	8	6

\* Cerebrospinal fluid.

### Bony Fusion in the Two Subgroups

We divided the MCs group into the n-HA/PA66 group and the PEEK group according to the type of cage. There was no significant difference in the bony fusion rate between the n-HA/PA66 and PEEK groups at 3 months, 6 months, 1 year or 2 years after surgery ( $15.0\%$  vs  $46.7\%$ ,  $P > 0.05$ ;  $52.6\%$  vs  $52.6\%$ ,  $P > 0.05$ ;  $65.0\%$  vs  $56.2\%$ ,  $P > 0.05$ ;  $76.0\%$  vs  $72.0\%$ ,  $P > 0.05$ ) (Table 4).

### Complications in the Two Groups

In the MCs group, there was one case of intraoperative cerebrospinal fluid leakage, two cases of intraoperative endplate injury and five cases of cage subsidence. In the non MCs group, there was one case of postoperative wound infection, one case of postoperative screw breakage, three cases of cage subsidence and one case of cage migration. There was no significant difference in complications between the MCs and non MCs groups ( $X^2 = 5.676$ ,  $P > 0.05$ ) (Table 5).

### Binary Logistic Regression Results of Risk Factors

The logistic regression analysis model, including sex, age, BMI, smoking and cage type, showed that BMI (OR, 1.735; CI, 1.107–2.721;  $P$ , 0.016) and smoking (OR, 5.659; CI, 1.092–29.331;  $P$  = 0.039) were independent risk factors for postoperative bone fusion in patients with MCs (Table 6).

### Discussion

To explore the influence of MCs on the short-term fusion rate after TLIF surgery and further compared the fusion performance of n-HA/PA66 and PEEK cages, we designed

**TABLE 6 Analysis of risk factors affecting bony fusion in modic changes patients**

Variable	$\beta$	Wald	P	Odds ratio	95% CI*
Sex <sup>†</sup>	1.264	2.005	0.157	3.541	0.615–20.374
Age	−0.069	2.606	0.106	0.934	0.859–1.015
BMI	0.551	5.769	0.016	1.735	1.107–2.721
Smoking	1.733	4.263	0.039	5.659	1.092–29.331
Cage type <sup>‡</sup>	0.011	0.000	0.989	1.011	0.201–5.090

\* CI, confidence interval.; <sup>†</sup> Take male as a reference.; <sup>‡</sup> Take PEEK as a reference.

this retrospective study. The results showed that the short-term fusion rate in patients with MCs at 3 months, 6 months, 1 year and 2 years after surgery was lower than that in patients without MCs, and the cage union ratio of the upper and lower endplates on the coronal and sagittal planes was also significantly lower in the MCs group than in the non MCs group. However, our study did not obtain positive results regarding screw loosening and cage migration, and there was no significant difference in the fusion rate between the n-HA/PA66 and PEEK groups, which may be explained by the small sample size. In addition, the results of binary logistic regression analysis showed that BMI and smoking were independent risk factors for bone fusion.

At present, the effect of MCs on the fusion rate after LIF surgery is still controversial. Liu *et al.*<sup>22</sup> and Erinc *et al.*<sup>10</sup> found that there was no significant difference in the fusion rate between patients with and without MCs. However, Kim *et al.*<sup>8</sup> and Kwon *et al.*<sup>9</sup> found a lower fusion rate in patients with MCs than in those without MCs. In addition, Li *et al.*<sup>23</sup> reported that the fusion rate in patients with type II sclerotic MCs was significantly lower than that in patients with type II nonsclerotic MCs or no MCs. The reason for the large heterogeneity of these results may be due to the study design, sample size, and follow-up time.

#### **Lower Fusion Rate and Poor Fusion in the MCs Group**

We speculated that the main reasons leading to the low short-term fusion rate in patients with MCs might be inflammatory factors and a reduced blood supply in the fusion area. Inflammatory factors such as TNF- $\alpha$  can be produced in the intervertebral space by low-toxicity infection of the intervertebral space, autoimmune reactions caused by exposure to the nucleus pulposus and intraoperative curettage of the endplate cartilage.<sup>24,25</sup> TNF- $\alpha$  inhibits the osteogenic differentiation of mesenchymal stem cells by activating the NF- $\kappa$ B pathway or Notch receptors,<sup>7,26</sup> which may lead to trabecular bone formation between the implanted bone and vertebral bone. It was previously thought that endplate sclerosis was generally only present in patients with type III MCs, but recent studies have revealed that endplate sclerosis can be present in patients with any type of MCs.<sup>27</sup> MCs with endplate sclerosis may result in a reduced blood supply to the vertebrae-cage interface, resulting in delayed or even failed fusion.

We also introduced the concept of the cage union ratio to evaluate the fusion of the cage in the two groups. The results showed that the cage union ratio was lower in the MCs group than in the non MCs group, which may be consistent with the difference in the fusion rate between the two groups. There may be little difference in the long-term fusion rate between the two groups, but the fusion quality is better in patients without MCs, which also reflects the effect of MCs on lumbar interbody fusion. Although, we found a lower short-term fusion rate after TLIF in the MCs group, further relevant basic studies are needed to explore the effect of MCs on fusion.

#### **Cage Subsidence in the Patients with MCs**

The cage subsidence rate after TLIF is reported to range from 0% to 51.2%, with a median subsidence rate of 21.4%.<sup>28</sup> In previous studies, the shorter the fusion time was, the lower the subsidence rate. Our study also confirms this conclusion; the cage subsidence rate was 10% (5/50) in the MCs group and 6% (3/50) in the non MCs group. In addition, Liu *et al.*<sup>22</sup> have demonstrated that MCs with endplate sclerosis may reduce the incidence of cage subsidence. Our results showed that cage subsidence occurred in one patient (1/12) with MCs and endplate sclerosis and in four patients (4/30) with MCs without endplate sclerosis, showing no significant difference. Thus, our study did not produce similar results. This lack of positive results may be because our subsidence rates were assessed from short-term follow-up data, and the sample size of patients with MCs and endplate sclerosis was small.

#### **n-HA/PA66 and PEEK Cage Achieve Comparable Fusion**

At present, conventional cages made of PEEK and titanium alloys are commonly used in clinical practice, as are some bioactive cages made of bioglass and n-HA/PA66. In patients with MCs, different cages may have different effects on the fusion outcome. According to the cage used in TLIF, the MCs group was further divided into the n-HA/PA66 group and the PEEK group. However, there was no significant difference in the fusion rate or fusion grade between the n-HA/PA66 group and the PEEK group. Although n-HA/PA66 can promote the polarization of macrophages toward the M2 phenotype<sup>29</sup> and is superior to PEEK in terms of bone integration, bioactivity and biocompatibility,<sup>30,31</sup> it does not seem to have notable benefits for patients with MCs patients. This may be due to the small sample size of the n-HA/PA66 subgroup in this study. Another possible reason is that the inflammatory environment in patients with MCs inhibits the bioactivity and osseointegration of n-HA/PA66 cages. Further experiments are needed to verify this hypothesis in the future.

#### **Risk Factors Affecting Fusion**

Our logistic regression analysis showed that BMI was an independent risk factor for LIF in patients with MCs. Because an increased BMI is associated with accelerated disc degeneration, an increased sacral slope, and increased L1-S1 lordosis, these postural changes may lead to increased lumbar instability, cage subsidence, and fusion failure.<sup>19</sup> In addition, as the patient's weight increases, the axial pressure on the endplate and on the cage after implantation increases,<sup>32</sup> which may lead to an increase in the cage subsidence rate and affect the fusion of the implanted and vertebral bone.

In our study, smoking was also a significant factor affecting LIF, which is consistent with previous findings.<sup>18</sup> Smoking can seriously interfere with the process of bone metabolism, reduce BMD, affect the process of bone healing in LIF, and reduce the fusion rate. Nicotine, as one of the main components in cigarettes, can stimulate sympathetic vascular constriction,

reduce cell metabolism, decrease neovascularization, and lead to bone nonunion.<sup>18</sup> The effects of smoking on fusion are mainly achieved via local vascular and metabolic factors. During fusion, growth factors released by platelets, macrophages and fibroblasts induce mesenchymal stem cells to differentiate into bone cells and promote bone healing; bone morphogenetic protein (BMP) is an important participant in this process and may be significantly affected by smoking.<sup>33</sup>

Previous studies have also reported that bone mineral density and age are also factors affecting LIF. Through biomechanical experiments, Hou *et al.*<sup>34</sup> found that bone mineral density was closely related to the failure load of the vertebral endplate, and a reduction in bone mineral density could lead to a reduction in the failure load of the vertebral endplate and increase the risk of cage subsidence. Park *et al.*<sup>35</sup> also reported that the risk of cage subsidence was 4.8 times higher in those with osteoporosis than in those without osteoporosis after TLIF surgery. Bone and muscle mass gradually decrease with aging, and middle-aged and elderly people are more prone to osteoporosis, which increases the risk of cage subsidence.

rhBMP-2 is an osteoinductive growth factor that stimulates pluripotential cells to migrate into the area and form bone and has been shown to result in high fusion rates after TLIF.<sup>36</sup> The off-label use of interbody rhBMP-2 with TLIF has been proven to be safe.<sup>37</sup> However, no relevant studies have reported the effect of rhBMP-2 on LIF in patients with MCs, so more research is needed.

### Strengths and Limitations

This study is the first to report the short-term follow-up outcomes and fusion dynamics in TLIF in patients with and without MCs. In addition, we introduced the cage union ratio to better assess the fusion state. However, our study also had some limitations. First, we did not obtain detailed data regarding the bone mineral density of patients, and the results of the logistic regression analysis may be biased. Second, due to the lack of follow-up MRI data, we did not consider the effect of postoperative transformation of the MCs type. Third, this was a retrospective study with a small sample from a single center, and prospective studies with larger samples are needed to support our conclusions in the future. Finally, the cage selection was not randomized, and the final results might be influenced by surgeon-related factors to a certain degree.

### Conclusion

This study demonstrated that the short-term fusion rate was lower in the MCs group than in the non MCs group and the

cage union ratio of the upper and lower endplates on the coronal and sagittal planes was significantly lower in the MCs group than in the non MCs group. In conclusion, MCs adversely affected bone fusion in the early postoperative period. The fusion performance of n-HA/PA66 and PEEK cages was comparable in patients with MCs. Smoking and BMI were independent risk factors for bone fusion in patients with MCs. Therefore, for obese and smoking patients, quitting smoking and losing weight after surgery may be beneficial.

### Author Contributions

All authors take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yang Xiao, Peng Xiu, and Xi Yang. Acquisition of data: Yang Xiao, Peng Xiu, Liang Wang, and Tao Li. Analysis and interpretation of the data: Yang Xiao and Peng Xiu. Manuscript draft: Yang Xiao, Tao Li, Liang Wang, and Quan Gong. Critical revision of the manuscript for important intellectual content: Limin Liu, Yueming Song, and Xi Yang. Statistical analysis: Yang Xiao and Peng Xiu. Study supervision: Yueming Song, and Xi Yang.

### Authorship Declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

### Acknowledgments

We would like to thank all patients who generously agreed to be interviewed for this study. Similarly, we are also grateful to those who helped with this research. This study was supported by the Science and Technology Department of Sichuan Province (2021YFG0240).

### Conflicts of Interest

The authors have no relevant financial or nonfinancial interests to disclose.

### Data Availability Statement

All data and material used in the elaboration of this article are available if requested, and stored only by the main author to ensure the privacy of patient information.

## References

1. Modic M, Steinberg P, Ross J, Masaryk T, Carter J. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*. 1988;166:193–9.
2. Modic MT, Masaryk TJ, Ross JS, Carter JR. Imaging of degenerative disk disease. *Radiology*. 1988;168(1):177–86.
3. Wu J, Chen Z, Wang H, Tian Y, Ma X, Lyu F, et al. The influence of Roussouly type on the prevalence, subtype, and distribution characteristics of Modic changes in patients with lumbar degenerative disc disease. *World Neurosurg*. 2023;169:e102–9.
4. Kanna RM, Shanmuganathan R, Rajagopalan VR, Natesan S, Muthuraja R, Cheung KMC, et al. Prevalence, patterns, and genetic association analysis of Modic vertebral endplate changes. *Asian Spine J*. 2017;11(4):594–600.
5. Mok FP, Samartzis D, Karppinen J, Fong DY, Luk KD, Cheung KM. Modic changes of the lumbar spine: prevalence, risk factors, and association with disc degeneration and low back pain in a large-scale population-based cohort. *Spine J*. 2016;16(1):32–41.



6. Hong L, Sharp T, Khorsand B, Fischer C, Eliason S, Salem A, et al. MicroRNA-200c represses IL-6, IL-8, and CCL-5 expression and enhances osteogenic differentiation. *PLoS One*. 2016;11(8):e0160915.
7. Wang N, Zhou Z, Wu T, Liu W, Yin P, Pan C, et al. TNF- $\alpha$ -induced NF- $\kappa$ B activation upregulates microRNA-150-3p and inhibits osteogenesis of mesenchymal stem cells by targeting  $\beta$ -catenin. *Open Biol*. 2016;6(3):150258.
8. Kim SM, Rhee W, Ha S, Lim JH, Jang IT. Influence of alendronate and endplate degeneration to single level posterior lumbar spinal interbody fusion. *Korean J Spine*. 2014;11(4):221–6.
9. Kwon YM, Chin DK, Jin BH, Kim KS, Cho YE, Kuh SU. Long term efficacy of posterior lumbar interbody fusion with standard cages alone in lumbar disc diseases combined with Modic changes. *J Korean Neurosurg Soc*. 2009;46(4):322–7.
10. Erinc S, Talmac MA, Kemah B, Ozdemir MH. The effect of modic changes on the fusion rates of posterior interbody fusion surgery modic changes and posterior interbody fusion. *J Neurosurg Sci*. 2021. <https://doi.org/10.23736/S0390-5616.21.05386-8>. Epub ahead of print. PMID: 34342195.
11. Kim DH, Hwang RW, Lee GH, Joshi R, Baker KC, Arnold P, et al. Comparing rates of early pedicle screw loosening in posterolateral lumbar fusion with and without transforaminal lumbar interbody fusion. *Spine J*. 2020;20(9):1438–45.
12. Aoki Y, Yamagata M, Nakajima F, Ikeda Y, Takahashi K. Posterior migration of fusion cages in degenerative lumbar disease treated with transforaminal lumbar interbody fusion: a report of three patients. *Spine*. 2009;34(1):E54–8.
13. Zhao FD, Yang W, Shan Z, Wang J, Chen HX, Hong ZH, et al. Cage migration after transforaminal lumbar interbody fusion and factors related to it. *Orthop Surg*. 2012;4(4):227–32.
14. Zhang Z, Hu BW, Wang L, Yang HL, Li T, Liu LM, et al. Comparison of long-term outcomes between the n-HA/PA66 cage and the PEEK cage used in transforaminal lumbar interbody fusion for lumbar degenerative disease: a matched-pair case control study. *Orthop Surg*. 2023;15(1):152–61.
15. Lee JH, Jeon DW, Lee SJ, Chang BS, Lee CK. Fusion rates and subsidence of morselized local bone grafted in titanium cages in posterior lumbar interbody fusion using quantitative three-dimensional computed tomography scans. *Spine*. 2010;35(15):1460–5.
16. Gum JL, Reddy D, Glassman S. Transforaminal lumbar interbody fusion (TLIF). *JBJS Essent Surg Tech*. 2016;6(2):e22.
17. Jiang C, Yin S, Wei JM, Zhao W, Wang X, Zhang Y, et al. Full-endoscopic posterior lumbar interbody fusion with epidural anesthesia: technical note and initial clinical experience with one-year follow-up. *J Pain Res*. 2021;14:3815–26.
18. Liao JC, Chen WJ, Niu CC, Chen LH. Effects of low-intensity pulsed ultrasound on spinal pseudarthrosis created by nicotine administration: a model of lumbar posterolateral pseudarthrosis in rabbits. *J Ultrasound Med*. 2015;34(6):1043–50.
19. Behrbalk E, Uri O, Parks RM, Musson R, Soh RC, Boszczyk BM. Fusion and subsidence rate of stand alone anterior lumbar interbody fusion using PEEK cage with recombinant human bone morphogenetic protein-2. *Eur Spine J*. 2013;22(12):2869–75.
20. Divi SN, Goyal DKC, Galetta MS, Fang T, Padua FG, Reyes AA, et al. How does body mass index influence outcomes in patients after lumbar fusion? *Spine*. 2020;45(8):555–61.
21. Zavras AG, Federico V, Nolte MT, Butler AJ, Dandu N, Munim M, et al. Risk factors for subsidence following anterior lumbar interbody fusion. *Global. Spine J*. 2022;20:21925682221103588.
22. Liu J, Ding W, Yang D, Wu H, Hao L, Hu Z, et al. Modic changes (MCs) associated with endplate sclerosis can prevent cage subsidence in oblique lumbar interbody fusion (OLIF) stand-alone. *World Neurosurg*. 2020;138:e160–8.
23. Li H, Chen S, Wei H, et al. Type 2 sclerotic Modic change affect fusion result in patients undergoing PLIF with pedicle screw instrumentation: a retrospective study. *BMC Musculoskelet Disord*. 2021;22(1):598.
24. Huang B, Liu J, Wei X, Li S, Xiang Y, Wu H, et al. Damage to the human lumbar cartilage endplate and its clinical implications. *J Anat*. 2021;238(2):338–48.
25. Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. *Eur Spine J*. 2016;25(11):3723–34.
26. Ye X, Huang H, Zhao N, Zhang J, Yang P. Inhibition of Runx2 signaling by TNF- $\alpha$  in ST2 murine bone marrow stromal cells undergoing osteogenic differentiation. *In Vitro Cell Dev Biol Anim*. 2016;52(10):1026–33.
27. Liu J, Huang B, Hao L, Shan Z, Zhang X, Chen J, et al. Association between Modic changes and endplate sclerosis: evidence from a clinical radiology study and a rabbit model. *J Orthop Translat*. 2019;16:71–7.
28. Parisien A, Wai EK, ElSayed MSA, Frei H. Subsidence of spinal fusion cages: a systematic review. *Int J Spine Surg*. 2022;16:1103–18.
29. Linares J, Fernández AB, Feito MJ, Matesanz MC, Sánchez-Salcedo S, Arcos D, et al. Effects of nanocrystalline hydroxyapatites on macrophage polarization. *J Mater Chem B*. 2016;4(11):1951–9.
30. Xiong Y, Ren C, Zhang B, Yang H, Lang Y, Min L, et al. Analyzing the behavior of a porous nano-hydroxyapatite/polyamide 66 (n-HA/PA66) composite for healing of bone defects. *Int J Nanomedicine*. 2014;9:485–94.
31. Rao PJ, Pelletier MH, Walsh WR, Mobbs RJ. Spine interbody implants: material selection and modification, functionalization and bioactivation of surfaces to improve osseointegration. *Orthop Surg*. 2014;6(2):81–9.
32. Schuller S, Charles YP, Steib JP. Sagittal spinopelvic alignment and body mass index in patients with degenerative spondylolisthesis. *Eur Spine J*. 2011;20(5):713–9.
33. Berman D, Oren JH, Bendo J, Spivak J. The effect of smoking on spinal fusion. *Int J Spine Surg*. 2017;11(4):29.
34. Hou Y, Yuan W. Influences of disc degeneration and bone mineral density on the structural properties of lumbar end plates. *Spine J*. 2012;12(3):249–56.
35. Park MK, Kim KT, Bang WS, Cho DC, Sung JK, Lee YS, et al. Risk factors for cage migration and cage retropulsion following transforaminal lumbar interbody fusion. *Spine J*. 2019;19(3):437–47.
36. Khan TR, Pearce KR, McAnany SJ, Peters CM, Gupta MC, Zebala LP. Comparison of transforaminal lumbar interbody fusion outcomes in patients receiving rhBMP-2 versus autograft. *Spine J*. 2018;18(3):439–46.
37. Crandall DG, Revella J, Patterson J, Huish E, Chang M, McLemore R. Transforaminal lumbar interbody fusion with rhBMP-2 in spinal deformity, spondylolisthesis, and degenerative disease-part 2: BMP dosage-related complications and long-term outcomes in 509 patients. *Spine*. 2013;38(13):1137–45.