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RESEARCH ARTICLE

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# Epidemiology of Modic changes in dogs: Prevalence, possible risk factors, and association with spinal phenotypes

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## Abstract

**Background:** Chronic low back pain, a leading contributor to disease burden worldwide, is often caused by intervertebral disc (IVD) degeneration. Modic changes (MCs) are MRI signal intensity changes due to lesions in vertebral bone marrow adjacent to degenerated IVDs. Only a few studies described the histopathological changes associated with MC to date. MC type 1 is suggested to be associated with bone marrow infiltration of fibrovascular tissue, type 2 with fatty infiltration, and type 3 with bone sclerosis in humans.

**Methods:** This study investigated whether the dog can be a valuable animal model to research MCs, by examining the prevalence, imaging, and histological characteristics of lumbar MCs in dogs (340 dogs, 2496 spinal segments).

**Results:** Logistic regression analysis indicated that the presence of lumbosacral MCs was associated with age and disc herniation (annulus fibrosis protrusion and/or nucleus pulposus extrusion). According to MRI analysis, MCs were mostly detected at the lumbosacral junction in dogs. Most signal intensity changes represented MC type 3, while previous spinal surgery seemed to predispose for the development of MC type 1 and 2. Histological analysis (16 dogs, 39 spinal segments) indicated that IVDs with MCs showed more histopathological abnormalities in the endplate and vertebral bone marrow than IVDs without MCs. Mostly chondroid proliferation in the bone marrow was encountered, while the histologic anomalies described in humans associated with MCs, such as fibrovascular or fatty infiltration, were scarcely detected.

**Conclusions:** Dogs spontaneously develop MCs, but may exhibit other pathological processes or more chronic bone marrow pathologies than humans with MCs. Therefore, more research is needed to determine the translatability of the MCs encountered in dog low-back-pain patients.

KEYWORDS
dog, histology, intervertebral disc, lumbosacral, Modic changes, MRI

## 1 | INTRODUCTION

Chronic low back pain (LBP) is the leading cause of years lived with disability in humans worldwide.[1,2] Although a specific cause of LBP can often not be accurately identified, intervertebral disc (IVD) degeneration (Figure 1) plays an important role in symptomatic individuals.[3,4] In a degenerated IVD, loading is converted to the annulus fibrosis (AF) and end plate (EPs), which can result in herniation (in this manuscript considered as protrusion of the AF and/or extrusion of the nucleus pulposus [NP]), tearing of the AF, fracturing/thickening of the EP, and subchondral vertebral bone marrow pathologies.[5,6]

Modic changes (MCs) are pathological magnetic resonance imaging (MRI) signal intensity changes in the vertebral bone marrow, typically adjacent to degenerated IVDs.[7,8] To date, the etiology of MCs remains elusive. Suggested risk factors are mechanical stress, IVD degeneration (IVDD), spondylodiscitis, an autoimmune response of the bone marrow triggered by the inflamed and herniated NP, genetics, altered metabolism and environmental factors/lifestyle (e.g., obesity and smoking).[9–15] Interestingly, many of these are also known risk factors for IVDD development.[16] MCs are some of the most clinically relevant spinal phenotypes in humans, often associated with LBP (primarily type 1 MCs).[4,17–27]

The general consensus in humans is that in type 1 MCs (hypointense on T1-weighted [T1W], hyperintense on T2-weighted [T2W] images[7–9]), fibrous and vascularized tissue (granulation tissue) replaces normal bone marrow, and edema and fissured EPs can be encountered (Figure 2). Type 2 MCs (hyperintense on T1W and T2W) are believed to represent the conversion of normal into fatty bone marrow (together with increased reactive bone and granulation/fibrotic tissue infiltration). Activation of the complement system, an indication for inflammation, has been demonstrated in human MC2 specimens, which has been suggested to be linked to resorption of the disrupted EP.[28] Type 3 MCs (hypointense on T1W and T2W) are believed to represent subchondral bone sclerosis. MC type 1 and 2 are interconvertible over time and can progress into MC type 3,[29–31] while about 20% of all MCs are of mixed type.[9] It must be noted, however, that abovementioned consensus was based on only a few studies that examined the histological features associated with the MC-related signal intensity changes,[7,9,32–35] as tissue specimens from human patients are scarce and small (surgical samples). Therefore, animal models are of high importance to study aspects of MCs that cannot be easily examined in humans, such as histological examination of spinal segments in which MCs were detected. In this manuscript, we examine whether the dog can be a useful animal model to study MCs.

Because of the similarities between humans and dogs in the etiology, pathology, and clinical representation of spontaneous IVDD-related LBP, dogs that are kept as companion animals are considered a good animal model to study human IVDD.[36] As such, studies on

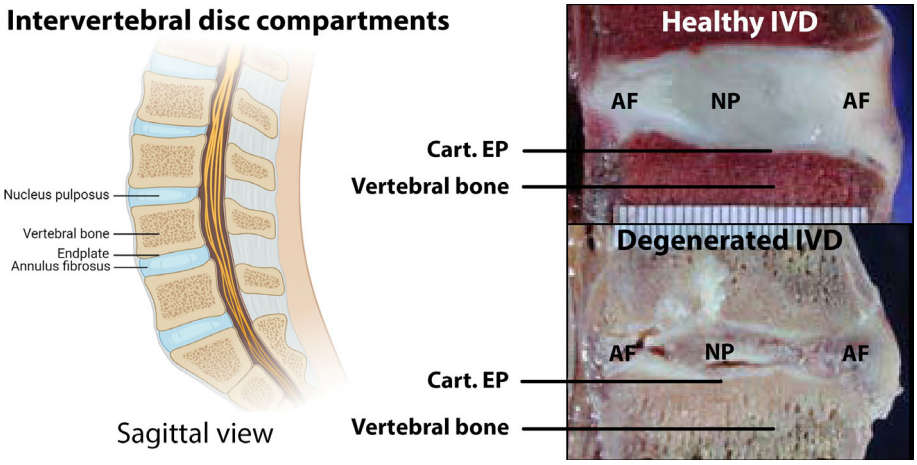


**FIGURE 1** Human intervertebral disc (IVD) compartments in health and disease. Left: Schematic representation of the different compartments in a healthy intervertebral disc. Figure created with Biorender (www.biorender.com). Right: macroscopic picture of a healthy (top) and degenerated (bottom) intervertebral disc.[5] AF, annulus fibrosus; Cart. EP, cartilaginous endplate; NP, nucleus pulposus.

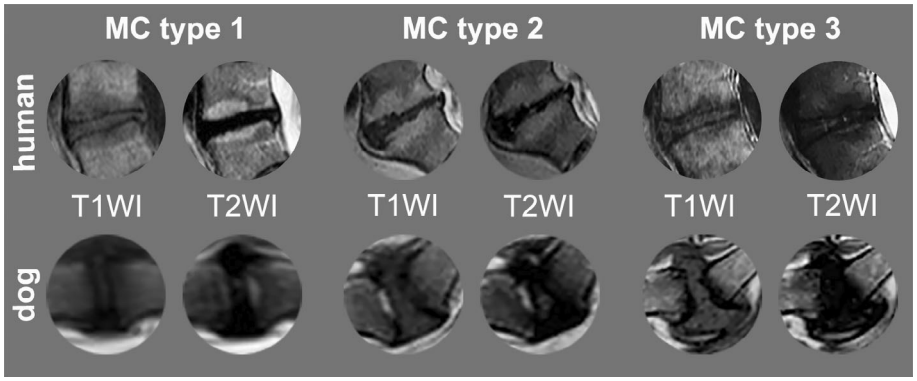


**FIGURE 2** Representative example of Modic changes (MCs) type 1, 2, and 3 detected in dogs (1.5 T MRI) in analogy to those detected in humans (3 T MRI) categorized according to their signal intensity in T1-weighted and T2-weighted MR imaging sequences (T1WI and T2WI, respectively).

MCs in dogs could also provide additional information for human patients. In the dog, breeds can be divided into chondrodystrophic (CD) and non-chondrodystrophic (NCD), based on their physical appearance. CD dog breeds have short bow-shaped legs because of disrupted endochondral ossification, which has strongly been linked with IVDD.[37] In CD dogs, IVD disease typically develops in the cervical or thoracolumbar spinal region at relatively young age and is considered to be polygenetic.[38,39] Large NCD dog breeds can also develop IVD disease in the caudal cervical or lumbosacral spine at a later age, mostly due to repetitive microtrauma or "wear and tear."[36,38]

Despite their clinical significance in humans, little is known about the prevalence, appearance, and risk factors for MCs in dogs.[40–42] Similarly as in humans, in low-virulent or early stages of discospondylitis (bacterial discitis and osteomyelitis[43,44]), MR signal intensity changes in the vertebrae can be encountered that resemble type 1 MCs.[45,46] Damage to the EPs is suggested to facilitate the development of MCs, as it promotes the interaction between IVD tissue and the vertebrae, thereby triggering an autoimmune response.[15,28] Interestingly, a significant association between vertebral EP changes detected on MRI and IVD disease of the adjacent disc was established in dogs,[47] indicating that dogs with IVD disease might also be prone to develop MCs. This is under scribed by that fact that companion dogs are exposed to similar risk factors as humans, for example, in-house smoking and obesity. There are also preliminary indications that the pathophysiology of MCs is different in dogs with respect to the autoimmune etiology.[48]

For the abovementioned reasons, the aim of the current retrospective study was multifaceted. First, we examined the prevalence and imaging characteristics of lumbar MCs in dogs with LBP and/or neurological deficits. Second, we investigated the level of association between the presence of MCs and demographic and imaging phenotypes (e.g., age, body weight, breed, the presence of IVDD, disc herniation, and previous spinal surgery). Finally, histological analysis was performed to determine the histological characteristics of spinal segments with and without MCs.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and animals

Patient owners approved the use of the anonymized imaging data for research purposes. MR images of client-owned dogs with LBP and/or neurological deficits that were referred for MRI of the lumbar spine to the Division of Diagnostic Imaging of the Department of Clinical Sciences, Utrecht University, the Netherlands, between December 2013 and November 2016, were retrospectively analyzed by a board-certified veterinary radiologist (MB). Inclusion criteria were the availability of sagittal T1- and T2-weighted turbo spin-echo sequences of the lumbar spine, which included the lumbosacral (LS) junction. Exclusion criteria were imaging findings of (para)spinal neoplasia.

In total, 340 dogs met the MRI inclusion criteria for this study, resulting in 2496 spinal segments for evaluation. Medical records were reviewed to record sex, age (years), body weight (kg), and breed. Also, the clinical history and location of previous spinal surgery was recorded to assess whether surgery is a risk factor for the development of MCs, as has been suggested in humans.[12,49] Fifteen of the 340 dogs underwent previous spinal surgery to the lumbar spine. Two of these dogs underwent surgical procedures at two locations, resulting in 17 spinal segments with surgical intervention.

The study included 154 female ($n = 111$ castrated) and 186 male ($n = 87$ castrated) dogs. The median age of the dogs was 6 years (range: 4 months–15.5 years). Arranging the dogs in age classes led to 9 young (<1 year old), 48 adolescent (1–2 years old), 195 adult (3–7 years old), and 88 senior (>8 years) dogs. Their median body weight was 25.1 kg (range: 2.5–88.0 kg). For statistical analysis, dogs were grouped in four weight classes: 60 small (<10 kg), 105 medium (10–25 kg), 156 large (25–50 kg), and 19 giant (≥50 kg) dogs. Breeds included 290 purebred dogs and 50 mixed breed dogs. The most represented breeds (more than 5 dogs/breed) were: Labrador retriever ($n = 24$), French bulldog ($n = 21$), German Shepherd dog ($n = 20$), Dachshund ($n = 17$), Golden retriever ($n = 12$), Border collie ($n = 9$), Bernese Mountain dog ($n = 7$), Boxer ($n = 7$), Jack Russell terrier ($n = 7$), Stabyhoun ($n = 6$), and Staffordshire bull terrier ($n = 6$). The following breeds in the population were considered CD: Basset Hound, Beagle, Cavalier King Charles Spaniel, (miniature) Dachshund, French/English bulldog, Pekingese, Shi Tzu, Tibetan spaniel, Toy Poodle, Pug, and Welsh Corgi.[38,50] Sixty-five dogs (19%) were CD breeds and 246 (72%) dogs were NCD breeds, while the breed of 29 dogs was not recorded or unknown (9%).

A second dataset was constructed of surplus research dogs that were euthanized in experimental studies (no reported history of back pain and no IVDD induced; $n = 10$) and dogs from other terminal experimental studies (in which IVDD was induced; $n = 9$) (project numbers AVD108002015285 and AVD108002015282).[40,51,52] These dogs were used for MRI and histological analysis. For the latter, animal procedures were approved and conducted in accordance with the Animal Experiments Committee guidelines, as required by Dutch regulation. In these studies, the effect of different intradiscal (cell- and nonsteroidal anti-inflammatory drug-based) treatments was determined using an in vivo model of IVDD employing Beagles, a CD dog breed. Briefly, IVDD was further induced under fluoroscopic guidance by a board-certified veterinary surgeon (BM) through partial NP removal and 4 to 6 weeks later 40–50 µL volume of the treatment (Mesenchymal stromal cell injection [50 µL; $1 \times 10^6$ MSCs], Notochordal cell-derived matrix injection [50 µL; 0.5 mg NCM]). TAA: Triamcinolone injection (40 µL; 8.4 µg TAA) was intradiscally injected in mildly (spontaneously) and moderately (induced) degenerated dog IVDs. Three and six months after intradiscal treatment, MRI analysis was performed. Spinal segments with MCs ($n = 16$) were selected for histological analysis and compared to a randomly selected set of segments without MCs ($n = 23$). For additional information regarding the intradiscal treatments, see previous manuscripts[40,51,52] and Supplementary File 1.

## 2.2 | MRI protocol and analysis

The MRI images in patients and experimental dogs were obtained using a high field 1.5 Tesla MRI (Philips Ingenia, Eindhoven, the Netherlands) and analyzed with Picture Archiving and Communication System software.

MRI was performed under general anesthesia. The dogs were positioned in dorsal recumbency with the pelvic limbs extending caudally. The clinical MRI protocol included sagittal T1-weighted (T1W) Turbo Spin Echo (time of repetition [TR] = 400 ms, time of echo [TE] = 8 ms), and T2-weighted (T2W) Turbo Spin Echo (TR = 2500 ms, TE = 110 ms) sequences. Slice thickness and field of view were optimized for patient size. Other sequences were available as part of the standard set of clinical sequences, but only used to diagnose discospondylitis. MCs were evaluated according to the criteria that apply in humans to enable comparison, analogous MRI of MCs in humans and dogs are provided in Figure 2. Furthermore, the following components were evaluated in the MRI analysis (Table 1).

**TABLE 1** MRI analysis criteria.

| MRI analysis | |
|---|---|
| Modic change type[7] | • MC type 1: hypointense on T1W images and hyperintense on T2W images<br>• MC type 2: hyperintense on both T1W and T2W images<br>• MC type 3: hypointense on both T1W and T2W images |
| Location | • Functional spinal unit (Th13-L1, L1-L2, L2-L3, L3-L4, L4-L5, L5-L6, L6-L7, and/or L7-S1)<br>• Cranial and/or caudal EP<br>• Dorsal (=posterior in human literature[9]), central and/or ventral (=anterior in human literature) part of the EP |
| Severity[a35] | • Mild: the largest cranial or caudal extent of the abnormality involves equal to or less than 25% of the vertebral body height;<br>• Moderate: the largest cranial or caudal extent of the abnormality involves between 25% and 50% of the vertebral body height;<br>• Severe: the largest cranial or caudal extent is equal to or more than 50% of the vertebral body height. |
| Disc degeneration[53,54] | • Per spinal segment, IVD degeneration was graded according to the modified Pfirrmann classification system for dogs (I–V) |
| Disc herniation[55] | • None<br>• Disc protrusion with <25% narrowing of the vertebral canal<br>• Disc protrusion with 25%–50% narrowing of the vertebral canal<br>• Disc protrusion with >50% narrowing of the vertebral canal or disc extrusion |
| Discospondylitis[41,44] | • Paravertebral Short Tau Inversion Recovery (STIR) hyperintensity or contrast enhancement<br>• Contrast enhancement of EPs or intervertebral disc<br>• EP erosion |

Abbreviations: EP, endplate; MC, Modic change; T1W, T1-weighted; T2W, T2-weighted.
[a]Vertebral body height was measured on a midsagittal image.

## 2.3 | Histological analysis

Research dogs that were used for histopathological analysis ($n = 19$) underwent MRI and *postmortem* spinal examination on the same day. Spinal segments with MCs ($n = 16$) were included in the current study and compared to a set of randomly selected segments without MCs ($n = 23$). These 39 segments originated from 19 research dogs (Supplementary File 1). The spinal segments (½ vertebral body—EP—NP/AF—EP—½ vertebral body) were harvested as described previously.[5] Briefly, the segments were transected in the sagittal plane, fixed in 4% buffered formaldehyde solution (Klinipath B.V., the Netherlands) for 14 days, decalcified in PBS with 0.5 M EDTA for 3 months and embedded in paraffin. Five µm sections were mounted on positively charged glass slides (KP-3056, B.V., the Netherlands) and stained with Hematoxylin and Eosin (H/E) and Picrosirius Red/Alcian Blue (PSR/AB).[56,57] The IVD, EP, and vertebral bone marrow were blindly evaluated (modified Boos score[6]) by a board-certified veterinary pathologist (GG) using an Olympus BX41 microscope (Olympus Nederland B.V., the Netherlands). The modified Boos score (0–29) is used to determine the degree of histological IVD degeneration and includes the following subcriteria: morphology of the AF, chondrocyte metaplasia in the AF, tear and cleft formation in NP and AF, chondrocyte proliferation in the NP, presence of notochordal cells in the NP, PSR/AB matrix staining of the NP, EP morphology, new bone formation, and subchondral bone sclerosis.[6] EP morphology was scored as: score 0 = regular thickness, homogenous structure, score 1 = slightly irregular thickness, score 2 = moderately irregular thickness, score 3 = severely irregular thickness with interruption of the EP. Bone sclerosis was scored as score 0 = no sclerosis, score 1 = mild sclerosis (2–4× thickness of the dorsal vertebral cortex), score 2 = moderate sclerosis (>4× the thickness of the dorsal vertebral cortex), score 3 = severe subchondral bone irregularities. The adjacent vertebral bone was furthermore assessed for infiltration of inflammatory cells, neovascularization, fatty infiltration, and the presence of chondroid cells, fibrous tissue, or Schmorl's nodes (NP tissue bulging into the adjacent vertebrae through an EP defect[58]).

## 2.4 | Statistical analysis

Statistical analysis was conducted with IBM SPSS Statistics (version 23.0, IBM Corp., USA). Descriptive statistics reported the prevalence,

severity, and location of MC types. Because the prevalence of MCs at the LS junction (61%) was far higher than at all other spinal segments, it was decided to perform the univariate analysis and multiple logistic regression models only with the data from the LS junction. This means that the study on associations of presence of MC with several factors/determinants was based on independent data ($n = 340$ LS junctions).

The strength of association of presence of MC with the categorical variables MCs, sex, age, weight, breed (CD/NCD), disc degeneration (Pfirrmann grade I-V), disc herniation (no, <25%, 25%–50% and >50% disc protrusion, and disc extrusion) and discospondylitis (yes/no) was assessed in two stages. First, a contingency table was constructed and univariable logistic regression of MC with each of determinants was applied to assess odds ratio (OR) with 95% confidence interval (CI). The chi-square test or Fisher's exact test (when expected frequencies were below 5) was applied to test independence of both factors. Second, a multivariable binary logistic regression for presence of MC was applied with the explanatory grouping variables sex, age, weight, breed (CD/NCD), disc degeneration, and disc herniation using stepwise backward and forward procedures with standard SPSS criteria, to assess the adjusted OR of the best fitting model. Both procedures assessed the same final model. No interactions were added to the model. During the backward stepwise approach, the change of the coefficients (beta) of each factor was studied for possible confounding effects (>20%). No confounders were, however, identified. The variable "other imaging characteristics of discospondylitis" was excluded from the multivariable analysis, because in a clinical setting discospondylitis is generally considered a separate disease entity.[41,46] For the binary logistic regression analysis, groups with low frequency were combined with the adjacent group, for example, dogs of <1 year old (added to 1–2 years old), Pfirrmann grade 1 (added to Pfirrmann grade 2) and Pfirrmann grade 5 (added to Pfirrmann grade 4). A low number of cases was also observed in the group dogs >50 kg without MCs ($n = 4$), but it was not combined with another group to avoid a very unequal range of weights within weight classes. Possible associations between each of the explanatory factors were studied and tested by chi-square test or Fisher's exact test (Supplementary File 2).

To investigate whether different types of MCs have different risk factors, univariable analyses were also performed between each of the different MC types and the aforementioned variables at the LS junction. To enable this, IVD segments presenting with multiple types were assigned to the dominating type: Type 1 MCs had the highest priority, followed by MC type 2 and last MC type 3. This prioritization was based on the clinical relevance and stability of MCs reported in the human literature.[7,17,59–61]

Finally, we used the dataset of all 2496 spinal segments to investigate whether previous spinal surgery was associated to MCs. Univariable logistic regression was performed with "previous surgery" as dependent variable and the determinants MC type 1, 2, and 3.

In all stages, ORs with 95% CI were presented as measures of association. To calculate the OR for variables with an empty cell (no subjects), 0.5 was added to each cell. All results were considered to be statistically significant when $p < 0.05$. Where applicable data is provided as mean ± SD.

# 3 | RESULTS

## 3.1 | CD and NCD dogs differ in age and weight

The univariable analysis model indicated that age and weight distribution were significantly different between NCD and CD dogs (Supplementary File 2). NCD dogs (mean 5.8 years ± 3.1) were older ($p < 0.01$) than the CD dogs (mean 5.1 years ± 2.1). Body weight of the large breed NCD dogs (mean 29.6 kg ± 14.8) was higher ($p < 0.001$) than that of the smaller breed CD dogs (mean 12.6 kg ± 7.2).

## 3.2 | MCs are mainly detected at the lumbosacral junction

MCs were observed in 66% (CI: 60.9–71.2) of the dogs (Figure 3B), of which the majority had MCs in only one spinal segment (56%, CI: 51–62), and a much lower prevalence had MCs in two segments (7%, CI: 5–10) or three or more segments (3%, CI: 1–5). In total, 89.3% (CI: 88.0–90.5) of the segments showed no MCs, 0.3% showed only type 1 MCs (CI: 0.1–0.6), 0.6% only type 2 MCs (CI: 0.4–1.0), 7.7% only type 3 MCs (CI: 6.7–8.9), and 2.1% showed mixed-type MCs (CI: 1.6–2.7) (Figure 3C). This means that 3% of all detected MCs was type 1, 6% was type 2, 72% was type 3, and 19% of the detected MCs was of a mixed type. Most MCs were detected at the LS junction (209 of 340 LS spinal segments; 61%, CI: 56–67; Figure 3D; $p < 0.001$ compared to the other vertebral segments). Within the affected LS junction, most MCs (71%, CI: 64–77) were located in the cranial EP of the sacrum (Figure 3E). Almost half (49%) of the MCs detected at the LS junction were present along the whole height of the EP, while almost 1/3 (31%) were located at the ventral (anterior) aspect of the EP (Figure 3F). The extension in a cranial or caudal direction was <25% of the vertebral body height in 83%, 25%–50% of the vertebral body height in 14% and >50% of the vertebral body height in 3% of the MCs in the LS junction.

Finally, 19 dogs showed other imaging signs consistent with discospondylitis at a single segment, all at the segment affected with MCs. Although discospondylitis is a different disease process, changes were classified as MCs for descriptive and univariate statistical analysis. In 18 of these 19 dogs, discospondylitis was diagnosed (at MRI level) at the LS junction.

## 3.3 | Predictors of LS MCs: age, weight, IVD degeneration, and herniation

The univariable analysis revealed that MCs (irrespective of type) at the LS junction (the segment with the highest prevalence of MCs) was more prevalent in dogs that were older, heavier, with more degenerated IVDs and/or a higher degree of disc herniation (Table 2). Presence of MCs at the LS junction was not associated with sex and breed type (CD/NCD).

The different MC types were also individually compared to the other variables. Type 1 MCs significantly correlated to disc degeneration and herniation (both $p < 0.001$). When set as dependent variable,

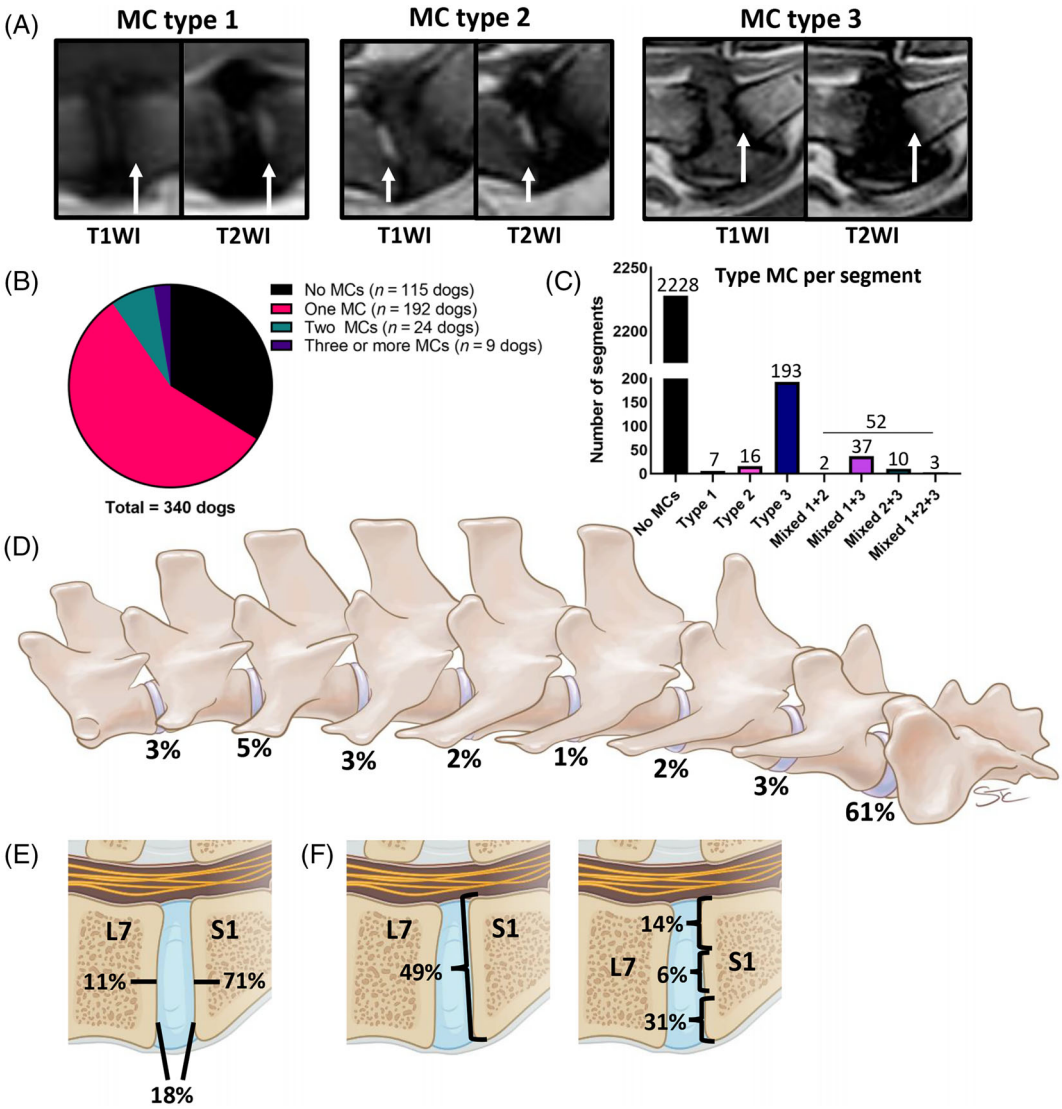


**FIGURE 3** Modic changes (MCs) type 1, 2, and 3, and mixed types detected in dogs. (A) T1 weighted (T1W) and T2W MRI sequences of the different MC types. (B) Number of dogs with no, one, or more MCs in their spinal segments. (C) The number of spinal segments in which the different (single or mixed) MC types were detected. © Copyright 2022 by The Curators of the University of Missouri, a public corporation. (D) The percentage of segments that showed MCs per intervertebral disc level. Most MCs were detected at the lumbosacral (L7-S1) junction. (E) and (F) The location of the detected MCs at the L7-S1 junction. Most MCs were detected at the cranial sacral endplate, mostly along the whole length of the endplate.

"other imaging characteristics of discospondylitis" at the LS junction was associated with type 1 MCs ($p < 0.001$). Type 2 MCs significantly correlated to disc degeneration and herniation (both $p < 0.01$). Because type 3 changes were most prevalent and dominated the overall results, they are similar to the overall results shown in Table 2 and are therefore not shown separately.

### 3.4 | Previous spinal surgery predisposes for the development of MC type 1 and 2 at the operated level

A univariate analysis was performed to test for associations between segments that underwent previous spinal surgery (17/2496 segments, found in 15/340 dogs) and the presence of MCs, since vertebral signal intensity changes are known to occur in both dogs and humans after surgery.[12,49,62,63] Hemilaminectomy and partial discectomy was performed at eight segments, dorsal laminectomy with partial discectomy at eight segments and dorsal laminectomy without discectomy at one segment. MCs were identified in 11 out of 17 (65%) of the operated segments. Prioritizing the MCs resulted in six segments with MCs type 1, three with MC type 2, and two segments with MC type 3. MCs developed between the pre and postoperative scans in 5 of the 12 segments of the client owned dogs that were scanned twice due to clinical signs related to spine pathology. Unfortunately, no preoperative MRI images were available for the remaining five of the 17 segments. Nevertheless, significantly more IVD segments that

**TABLE 2** Univariable logistic regression analysis for risk factor associations of lumbosacral Modic changes (MCs).

| Variables | Categories | MCs present (%) [$n = 209$ (61%)] | No MCs (%) [$n = 131$ (39%)] | Odds ratio | 95% CI | $p$-Value* |
|---|---|---|---|---|---|---|
| Sex | Male | 118 (63.4) | 68 (36.6) | 1.0 | Ref[a] | 0.435 |
| | Female | 91 (59.1) | 63 (40.9) | 0.8 | 0.5–1.3 | |
| Age | <1 year old | 2 (22.2) | 7 (77.8) | 1.0 | Ref[a] | 0.001 |
| | 1–2 years old | 21 (43.8) | 27 (56.3) | 2.7 | 0.5–14.5 | |
| | 3–7 years old | 122 (62.6) | 73 (37.4) | 5.8 | 1.2–28.9 | |
| | >7 years old | 64 (72.7) | 24 (27.3) | 9.3 | 1.8–48.1 | |
| Weight | <10 kg | 24 (40.0) | 36 (60.0) | 1.0 | Ref[a] | <0.001 |
| | 10–25 kg | 62 (59.0) | 43 (41.0) | 2.2 | 1.1–4.1 | |
| | 25–50 kg | 108 (62.2) | 48 (30.8) | 3.4 | 1.8–6.3 | |
| | ≥50 kg | 15 (78.9) | 4 (21.1) | 5.6 | 1.7–19.0 | |
| Chondrodystrophy | CD | 36 (55.4) | 29 (44.6) | 1.0 | Ref[a] | 0.316 |
| | NCD | 155 (63.0) | 91 (37.0) | 1.4 | 0.8–2.4 | |
| | Breed type unknown | 18 (62.1) | 11 (37.9) | 1.3 | 0.5–3.2 | |
| IVD degeneration grade (Pfirrmann) | Grade 1 | 9 (50.0) | 9 (50.0) | 1.0 | Ref[a] | <0.001 |
| | Grade 2 | 61 (50.0) | 61 (50.0) | 1.0 | 0.4–2.7 | |
| | Grade 3 | 63 (58.9) | 44 (41.1) | 1.4 | 0.5–3.9 | |
| | Grade 4 | 68 (80.0) | 17 (20.0) | 4.0 | 1.4–11.6 | |
| | Grade 5 | 8 (100.0) | 0 (0.0) | 17.0[b] | 0.9–338.3 | |
| Disc herniation | No | 44 (38.3) | 71 (61.7) | 1.0 | Ref[a] | <0.001 |
| | Protrusion, <25% vertebral canal stenosis | 55 (62.5) | 33 (37.5) | 2.7 | 1.5–4.8 | |
| | Protrusion, 25%–50% vertebral canal stenosis | 39 (66.1) | 20 (33.9) | 3.1 | 1.6–6.1 | |
| | Protrusion, >50% vertebral canal stenosis | 48 (90.6) | 5 (9.4) | 15.4 | 5.7–41.9 | |
| | Disc extrusion | 23 (92.0) | 2 (8.0) | 18.6 | 4.2–82.6 | |
| Other imaging characteristics of discospondylitis | No | 191 (59.3) | 131 (40.7) | 1.0 | Ref[a] | <0.001 |
| | Yes | 18 (100.0) | 0 (0.0) | 25.4[b] | 1.5–425.3 | |

Abbreviation: CI, confidence interval.

[a]"Ref" Reference category.

[b]To calculate the odds ratio for variables with an empty cell, 0.5 was added to each cell.

*Fisher's exact test.

underwent previous spinal surgery showed MCs (65%) than non-operated segments (10.3%; $p < 0.001$). When "previous surgery" was set as dependent variable, a significant association was found with both MCs type 1 and 2 (MC type 1, OR = 49.8, $p < 0.001$; MC type 2, OR = 45.7, $p < 0.001$). Two dogs had suspicion of a post-operative discospondylitis based on imaging findings.

## 3.5 | Age and IVD herniation are associated with the development of MCs at the lumbosacral junction

A multiple logistic regression model demonstrated that age and disc herniation were significantly associated with the presence of MCs at the LS junction (Table 3). Dogs of 3–7 years of age were 2.1 times more likely to have MCs than dogs that were ≤2 years old ($p < 0.05$). Dogs older than 7 years old were 3.0 times more likely to have MCs than dogs ≤2 years old ($p < 0.01$). The likelihood of developing LS MCs increased when disc protrusion was more severe or when disc extrusion was present. Especially disc protrusion that caused more than 50% vertebral canal stenosis or disc extrusion strongly increased the odds of the presence of LS ($p < 0.001$).

## 3.6 | Other associated variables

In addition to the comparison with the presence of MCs, the association between each of explanatory factors was studied. All variables showed pairwise significant association except for "disc herniation" and "sex" or "breed (CD/NCD)," and between "age" and "sex" (Supplementary File 2). Nevertheless, this did not distort

**TABLE 3** Multiple logistic regression model with variables associated with lumbosacral Modic changes.

| Variables | Categories | Odds ratio | 95% CI |
|---|---|---|---|
| Age | 0–2 year old | 1.0 | Ref[a] |
| | 3–7 years old | 2.1 | 1.02–4.2 |
| | >7 years old | 3.0 | 1.3–6.7 |
| Disc herniation | No | 1.0 | Ref[a] |
| | Protrusion, <25% vertebral canal stenosis | 2.8 | 1.5–5.2 |
| | Protrusion, 25%–50% vertebral canal stenosis | 3.0 | 1.5–6.2 |
| | Protrusion, >50% vertebral canal stenosis or extrusion | 11.4 | 4.6–27.9 |

*Note*: The full model included the variables sex, age, weight, chondrodystrophy, disc degeneration, and disc herniation.
Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Reference category.

the backward procedure of the multivariable binary logistics regression.

## 3.7 | Histology

For histological purposes, spinal segments from surplus research dogs (no reported history of back pain, no degeneration induced) and research dogs from other experimental studies where IVDD was induced by partial nuclectomy were used (Supplementary File 1). Lumbar spines of 16 dogs were available for histological analysis, providing a total of 39 spinal segments. In six of these segments, type 1 MCs were encountered on MRI, nine segments showed type 3 MCs on MRI, and one segment demonstrated both type 1, 2, and 3 MCs on MRI (Figure 4A; Supplementary File 1).

### 3.7.1 | IVDs with MCs showed histopathological changes in the vertebral bone

Most dog spinal segments without observed MCs on MRI also showed no histopathological abnormalities in the vertebral body (Figure 4B). Chondroid areas infiltrating the bone marrow were, however, observed in the vertebrae of two dogs without MCs. Four of the six segments in which type 1 MCs were observed showed chondroid areas in the vertebral bone, adjacent to the EP (Figure 4B,H,I). In one spinal segment with MC type 1, fibrous tissue replaced normal bone marrow (Figure 4B,F,G). Also, plasma cells were present in the vertebral bone marrow of this spinal segment, suggesting the presence of inflammation. The last spinal segment with type 1 MCs showed a Schmorl's node and some fibrous tissue within the vertebral bone marrow. Of the nine segments in which type 3 MCs were observed, abnormal findings were detected in the vertebral bone marrow of four segments: one segment revealed chondroid areas, two segments showed fibrous tissue infiltration, and one segment exhibited mild signs of inflammation and chondroid islets within bone trabecula (Figure 4B). The spinal segment of the only dog with mixed MCs (type 1, 2, and 3) revealed chondroid areas in de vertebral bone marrow and mild inflammation, together with a Schmorl's node (Figure 4B). Altogether, this indicates that spinal segments with MCs showed more histopathological abnormalities in the vertebral bone marrow than segments without MCs and that chondroid areas were mainly detected in type 1 MCs.

### 3.7.2 | Endplate pathologies and vertebral bone sclerosis are detected in dog IVDs showing MCs

The total modified Boos score was not considerably different between spinal segments with and without detected MCs (Figure 4C), indicating that segments with MCs have a histological IVD degeneration grade comparable to segments without MCs. As damage to the EP is classified as a risk factor for the development of MCs,[9] we further focused on the sub criteria addressing EP and vertebral bone morphology. All spinal segments in which MCs were detected showed a varying degree of abnormal histologic findings in the EP (score 1 for four segments, score 2 for eight segments, score 3 for four segments) (Figure 4D). However, 17 out of 23 segments without detected MCs (74%) also showed abnormal histologic findings for the EP (score 1 for seven segments, score 2 for seven segments, and score 3 for three segments). Finally, only one segment (with MC type 3) was assigned as "severe subchondral bone sclerosis," while all other segments were histologically graded as "no subchondral bone sclerosis" (Figure 4E). Altogether, this indicates that more histological EP and bone marrow pathologies are detected in MC-containing dog spinal segments than in dog segments without MCs.

## 4 | DISCUSSION

Although dogs suffer from IVD-related LBP like humans, little was known about MCs in this species. Previous work indicated an association between MRI-detected vertebral EP changes and disease of the adjacent disc in dogs.[47] That study, however, did not identify factors associated with MC nor did it specify MC types, evaluated the whole spinal column (with spinal segments containing relatively few MCs compared with LS spinal segments) and had a lower power compared with the current study. The current study expands the knowledge on dog MCs as it identified the prevalence, possible associated risk factors, imaging, and histological characteristics of lumbar dog MCs.

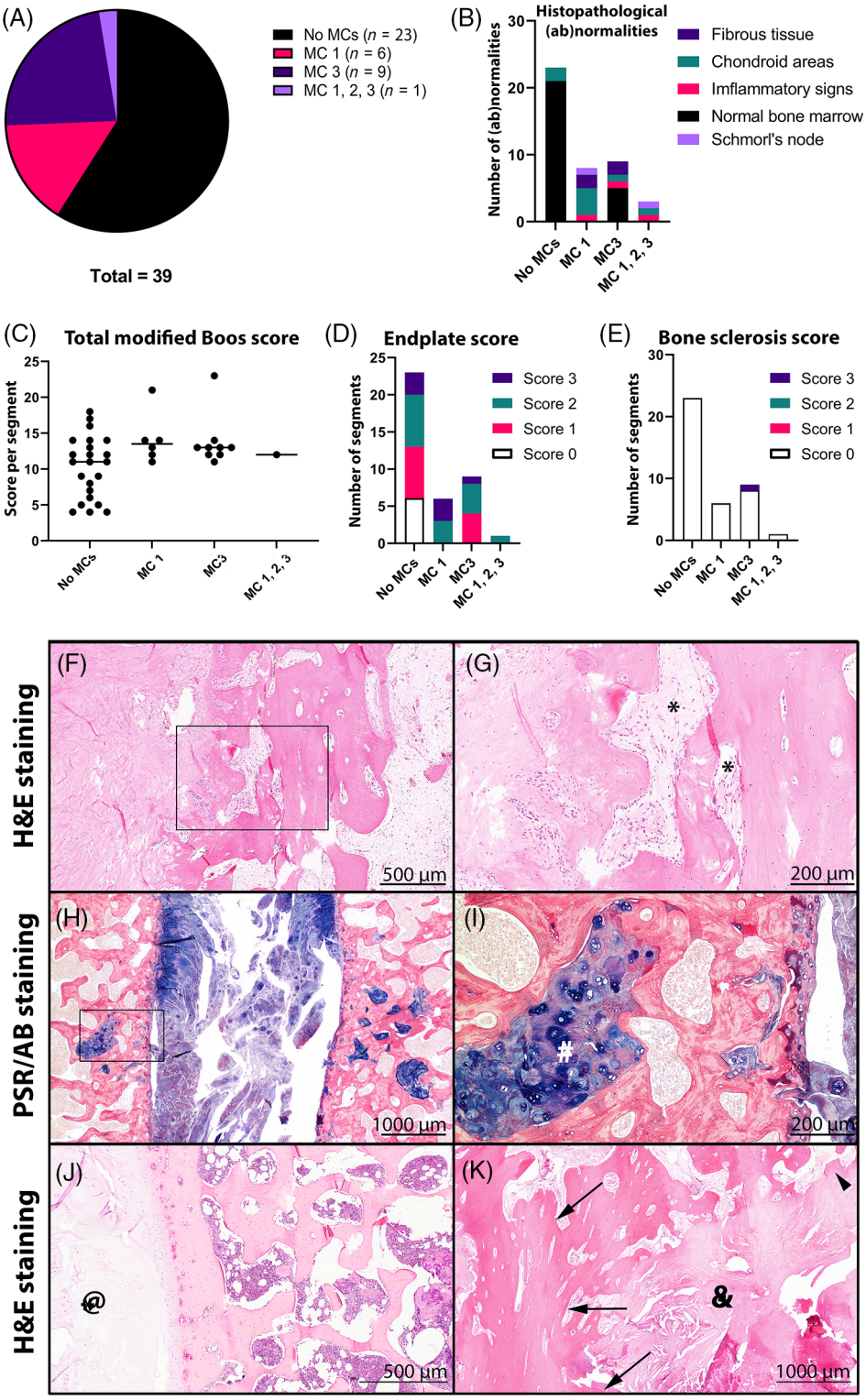


**FIGURE 4** Histopathological features observed in dog spinal segments with and without Modic changes (MCs). (A) Overview of all spinal segments used in the current histological study ($n = 39$). (B) Histopathological abnormalities detected in the vertebral bodies (VB); abnormalities may co-exist in one VB. (C) The total modified Boos score for every included spinal segment (with/without detected MCs at MRI). (D) Overview of the endplate (EP) score for all segments (score 0 = regular thickness, homogenous structure, score 1 = slightly irregular thickness, score 2 = moderately irregular thickness, score 3 = severely irregular thickness with interruption of the EP). (E) Overview of the bone sclerosis score for all segments (0 = no sclerosis, 1 = mild sclerosis [2–4× thickness of the dorsal vertebral cortex], 2 = moderate sclerosis [>4× the thickness of the dorsal vertebral cortex], 3 = severe subchondral bone irregularities). (F) and (G) H&E stained sections demonstrating infiltration of fibrous tissue (*) in the vertebral bone marrow of a dog with MC type 3. (H) and (I) PSR/AB stained sections demonstrating chondroid change (#) in the vertebral bone marrow of a dog with MC type 1. (J) H&E stained section demonstrating normal IVD tissue and bone marrow, @: NP tissue. (K) H&E stained section showing subchondral bone sclerosis (arrow), and an area with less sclerosis (arrow point) in the vertebral bone of a dog with MC type 1, &: IVD tissue.

## 4.1 | Prevalence of MCs

The prevalence of MCs in the lumbar spine of the studied dog patient population was 66%, which is higher than the 25% and 5.6% previously reported.[41,42] This could potentially be explained by patient selection in a second and third-line referral academic veterinary hospital. All scans in our study included the LS junction, the spinal segment with by the largest prevalence of MCs in the current study, whereas previous studies included cervical and thoracic scans,[41] or did not include the LS junction,[42] likely lowering the prevalence of detected MCs. The results of our study and previous studies indicate that the dog is, to our knowledge, the first animal species in which spontaneously developed MCs are detected. Inherent to the retrospective nature and study design based on availability of complete MRI

records, however, most dogs in the current study were referred for imaging with clinical indication (LBP or neurological deficits). The prevalence of MCs in asymptomatic dogs remains to be determined but is expected to be lower than observed in the current study.

The reported prevalence of human MCs is about 43% in patients with nonspecific LBP and/or sciatica and about 6% in nonclinical populations, but varies between studies.[10,24,25,46] Presumably, LBP is noticed later in the disease process in dogs, because of mild, nonspecific initial clinical signs that are not recognized as such by the dog owner or the first line veterinary practitioner. This probably leads to relatively delayed diagnostic imaging for LBP (and MCs), possibly explaining the higher MC prevalence in dogs. The MC prevalence in humans varies between ethnicities, suggesting that genetic variation may play a role.[25] Also in dogs there might be an association with breed.[38] MRI settings can also influence the observed prevalence, as classification of MCs depends on MRI field strength.[64] In humans, STIR images have been used, which may visualize a different spectrum MC presence and types, possibly explaining differences between human and dog. Concluding, the current study detected a high prevalence of MCs in dogs with LBP and/or neurological deficits compared with humans, possibly because LBP is later noticed and treated in dogs.

## 4.2 | MC type 3 is most commonly detected

MC type 3 was most often encountered in the current dog study (72%). In contrast, in humans mostly MC type 2 is encountered (16%–50%), followed by MC type 1 (4%–18.5%), and MC type 3 (1.3%–2.8%).[7,21,25,30,65,66] We can only speculate what causes this difference between species. Dogs have thicker subchondral cortices and thinner cartilaginous EPs compared to humans,[36] but whether this leads to differences in MC development is unknown. Because MCs may convert to other MC types and because mixed type MCs exist (20% in humans[9] and 19% in this dog study), it is suggested that MCs may represent different consecutive phases of the degenerative/reactive process.[7,17] MCs type 1 have been associated with rapid and progressive IVDD and might therefore be part of a distinct process different from the process associated with MC type 2 and 3.[67,68] MC type 2 is thought to remain more stable in time compared to type 1.[7,69]

The fact that mainly type 3 MCs were detected in the current study may again indicate that dogs with LBP are scanned at a more chronic disease stage. This probably relates to the fact that people do not timely recognize clinical signs that relate to lower back pain in their dogs and the first line veterinarian also often has difficulties recognizing those. In addition, MRI is a relatively expensive modality and as such this diagnostic tool is often reserved for the chronic conditions not responding to conservative treatment. The overlap in histologic findings between type 1 and type 3 MCs also supports the theory that type 3 MCs can be preceded by type 1 changes[27,67,69] and can be regarded as a metaplastic change in the reactive tissue and thus, that MCs in dogs are also interconvertible over time. To validate this hypothesis, more longitudinal studies in more dog patients, and proper characterization of clinical phenotypes is needed. Finally, MCs have been proposed as a cause of human LBP, but this proposition remains controversial.[46,70] Since the current study included MRIs of client-owned dogs with LBP and/or neurological deficits, analyzed in retrospective fashion and in the absence of longitudinal quantitative and qualitative pain assessment, no conclusions on the association between MCs and LBP in dogs can be made.

## 4.3 | MCs mostly detected at the lumbosacral junction

The current study mainly detected dog MCs at the L7-S1 junction, in accordance with previous research.[41] More specifically, MCs were mainly present along the whole height of the sacral EP, while in humans they are mostly present at the anterior part of the vertebra.[71] Additionally, only 18% of dog MCs were present in both cranial and caudal EPs, while this is most commonly the case in humans (78%).[30] Similarly as in dogs, human MCs are also mainly present at the L5-S1 junction.[72] An explanation for this predilection site is the known association between MCs and IVDD,[7,24,31,65,67] as the latter is known to be most prevalent at the LS junction.[38] Another explanation is a high flexion and extension mobility and a small rotational stiffness in the dog LS spinal segment, which can cause repetitive stress and eventually degeneration.[73] Dog IVDs are often considered to be under different loads than their human counterparts because of the horizontal versus vertical spinal orientation. To keep the dog spine in a horizontal position, however, considerable muscle and ligamental forces are necessary.[74,75] Thus, dog spine biomechanics are not much different from the human situation. Affirmatively, in humans, the L5-S1 spinal segment also has the highest flexion and extension mobility,[76,77] and a correlation between MC and biomechanics was established.[72] Finally, there is a breed disposition for LS disease in German Shepherd dogs, indicating that genetics may also play a role in dogs.[78] Because the prevalence of MCs at other sites was too low for reliable statistical analysis, this study focused on possible risk factors for MC presence at the LS junction. Whether these possible associated factors also apply to other spinal locations remains to be determined. Concluding, in both humans and dogs, most MCs are detected at the LS junction, presumably because of their association with IVDD and biomechanics.

## 4.4 | Etiology of MCs at the lumbosacral junction

### 4.4.1 | IVDD

The multivariate analysis of this study indicated that LS MCs in dogs were associated with age and disc herniation. This is rather similar in humans, as their MCs are also associated with IVDD.[7,24,31,65,67] The association between dog MCs and IVDD was significant in the univariable, but not in the multivariable analysis, indicating that although IVDD plays a role in MC development, age and herniation appear to

be even more important. Nevertheless, a relationship between dog MCs and IVDD seems plausible, as IVDD correlates to age[79–81] and predisposes for IVD herniation.[73,82,83] Lumbosacral MCs were present in both the cranial and caudal EPs in only 18% of dogs, with the majority affecting the sacral EP. This seems to contradict with the idea that the development of MCs is mainly disc driven (as inflammatory mediators from an abnormal disc would affect both sides equally). To this end, the present data suggests EP pathology to be involved in the development of MCs in dogs. The importance of the EP is also supported by the relatively large number of dogs in this study with MC type 3 (thought to represent late stage of disease) that had a low Pfirrmann grade. Nonetheless, the field of etiopathogenesis of MCs is under heavy debate, and the study design does not allow for such speculations and leaves the question unanswered (as MCs may depend on the population studied, time point of assessment in lifespan, and the initiating factor may be relating to many different variables, including the disc, the endplate, the paraxial muscles, and the facet joints).

Despite an abundance of imaging data from MC studies, few reports detail the histology of MCs. In the current study, 39 spinal segments of dogs with and without MCs were histologically analyzed. To gain enough power for proper statistical analysis of the histological results, we also included spinal segments in which IVD degeneration was mechanically induced and/or that received intradiscal treatment. Whether this resulted in different histological changes than in dogs without these interventions is unknown, and more research is needed on spontaneously developed MCs in dogs.

In the current study, most EP and vertebral bone marrow abnormalities were detected in segments with MCs compared to segments without MCs, in line with previous reports where vertebral bone and EP pathologies were associated with MCs.[7,9] Affirmatively, EP pathologies were also associated with IVDD and have been implicated to contribute to their development,[47,84] which seems logical from a pathological perspective as the EP provides nutrition to the avascular IVD.[85]

In the vertebral bone marrow, chondroid areas, fibrous tissue, and inflammation were observed in dogs with MC type 1 and 3. Since no MRI-confirmed MC type 2 samples were available for histological purposes, no conclusions can be drawn for this MC type. A T2W sequence with fat saturation can give additional information, but since this sequence was not routinely used, subtle MC type 1 or 2 changes might not have been detected.[41] As two spinal segments without MCs also revealed chondroid areas in the vertebral bone marrow, MRI analysis is apparently not sensitive enough to detect all histological abnormalities, especially using a magnet with a relatively low field strength of 1.5 T (and therefore limited resolution).[64] Only one previous microscopic study studied 6 spinal segments and indicated that human MC type 3 represents subchondral bone sclerosis,[33] but in our study only one out of nine spinal segments with MC type 3 showed sclerosis histologically. The question remains whether MRI is more sensitive to find changes in the vertebral bone or are we overinterpreting MRI data? Another explanation might be that by using MRI, the whole IVD and adjacent vertebral tissue is analyzed, while for histology only a single or limited numbers of 5 µm tissue slides are examined at specific tissue level(s), and as a consequence pathology can be missed when not sectioned. In future studies, micro-CT analysis might help in determining bone volume fraction.

Interestingly, previous work indicated that specimens with idiopathic vertebral lesions showed dense collagenous tissue histologically, while signal intensity changes comparable with MC type 3 were observed with MRI.[86] Furthermore, loose fibrous tissue (with vessels and edema) and cartilage metaplasia both exhibited imaging characteristics comparable with MC type 1.[86] Finally, bone sclerosis not consistently showed hypointense on T1W and T2W,[86] indicating that type 3 MCs can be missed with imaging. Altogether, this indicates that a specific tissue type with variable density of its fiber arrangement and especially a difference in composition of the extracellular matrix, may represent different on MRI and hence lead to a different MC type classification. Additionally, the current study shows that at least in dogs, other pathologies than the ones known in humans can be encountered in spinal segments with MCs, such as chondroid tissue proliferation. This implies that dogs may exhibit different or more chronic bone marrow pathologies than humans with MCs. Because only limited histological studies on (human) spinal segments with MCs are available, however, more research on the histology of MCs in different species is strongly recommended.

### 4.4.2 | Discospondylitis

The diagnosis of discospondylitis in our patient population was based on imaging characteristics, as biopsies and bacteriological culture were unavailable in most dogs due to the location of the presumed infection. MRI characteristics compatible with discospondylitis were found in 5.5% (19/340) of dogs referred for MRI analysis of the lumbar spine. Previous work found a comparable prevalence (3.4%) in dogs referred for spinal imaging.[87] A significant association was furthermore detected between discospondylitis (diagnosed with MRI based on imaging characteristics such as end plate lysis) and MC type 1, indicating that MC type 1 is associated with characteristics that are also commonly encountered in discospondylitis. Affirmatively, MRI signal intensity changes are common findings in dogs with discospondylitis and resemble type 1 (acute phase) or type 3 MC.[44,88] Although spondylodiscitis, the human variant of discospondylitis in dogs, is not common (incidence of between 0.2 and 3.7/100000 per year[89]), a bacteriological etiology has also been suggested as cause for human MCs.[9,45,46] Concluding, MCs can be caused by pathological EP/vertebral bone changes due to IVDD, but also by infections, and therefore it is recommended to look for (other) characteristics of infections when MCs are encountered.

### 4.4.3 | Previous spinal surgery

By analyzing MRIs of 15 (out of 340) dogs with previous surgery, this study demonstrated that previous spinal surgery increased the

likelihood of developing MCs (>6 times), especially MC type 1 and 2, as is also known in humans.[12] Noteworthy, dogs were only scanned after a surgical procedure when clinically indicated (i.e., persistent or recurrent pain and/or neurologic deficits), implying that the true prevalence of MCs after surgery is not exactly known, but is probably lower. Besides, inherent to the retrospective nature of the study, it was not known for all dogs whether the MCs were already present before surgery, and if the MCs converted over time. Spinal surgery, that may include partial discectomy, probably induced MCs by iatrogenic damage or postoperative infections. The latter was suspected in two dogs in this study. In our previous study, more severe IVDD was mechanically induced by partial NP removal (different from the spontaneous process of mild IVDD[36,38,40]) in dogs. After 6 months, 6 out of 20 of these spinal segments had developed MCs, whereas no MCs had developed in the spinal segments in which no degeneration was induced,[40] indicating that the MCs were caused by iatrogenic trauma. Previous work supported this, as dog EPs and subchondral bone showed histological abnormalities such as microfractures and sclerosis after discectomy[62,63] and in an induced IVDD model.[90] Also in humans, EP intensity changes can be observed after (non-specified) surgery for herniated discs.[49] Altogether, MCs were detected in dogs that underwent pervious spinal surgery, but it remains to be determined whether these MCs were caused by IVDD that was already present before surgery, by postoperative infections, or by mechanical damage due to the surgical procedure or a combination of these factors.

## 5 | CONCLUSIONS

This study shows that as in humans, MCs in dogs were most often detected at the lumbosacral junction. MRI signal intensity changes mostly represented MC type 3, while previous spinal surgery was associated with the presence of MC type 1 and 2. As in humans, MCs in dogs were associated with age and disc herniation. Finally, spinal segments with MCs showed more histological abnormalities in the endplate and vertebral bone marrow than those without MCs. Mostly chondroid infiltration was encountered, while the histologic anomalies described for humans were scarcely detected. This implies that dogs may exhibit other or more chronic vertebral bone marrow pathologies than humans with MCs. Comparative histological analysis of endplate changes associated with MC may increase the understanding on endplate pathology related to LBP. Finally, more research is needed to determine the translatability of MCs observed in dogs suffering from LBP toward those observed in human LBP patients.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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## SUPPORTING INFORMATION

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