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Relationship Between Lumbar Multifidus Morphometry and Pain/Disability in Individuals With Chronic Nonspecific Low Back Pain After Considering Demographics, Fear-Avoidance Beliefs, Insomnia, and Spinal Degenerative Changes

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ABSTRACT

Background: Although individuals with chronic low back pain (CLBP) show increased fatty infiltration in the lumbar multifidus muscle (LMM), it remains unclear whether LMM changes are related to clinical outcomes (such as pain and disability) after considering confounders (spinal phenotypes, fear-avoidance beliefs [FABs] and insomnia). This study examined: (1) differences in confounders and LMM characteristics between individuals with and without CLBP; and (2) associations between confounders, LMM parameters, and clinical outcomes in the CLBP group alone.

Methods: Participants (CLBP = 70 and asymptomatic people = 67) underwent lumbar magnetic resonance imaging. Outcome measures comprised the numeric pain rating scale, the Roland–Morris Disability Questionnaire, the Fear-Avoidance Beliefs Questionnaire (FABQ), and the Insomnia Severity Index (ISI) Scale. LMM morphometry at L3-S1 (cross-sectional area, total volume, and fatty infiltration) was measured using a customized MATLAB program. Spinal phenotypes (disc degeneration, high-intensity zones, Modic changes [MCs], Schmorl's nodes, facet joint degeneration [FJD], and facet tropism [FT]) were scored. The between-group differences were analyzed using linear mixed models and chi-squared/Fisher's exact tests. Univariate and multivariate analyses evaluated associations between clinical outcomes and other outcome measures in the CLBP group.

Results: The CLBP group demonstrated more severe disc degeneration and FJD at all levels, and greater FT at L5/S1 than asymptomatic participants ($p < 0.05$). The average LMM total volume at L3/4 and the percentage of fatty infiltration in LMM in the L3-S1 region were greater in the CLBP group than in asymptomatic counterparts ($p < 0.05$). The presence of MC at L4 and

FJD at L4/5 and L4-S1 was significantly related to pain intensity in the CLBP group. Similarly, FABQ-Work and ISI scores were significantly related to pain intensity (explaining 37% of the variance in pain).
Conclusions: The CLBP group displays more fatty infiltration in the LMM, but their LMM morphometric parameters are unrelated to pain/disability after considering spinal phenotypes, FABs, and insomnia.

1 | Introduction

A global prevalence of 568.4 million low back pain (LBP) cases was reported in 2019, indicating that LBP is one of the major public health concerns. Approximately 90% of LBP cases have unknown causes and are diagnosed as nonspecific LBP [1]. Although 95% of LBP cases recover spontaneously, more than two-thirds of these cases relapse within 12 months and 20% may develop chronic LBP (CLBP) lasting for at least 12 weeks [2–4].

Compared to asymptomatic individuals, those with CLBP may show functional and morphological changes in the lumbar multifidus muscle (LMM) (e.g., smaller total cross-sectional area [CSA] and/or more intramuscular fatty infiltration) [5]. Although it is thought that these changes in LMM morphometry may be related to the development/maintenance of CLBP, baseline or temporal changes in LMM morphometry (e.g., fatty infiltration/thickness) may not necessarily be related to clinical outcomes (e.g., pain/disability) in individuals with CLBP [6–8]. While a study involving a mixed cohort of individuals with acute and chronic LBP found significant positive correlations between fatty infiltration in LMM and pain or disability [9], other investigations showed that the percentage of fatty infiltration in LMM among CLBP patients was not significantly related to pain intensity/disability [10].

The inconsistent associations between LMM morphometry and LBP-related clinical outcomes may be partly attributed to the fact that the CSA of LMM is not a true measure of LMM morphometry as compared to LMM volume. Unfortunately, prior research has not investigated the correlation between LMM volume and clinical outcomes among patients with CLBP.

Additionally, various spinal phenotypes, psychological factors (e.g., fear-avoidance beliefs [FABs]), and insomnia may also confound the associations between LMM morphometry and LBP/LBP-related disability in individuals with CLBP [11]. Several lumbar degenerative phenotypes (e.g., intervertebral disc [IVD] degeneration, high-intensity zones [HIZs], Modic changes [MCs], Schmorl's nodes [SNs], facet joint degeneration [FJD], and facet joint tropism [FT]) as observed on magnetic resonance images (MRIs) have been separately found to be associated with LBP [12–16]. Notably, the presence of IVD degeneration [17–19] or MC type 1 (MC1) [20, 21] is significantly related to higher LBP intensity. Additionally, IVD degeneration and FJD may impact kinematics and compromise lumbar stability, resulting in accelerated LMM degeneration [22]. Psychological factors like FABs are associated with clinical outcomes (pain intensity and/or disability) in individuals with CLBP [23]. Likewise, sleep disturbances/insomnia have been found to be associated with pain intensity in patients with CLBP [24]. Given the proximity of LMM, vertebrae, IVDs, and facets, LMM characteristics, spinal phenotypes, and LBP-related clinical outcomes may mutually affect one another. However, no prior research has investigated these inter-relations nor the associations between LMM morphometry and clinical outcomes after accounting for the confounding effects of demographics, spinal degenerative phenotypes, FABs, and insomnia in individuals with CLBP.

Given the above, the primary objective of the study was to compare FABs, insomnia, spinal phenotypes, and LMM characteristics between individuals with and without nonspecific CLBP. The secondary objective was to quantify the correlations between FABs, insomnia, LMM characteristics, and other spinal phenotypes with clinical outcomes (i.e., pain intensity and disability) in individuals with CLBP.

2 | Methods

This case–control study was approved by the Human Subjects Ethics Sub-committee of a university (HSEAR20151027007-01) and was conducted at a single center.

2.1 | Participants

The sample size was calculated based on a previous study, in which the lean muscle CSA to fatty CSA index in LMM was significantly higher in the LBP group than in healthy controls, with Cohen's *d* effect size of 0.9 and a standard deviation of 3.8 [25]. By assuming the same effect size, a sample of at least 34 participants per group was required to find a significant difference with an alpha level of 0.05% and 80% statistical power.

Individuals aged between 18 and 65 years were recruited. Participants with CLBP ($n = 78$) were recruited from a tertiary referral center for spinal pathologies and were screened by specialists to rule out pathologies that required surgical interventions. Age- and sex-matched asymptomatic participants ($n = 73$) were recruited through posters posted on the university campus (Figure 1). People with CLBP were recruited if: (1) they experienced nonspecific CLBP (NSCLBP) (defined as LBP that is not attributed to a recognizable pathology [26]) with or without leg pain that lasted for 3 months or more in the last 12 months, requiring surgical intervention; and (2) their LBP intensity was at least 5/10 on an 11-point numeric pain rating scale (NPRS), because LBP intensity between 5 and 6 is considered moderate in people with LBP [27, 28]. Asymptomatic participants were required to be free of LBP during the visit, free of LBP history within the past 12 months, and free of LBP that lasted more than a week in the previous 36 months. Individuals with neurological deficits/disease, spondylolisthesis, spinal tumors/cancer, spinal fractures, spinal operations, systemic inflammatory disease, metabolic disorders, or pregnancy (confirmed or suspected) were excluded from the study.

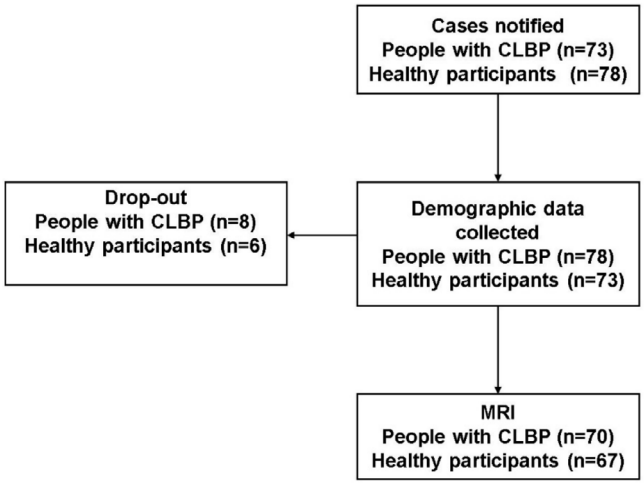

FIGURE 1 | Case reporting and completeness of data collection.

2.2 | Procedures

Participants completed a set of questionnaires to provide their demographic information, pain intensity, LBP-related disability, fear avoidance beliefs, and the severity of insomnia. Participants then underwent lumbar MRI from L1 to S1 levels in a 1.5 MRI scanner (Siemens, Berlin and Munich, Germany; or Philips, Amsterdam, and the Netherlands) and both T1 and T2 weighted images were obtained. The MRI sequence is described in Appendix S1.

2.3 | Clinical Outcome Questionnaires

Pain intensity was measured using the 11-point NPRS [29, 30], where 0 was defined as no pain and 10 as the worst imaginable pain. Participants rated their current pain intensity, as well as their least pain intensity and worst pain intensity during the past 24 h [31]. The three ratings were averaged to determine the pain intensity over the past 24 h [32].

LBP-related disability was measured using a validated Hong Kong-Chinese version of the Roland-Morris Disability Questionnaire (RMDQ) [33]. It consisted of 24 yes/no items to describe the negative impacts of LBP on individuals. Higher scores indicated more disability.

2.4 | Psychological Factors and Insomnia

Pain-related fear avoidance beliefs were assessed using a validated Hong Kong Chinese version of the 16-item Fear-Avoidance Beliefs Questionnaire (FABQ) [34]. It comprised two subscales to determine: (1) beliefs that physical activities cause damage; and (2) beliefs that work-related activities cause damage. By adding both subscale scores, the overall score was calculated [35]. Higher scores imply more fear avoidance beliefs.

The Chinese version of a 7-item Insomnia Severity Index (ISI) was used to assess the severity of insomnia [36]. A 5-point Likert scale was used to rate each item (e.g., 0 = *no insomnia*; 4 = *very severe insomnia*) [37]. A total score of 0 indicates no insomnia [37].

2.5 | Phenotype Grading

Prior to the measurements, one author was trained by a spinal specialist to perform the assessments. Each participant's spinal phenotypes at the L3 to S1 levels were rated by validated scales. Specifically, IVD degeneration was graded on T2-weighted MR images by a 5-point Pfirrmann grading system [38] (Appendix S2). HIZs in the disc were graded on T2-weighted MR images and were dichotomized as presence/absence regardless of the location, shape, or signal intensity [12] (Appendix S3). The presence/absence of MCs at a given disc level was determined based on the existence of any type of MCs in adjacent vertebrae [39] (Appendix S4). The presence/absence of SNs on the caudal endplate of the upper vertebra/cephalic endplate of the lower vertebra [40] was documented (Appendix S5). Bilateral FJD was graded by a validated 4-point scale developed by Weishaupt et al. [41] (Appendix S6). FT was dichotomized as presence/absence at each level [42] (Appendix S7).

2.6 | LMM Measurements

One trained author with a physiotherapy background performed the assessments. The CSAs of bilateral LMM were manually traced according to the recommendation of previous research [43, 44] using a customized MATLAB program (R2019b, The MathWorks Inc., Natick, MA, USA) (Appendix S8). After demarcating the region of interest of bilateral LMM from the L3 to S1 levels, the program automatically measured the respective total CSA, lean muscle CSA, and intramuscular fatty infiltration. The total muscle volume was estimated based on the thickness of each slide (4 mm) multiplied by the number of slides per vertebral level (4). The percentages of fatty infiltration and lean muscle volume at L3/4, L4/5, L5/S1, L3-S1, and L4-S1 level(s) were calculated starting from the cephalic endplate of L3 to L3/4 disc to estimate L3 LMM volume using the thresholding method. The process was repeated for the other levels. The CSA for each level was measured on the slide on the caudal IVD level. To measure the intra-observer reliability of each spinal phenotype grading and LMM CSA measurement, these parameters were remeasured on the MR images of 20 randomly selected participants after 3 weeks.

2.7 | Statistical Analysis

Descriptive and frequency analyses were conducted on all data. Statistical tests were performed using SPSS software (Version 25, IBM Corp., Armonk, NY, USA). Pfirrmann grading was dichotomized as "no/mild degeneration (Grades 1–3)" and "severe degeneration (Grade 4 or 5)" [45], and MCs were dichotomized as presence/absence regardless of the type at each of the L3/4 to L5/S1 levels. FJD was dichotomized as "no/mild degeneration (Grade 0 or 1)" or "severe degeneration (Grade 2 or 3)" on both sides. Further, FJD was dichotomized as presence/absence using a cutoff of Grade 2 irrespective of right/left side [46]. Cohen's Kappa (κ) was used to evaluate the intra-rater reliability of grading spinal phenotypes [47]. The agreement was interpreted as none to slight ($\kappa = 0.01–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), good agreement ($\kappa = 0.61–0.80$), or almost perfect ($\kappa = 0.81–1.00$) [47]. The intra-class correlation

TABLE 1 | Characteristics of participants with chronic low back pain (CLBP) and asymptomatic individuals (median [interquartile range]).

Characteristics	CLBP	Asymptomatic
Age (years)	46.0 (35.8–54.0)	48.0 (30.0–54.5)
Body mass index (kg/m^2)	23.0 (21.0–25.0)	22.0 (20.0–24.0)
Gender male, *n* (%)	32 (41.0%)	36.6% (26)
Education level, *n* (%)		
Less than college	34 (44.7%)	20 (28.2%)
College or above	42 (55.3%)	51 (71.8%)
Occupation, *n* (%)		
Employed	53 (74.7%)	50 (75.8%)
Unemployed/ retired	18 (25.4%)	16 (24.2%)
Marital status, *n* (%)		
Married	49 (66.2%)	30 (47.6%)
Others	25 (33.8%)	33 (52.4%)
Smoking status, *n* (%)		
No	72 (94.7%)	69 (97.2%)
Yes	4 (5.3%)	2 (2.8%)
Alcohol use, *n* (%)		
No	54 (71.1%)	53 (74.6%)
Yes	22 (28.9%)	18 (25.4%)

Note: Married and others (unmarried/divorced/widowed). BOLD = $p < 0.05$ for comparisons between individuals with CLBP and asymptomatic participants. Calculation of *p* values was performed using Mann–Whitney *U*-test (for continuous variables) and chi-square test (for nominal and ordinal variables).

TABLE 2 | Summary of pain intensity, disability, FABQ, and insomnia scores.

Characteristics	CLBP	Asymptomatic
Pain intensity	4.2 (3.0–5.6)	0.0 (0.0–0.0)
Disability	5.5 (3.0–9.0)	0.0 (0.0–1.0)
FABQ-total	44.0 (27.0–53.0)	0.0 (0.0–22.0)
FABQ-PA	18.0 (14.0–21.0)	0.0 (0.0–11.3)
FABQ-W	22.0 (10.0–27.0)	0.0 (0.0–8.0)
ISI	12.0 (7.3–15.0)	5.0 (3.0–11.0)

Note: BOLD = $p < 0.05$ for comparisons between individuals with CLBP and asymptomatic participants.
Abbreviations: FABQ = fear-avoidance beliefs questionnaire; FABQ-PA = fear-avoidance beliefs questionnaire-physical activity; FABQ-W = fear-avoidance beliefs questionnaire-work; ISI = insomnia severity index.

coefficient (ICC), two-way random effects model, and single rater ($ICC_{2,1}$) were used to determine the intra-rater reliability of LMM CSA measurements [48, 49]. The reliability was defined as excellent (ICC > 0.90), good (ICC = 0.75–0.90), moderate (ICC = 0.50–0.75), or poor (ICC < 0.50) [49]. Chi-squared or Fisher's exact tests were used for categorical variables. To compare between-group differences in LMM parameters, linear mixed models were used after adjusting for age and sex [50]. Age and sex adjustments were conducted because they were significantly correlated with LMM parameters in people with CLBP [50]. Separate point-biserial tests were used to determine the correlation between each spinal phenotype and LBP intensity or LBP-related disability scores. Spearman's rank correlation coefficients were used to evaluate the correlations between: (1) demographic characteristics (age, gender, and body mass index) and LMM parameters; (2) FABQ or ISI scores and LBP intensity/LBP-related disability, respectively; and (3) CSA and total volume of LMM. The strength of the correlation was classified as very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), or very strong (0.80–1.00) [51]. All possible confounders (demographic characteristics, LMM parameters, FABQ scores, ISI scores, and spinal phenotypes) were assessed for their correlations with LBP intensity and/or LBP-related disability in univariable analyses. Variables with $p \leq 0.20$ were then entered into a hierarchical linear regression to evaluate which variables were independently related to LBP intensity or LBP-related disability in people with CLBP. Unstandardized regression coefficients (*B*), standard error of *B* (SE-B), standardized regression coefficient (β), and *p* values were calculated. Missing data were excluded from the analysis. The statistical significance was set at $p < 0.05$ with a 95% confidence interval (CI).

3 | Results

3.1 | Demographic Data

Demographic data and self-reported questionnaire results of 70 individuals with CLBP and 67 asymptomatic controls are shown in Table 1. There were no significant differences in age, body mass index, percentage of males, occupation (employed/[unemployed/retired)], smoking status, and alcohol use, except for education levels and marital status between groups. Excellent intra-rater reliability was noted for IVD degeneration ($\kappa = 0.86$), HIZ ($\kappa = 0.88$), MC ($\kappa = 0.91$), SN ($\kappa = 0.88$), FJD ($\kappa = 0.95$), and FT ($\kappa = 0.89$). Likewise, good intra-rater reliability of LMM CSA was noted with ICC of 0.83 (95% CI: 0.76–0.88).

3.2 | Comparisons Between Individuals With and Without CLBP

Participants with NSCLBP had significantly higher LBP intensity, RMDQ scores, FABQ scores, and ISI scores than asymptomatic controls ($p < 0.05$) (Table 2). Individuals with CLBP demonstrated significantly more severe IVD degeneration and FJD at L3/4, L4/5, and L5/S1 levels than asymptomatic controls ($p < 0.05$) (Table 3). Likewise, FT at the L5/S1 level was significantly greater in individuals with CLBP than asymptomatic controls (Table 3).

Because age and sex were significantly correlated with LMM parameters at all levels, these covariates were used in the between-group comparisons of LMM parameters.

After adjusting for age and sex, the mean total volume of LMM at the L3/4 level was significantly greater in individuals with

TABLE 3 | Between-group comparisons of spinal phenotypes.

Variables	CLBP		Asymptomatic	
	No/mild degeneration % (*n*)	Severe degeneration % (*n*)	No/mild degeneration % (*n*)	Severe degeneration % (*n*)
Pfirrmann L3/4	87.1% (61)	12.9% (9)	100% (68)	0% (0)
Pfirrmann L4/5	67.9% (53)	21.8% (17)	100% (68)	0% (0)
Pfirrmann L5/S1	62.9% (44)	37.1% (26)	98.5% (67)	1.5% (1)
	Present % (*n*)	Absent % (*n*)	Present % (*n*)	Absent % (*n*)
MC at L3/4	2.6% (2)	87.2% (68)	2.9% (2)	97.1% (66)
MC at L4/5	5.7% (4)	94.3% (66)	2.9% (2)	97.1% (66)
MC at L5/S1	5.7% (4)	94.3% (66)	7.4% (5)	92.6% (63)
	Present % (*n*)	Absent % (*n*)	Present % (*n*)	Absent % (*n*)
HIZ at L3/4	15.7% (11)	84.3% (59)	7.4% (5)	92.6% (63)
HIZ at L4/5	10.0% (7)	90.0% (63)	10.3% (7)	89.7% (61)
HIZ at L5/S1	12.9% (9)	87.1% (61)	10.3% (7)	89.7% (61)
SN at L3/4	5.7% (4)	94.3% (66)	2.9% (2)	97.1% (66)
SN at L4/5	11.4% (8)	88.6% (62)	4.4% (3)	95.6% (65)
SN at L5/S1	5.7% (4)	94.3% (66)	2.9% (2)	97.1% (66)
	No/mild degeneration % (*n*)	Severe degeneration % (*n*)	No/mild degeneration % (*n*)	Severe degeneration % (*n*)
FJD at L3/4	80.0% (56)	20.0% (14)	94.1% (64)	5.9% (4)
FJD at L4/5	57.1% (40)	42.9% (30)	92.5% (62)	7.5% (5)
FJD at L5/S1	58.6% (41)	41.4% (29)	95.5% (64)	4.5% (3)
	Present % (*n*)	Absent % (*n*)	Present % (*n*)	Absent % (*n*)
FT at L3/4	27.1% (19)	72.9% (51)	22.4% (15)	77.6% (52)
FT at L4/5	28.6% (20)	71.4% (50)	20.9% (14)	79.1% (53)
FT at L5/S1	41.4% (29)	58.6% (41)	19.4% (13)	80.6% (54)

Note: BOLD = $p < 0.05$ for comparison between individuals with CLBP and asymptomatic participants.
Abbreviations: FJD = facet joint degeneration; FT = facet joint tropism; HIZ = high-intensity zones; MC = Modic changes; SN = Schmorl's nodes.

CLBP than in asymptomatic controls ($p < 0.05$). However, there was no significant between-group difference in the total volume of LMM at L4/5, L5/S1, L3-S1, and L4-S1 levels ($p > 0.05$). Compared to asymptomatic controls, the absolute percentage of lean muscle volume of LMM at the L3-S1 region was significantly smaller in people with CLBP (Table 4).

3.3 | Correlations

3.3.1 | Correlations Between FABQ Scores, ISI Scores, and Clinical Outcomes

Pain intensity was weakly associated with FABQ-Total scores ($\rho = 0.30$, $p < 0.05$) and FABQ-Work scores ($\rho = 0.39$, $p < 0.05$), but moderately associated with ISI scores ($\rho = 0.44$, $p < 0.05$) (Table 5). RMDQ scores were positive and weakly correlated with FABQ-Total scores ($\rho = 0.34$, $p < 0.05$), FABQ-physical activity (FABQ-PA) ($\rho = 0.24$, $p < 0.05$), FABQ-Work ($\rho = 0.26$, $p < 0.05$), and ISI scores ($\rho = 0.24$, $p < 0.05$) (Table 5).

3.3.2 | Correlations Between Various Spinal Phenotypes and Clinical Outcomes

Point-biserial correlation analysis revealed that only MC at L4/5 (point-biserial = 0.26), FJD at L4/5 (point-biserial = 0.30), and FJD at L4-S1 (point-biserial = 0.28) were significantly correlated with pain intensity in individuals with CLBP. There were no significant correlations between IVD degeneration, HIZ, SN, and FT at L3/4, L4/5, L5/S1, L3-S1, and L4-S1 levels and pain intensity. Similarly, no significant correlations were found between IVD degeneration, HIZ, MC, SN, FJD, or FT and RMDQ scores (Table 6).

3.3.3 | Correlations Between LMM Parameters and Clinical Outcomes

There was no significant correlation between total volume or percentage of lean muscle volume at the L3/4, L4/5, L5/S1, L3-S1, or L4-S1 level and LBP intensity in individuals with CLBP (Table 8). Similarly, no significant correlations were found between the total volume or percentage of lean muscle volume at each of the L3 to S1 levels or L3-S1 levels and RMDQ scores in individuals with CLBP (Table 7).

3.4 | Factors Explaining Pain Intensity

A three-stage hierarchical linear regression analysis was used to predict the pain intensity reported by individuals with CLBP. In the first block, demographics were entered. Psychological variable scores and ISI scores were entered as covariates, and spinal phenotypes were entered as the primary variables of interest in the second block (Table 8). In the third block, LMM parameters were entered. FABQ-Work and ISI scores were significant covariates. For the final block, the model was statistically significant, F (5, 67) =7.359, $R^2 = 0.372$, adjusted $R^2 = 0.322$. The FABQ-Work and ISI scores together accounted for 37% of the variance of pain intensity. The variance explained by each of the two independent variables indexed by the squared semi-partial correlations was low (ISI and FABQ-Work scores accounted for approximately 8% and 9% of the variance of pain intensity, respectively).

3.5 | Factors Explaining Disability

A three-stage hierarchical linear regression analysis was also used to determine factors predicting the pain intensity reported by individuals with CLBP. In the first block, demographics were entered. In the second block, psychological variable scores, ISI scores, and spinal phenotypes were entered as a covariate. LMM parameters were entered in the third block. The regression analysis found no significant predictors of LBP-related disability.

4 | Discussion

Individuals with CLBP had significantly more severe IVD degeneration and FJD at the L3/4, L4/5, and L5/S1 levels than asymptomatic controls. Individuals with CLBP had a significantly higher frequency of FT at the L5/S1 level than asymptomatic controls. Compared to asymptomatic controls, individuals with CLBP had significantly smaller LMM lean muscle volume over the L3-S1 region. FABQ-Work scores, ISI scores, MC at the L4/5 level, and FJD at the L4/5 and L4-S1 levels separately showed significant associations with pain intensity in individuals with CLBP. After considering all these factors, only FABQ-Work and ISI scores together explained 37% of the variance of pain intensity in individuals with CLBP. No LMM characteristics nor spinal phenotypes were related to RMDQ scores.

Since IVD and facet joints form a three-joint complex at each level, they are responsible for bearing the loading of the lumbar spine [52, 53]. An abnormality in any of these three joints may overload the facet joints and IVD at the same level, accelerating the IVD degeneration, FJD, and FT, which may result in CLBP [54]. Our results supported this notion because participants with CLBP had more severe IVD and FJD at the L3/4, L4/5, and L5/S1 levels than asymptomatic controls.

4.1 | Correlations Between Spinal Phenotypes and Clinical Outcomes

Significant correlations were found between the presence of MC at the L4/5 level and pain intensity in participants with CLBP. It is noteworthy that most of the identified MCs belonged to type 1. This finding concurred with a systematic review that concluded a significant positive association between MC and CLBP [55]. The mechanical cause of MC is microtraumas of the vertebral endplates [56]. Basivertebral nerves from damaged endplates transmit nociceptive signals to the brain. As the severity of endplate defects increases, the number of nerves also increases, which may cause pain in individuals with CLBP [57–59].

At the molecular and cellular levels, granulation and fibrotic tissues have been identified in surgical specimens of MC. Granulation tissue, indicative of inflammation during active

TABLE 4 | Between-group comparisons of morphometric changes of lumbar multifidus muscle.

	CLBP ($n=70$)			Asymptomatic ($n=67$)		
Variables	**Mean**	**Right**	**Left**	**Mean**	**Right**	**Left**
CSA at L3 (mm^2)	717.40 (571.25–944.66)	706.25 (547.18–950.38)	728.85 (601.18–909.60)	613.85 (526.35–708.10)	617.90 (519.30–703.50)	594.60 (529.30–731.10)
CSA at L4 (mm^2)	1002.25 (856.08–1127.43)	1022.60 (814.93–1157.13)	980.60 (847.83–1105.56)	919.75 (828.40–1024.10)	918.30 (838.10–1031.20)	895.00 (807.10–1034.30)
CSA at L5 (mm^2)	1159.77 (993.74–1285.44)	1144.40 (986.20–1298.43)	1158.60 (952.18–1316.50)	1050.70 (976.50–1167.15)	1048.10 (960.90–1187.60)	1044.80 (976.40–1150.10)
Total volume at L3/4 (mm^3)	22 678.90 (16 486.04–33 102.76)	22 577.45 (16 514.58–30 894.75)	22 481.30 (17 500.70–31 271.73)	18 213.60 (15 215.25–21 511.75)	17 842.10 (15 487.20–21 575.50)	18 763.60 (15 491.00–21 758.50)
Total volume at L4/5 (mm^3)	31 210.15 (25 522.80–36 962.73)	31 802.50 (25 108.38–37 862.88)	30 959.90 (25 481.40–36 302.88)	27 696.15 (24 472.75–33 098.20)	27 279.20 (24 020.40–32 894.50)	27 283.80 (24 276.70–34 070.80)
Total volume at L5/S1 (mm^3)	64 319.00 (54 930.59–75 249.58)	64 525.00 (55 091.48–74 905.55)	65 126.45 (54 694.23–76 277.70)	61 946.60 (55 748.10–70 108.95)	61 207.40 (55 049.00–68 284.30)	62 910.80 (56 718.80–68 814.40)
Total volume at L4-S1 (mm^3)	92 507.75 (84 499.62–109 883.73)	92 292.45 (84 346.28–109 471.78)	91 627.60 (83 745.33–110 537.70)	91 039.85 (81 082.45–100 137.50)	89 993.20 (81 309.00–99 398.30)	91 167.20 (81 075.60–100 314.50)
Total volume at L3-S1 (mm^3)	124 777.65 (102 586.56–164 138.98)	121417.35 (101805.60–151444.90)	119665.10 (102407.50–147924.43)	114056.65 (100150.50–121445.20)	111892.10 (100514.30–120472.60)	113978.50 (99192.00–122230.90)
Lean muscle volume at L3/4 (mm^3)	17 271.13 (12 922.98–27 805.76)	16 521.65 (12 695.60–25 657.75)	18 138.85 (13 221.78–26 522.23)	15 030.05 (11 614.50–18 068.08)	14 705.30 (10 911.33–17 729.43)	15 167.60 (12 216.35–18 930.35)
Lean muscle volume at L4/5 (mm^3)	23 597.20 (18 531.34–28 230.71)	23 976.10 (17 734.90–28 326.48)	23 046.20 (18 491.10–28 705.85)	21 307.35 (17 658.30–26 735.35)	20 951.40 (16 703.10–25 887.00)	22 064.50 (18 437.10–27 095.40)
Lean muscle volume at L5/S1 (mm^3)	43 063.58 (36 955.41–56 393.11)	43 178.00 (36 050.60–57 153.43)	42 781.70 (35 668.58–57 998.33)	45 898.70 (38 592.90–52 773.75)	44 719.30 (37 862.10–51 654.30)	45 273.90 (38 297.00–53 458.40)
Lean muscle volume at L4-S1 (mm^3)	66 155.95 (54 467.08–86 062.35)	66 984.75 (54 771.63–84 092.58)	65 762.35 (54 954.18–86 916.35)	67 861.25 (57 496.90–78 326.75)	65 294.70 (56 943.10–79 652.20)	69 078.60 (58 315.50–78 229.40)
Lean muscle volume at L3-S1 (mm^3)	89 460.75 (68 443.49–127 904.65)	89 025.55 (66 849.53–120 457.70)	84 998.90 (67 701.25–124 473.33)	85 140.95 (70 528.15–99 317.10)	83 435.80 (71 000.00–97 896.30)	87 254.70 (73 099.30–99 231.20)
Percentage of lean muscle volume at L3/4 (%)	78.42 (69.04–84.30)	77.17 (68.77–84.69)	79.78 (71.07–86.26)	79.67 (75.31–85.35)	80.03 (72.63–83.47)	82.06 (77.51–87.08)

(Continues)

TABLE 4 | (Continued)

	CLBP ($n = 70$)			Asymptomatic ($n = 67$)		
Variables	**Mean**	**Right**	**Left**	**Mean**	**Right**	**Left**
Percentage of lean muscle volume at L4/5 (%)	76.62 (69.61–82.21)	75.65 (68.87–80.62)	77.45 (71.64–83.76)	78.04 (72.89–83.53)	77.10 (69.89–82.51)	79.37 (74.70–85.05)
Percentage of lean muscle volume at L5/S1 (%)	70.77 (64.16–75.36)	71.56 (64.29–75.74)	70.20 (63.14–76.03)	72.69 (65.62–80.14)	71.47 (64.15–79	72.49 (66.36–80.90)
Percentage of lean muscle volume at L4-S1 (%)	72.80 (65.80–77.77)	72.33 (66.27–77.33)	73.00 (67.33–78.44)	73.50 (67.30–81.46)	72.88 (66.50–81.03)	74.12 (68.10–81.59)
Percentage of lean muscle volume at L3-S1 (%)	73.14 (66.37–79.00)	72.73 (66.43–78.40)	74.22 (67.26–80.16)	74.60 (67.30–81.46)	73.76 (68.71–80.91)	75.91 (69.89–82.40)
Percentage of fatty infiltration in LMM at L3/4 (%)	21.58 (15.70–30.96)	22.83 (15.31–31.23)	20.22 (13.74–28.93)	20.33 (14.65–24.69)	21.66 (16.58–32.74)	18.99 (13.19–23.84)
Percentage of fatty infiltration in LMM at L4/5 (%)	23.38 (17.79–30.39)	24.35 (19.38–31.13)	22.55 (16.24–28.37)	21.96 (16.47–27.11)	23.58 (17.74–33.25)	21.45 (15.42–29.66)
Percentage of fatty infiltration in LMM at L5/S1 (%)	29.23 (24.64–35.84)	28.44 (24.26–35.71)	29.80 (23.97–36.86)	27.31 (19.86–34.38)	30.39 (20.74–37.50)	28.19 (19.81–35.96)
Percentage of fatty infiltration in LMM at L4-S1 (%)	27.19 (22.23–34.20)	27.67 (22.67–33.73)	27.00 (21.56–32.67)	26.50 (18.54–32.70)	29.11 (19.73–36.36)	26.05 (18.71–33.37)
Percentage of fat infiltration in LMM at L3-S1 (%)	26.86 (21.00–33.63)	27.27 (21.60–33.57)	25.78 (19.84–32.74)	25.40 (18.16–30.60)	27.52 (19.48–35.16)	25.04 (18.00–32.93)

Note: BOLD = $p < 0.05$ for comparison between individuals with CLBP and asymptomatic participants.

TABLE 5 | Correlation between fear-avoidance beliefs, insomnia severity index, and clinical outcomes in people with CLBP.

	FABQ-Total	FABQ-Physical Activity	FABQ-Work	Insomnia severity index
Pain intensity	**0.30**	0.04	**0.39**	**0.44**
Disability	**0.34**	**0.24**	**0.26**	**0.24**

Note: Spearman rank correlation coefficient; BOLD = $p < 0.05$.

healing, is characterized by loose extracellular matrix and myeloid cells. Conversely, fibrotic tissue, marked by high collagen content, results from ongoing healing efforts and chronic inflammation. These changes suggest that myeloid cells arise from repeated cycles of inflammation and healing [60], playing a significant role in the pain response. Targeting myeloid cell functions and their mediators offers novel therapeutic opportunities for pain management. Modulating these immune responses could alleviate chronic pain and improve treatment outcomes for patients with CLBP [61, 62]. Additionally, research indicates a subtype of MC caused by a low-grade bacterial infection within the IVD, leading to inflammation and endplate bone marrow changes in adjacent vertebral bodies [56, 63]. Oral antibiotics may be beneficial for these patients [64].

Our findings of significant correlations between FJD at L4/5 or L4-S1 levels and pain intensity in participants with CLBP align with prior findings. FJD is considered a major cause of LBP [65], as it can damage surrounding tissues and cause inflammation. This inflammation leads to increased production of inflammatory chemicals and cartilage-degrading enzymes, which stimulate joint nociceptors and cause pain [59, 66]. At the cellular level, elevated NGF (nerve growth factor) levels can sensitize nociception neurons, heightening pain afferents from degenerated facet joints [66]. Understanding the role of inflammatory mediators can guide the use of anti-inflammatory treatments, such as corticosteroids, while targeting NGF with specific inhibitors could offer a novel approach to managing pain in patients with FJD [67].

While our results substantiated the important role of FJD in individuals with CLBP, the lack of significant correlation between spinal phenotypes and LBP-related disability in our study might be partly attributed to the fact that spinal degenerative changes seen on MRI are part of the aging process that were unrelated to LBP-related disability [68]. Even though FJD might be related to LBP, the pain intensity might not be large enough to cause LBP-related disability.

4.2 | LMM Characteristics Between Individuals With and Without CLBP

Individuals with CLBP had significantly higher total fatty infiltration and smaller lean muscle volume in LMM in the L3-S1 region than asymptomatic individuals. These results concur with the findings from another study, which found that the CSA at L4/5 and L5/S1 levels in individuals with

TABLE 6 | Correlation between spinal phenotypes and clinical outcomes in people with chronic low back pain.

	Pfirrmann grading					High-intensity zones					Modic change					Schmorl's nodes					Facet joint degeneration					Facet tropism				
	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3	L4	L5	S1	L4-S1	L3	L4	L5	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1
Pain-intensity	**0.09**	−0.13	−0.04	0.13	0.03	−0.08	0.09	0.05	0.10	0.02	−0.13	**0.26**	0.06	0.04	0.15	−0.09	0.19	0.06	0.18	−0.18	0.22	−0.08	−0.13	−0.01	−0.18	0.22	−0.08	−0.13	−0.01
Disability	**0.16**	0.01	0.10	0.12	0.21	0.01	−0.05	0.06	−0.08	−0.03	−0.02	−0.07	0.11	0.19	0.00	−0.10	−0.21	0.11	0.02	−0.07	−0.00	−0.10	0.01	−0.09	−0.07	−0.00	−0.10	0.01	−0.09

Note: Spearman rank correlation coefficient; BOLD = $p < 0.05$.

TABLE 7 | Correlation between LMM parameters and clinical outcomes in people with chronic low back pain.

	Total volume					Percentage of lean muscle volume				
	L3/4	**L4/5**	**L5/S1**	**L4-S1**	**L3-S1**	**L3/4**	**L4/5**	**L5/S1**	**L4-S1**	**L3-S1**
Pain-intensity	−0.07	−0.03	−0.30	−0.04	0.02	−0.20	−0.21	−0.21	−0.22	−0.22
Disability	−0.12	0.04	−0.17	−0.13	−0.12	−0.03	−0.10	−0.19	−0.16	−0.08

Note: Spearman rank correlation coefficient.

TABLE 8 | Summary of hierarchical regression model predicting pain intensity.

Block	**Dependent variable**	R^2	**Model**	***B***	**SE-B**	***β***
1	Pain intensity	0.530	Constant			
			FABQ-Work	0.046	0.016	0.315
			Insomnia severity index	0.097	0.034	0.324
2	Pain intensity	0.610	Constant			
			FABQ-Work	0.042	0.016	0.290
			Insomnia severity index	0.093	0.033	0.308

Note: Adjusted $R^2 = 0.322$. $R^2 = 0.610$. $F(5, 67) = 7.359$; BOLD = $p < 0.05$.
Abbreviations: B = regression coefficient; β = standardized regression coefficient; FABQ = fear-avoidance beliefs questionnaire; SE-B = standard error of B.

CLBP was significantly smaller than in healthy participants [69]. The relatively more fatty infiltration and smaller lean muscle volume in participants with CLBP were noted because NSCLBP might cause diffuse LMM structural changes due to disuse/deconditioning that are not specific to a particular spinal level. Disuse of back muscles may decrease fatty acid oxidation in the muscles, which causes increased intramuscular fatty infiltration and atrophy of LMM in individuals with CLBP [70]. In addition to evaluating morphological changes of the LMM, future prospective studies should also evaluate histochemical changes and electromyographic activity of LMM to better understand the etiopathology of LMM alterations in individuals with CLBP.

4.3 | Correlations Between LMM Characteristics and Clinical Outcomes in Individuals With CLBP

Our nonsignificant associations between lean muscle volume at L3 to L5 levels and pain intensity or LBP-related disability agree with previous research [10]. Mengiardi et al. found that the percentage of fatty infiltration in LMM among 25 individuals with CLBP was unrelated to pain intensity or disability [10]. Further, the LMM thickness as measured by ultrasonography in the current cohort also found that LMM thickness at rest or during contraction was unrelated to pain or disability after adjusting for psychological variables [11]. Two earlier systematic reviews also revealed that changes in LMM resting thickness, CSA, or endurance after treatment were not associated with the corresponding changes in pain intensity or disability among individuals with LBP [6, 7]. These consistent findings suggest that morphometric characteristics (i.e., CSA, volume, and thickness) of LMM are not good imaging biomarkers for indicating the severity of symptoms and disability among individuals with CLBP. Other factors may mediate or moderate pain and disability in individuals with CLBP. While LMM did not show a significant association with clinical outcomes, changes in morphometry of other paravertebral muscles, such as the psoas muscles, may be related to clinical outcomes in individuals with CLBP [71]. Future studies should investigate the associations between the morphometric or biomechanical properties of various paravertebral muscles and LBP intensity or disability in individuals with CLBP, while controlling for psychosocial factors.

4.4 | Factors Explaining Pain Intensity and Disability in Individuals With CLBP

Prior research has shown that FABs are associated with pain intensity and LBP-related disability among individuals with CLBP [72, 73]. It is possible that pain or fear may interfere with the neural control pathway for automaticity, which may result in deficits in trunk motor control causing reduced trunk stability, which may affect daily living activities [74]. Furthermore, some individuals with CLBP believe that any painful movement may worsen their condition [75]. Therefore, they may choose to reduce movements, which in turn may lead to deconditioning/disuse of trunk muscles [76], and/or altered trunk muscle recruitment, resulting in more spinal loading [77], and increased likelihoods of LBP and disability [74].

Our results reveal a significant association between sleep, pain intensity, and LBP-related disability. This concurs with prior research indicating that sleep deprivation increases pain sensitivity and affects balance in individuals with CLBP [78–80], with those suffering from comorbid CLBP and insomnia experiencing the highest pain sensitivity [81]. Clinicians should routinely assess sleep quantity and quality in these patients and offer timely, personalized treatment [82].

4.5 | Clinical Implications

The current study found an average 1% increase in fat infiltration in the LMM of individuals with CLBP compared to asymptomatic controls, but the clinical significance of this finding is uncertain. A previous cross-sectional study involving 58 participants with and 14 without CLBP found that higher fat content in the LMM was related to greater pain intensity and disability in those with CLBP after adjusting for age, gender, BMI, physical activity, and muscle CSA [83]. However, it did not report actual LMM measurements for both groups. Another cross-sectional study involving 493 patients with CLBP found that fat infiltration in paraspinal muscles was associated with structural abnormalities in the lumbar spine, potentially affecting pain and physical function [84]. However, this study did not examine the association between muscle morphometry and clinical symptoms, nor did it include asymptomatic controls for comparison. Future large-scale studies should compare paraspinal phenotypes between individuals with and without CLBP and explore their associations with clinical symptoms.

Given the multifactorial causes of CLBP, both physical and psychological factors can affect clinical symptoms [85]. For instance, lumbar flexion range of motion and isometric lumbar muscle strength are negatively associated with RMDQ scores in individuals with CLBP [85]. A cross-sectional study revealed a significant correlation between abnormal flexion relaxation ratio/muscle variability of the erector spinae and LBP-related disability in individuals with CLBP [86]. This suggests that back muscle performance/activation, including the erector spinae, may impact physical dysfunction. Additionally, FABs, pain catastrophizing, and depression can predict pain and/or LBP-related disability levels [11, 72, 73, 87]. Patients with depression often experience greater pain intensity, increased disability, and reduced quality of life [88]. Clinicians should consider biopsychosocial factors when determining treatment options.

4.6 | Strengths and Limitations

This is the first study to determine the association between LMM parameters and pain intensity or LBP-related disability after controlling multiple factors such as demographics, psychological factors, insomnia, and spinal phenotypes in individuals with CLBP. Our findings suggest that clinicians should assess FABs and sleep disturbances in patients with CLBP during routine clinical evaluations. For patients with moderate to severe FABs or insomnia, referral for behavioral psychological interventions, such as cognitive behavioral therapy [89, 90] or acceptance and commitment therapy [91], should be considered to address their issues.

Like other studies, this study had several limitations. First, cross-sectional data could not determine the causal relationship between various spinal phenotypes or LMM characteristics and pain intensity/disability in individuals with CLBP. Future prospective studies should determine whether the presence of one or more spinal phenotypes/LMM parameters can predict pain intensity/disability in the future. Second, only 43% of individuals with CLBP had pain for more than 3 years. It remains unclear whether people with longer pain duration might have different associations between LMM characteristics and pain intensity/disability. Third, research indicates that a sedentary lifestyle is related to pain and disability in individuals with CLBP [92–94], and physical inactivity is associated with increased fatty infiltration in LMM [83]. Future studies should examine the association between LMM morphology and LBP/LBP-related disability after controlling for factors such as physical activity levels, FABQ scores, and sleep quality. Fourth, multiple correlation analyses were conducted without adjusting for multiplicity in the statistical analyses of the secondary objective. Consequently, the findings should be considered exploratory due to the potential for type I error [95]. Fifth, the current study did not include individuals aged 65 years or above. Future research should examine the morphometry of LMM and its associations with clinical outcomes while controlling for other age-related factors, such as sarcopenia or osteoporosis [96]. Sixth, individuals with neuropathic pain may experience more severe pain and disability due to somatosensory nerve lesions [97], which could affect our analysis of the association between LMM morphometry and clinical symptoms. However, the risk of having patients with neuropathic pain is low since we excluded patients with neurological deficits.

5 | Conclusions

This is the first study to evaluate the associations among various spinal phenotypes, LMM volumetric parameters, and clinical outcomes in individuals with CLBP after considering other psychological factors. Instead of comparing the CSA of LMM at a given spinal level, we evaluated the total volume and lean muscle volume of LMM at each level from L3 to S1, which were supposed to provide more comprehensive information on the LMM morphology in individuals with and without CLBP. Our results revealed that LMM characteristics and spinal degeneration (MC and FJD) were unrelated to clinical outcomes after adjusting for FABQ and ISI scores.

Author Contributions

Sabina M. Pinto and Arnold Y.L. Wong contributed to the conceptualization and research design. Sabina M. Pinto and Arnold Y.L. Wong performed the recruitment of participants and data collection. Sabina M. Pinto, Arnold Y.L. Wong, Marco Y.C. Pang, Jason P.Y. Cheung, Dino Samartzis, Jaro Karppinen, and Maryse Fortin contributed to the data analysis and interpretation of data. Sabina M. Pinto and Arnold Y.L. Wong wrote the original manuscript. All the authors critically revised the draft and approved the final submission of this manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.