The Development of Modic Changes after Lumbar Surgical Procedures and their Association with Patients' Baseline Demographic Characters and Disc Degeneration

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ABBREVIATIONS

CLBP	Chronic low back pain
IVD	Intervertebral disc
MCs	Modic changes
MRI	Magnetic resonance imaging
IDD	Intervertebral disc degeneration
aMCs	Accentuated Modic changes
AF	Annulus fibrosus
CEP	Cartilage endplate
BEP	Bony endplate
NP	Nucleus pulposus
LDDD	Lumbar disc degenerative disease
T1WI	T1-weighted images
T2WI	T2-weighted images
MC0	Modic type 0 change
MC1	Modic type 1 change
MC2	Modic type 2 change
MC3	Modic type 3 change
nMCs	New Modic changes
LDH	Lumbar disc herniation
IL	Interleukin
PG	Prostaglandin

ABBREVIATIONS

TNF	Tumour necrosis factor
hsCRP	High-sensitivity C-reactive protein
NLPs	NOD-like receptors
TLRs	Toll-like receptors
MMP	Matrix metalloproteinases
NF-kB	Nuclear factor-kB
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
CT	Computed tomography
ODI	Oswestry Disability Index
ZA	Zoledronic acid
NSAIDs	Nonsteroidal anti-inflammatory drugs
VAS	Visual analogue scale
RCT	Randomized controlled trial
ICSI	Intradiscal corticosteroid injection
Ldis	Lumbar discectomy
Lfus	Lumbar fusion
LTDR	Lumbar total disc replacement
Lseq	Lumbar sequestrectomy
Ldec	Lumbar decompression
ST	Slice thickness
TR	Time of repetition
TE	Time to echo
FOV	Field of view
CSF	Cerebrospinal fluid

ABBREVIATIONS

BMI	Body mass index
WBC	White blood cell
mm	Millimetre
n	Number
cm^3	Cubic centimetre
M	Male
F	Female
kg	Kilogram
m^2	Square metre
L	Litre
mg	Milligram
LLS	Lumbar spinal stenosis
ASD	Adjacent segmental degeneration

I. INTRODUCTION

Chronic low back pain (CLBP) is a common symptom that bothers a considerable proportion of the population (1,2). Because of the growth of disability and use of healthcare services, it is also the worldwide disabling condition with detrimental consequences (2,3). According to current epidemiological studies, we still cannot give an accurate number or rate to depict the prevalence of CLBP due to the existence of heterogeneity. However, Cassidy et al. (4) reported that over 80% of individuals got at least one episode of CLBP at some point during their lifetime. Obviously, not only does CLBP exert essential impacts on the individual, but it also has negative effects on communities and health care systems (1,2).

Despite the medical and socioeconomic importance of CLBP, there is professional uncertainty about the pathological mechanism of CLBP and optimal treatment options. However, degenerative changes involving intervertebral discs (IVD), ligaments and bony structures are thought to be the most common sources of CLBP (2). Modic changes (MCs), i.e. vertebral endplate-related signal abnormalities in the subchondral bone marrow, which are visible on magnetic resonance imaging (MRI), have also been found to contribute to CLBP (5,6). Unfortunately, a certain amount regarding MCs remain either controversial or unknown over three decades of studies.

A previous study (7) has revealed that most of CLBP patients with MCs fail to have long-term benefits from nonsurgical treatments. However, the commonly used lumbar surgical procedures seem to alter directly lumbar biomechanical properties at a micro-structural level and pre-dispose the adjacent vertebral bodies to MCs (8). Therefore, a research aiming at comparing the incidences of MCs after these lumbar surgical procedures is needed, which is one of the important research parts of this retrospective study.

In addition, we investigate the correlation between the patients' demographic,

inflammatory indicators, intervertebral disc degeneration (IDD) scores, and MCs, as well as for the first time provide new insights into the risk factors of the development of accentuated MCs (aMCs) following lumbar surgery, which will help to further understand the aetiology of MCs and find a better therapeutic option.

1. The structures and functions of the vertebral endplate

In order to understand the pathological mechanism of CLBP, it is necessary to understand its anatomy. The inner and outer annulus fibrosus (AF) are tightly connected with the cartilage endplate (CEP) and the bony endplate (BEP), respectively. Together with the internal nucleus pulposus (NP), these three parts constitute the intact structure of the IVD (9) (**Fig. 1**). Structural changes in even one of these three parts are the cause of lumbar disc degenerative diseases (LDDD). As the key component of the IVD, the vertebral endplate directly affects the normal physiological state of the lumbar spine and is affected by pathological changes in this region.

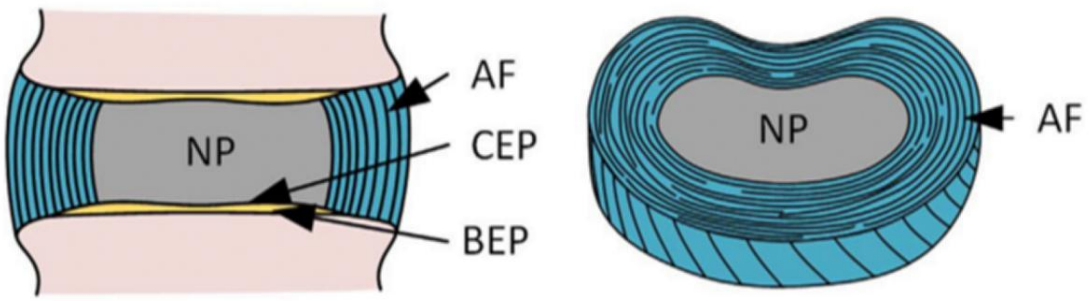

Fig. 1: The structure of the intervertebral disc (10). NP, nucleus pulposus; AF, annulus fibrosus; CEP, cartilage endplate; BEP, bony endplate. [Reprinted by permission from Elsevier Science & Technology Journals: J Mech Behav Biomed Mater, Biomechanics of the human intervertebral disc: a review of testing techniques and results, N Newell et al., Copyright ©2017.]

1.1 Structures

The vertebral endplate is composed of two parts: the CEP and the BEP. Although the structures of the two vertebral endplates alter, their functions are similar, and current imaging techniques cannot detect the boundary between them. Therefore, they are often regarded as a unitary structure.

The CEP, which consists of a layer of hyaline cartilage, lies at both the upper and the lower end of the vertebral body. Its centre, which is located near the NP, is its thinnest part and thus the weakest part of the spine (11). In addition to the AF surrounding the peripheral cortical bone of the BEP, the BEP is covered by the CEP. The vertebral endplates composed of these two types of tissue effectively prevent the NP from protruding into the vertebral body (11).

The adult vertebral endplate can assume one of three principal sagittal shapes: flat, oblong or excentric, with the excentric shape being the most common (12). The vertebral endplate is located at the upper and lower end of the IVD and is a thin concave structure. Different vertebral levels have different degrees of concavity and the degree of concavity of the inferior vertebral endplate is greater than the one of the superior vertebral endplate in the same intervertebral space (13,14). The degree of concavity of the vertebral endplate is correlated with IDD; i.e. the more severe the degree of the IDD, the greater the degree of the vertebral endplate concavity is (15).

1.2 Functions

1.2.1 Stress buffer

The IVD and the vertebral endplate together maintain the physiological function of the spine, especially in the redistribution of load on the IVD and regarding stress transmission (16). The normal CEP exerts a cushioning effect that maintains the mechanical stability of the IVD. Once the NP is squeezed by an external load, the pressure transmitted to the vertebral endplate causes the CEP to protrude into the bone

medullary cavity (17), thereby passively increasing the volume of the IVD and reducing the compression of the NP to the AF (18).

Under physiological conditions, the centre of the vertebral endplate is the main area of stress transmission in lumbar IVD. However, when IDD occurs, the force acting on the vertebral endplate can be transmitted from the central region to its periphery. Thus, long-term stress load causes the vertebral endplate to be structurally remodelled, becoming stiff and gradually losing its cushioning effect (19,20). Once the stress effect exceeds the limit of the vertebral endplate, the formation of vertebral osteophytes and Schmorl nodes formed by the protrusions of the nucleus (21) causes the vertebral endplate to assume an irregular shape. This shape is one aspect explaining why the vertebral endplate undergoes a change from the concave shape to a flat or irregular shape.

Additionally, the composition of the vertebral endplate provides a structural basis for its resistance to stress. The main components of the extracellular matrix of the CEP include proteoglycan and type II collagen. Proteoglycan, which carries a negative charge, can absorb water and thereby plays a role in resisting pressure and contributing a cushioning effect (10,11). Type II collagen can form a collagen skeleton by itself or in connection with the NP tissue, which has an anti-tensile strength effect (22). However, the synthesis of these components decreases with age, which affects their own ability to exert their physiological functions.

1.2.2 Nutritional function

IDD is a consequence of various internal environmental factors. A shortage of nutrient supply to the NP and the AF is fundamental to its occurrence. The vertebral endplate and the AF are two important structures through which lumbar discs (the avascular structures) obtain nutrients. A previous study has shown that the CEP is the main path for IVD nutrition (**Fig. 2**) and that it supplies two-thirds of the nutrients required by the AF and the NP (23).

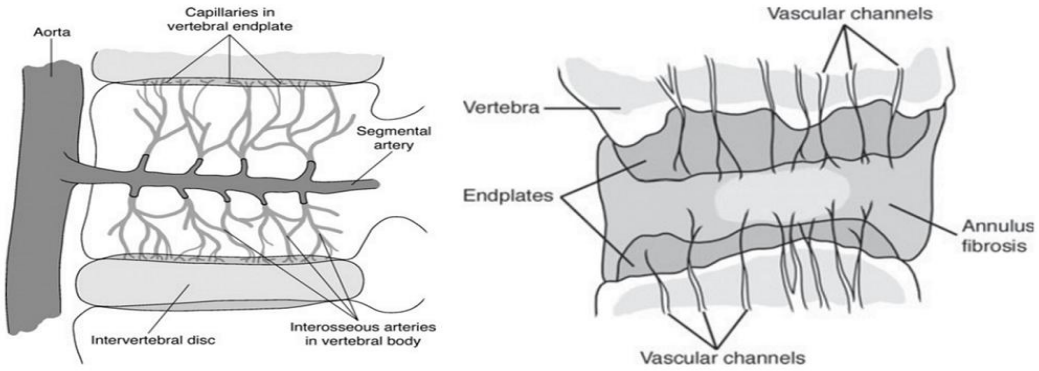

Fig. 2: Distribution of blood vessels branching of vertebral body and endplate (9). [Reprinted by permission from John Wiley and Sons: Pain Pr, Intervertebral disc: anatomy-physiology-pathophysiology-treatment, PP Raj et al., Copyright ©2008.]

The vertebral endplate is rich in lamellar pore structure composed of trabecular bone (24). Approximately 10% of the vertebral venous sinusoids are directly in contact with the CEP, and another 20% of the sinusoids are separated from the CEP by a layer of permeable tissue. At the interface between the CEP and the BEP lies a large number of terminal vascular loops that directly enter the bone medullary cavity. The branches of these vascular loops enter the CEP through the lamellar pore structure to form a vascular branching structure (25) that not only nourishes the CEP but also the NP and the AF through osmosis (26).

Moreover, the composition of different regions of the vertebral endplate alters. As one moves from the NP to the vertebral body, the proteoglycan and water content of the CEP gradually increases and the collagen fibre content gradually decreases (11,27). This structural difference facilitates the entry of nutrients into the IVD tissue from the central region of the vertebral endplate and the removal of metabolic products (11).

2. Vertebral endplate degeneration and Modic changes

The vertebral endplate undergoes structural remodelling with aging, also known as the physiological degeneration of the vertebral endplate. During remodelling, the cells of the CEP undergo apoptosis and density loss and are gradually transformed into calcified bone tissue (28). The calcification of the CEP increases the thickness of the vertebral endplate and destroys the contact channels between the pores of the CEP and the bone marrow. Furthermore, the decrease in the permeability of the vertebral endplate could reduce the ability of the vertebral endplate to function properly in the exchange of nutrients and metabolites (29). Because of this degeneration, the apoptosis of the CEP cells could increase (30), resulting in a decrease in both the number of vertebral endplate chondrocytes and matrix synthesis (31). In addition, genes play a certain role in the degeneration of the vertebral endplate (32,33).

In general, the degeneration of the vertebral endplate is the basis of its damage. When the pressure load on the vertebral endplate exceeds the maximum load it can bear, the trabecular bone may undergo microfracture. Vertebral endplate microfractures are an important biomechanical factor for the occurrence of MCs (34,35). The damaged vertebral endplate can no longer function as a barrier. Substances that previously could not enter the IVD permeate into the NP and cause degradation of the extracellular matrix (36). The inflammatory factors and metabolites in the IVD directly flow into the vertebral body and cause MCs of the vertebral body (35). In summary, the degeneration and damage of the vertebral endplate are important prerequisites for MCs.

3. Modic changes (MCs)

3.1 Overview of MCs

3.1.1 Definition and classifications

With the advance in imaging technology, the vertebral endplate, as the part of the spinal structure, can clearly manifest on MRI, which is a commonly used examination tool to evaluate lumbar IDD. In 1987, de Roos *et al.* (37) first reported that signal abnormalities in the subchrondral body marrow in close proximity to the endplates were visible on the MRI of patients with lumbar IDD. Subsequently, the histological features and classifications of vertebral endplate signal changes, also known as MCs, were described systematically by Modic *et al.* (38,39).

MCs are classified by three inter-convertible types according to their specific imaging findings on T1-weighted images (T1WI) and T2-weighted images (T2WI) (38,39). Modic type 1 change (MC1) is characterized by subchondral bone marrow oedema, which is related to the increase in granulation tissue and the vascularization of bone marrow after the rupture of the vertebral endplate (**Fig. 3**), as shown by a hypointense on T1WI and a hyperintense on T2WI (38). Fatty degeneration, associated with red bone marrow being replaced by yellow bone marrow (**Fig. 3**) and a large number of adipocytes deposited in the vertebral endplate and subplate area, can be observed in the population with Modic type 2 change (MC2) and displays a hyperintense on T1WI and an isointense or hyperintense on T2WI (38). Conversely, bone marrow fat deposition is replaced by sclerosing bone over time. Modic type 3 change (MC3), the stage of sclerotic changes, is reflected as hypointense signalling on both T1WI and T2WI (39).

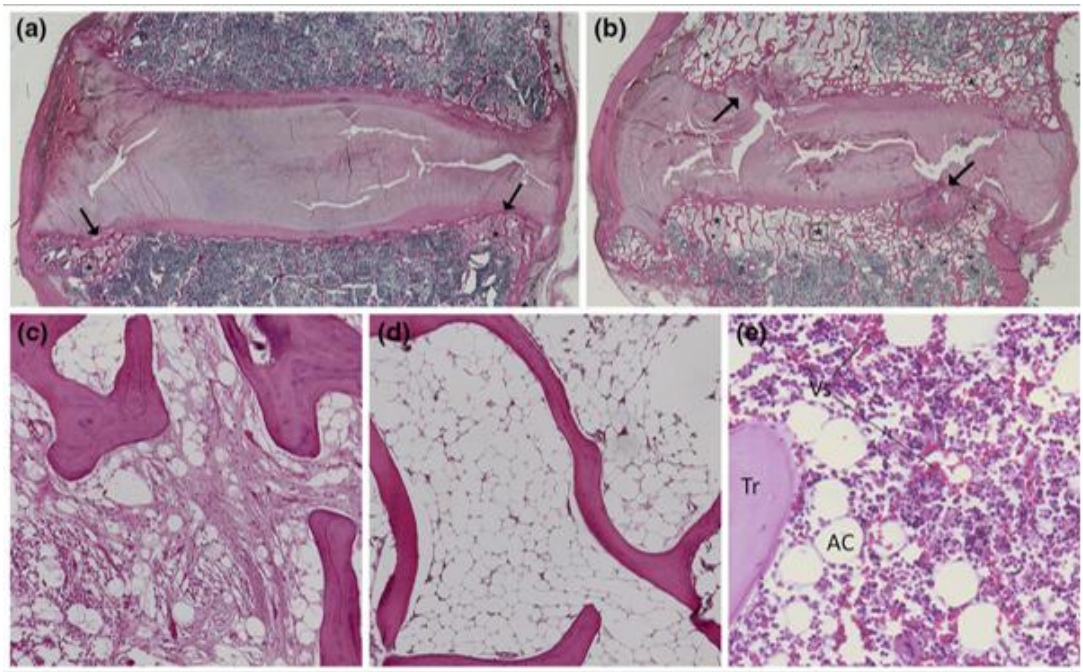

Fig. 3: The histological sections of Modic changes (35). a) and c), Modic type 1 change (fibrovascular tissue and trabecular thickening). b) and d), Modic type 2 change (fatty marrow replacement). e), Healthy vertebral bone marrow; Tr, trabecular bone; AC, adipocytes; VS, vascular sinus. [Reprinted by permission from Springer Nature: Eur Spine J, Pathobiology of Modic changes, S Dudli et al., Copyright ©2016.]

Although the MCs classification system is widely recognized, subdivisions and improvements must be made to this system. In actual clinical work, mixed MCs were reported consecutively in several studies (40–42). Both bone marrow oedema and fatty degeneration can be observed simultaneously on MRI, which makes it impossible to divide them into pure MC1 or MC2. To solve this problem, Fayad *et al.* (43) introduced two other types based on the Modic classification: Modic I-2 (both bone marrow oedema and fatty degeneration are present, but mainly bone marrow oedema) and Modic II-1 (both bone marrow oedema and fatty degeneration are present, but mainly fatty degeneration). The mixed MCs can be observed because an

acute ongoing inflammatory process in some MC2 causes the yellow marrow to transmute into red marrow (41).

3.1.2 Epidemiology

Given the differences in study designs and samples, the incidence of MCs in different populations varies greatly. The average incidence of MCs is 43% in patients with non-specific CLBP, but only 6% in asymptomatic people (44). MC1 and MC2 are the most common types of MCs. However, controversy still exists regarding which type of MCs has the higher incidence. Jensen *et al.* (45) performed a 4-year prospective longitudinal study that included 344 people sampled from the Danish general population. The data indicates that MC1 was the most common type of new MCs (nMCs) identified. Conversely, 809 patients were examined by MRI in the study of Kanna *et al.* (46) and found that the prevalence of MCs was 13% (107/809) and that MC2 was the most commonly observed pattern (66/107, 88%), followed by MC1 (7/107, 9.3%).

MCs can affect all parts of the human spine and even the spine of some animals (47). Because the lower lumbar segments are more prone to bearing more mechanical stress than the upper lumbar spine (48), MCs are mainly distributed at the lumbar levels of L4/5 and L5/S1 among different lumbar segments (38,42,44,49). Additionally, a recent systematic review reported that MCs had a higher likelihood of occurring at the level of L5/S1 than that of at L4/5 level (50). Notably, MCs may be related to LDDD since most lumbar disc herniation (LDH) appear at the L4/5 or L5/S1 level (15). The degree of lumbar IDD is aggravated as age increases. Similarly, as age increases, the incidence of MCs also increases (41,51).

3.1.3 Turnover

In terms of histopathology, there are three types of MCs that can be considered focusing on the dynamic process of the transformation from acute to chronic stage. Namely, from the inflammatory reaction of MC1 to the relatively stable state of MC2 with aggravated degeneration and remission of inflammation, some patients can finally obtain the stable state of MC3. A phenomenon where different types of MCs coexist at the same lumbar level (i.e., mixed MCs) (52) can explain that these three types of MCs can be transformed into each other over time. However, there is still regarding consensus on the time frame for the transformation of MCs to occur.

In general, vertebral endplate bone marrow lesions start with MC1. Following this state, they convert from MC1 to MC2 or to MC3. Mitra *et al.* (53) in their longitudinal study reported that over 50% of MC1 patients can be completely or partially converted to MC2 within 2 to 3 years, and MC2 and MC3 tend to be stable. However, the process of transformation of these three types of MCs does not always follow this conventional direction. A study performed by Hutton *et al.* (54) aiming at the natural course of MCs found that, of 22 patients with preexisting MC2, 4 patients converted to MC1 at the final follow-up. Although this situation is not common, it can be confirmed that the transformation of MCs is mutual and reversible. Kuisma *et al.* (41) conducted a 3 years study examining 70 lumbar segments with MC2. Although only 10 lumbar segments changed from the preexisting MC2 to MC1, the extent of vertebral involvement for the remaining 60 lumbar segments with MC2 was significantly larger than according to the baseline. Thus, one can consider that the MC2 might not be as stable as previously reported.

Moreover, the conversion progress of MCs can also be reversed by surgery in the clinical practice. Based on the imaging data of patients with MC1 or MC2 who underwent posterolateral fusion, Ohtori *et al.* (55) found that with the increase of spinal stability after fusion, the structure between vertebral body and endplate would be rebuilt and regenerated, leading to a reversal of the pathological process, and even

a disappearance and normal pathological signal of imaging. In addition, the sizes of MCs were also positively associated with their transformation. Although 40% of cases were transformed from MC1 to MC2 or to MC3 in the Jensen *et al.* (56) study, the larger the shape was, the more difficult it was to change.

3.2 Potential pathogenesis of MCs

At present, the pathogenesis of MCs remains unclear. A variety of risk factors contribute to the occurrence of MCs (35) (**Fig. 4**). Abnormal gene fragments may underlie the development of MCs (46,57). Vertebral endplate and IVD lesions are the results of biomechanical imbalances, which is one of the most important conditions for the subsequent immune responses (35). Autoimmune reactions and inflammation induced by inflammatory mediators and extracellular matrix catabolites will gradually aggravate both the degree of IDD and vertebral body marrow defect (35,58,59). Biomechanical, biochemistry and genomics factors that are considered closely related to the occurrence of MCs have become research hotspots.

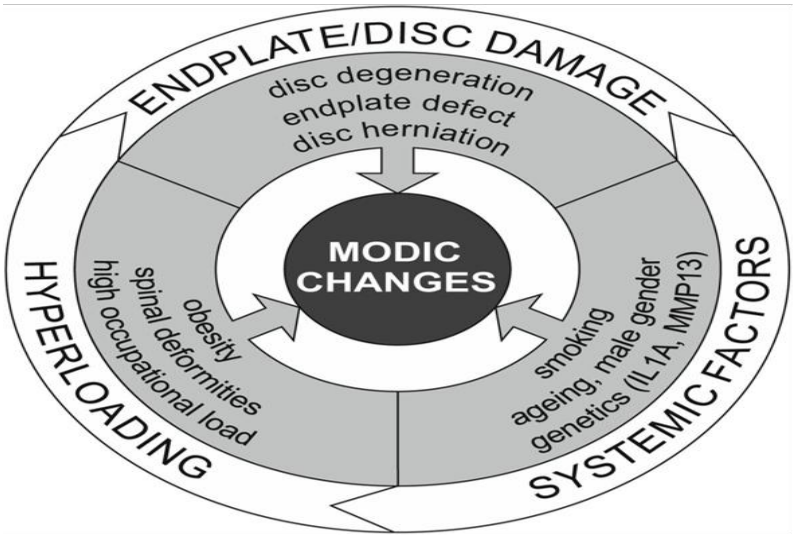

Fig. 4: The risk factor of Modic changes (35). [Reprinted by permission from Springer Nature: Eur Spine J, Pathobiology of Modic changes, S Dudli et al., Copyright ©2016.]

3.2.1 Biomechanical factors

The structure of the vertebral endplate is known to determine its primary biomechanical role in upright-walking humans. Although some studies have shown that the vertebral endplate is a weak link in the spine, vertebral endplate lesions commonly usually occur before IDD, regardless of the degrees of lesions in IDD (60). However, the sequence of their occurrence remains unclear. The current view is more inclined to hold that vertebral endplate lesions and IDD have mutual influences and reciprocal inducements.

Physiological IVDs contain a large amount of water, mucopolysaccharide complexes, and collagen fibres. With increasing age, IVDs will have corresponding degenerative changes, including a loss of water and a reduced cell matrix synthesis. NP dehydration caused by the loss of indispensable materials (61) will result in significantly reduced pressure in the IVD (62). Subsequently, the posterior AF will become the major structure that bears the pressure load in the spine (62). These biochemical changes cause IVDs to lose their buffer function, and their stress tolerance ability also gradually decreases. As the weakest structure in the entire IVD, the vertebral endplate is particularly sensitive to mechanical injuries. The vertebral endplate microfracture that is common in cadaver spine specimens (63) or biomechanical studies (11,64,65) is usually caused by long-term chronic mechanical loading.

For normal or mildly degenerated IVD, the occurrence of vertebral endplate microfractures often require large or sustained mechanical loads. Repeated loading on the IVD can cause changes in its volume and morphology. When the load is too large or cannot be removed in a certain time, the load can further act on the vertebral endplate, causing irreversible degenerative damage to the vertebral endplate and subchondral bone trabeculae, and eventually leading to the occurrence of vertebral endplate microfracture (65,66). However, an IVD with severe degeneration has lost its buffering capacity, and a small mechanical load can increase the shear force on the

endplate, resulting in the occurrence of vertebral endplate microfracture (63) Thus, regardless of degeneration or repeated mechanical loading, an eventual occurrence of vertebral endplate microfractures are the key to the emerge of MCs.

Furthermore, the time frame regarding the occurrence of the vertebral endplate microfracture may also provide a certain theoretical basis for histopathological features of the different types of MCs. If the vertebral endplate microfracture was recent, imaging results may show the hypointensity on T1WI and hyperintensity on T2WI consistent with that of MC1 inflammatory ooedema. After that, the body will turn on the repair mechanism of vertebral endplate microfracture to cause the inflammatory ooedema to subside, adipogenesis or ossification, and imaging signs consistent with that of MC2 or MC3 will arise.

3.2.2 Biochemical factors

Undoubtedly, vertebral endplate structural damage critically contributes to the pathogenesis of MCs. The increase in pressure in the vertebral body and IVD does not only destroy the metabolic balance in the cell but also accelerates the exchange of inflammatory mediators and metabolites of the extracellular matrix between the IVD and bone marrow (67). Generally, inflammatory stimuli can trigger a healing mechanism via the growth of fibrous granulation tissue. However, if inflammatory stimuli persist and the repair mechanism does not work effectively, three typical pathological changes may occur: inflammation, fibrosis and high bone turnover (35,38).

The theory of internal IVD disruption (68) suggests that degeneration of the IVD can produce inflammatory cytokines inside the NP, such as interleukin (IL)-6, IL-8 and prostaglandin (PG) E2, which can cause the occurrence of MCs and CLBP. This theory has been repeatedly confirmed by subsequent studies and has made the biochemical-related mechanisms of MCs a research hotspot. The segments with MCs do not only have a high inflammatory factor expression but also have a close

correlation with their classification. Schroeder *et al.* (69) compared the expression levels of intervertebral cytokines in the segments with or without MCs and found that higher expression levels of IL-1β, granulocyte macrophage stimulating factor, extractable nuclear antigen-78, and tumor necrosis factor (TNF) were detected at the lumbar segments with MCs in comparison with the normal segments. A previous study (70) has also shown that the expression levels of inflammatory mediators, such as ILs, PG9.5, and TNF, are higher in segments with MCs than in normal IVD, and that the positive expression of TNF in segments with MC1 is higher than in segments with MC2. The inflammatory factors detected in degenerated IVD with MCs are mostly related to pain (68) and therefore are considered to be a main causes of CLBP in patients with MCs. Significantly elevated level of high-sensitivity C-reactive protein (hsCRP) was detected in MC1 patients with CLBP, as well as frequent nocturnal and morning pain in these patients (71). It indicates that MC1 was more closely associated with elevated pro-inflammatory mediators and CLBP. The improvement of patients' symptoms after anti-inflammatory treatment further confirmed this view (72).

The release of inflammatory factors is affected by multiple pathways. However, NOD-like receptors (NLPs) and Toll-like receptors (TLRs) play an important role in the occurrence of MCs. Other pattern recognition receptors involved in the degeneration of the IVD and vertebral endplate warrant further studies. Tang *et al.* (73) found that the CEP with MCs had higher expression levels of NLRP3, caspase-1, and IL-1β than those without MCs. This is mainly because the NLRP3 inflammasome composed of NLRs can activate caspase-1 and further cleave pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18. The function of TLRs is mainly to promote the release of inflammatory mediators and matrix metalloproteinases (MMP). Klawitter *et al.* (74) reported that in human IVD degeneration, the expression levels of TLR1/2/4/6, which are related to the release of TNF-a and IL-1β, are increased. In addition, TNF-a and IL-1β can also promote the secretion of IL-6 and IL-8 mediated by TLR2 in IVD cells. Furthermore, as an important signalling pathway for osteoarthritis and IVD

degeneration, the activation of the nuclear transcription factor nuclear factor-kB (NF-kB) and mitogen-activated protein kinase are also regulated by TLR (75).

With age, the NP tissue is no longer in contact with the circulatory system and immune system of the body after the formation of the IVD. In cases with microfracture of the CEP, the NP can enter the upper and lower vertebral endplates through fracture sites and again connect to the blood circulation. This restored connection can cause a strong immune response that generates many inflammatory factors and thereby induces signal changes in the vertebral body (76). The NP cells mediate lymphocyte apoptosis mainly by expressing Fas ligand and thereby producing an effect of immune exclusion (77). High concentrations of Fas ligands have also been detected in the vertebral endplates with MCs, and the ability of the NP to stimulate an autoimmune response has been confirmed in animal models (78). Autologous transplantation of the NP tissue into immunologically active tissues can result in the expression of a large number of inflammatory factors, macrophages, and activated T and B cells (79). In addition, both the promotion of intervertebral proteoglycans to lymphocyte transport (80) as well as the enhanced monocyte infiltration of chondrocyte proteoglycans (81) show that the extracellular matrix of the IVD is also involved in the immune response. This immune response causes the cells to secrete many degrading enzymes of the cell matrix, which do not only accelerate the degradation of the IVD matrix but also causes the persistent symptoms in patients with CLBP (80).

3.2.3 Bacterial infection

After IVD and a vertebral endplate injury, anaerobic bacteria can follow the blood circulation to reach the IVD, a tissue that lacks blood circulation; once arrived, the bacteria can continue to grow and can spread to the vertebral endplate and its adjacent bone marrow (82). Therefore, a low-toxicity bacterial infection may be a pathogenic mechanism of MCs. This mechanism was first proposed by Stirling *et al.*

(82). Subsequently, Albert *et al.* (83) demonstrated the mechanism by which low-toxicity anaerobic bacterial infections led to the occurrence of MC1; To summarize, anaerobic bacteria infections can cause inflammation and oedema in the surrounding tissues and produce cytokines that affect bone quality.

Currently, controversy still exists in the academic community concerning the contribution of this mechanism to the MCs development (84,85). By culturing herniated NP tissue from 61 patients with LDH, Albert *et al.* (86) found that microorganisms were present on the herniated NP tissue of 26 patients, with the anaerobic bacterium *Propionibacterium acnes* being the most common, and found nMCs in the neighbourhood of the herniated segments in 80% of the patients. Subsequently, Aghazadeh *et al.* (87) performed bacterial culture on surgically removed IVD from 120 patients and found that 36 among the 87 patients with MCs had a positive bacterial culture and that 78% of the bacterial culture results showed *Propionibacterium acnes*. This finding may be related to the fact that the normal flora parasitizing the oral mucosa and skin can enter the blood system, propagate in the IVD and cause MCs (88). However, the results of some studies are contrary to the above results. Wedderkopp *et al.* (89) performed sterile IVD aspiration biopsy in 24 patients with MC1 in the lumbar spine and took 2 specimens for bacterial culture. However, no specimens showed anaerobic bacterial growth except for 1 specimen in which coagulase-negative staphylococci were cultured. Moreover, the clinical symptoms and imaging results of the patients were not significantly improved by antibiotic treatment. Similar results have been documented by other reports (90,91). The authors of these studies are convinced that surgically removed IVD are highly likely to be contaminated by skin or muscle surrounding of the operating field, thereby affecting the bacterial culture results (91).

In general, the relationship between MCs and low-toxicity anaerobic bacterial infections is unclear (85), and further studies need to be conducted in order to reach more certain conclusions. In terms of the mechanism by which bacteria enter the IVD and cause MCs, 2 more reasonable views have been proposed (86): (1) when the AF

of the IVD ruptures, bacteria enter the IVD in an anaerobic environment through a breach, causing an inflammatory response in the bone beneath the vertebral endplate; and (2) macrophages that carry anaerobic bacteria and enter the IVD through the ruptured AF start to die, while the anaerobic bacteria are released to cause inflammatory responses. If the results of further studies support this theory, there might be an improvement for patients with CLBP, since these findings may change the routine diagnosis and treatment and provide new ideas for the treatment of CLBP.

3.2.4 Bone marrow microenvironment

The theories that were previously displayed do all provide reasonable explanations for the aetiology of MCs. However, they cannot explain why almost all MCs occur in patients with IDD, particularly in patients with severe degeneration. To answer this question, the ability of the bone marrow to respond to IVDs after inflammation stimulation should be considered.

Tissue sections of MC1 show trabecular bone thickening, and the high bone turnover in biopsy is most likely the result of inflammatory stimulation, whereas MC2 shows a reduced bone formation and MC3 mainly exhibits osteosclerosis (92). These characteristics of bone tissue changes are all associated with cytokines. These cytokines, such as receptor activator of NF-kB ligand, macrophage colony stimulating factor and the nuclear factor of activated T-cells, runt-related transcription factor 1, are all abundant in degenerative IVDs that have MCs (93). They do not only interfere with adjacent bone marrow cells but can also affect the regulation of trabecular bone mass. Therefore, the structure of the vertebral endplate after inflammatory stimulation is directly affected by the ratio of osteoblasts and osteoclasts in the bone marrow.

There is still no evidence that can clearly elucidate the correlation between fat metabolism and MCs. Based on the similarity of the structures between articular cartilage and the vertebral endplate and the association between osteoarthritis and IVDs (94), one can obtain some inspiration from studies of bone marrow lesions in

osteoarthritis. Similar to the distribution characteristics of MCs, bone marrow adipose tissues are extensively distributed in the lower lumbar spine of the human body (95). These bone marrow adipose tissues contain large amounts of saturated fatty acids and low-density lipoproteins that can activate TLR2/4 (96). Fat hypertrophy and hyperplasia caused by the chronic stimulation of TLR (97) is responsible for the yellow bone marrow conversion in MC2. In addition, high blood lipid aggregation will increase advanced glycation end-products (98) and decrease hydrophilic proteoglycan synthesis to directly or indirectly promote tissue sclerosis (99). The vertebral endplate structure presents as osteosclerosis in MC3.

Stress overload is a biomechanical factor that promotes the development of MCs. Wolff's law suggests that a mutual relationship between mechanical and biological factors and says load will change bone metabolism (100). The complicated coregulation of osteogenesis, adipogenesis, and hematopoietic function further (101) indicates that a chronic overload also influences adipogenesis and hematopoietic function. Obesity is closely associated with the development of MCs because it not only increases spinal load but, more importantly, affects bone and fat formation and the hematopoietic process (101).

3.2.5 Genetic factors

Genetic abnormalities play a significant role in IDD (102). MCs may also be closely associated with genetics. Although the genetic background of MCs is currently still unclear, the heritability is estimated at 16-43% (57). The probability that identical twins will both develop MCs is significantly higher than the one of nonidentical twins (57). Perera *et al.* (103) typed single-nucleotide variants to analyse the metabolic pathway of proteoglycans in MCs and showed that the IL-1 gene cluster, the a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) 4 gene, and the ADAMTS5 gene played important roles in the development of MCs. Furthermore, MMP3 has an active association with MCs; it is significantly associated

with the development of MC2 (104). In the degenerative vertebral endplate, the expression of both the Fas receptor gene and apoptotic cells is significantly higher than in the normal vertebral endplate, indicating that this receptor might be involved in the development of MCs through apoptosis (78).

Currently, there are a few studies on MCs regarding the genetic level, however, no study has confirmed an association between a single gene and the development of MCs. There are likely other genes involved in the occurrence and development of MCs. Therefore, further studies at the gene level are expected to better explain the pathogenetic mechanism of MCs.

3.3 The relationships between MCs and intervertebral disc degeneration (IDD)

In anatomical structures, the primary way that IVDs without blood flow obtain nutrients depends on the osmotic function of the vertebral endplate (26). Lesions, degeneration, biochemical changes, and disorders of nutritional metabolism in the vertebral endplate will result in IDD. IDD causes biomechanical changes in the spinal motion unit, which in turn promotes the vertebral endplate degeneration. Therefore, IDD is considered to be one of the risk factors for MCs (105).

Kokkonen *et al.* (106) performed lumbar MRI and computed tomography (CT)-guided discography on the discogenic LBP patients and revealed that MCs patients all had different degrees of IDD. They believed that these imaging changes were caused by IDD. However, for patients with CLBP, the magnitude of MCs was usually positively correlated with the degree of reduction in the disc height; thus, the role of MCs in acceleration of IDD cannot be ruled out (5). Although studies to date have not established the order of their occurrence, it is certain that MCs and DD have a close relationship.

3.4 Optional treatments for MCs

3.4.1 Conservative treatments

3.4.1.1 Physical therapy

Exercise therapy is recommended as a first-line treatment method for nonspecific CLBP in the clinical guidelines (107). Because of its complicated aetiology, the effect of exercise therapy on different population varied greatly. Although the combination of IDD and MCs are positively associated with CLBP (5,6), they are not the only cause for CLBP (85). Therefore, it is difficult to determine the significance of exercise therapy regarding the treatment of patients with MCs. A previous study by Jensen *et al.* (108) revealed that there was no statistical difference in any measured value between exercise therapy and rest in patients with MCs and CLBP. However, their subgroup analysis showed that patients with MC1 were 0.17 points (0.17; 95% -1.28 to 0.93) worse in terms of rest than exercise, patients with larger MCs were 0.41 points (0.41; 95%CI -1.62 to 0.79) worse after rest than after exercise, and the whole group of patients with larger MC1 were 0.61 points (0.61; 95%CI -1.82 to0.61) worse in terms of rest than exercise (109). Therefore, patients with all of the MRI findings shown above might obtain more benefit from exercise therapy than from rest.

Guiding patients with different baseline characteristics by using the same treatment method resulted in large differences. This phenomenon was also present in the studies of Annen *et al.* (110,111) that aimed at investigating the efficacy of chiropractic treatment in CLBP patients with MCs. The interventional measures used in these two studies were both spinal manipulations, and the study protocols were also very similar. The largest difference was whether the target patient population had combined LDH. Among CLBP patients with LDH, MCs-positive patients had higher clinical improvement rates and significantly lower CLBP, leg pain, and Oswestry Disability Index (ODI) scores in the short terms (less than 1 year). Furthermore, by comparing patients with MC1 and MC2, the response of patients with MC2 was more positive and effective to chiropractic manipulation (110). However, for CLBP patients

without LDH, the clinical improvement rate or deterioration rate and the numerical rating scale/Bournemouth Questionnaire changes did not differ significantly at any follow-up point between those with and without MCs and their types (111).

Based on these results, one can conclude that the strict selection of suitable patients is a prerequisite for physical therapy to be effective in symptomatic MCs patients, although indications for this therapy still require continuous exploration and in-depth research.

3.4.1.2 Medication

The pathological processes underlying MCs primarily include inflammation, high bone turnover, and fibrosis (35,112). Chemical and mechanical stimulation of nociceptors close to the injured vertebral endplate may be the source of pain (113). Patients who using zoledronic acid (ZA) rarely show bone marrow lesions because it can inhibit osteoclast functions and promote apoptosis (114). Calcitonin, which is used for treating metabolic bone diseases characterized by high bone turnover, can also effectively inhibit osteoclast functions through specific receptors (115). Therefore, they are considered as the potential treatment options for symptomatic MCs. Koivisto *et al.* (116) successively used clinical and imaging indicators to evaluate the efficacy of ZA in CLBP patients with MCs. ZA effectively reduced the CLBP intensity within a short time and decreased the use of nonsteroidal anti-inflammatory drugs (NSAIDs) within the time span of 1 year among these patients. This active effect might be caused by the tendency of ZA to accelerate the conversion of MC1-domination MCs into MC2-domination MCs and the reduction in the volume of MC1-domination MCs (113). Among patients who received calcitonin treatment, the significant improvements in the visual analogue scale (VAS) score and ODI score also led by Zhou *et al.* (117) to conclude that the short-term therapeutic effect of calcitonin is superior to that of diclofenac in CLBP patients with MC1.

The pathological process of MCs involves many proinflammatory factors (35). Therefore, treatment methods that target one or more types of proinflammatory factors have also been introduced into clinical practice. Because glucosamine sulphate can target IL-1β, a cytokine related to the inflammation in the degenerative process of osteoarthritis (118), Wilkens *et al.* (119) introduced it into the treatment of MCs patients. Unfortunately, no clear clinical effect was identified. Furthermore, due to the late-onset effect of the antibiotic treatment, Jensen *et al.* (120) speculated that the effects of antibiotics might have depended on changes in intestinal flora; in other words, symbiotic bacteria in the intestine caused changes in the immune system. Therefore, a randomized controlled trial (RCT) was performed with a 1 year follow-up and found that treating CLBP patients with MC1 or mixed MCs with probiotics for 100 days did not lead to a solid clinical improvement. Probiotic treatment can reduce the concentrations of the pro-inflammatory cytokines TNF-α, IL-6, and IL-12 and increase the regulatory cytokine IL-10 (121). Theoretically, the efficacy of probiotics in the treatment of MCs should be positive. The negative results in current studies might be associated with a lack of analysis of stool samples, lower probiotic doses, or treatment courses that are too short.

One hypothesis considers whether the development of MCs and CLBP is caused by low-toxicity bacterial infection (122). This theory also provides a new idea for treating MCs patients. The uncontrolled observational study of Albert *et al.* (123) on highly selected CLBP patients with MC1 reported that the clinical effects of antibiotic treatment in MCs patients with persistent CLBP after LDH were strong, and these results also provided preliminary evidence for a hypothesis in which bacterial infection plays a critical role in CLBP with MCs. Later, they performed a 1-year RCT on 162 CLBP patients with MC1 (124) and patients in the antibiotic group received amoxicillin-clavulanate (500mg/125mg), three times daily (one or two tablets per dose) for 100 consecutive days. During a 1 year of follow-up, antibiotic treatment was better than the placebo in improving all outcome indicators. Thus, this led to more clinically significant improvements in the main outcome indicators, and reduced the

volume of MCs to a greater extent. In addition, the dose–response relationship showed a positive trend, and double-dose antibiotics seemed to be more effective. However, antibiotic treatment was associated with a higher incidence of adverse events. Conversely, one recent study of patients with CLBP with MCs and previous LDH found that 3 months of treatment with amoxicillin did not provide a clinically relevant benefit (125).

Opposite conclusions from different research groups will surely confuse clinicians when considering whether to treat similar patients with antibiotics; in particular, current guidelines do not support or oppose antibiotics for persistent CLBP and MCs (126). Therefore, unless MCs are confirmed to be a bacterial infectious disease, one must be cautious about the rationality of antibiotic use, antibiotic selection, and duration of treatment.

3.4.2 Surgical Treatments

3.4.2.1 Intradiscal corticosteroid injection

Local inflammation in the subchondral bone marrow adjacent to the vertebral endplate provides a reasonable theoretical basis for local intradiscal corticosteroid injection (ICSI) in chronic CLBP patients with MCs. One recent study (127) found that ICSI for MC1 patients with severe CLBP had very good analgesic effects. Patients with combined MC1 may derive the largest benefit from this treatment option. This speculation has been supported by a study (40) that evaluated the relationship between the severity of inflammatory vertebral endplate changes on MRI of nonspecific CLBP and the clinical responses to ICSI and concluded that the reduction in pain scores in patients with MC1 after treatment was significantly better than that of patients with MC2. MC1 usually exhibits more active inflammation, which seems to be mediated by TNF-α (70), whereas MC2 and MC3 occur during the resting stages of the course. Furthermore, repetitive IVD injuries might also cause the production of inflammatory substances in the NP. These are all being reasons why ICSI yields

excellent clinical responses in MC1. Accelerating the conversion of MC1 into MC0 by ICSI also has active functions in pain reduction (128).

3.4.2.2 Lumbar discectomy

Most patients with MCs cannot obtain long-term benefits from a conservative treatment (7). Therefore, lumbar discectomy (Ldis) is usually an important surgical method for CLBP patients without spinal instability who have troublesome symptoms. Regardless of whether having combined MCs, Ldis can successfully address the major symptoms of these patients, but the postoperative efficacy in CLBP patients without MCs is even more evident (129). Some scholars have found that patients with or without MCs all show a similar increase in postoperative CLBP scores, and MCs did not influence the postoperative efficacy of Ldis (130). However, in a systematic review, Laustsen *et al.* (131) comprehensively analysed the effect of MCs on Ldis and showed that MCs, particularly MC1, were an important risk factor affecting postoperative symptom relief and functional recovery.

Clearly, this topic still lacks an unified opinion. Generally, for LDH patients with MCs, the poor postoperative efficacy of Ldis is mainly present regarding the improvement of CLBP (132). This situation occurs essentially because Ldis can only remove the herniated NP but denies to resolve the issue of the endplate, which may be the source of the CLBP. Additionally, Ldis is a potential risk factor affecting lumbar stability, and MCs hinder lumbar stability (133,134), which certainly contributes to the poor long-term efficacy after surgery.

Whether Ldis can have a greater clinical efficacy in patients with MCs still requires support of high-level evidence. However, this surgical method may contribute to the development of MCs. A 3- to 5-year study focusing on 41 patients who received Ldis showed that the incidence of MCs increased from 46% to 78%, and the majority of patients had a new onset MC1 coming from MC0, and Ldis tended to accelerate the conversion of MC1 into MC2 (135). MCs occurred more frequently

in patients who had recurrent disc herniation and received Ldis (136,137). Although current studies still cannot clearly explain how Ldis affects the course of MCs, the development mechanism of MCs after surgery is very complicated and definitely not just an increase in quantity. A possible explanation is that Ldis, under its conditions of annular disruption and disc herniation, may directly change the biomechanics at the microstructure level and creates this segment and its adjacent segments vulnerable to MCs (8).

3.4.2.3 Lumbar fusion

In comparison with other types of MCs, MC1 is more often associated with spinal instability (133) and CLBP (48). Therefore, an extra surgery to stabilize the spine may be necessary for preexisting MC1. A previous small study (138) evaluated the effect of posterior lumbar fusion (Lfus) on CLBP patients with MC1 and reported a great improvement of clinical outcomes and imaging presentations (23.5% of MC1 was converted into normal vertebral endplates, and 76.5% of patients converted from MC1 to MC2). Lfus accelerated the conversion of the unstable MC1 into mechanical stability, which might be used as an indicator of the excellent prognosis of Lfus. The above conclusion was strengthened by subsequent study (139).

Nevertheless, Lfus does not have an excellent efficacy in all types of MCs. Esposito *et al.* (140) classified 60 patients with single-level LDD into different groups based on their MCs' type. The results showed that MC1 could obtain better benefits from Lfus than MC2. Kwon *et al.* (141) found that Lfus was an effective surgical method for relieving symptoms of patents with MCs. However, the effect on the MC3 type was poor. In addition, the postoperative fusion rate of MC1 and MC2 reached more than 81%, whereas the fusion rate of MC3 was only 54.5%.

Compared to Ldis, Lfus can yield a better symptom relief and an improved function in the treatment of LDH combined with MCs, particularly for the relief of back pain symptoms (142). These benefits originate mainly from the complete

removal of IVD by the Lfus, which prevents the reherniation of IVDs caused by MCs that compress nerves, effectively restores spinal stability, and relieves LBP caused by MCs by scraping some diseased vertebral endplates. Furthermore, an immediate stabilization of the lumbar spine after a surgery is the key for obtaining the best efficacy for MC1, as MC2 and MC3 are usually considered to be relatively stable and to be the final stable phase of lumbar segmental motion (133,134,143). Lang *et al.* (144) showed that patients with excellent bone fusion all had MC2, and most patients without bone fusion developed MC1. Therefore, the presence of MCs after a surgery and their types also provide new evaluation indicators for the assessment of bone fusion after lumbar fusion. The histopathological features of osteosclerosis in MC3 also provide reasonable explanations for its low fusion rate.

3.4.2.4 Lumbar total disc replacement

With the rise of a nonfusion technology, lumbar total disc replacement (LTDR) has also gradually been applied by patients with LDD combined with MCs. Siepe *et al.* (145) performed a detailed analysis of 92 patients who received LTDR, including patients with degeneration combined with MCs. Considering the final follow-up, all patients reported a significant clinical improvement. However, patients with MCs were not doing as well as the other groups, and no statistical difference was detected between patients with MC1 and MC2. Opposite results were reported in the prospective study of Blondel *et al.* (146), which aimed to evaluate the effect of LTDR on the clinical outcomes of different types of MCs over a period of more than 2 years of follow-ups. The results have indicated that regardless of whether patients had combined MCs before surgery, the overall results 2 years after LTDR treatment showed a significant clinical improvement. In addition, an analysis of different types of MCs has revealed that patients with MC1 had better clinical results. Because there is currently little clinical evidence, the treatment of this subset of patients by LTDR remains controversial. Therefore, the efficacy of LTDR in the treatment of MCs and

whether MCs affect the clinical results of LTDR still require further long-term follow-up studies.

4. The purposes of the study

Nowadays, there are only a few studies focusing on the impact of lumbar surgeries regarding in the development of MCs. These studies do mainly focus on the natural course of MCs after a specific lumbar surgery, with a particular focus on investigating Ldis (8,135). Only one study was found (147) that compared the effects of Ldis with lumbar sequestrectomy (Lseq) on MCs. However, many commonly used lumbar surgical procedures may affect MCs. Therefore, comparing the impact of different types of lumbar surgeries on MCs can not only determine the characteristics of the impact of these surgical procedures on the course of MCs but also may provide spinal surgeons with a certain reference for selecting the surgical plan, for example, by selecting the plan with the least impact on MCs in multiple lumbar surgical procedures.

Previous studies (135,148) have reported that a lumbar surgery can increase the size of MCs, but the methods used by these studies to measure the size of MCs varied and were all semi-quantitative. Moreover, almost all MCs appear to have an irregular shape. The qualitative or two-dimensional semi-quantitative measurement methods undoubtedly have greater errors, leading to inaccurate data and unreliable conclusions. Therefore, a three-dimensional quantitative analyses to calculate the volume of MCs may provide a more accurate understanding of MCs after undergoing different lumbar surgical procedures.

At present, the focus of the debate on the aetiology of MCs in the academic community mainly lies in whether MCs reflect inflammatory changes or more serious degenerative changes. A previous study (71) has shown that hsCRP and other inflammatory indicators are positively correlated with MCs, but studies with small sample sizes and a limited number of similar studies have limited the availability to

obtain high-quality evidence. In addition, MCs are usually accompanied by severe IDD (149), but the relationship between them has not been well explained. The various standards for evaluating IDD have their own limitations, thus multiple IDD evaluation standards must also be used.

In summary, the main purposes of this study are:

1) To investigate the impact of four commonly used lumbar surgical procedures on the development of MCs and to compare the incidence of postoperative nMCs to identify surgical methods with the least impact on MCs.

2) To perform a three-dimensional quantitative analysis to calculate the volume change of MCs before and after surgery and to provide more accurate data for evaluating the impact of lumbar surgery on MCs.

3) To repeat the previous studies aiming at investigating the association between hsCRP and MCs; based on the existing investigation of the correlation between IDD and MCs, multiple IDD evaluation standards are used to further validate their research conclusions and obtain stronger evidence on the aetiology of MCs;

4) To investigate the baseline of MCs and accentuated MCs (aMCs) to determine their epidemiological characteristics.

II. MATERIALS AND METHODS

1. Subject selection and groups

In this retrospective study, 270 adult patients (≥ 18 years of age) who sought treatment in our university hospital due to LDD between January 2012 and December 2018 were included. The study protocol was approved by the Ethics Committees of University Hospital (No. AZ139/20). The principles of the Helsinki Declaration served as the ethical guidance for implementation of this study.

Patients who fulfilled the following criteria were enrolled in this study: 1) patients who had surgical indicators of one of the four types of surgery (Ldis, Lseq, lumbar decompression (Ldec), and Lfus) and received one of the above lumbar surgical procedures that were previously presented and 2) patients who received standard lumbar MRI examinations both before and after surgery and had clear and complete imaging data. The exclusion criteria included patients who had a prior lumbar surgery, a history of inflammatory or infectious disease, and patients who took medication that might have influenced the progression of MCs before and/or after surgery, such as antibiotics and calcitonin.

Those categories meeting the inclusion-exclusion criteria were classified into the following groups according to the study protocol: 1) The patients were allocated and divided into one of four groups (Ldis, Lseq, Ldec, and Lfus) based on the lumbar surgical procedures to investigate the influence of these surgical procedures on the development of MCs. 2) Based on the time of follow-up after surgery, the patients were divided into three groups (<12 months, 12-24-months, and >24-months) to investigate the active phases of the occurrence of nMCs and their types after undergoing different surgical methods. 3) The patients were divided into MCs and non-MCs groups based on the presence of MCs on their preoperative MRI to explore which baseline or outcome indicators are related to MCs. 4) The patients were divided into the new/accentuated MCs and non-new/non-accentuated MCs groups based on

whether the postoperative MRI showed evidence of new/accentuated MCs to examine the association between the baselines, outcome indicators and new/accentuated MCs.

2. MRI parameters

Patients were put in the supine position and examined with the magnetic resonance unit in according to the standard procedure. The scan area ranged from T12 to sacrum. Two types of magnetic resonance units (1.5 T and 3.0 T) were used.

The following parameters were performed with the 1.5 T unit (Espree, Siemens, Germany): the sagittal T1WI (slice thickness (ST): 3 mm, time of repetition (TR): 620 ms, time to echo (TE): 13 ms, field of view (FOV): 280 mm), the sagittal T2WI (ST: 3 mm, TR: 4850 ms, TE: 81 ms, FOV: 280 mm); and axial T2WI (ST: 3 mm, TR: 5000 ms, TE: 97 ms, FOV: 220 mm).

The following parameters were performed with the 3.0 T unit (Skyra, Siemens, Germany): the sagittal T1WI (ST: 3 mm, TR: 650 ms, TE: 9.9 ms, FOV: 280 mm), the sagittal T2WI (ST: 3 mm, TR: 3000 ms, TE: 102 ms, FOV: 280 mm); and axial T2WI (ST: 3 mm, TR: 3500 ms, TE: 108 ms, FOV: 210 mm).

All images were evaluated by spinal surgeons with more than a three-year clinical experience. The dispute regarding evaluation results was resolved by consulting an extra reviewer with more than ten-year clinical experience.

3. Definition of MCs, new MCs (nMCs), and accentuated MCs (aMCs)

3.1 MCs

Based on their appearance on T1WI and T2WI, Modic *et al.* (38,39) classified MCs into three types and described their imaging characteristics. MC1 was

characterized by a hypointensity on T1WI and a hyperintensity on T2WI. MC2 exhibited hyperintensity on both T1WI and T2WI, whereas MC3 showed hypointensity on both T1WI and T2WI (**Fig. 5**). Some patients might have both a MC1 and MC2 image presentation together, also known as mixed MCs, since these three types could be transformed into each other. The mixed MCs that could not be simply be classified into one of these three types, were classified as the such: Those mainly with a hyposignal (bone marrow oedema) were characterized into MC1 while those mainly with a hypersignal (fat degeneration) into MC2 (150).

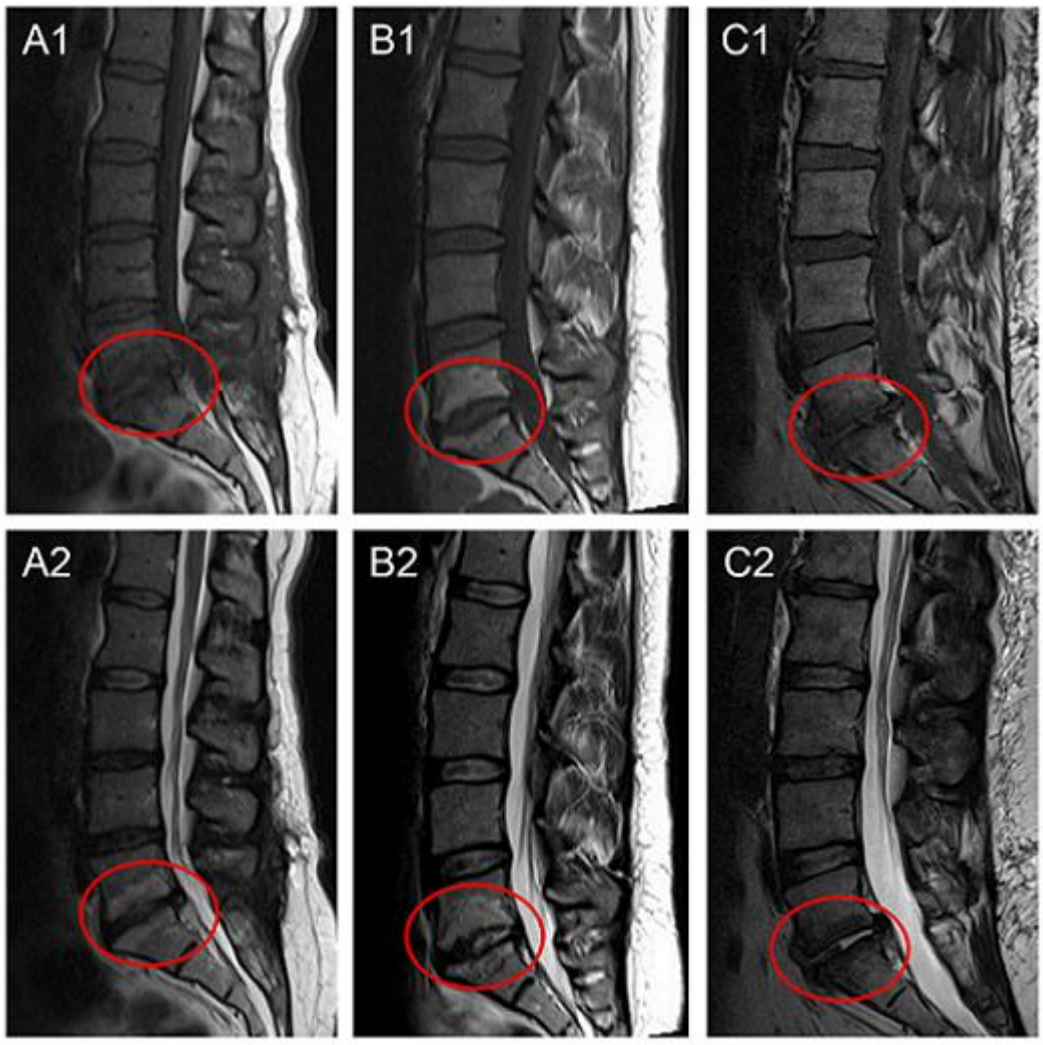

Fig. 5: The appearance of Modic changes at the level of L5/S1. **A.** Modic type 1 change: hypointense on T1-weighted images (A1) and hyperintense on T2-weighted images (A2); **B.** Modic type 2 change: hyperintense on both T1- (B1) and

T2-weighted images (B2); **C.** Modic type 3 change: hypointense on both T1- (C1) and T2-weighted images (C2).

3.2 New Modic changes (nMCs)

Guided by the established research protocol, we only took into account MCs that occurred at the surgical levels and their adjacent levels. Lumbar levels with one of the following conditions were defined as nMCs: 1) preoperative MRI scanning did not discover MCs at the surgical segments and their adjacent segments, but MCs were present at the surgical and/or adjacent segments after surgery (**Fig. 6-1**); 2) preoperative MRI scanning suggested MCs at the surgical (or adjacent) segments, and MCs were present at the adjacent (or surgical) segments after surgery (**Fig. 6-2**).

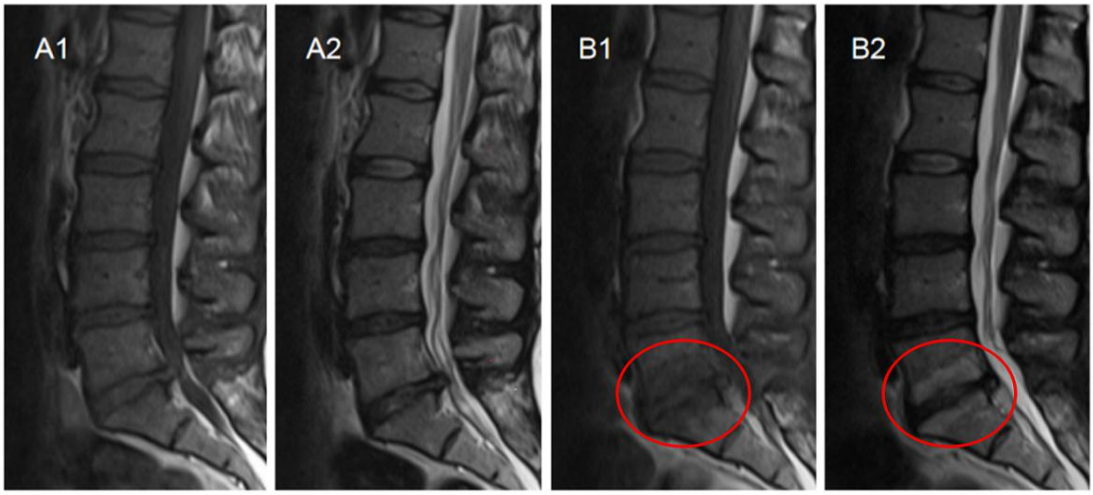

Fig. 6-1: New Modic changes (MCs) at the surgical level. **A.** No MCs at the surgical level and its adjacent levels both on the preoperative T1-weighted images (A1) and T2-weighted images (A2). **B.** Postoperative magnetic resonance imaging scanning shown a hypointense on T1-weighted images (B1) and a hyperintense on T2-weighted images (B2), indicating the evidence of new Modic type 1 change at the surgical level (L5/S1).

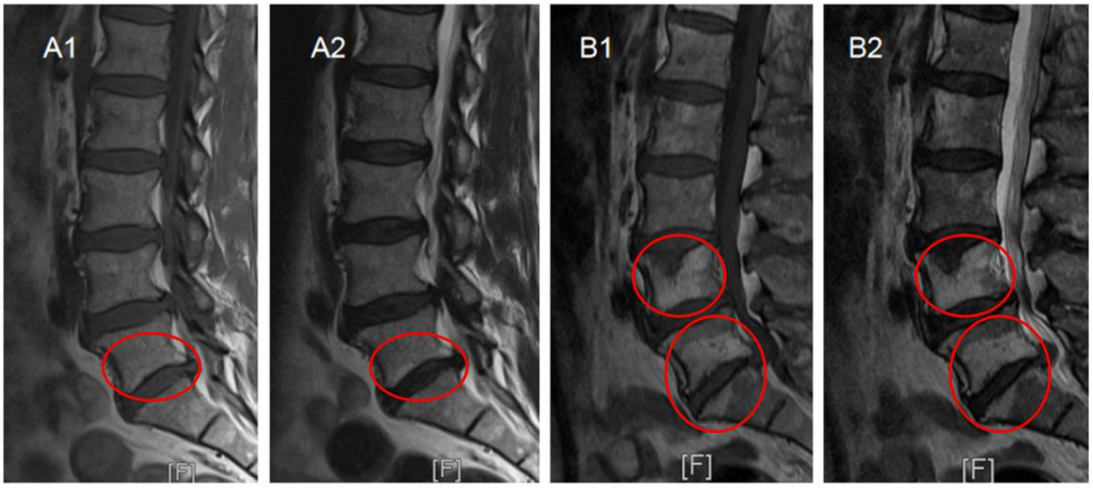

Fig. 6-2 New Modic changes at the adjacent level. **A.** Modic type 2 change (MC2) with hyperintense both on T1- (A1) and T2-weighted images (A2) was detected at the surgical level (L5/S1) on the preoperative magnetic resonance imaging (MRI) scanning. **B.** Postoperative MRI was with evidence of new MC2 (hyperintense both on T1- (B1) and T2-weighted images (B2)) at its adjacent level (L4/5) and the volume of preexisting MC2 at the level of L5/S1 significantly increased after surgery.

3.3 aMCs

MC1 is usually considered to be an early lesion in the vertebral endplate and bone marrow. In other words, the conversion route of MCs usually begins with MC1, followed by MC2 and MC3 (119). There is a negative association between their types and clinical symptoms in the progression of MCs; MC1, which is characterized by inflammation, is the type usually reported to be closely associated with CLBP (6). Therefore, if nMCs were observed or the normal conversion route of MCs was reversed, i.e., the conversion of MC3 or MC2 into MC1, were defined as aMCs (**Fig. 7**).

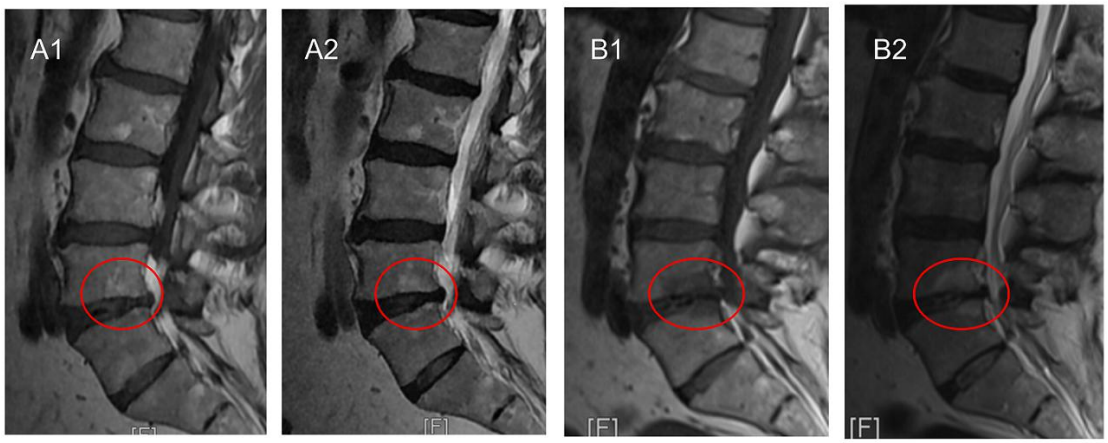

Fig .7: The appearance of accentuated Modic changes (MCs) at the level of L4/5. **A.** Preoperative magnetic resonance imaging scanning revealed that a Modic type 2 change (MC2) with the evidence of hyperintense both on T1- (A1) and T2-weighted images (A2) was observed at the surgical segments (L4/5). **B.** MC2 was converted to Modic type 1 change (hypointense on T1-weighted images (B1) and a hyperintense on T2-weighted images (B2)) after surgery and the volume of postoperative MCs was significantly larger in comparison prior to the surgery.

4. Evaluating disc degeneration

4.1 Pfirrmann classification

Pfirrmann's classification was accredited as a reliable and effective method for evaluating IDD on MRI in a systematic review of existing classification systems for LDD. It was proposed after Pfirrmann *et al.* (151) summarized and analysed the MRI data of 60 patients with an average age of 40 years. This method classified those patients into five categories based on their disc structure, distinction of nucleus and annulus, signal intensity, and disc height on lumbar MRI (**Table 1**). A higher class indicates more severe IDD.

Table 1 Pfirrmann classification

Items	Descriptions			
	Structure	Distinction of Nucleus and Annulus	Signal Intensity	Disc height
Grade I	Homogeneous, bright white	Clear	Hyperintense, isointense to CSF	Normal
Grade II	Inhomogeneous with or without horizontal bands	Clear	Hyperintense, isointense to CSF	Normal
Grade III	Inhomogeneous, gray	Unclear	Intermediate to CSF	Normal to slightly decreased
Grade IV	Inhomogeneous, gray to black	Lost	Intermediate to hypointense to CSF	Normal to moderately decreased
Grade VIII	Inhomogeneous, black	Lost	Hypointense to CSF	Collapsed

CSF, cerebrospinal fluid**.**

4.2 Modified Pfirrmann classification

Although the Pfirrmann classification covers more lumbar MRI features, the evaluation results of patients in different age groups (younger and elderly subjects) reported large differences. Therefore, Griffith *et al.* (152) modified this five-point system and proposed a more detailed classification. The modified grading method includes the signal intensity of the nucleus and fibres of annulus, intervertebral disc height and the distinction between the annulus, to give an 8 point grading system (**Table 2**).

Table 2 Modified Pfirrmann classification

Items	Descriptions		
	Signal from nucleus and inner fibres of annulus	Distinction between inner and outer fibres of annulus at posterior aspect of disc	Disc Height
Grade I	Uniformly hyperintense, equal to CSF	Distinct	Normal
Grade II	Hyperintense	Distinct	Normal
Grade III	Hyperintense but less than presacral fat	Distinct	Normal
Grade IV	Mildly hyperintense	Indistinct	Normal
Grade V	Hypointense	Indistinct	Normal
Grade VI	Hypointense	Indistinct	<30% reduction in disc height
Grade VII	Hypointense	Indistinct	30%-60% reduction in disc height
Grade VIII	Hypointense	Indistinct	>60% reduction in disc height

CSF, cerebrospinal fluid

4.3 Riesenburger scoring system

The two methods that were previously presented still lack some factors that might be associated with IDD. Therefore, we simultaneously introduced a novel classification system for IDD proposed by Riesenburger *et al.* (153) that incorporated multiple radiographic indicators including disc structure and brightness, MCs, high intensity zone, and disc height, to evaluate the degree of disc degeneration at each level in the spine. The detailed items are shown in **Table 3**.

Table 3 Riesenburger scoring system

Items	Descriptions	Score
Disc structure and brightness	Presence of a distinct annulus fibrosis and nucleus pulposus; nucleus pulposus T2-weighted signal isointense to CSF	0
	Lack of a distinction of annulus fibrosis and nucleus pulposus; nucleus pulposus T2-weighted signal hypointense to CSF but not completely black	1
	Lack of a distinction of annulus fibrosis and nucleus pulposus; nucleus pulposus T2-weighted signal completely hypointense (black or dark disk)	2
Modic changes	No type I or II changes	0
	Type I or II changes present	1
High intensity zone	Absent	0
	Present	1
Disc height	Greater or equal to 5 mm	0
	Less than 5 mm	1

CSF, cerebrospinal fluid; mm, millimetre.

5. Calculating the volume of MCs

Considering that MCs have an irregular morphology, the qualitative or two-dimensional quantitative measurement of their areas usually results in larger errors. Therefore, we used a clinical three-dimensional quantitative calculation method for pituitary adenoma volume, i.e., the platform-like volume calculation formula proposed by Wang *et al.* (154). This method was based on the Cavalieri principle in stereology: According to the method of isometric sampling, the total area of all sections of the object is multiplied by the cross-section spacing in any direction, that is, the unbiased estimation of the volume of the object.

The MCs in each lumbar level were divided into multiple scanning layers after MRI scanning, with the interval between two scanning layers remaining the same. Layers on horizontal sections that contained MCs were selected. The boundary between the MCs and normal vertebral tissues in each scanning layer was delineated using the paintbrush in the medical imaging system to automatically calculate the area of the MCs in this layer. The section of MCs between two scanning layers in the MRI was regarded as an independent platform. The volume of each platform was calculated using the formula: $v=(S_1+S_2)*h/2$, in which S_1 and S_2 are the areas of the upper layer and lower layer of a platform, respectively, and h is the distance between two layers. The total volume of MCs was calculated by summing up the volumes of multiple platforms: $V=(S_1+2S_2+2S_3+.....+2S_{n-1}+S_n)*h/2$.

6. Statistical analysis

SPSS software (version 22.0, SPSS Inc., Chicago, Illinois, USA) was used to analyse the original data. Percentage (%) was used in order to describe the incidence of MCs. The continuous data, such as patients' age, body mass index (BMI), white blood cell (WBC), hsCRP and the volumes of MCs, was expressed as the mean ± standard deviation (x ± s). If the continuity data conforms to a normal distribution, we used the *t*-test to analyse the differences between groups. Otherwise, Mann-Whitney *U* test is used. The *Chi-square* test for the categorical data was used to compare the difference between the groups. A *p* value with two tails less than 0.05 was considered statistically significant.

III. RESULTS

1. The prevalence of nMCs

Data of 270 patients, including 130 males and 140 females, were retrospectively analysed in this study. The mean follow-up period was 267.63±427.82 days. The subjects undergoing Ldis, Lseq, Ldec and Lfus were 93 cases, 60 cases, 74 cases and 43 cases, respectively.

The total incidence of postoperative nMCs was 36.30% (98/270, **Fig. 8-1**), of which more than half were MC2 (70.41%, 69/98), followed by MC1 (24.49%, 24/98) and MC3 (5.10%, 5/98, **Fig. 8-2**). The operative levels were the most affected sites of nMCs (**Fig. 8-3**), accounting for more than half of the total incidence of nMCs (54.09%, 53/98). The postoperative incidence of nMCs at the adjacent levels was 29.59% (29/98). nMCs occurred at both the operative levels and their adjacent levels in 16 patients (16.32%) after the operation.

The postoperative incidence of nMCs in patients receiving the four lumbar surgical procedures ranged between 30.23% and 38.71% (**Fig. 8-1**). We did not detect a significant difference in the incidence of postoperative nMCs between those four groups ($P>0.05$). However, the incidence of nMCs in patients after Ldis (38.71%, 36/93) was the highest, and that after Lfus (30.23%, 13/43) was the lowest. MC2 was the main type of nMC (**Fig. 8-2**), and operative level was the main affected site of nMCs following these four surgeries (**Fig. 8-3**).

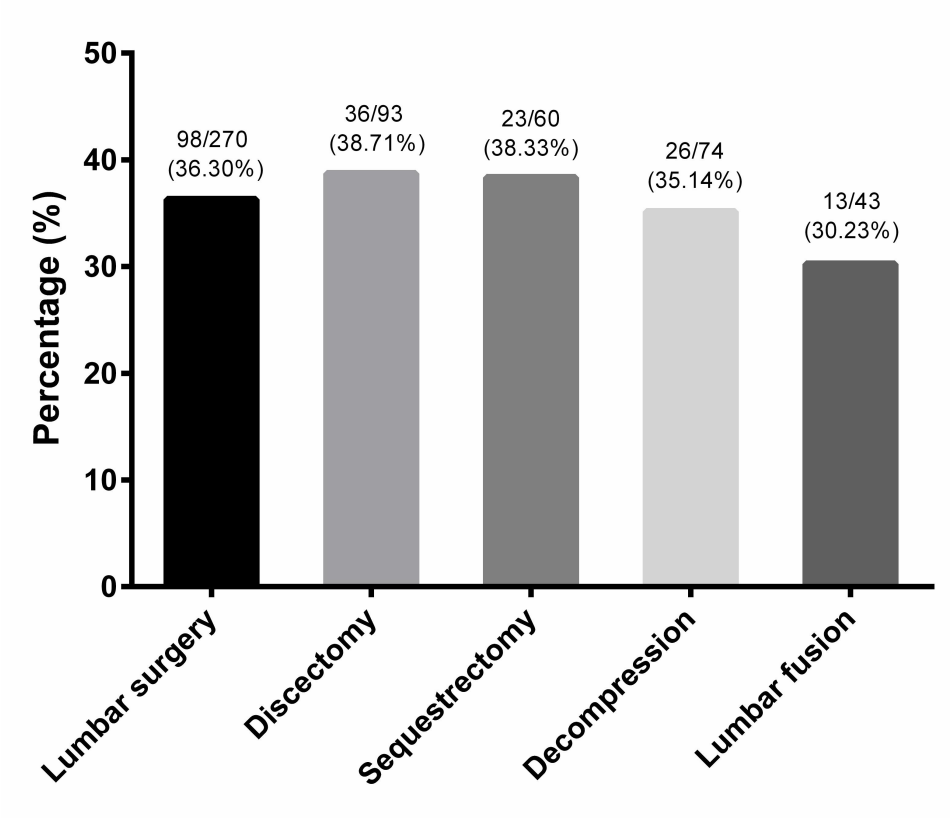

Fig. 8-1: The incidence of new Modic changes following lumbar surgical procedures.

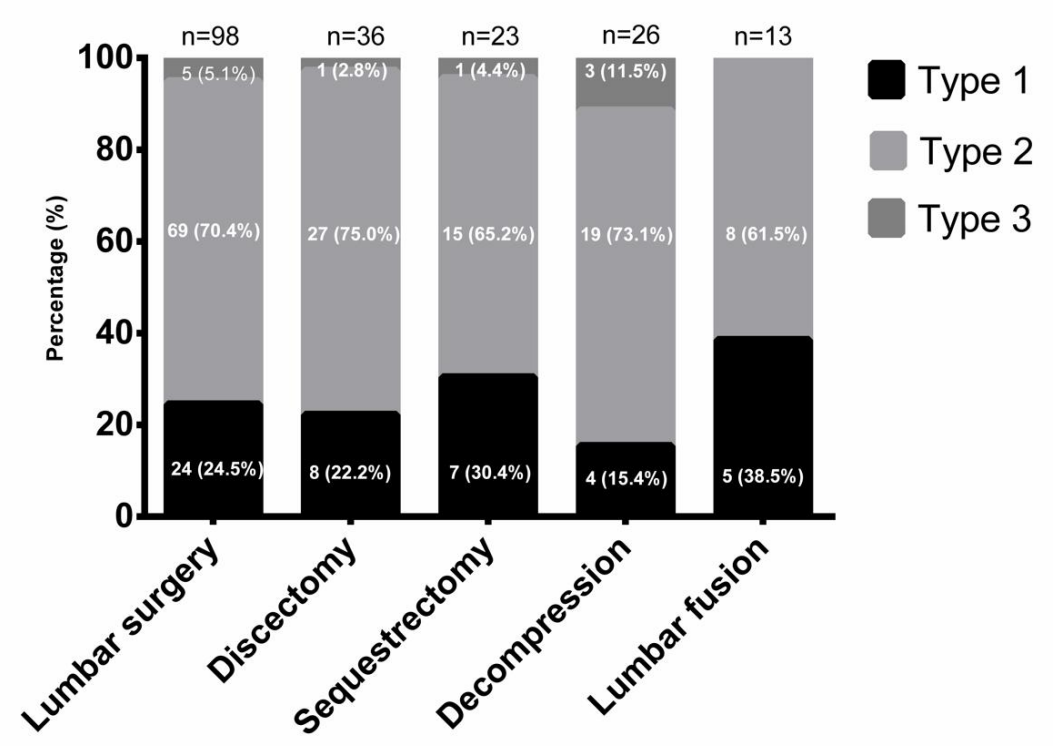

Fig. 8-2: Type distribution of new Modic changes following lumbar surgical

procedures.

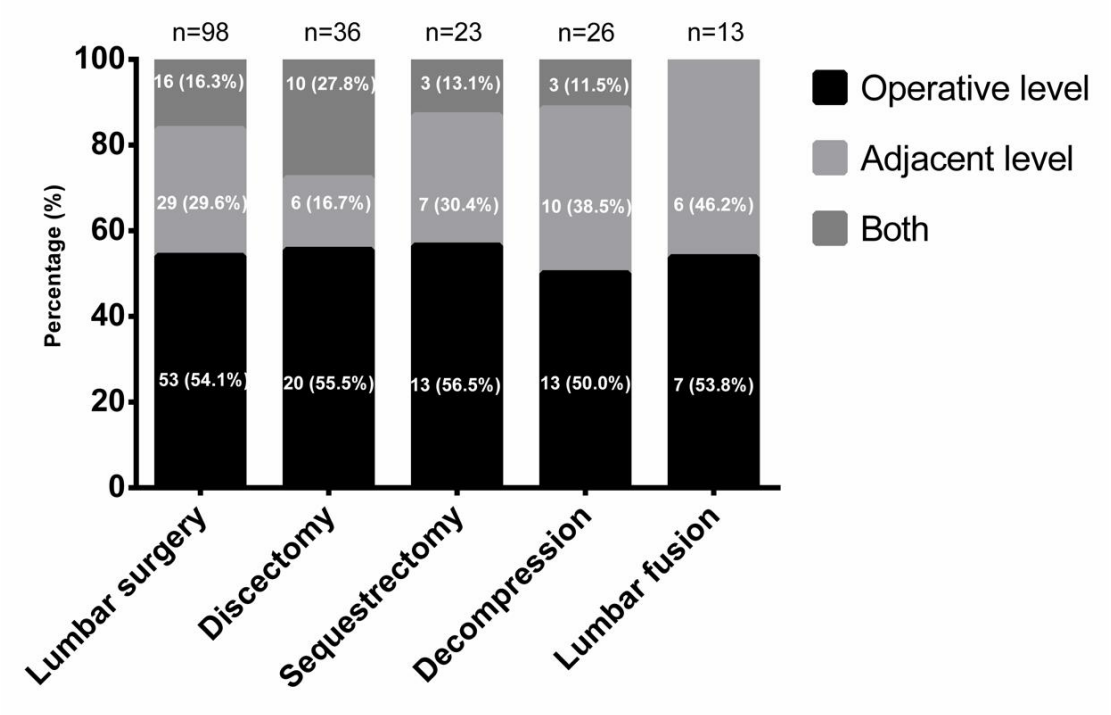

Fig. 8-3: Lumbar level distribution of new Modic changes following lumbar surgical procedures.

Based on the characteristics of the case data and the distribution of the study subjects, the cut-points of follow-up intervals were set to 12 months and 24 months. The incidence and type of nMCs in different groups of patients at different follow-up intervals are shown in **Table 4**. nMC1 and nMC2 were observed at any stage of postoperative follow-up. However, regardless which lumbar surgical procedures was chosen, nMCs seemed to occur most often in the first year after the surgery. The incidence of different types of nMCs in each follow-up interval was different (**Fig. 9**), and nMC2 mostly occurred within one year after surgery. After Ldis, Lseq and Ldec, nMC1 seemed to be more likely to occur within the postoperative 1 year. However, for patients undergoing Lfus, no difference in the incidences of nMC1 at different follow-up groups was detected. The epidemiological characteristics of nMC3 could not be analysed because of its rare postoperative occurrence.

Table 4 Type distribution of nMCs after lumbar surgical procedures in the different follow-up intervals

Groups	new MC1	new MC2	new MC3
Discectomy (n=36)			
<12 months (n, %)	5 (13.89)	18 (50.00)	1 (2.78)
12-24 months (n, %)	3 (8.33)	3 (8.33)	0
>24 months (n, %)	0	6 (16.67)	0
Sequestrectomy (n=23)			
<12 months (n, %)	6 (26.08)	8 (34.78)	1 (4.35)
12-24 months (n, %)	1 (4.35)	4 (17.39)	0
>24 months (n, %)	1 (4.35)	2 (8.70)	0
Decompression (n=26)			
<12 months (n, %)	3 (11.54)	14 (53.86)	2 (7.69)
12-24 months (n, %)	1 (3.84)	3 (11.54)	0
>24 months (n, %)	0	2 (7.69)	1 (3.84)
Fusion (n=13)			
<12 months (n, %)	2 (15.39)	6 (46.15)	0
12-24 months (n, %)	1 (7.69)	1 (7.69)	0
>24 months (n, %)	2 (15.39)	1 (7.69)	0

nMCs, new MCs, MC1, Modic type 1 change; MC2, Modic type 2 change; MC3, Modic type 3 change; n, number.

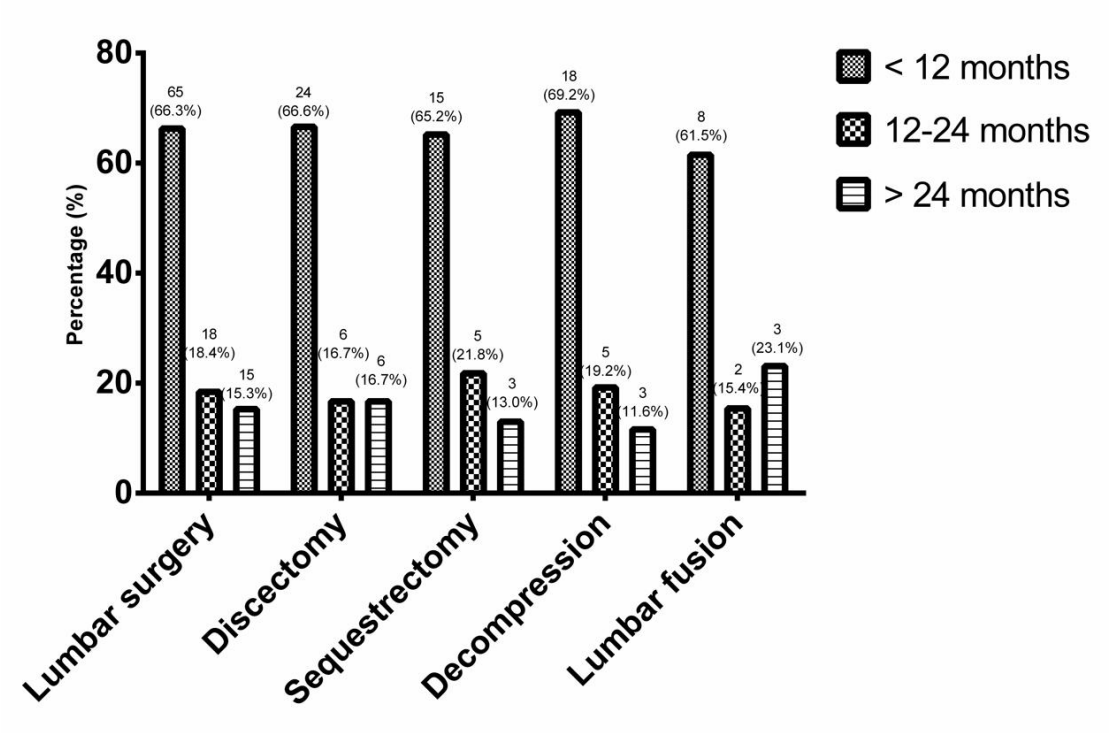

Fig. 9: The incidence of new Modic changes in the different follow-up intervals.

2. Comparison of the preoperative and postoperative volume of MCs

The measurements of MCs volumes before and after surgery in patients undergoing the four different lumbar surgical procedures are shown in **Table 5**. The volume of postoperative MCs in patients receiving lumbar surgery was significantly larger than the one before surgery ($P<0.01$), indicating that lumbar surgery had a promoting impact on the development of MCs. The subgroup analysis found that the volumes of MCs after Ldis, Lseq, and Ldec were significantly different from those before surgeries ($P<0.01$). However, for the patients in the Lfus group, a surgery did not lead to significant postoperative MCs volume change ($P>0.05$).

Table 5 The volume of MCs before and after surgery

Groups	Preoperative volume (cm^3)	Postoperative volume (cm^3)	Follow-up (days)	*t*	*p*
Total (n=270)	4.25±5.62	7.42±6.70	267.63±427.82	-10.76	**<0.01**
Discectomy (n=93)	3.33±4.64	7.03±6.45	283.08±439.76	-8.95	**<0.01**
Sequestrectomy (n=60)	3.82±4.71	8.05±7.40	228.20±474.12	-5.63	**<0.01**
Decompression (n=74)	4.36±5.89	7.71±6.17	270.19±366.81	-9.20	**<0.01**
Fusion (n=43)	6.60±7.30	6.97±7.38	284.86±442.65	-0.34	>0.05

MCs, Modic changes; cm^3, cubic centimetre; n, number. Mean ± standard deviation.

3. Comparison of the baseline between patients with or without MCs

Preoperative MRI showed that 164 patients had MCs. Compared with the 106 patients without MCs, the patients with MCs were older, but with no significant difference (P=0.067), and there was no significant difference in gender, BMI and WBC (P>0.05, **Table 6-1**). However, a higher hsCRP value of patients in the MCs group was detected compared with that in the non-MCs group (P<0.05), indicating that MCs may be an imaging sign associated with inflammation.

Table 6-1 Comparison of the baseline characteristic between patient with MCs and without MCs

Groups	Age (years)	Gender (M/F)	BMI (kg/m^2)	WBC ($10^9/L$)	CRP (mg/L)
MCs (n=164)	64.33±15.42	73/91	29.34±5.47	8.52±3.40	9.17±21.79
No MCs (n=106)	60.51±15.88	56/50	28.98±6.61	8.43±2.84	4.41±6.71
p	>0.05	>0.05	>0.05	>0.05	**<0.01**

MCs, Modic changes; M, male; F, female; BMI, body mass index; kg, kilogram; m^2,

square metre; L, litre; mg, milligram; WBC, white blood cell; CRP, C-reaction protein; n, number. Mean ± standard deviation.

In the analysis of various surgical subgroups, the small sample size may be the main reason for the discrepancy in the statistical results of various baseline indicators (**Table 6-2**). Among patients receiving Ldis, MCs were more common in females (P<0.01); among patients undergoing Lseq, age and hsCRP had significant inter-group differences (P<0.05). We did not find a significant differences in other baseline characteristics between the MCs and non-MCs groups (P>0.05).

Table 6-2 Comparison of the baseline between patient with MCs and without MCs (surgical subgroup analysis)

Groups		Age (years)	Gender (M/F)	BMI (kg/m^2)	WBC ($10^9/L$)	CRP (mg/L)
Discectomy (n=93)	MCs (n=49)	54.78±13.43	19/30	29.76±5.85	9.25±3.23	8.12±22.22
	No MCs (n=44)	57.66±16.35	29/15	28.64±7.42	8.76±3.17	4.55±7.17
	p	>0.05	**<0.01**	>0.05	>0.05	>0.05
Sequestrectomy (n=60)	MCs (n=35)	60.94±15.41	17/18	29.32±6.12	9.07±3.37	5.31±10.80
	No MCs (n=25)	52.44±14.52	12/13	28.37±6.22	8.85±3.32	2.56±5.14
	p	**<0.05**	>0.05	>0.05	>0.05	**<0.05**
Decompression (n=74)	MCs (n=51)	74.94±11.31	25/26	28.91±4.73	7.61±2.86	12.63±29.94
	No MCs (n=23)	70.87±9.93	10/13	29.31±6.03	7.83±1.91	5.34±7.07
	p	>0.05	>0.05	>0.05	>0.05	>0.05
Fusion (n=43)	MCs (n=29)	65.90±13.31	12/17	29.44±5.44	8.24±4.27	9.49±11.49
	No MCs (n=14)	66.86±14.50	6/8	30.61±5.79	7.66±1.83	5.73±7.08
	p	>0.05	>0.05	>0.05	>0.05	>0.05

MCs, Modic changes; M, male; F, female; BMI, body mass index; kg, kilogram; m^2, square metre; L, litre; mg, milligram; WBC, white blood cell; CRP, C-reaction protein; n, number. Mean ± standard deviation.

4. Comparison of the baseline between patients with or without aMCs

109 patients showed aMCs (40.37%, 109/270) after surgery. Patients with aMCs were older and had a higher BMI compared to those without aMCs (P<0.05), and aMCs were more prone to appear in male patients. However, there were no significant differences in WBC and hsCRP values between the two groups (P>0.05, **Table 7-1**).

Table 7-1 Comparison of the baseline between patient with aMCs and without aMCs

Groups	Age (years)	Gender (M/F)	BMI (kg/m^2)	WBC ($10^9/L$)	CRP (mg/L)
aMCs (n=109)	65.78±13.89	61/48	30.45±6.69	8.13±2.61	8.72±21.83
No aMCs (n=161)	60.83±16.54	69/92	28.36±5.22	8.73±3.51	6.34±14.08
p	**<0.05**	**<0.05**	**<0.01**	>0.05	>0.05

aMCs, accentuated Modic changes; M, male; F, female; BMI, body mass index; kg, kilogram; m^2, square metre; L, litre; mg, milligram; WBC, white blood cell; CRP, C-reaction protein; n, number. Mean ± standard deviation.

For patients undergoing different surgical procedures, the baseline indicators between the groups were also different (**Table 7-2**). Significant differences in age were only detected between the Ldis and Lseq groups (P<0.05). Compared with patients without aMCs, the aMC patients with higher BMI only appeared in the Lseq and Ldec groups (P<0.05), and the male patients receiving Ldec were more prone to aMCs after surgery. However, we did not find a significant difference in baseline

characteristics for patients undergoing Lfus (P>0.05).

Table 7-2 Comparison of the baseline between patient with aMCs and without aMCs (surgical subgroups analysis)

Groups		Age (years)	Gender (M/F)	BMI (kg/m^2)	WBC ($10^9/L$)	CRP (mg/L)
Discectomy (n=93)	aMCs (n=40)	61.28±14.40	20/20	29.55±8.34	8.28±2.32	5.05±7.11
	No aMCs (n=53)	52.26±14.15	28/25	28.99±5.03	9.57±3.64	7.48±21.52
	p	**<0.01**	>0.05	>0.05	>0.05	>0.05
Sequestrectomy (n=60)	aMCs (n=24)	62.33±15.54	14/10	30.90±5.47	8.47±2.87	5.04±12.66
	No aMCs (n=36)	54.11±14.80	15/21	27.61±6.26	9.32±3.59	3.59±5.33
	p	**<0.05**	>0.05	**<0.05**	>0.05	>0.05
Decompression (n=74)	aMCs (n=31)	73.26±9.42	21/10	30.67±5.19	8.07±2.96	16.92±37.46
	No aMCs (n=43)	73.98±12.11	14/29	27.85±4.80	7.39±2.29	5.64±7.54
	p	>0.05	**<0.01**	**<0.05**	>0.05	>0.05
Fusion (n=43)	aMCs (n=14)	68.00±11.18	6/8	31.78±6.56	7.25±2.12	7.38±7.55
	No aMCs (n=29)	65.34±14.65	12/17	28.87±4.77	8.44±4.16	8.69±11.53
	p	>0.05	>0.05	>0.05	>0.05	>0.05

aMCs, accentuated Modic changes; M, male; F, female; BMI, body mass index; kg, kilogram; m^2, square metre; L, litre; mg, milligram; WBC, white blood cell; CRP, C-reaction protein; n, number. Mean ± standard deviation.

5. Comparison of the IDD extents between lumbar levels with or without MCs

This study evaluated the extent of IDD at lumbar levels with MCs compared

with those without MCs at the same lumbar level. The results showed that under three different IDD evaluation classifications, the extents of IDD in patients with MCs at the levels of L3/4, L4/5, and L5/S1 were significantly more severe than those at the same lumbar level in patients without MCs (P<0.05, **Table 8-1, 8-2 and 8-3**).

Table 8-1 Comparison of disc degeneration extents between lumbar levels with MCs and without MCs (Pfirrmann grading classification)

Levels	Level with MCs	No.	Pfirrmann grading system					p
			V	VI	III	II	I	
L3/4	Yes	49	36	10	3	0	0	**<0.05**
	No	104	29	34	23	13	5	
L4/5	Yes	67	34	30	3	0	0	**<0.05**
	No	106	40	44	12	6	4	
L5/S1	Yes	96	52	35	8	0	1	**<0.05**
	No	106	39	44	15	7	1	

MCs, Modic changes; No., number.

Table 8-2 Comparison of disc degeneration extents between lumbar levels with MCs and without MCs (modified Pfirrmann grading classification)

Levels	Level with MCs	No.	Modified Pfirrmann grading system								p
			VIII	VII	VI	V	VI	III	II	I	
L3/4	Yes	49	12	19	11	1	4	2	0	0	**<0.05**
	No	104	5	8	27	11	20	19	7	7	
L4/5	Yes	67	12	15	28	1	10	1	0	0	**<0.05**
	No	106	6	8	39	14	20	12	3	4	
L5/S1	Yes	96	15	31	21	5	20	3	0	1	**<0.05**
	No	106	4	21	28	6	30	11	5	1	

MCs, Modic changes; No., number.

Table 8-3 Comparison of disc degeneration extents between lumbar levels with MCs and without MCs (Riesenburger scoring system)

Levels	Level with MCs	No.	Scores	p
L3/4	Yes	49	3.18±0.91	**<0.05**
	No	104	1.18±0.75	
L4/5	Yes	67	2.60±0.76	**<0.05**
	No	106	1.32±0.71	
L5/S1	Yes	96	2.94±0.86	**<0.05**
	No	106	1.41±0.84	

MCs, Modic changes; No., number; Mean ± standard deviation.

6. Comparison of the IDD scores between lumbar levels with or without aMCs

There were differences in the IDD extents between varying lumbar levels with vs. without aMCs (**Table 9-1a, 9-1b and 9-1c**). The results showed that under modified Pfirrmann grading system and Riesenburger scoring system,the extents of IDD were more severe in patients with aMCs at the L3/4 segment than in patients without aMCs ($P<0.05$, **Table 9-1b and 9-1c**). However, at the level of L4/5, aMCs patients only showed a significant difference in IDD extent from patients without aMCs in the Riesenburg classification ($P<0.05$, **Table 9-1c**). A significant difference in the IDD grade of the L5/S1 segment was detected between the groups in Pfirrmann grading system ($P<0.05$, **Table 9-1a**).

Table 9-1a Comparison of disc degeneration extents between lumbar levels with aMCs and without aMCs (Pfirrmann grading classification)

Levels	Level with aMCs	No.	Pfirrmann grading classification					p
			V	VI	III	II	I	
L3/4	Yes	74	36	24	10	4	0	>0.05
	No	152	55	50	25	15	7	
L4/5	Yes	89	39	39	9	2	0	>0.05
	No	151	70	53	18	6	4	
L5/S1	Yes	77	31	34	6	3	3	**<0.05**
	No	153	70	53	24	6	0	

aMCs, accentuated Modic changes; No., number.

Table 9-1b Comparison of disc degeneration extents between lumbar levels with aMCs and without aMCs (modified Pfirrmann grading classification)

Levels	Level with aMCs	No.	Modified Pfirrmann grading classification								p
			VIII	VII	VI	V	VI	III	II	I	
L3/4	Yes	74	10	11	25	12	11	2	3	0	**<0.05**
	No	152	11	14	38	26	24	21	11	7	
L4/5	Yes	89	12	16	20	12	24	3	1	1	>0.05
	No	151	18	20	49	23	23	10	4	4	
L5/S1	Yes	77	12	11	15	18	12	4	3	2	>0.05
	No	153	20	32	32	20	30	16	3	0	

aMCs, accentuated Modic changes; No., number.

Table 9-1c Comparison of disc degeneration extents between lumbar levels with aMCs and without aMCs (Riesenburger scoring system)

Levels	Level with aMCs	No.	Score	p
L3/4	Yes	74	2.07±1.14	**<0.05**
	No	152	1.41±1.01	
L4/5	Yes	89	2.25±1.01	**<0.05**
	No	151	1.74±1.01	
L5/S1	Yes	77	2.17±1.09	>0.05
	No	153	1.99±1.09	

aMCs, accentuated Modic changes; No., number; Mean ± standard deviation.

The subgroup analysis by surgical methods was based on the fact, that surgical procedures may be correlated with the IDD of aMCs patients. Compared to those without aMCs, the significant differences in the IDD scores at the L3/4-L5/S1 levels were observed in aMC patients after Ldis using the Riesenburg classification (P<0.05, **Table 9-2a-c**),and the significant differences in the extents of IDD at the level of L3/4 were detected using the Pfirrmann and modified Pfirrman grading systems (P<0.05). In addition, the IDD scores of aMC patients in the Lseq group (L3/4 level, **Table 9-3a-c**) and in the Ldec group (L4/5 level, **Table 9-4a-c**) were significantly higher than those of patients without aMCs using the Riesenburg classification (P<0.05). The extents of IDD of aMC patients in the Lfus group were similar to those without aMCs **(Table 9-5a-c)**.

Table 9-2a Comparison of disc degeneration extents between patients with aMCs and without aMCs after discectomy (Pfirrmann grading classification)

Levels	Level with aMCs	No.	Pfirrmann grading classification					p
			V	VI	III	II	I	
L3/4	Yes	28	16	7	4	1	0	**<0.05**
	No	53	12	17	11	9	4	
L4/5	Yes	37	23	10	3	1	0	>0.05
	No	53	20	21	8	2	2	
L5/S1	Yes	31	16	12	2	1	0	>0.05
	No	53	24	21	5	3	0	

aMCs, accentuated Modic changes; No., number.

Table 9-2b Comparison of disc degeneration extents between lumber levels with aMCs and without aMCs after discectomy (modified Pfirrmann grading classification)

Levels	Level with aMCs	No.	Modified Pfirrmann grading classification								p
			VIII	VII	VI	V	VI	III	II	I	
L3/4	Yes	28	4	3	10	8	2	0	1	0	**<0.05**
	No	53	1	5	12	8	7	10	6	4	
L4/5	Yes	37	7	8	9	7	4	1	0	1	>0.05
	No	53	7	8	18	9	3	5	1	2	
L5/S1	Yes	31	7	4	5	11	3	0	1	0	>0.05
	No	53	9	9	17	10	3	4	1	0	

aMCs, accentuated Modic changes; No., number.

Table 9-2c Comparison of disc degeneration between lumber levels with aMCs and without aMCs after discectomy (Riesenburger scoring system)

Levels	Level with aMCs	No.	Score	p
L3/4	Yes	28	1.89±1.13	**<0.05**
	No	53	1.13±0.96	
L4/5	Yes	37	2.27±1.12	**<0.05**
	No	53	1.70±1.10	
L5/S1	Yes	31	2.42±1.06	**<0.05**
	No	53	1.92±1.09	

aMCs, accentuated Modic changes; No., number; Mean ± standard deviation.

Table 9-3a Comparison of disc degeneration between lumber levels with aMCs and without aMCs after sequestrectomy (Pfirrmann grading classification)

Levels	Level with aMCs	No.	Pfirrmann grading classification					p
			V	VI	III	II	I	
L3/4	Yes	19	9	5	1	4	0	>0.05
	No	36	10	12	7	5	2	
L4/5	Yes	22	5	14	2	1	0	>0.05
	No	36	14	14	4	3	1	
L5/S1	Yes	18	6	6	3	1	2	>0.05
	No	36	10	14	10	2	0	

aMCs, accentuated Modic changes; No., number.

Table 9-3b Comparison of disc degeneration between lumber levels with aMCs and without aMCs after sequestrectomy (modified Pfirrmann grading classification)

Levels	Level with aMCs	No.	Modified Pfirrmann grading classification								p
			VIII	VII	VI	V	VI	III	II	I	
L3/4	Yes	19	1	4	6	1	1	3	2	0	>0.05
	No	36	1	3	8	8	4	6	4	2	
L4/5	Yes	22	1	4	4	1	10	1	1	0	>0.05
	No	36	2	4	13	3	9	2	2	1	
L5/S1	Yes	18	0	5	4	0	4	2	2	1	>0.05
	No	36	1	9	6	0	12	7	1	0	

aMCs, accentuated Modic changes; No., number.

Table 9-3c Comparison of disc degeneration between lumber levels with aMCs and without aMCs after sequestrectomy (Riesenburger scoring system)

Levels	Level with aMCs	No.	Score	p
L3/4	Yes	19	2.18±1.29	**<0.05**
	No	36	1.17±0.88	
L4/5	Yes	22	1.86±0.83	>0.05
	No	36	1.56±1.00	
L5/S1	Yes	18	1.67±0.91	>0.05
	No	36	1.86±1.11	

aMCs, accentuated Modic changes; No., number; Mean ± standard deviation.

Table 9-4a Comparison of disc degeneration extents between lumber levels with aMCs and without aMCs after decompression (Pfirrmann grading classification)

Levels	Level with aMCs	No.	Pfirrmann grading classification					p
			V	VI	III	II	I	
L3/4	Yes	28	11	12	5	0	0	>0.05
	No	43	25	13	4	1	0	
L4/5	Yes	26	10	12	4	0	0	>0.05
	No	43	26	12	4	1	0	
L5/S1	Yes	25	10	13	1	1	0	>0.05
	No	42	25	10	6	1	0	

aMCs, accentuated Modic changes; No., number.

Table 9-4b Comparison of disc degeneration between lumber levels with aMCs and without aMCs after decompression (modified Pfirrmann grading classification)

Levels	Level with aMCs	No.	Modified Pfirrmann grading classification								p
			VIII	VII	VI	V	VI	III	II	I	
L3/4	Yes	28	5	3	10	2	7	1	0	0	>0.05
	No	43	6	4	13	9	8	2	1	0	
L4/5	Yes	26	4	3	5	4	9	1	0	0	>0.05
	No	43	4	5	15	10	7	1	1	0	
L5/S1	Yes	25	5	3	6	5	4	2	0	0	>0.05
	No	42	7	8	6	9	7	4	1	0	

aMCs, accentuated Modic changes; No., number.

Table 9-4c Comparison of disc degeneration extents between lumber levels with aMCs and without aMCs after decompression (Riesenburger scoring system)

Levels	Level with aMCs	No.	Score	p
L3/4	Yes	28	2.08±1.04	>0.05
	No	43	1.81±0.88	
L4/5	Yes	26	2.48±0.96	**<0.05**
	No	43	1.88±0.88	
L5/S1	Yes	25	2.25±1.15	>0.05
	No	42	2.12±1.13	

aMCs, accentuated Modic changes; No., number; Mean ± standard deviation.

Table 9-5a Comparison of disc degeneration between lumber levels with aMCs and without aMCs after fusion (Pfirrmann grading classification)

Levels	Level with aMCs	No.	Pfirrmann grading classification					p
			V	VI	III	II	I	
L3/4	Yes	5	2	3	0	0	0	>0.05
	No	21	8	9	3	0	1	
L4/5	Yes	5	2	3	0	0	0	>0.05
	No	20	10	7	2	0	1	
L5/S1	Yes	6	1	4	0	0	1	>0.05
	No	23	11	9	3	0	0	

aMCs, accentuated Modic changes; No., number.

Table 9-5b Comparison of disc degeneration between lumber levels with aMCs and without aMCs after fusion (modified Pfirrmann grading classification)

Levels	Level with aMCs	No.	Modified Pfirrmann grading classification								p
			VIII	VII	VI	V	VI	III	II	I	
L3/4	Yes	5	0	0	5	0	0	0	0	0	>0.05
	No	21	3	2	6	1	5	3	0	1	
L4/5	Yes	5	1	0	2	0	2	0	0	0	>0.05
	No	20	5	3	3	1	5	2	0	1	
L5/S1	Yes	6	1	1	0	2	1	0	0	1	>0.05
	No	23	3	6	4	1	8	1	0	0	

aMCs, accentuated Modic changes; No., number.

Table 9-5c Comparison of disc degeneration between lumber levels with aMCs and without aMCs after fusion (Riesenburger scoring system)

Levels	Level with aMCs	No.	Score	p
L3/4	Yes	5	2.75±1.26	>0.05
	No	21	1.75±1.25	
L4/5	Yes	5	2.60±0.89	>0.05
	No	20	1.89±1.10	
L5/S1	Yes	6	2.00±1.41	>0.05
	No	23	2.09±1.06	

aMCs, accentuated Modic changes; No., number; Mean ± standard deviation.

IV. DISCUSSION

1. The impacts of lumbar surgical procedures on the development of MCs

1.1 The prevalence of MCs following lumbar surgical procedures

1.1.1 Lumbar discectomy (Ldis)

In comparison with other lumbar surgical procedures, most studies have investigated the natural course of MCs after Ldis. Rahme *et al.* (135) reported that the incidence of MCs increased from 46% before surgery to 78% 3-5 years after Ldis, and most of them were mainly MC2. A recent prospective study with 2-year follow-up (8) showed that the incidence of nMCs was 26.9% and 37.4% in the first 1 and 2 year after Ldis, respectively. The follow-up in these studies differed; however, the incidence and main types of nMCs were essentially consistent with our research results. Additionally, we found that nMCs mainly occur at the surgical levels, although the adjacent levels can also be involved.

Weiner *et al.* (59) reported that 30-40% of new MC1 developed in the first 3 years after Ldis, and this proportion decreased over time. Nearly 80% of patients had MC2 5 years after surgery. However, Bostelmann *et al.* (8) showed that the incidence of new MC1 and MC2 in the postoperative 1 year were 16.5% and 10.4%, respectively; the incidences 2 years after surgery were 17.4% and 20%, respectively. Moreover, 33.1% of MC2 was converted to MC1 and 20% of MC1 was converted to MC2 at the follow-up point of postoperative 1-year. Moreover, during the 2-year follow-up, nearly half of the MCs types did not change compared with the preoperative MCs. Therefore, they believe that the transformation of MCs after Ldis followed different patterns. However, our study, which had a mean follow-up of 283 days, found that more than 60% of new MC1 and MC2 occurred within 1 year after surgery. Because these studies have different follow-up periods, we were unable to obtain the accurate incidence of different types of nMCs after Ldis. In our opinion

transient segment instability caused by lumbar surgery may lead to the occurrence of new MC1 in the early stage (155), and the subsequent self-repair, which usually occurs within 1 year of surgery and involves the formation of fibrous scar, solving the segmental instability caused by surgery, thereby promoting the conversion of MC1 to MC2 (135).

1.1.2 Lumbar sequestrectomy (Lseq)

Both Ldis and Lseq are classic and commonly used procedures for patients suffering symptomatic LDH and seeking surgical treatment (156). At present, clinical studies mainly focus on the comparison of symptom improvement and the postoperative disc herniation recurrence between the two surgical procedures. No sufficient information in exploring the effect of Lseq on the development of MCs was available. To our best knowledge, a study performed by Barth *et al.* (147), which aimed to compare imaging changes between Ldis and Lseq before and after surgery, was the first study to report the effect of Lseq on MCs. They found that the changes in MCs before and after surgery in patients receiving Lseq were rather stable (preoperative: 28 cases; postoperative: 34 cases), whereas the ratio of postoperative MC2 and MC3 in the Ldis group was twice that of preoperation (21% before surgery and 42% at follow-up) (147). Their subsequent study also supported the conclusion that Lseq had no relevant effect on MCs (157). However, in this study, 38.33% of nMCs following Lseq were detected, and there was no significant difference compared with Ldis, indicating that our results are inconsistent with the findings presented above. We suspect that this difference may have occurred because the Ldis procedure they used was minimally invasive, and more limited disc tissues were removed than in our procedure.

1.1.3 Lumbar decompression (Ldec)

The efficacy of Ldec in the treatment of patients with MCs has been confirmed

by a study previously conducted (158). However, no studies have discussed image changes of the endplate after Ldec. To our knowledge, this is the first study to report the effect of Ldec on the development of MCs. In this study, the postoperative incidence of nMCs of 35.15%, with MC2 at the surgical levels being the most common, was essentially consistent with that after Ldis and Lseq. The following reasons may explain the above findings: although some patients develop lumbar spinal stenosis (LLS) caused by thickening of the posterior yellow ligament or hyperplasia of bone tissue, the IDD-induced LSS is still the primary clinical cause. The pathological changes in IVDs are strongly related to MCs and will gradually transform into LLS over time (159). Therefore, the IVD tissue should also be processed during the operation, which results in biomechanical and biochemical changes similar to those after Ldis and Lseq.

1.1.4 Lumbar fusion (Lfus)

MCs are considered to be one stage in the process of IDD (160,161) that contributes to lumbar instability (133,134). Therefore, Lfus for patients with lumbar IDD with MCs appears reasonable, although this decision should still be made in combination with the patient's actual clinical conditions.

We retrieved only two studies (55,138) that reported the effect of Lfus on the progression of MCs at the surgical segment. Vital *et al.* (138) analysed the data of 17 CLBP patients with single-level MC1 who received posterolateral fusion and found that MC1 converted to MC2 in 13 patients 6 months after surgery; the remaining four patients all returned to normal. Ohtori *et al.* (55) conducted a 2-year follow-up of patients with LSS after posterolateral fusion and found that in 21 patients with MC1, nine were converted to MC2 and two returned back to normal; controversy, only two of 12 patients with MC2 returned to normal and the others displayed no changes. However, both studies only investigated patients with preexisting MCs, while ignoring the potential possibility for Lfus to cause nMCs in patients without MCs

before surgery and their impact on the adjacent levels of surgical site. We found that 30.23% of patients developed nMCs after Lfus, and the occurrence of nMCs was not limited by the surgical levels. nMCs occurred at the adjacent levels as well, which may provide some guidance for studying the aetiology of adjacent segmental degeneration (ASD) after Lfus (162).

1.1.5 The underlying mechanism of the development of MCs after lumbar surgeries

As mentioned earlier, inflammatory factors secondary to endplate injury and bone marrow stimulation are some of the most important factors leading to MCs. The endplate lesion is the result of the original disc herniation (163) but is also directly related to the surgical procedures (164). These four lumbar surgical procedures in this study need to destroy the posterior soft and bone tissues of the lumbar spine and remove the protruding IVD or hyperplastic tissue in order to relieve the spinal canal or nerve root compression. The destruction of the normal structure of the lumbar spine will cause stress redistribution (165), and the direct mechanical operation of the IVD will lead to a reduction in intradiscal pressure (166), which will affect the lumbar stability. Therefore, this theory may provide a reasonable explanation for the increased volume of the preexisting MCs and the occurrence of nMCs in patients undergoing Ldis, Lseq, and Ldec. In addition, Ldis, Lseq, and Lfus requires a removal of the herniated or whole disc tissue, and Lfus must scrape the vertebral endplate to increase the fusion rate of the bone graft. These direct mechanical operations on IVDs make the vertebral endplate and its adjacent bone marrow prone to MCs at biomechanical and biochemical levels. However, the implantation of the fusion device during Lfus allows the lumbar spine to both obtain immediate stability and reconstruct spinal sagittal balance (167). Therefore, it may have a smaller impact on the development of MCs compared to the other three procedures.

Regardless of the surgical procedures, postoperative nMCs were mainly MC2,

which may be related to the acceleration of fat degeneration in the subchondral bone marrow caused by lumbar surgery (135). Meanwhile, MC1 is considered to be closely related to biomechanical instability, while MC2 is relatively biomechanically stable (138). Ldis can accelerate the transition process of segmental instability to fixed deformity at the operative levels (135), which can also explain why MC2 predominated so far. The incidences of new MC1 in the first year after Ldis, Lseq and Ldec were high but lacked a difference in the follow-up intervals after Lfus, indicating the promoting effect of lumbar transient instability on the occurrence of MCs, especially for MC1. However, we did not count the number of cases of postoperative MCs-type conversion, as it was done in similar studies, mainly because of the difficulty in obtaining accurate results in a retrospective study, as it was impossible to control the consistent follow-up time of the enrolled population.

In addition, more than half of nMCs occurred at the operative levels, and at least 20% of nMCs were observed at the adjacent levels, revealing that the impact of surgical procedure on the lumbar spine is not limited to the surgical sites but can expand to their adjacent segments. Importantly, different mechanisms may work on the occurrence of nMCs that do occur at the surgical levels and their adjacent levels. We believe that nMCs at the operative level may be the combined effect of local biomechanical changes caused by posterior structural damage of lumbar spine and accelerated degeneration caused by a disc or vertebral endplate injury due to the operation (168), while the nMCs at the adjacent levels are more likely to be associated with changes in local biomechanics only. The acceleration of IDD caused by the increased stress of adjacent levels following fusion (169) may explain why nearly half of the nMCs occurred at the adjacent levels after Lfus.

1.2 The volume changes of MCs after lumbar surgical procedures

The size of MCs was positively correlated with CLBP intensity (6,149,170), and the size of MCs in patients who underwent Ldis showed different degrees of progress

(148,171). However, the measurement of MCs size is mainly based on two-dimensional qualitative or semiquantitative analysis. Karchevsky *et al.* (149) divided the vertebral body into 15 small units on the horizontal plane and assessed the size of reactive vertebral endplate marrow changes by summing up the involvement of MCs in the small units. According to the standard classification recommended by the Nordic Modic Consensus Group, Jensen *et al.* (56) divided MCs into four categories based on the relative extension depth of MCs in the vertical height of the vertebral body: endplate only, <25%, 25-50%, and >50%. Hanımoğlu *et al.* (172) separated the vertebral body to four parts (16 small units) on the anterior-posterior and cranial-caudal planes. Considering that only the sagittal or axial single plane cannot reflect the actual size of MCs, Kuisma *et al.* (41) combined the overall size of MCs on the sagittal (measurement of the maximum vertical depth of MCs on sagittal T2WI) and axial plane (dividing the vertebral body into four small units on the axial T1WI and measuring the maximum area of MCs) to evaluate the changes in MCs size from before to after follow-up.

To our best knowledge, this is the first study to use a three-dimensional quantitative methods to measure the volume of MCs before and after lumbar surgical procedures. Interestingly, the volume of MCs significantly increased in patients undergoing Ldis, Lseq and Ldec, while the volume of MCs did not change drastically after Lfus. These four common lumbar surgical procedures have the common feature of intraoperatively destroying the integrity of posterior bone and soft tissue of lumbar spine. The largest difference between Lfus and the other three lies in the extra stabilizing device applied to the operative site during the surgery. Therefore, this study indicates that the effects of different surgical procedures on the occurrence of MCs may be different, and it may also indirectly reveal that lumbar instability may contribute to the occurrence of MCs. Unfortunately, we cannot conclude that Lfus is the most ideal surgical procedure for the treatment of patients with CLBP and MCs, as our main focus was to evaluated the impact of these surgical procedures on MCs from the perspective of imaging and did not compare relevant clinical indicators.

2. The relationships between patients baselines and MCs / aMCs

2.1 Baselines

Although several studies have investigated the risk factors for MCs, the correlations between age, sex, BMI, and MCs are still controversial. Barth *et al.* (147) reported that age (p=0.889) and gender (p=0.293) were not correlated with MCs in the population undergoing surgical treatment, but two studies conducted later (48,173) showed that age and BMI clearly were risk factors for MCs. A study reported that there was higher incidence in male with MCs than that in female (149). Oppositely, Xiao *et al.* (174) reported that the incidence rate of MCs in females was higher than that in the males (Female/Male: 63/57), although these two groups had no statistical significance. Our study compared the age, sex, and BMI of the 164 patients with MCs and the 106 patients without MCs, but no significant difference was identified. The findings of our study may be related to the fact that the study included patients with a clear indication for a surgical treatment, in line with Barth *et al.* (147). However, compared with other studies that reported MCs-related factors, the large differences in the results of our study may be related not only to the different study subjects and small sample size but also to the lifestyle of the patients and whether the endplate and disc pathological changes were combined (48).

This is also the first retrospective study as far as we known to investigate the baseline characteristics of aMCs. The elderly male patients with high BMI were more prone to aMCs. A reasonable explanation may be that male patients are engaged in moderate to heavy physical labour, combined with obesity and other factors, and repeated mechanical loads are prone to cause cumulative injuries, resulting in secondary damage to the endplate. The incidence of arteriosclerosis in older patients is high (175), and the number of small arteries surrounding the vertebral body will also decrease while aging (176). These changes may lead to blood circulation disorders at the vertebral endplate and disc, accelerate their degeneration, and result in aggravation of endplate damage. Although the findings of the current study may

provide guidance for the assessment of aMCs-susceptible populations, these findings apply only to the included patient population, and the results in different surgical subgroups were not consistent, which may have been caused by the small size of each subgroup. Therefore, further studies with a large-sample, multi-centre, well-design are expected to examine the findings provided previously.

2.2 Inflammatory indicators (WBC and CRP)

Intervertebral intradiscal increasing IL-6 and TNF factors in CLBP patients with MCs (93) indicated that endplate marrow signal changes may be associated with local inflammation. Based on this expectation, the expression of proinflammatory mediators in discs may be a pathway closely related to the aetiology of MCs. IL-6, enriched in the IVD with MCs, is the main stimulator that upregulates CRP gene expression. Therefore, hsCRP can be used as a sensitive indicator of low-grade inflammation (177). Rannou *et al.* (71) divided 36 patients with CLBP into three groups (MC0, MC1, and MC2) according to the types of MCs, and compared the differences in hsCRP between the groups for the first time. They found that high concentrations of hsCRP were tested in the serum of MC1 patients, indicating a strong correlation between MC1 and local inflammation (71). However, a subsequent study with a small sample size (11 cases with MCs) (178) failed to detect the statistical differences in serum hsCRP between CLBP patients with MCs and that of without MCs.

Our study compared the differences between two inflammatory indicators, WBC and hsCRP, of patients with and without MCs and between patients with and without aMCs. Among all included patients, the hsCRP of MCs patients (9.17±21.79) was significantly different from that of patients without MCs (4.41±6.71). This conclusion was contrary to the findings of Briggs *et al.* (178). The inconsistency may have been mainly due to small sample sizes they included in the observation group (11 cases with MCs). Due to the limited sizes of MC1 and MC3 represented in this study, we

were unable to perform stratification analysis on these patients according to the types of MCs. However, the results of this study may suggest a positive correlation between MCs and hsCRP. In addition, this study indicated not only that MC1 is correlated with hsCRP, as Rannou *et al.* (71) found, but also that MC2 may have a strongly correlation with hsCRP because in this study MC2 accounted for more than 70% of the total cases. High hsCRP in MCs patients should be related to the increased IL-6 content in IVD tissues because the activation of hsCRP after being synthesized in hepatocytes often requires a signal from a cytokine, especially IL-6 (179).

Current views tend to agree that MC1 is the type of MCs that is most associated with CLBP (6,48) and inflammation (71), and it will gradually develop into stable MC2 or MC3 over time (53). Based on this, we expect that the reversal of MCs (aMCs) may also lead to the recurrence of clinical symptoms. The mechanism explaining why CLBP is closely related to MCs may be the results of inflammation and other chemical stimuli (113). However, the results of current studies do not support our hypothesis that WBC and hsCRP levels are higher in the serum of aMC patients than in those without aMCs. Combining these findings with our previous finding that hsCRP is correlated with MCs, these inflammation indicators may not have a significant correlation with the types of MCs but may only related to whether patients have MCs.

3. The relationships between IDD and MCs / aMCs

In the general population, IDD occurs more frequently in lumbar levels with MCs (51). Previous studies (48,133,174) have reported a positive correlation between MC1 or MC2 and IDD. A study (133) using the Pfirrmann classification to evaluate the IDD score of each lumbar level and test its correlation with MCs showed that the IDD scores of all lumbar levels with MCs were significantly higher than those without MCs. Although we could not analyse the IDD scores at the levels of L1/2 and L2/3 due to the lack of not having enough samples, our results at the L3/4, L4/5, and

L5/S1 segments support the findings provided above. Conversely, Teichtahl *et al.* (180) reported that there was no significant correlation between MCs and IDD at the level of L5/S1 as calculated with the DD score. They believed that this is because L5/S1 is the transition point of the spine, thus the association between MCs at this segment and LDD may be different from the one between MCs at other lumbar levels and LDD (180). The IDD was severe in their included population, which may also be the reason why they obtained opposite results from other studies.

There is no available information on the correlation between aMCs and IDD. To ensure the accuracy of the evaluation, we used three commonly used IDD classifications to evaluate the degree of IDD. However, only the extents of IDD of aMCs at the L3/4 segment were significantly higher than those at the level of L3/4 without aMCs under modified Pfirrmann grading system and Riesenburger scoring system. This may be because both MCs and IDD often occurred at lower lumbar levels (181), resulting in the IDD degree of the L4/5 and L5/S1 segments being more severe than that of the L3/4 segments. Under the same stimulating factors, the increase regarding the degree of degeneration in lower lumber levels may be less than that of the superior lumbar levels as there is mild degeneration.

In subgroup analysis, aMCs patients who only underwent Ldis had significantly different in IDD scores from those without aMCs, while aMCs and non-aMCs patients undergoing other surgical procedures did not show significant differences. The finding presented above may be explained by the following: Ldis usually requires the removal of more NP tissue than Lseq and Ldec, so disc space narrowing is more likely to occur after Ldis. The reduction in disc height is one of the most important indicators in the IDD classification (151–153). Therefore, IDD scores following Ldis will be higher than after other surgical procedures. In addition, due to the removal of the whole disc during the fusion operation, it was impossible to evaluate the IDD at the operative levels. Therefore, we only compared the IDD scores of the adjacent levels in aMCs patients with those of the same adjacent levels in the patients without aMCs. Theoretically, a fusion can easily lead to the occurrence of ASD after the

operation, resulting in higher IDD scores. However, this pathological process does not arise in the short term, so it could not be well observed in this study with mean follow-up of 283 days.

IDD generally does not occur in the short-term. For patients with long follow-up, the IDD at the final follow-up may be more severe than at earlier times. Limited by the retrospective nature of this study, we could not control the postoperative follow-up time of patients to a more consistent interval, which may be one of the reasons underlying the large difference in results. A careful interpretation of the results of this study suggests that aMCs may be associated with IDD, and the disc with aMCs may more easily degenerate after Ldis.

4. Strengths and Limitations

However, similar to other studies, this study has several limitations. Firstly, this is a retrospective study focusing on a specific population undergoing lumbar surgery due to LDD. It has the limitations of a retrospective study. For example, related indicators cannot be included in the study for analysis, because the tests for its indicators were not performed during the patients' visits or follow-up. Moreover, the results cannot be applied to all subjects, that is, the results lack universality. Secondly, although we have expanded the search time span as much as possible to obtain more case data, this study is still limited by its relatively small sample size due to the limited number of patients undergoing lumbar MRI during follow-up. Furthermore, nonidentical follow-up times may affect the reliability of the current conclusions. The three-dimensional quantitative measurement method is more accurate for calculating the volume of MCs. Although we tried our best to minimize errors, we still cannot completely avoid measurement errors. This is a common limitation of all studies involving parameter measurement. The current study has obtained significant results, but because of its limitations, some results still cannot be used to give a definitive recommendation. To that end, we wish to perform long-term follow-up in addition to

large-sample-sized and high-quality studies to further verify or enhance the evidence of this current study.

V. SUMMARY

Modic changes (MCs) are vertebral endplate-related signal abnormalities in the subchondral bone marrow, which are visible on MRI. Depending on the changes in the MRI they are classified in three different types (MC1, MC2, MC3). These changes were found to contribute to chronic low back pain. As lumbar surgery may alter biomechanical properties at a micro-structural level they may cause or aggravate preexisting MCs.

Almost all studies that were previously conducted have focused on investigating the effect of a specific type of lumbar surgery on the development of Modic changes (MCs) in the levels operated on, but have ignored that different type of operations may have different effects on the operated and their adjacent levels. It still remains to be determined whether the etiological factor of MCs are degenerative changes or inflammation, and whether the patients' baseline demographic characters are associated with the development of MCs. Therefore, this study aimed to compare the effects of four common types of lumbar surgery (fusion, decompression, sequestrectromy and discectomy) on MCs at the operated levels and their adjacent levels on MCs. Additionally, three classifications of intervertebral disc degeneration (IDD) and serum inflammation indexes were used in this study to further explore the relationship between IDD, inflammation, and MCs.

In order to address the above scientific questions, 270 patients, who underwent one of the above mentioned lumbar surgical procedures were retrospectively analysed. Patients' baseline characteristics were evaluated. The incidence of postoperative MCs and the volume changes of MCs meausured on MRI-images using an image analysis system, were used to systematically evaluate the impact of the different types of lumbar surgeries on the development of MCs. We evaluated lumbar IDD on MRI by using three different classification standards.

The data show that 1) all four commonly used types of lumbar surgeries can lead to the occurrence of postoperative MCs. Based on their incidence and the volume

changes of MCs in MRI before and after surgery, lumbar fusion seems to have a smaller impact on the development of MCs. 2) Modic changes type 2 are the primary type of MCs that occur after lumbar surgery. In terms of location, MCs can occur at the operative levels as well as at their adjacent levels, or at both locations. However, MCs were mainly observed at the operative levels. The three types of MCs may be found at any time after surgery. The first year after surgery appears to be the most active period for the occurrence of Modic changes Type 1 and Modic changes Type 2, whereas Modic changes Type 3 tend to represent a more stable state of bone marrow lesions. 3) Lumbar instability caused by surgery might be an important risk factor to contribute to the occurrence of MCs following lumbar surgical procedures. 4) The current study did not find any correlation between MCs and age, sex or BMI in the patients requiring surgical treatment. However, higher levels of C-reactive protein in MCs patients may reveal, that MCs might be associated with inflammation. 5) This study reinforces the conclusion that IDD and MCs are positively correlated, but there is still insufficient evidence that acute MCs have more severe imaging presentation of disc degeneration than non-acute MCs.

VI. ZUSAMMENFASSUNG

Modic-Veränderungen (MCs) sind pathologische Veränderungen im subchondralen Knochenmark nahe der Deck- und Bodenplatten von Wirbelkörpern, die im MRT nachweisbar sind. In Abhängigkeit vom Ausmaß der Veränderungen werden diese in drei verschiedene Typen eingeteilt (MC1, MC2, MC3). Diese Veränderungen sind oft mit chronischen Rückenschmerzen assoziiert. Da durch operative Eingriffe an der Lendenwirbelsäule die biomechanischen Eigenschaften auf der mikrostrukturellen Ebenen verändert werden können, kann es infolge dieser Eingriffe zur Entstehung oder zur Verschlimmerung von bereits bestehenden MCs kommen.

Die meisten Studien, die bisher zur Entstehung der sogenannten Modic-Veränderungen (MCs) in Wirbelkörpern durchgeführt wurden, haben sich auf die Entstehung dieser Veränderungen in den operierten Segmenten konzentriert. Es wurde aber außer Acht gelassen, dass verschiedene Operationsverfahren zu unterschiedlichen Veränderungen in der operierten Höhe aber auch den angrenzenden Segmenten führen können. Insbesondere ist weiter unklar, ob die Ursache für die Entstehung der MCs degenerativer Art ist, auf eine entzündliche Ursache zurückzuführen ist oder ob patientenspezifische Charakteristika eine Rolle spielen. Ziel der vorliegenden Arbeit war es daher, den Einfluss von vier verschiedenen lumbalen Eigriffen (lumbale Sequesterektomie, lumbale Dekompression, lumbale Diskektomie, lumbale Fusion) auf die Entstehung von MCs in den operierten und den angrenzenden Wirbelkörpersegmenten zu untersuchen, indem die Inzidenz der postoperativen MCs analysiert und das Volumen der MCs dreidimensional in einer quantitativen Analyse basierend auf MRT-Bildern berechnet wurde. Darüber hinaus wurden in dieser Studie drei Klassifikationen der Bandscheibendegeneration sowie Entzündungsparameter verwendet, um den Zusammenhang zwischen MCs, Bandscheibendegeneration und Entzündung näher zu untersuchen.

Um die oben genannten Fragen zu beantworten wurden 270 Patienten analysiert, die sich einer der vier obengenannten lumbalen Operation unterziehen mussten. Die Patientencharakteristika und die relevanten Parameter wurden retrospektiv aus den Patientenunterlagen extrahiert. Das Volumen der MCs prä- und postoperativ wurde mit einem medizinischen Bildanalyseprogramm anhand der MRT-Bildgebung quantifiziert. Die Inzidenz der postoperativen MCs und die Volumenänderung wurden kombiniert, um die Auswirkungen der vier Operationstechniken auf die Entwicklung von MCs systematisch zu bewerten.

Nach statistischer Analyse und sorgfältiger Interpretation der Daten lassen sich die Ergebnisse wie folgt zusammenfassen: 1) alle vier Lumbaloperationen können zur Entstehung von postoperativen MCs führen. Nach ihrer Inzidenz und den Volumenänderungen der MCs vor- und nach der Operation scheint die Lumbalfusion einen geringeren Einfluss auf die Entwicklung der MCs zu haben. 2) MC2 ist der Haupttyp von MCs, die nach einer lumbalen Operation auftreten. In Bezug auf das Wirbelsäulensegment können MCs auf der operierten Höhe, dem benachbarten Segment oder in beiden Höhen auftreten. MCs wurden jedoch hauptsächlich auf der operierten Höhe beobachtet. Die drei Arten von MCs können in jeder Phase nach der Operation nachgewiesen werden. Im ersten Jahr nach der Operation treten vor allem MC1 und MC2 auf, während MC3 tendenziell einen stabileren Zustand von Knochenmarkläsionen darstellt. 3) Die durch eine Operation verursachte Instabilität an der Lendenwirbelsäule könnte ein wichtiger Faktor sein, der zum Auftreten von MCs nach lumbalen chirurgischen Eingriffen beiträgt. 4) In der aktuellen Studie fand sich kein Zusammenhang zwischen MCs und Alter, Geschlecht oder BMI. Ein erhöhtes C-reaktives Protein bei den MCs-Patienten ist mit dem Nachweis von MCs assiziiert, was auf eine entzündliche Genese hindeutet. 5) Die Daten zeigen ebenfalls, dass MCs mit einer Bandscheibendegeneration einhergehen. Aber es gibt immer noch unzureichende Nachweise dafür, dass aMCs im Vergleich mit Non-aMCs eine signifikantere stärkere Bandscheibendegeneration aufweisen.

VII. REFERENCES

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VIII. ACKNOWLEDGEMENTS

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IX. CURRICULUM VITAE

Personal Details

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Educational Backgrounds

December 2017—November 2020	Doctoral student in the research group of Prof. Dr. med. Eberhard Uhl, Department of Neurosurgery, Justus-Liebig-University Giessen, Germany.
September 2014—July 2017	Master of Medicine, Orthopaedics, Ruikang Clinical Faculty, Guangxi University of Chinese Medicine, Nanning, China.
September 2009—July 2014	Bachelor of Medicine, Clinical Discipline of Chinese and Western Integrative Medicine, Faculty of Chinese Medicine Science, Guangxi University of Chinese Medicine, Nanning,

Clinical Training

July 2015—June 2017	Resident, Department of Orthopaedics, People's Hospital of Guangxi Zhuang Autonomous Region.
October 2014—June 2015	Subspecialty Training in Surgery, Ruikang Hospital Affiliated to Guangxi University of

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May 2013—April 2014	Intern, People's Hospital of Shucheng County.

Research Activities

2016-2017	Biomechanical study: impact of adjacent pressure on adjacent intervertebral disc after lumbar fusion and internal fixation of goats.
2014-2017	Master thesis: perioperative blood loss for patients who underwent a modified lumbar fusion.
2015-2016	Clinical study: microendoscopic discectomy for huge lumbar disc herniation

Award

June 2018	Chinese Government Scholarship

Review Activities

Spine (Phila Pa 1976)

Journal of International Medical Research

Chinese Journal of Tissue Engineering Research

X. LIST OF PUBLICATIONS

1. Publications originally from this thesis

- **Xiaoping Mu**, Seongwoong Kim, Eberhard Uhl, Karsten Schöller. New insights into the effects of four lumbar surgical procedures on the development of Modic changes. (Manuscript in preparation)
- **Xiaoping Mu**, Seong Woong Kim, Michael Bender, Eberhard Uhl, Karsten Schöller. Influence of discectomy on lumbar Modic endplate changes. 70th Annual Meeting of the German Society of Neurosurgery (DGNC). Würzburg, May 2019. (ePoster presentation)
- Seong Woong Kim, **Xiaoping Mu**, Michael Bender, Karsten Schöller. Are Modic changes associated with lumbar disc degeneration? A systematic review of MRI studies [C]. 69th Annual Meeting of the German Society of Neurosurgery (DGNC). Münster, June 2018. (ePoster presentation)

2. Other publications

- **Xiaoping Mu**, Jianxun Wei , Chenglong Wang, Yufu Ou, Dong Yin, Bin Liang, et al. Intravenous administration of tranexamic acid significantly reduces visible and hidden blood loss compared with its topical administration for Double-segment posterior lumbar interbody fusion: a single-center, placebo-controlled, randomized trial. World Neurosurg. 2019;122:e821-7.
- **Xiaoping Mu**, Zhuhai Li, Dong Yin, Bin Liang, Yufu Ou, Jianxun Wei. Biomechanical effects of fixation of different segments of goat lumbar spine on adjacent segmental motion and intradiscal pressure change. Med Sci Monit. 2019;25:4885-91.
- Chengxin Xie, **Xiaoping Mu**, Zhuangming Hu, Wei Wang, Wenwen Huang, Ge Huang, et al. Impact of pharmaceutical care in the orthopaedic department. J Clin Pharm Ther. 2020; 45(3):401-7.

XI. EHRENWÖRTLICHE ERKLÄRUNG

Ich erkläre: Ich habe die vorgelegte Dissertation selbständig und ohne unerlaubte fremde Hilfe und nur mit den Hilfen angefertigt, die ich in der Dissertation angegeben habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nicht veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Giessen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten.

I declare that I have completed this dissertation single-handedly without the unauthorized help of a second party and only with the assistance acknowledged therein. I have appropriately acknowledged and referenced all text passages that are derived literally from or are based on the content of published or unpublished work of others, and all information that relates to verbal communications. I have abided by the principles of good scientific conduct laid down in the charter of the Justus Liebig University of Giessen in carrying out the investigations described in the dissertation.

Giessen, den _____

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