

Baseline predictors of treatment response to Chinese tuina and manual physical therapy in knee osteoarthritis: a secondary analysis of a randomized controlled trial

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ABSTRACT

Introduction Although manual therapy, including traditional Chinese tuina and manual physical therapy, is generally effective for knee osteoarthritis (KOA), individual responses vary considerably. This secondary analysis aimed to identify the quantifiable baseline characteristics that predict treatment response, thereby supporting personalized care. **Methods** Data from a randomized controlled trial comparing tuina and manual physical therapy for KOA were analyzed. At week 4, 59 of 127 patients (46.5%) were responders by Outcome Measures in Rheumatology–Osteoarthritis Research Society International (OMERACT–OARSI) criteria. Candidate variables were screened by univariate analysis ($P < 0.25$). Multivariate logistic regression identified independent predictors. Internal validation used 1000 bootstrap resamples, with sensitivity analyses including least absolute shrinkage and selection operator (LASSO) and stepwise regression based on Akaike information criterion or Bayesian information criterion. **Results** Univariate analysis identified disease duration, Kellgren-Lawrence grade, prior treatment satisfaction, all Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales, numeric rating scale (NRS) pain score, 12-item short form health survey (SF-12) mental health score, functional tests, and treatment expectations as associated with response ($P < 0.25$). Multivariate logistic regression revealed two independent predictors: higher baseline WOMAC pain score (odds ratio [OR] = 1.56, 95% confidence interval [CI]: 1.31, 1.87, $P < 0.001$) and higher baseline SF-12 mental health score (OR = 1.06, 95% CI: 1.01, 1.12, $P = 0.023$). The model showed good discrimination (apparent area under the curve [AUC] = 0.838). Internal validation yielded an optimism-corrected AUC of 0.763 and Brier score of 0.169. Calibration and decision curve analyses indicated acceptable fit and net benefit. **Conclusion** Patients with more severe baseline pain and better mental health are more likely to respond favorably to either tuina or manual physical therapy. These findings bridge pain and mental health as predictors, providing evidence for precision manual therapy in KOA; external validation in larger cohorts is required.

Registration: This study was registered with ClinicalTrials.gov (<https://clinicaltrials.gov/>, NCT03966248).

KEYWORDS

knee osteoarthritis, manual therapy, predictors, pain, mental health, logistic models

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1. Introduction

Osteoarthritis of the knee is a common chronic degenerative joint disease characterized by persistent pain, joint stiffness, and progressive functional loss. It is a leading cause of reduced quality of life and disability in middle-aged and older adults.¹ Manual therapy, an important branch of non-pharmacological treatment, plays a key role in the management of knee osteoarthritis (KOA). Tuina is a form of manual therapy originating from traditional Chinese medicine (TCM), involving rhythmic compression, stretching, and manipulation of soft tissue and joints. In the context of KOA, tuina is thought to alleviate pain by improving local blood circulation, reducing inflammation, and modulating peripheral nociceptive signals. Additionally, it may enhance joint mobility and muscle function by relaxing periarticular soft tissues and activating mechanoreceptors.² A large body of clinical evidence indicates that both traditional Chinese tuina and modern manual physical therapy effectively relieve pain and improve knee function,^{3,4} and therefore they have been endorsed in several international clinical guidelines.^{5,6}

Our previous randomized controlled trial (RCT) confirmed that both

tuina therapy and manual physical therapy produced significant clinical improvements in patients with KOA.⁷ However, despite their overall effectiveness, individual responses to treatments vary greatly. This suggests that the efficacy of manual therapy arises from a complex interplay between specific effects (such as biomechanical adjustment and neurophysiological inhibition) and nonspecific effects (such as contextual and psychological factors).^{8,9} Research has begun to outline the factors influencing this system. Emotional factors (e.g., depression and anxiety) have been shown to significantly modulate pain perception and outcomes after manual intervention.¹⁰ Treatment parameters (e.g., technique type and dose) directly affect efficacy,¹¹ and enhanced interventions (e.g., combined with structured home exercises) can consolidate and improve long-term outcomes.¹² In addition, qualitative and expert consensus studies have emphasized that disease selection, patient expectations, and therapeutic relationships are crucial prognostic factors.^{13–15}

Despite everything that has been learned, a key question remains unanswered in the field of KOA: Which quantifiable baseline patient characteristics (including disease severity and physical and mental health status) can systematically predict the likelihood of responding to manual therapy? Answering this question is a prerequisite for determining whether a patient with KOA is more likely to benefit from tuina or from manual physical therapy. To address this gap, we performed a preplanned secondary analysis of data from a RCT that compared tuina and manual physical therapy. This analysis aimed to go beyond the average treatment effects, exploring how multidimen-

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sional baseline features, including pain severity, physical function, and mental health, jointly influence the final response. This was an exploratory predictor identification study rather than a validated clinical prediction model. A pre-specified statistical analysis plan was developed and is provided as supplementary material. These results provide empirical support for the development of personalized treatment decision pathways in clinical practice.

2. Methods

2.1. Study design

This was a secondary analysis of a previously-published, parallel-group RCT.⁷ Patients with KOA were allocated in a 1:1 ratio to either the tuina group or the modern manual physical therapy group using a computer-generated random sequence. Randomization was performed by an independent statistician, and allocation concealment was ensured using sealed envelopes. Owing to the nature of the interventions, the patients and therapists could not be blinded, but the outcome assessors were blinded to the group assignment. The sample size calculation for the original trial was based on the primary outcome, the total score of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), assuming $\alpha = 0.05$, $\beta = 0.2$, which required 140 patients (70 per group) to detect a minimal clinically important difference between groups. Ultimately, 127 patients with KOA completed the 4-week assessment and were included in the present study. Because this is a secondary analysis, the available sample size served as a fixed constraint inherited from the parent trial, rather than being determined by a priori power calculation.

The study was conducted in the Department of Massage and Pain Management, Dongzhimen Hospital, Beijing University of Chinese Medicine (Beijing, China) following the Declaration of Helsinki. It was approved by the Ethics Committee of Dongzhimen Hospital, Beijing University of Chinese Medicine (approval no.: DZMEC-KY-2019-06). The original trial protocol also covered this secondary analysis under the same approval number.⁷

2.2. Participants

All patients with KOA were diagnosed according to the “Guidelines for Diagnosis and Treatment of Osteoarthritis” and the clinical criteria of the American College of Rheumatology, with Kellgren-Lawrence grade II or III.^{16–18} The inclusion criteria were being 40–75 years of age, having frequent knee pain within the 3 months before screening, and having a numeric rating scale (NRS) pain score of at least 4 at enrollment. The exclusion criteria were as follows: secondary osteoarthritis, knee surgery or intra-articular injection within the previous 6 months, serious systemic diseases, contraindications to tuina or physical therapy, and pregnancy or breastfeeding. All eligible participants provided written informed consent prior to enrollment. Treatment adherence and therapist consistency were monitored weekly; detailed data are available in the original RCT.

2.3. Interventions

Both groups received a total of 8 treatment sessions over 3 weeks, with 3 sessions per week (at least one day between sessions); each session lasted 20 min. In the tuina group, patients received a standardized tuina protocol developed by a senior tuina physician with more than 20 years of experience. This protocol was performed by certified tuina therapists who received uniform training. The core techniques included kneading and rolling to relax the muscles around the knee, point pressing to stimulate key acupoints, and rocking and stretching to passively mobilize the knee joint. All manipulations were applied to the degree that the patient felt soreness, numbness, distension, or warmth, without exceeding the threshold of tolerance. In the manual physical therapy group, patients received a standardized protocol developed by an experienced physical therapist, designed to match the tuina intervention in terms of treatment time and attention but without specific traditional Chinese tuina techniques. The core techniques included soft tissue mobiliza-

tion, joint mobilization, and muscle strengthening.

After enrollment, all patients received a uniformly printed health education booklet containing information on KOA, self-management guidance, and home exercise instructions. If both knees were affected, only the more symptomatic side was treated, to ensure a consistent treatment dose. The therapists recorded adherence in both groups.

2.4. Secondary analysis design

This secondary analysis used a backward-elimination logistic regression model to explore the characteristics associated with treatment response. Responders were defined according to the Outcome Measures in Rheumatology (OMERACT)–Osteoarthritis Research Society International (OARSI) responder criteria adapted from the present data. At week 4, a responder met at least one of the following conditions: (I) the WOMAC pain subscale score or function subscale score improved by at least 50% from baseline, with an absolute improvement of at least 20 points; or (II) at least two of the following three criteria were satisfied: (a) at least 20% improvement with an absolute change of at least 10 points in WOMAC pain subscale, (b) at least 20% improvement with an absolute change of at least 10 points in the WOMAC function subscale, or (c) at least moderate improvement (score ≤ 4) on a 15-point Patient Global Impression of Change scale. The dependent variable was responder status (responder vs. non-responder).

We hypothesized that baseline characteristics might be associated with treatment response. The analyzed factors included: (I) demographic data (sex, body mass index [BMI], ethnicity, marital status, occupation, education level, history of KOA, treated side, Kellgren-Lawrence grade, previous treatments, satisfaction with previous treatment, comorbidities); (II) WOMAC scores (total, pain, stiffness, function subscales); (III) NRS pain score; (IV) functional tests (30-second sit-to-stand test, single-leg stance test, timed up-and-go test); (V) SF-12 scores (mental and physical health dimensions); and (VI) treatment group.

Week 4 was selected as the primary endpoint because it represented the end of the treatment period, reflecting the immediate effects of manual therapy. Follow-up assessments at weeks 8 and 12 had higher dropout rates (>20%) and were subject to additional confounding factors (e.g., home exercises and co-interventions); therefore, they were not used as the primary analysis time points. Sensitivity analyses using week 8 data showed a consistent direction of the effects, albeit with a reduced magnitude.

2.5. Statistical analysis

Statistical analyses were performed using R version 4.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 24.0 (IBM Corp., Armonk, NY). A complete-case analysis was performed (no missing data on key variables). Missing pattern analysis was also performed, which confirmed that the missing data were completely random. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed variables are presented as mean (standard deviation [SD]) and were compared using an independent *t*-test; non-normally distributed variables are presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney U test. Categorical variables are presented as *n* (%) and were compared using the chi-square or Fisher's exact test.

(I) Variable selection: Variables with $P < 0.25$ in univariate analysis were entered into the multivariate logistic regression model. This purposeful selection threshold followed the methodological evidence that a traditional significance level of 0.05 may fail to identify important variables.^{19,20} This approach has been adopted in previous KOA prediction studies.²¹ In addition, age, BMI, and comorbidity count were forced into the model as predefined clinically important confounders regardless of their univariate *P*-values. Multicollinearity was assessed using the variance inflation factor (VIF), with a VIF < 5 considered acceptable.

(II) Linearity assumption: The linearity assumption for the continuous predictors was examined using restricted cubic splines (four knots). When significant nonlinearity was detected ($P < 0.05$), the variable was retained

using spline transformation.

(III) Model building: A backward stepwise elimination method (removal criterion, $P > 0.05$) was used to construct the final multivariate logistic regression model. Sensitivity analyses were conducted using least absolute shrinkage and selection operator (LASSO) regression (10-fold cross-validation) and stepwise regression based on Akaike information criterion (AIC) or Bayesian information criterion (BIC) to confirm the robustness of the variable selection.

(IV) Internal validation: To avoid overfitting, internal validation was performed using bootstrap resampling with 1000 iterations; the optimism-corrected C-index (AUC) and a calibration plot were derived. The Brier score was calculated as an overall measure of the prediction error.

Clinical utility decision curve analysis was used to evaluate the net clinical benefit across clinically reasonable threshold probabilities (20%–50%). All statistical tests were two-sided, and $P < 0.05$ was considered statistically sig-

nificant.

3. Results

3.1. Study population and univariate analysis

A total of 127 patients with KOA were included in the secondary analysis. Among them, 59 (46.5%) were classified as treatment responders and 68 (53.5%) as non-responders at week 4. Table 1 compares the baseline demographic and clinical characteristics of the responders and non-responders. Univariate analysis (Table 1) showed that several variables were associated with treatment response at the $P < 0.25$ level: disease duration, Kellgren-Lawrence grade, previous treatment satisfaction, all WOMAC subscale scores (total, pain, stiffness, function), NRS pain score, SF-12 mental health score, 30-second sit-to-stand test times, timed up-and-go test time, and treatment

Table 1 Univariate analysis of baseline characteristics between responders and non-responders

Variable	Non-responder (<i>n</i> = 68)	Responder (<i>n</i> = 59)	Total (<i>n</i> = 127)	OR (95% CI)	Test statistic (<i>t/z/χ</i> ²)	<i>P</i>
Treatment group, <i>n</i> (%)					0.009	0.924
Tuina	34 (50.0)	29 (49.2)	63 (49.6)	Ref.		
mPT	34 (50.0)	30 (50.8)	64 (50.4)	0.967 (0.481, 1.942)		
Age, median (IQR), y	62.93 (58.03, 68.74)	63.77 (59.15, 69.10)	63.18 (58.30, 68.74)	1.005 (0.961, 1.052)	−0.331	0.741
Female, <i>n</i> (%)	51 (75.0)	45 (76.3)	96 (75.6)	0.933 (0.414, 2.104)	0.028	0.868
BMI, median (IQR), kg/m ²	24.89(23.52, 26.57)	25.26 (22.89, 26.90)	25.06 (23.39, 26.81)	1.029 (0.917, 1.155)	−0.181	0.856
Ethnicity, <i>n</i> (%)					0.026	0.871
Han	66 (97.1)	56 (94.9)	122 (96.1)	Ref.		
Minority	2 (2.9)	3 (5.1)	5 (3.9)	0.566 (0.091, 3.506)		
Disease duration, median (IQR), m	37 (25, 87)	49 (25, 100)	42 (25, 92)	1.003 (0.996, 1.010)		0.188
KL grade, <i>n</i> (%)					1.585	0.208
Kellgren II	41 (60.3)	29 (49.2)	70 (55.1)	Ref.		
Kellgren III	27 (39.7)	30 (50.8)	57 (44.9)	0.637 (0.315, 1.288)		
Comorbidities, <i>n</i> (%)					2.888	0.409
0	34 (50.0)	22 (37.3)	56 (44.1)	Ref.		
1	19 (27.9)	23 (39.0)	42 (33.1)	1.078 (0.234, 4.973)		
2	10 (14.7)	11 (18.6)	21 (16.5)	2.018 (0.426, 9.553)		
≥3	5 (7.4)	3 (5.1)	8 (6.3)	1.833 (0.346, 9.719)		
Education, <i>n</i> (%)					1.587	0.452
High school or below	30 (44.1)	28 (47.5)	58 (45.7)	Ref.		
College	32 (47.1)	29 (49.2)	61 (48.0)	2.800 (0.521, 15.041)		
Higher degree	6 (8.8)	2 (3.4)	8 (6.3)	2.719 (0.508, 14.549)		
Occupation, <i>n</i> (%)					2.411	0.300
Employed	31 (45.6)	33 (55.9)	64 (50.4)	Ref.		
Retired	31 (45.6)	24 (40.7)	55 (43.3)	3.194 (0.599, 17.028)		
Other	6 (8.8)	2 (3.4)	8 (6.3)	2.323 (0.430, 12.546)		
Marital status, <i>n</i> (%)					0.009	0.923
Married	62 (91.2)	55 (93.2)	117 (92.1)	0.752 (0.202, 2.803)		
Previous treatments, <i>n</i> (%)						
Medication	60 (88.2)	49 (83.1)	109 (85.8)	1.531 (0.561, 4.175)	0.698	0.403
Interventional	36 (52.9)	29 (49.2)	65 (51.2)	1.164 (0.579, 2.339)	0.181	0.670
Physiotherapy	38 (55.9)	34 (57.6)	72 (56.7)	0.931 (0.461, 1.883)	0.039	0.843
Other	4 (5.9)	5 (8.5)	9 (7.1)	0.675 (0.173, 2.640)	0.049	0.825

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Variable	Non-responder (<i>n</i> = 68)	Responder (<i>n</i> = 59)	Total (<i>n</i> = 127)	OR (95% CI)	Test statistic (<i>t/z/χ</i> ²) <i>P</i>
Satisfaction with previous treatment, median (IQR)	5.00 (3.00, 6.00)	5.00 (4.00, 6.00)	5.00 (3.00, 6.00)	1.141 (0.973, 1.338)	−1.318 0.187
WOMAC, median (IQR)					
Total	12.00 (7.00, 18.00)	20.00 (14.00, 32.00)	15.00 (10.00, 27.00)	1.065 (1.030, 1.102)	−4.465 <0.001
Pain	3.00 (2.00, 5.00)	5.00 (3.00, 8.00)	4.00 (2.00, 6.00)	1.425 (1.212, 1.676)	−5.182 <0.001
Stiffness	1.00 (0.00, 2.00)	2.00 (0.00, 4.00)	1.00 (0.00, 2.00)	1.466 (1.155, 1.861)	−2.975 0.003
Function	7.50 (5.00, 13.00)	13.00 (9.00, 21.00)	10.00 (6.00, 19.00)	1.071 (1.027, 1.117)	−3.858 <0.001
NRS pain score, median (IQR)	5.00 (4.00, 7.00)	6.00 (5.00, 7.00)	5.50 (4.50, 7.00)	1.353 (1.064, 1.719)	−2.367 0.018
SF-12					
Physical health, mean (SD)	38.31 (7.55)	36.84 (8.53)	37.62 (8.02)	0.977 (0.935, 1.021)	1.033 0.304
Mental health, median (IQR)	50.13 (41.40, 57.89)	53.19 (44.18, 59.90)	50.83 (42.77, 59.26)	1.023 (0.987, 1.060)	−1.259 0.208
30-second sit-to-stand, mean (SD), rep	11.53 (3.53)	10.31 (3.64)	10.96 (3.62)	0.907 (0.820, 1.004)	1.920 0.057
Timed up-and-go, median (IQR), s	10.65 (9.08, 12.40)	11.12 (9.83, 13.82)	10.96 (9.36, 12.57)	1.182 (1.024, 1.365)	−1.936 0.053
Single-leg stance, median (IQR), s	21.40 (9.1525, 30.00)	19.58 (7.15, 30.00)	19.58 (8.11, 30.00)	0.992 (0.960, 1.025)	−0.848 0.396
Target knee, <i>n</i> (%)					0.009 0.924
Left	34 (50.0)	29 (49.2)	63 (49.6)	Ref.	
Right	34 (50.0)	30 (50.8)	64 (50.4)	0.967 (0.481, 1.942)	
Credibility/expectation questionnaire, median (IQR)					
Credibility	0.21 (−0.46, 0.66)	0.25 (−0.40, 0.83)	0.25 (−0.40, 0.75)	1.241 (0.789, 1.952)	−0.913 0.361
Expectation	−0.01 (−1.19, 0.58)	−0.01 (−0.60, 1.17)	−0.01 (−0.96, 0.58)	1.295 (0.910, 1.842)	−1.583 0.113

Notes: BMI: body mass index; CI: confidence interval; IQR: interquartile range; KL: Kellgren-Lawrence grade; m: month; mPT: manual physical therapy; *n*: number; NRS: numeric rating scale; OR: odds ratio; Ref.: reference; rep: repetition; s: second; SD: standard deviation; SF-12: 12-item short form health survey; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; *y*: year. OR values were obtained from univariate logistic regression for each individual variable. For continuous variables, the OR represents the change in odds per unit increase.

expectation. Importantly, the treatment group (tuina vs. manual physical therapy) did not differ significantly between responders and non-responders (tuina, 49.2% vs. manual physical therapy, 50.8%; $P = 0.924$). Other factors such as age, sex, BMI, ethnicity, marital status, education level, number of comorbidities, previous specific treatments (medication, interventional procedures, physical therapy, others), and SF-12 physical health score were not significantly associated ($P \geq 0.25$).

3.2. Multivariate logistic regression analysis

The 12 candidate variables identified by univariate analysis ($P < 0.25$) were entered into a multivariate logistic regression model. All variance inflation factors were below 5, indicating no serious multicollinearity. Table 2 presents three logistic regression models (unadjusted, minimally adjusted, and fully adjusted); the fully adjusted model (Model 3) was the final model, which identified two independent significant predictors: higher baseline WOMAC pain subscale score (odds ratio [OR] = 1.56, 95% confidence interval [CI]: 1.31, 1.87, $P < 0.001$) and higher baseline SF-12 mental health score (OR = 1.06, 95% CI: 1.01, 1.12, $P = 0.023$). After adjusting for other confounders, patients with more severe baseline pain (higher WOMAC pain score) and better baseline mental health (higher SF-12 mental score) were more likely to respond to treatment (tuina or manual physical therapy). Other variables, including disease duration, Kellgren-Lawrence grade, previous treatment satisfaction, WOMAC function and stiffness subscales, NRS pain score, functional tests (30-second sit-to-stand, timed up-and-go), and treatment expectation, did not show independent predictive values ($P > 0.05$).

3.3. Nonlinearity and interaction

Restricted cubic spline analysis revealed that the relationship between baseline WOMAC pain score and the log odds of response was significantly nonlinear (overall $P = 0.0001$, nonlinear component $P = 0.0215$). The associa-

tion between SF-12 mental health score and response was linear ($P > 0.05$). An exploratory interaction test (without splines) suggested a significant multiplicative interaction between WOMAC pain and SF-12 mental health ($P = 0.028$), but this interaction was not included in the final model to avoid overfitting due to the limited sample size.

The VIF values for all candidate variables are provided in Table 3. The VIF was 2.75 for WOMAC pain and 1.21 for NRS pain, both well below the threshold of 5, indicating no problematic multicollinearity. To further assess the specificity of pain measures, we also conducted a principal component analysis which combined WOMAC pain and NRS pain into a single component (explaining 81.5% of variance); the model based on this analysis yielded consistent results (data not shown).

The stepwise elimination process, which shows the order and AIC changes at each step, is presented in Table 4. The final model retained WOMAC pain and SF-12 mental health with an AIC of 147.6.

3.4. Model evaluation

The final multivariate logistic regression model incorporated a restricted cubic spline for WOMAC pain (4 knots, nonlinear component, $P = 0.0215$) and linear terms for the other variables. The model demonstrated good goodness-of-fit (Hosmer–Lemeshow $P = 0.284$). The discriminative ability was acceptable, with an apparent AUC of 0.838 (95% CI: 0.765, 0.911). Internal validation using 1000 bootstrap resamples yielded an optimism-corrected AUC of 0.763. The calibration plot showed a good agreement between the predicted and observed probabilities (Figure 1). The Brier score was 0.169, and decision curve analysis indicated a positive net benefit across clinically reasonable threshold probabilities (20%–50%) (Figure 2). Sensitivity analyses using LASSO and stepwise regression consistently identified the WOMAC pain and SF-12 mental health scores as the most important predictors (Table 5). LASSO regression (lambda.min) selected WOMAC pain, SF-12 mental

Table 2 Multivariable logistic regression models predicting treatment response

Variable	Model 1 (unadjusted, OR, 95% CI)	Model 2 (minimally adjusted, OR, 95% CI)	Model 3 (fully adjusted, OR, 95% CI)
Predictors			
WOMAC pain score	1.55 (1.31, 1.84)***	1.57 (1.32, 1.88)***	1.56 (1.31, 1.87)***
SF-12 mental health score	1.07 (1.02, 1.12)**	1.07 (1.02, 1.12)**	1.06 (1.01, 1.12)*
Age	—	0.98 (0.93, 1.03)	0.98 (0.92, 1.03)
BMI	—	1.03 (0.90, 1.18)	1.01 (0.88, 1.16)
Comorbidity (ref. = 0)	—	—	—
1			1.47 (0.57, 3.86)
2			1.53 (0.44, 5.71)
3			2.17 (0.17, 26.6)
4			0.37 (0.01, 4.45)
Previous treatment satisfaction	—	—	1.13 (0.93, 1.39)
Model fit statistics			
Hosmer-Lemeshow P	0.402	0.311	0.284
AUC (apparent)	0.828	0.836	0.838
Brier score	—	—	0.169

Notes: AUC: area under the receiver operating characteristic curve; BMI: body mass index; CI: confidence interval; OR: odds ratio; ref: reference; SF-12: 12-item short form health survey; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. For continuous variables (WOMAC pain, SF-12 mental health, age, BMI, previous treatment satisfaction), the OR represents the change in the odds of being a responder for each one-unit increase in the variable. For the categorical variable comorbidity, the OR for each level is compared with the reference group (ref. = 0, i.e., no comorbidities). **P* < 0.05; ***P* < 0.01; ****P* < 0.001. “—” indicates the variable was not included in the model. Model 1: unadjusted; Model 2: adjusted for age and BMI; Model 3: adjusted for age, BMI, comorbidities, and previous treatment satisfaction. The three models are presented separately to show the stability of the predictors under different adjustment sets, not for direct comparison between models.

Table 3 Variance inflation factor values

Variable	VIF
Disease duration	1.212
Satisfaction with previous treatment	1.109
NRS pain score	1.216
30-second sit-to-stand	1.496
Timed up-and-go	1.162
WOMAC pain scores	2.753
WOMAC stiffness scores	1.821
WOMAC function scores	3.066
SF-12 mental health	1.208
Expectation	1.091
KL grade	1.248

Notes: KL: Kellgren-Lawrence; NRS: numeric rating scale; SF-12: 12-item short form health survey; VIF: variance inflation factor; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

health, previous treatment satisfaction, and expectation. AIC-based stepwise regression also retained expectation (*P* = 0.073), while BIC-based stepwise regression selected only WOMAC pain and SF-12 mental health, confirming the robustness of the two main predictors. The intercept (constant) of the final logistic model was −2.874. As shown in Table 2, the AUC values for the unadjusted, minimally adjusted, and fully adjusted models were 0.828, 0.836, and 0.838, respectively, indicating that the adjustment for confounders did not materially alter model discrimination.

4. Discussion

In this secondary analysis of a RCT comparing tuina and manual physical therapy for KOA, we identified the baseline WOMAC pain score and SF-12 mental health score as independent predictors of treatment response. This

Table 4 Backward stepwise elimination process (removal criterion *P* > 0.05)

Step	Variable removed	Remaining variables	AIC
0	—	12	158.2
1	30 sec sit to stand	11	156.5
2	KL grade	10	155.0
3	Timed up-and-go	9	153.8
4	Disease duration	8	152.4
5	NRS pain score	7	151.0
6	Age	6	149.7
7	BMI	5	148.3
8	Comorbidity	4	147.0
9	Previous treatment satisfaction	3	146.2
10	Expectation	2	147.6 (final model)

Notes: AIC: Akaike information criterion; BMI: body mass index; KL: Kellgren-Lawrence; NRS: numeric rating scale; sec: second. “—” indicates the variable was not included in the model.

finding has important clinical implications and offers novel insights from the perspective of integrated traditional Chinese and Western medicine.

4.1. Interpretation of main findings and scientific basis

Patients with more severe baseline pain (higher WOMAC pain score) showed better response to either tuina or manual physical therapy. This aligns with the clinical intuition that more severe conditions require stronger interventions and yield greater absolute benefits. In TCM, KOA belongs to the category of *Bi* pattern (related to rheumatic diseases), with the core pathogenesis being “meridian blockage and qi-blood stagnation.”²² As stated in the *Yellow Emperor’s Canon of Medicine* (*Huang Di Nei Jing*), “Obstruction leads

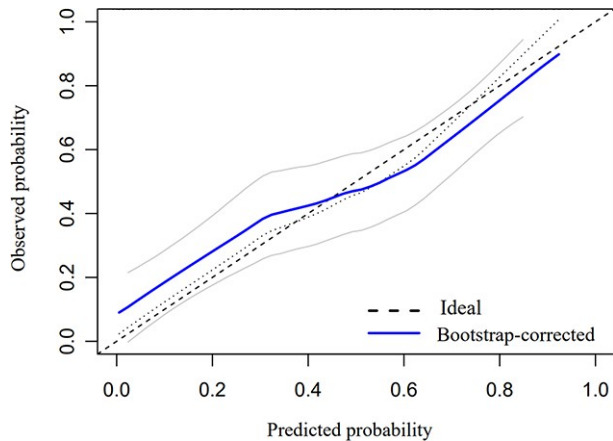


Figure 1 Calibration plot comparing observed and predicted probabilities for treatment response in Model 3

Notes: Model 3 was adjusted for age, body mass index, comorbidities, and previous treatment satisfaction. The diagonal dashed line represents ideal calibration (observed probability = predicted probability). The solid line represents the bootstrap-corrected calibration curve, with gray lines indicating 95% confidence intervals.

Hosmer–Lemeshow $P = 0.284$ indicates good model calibration.

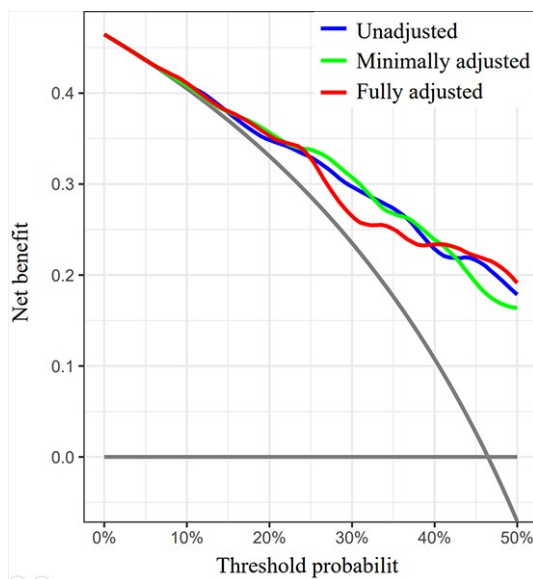


Figure 2 Decision curve analysis comparing the net benefit of three logistic regression models for predicting treatment response

to pain, and pain indicates obstruction.” Severe baseline pain reflects a pronounced state of blockage. Tuina, by promoting qi circulation, activating blood, and relaxing meridians, can effectively break up the entrenched pathogenic factors, restore the flow of qi and blood, and thus produce a notable “free flow stops pain” effect.^{13,23} In other words, the stronger the

pathogenic factor, the greater the applicability and apparent effect of this external therapy. From a modern medical perspective, higher baseline pain levels are often associated with more pronounced peripheral and central sensitization.²⁴ Manual therapy has been shown to modulate descending pain inhibitory pathways, reduce pro-inflammatory cytokine levels, and improve local tissue mechanical properties.²⁵ For patients with more severe sensitization, these modulatory effects may produce larger absolute gains, translating into a better treatment response.²⁶ Basic research has also demonstrated that acupoint pressing around the knee can significantly improve pain and depression in a rat model of KOA, while promoting the expression of postsynaptic density protein 95 and synaptophysin and protecting neurons and synapses in the anterior cingulate cortex.²⁷

Another key finding was that patients with better baseline mental health (higher SF-12 mental health scores) were more likely to benefit from treatment. These findings highlight the central role of psychological factors in the rehabilitation of patients with somatic diseases. TCM emphasizes the unity of physical “form” and mental-emotional “spirit”, proposing a dynamic and reciprocal interaction between the body and mind.^{28,29} The Classified Classic (*Lei Jing*), a Ming-dynasty medical text compiled by Zhang Jingyue (1563–1640), systematically reorganized and annotated the *Yellow Emperor's Canon of Medicine*, “in acupuncture, the essence is to first regulate the spirit (mind).” Whether the “spirit” of the patient is calmed and free directly influences the circulation of qi and blood, as well as the therapeutic effect. Patients who are mentally healthy and emotionally stable have a well-regulated qi mechanism, which better facilitates the treatment and allows the induced “de qi (qi arrival)” sensation and physiological effects to fully unfold: a concept known as “spirit driving qi.”³⁰ Conversely, patients with depression or anxiety may have liver-qi stagnation and disordered qi movement, which are associated with poorer treatment outcomes.^{31,32} Moreover, studies have shown that pain during physical activity is associated with neural characteristics indicating a lack of compensatory pain mechanisms (reduced cortical inhibition, elevated β -band oscillations, and conditioned pain modulation deficits); unlike resting pain measured by visual analogue scale, this is mainly related to the dysfunction of emotional circuits.³³ Within the modern psychosomatic medicine framework, better mental health generally implies less pain catastrophizing,³⁴ higher self-efficacy,³⁵ and better treatment adherence. These factors have been shown to positively modulate pain perception and processing in the brain, enhance placebo effects,³⁶ and encourage patients to continue home exercise programs, thereby collectively improving overall treatment outcomes. Although we used baseline mental health to predict subsequent responses, the relationship may be bidirectional. Future studies using cross-lagged or mediation analyses are needed to clarify causality. However, these mechanistic interpretations remain speculative, requiring further empirical investigation in future studies.

4.2. Comparison with previous studies

Our findings regarding baseline pain align with previous research. For example, several studies on physical therapy and nonsteroidal anti-inflammatory drugs for KOA have also reported baseline pain severity as a predictor of positive outcomes,^{37–39} although it should be noted that those studies mainly involved drug or surgical treatments, so comparisons should be made with caution. Regarding psychological factors, a systematic review indicates that pretreatment depression and anxiety are strong predictors of poor prognosis in patients with KOA,⁴⁰ which logically aligns with our finding that better

Table 5 Sensitivity analyses: variables selected by different methods

Method	Selected variables
LASSO (lambda.min)	WOMAC pain, SF-12 mental health, previous treatment satisfaction, expectation
AIC stepwise	WOMAC pain, SF-12 mental health, expectation
BIC stepwise	WOMAC pain, SF-12 mental health

Notes: AIC: Akaike information criterion; BIC: Bayesian information criterion; LASSO: least absolute shrinkage and selection operator; SF-12: 12-item short form health survey; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

mental health predicts a better response.

Conversely, other studies have found that lower baseline pain is associated with better functional improvement,^{41,42} or have found no association between psychological factors and outcomes.⁴³ These discrepancies may arise from differences in study populations, interventions (e.g., surgery vs. conservative care), outcome definitions, and statistical models. The present study focused on two manual therapies, the mechanisms of which may rely more on holistic neurophysiological regulation than those of drugs or surgery. Therefore, our results highlight that the predictors may be treatment-specific.

4.3. Strengths and limitations

The strengths of this study include the use of high-quality data from a methodologically rigorous RCT, adoption of the widely accepted OMERACT-OARSI criteria to define treatment response (enhancing clinical relevance), and a comprehensive statistical analysis that followed prediction modeling standards, including collinearity diagnostics and model performance evaluation.

Several limitations must be acknowledged. First, this was a single-center study with a relatively small sample size (59 respondents, 12 candidate variables). The events per variable ratio was approximately 4.9, below the recommended range of 10–15, which increases the risk of overfitting. Although we performed internal validation and sensitivity analyses, external validation in larger multicenter cohorts is required. Second, the follow-up duration was only 4 weeks, which captures the immediate treatment effect, but does not address the long-term stability of the response. Third, we did not measure some potentially important confounders, such as pain catastrophizing, social support, coping strategies, and therapeutic alliance. Fourth, owing to the exploratory nature and limited sample size, we did not derive clinical cutoff values or calculate the Net Reclassification Improvement/Integrated Discrimination Improvement; these will be addressed in future validation studies. Fifth, as a secondary analysis, causal inference is limited, and all findings should be interpreted as associations.

4.4. Implications for clinical practice and future research

Our findings have important implications for advancing the precision management of KOA. In clinical practice, physicians and therapists can easily use baseline pain scores and mental health screening tools to quickly identify the patients with KOA who are most likely to benefit from tuina or manual physical therapy. This can help allocate healthcare resources efficiently and provide patients with more personalized prognostic counseling. In future studies, we recommend the development and validation of a clinical prediction model that integrates pain, mental health, and other key baseline characteristics. Further investigation into the neurobiological mechanisms by which manual therapy modulates pain-emotion interactions is warranted, using neuroimaging techniques to provide evidence for the modern scientific understanding of the “unity of form and spirit.” Finally, targeted strategies (e.g., combining cognitive-behavioral therapy) should be designed and evaluated to improve treatment outcomes in patients with poor mental health.

5. Conclusion

This exploratory secondary analysis suggests that patients with more severe baseline pain and better baseline mental health may respond better to either tuina therapy or manual physical therapy for KOA. These findings provide preliminary evidence for precision manual therapy. However, confirmation in large-scale multicenter external validation studies is required. Future research should aim to validate this prediction model in broader populations and explore the underlying biological mechanisms, ultimately enabling individualized treatment and enhancing the scientific basis and clinical effectiveness of non-pharmacological therapies.

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Data Availability

Additional data related to this paper may be obtained from the corresponding author upon reasonable request.

Author Contribution Statement

Ying Wang: Software, formal analysis, writing – original draft, visualization, and writing – review & editing. **Xi-you Wang:** Methodology, visualization, funding acquisition, project administration, and writing – review & editing. **Ya-nan Sun:** Formal analysis and writing – review & editing. **Chang-he Yu:** Conceptualization, formal analysis, supervision, funding acquisition, project administration, and writing – review & editing.

Use of AI Statement

None.

Declaration of Competing Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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