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Predictive factors associated with neck pain in patients with cervical disc degeneration
A cross-sectional study focusing on Modic changes

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Abstract

The predictive factors associated with neck pain remain unclear. We conducted a cross-sectional study to assess predictive factors, especially Modic changes (MCs), associated with the intensity and duration of neck pain in patients with cervical disc degenerative disease.

We retrospectively reviewed patients in our hospital from January 2013 to December 2016. Severe neck pain (SNP) and persistent neck pain (PNP) were the 2 main outcomes, and were assessed based on the numerical rating scale (NRS). Basic data, and also imaging data, were collected and analyzed as potential predictive factors. Univariate analysis and multiple logistic regression analysis were performed to assess the predictive factors for neck pain.

In all, 381 patients (193 males and 188 females) with cervical degenerative disease were included in our study. The number of patients with SNP and PNP were 94 (24.67%) and 109 (28.61%), respectively. The NRS of neck pain in patients with type 1 MCs was significantly higher than type 2 MCs (4.8 ± 0.9 vs 3.9 ± 1.1; $P = .004$). The multivariate logistic analysis showed that kyphosis curvature (odds ratio [OR] 1.082, 95% confidence interval [CI] 1.044–1.112), spondylolisthesis (OR 1.339, 95% CI 1.226–1.462), and annular tear (OR 1.188, 95% CI 1.021–1.382) were factors associated with SNP, whereas kyphosis curvature (OR 1.568, 95% CI 1.022–2.394), spondylolisthesis (OR 1.486, 95% CI 1.082–2.041), and MCs (OR 1.152, 95% CI 1.074–1.234) were associated with PNP.

We concluded that kyphosis curvature, spondylolisthesis, and annular tear are associated with SNP, whereas kyphosis curvature, spondylolisthesis, and MCs are associated with PNP. This study supports the view that MCs can lead to a long duration of neck pain.

Abbreviations: BMI = body mass index, CI = confidence interval, MCs = Modic changes, MRI = magnetic resonance imaging, NRS = numerical rating scale, OR = odds ratio, PNP = persistent neck pain, SNP = severe neck pain.

Keywords: cervical disc degeneration, Modic changes, multivariable analysis, neck pain

1. Introduction

Neck pain is the second most common complaint, after lower back pain, in patients with spinal disc degeneration.[1,2] The prevalence of neck pain has increased steadily over the past 20 years,[3] with a 1-year incidence of between 10.4% and 21.3%.[4] In these patients, the cause of pain cannot be definitively attributed to a specific pathology and thus are labeled as nonspecific pain. Relieving such neck pain would be a major

breakthrough for clinicians, but currently there is a lack of strong evidence for any effective preventative approach. Many reports suggest that nonspecific neck pain may not be 1 distinct condition, but may consist of several different subgroups.[5,6] In this case, a generic "one-size-fits-all" approach should be replaced by targeted treatment. Although neck pain is widely considered a multifactorial condition, to our knowledge, risk factors for neck pain have not been clearly identified. Given the limited understanding of the etiology and risk factors for developing neck pain, a lack of effective interventions for preventing it is not surprising.[7]

Modic changes (MCs) are the signal intensity changes of vertebral end plates and subchondral bone on magnetic resonance imaging (MRI). These were first described by de Roos et al[8] and classified by Modic et al[9] into 3 types: types 1, 2, and 3. Histological studies show that type 1 MCs consist of fissured endplates and vascular granulation tissue adjacent to the endplate; type 2 is characterized by a disruption of the endplates and fatty degeneration of the adjacent bone marrow; and type 3 appears to be sclerosis of the bone marrow.[9] The causes of MCs are unclear, and degenerative or infectious causes have been suggested.[10,11] According to previous studies, the incidence of MCs in the cervical spine ranges from 3.3% to 19.2% in different populations.[12,13] Ohtori et al[14] reported that the vertebral endplates observed on MRI in patients with MCs have significantly more immunoreactive cells compared with patients with normal endplates. Although the etiology and pathobiology of MCs are not totally clear, there is much evidence that they are

painful.[15–17] In several published studies, MCs, especially type 1, have been proposed to contribute to lower back pain,[16,17] but whether MCs have an effect on neck pain is currently undetermined. Furthermore, as MCs are frequently observed in patients with disc degeneration, it remains unclear whether MCs are simply an adjunct feature of disc degeneration or if they are associated with spinal pain directly.

To the best of our knowledge, few previous studies have investigated the impact of MCs on neck pain, which has limited our understanding and further treatment of it. The main objective of our study was to investigate the predictive factors associated with neck pain, particularly the predictive value of MCs, in patients with cervical disc degenerative disease using multivariate analysis. The secondary aim was to determine the association between MCs and components of disc degeneration. Our null hypothesis was that MCs are not associated with neck pain.

2. Methods

2.1. Patient population

This was a cross-sectional study retrospectively reviewing patients between January 2013 and December 2016 in the Third Hospital of Hebei Medical University. Patients with cervical disc degenerative disease, such as cervical disc herniation or cervical spondylotic myelopathy, were analyzed. The inclusion criteria were adults aged between 18 and 70 years, having symptoms of radiculopathy or myelopathy, with or without neck pain. Patients were excluded if they had acute cervical trauma, prior cervical spinal surgery, ossification of the posterior longitudinal ligament, amyotrophic lateral sclerosis, spinal tuberculosis, or spinal infection. This was a retrospective study using data routinely collected, and patients signed informed consent before their procedures, so specific ethics approval for this study was not required according to a waiver issued by the ethics committee.

2.2. Assessment of neck pain

Patients' neck pain was assessed using the numerical rating scale (NRS), which is an 11-point rating scale with 0 being no pain and 10 being the worst pain imaginable.[18] It has been demonstrated to be an accurate, reliable, repeatable, and sensitive measurement of pain intensity.[19] A recording of more than 3 points on the scale was considered to indicate the existence of neck pain. The primary outcome of this study was the intensity of neck pain, with severe neck pain (SNP) defined as at least 5 points on the NRS. The secondary outcome was the duration of neck pain, with persistent neck pain (PNP) defined as neck pain of at least 3 points for more than 12 months. The patients' allocation is shown in Fig. 1.

2.3. Parameter evaluation

Both basic data and imaging data were collected and analyzed as potential predictive factors. Demographic data were collected from medical records, including age, sex, body mass index (BMI), history of smoking, and academic level. Academic level was categorized by completion of less than elementary school, elementary school, high school, or university. Participants with university level education were considered highly educated.

All patients underwent plain radiograph tests. From standing lateral radiographs, cervical lordosis was assessed by C2–7 Cobb angle. An alignment of C2–7 Cobb angle more than 0 was defined as lordosis, and an alignment of C2–7 Cobb angle of 0
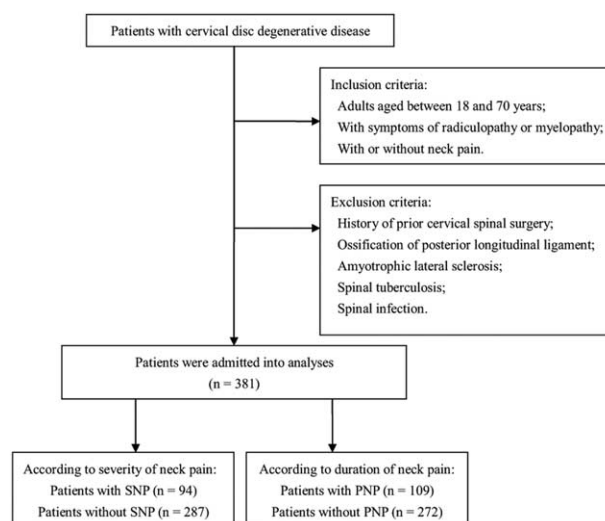

Figure 1. Flow diagram showing patient allocation.

or less was defined as kyphosis.[20] Cervical degenerative spondylolisthesis was then described according to the degree of severity. The measured values of the maximum horizontal displacement on radiographs were obtained by flexion and extension radiography. Patients with spondylolisthesis were defined as having unequivocal horizontal displacement of 2 mm or more.[21]

Participants also underwent MRI scans of the cervical spine on a single high-field strength system (3.0-T Siemens Magnetom Symphony; Siemens, Berlin, Germany) with a multichannel phased array spine surface coil. A standardized protocol was used for all participants, including sagittal fast spin echo T1 and T2, sagittal short tau inversion recovery (STIR), and axial T2 scans. According to the definition of Modic et al[9], the MCs were classified as type 1, type 2, or type 3. Type 1 MCs show hypointense signals on T1 sequences and hyperintense signals on T2 sequences; type 2 shows hyperintense signals on T1 sequences and hyper or isointense signals on T2 sequences; and type 3 shows hypointense signals on both T1 and T2 sequences. As type 3 MCs are seldom seen, only type 1 and type 2 were investigated in our study (Fig. 2). Disc degeneration was assessed based on the Pfirrmann scale ranging from 1 to 5.[22] Grade 4 or more at any cervical level was considered a positive finding. Disc height loss was categorized as mild, moderate, or severe, and severe disc height loss at any cervical level was regarded as a positive finding.[23] Annular tear was defined as a positive finding when present at any cervical level.[24] All parameters were evaluated by 2 independent investigators. Disagreements between the 2 investigators were settled by discussion, and if no consensus could be reached, a third investigator made the final decision.

2.4. Data analysis

Continuous variables are shown as mean ± SD, and categorical variables are shown as the number (percentage). The Kappa statistic was used to evaluate the interobserver and intraobserver reliability of the presence of MCs from MRI. The minimum sample size for multiple logistic regression analysis was estimated by a power analysis.[25] To be statistically significant at 95% of power with an anticipated effect size (f^2) of 0.15, six possible
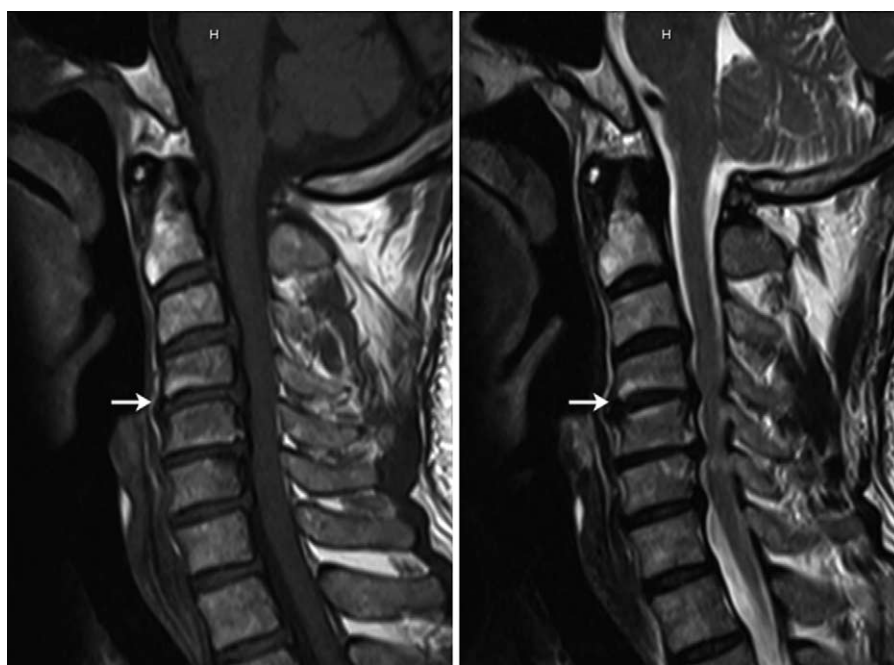
Figure 2. A Modic change at the C4–5 level on cervical magnetic resonance images.

predictors, and an alpha level of 0.05 required 146 patients. Simple logistic regression was used to compute crude odds ratios (ORs) with 95% confidence intervals (CIs) for variables. Variables with a $P < .10$ were included in the multivariate logistic regression analysis to estimate adjusted ORs with 95% CIs. A forward method was used in the multivariate logistic regression model. Any missing data were not included in the multivariate analysis. Before logistic regression analysis, continuous variables were converted to categorical variables according to cut-off values with clinical meaning. The variables used for analysis included age (<50 years, ≥50 years), sex (male, female), BMI (<25 kg/m², ≥25 kg/m²), history of smoking (yes, no), academic level (low, high), cervical curvature (lordosis, kyphosis), spondylolisthesis (yes, no), MCs (yes, no), severe disc degeneration (yes, no), disc height loss (yes, no), and annular tear (yes, no). Statistical analyses were performed using SPSS for Windows, version 16 (SPSS Inc., Chicago, IL). The statistical threshold for significance was set at $P < .05$.

3. Results

3.1. Baseline characteristics

In all, 381 patients (193 males and 188 females) with cervical degenerative disease were included in our study. The mean age of these patients was 50.7±12.9 years. Of these participants, 47 patients (12.34%) had MCs, and the other 334 (87.66%) did not. Kappa values for the intra and interobserver analysis of the presence of MCs were 0.89 and 0.11, indicating excellent reliability. The number of patients with type 1 and type 2 MCs were 21 (44.68%) and 26 (55.32%), respectively. The NRS of neck pain in patients with type 1 MCs was significantly higher than type 2 MCs (4.8±0.9 vs 3.9±1.1; $P = .004$). Of the 381 patients, 94 had SNP, and 109 had PNP. Details concerning demographic data and clinical characteristics of all patients are given in Table 1.

3.2. Predictive factors associated with neck pain

Table 2 shows the predictive factors associated with SNP. We calculated the crude ORs using simple logistic regression, and the results showed that age (crude OR 1.539, 95% CI 0.963–2.461), cervical curvature (crude OR 2.355, 95% CI 1.185–4.677), spondylolisthesis (crude OR 2.464, 95% CI 1.332–4.559), MCs (crude OR 2.603, 95% CI 1.382–4.903), and annular tear (crude OR 1.582, 95% CI 0.991–2.527) were factors that could enter the multivariate logistic regression analysis ($P < .10$). The final results of multivariate analysis showed that kyphosis curvature (adjusted OR 2.615, 95% CI 1.323–5.170), spondylolisthesis

Table 1

Baseline characteristics of participants.

Variables	Value (n=381), %
Age, y	50.7±12.9
Sex	
Male	193 (50.65)
Female	188 (49.34)
BMI, kg/m²	24.4±5.7
History of smoking	
Yes	100 (26.25)
No	281 (73.75)
Academic level	
Less than elementary school	74 (19.42)
Elementary school	109 (28.61)
High school	117 (30.71)
University	81 (21.26)
Types of lesion	
Radiculopathy	102 (26.77)
Myelopathy	183 (48.03)
Both	96 (25.20)
No. of patients with MCs	47 (12.34)
No. of patients with SNP	94 (24.67)
No. of patients with PNP	109 (28.61)

BMI = body mass index, MCs = Modic changes, PNP = persistent neck pain, SNP = severe neck pain.

Table 2

Predictive factors associated with SNP.

Variable	With SNP (n=94)	Without SNP (n=287)	Crude			Adjusted		
			OR	95% CI	P	OR	95% CI	P
Age, y								
<50	41	156	Reference			Reference		
≥50	53	131	1.539	0.963–2.461	.075	1.420	0.885–2.279	.151
Sex						—*	–	——
Female	49	139	Reference			—	—	—
Male	45	148	0.863	0.541–1.375	.554	—	—	—
BMI, kg/m²						—	—	—
<25	51	167	Reference			—	—	—
≥25	43	120	1.173	0.734–1.875	.549	—	—	—
History of smoking						—	—	—
No	71	210	Reference			—	—	—
Yes	23	77	0.883	0.516–1.513	.688	—	—	—
Academic level						—	—	—
High	19	62	Reference			—	—	—
Low	75	225	1.088	0.611–1.936	.885	—	—	—
Cervical curvature								
Lordosis	78	264	Reference			Reference		
Kyphosis	16	23	2.355	1.185–4.677	.018	2.615	1.323–5.170	.010
Spondylolisthesis								
No	73	257	Reference			Reference		
Yes	21	30	2.464	1.332–4.559	.005	2.892	1.572–5.321	.001
Modic changes								
No	74	260	Reference			Reference		
Yes	20	27	2.603	1.382–4.903	.004	1.874	0.969–3.623	.066
Severe disc degeneration								
No	29	109	Reference			—	—	—
Yes	65	178	1.373	0.834–2.259	.220	—	—	—
Disc height loss								
No	31	103	Reference			—	—	—
Yes	63	184	1.138	0.695–1.863	.709	—	—	—
Annular tear								
No	45	170	Reference			Reference		
Yes	49	117	1.582	0.991–2.527	.056	1.752	1.098–2.794	.023

CI = confidence interval, OR = odds ratio, SNP = severe neck pain.

* Variables with a P ≥ 0.10 were not included in the multivariate logistic regression analysis.

(adjusted OR 2.892, 95% CI 1.572–5.321), and annular tear (adjusted OR 1.752, 95% CI 1.098–2.794) were 3 significant independent factors associated with SNP in patients with cervical degenerative disease (P < .05).

Predictive factors associated with PNP were listed in Table 3. The crude ORs calculated by simple logistic regression showed that age (crude OR 1.539, 95% CI 0.984–2.408), cervical curvature (crude OR 2.364, 95% CI 1.205–4.637), spondylolisthesis (crude OR 2.562, 95% CI 1.402–4.681), MCs (crude OR 2.498, 95% CI 1.340–4.658), and annular tear (crude OR 1.556, 95% CI 0.995–2.433) were factors that could enter the multivariate logistic regression analysis (P < .10). The final results of multivariate analysis showed that kyphosis curvature (adjusted OR 2.758, 95% CI 1.398–5.442), spondylolisthesis (adjusted OR 2.506, 95% CI 1.311–4.792), and MCs (adjusted OR 2.308, 95% CI 1.244–4.282) were 3 significant independent factors are associated with SNP in patients with cervical degenerative disease (P < .05).

3.3. MCs and components of disc degeneration

In the model investigating the association between MCs and disc degeneration components, we found that severe disc degeneration (crude OR 2.299, 95% CI 1.105–4.783) and disc height loss

(crude OR 2.525, 95% CI 1.181–5.398) were 2 factors that could enter the multivariate logistic regression analysis (P < .10). The final results of multivariate analysis showed that severe disc degeneration (adjusted OR 2.423, 95% CI 1.169–5.023) and disc height loss (adjusted OR 2.381, 95% CI 1.110–5.108) were 2 factors that are associated with MCs (P < .05). The details of these results are shown in Table 4.

4. Discussion

4.1. Main findings of the present study

Our main finding was that kyphosis curvature, spondylolisthesis, and annular tear are associated with SNP, whereas kyphosis curvature, spondylolisthesis, and MCs are associated with PNP. In comparison with type 2 MCs, patients with type 1 MCs showed high NRS. MCs can lead to long duration of neck pain, and type 1 MCs contribute to SNP. Furthermore, our results show that severe disc degeneration and disc height loss are associated with the prevalence of MCs.

4.2. Comparison with other studies

Previous researches have reported the associations of predictive factors and neck pain among different populations. Most studies

Table 3

Predictive factors associated with PNP.

Variable	With PNP (n=109)	Without PNP (n=272)	Crude OR	Crude 95% CI	Crude P	Adjusted OR	Adjusted 95% CI	Adjusted P
Age, y								
<50	48	149	Reference			Reference		
≥50	61	123	1.539	0.984–2.408	.069	1.444	0.924–2.257	.113
Sex								
Female	55	133	Reference			—*	—	—
Male	54	139	0.939	0.602–1.465	.821	—	—	—
BMI, kg/m²								
<25	59	159	Reference			—	—	—
≥25	50	113	1.192	0.762–1.865	.492	—	—	—
History of smoking								
No	83	198	Reference			—	—	—
Yes	26	74	0.838	0.501–1.403	.523	—	—	—
Academic level								
High	23	58	Reference			—	—	—
Low	86	214	1.013	0.58888–1.746	.962	—	—	—
Cervical curvature								
Lordosis	91	251	Reference			Reference		
Kyphosis	18	21	2.364	1.205–4.637	.015	2.758	1.398–5.442	.004
Spondylolisthesis								
No	85	245	Reference			Reference		
Yes	24	27	2.562	1.402–4.681	.003	2.506	1.311–4.792	.007
Modic changes								
No	87	247	Reference			Reference		
Yes	22	25	2.498	1.340–4.658	.005	2.308	1.244–4.282	.010
Severe disc degeneration								
No	34	104	Reference			—	—	—
Yes	75	168	1.366	0.851–2.192	.238	—	—	—
Disc height loss								
No	37	97	Reference			—	—	—
Yes	72	175	1.079	0.676–1.722	.813	—	—	—
Annular tear								
No	53	162	Reference			Reference		
Yes	56	110	1.556	0.995–2.433	.053	1.500	0.955–2.357	.083

CI=confidence interval, OR=odds ratio, PNP=persistent neck pain.
* Variables with a P≥.10 were not included in the multivariate logistic regression analysis.

collected clinical characteristics, physical status, and psychological factors as potential predictive factors.[26,27] However, to our knowledge, few studies have focused on radiological features, especially MCs. The incidence of MCs in the lumbar spine is significantly higher than in the cervical spine, resulting in a focus in most of the literature on MCs on the lumbar spine, with few studies reporting on the cervical spine. However, we can get some clues from previous studies of the lumbar spine. A study by Kjaer et al[15] investigated 412 Danes, and indicated a strong association between MCs and nonspecific lower back pain. Kuisma et al[17] showed that MCs at a specific level and type 1 MCs are more likely to be related to lower back pain. Luoma et al[28] collected 49 patients with severe, nonspecific low back pain, and found that decrease of type 1 MCs predicted decrease of pain. In line with these results, our study found an association between MCs and neck pain. Patients with MCs are prone to neck pain of long duration. Meanwhile, type 1 MCs are associated more SNP than type 2.

In those studies where the relationship between MCs and disc degeneration has been assessed previously, MCs frequently occur at sites with degenerative disc disease.[29,30] In a study by Maatta et al, the authors found that disc narrowing and disc signal loss were associated with prevalent MCs, even in multivariable analysis.[31] Kerttula et al reviewed 54 patients with large MCs

and concluded that MCs were associated with decrease of disc height and change in disc signal intensity.[32] Our results also show that severe disc degeneration and disc height loss are associated with MCs in the cervical spine. Although an association has been found between disc degeneration and MCs, we cannot draw a definite conclusion that there is a cause-effect relationship between them.

4.3. Implication and explanation of findings

In the current study, we included cervical curvature, spondylolisthesis, annular tear, and other factors as important features of cervical degeneration, and our multivariable analysis showed that both kyphosis curvature and spondylolisthesis are independently associated with the intensity and duration of neck pain. We assumed that the pathogenic mechanisms of the 2 degenerative features causing neck pain might be different. In spines with kyphosis, the cause of pain is mainly from muscle tissue with unbalanced tension, whereas in spines with spondylolisthesis, the pain might be caused by intervertebral instability. These results strengthen the fact that cervical degeneration is associated with neck pain, and kyphosis curvature and spondylolisthesis are 2 important features in radiography. Additionally, annular tear is an important

Association of disc degeneration components with MCs.

Variable	MC (+) (n=47)	MC (−)(n=334)	Crude OR	Crude 95% CI	P	Adjusted OR	Adjusted 95% CI	P
Spondylolisthesis								
No	39	291	Reference			—*	—	—
Yes	8	43	1.388	0.608–3.169	.491	—	—	—
Severe disc degeneration								
No	10	128	Reference			Reference		
Yes	37	206	2.299	1.105–4.783	.024	2.423	1.169–5.023	.016
Disc height loss								
No	9	125	Reference			Reference		
Yes	38	209	2.525	1.181–5.398	.014	2.381	1.110–5.108	.030
Annular tear								
No	26	189	Reference			—	—	—
Yes	21	145	1.053	0.570–1.946	.876	—	—	—

CI = confidence interval, MC = Modic change, OR = odds ratio.

* Variables with a $P \geq .10$ were not included in the multivariate logistic regression analysis.

pathology identified on MRI, and is demonstrated to be mainly associated with the severity of neck pain. This may be why some patients with no signs in radiography had SNP. An annular tear on MRI may better explain the source of the neck pain. What's more, MCs were demonstrated to be associated with persistent neck pain. Although this correlation is weak compared with kyphosis and spondylolisthesis in multivariable analysis, the mechanism of neck pain result from MCs needs further study.

Though MCs are commonly seen in patients with spinal degenerative diseases, the exact pathogenesis and their role in the process of disc degeneration is poorly understood so far.[12] Currently, there are 2 main theories of the pathophysiology of MCs: one is biomechanical, which regards the MCs as a result of mechanical stress at the vertebral endplate; the other is infection, which implies that edema in the vertebral endplate is caused by pyogenic infection of the disc and adjacent endplates.[10,11] Some investigators considered that MCs in the cervical spine are a dynamic phenomenon: type 1 MCs can convert to type 2 MCs, and type 2 MCs correspond to clinical and biological healing stages, which are associated with decreased inflammation-related symptoms.[33,34] On the basis of this theory, it is reasonable to see that type 1 MCs were more associated with clinical symptoms than other types.

4.4. Strengths and limitations

Strengths of this study include the strict inclusion criteria and the absence of significant differences in the general characteristics between the patient groups. However, there are several limitations in our study. First of all, in comparison with the lumbar spine, the size of MCs in the cervical spine was usually small. Thus, we did not account for the size of MCs in our study. The absence of this information in this cross-sectional study may not significantly affect our overall interpretations of the clinical relevance of MCs, but further investigation of MCs size may provide more valuable information. Besides, our study had only a moderate sample size. As the prevalence of MC is less commonly seen in the cervical spine, further studies with larger sample sizes are required. Though the association between MCs and PNP was found, subgroup and sensitivity analyses are necessary if we go a step further to investigate this association. Finally, our results were based on patients with cervical disc degenerative disease. Additional studies of patients without severe disc degenerative are needed to confirm generalisability of these findings.

4.5. Conclusion, recommendation, and future directions

Although it is 1 of the most common disorders of middle and old age, neck pain is often difficult to explain in terms of etiology. Finding an effective conservative treatment for neck pain is challenging because of its heterogeneous pathophysiological mechanism. The identification of subgroups of patients with neck pain could help in the search for specific therapeutics. For example, in a previous study, Bailly et al[16] reported a better effect of corticosteroids than NSAIDs in patients with type 1 MCs. Since we have identified that MCs are associated with long duration of neck pain. For those with MCs, corticosteroids may be a better choice. However, randomized trials and long-term follow-ups are needed to determine the magnitude of the effect and the impact of side effects before this treatment can be recommended widely. Similarly, for patients with severe cervical disc degeneration requiring surgery, the correction of kyphosis curvature and fusion procedures may play an important role in relieving neck pain.

5. Conclusions

In conclusion, this study shows that kyphosis curvature, spondylolisthesis, and annular tear are associated with SNP, whereas kyphosis curvature, spondylolisthesis, and MCs are associated with PNP. These results support the view that MCs can lead to a long duration of neck pain and that type 1 MCs contribute to SNP. Furthermore, this study indicates that severe disc degeneration and disc height loss are associated with the prevalence of MCs.

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