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Five-Year Matched Cohort Evaluation of the Relationship between Traditional Chinese Medicine and Osteoarthritis Outcomes

Markus Huber[1], Florian Meier[1], Tobias König[1]*

[1]Department of Clinical Systems Medicine, Faculty of Medicine, University of Zurich, Zurich, Switzerland

***E-mail** ✉ tobias.koenig.med@gmail.com

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ABSTRACT

This study aimed to clarify how Traditional Chinese Medicine (TCM) influences several key outcomes in individuals diagnosed with osteoarthritis (OA), including pain relief, risk of hospital readmission, and likelihood of undergoing joint replacement. Patterns of Chinese herbal medicine (CHM) prescriptions were further explored to verify their connection with patient prognosis and overall quality of life.A retrospective cohort of 3,850 inpatients with OA admitted between January 2018 and December 2022 was identified through the hospital's HIS database. Propensity score matching (PSM) was applied to balance baseline characteristics between comparison groups. A Cox proportional hazards model was utilized to quantify the effect of clinical and treatment-related factors on pain deterioration, readmission risk, and incidence of joint replacement. Kaplan–Meier survival analysis was performed to compare outcomes across different durations of TCM exposure. Additionally, data mining techniques—including association rule analysis, clustering, and random walk algorithms—were incorporated to evaluate the therapeutic role of TCM.TCM was used by 67.01% of OA patients (2,511/3,747). Following PSM, 1,228 TCM users were matched with 1,228 non-users. Rates of pain exacerbation, hospital readmission, and joint replacement were significantly higher in the non-TCM cohort than in TCM users ($p < 0.05$). According to the Cox model, TCM served as an independent protective variable. Relative to non-users, patients receiving TCM demonstrated a 58.4% reduction in pain deterioration, a 51.1% decrease in readmissions, and a 42% lower likelihood of joint replacement. Furthermore, individuals with prolonged exposure to TCM (＞24 months) exhibited substantially fewer adverse outcome events than those with shorter exposure (≤24 months). Mining analyses additionally indicated that TCM interventions were associated with improvements in immune-inflammatory markers, VAS scores, and SF-36 quality-of-life metrics.TCM appears to function as a significant protective intervention for individuals with OA, with extended herbal medicine use conferring even greater prognostic benefits.

Keywords: Random walking, Traditional Chinese medicine, Osteoarthritis, Data mining, Cohort study

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Introduction

Osteoarthritis (OA) is a progressive degenerative disorder of the joints [1], arising from a complex interplay of mechanical stress, inflammatory processes, aging, and metabolic imbalances, ultimately leading to joint deterioration, functional impairment, and persistent pain [2, 3]. Conventional management strategies include nonsteroidal anti-inflammatory drugs (NSAIDs), glucosamine, and other analgesics [4], whereas joint replacement remains the definitive option for patients with severe, treatment-resistant pain [5]. With global trends showing increases in aging populations and obesity, OA prevalence is expected to rise, posing a major public health burden [6]. The disease often results in pain, restricted mobility, deformities, and reduced quality of life, causing significant physical and psychological distress.

Inflammatory pathways are central to OA progression [7], triggering cascades of cellular and molecular responses. Cytokines such as IL-1β, TNF-α, and IL-6 are implicated in OA-associated pain by interacting with peripheral sensory nerves [8]. Traditional Chinese Medicine (TCM) has been shown to modulate both cellular and

extracellular inflammatory responses, including the suppression of proinflammatory cytokines like ILs and TNF [9, 10]. Chinese herbal medicine (CHM), a cor

nerstone of TCM, has demonstrated benefits in reducing pain scores measured by the visual analogue scale (VAS) and improving physical function, making it a widely used intervention in OA [11]. Although numerous systematic reviews and randomized controlled trials support the efficacy and safety of CHM in OA treatment [12–14], there is limited research on how specific prescription patterns or treatment routines influence patient-reported outcomes such as VAS and SF-36 scores.

In light of these gaps, this single-center, retrospective cohort study employed advanced data mining approaches to investigate the impact of CHM on OA outcomes, including pain progression, hospital readmissions, and joint replacement. Methods such as cluster analysis, association rule mining, network visualization, propensity score matching, and random walk models were applied to explore prescribing patterns and link them with both clinical outcomes and quality of life, offering a comprehensive evaluation of CHM's therapeutic potential in OA management.

Materials and Methods

Data source and participants

The study was conducted in accordance with the Declaration of Helsinki. Telephone-based follow-up ensured confidentiality and did not affect ongoing patient treatment. The patient selection process is summarized in **Figure 1.**

Following approval from the Institutional Review Board, electronic health records from 3,850 OA patients admitted to the First Affiliated Hospital of Anhui University of Chinese Medicine between January 2018 and December 2022 were retrospectively analyzed. Ethics approval was granted by the hospital's review board (Review No. 2022MCZQ01), with informed consent waived due to the use of de-identified secondary data.

Inclusion criteria were: (1) meeting the 2018 Chinese Medical Association Orthopaedic Society guidelines for OA diagnosis and treatment [15]; (2) consent to participate and undergo regular follow-up; and (3) exclusive use of oral CHM without additional interventions such as topical proprietary medicines or needle-knife therapy.

A total of 103 patients were excluded for the following reasons: presence of other rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, spondyloarthritis, or secondary rheumatic conditions due to endocrine, infectious, or neoplastic diseases; n = 20), age under 45 or over 75 (n = 13), severe comorbidities affecting cardiovascular, respiratory, hematopoietic, or other organ systems (n = 50), and incomplete clinical data (n = 20). After exclusions, 3,747 OA patients remained for analysis.

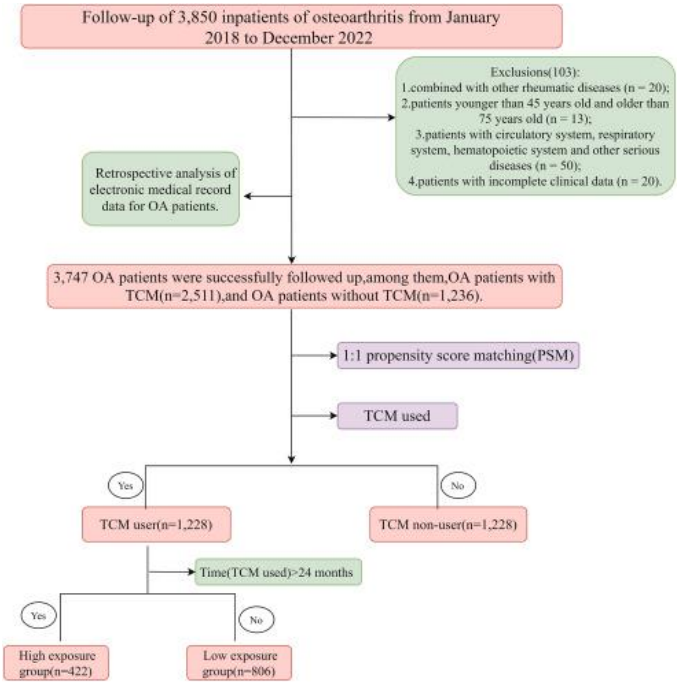


Figure 1. Flowchart of the study.

Use of CHM (Exposure)

Patients were categorized into TCM users and non-users through a structured procedure. Initially, inpatient medical records for OA patients were extracted from the hospital information system (HIS), including demographic data, contact information, diagnostic details, CHM prescriptions, and co-morbidities. These records were subsequently verified through telephone follow-ups, which collected additional information on essential medications and their durations, CHM use and duration, underlying health conditions, and clinical outcomes. Patients who received TCM treatment for at least 30 days during the follow-up period were classified as TCM users (n = 2,511), while those who did not meet this criterion were assigned to the TCM non-user group (n = 1,236). Propensity score matching (PSM) was then employed to balance baseline characteristics, resulting in 1,228 matched pairs of TCM users and non-users for the final analysis. All CHM prescriptions were managed by specialized Chinese medicine rheumatologists trained in both traditional and modern medical practices [16].

To explore the dose-response relationship, TCM users were further divided based on treatment duration using a sensitivity analysis: the high-exposure group (>24 months) and the low-exposure group (≤24 months). Data mining techniques were also applied to evaluate the effects of specific CHM formulations reported to alleviate OA symptoms.

Assessment of OA patient outcomes

During baseline and follow-up assessments, participants were queried about joint pain affecting the hips, knees, or hands using the question: “During the past 12 months, have you experienced pain, stiffness, or soreness in or around your hand, hip, or knee joints on most days?” Pain severity was quantified using the Visual Analogue Scale (VAS), ranging from 0 cm (no pain) to 10 cm (maximum pain) [17]. Follow-ups were conducted by rheumatology specialists, with each assessment performed by one physician and supervised by two others to ensure accuracy.

The primary outcomes analyzed were: (1) pain worsening, defined as either a ≥14% increase in VAS from baseline or new onset of joint pain during follow-up [18, 19]; (2) increased joint pain resulting in hospital readmission; and (3) joint replacement surgery.

Covariates

Potential confounding variables were identified and collected from medical records, patient-reported outcomes (PROs), and medication histories. Demographic factors included age, sex, and body mass index (BMI), while clinical variables encompassed immune-inflammatory indices, VAS scores, and the Short Form-36 (SF-36) health survey. The SF-36, Danish version, evaluates health-related quality of life across eight domains—physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH)—scored from 0 (maximal impairment) to 100 (no impairment) [20, 21]. Co-morbidities were considered present if diagnostic codes were recorded prior to OA diagnosis, including osteoporosis, hyperlipidemia, hyperuricemia, chronic gastritis, diabetes, fatty liver, cerebrovascular disease, hypertension, and coronary artery disease. Use of Western medications, such as NSAIDs (meloxicam, celecoxib, lornoxicam) and glucosamine, between the initial diagnosis and study endpoint was also documented.

Data mining approaches

Cluster analysis

CHM treatments were coded as “T” (used) or “F” (not used). Post-treatment, patients receiving CHM exhibited decreases in ESR, immunoglobulins (IgA, IgG, IgM), C-reactive protein (CRP), complement components (C3, C4), and VAS scores, whereas non-users showed stability or increases. Conversely, SF-36 scores improved in the TCM group and decreased in the non-user group. Cluster analysis was performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) to investigate compatibility patterns among CHM prescriptions.

Network analysis

CHM prescription networks were visualized using the “network” node in SPSS Clementine v.11.1 (IBM Corp., Armonk, NY, USA). Stronger connections between herbs were represented by thicker lines, while weaker connections were thinner or dashed, with a maximum of 80 links displayed. Link sizes varied continuously, with thresholds set to highlight both strong and weak associations, producing an intuitive global network of CHM interactions.

Association rule mining

The Apriori algorithm was employed to identify hidden relationships between commonly used CHM combinations [22]. In these analyses, an association rule takes the form X → Y, where X (antecedent or left-hand side) and Y (consequent or right-hand side) are sets of items within the dataset. Support, confidence, and lift metrics were calculated to quantify the strength and significance of these associations [23]:

$$Support(X) = \frac{X}{M} \tag{1}$$

$$Confidence(X \rightarrow Y) = \frac{Support(X \cup Y)}{Support(X)} \tag{2}$$

$$Lift(X \rightarrow Y) = \frac{Confidence(X \rightarrow Y)}{Support(Y)} = \frac{Support(X \cup Y)}{Support(X) * Support(Y)} \tag{3}$$

Random walk analysis

A random walk model was applied to assess longitudinal changes in immuno-inflammatory markers following TCM interventions, aiming to clarify the long-term relationship between treatment and disease improvement. The computational formula and methodology for the random walk model were adopted from prior studies [10, 24].

Statistical analysis

All analyses were conducted using IBM SPSS version 22.0 (IBM Corp., NY, USA). Data normality was evaluated with the Shapiro-Wilk test. Continuous variables following a normal distribution were reported as mean ± standard deviation, whereas non-normally distributed variables were summarized as median (P25–P75). Categorical data were expressed as counts and percentages. Depending on variable type and distribution, the Mann–Whitney U test, Student's t-test, Wilcoxon signed-rank test, or chi-square test was applied to determine statistical significance. Kendall's tau-b was used for correlation analyses. Two-sided tests were employed with a significance threshold of $p < 0.05$.

Survival probabilities were estimated using Kaplan-Meier (K-M) curves, with differences between groups tested via the log-rank method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using univariate and multivariate Cox proportional hazards regression. Model selection utilized both the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), where lower values indicated better model fit [25]. Stepwise regression identified significant variables ($p < 0.05$) for inclusion in nomogram construction. Nomogram calibration was assessed by comparing calibration curves to the ideal diagonal line [26]. The predictive accuracy and discrimination ability of the model were evaluated using the concordance index (C-index) and time-dependent area under the receiver operating characteristic curve (AUC), derived via bootstrapping; values range from 0.5 (random chance) to 1.0 (perfect prediction), with values above 0.7 considered acceptable [26, 27]. Calibration was further evaluated using the Hosmer-Lemeshow test ($p > 0.05$ indicated good fit) [28]. Internal validation was performed using 1,000 bootstrap resamples to minimize overfitting bias. Decision curve analysis (DCA) was conducted to examine the clinical utility of the nomogram by estimating net benefit across varying probability thresholds [29]. R software (version 4.0.1, R Foundation for Statistical Computing) was employed to generate the nomogram, prediction models, and decision curves.

Results and Discussion

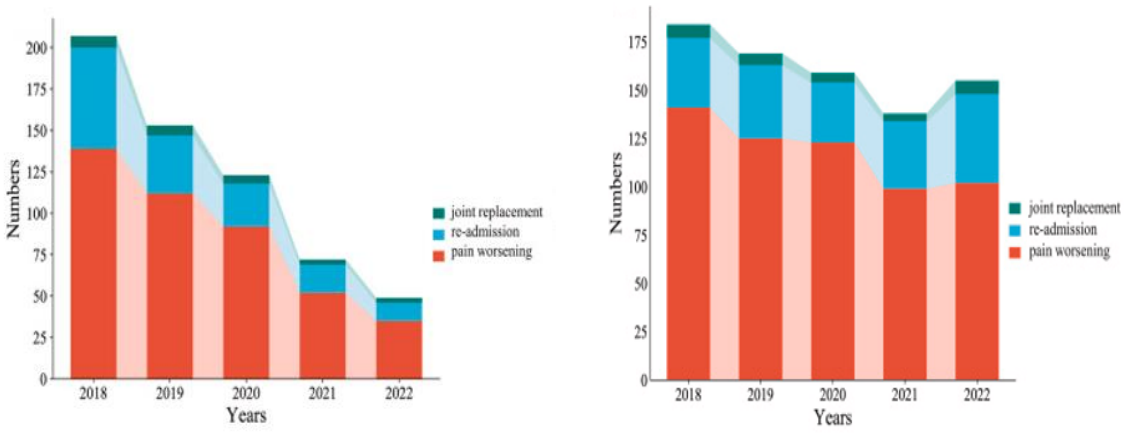
Baseline characteristics

The study cohort included 3,747 OA patients, of whom 2,963 (79.08%) were female and 784 (20.92%) male, with a mean age of 59.83 ± 12.27 years. Among these, 2,511 patients received TCM, whereas 1,236 did not. Significant differences were observed between the groups in BMI, sex distribution, presence of hypertension, coronary artery disease, and cumulative NSAID exposure. Additionally, baseline measures of ESR, CRP, IgA, IgM, as well as SF-36 domains (RE, BP, SF, MH) differed between the groups.

To minimize confounding from baseline imbalances, propensity score matching (PSM) was applied, resulting in 1,228 matched pairs of TCM users and non-users (n = 2,456). Post-matching, no significant differences remained

in age, sex, comorbidities, essential medication use, baseline immuno-inflammatory markers, VAS scores, or SF-36 scores.

Analysis of outcomes revealed that the TCM non-user group experienced higher rates of pain exacerbation, hospital readmission, and joint replacement compared to the TCM user group **(Table 1)**. Annual trends in these outcomes are summarized in illustrated in **Figures 2a–2b**.



a) b)

Figure 2. Annual trends of outcome events in propensity score–matched OA patients: (a) TCM user group and (b) TCM non-user group.

Table 1. Characteristics of the participants were classified according to their baseline use of TCM.

Characteristic	Before PSM matched			*p-value*	After PSM matched			*p-value*
	Total (n = 3,747)	**TCM user (n = 2,511)**	**TCM non-user (n = 1,236)**		**Total (n = 2,456)**	**TCM user(n = 1,228)**	**TCM non-user(n = 1,228)**	
Demographic characteristics								
Age (years)	59.83 ± 12.27	59.63 ± 11.86	60.25 ± 13.04	0.141	59.78 ± 12.84	59.46 ± 12.04	60.10 ± 12.94	0.178
≤60, n (%)	2,033(54.26)	1,382(55.04)	651(52.67)	/	1,117(45.48)	540(43.97)	577(46.99)	/
>60, n (%)	1,714(45.74)	1,129(44.96)	585(47.33)	/	1,339(54.52)	788(64.17)	551(44.87)	/
Gender, n(%)								

Female	2,963(79.08)	2,031(80.88)	932(75.40)	<0.001	1,882(76.63)	950(77.36)	932(75.90)	0.365	
Male	784(20.92)	480(19.12)	304(24.60)	Reference	574(23.37)	278(22.64)	296(24.10)	Reference	
BMI, kg/m2	28.34 ± 6.24	29.16 ± 6.10	27.56 ± 6.12	<0.001	27.28 ± 5.67	27.23 ± 5.98	27.31 ± 6.03	0.054	
Hip OA	625(16.68)	502(19.99)	123(9.95)	0.011	250(10.18)	130(10.59)	120(9.77)	0.231	
Knee OA	2,620(69.92)	1,632(64.99)	988(79.94)	0.146	1,914(77.93)	947(77.12)	967(78.75)	0.312	
Hand OA	502(13.40)	377(15.01)	125(10.11)	0.177	292(11.89)	151(12.30)	141(11.48)	0.227	
Comorbidity									
Osteoporosis, n (%)	774(20.66)	515(20.51)	259(20.95)	0.752	554(22.56)	299(24.35)	255(20.77)	0.187	
Hyperlipemia, n (%)	293(7.82)	192(7.65)	101(8.17)	0.574	201(8.18)	101(8.22)	100(8.14)	0.941	
Chronic gastritis, n (%)	505(13.48)	350(13.94)	155(12.54)	0.239	307(12.50)	152(12.38)	155(12.62)	0.855	
Diabetes, n (%)	428(11.42)	282(11.23)	146(11.81)	0.599	283(11.52)	138(11.24)	145(11.81)	0.658	
Fatty liver, n (%)	607(16.20)	401(15.97)	206(16.67)	0.586	423(17.22)	218(17.75)	205(16.69)	0.487	

										Cerebrovascular disease, n (%)	749(19.99)
											504(20.07)
											245(19.82)
											0.857
											491(19.99)
											246(20.03)
											245(19.95)
											0.960
										Hypertension, n (%)	631(16.84)
											387(15.41)
											244(19.74)
											0.001
											455(18.53)
											218(17.75)
											237(19.30)
											0.324
										Coronary artery disease, n (%)	165(4.40)
											86(3.42)
											79(6.39)
											<0.001
											137(5.58)
											66(5.37)
											71(5.78)
											0.660
										NSAID accumulation duration, n (%)	2,021(53.94)
											1,255(49.98)
											766(61.97)
											0.023
											1,108(45.11)
											547(44.54)
											561(45.68)
											0.117
										≤60d	469(12.52)
											285(11.35)
											184(14.89)
											/
											361(14.70)
											197(16.04)
											164(13.36)
											/
										60-180d	830(22.15)
											605(24.09)
											225(18.20)
											/
											457(18.61)
											246(20.03)
											211(17.18)
											/
										≥180d	722(19.27)
											365(14.54)
											357(28.88)
											/
											290(11.81)
											104(8.47)
											186(15.15)
											/
										Glucosamine accumulation duration, n (%)	3,170(84.60)
											2,096(83.46)
											1,074(86.89)
											0.731
											2,061(83.92)
											1,027(83.63)
											1,034(84.20)
											0.537
										≤60d	1,053(28.10)
											632(25.17)
											421(34.06)
											/
											736(29.97)
											321(26.14)
											415(33.79)
											/
										60-180d	895(23.89)
											703(27.99)
											192(15.53)
											/
											588(23.94)
											401(32.65)
											187(15.23)
											/
										≥180d	1,222(32.61)
											761(30.31)
											461(37.30)
											/
											737(30.01)
											305(24.84)
											432(35.18)
											/

Immuno-inflammatory indexes

VAS (cm)	PROs	C4(g/L)	C3(g/L)	IGM(g/L)	IGG(g/L)	IGA(g/L)	CRP (mg/L)	ESR (mm/h)
/		/	/	/	/	/	/	/
5.39 ± 1.20		19.20(0.31,26.70)	88.65(1.17,109.60)	3.02(0.74,4.42)	11.14(9.44,12.85)	5.90(1.45,8.49)	22.45(1.12,30.23)	42(6,62)
5.26 ± 1.39		19.40(0.33,26.90)	89.50(1.22,109.9)	2.98(0.73,4.34)	11.29(9.77,13.12)	5.01(1.49,8.29)	18.04(2.19,27.09)	33(7,51)
0.481		0.403	0.275	0.022	0.103	0.002	0.035	0.031
/		/	/	/	/	/	/	/
5.29 ± 1.20		19.40(0.32,26.60)	90.10(1.19,110.4)	3.01(0.73,4.40)	11.17(9.48,12.74)	5.89(1.46,8.42)	19.12(1.45,29.56)	36(7,58)
5.27 ± 1.26		19.35(0.34,26.80)	89.30(1.22,109.9)	2.98(0.74,4.34)	11.19(9.78,13.05)	5.17(1.52,8.07)	18.87(2.21,26.78)	34(8,40)
0.073		0.917	0.860	0.247	0.185	0.057	0.783	0.139
SF-36								

	MH (score)	VT (score)	GH (score)	RP (score)	PF (score)	SF (score)	BP (score)	RE (score)
End event								
	/	/	/	/	/	/	/	/
	35.00(22.00,45.00)	33.00(19.00,50.00)	20.00(15.00,45.00)	14.61(9.00, 27.75)	29.00(10.00,42.00)	32.00(20.00,44.00)	22.00(18.00.31.00)	12.00(8.00,25.00)
	38.00(26.00,52.00)	31.00(20.00,52.00)	22.00(16.00,48.00)	13.00(7.00,28.00)	25.00(9.00,42.00)	28.50(18.00,45.00)	26.00(17.00,30.00)	16.00(10.00,32.00)
	0.045	0.056	0.066	0.072	0.065	0.032	0.015	0.024
	/	/	/	/	/	/	/	/
	36.00(20.00,42.00)	32.00(26.00,48.00)	20.00(18.00,40.00)	14.00(9.00, 24.50)	28.00(11.00,40.00)	30.00(18.00,42.00)	23.00(19.00,29.00)	13.00(8.67,24.00)
	37.00(27.00,51.00)	32.00(22.00,49.00)	21.00(17.00,42.00)	14.00(8.00,25.00)	26.00(12.00,38.00)	28.90(20.00,41.00)	24.09(18.00,29.00)	14.86(8.33,30.00)
	0.067	0.081	0.064	0.058	0.070	0.066	0.064	0.057

Pain worsening, n (%)	1,958(52.26)	1,155(46.00)	803(64.97)	<0.001	1,020(41.53)	430(35.02)	590(48.05)	0.031
Re-admission, n (%)	616(16.44)	344(13.70)	272(22.01)	<0.001	336(13.68)	150(12.21)	186(15.15)	0.035
Joint replacement, n (%)	86(2.30)	54(2.15)	32(2.59)	<0.001	53(2.16)	24(1.95)	29(2.36)	0.043

Note: PSM= propensity score matching; BMI= body mass index; NSAID= nonsteroidal anti-inflammatory drugs; VAS= visual analog scale; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; IGA= immunoglobulin A; IGG= immunoglobulin G; IGM= immunoglobulin M; C3= complement component 3; C4= complement component 4; PROs= patient reported outcomes; SF-36= short form-36 health survey; RE= role-emotional; BP= bodily pain; SF= social function; PF= physical function; RP= role-physical; GH= general health; VT= vitality; MH= mental health.

TCM use and patient outcomes

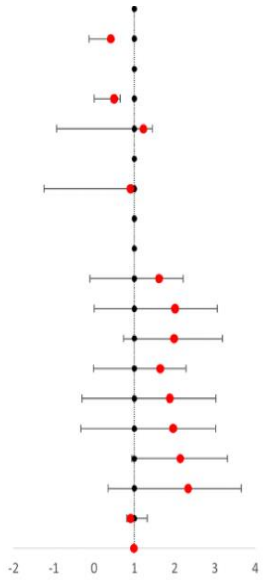
As detailed in **Table 2**, Cox regression analyses were conducted to evaluate how baseline characteristics influenced outcomes in OA patients. In univariate analysis, TCM use was identified as an independent protective factor, significantly reducing the risk of pain (HR = 0.405, 95% CI = 0.325–0.966, $p < 0.001$), hospital readmission (HR = 0.555, 95% CI = 0.204–0.942, $p < 0.001$), and joint replacement (HR = 0.402, 95% CI = 0.205–0.991, $p < 0.001$). Similarly, NSAID and glucosamine therapy were associated with lower rates of pain and joint replacement. Conversely, increasing age significantly increased the likelihood of pain worsening (HR = 1.115, 95% CI = 1.001–3.325, $p = 0.044$), readmission (HR = 1.401, 95% CI = 1.118–3.756, $p = 0.003$), and joint replacement (HR = 1.362, 95% CI = 1.184–3.714, $p = 0.003$). Additional risk factors for pain exacerbation included osteoporosis (HR = 1.036, 95% CI = 1.002–3.381, $p = 0.001$), diabetes (HR = 1.504, 95% CI = 1.005–3.327, $p = 0.043$), and coronary artery disease (HR = 1.129, 95% CI = 1.103–3.618, $p = 0.022$). Osteoporosis (HR = 1.426, 95% CI = 1.022–4.989, $p = 0.037$) and hypertension (HR = 1.602, 95% CI = 1.131–4.269, $p = 0.008$) were associated with higher readmission risk, while osteoporosis (HR = 1.327, 95% CI = 1.003–2.546, $p = 0.029$) and diabetes (HR = 1.406, 95% CI = 1.068–2.421, $p = 0.023$) predicted increased likelihood of joint replacement. After adjustment for potential confounding variables in multivariate Cox models, TCM use remained strongly linked to reduced pain (HR = 0.416, 95% CI = 0.402–0.954, $p = 0.025$), readmission (HR = 0.489, 95% CI = 0.133–0.967, $p = 0.022$), and joint replacement (HR = 0.580, 95% CI = 0.135–0.982, $p = 0.021$). Relative to non-users, patients receiving TCM experienced 58.4% lower pain incidence, 51.1% fewer readmissions, and 42% fewer joint replacements. Age persisted as a significant risk factor across all outcomes, and comorbidities such as osteoporosis and diabetes continued to elevate risk. Notably, longer durations of herbal therapy were associated with progressively lower incidences of adverse outcomes.

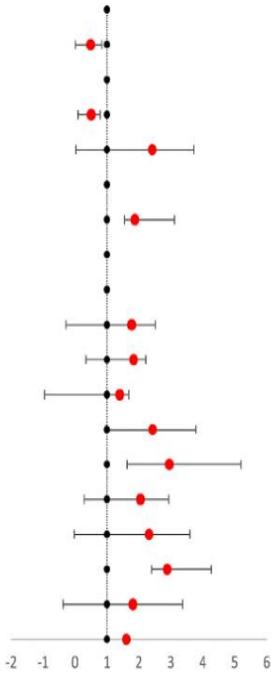
All independent predictors identified via Cox regression were incorporated into a nomogram to estimate the probability of pain worsening, hospital readmission, and joint replacement. Each variable was assigned a point value, and the total score was calculated by summing these points **(Figure 3a)**. The C-index, reflecting discriminative performance, was 0.873 (95% CI = 0.831–0.916) in the training cohort (TCM users) and 0.819 (95% CI = 0.767–0.871) in the validation cohort (TCM non-users), indicating robust prediction accuracy. Calibration curves based on the Hosmer-Lemeshow test demonstrated good agreement between predicted and observed outcomes in both the training ($p = 0.287$) and validation ($p = 0.231$) datasets **(Figures 3c–3d).**

The predictive capability of the nomogram was further supported by AUC values in the training cohort: pain worsening (0.873), readmission (0.864), and joint replacement (0.727), all exceeding the corresponding AUCs in the validation cohort **(Figures 3e–3f)**. Decision curve analysis (DCA) confirmed the clinical usefulness of the model, showing significant net benefit across a wide range of risk thresholds **(Figure 3b)**. Collectively, these results indicate that the nomogram provides strong discriminatory power, accurate calibration, and meaningful clinical utility for predicting outcomes in OA patients.

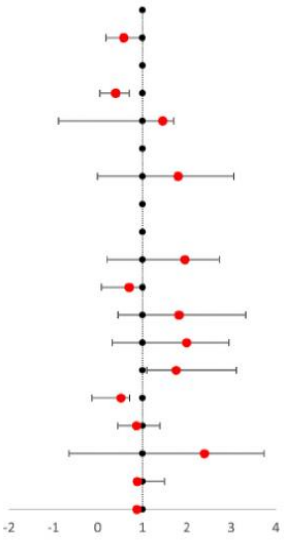
Table 2. Association between baseline use of TCM and incident patient outcomes.

Items	Univariate analysis			Multivariate analysis		
	Hazard Ratio	**95% CI**	***p*-value**	**Adjust hazard ratio**	**95% CI**	***p*-value**
Pain worsening						
TCM used	0.405	0.325-0.966	<0.001	0.416	0.402-0.954	0.025*
Low exposure (≤24 months)	Reference	Reference	Reference	Reference	Reference	Reference
High exposure (>24 months)	0.411	0.365-0.946	<0.001	0.501	0.359-0.999	0.013*
Age/year	1.115	1.001–3.325	0.044	1.225	1.005-3.382	0.045*
Gender	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.885	0.764-4.025	0.104	0.901	0.776-3.045	0.168
Male	Reference	Reference	Reference	Reference	Reference	Reference
Comorbidity						
Osteoporosis	1.036	1.002–3.381	0.001	1.611	1.004-3.321	0.039*
Hyperlipemia	1.990	0.969-3.011	0.326	2.012	0.966-4.019	0.562
Chronic gastritis	1.165	0.931-3.457	0.181	1.985	0.786-3.236	0.299
Diabetes	1.504	1.005-3.327	0.043	1.645	1.004-3.302	0.048*
Fatty liver	1.082	1.020-4.212	0.447	1.879	0.726-4.063	0.583
Cerebrovascular disease	1.774	0.914-5.260	0.386	1.962	0.900-4.252	0.476
Hypertension	1.911	0.851-4.155	0.311	2.139	0.964-3.346	0.425
Coronary artery disease	1.129	1.103-3.618	0.022	2.333	1.009-4.320	0.058
NSAID used	0.893	0.474-0.995	<0.001	0.905	0.492-0.998	0.034*
Glucosamine used	0.796	0.468-0.999	<0.001	0.985	0.465-1.000	0.054
Re-admission						
TCM used	0.555	0.204-0.942	<0.001	0.489	0.133-0.967	0.022*
Low exposure (≤24 months)	Reference	Reference	Reference	Reference	Reference	Reference
High exposure (>24 months)	0.419	0.228-0.953	0.022	0.503	0.213-0.912	0.033*
Age/year	1.401	1.118-3.756	0.003	2.415	1.110-4.802	0.025*
Gender	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.801	0.218-1.038	0.094	1.874	0.640-2.195	0.400
Male	Reference	Reference	Reference	Reference	Reference	Reference
Comorbidity						
Osteoporosis	1.426	1.022-4.989	0.037	1.773	1.029-3.832	0.041*
Hyperlipemia	1.025	0.773-3.358	0.565	1.834	1.452-3.317	0.601
Chronic gastritis	1.175	0.922-3.497	0.194	1.401	1.118-3.756	0.403
Diabetes	2.300	0.937-4.805	0.116	2.428	1.070-3.905	0.216
Fatty liver	1.862	0.638-3.165	0.334	2.952	0.714-4.270	0.738
Cerebrovascular disease	1.041	0.816-3.328	0.745	2.048	1.161-3.805	0.541
Hypertension	1.602	1.131-4.269	0.008	2.316	1.044-4.657	0.220
Coronary artery disease	1.236	0.950-3.609	0.115	2.886	1.502-3.369	0.213
NSAID used	1.808	0.797-3.019	0.151	1.811	0.252-3.993	0.221

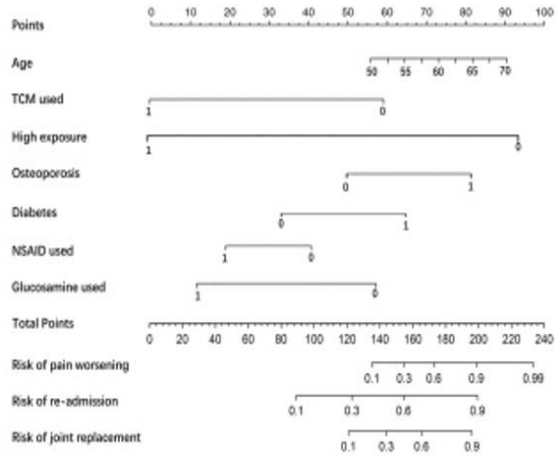




Glucosamine used	1.393	0.283-2.994	0.231	1.608	0.201-3.997		0.144
Joint replacement							
TCM used	0.402	0.205-0.991	<0.001	0.580	0.135-0.982		0.021*
Low exposure (≤24 months)	Reference	Reference	Reference	Reference	Reference		Reference
High exposure (>24 months)	0.328	0.091-0.771	0.002	0.401	0.095-0.756		0.016*
Age/year	1.362	1.184-3.714	0.003	1.456	1.212-3.793		0.022*
Gender	Reference	Reference	Reference	Reference	Reference		Reference
Female	1.709	0.523-3.691	0.510	1.801	0.544-3.604		0.485
Male	Reference	Reference	Reference	Reference	Reference		Reference
Comorbidity							
Osteoporosis	1.327	1.003-2.546	0.029	1.957	1.180-3.706		0.043*
Hyperlipemia	0.583	0.171-1.975	0.386	0.707	0.376-1.331		0.283
Chronic gastritis	1.675	0.222-4.114	0.670	1.825	0.326-3.198		0.157
Diabetes	1.406	1.068-2.421	0.023	1.995	1.042-3.666		0.037*
Fatty liver	1.485	0.354-2.227	0.589	1.757	0.404-2.420		0.385
Cerebrovascular disease	0.481	0.356-1.008	0.160	0.522	0.330-1.176		0.144
Hypertension	0.776	0.173-2.421	0.342	0.869	0.346-1.291		0.230
Coronary artery disease	1.039	0.988-2.239	0.061	2.393	1.056-5.427		0.137
NSAID used	0.675	0.167-0.912	0.037	0.886	0.273-0.929		0.042*
Glucosamine used	0.688	0.176-0.908	0.031	0.876	0.232-0.977		0.041*



Note: *$p < 0.05$.



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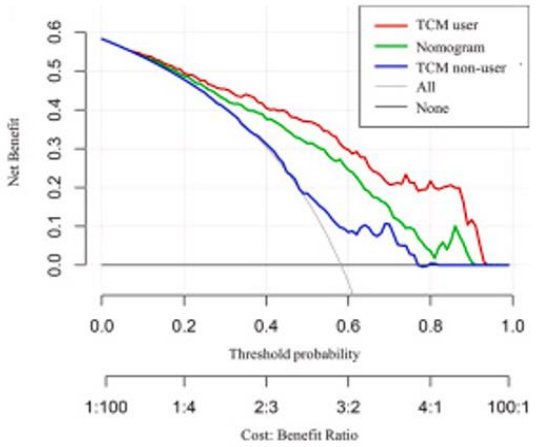

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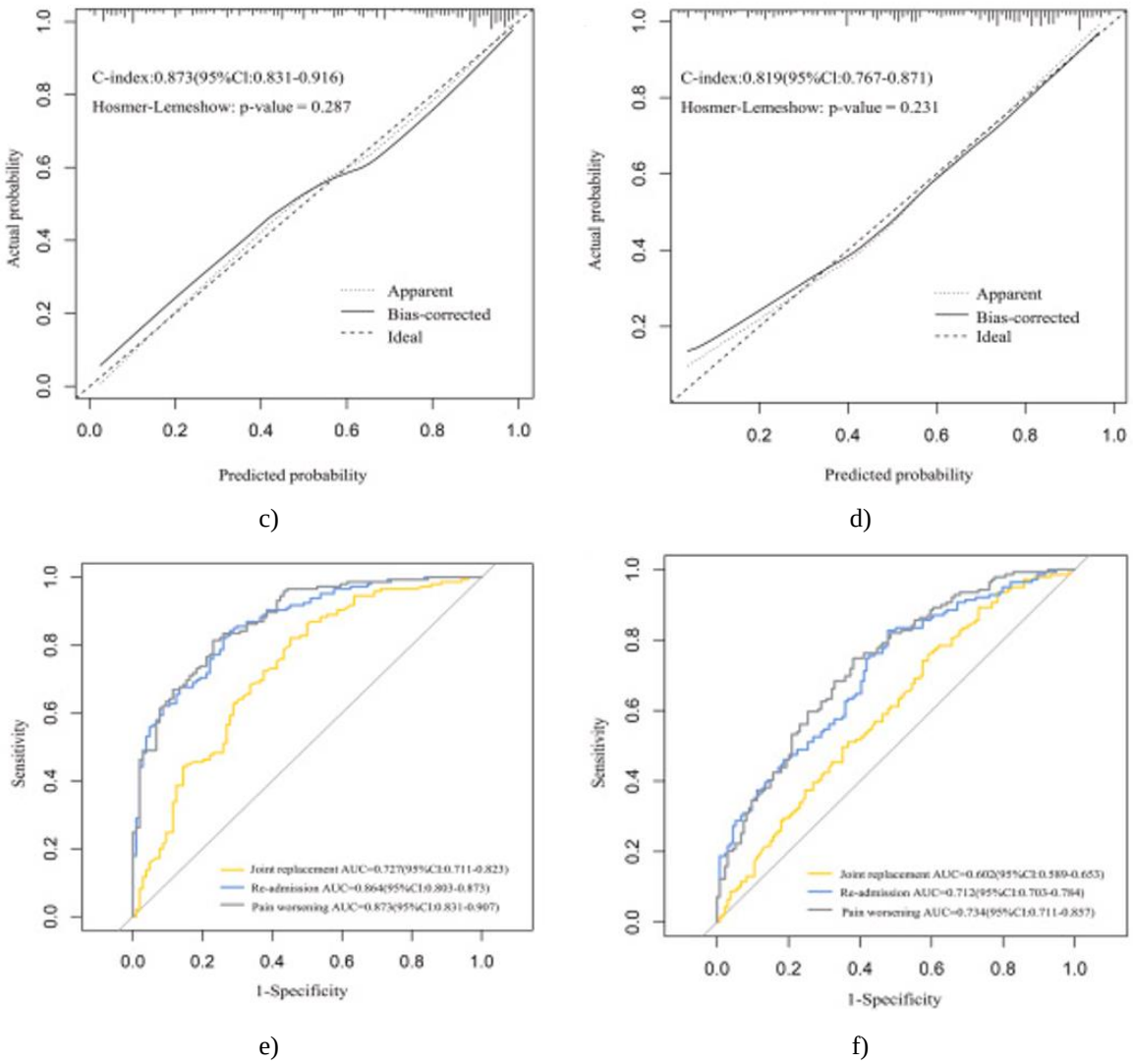


Figure 3. (a) The nomogram of the regression model incorporates seven predictors. To use it, locate each predictor's corresponding point on the top scale and sum the points. The total points projected onto the bottom scale indicate the predicted probability of outcome risk. (b) Decision curve analysis (DCA) for the training and validation cohorts. The y-axis represents net benefit, while the x-axis shows thresholds of predicted risk. Across a range of clinically relevant thresholds, the net benefit of using the TCM user cohort (red line) exceeds that of the TCM non-user cohort (blue line). (c–d) Calibration curves for the training (c) and validation (d) cohorts. Perfect predictions align with the 45° gray line; dashed lines represent observed outcomes for all cohorts, and solid lines show bias-corrected predictions via bootstrapping (B = 1,000). Closer alignment indicates higher predictive accuracy. (e–f) Receiver operating characteristic (ROC) curves for training (e) and validation (f) datasets. (For color references in this figure legend, see the Web version of the article.)

Kaplan-meier survival analysis of TCM effects

Kaplan-Meier survival curves were used to assess the influence of TCM use on patient outcomes **(Figure 4).** Compared to the non-user group, the TCM user group demonstrated significantly lower risks of pain progression (log-rank $p < 0.0001$); **(Figure 4a)**, hospital readmission (log-rank $p < 0.0001$); **(Figure 4b)**, and joint replacement (log-rank $p = 0.0095$); **(Figure 4c)**. To evaluate the effect of treatment duration, TCM users were stratified into low-exposure (≤24 months) and high-exposure (>24 months) groups. Patients in the high-exposure group showed markedly lower risks for all outcomes compared with the low-exposure group (log-rank $p < 0.001$); **(Figures 5a–5c**).

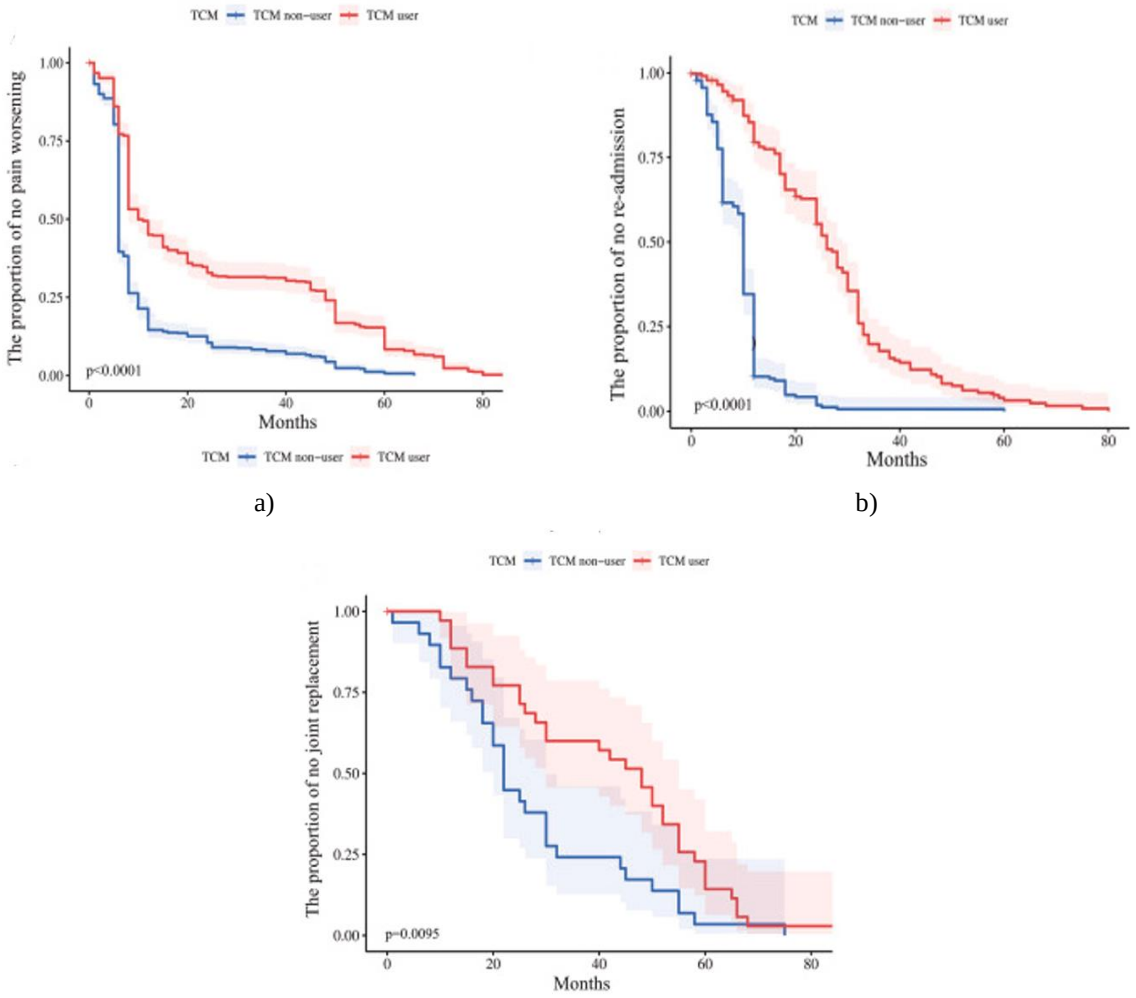
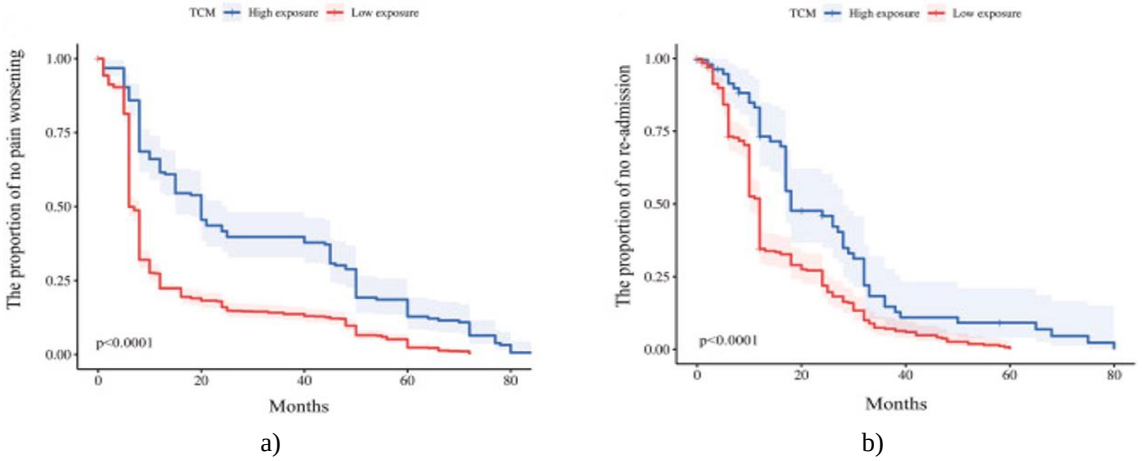
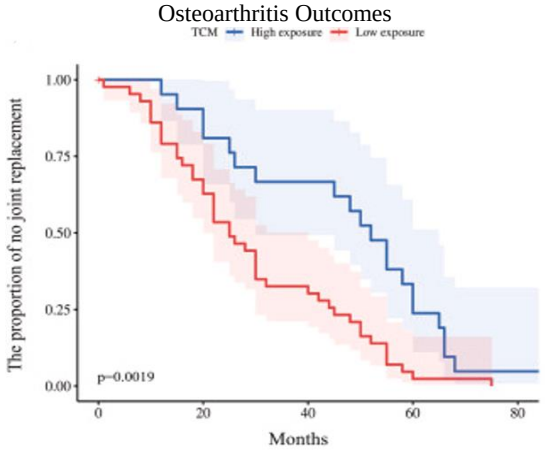


Figure 4. Kaplan-Meier survival curves illustrating the risk of outcomes in TCM users versus non-users: (a) progression of pain, (b) hospital readmission, and (c) joint replacement.





c)

Figure 5. Kaplan-Meier curves depicting outcome risks in patients based on TCM exposure duration: (a) worsening of pain, (b) hospital readmissions, and (c) joint replacement, comparing high-exposure and low-exposure groups.

CHM prescription patterns in the TCM user cohort

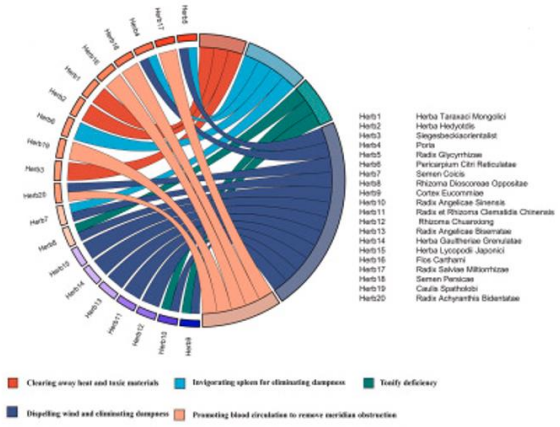
Among OA patients receiving TCM, the 20 most commonly prescribed Chinese herbal medicines were classified into five therapeutic categories: clearing heat and toxins, reinforcing the spleen to eliminate dampness, tonifying deficiencies, enhancing blood circulation to relieve meridian obstructions, and dispelling wind-dampness (**Figure 6a)**.

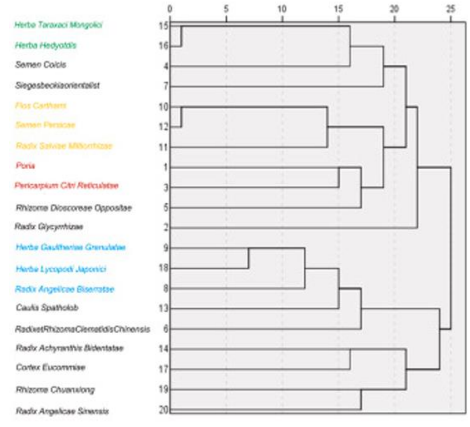
A systematic cluster analysis of CHM combinations revealed four distinct clusters when the Euclidean distance was set at 15 **(Figure 6b)**:

- Cluster 1: Herba Taraxaci Mongolici, Herba Hedyotdis
- Cluster 2: Flos Carthami, Semen Persicae, Radix Salviae Miltiorrhizae
- Cluster 3: Poria, Pericarpium Citri Reticulatae
- Cluster 4: Herba Gaultheriae Grenulatae, Herba Lycopodii Japonici, Radix Angelicae Biserratae

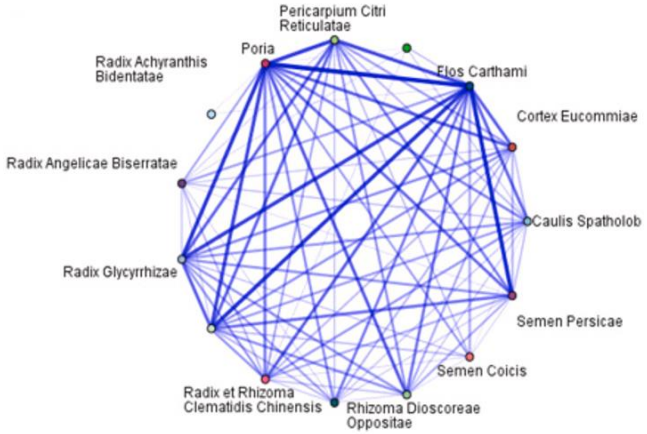
To visualize the relationships between frequently used herbs, a correlation network was constructed **(Figure 6c).** Herbs such as Poria, Radix Glycyrrhizae, Flos Carthami, Semen Persicae, Radix Salviae Miltiorrhizae, and Pericarpium Citri Reticulatae were highly interconnected, often co-prescribed, and formed the core of treatment combinations.

Cox regression analysis further highlighted the herbs most strongly associated with improved outcomes: Radix Achyranthis Bidentatae and Radix Salviae Miltiorrhizae were linked to reduced pain; Poria and Flos Carthami were associated with lower readmission rates; and Flos Carthami along with Radix Salviae Miltiorrhizae were connected to decreased rates of joint replacement **(Table 3).**





a) b)



c)

Figure 6. (a) Therapeutic classification of the 20 most frequently used herbs. (b) Systematic cluster analysis of CHM prescriptions among TCM users. (c) Network diagram visually representing the relationships among CHM prescriptions in the TCM user group.

Table 3. Adjusted Cox proportional hazards model for commonly used Chinese herbal medicines (CHM) with cumulative use >24 months

Outcome	Chinese Herbal Medicine	Adjusted Hazard Ratio (95% CI)	p-value (AIC / BIC)
Pain worsening [a]			
	Radix Achyranthis Bidentatae	0.409 (0.212–0.793)	0.008 (112.311 / 204.211)
	Radix Salviae Miltiorrhizae	0.375 (0.195–0.721)	0.003 (202.311 / 234.111)
Re-admission [b]			
	Poria	0.319 (0.131–0.777)	0.012 (232.301 / 274.121)
	Flos Carthami	0.584 (0.392–0.871)	0.009 (108.511 / 209.221)
Joint replacement [c]			
	Flos Carthami	0.395 (0.213–0.732)	0.003 (235.312 / 298.111)
	Radix Salviae Miltiorrhizae	0.496 (0.287–0.857)	0.011 (119.020 / 232.151)

Note:
a Adjusted for age, osteoporosis, diabetes, and NSAID use.
b Adjusted for age and osteoporosis.
c Adjusted for age, osteoporosis, diabetes, NSAID use, and glucosamine use.
AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Impact of TCM on immune-inflammatory markers and patient-reported outcomes in OA

Following treatment, patients in the TCM non-user group showed decreased ESR, CRP, and IGA levels and reduced VAS scores, accompanied by improvements in SF-36 scores compared to baseline ($p < 0.05$). In the TCM user group, reductions were observed not only in ESR, CRP, and IGA but also in IGG, IGM, C3, and C4, alongside lower VAS scores and higher SF-36 scores ($p < 0.05$ or $p < 0.01$). Importantly, TCM users demonstrated significantly greater improvements than non-users in lowering ESR, CRP, C4, and VAS scores, as well as enhancing multiple SF-36 subdomains ($p < 0.05$); **(Table 4**).

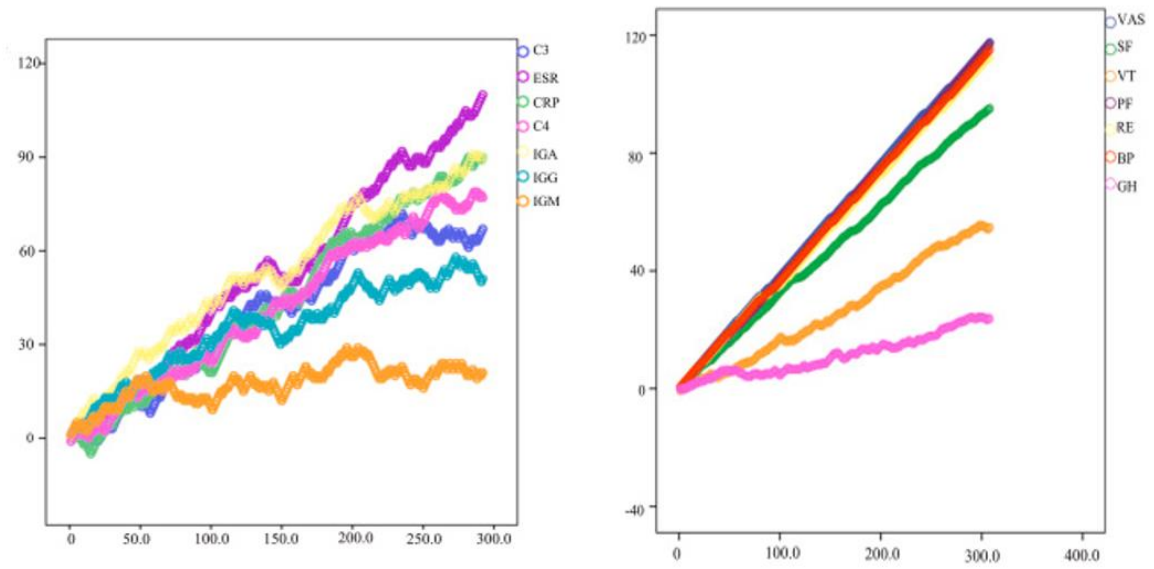
To examine the dynamic effects of TCM on immune-inflammatory parameters and patient-reported outcomes, a random walk model was employed **(Figure 7)**. The analysis revealed a strong positive correlation between TCM use and reductions in ESR, CRP, IGA, IGG, C3, and C4 **(Figure 7a)**, as well as improvements in VAS and SF-36 scores **(Figure 7b)**. For example, CRP was evaluated across 623 assessments, with a patient improvement coefficient of 0.311, indicating that approximately 8 steps were needed to achieve a unit improvement in the composite patient index. Overall, the random walk results **(Figure 7)** show that post-treatment immune-inflammatory markers and patient-reported outcomes improved compared to pre-treatment, though changes in IGM, GH, RP, and MH were modest.

Table 4. Effects of TCM on immune-inflammatory indexes and PROs in OA patients.

Index	TCM non-user (n = 1,228)	TCM user (n = 1,228)

	Before treatment	After treatment	Before treatment	After treatment
ESR (mm/h)	34(8,40)	15(7,20)#	36(7,58)	9(6,18)・・△
CRP (mg/L)	18.87(2.21,26.78)	2.01(0.33,3.53)##	19.12(1.45,29.56)	0.65(0.32,2.18)・・△
IGA(g/L)	5.17(1.49,8.37)	2.07(1.49,2.56)#	5.89(1.46,8.48)	1.75(1.46,2.46)・・△
IGG(g/L)	9.76(8.28,13.1)	8.25(7.64,13.0)	11.17(9.48,12.9)	8.11(6.5,11.8)・
IGM(g/L)	2.98(0.74,4.34)	1.09(0.63,1.36)	3.01(0.73,4.40)	0.87(0.62,1.4)・
C3(g/L)	89.30(1.22,109.9)	87.70(1.2,109.4)	90.10(1.19,110.4)	81.1(1.18,109.95)・
C4(g/L)	19.35(0.34,26.8)	18.9(0.33,26.3)	19.40(0.32,26.6)	15.2(0.31,26.3)・・△
VAS (cm)	5.27 ± 1.26	3.23 ± 0.76#	5.29 ± 1.20	1.84 ± 0.83・・△
RE (score)	14.86(8.33,30.00)	66.60(33.30,80.00)#	13.00(8.67,24.00)	86.60(33.30,100.00)・・△
BP (score)	24.09(18.00,29.00)	60.29(42.00,78.00)#	23.00(19.00,29.00)	70.29(52.00,82.00)・・△
SF (score)	28.90(20.00,41.00)	43.50(33.00.62.00)#	30.00(18.00,42.00)	75.50(40.00.85.00)・・△
PF (score)	26.00(12.00,38.00)	55.00(30.00,75.00)#	28.00(11.00,40.00)	75.00(35.00,88.00)・・△
RP (score)	14.00(8.00,25.00)	50.00(0.00,80.00)#	14.00(9.00, 24.50)	60.00(0.00,80.00)・
GH (score)	21.00(17.00,42.00)	48.00(32.00,75.00)#	20.00(18.00,40.00)	55.00(42.00,74.00)・・
VT (score)	32.00(22.00,49.00)	55.00(48.00,75.00)#	32.00(26.00,48.00)	65.00(50.00,80.00)・・△
MH (score)	37.00(27.00,51.00)	68.00(47.00,78.00)#	36.00(20.00,42.00)	78.00(56.00,88.00)・

Note. Compared with the TCM non-user group before treatment, #p < 0.05, ##p < 0.01. Compared with the TCM user group before treatment, ・p < 0.05, ・・p < 0.01. Compared with the TCM non-user group difference (after treatment−before treatment), Δp < 0.05. ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; IGA=immunoglobulin A; IGG= immunoglobulin G; IGM= immunoglobulin M; C3= complement component 3; C4= complement component 4; VAS= visual analog scale; RE= role-emotional; BP= bodily pain; SF= social function; PF= physical function; RP= role-physical; GH= general health; VT= vitality; MH= mental health.



a) b)

Figure 7. Random walking model of immune-inflammatory indices (a) and PROs (b) in the TCM user group. Note: The horizontal axis length increases with the number of walking steps, while the vertical axis height reflects the magnitude of intervention efficacy and response. ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; IgA= immunoglobulin A; IgG= immunoglobulin G; IgM= immunoglobulin M; C3= complement component 3; C4= complement component 4; VAS= visual analog scale; RE= role-emotional; BP= bodily pain; SF= social function; PF= physical function; GH= general health; VT= vitality.

Effects of TCM on kidney and liver function in OA patients

In the TCM non-user group, post-treatment levels of UA and BUN were significantly lower than baseline ($p < 0.05$; **Table 5**). In the TCM user group, UA and BUN levels decreased significantly after treatment ($p < 0.01$), while CREA, ALT, and AST showed no significant changes ($p > 0.05$). Additionally, the TCM user group demonstrated a notably greater reduction in UA and BUN levels compared with the non-user group ($p < 0.05$; **Table 5**).

Table 5. Effects of TCM on kidney and liver function in OA patients.

Index	TCM non-user (n = 1,228)		TCM user (n = 1,228)	
	Before treatment	After treatment	Before treatment	After treatment
ALT	18(13,28)	17(12,25)	18(13,27)	16(12,23)
AST	20(16,25)	19(16,23)	19(16,24)	18(16,22)
CREA	53.9(47.4,62.4)	53.8(47.5,62.10)	53.90(47.30,64.40)	53.60(48.00,64.80)
UA	277(230,334.5)	269(221.5,322)$^{\#}$	275(226.75,336.00)	259(225.00,328.00)$^{\cdot\cdot\triangle}$
BUN	5.30(4.40,6.33)	4.94(4.19,5.99)$^{\#}$	5.35 (4.56,6.43)	4.81(4.23,6.13)$^{\cdot\cdot\triangle}$

Note: Compared with the TCM non-user group before treatment, $^{\#}p < 0.05$. Compared with the TCM user group before treatment, $^{\cdot\cdot}p < 0.01$. Compared with the TCM non-user group difference (after treatment and before treatment), $^{\triangle}p < 0.05$. CREA= serum creatinine; BUN= blood urea nitrogen; UA= uric acid; ALT= alanine aminotransferase; AST=aspartate transferase.

Association rule analysis of CHM correlations with immune-inflammatory markers and patient outcomes in the TCM user group

We applied association rule analysis by treating the TCM interventions as the antecedents and the improvements in laboratory and clinical outcomes as the consequents. The analysis showed that Herba Taraxaci Mongolici, Semen Coicis, and Rhizoma Chuanxiong were highly connected with reductions in inflammatory indicators, including ESR and CRP. A combination of Flos Carthami, Poria, and Radix Salviae Miltiorrhizae was closely tied to increases in immune-related markers such as C3, C4, IgA, IgG, and IgM **(Table 6)**. Improvements in VAS and BP scores were predominantly associated with Radix Salviae Miltiorrhizae and Radix et Rhizoma Clematidis Chinensis, while PF and RP enhancements correlated strongly with Poria, Radix et Rhizoma Clematidis Chinensis, and Radix Angelicae Sinensis. Moreover, better scores in SF, RE, MH, VT, and GH were linked to Semen Coicis, Radix Angelicae Sinensis, and Poria.

To further investigate CHM associations with clinical outcomes in OA patients, we defined the occurrence of an event as F and its absence as T. The analysis revealed that Herba Taraxaci Mongolici and Radix Achyranthis Bidentatae were strongly related to lower pain events, while the combination of Flos Carthami and Poria was associated with fewer readmissions. Reductions in joint replacement procedures were mainly linked to Radix Angelicae Biserratae and Flos Carthami **(Table 7).** Overall, the identified rules demonstrated high reliability, with support levels above 50%, confidence exceeding 80%, lift values greater than 1, and rule support above 40% **(Table 7).**

Table 6. Analysis of association rules between CHM and immune-inflammatory indexes and PROs in the TCM user group.

LHS	RHS	Support (%)	Confidence (%)	Rule support (%)	Lift
Herba Taraxaci Mongolici, Semen Coicis	ESR↓	51.279	81.545	47.489	1.045
Semen Coicis, Rhizoma Chuanxiong	CRP↓	50.048	80.597	43.835	1.027
Flos Carthami, Poria	C3↓	59.679	89.836	53.612	1.023

Flos Carthami, Poria	C4↓	59.678	92.974	55.486	1.011
Poria	IGA↓	75.558	90.673	68.510	1.014
Flos Carthami, Poria	IGG↓	57.679	90.135	53.791	1.010
Radix Salviae Miltiorrhizae, Flos Carthami	IGM↓	57.003	87.011	49.599	1.045
Radix Salviae Miltiorrhizae, Radix et Rhizoma Clematidis Chinensis	VAS↓	48.789	88.567	47.890	1.015
Semen Coicis, Radix Angelicae Sinensis	RE↑	51.678	87.679	48.957	1.014
Radix Salviae Miltiorrhizae, Radix et Rhizoma Clematidis Chinensis	BP↑	52.341	88.986	51.568	1.011
Poria, Radix Angelicae Sinensis	SF↑	65.456	89.453	50.567	1.012
Poria, Radix et Rhizoma Clematidis Chinensis	PF↑	64.789	88.345	50.457	1.113
Poria, Radix Angelicae Sinensis	RP↑	65.894	87.975	49.897	1.034
Semen Coicis, Radix Angelicae Sinensis	GH↑	54.568	87.679	49.985	1.043
Radix Salviae Miltiorrhizae, Poria	VT↑	55.876	88.982	50.234	1.034
Semen Coicis, Radix Angelicae Sinensis	MH↑	54.345	89.045	49.087	1.022

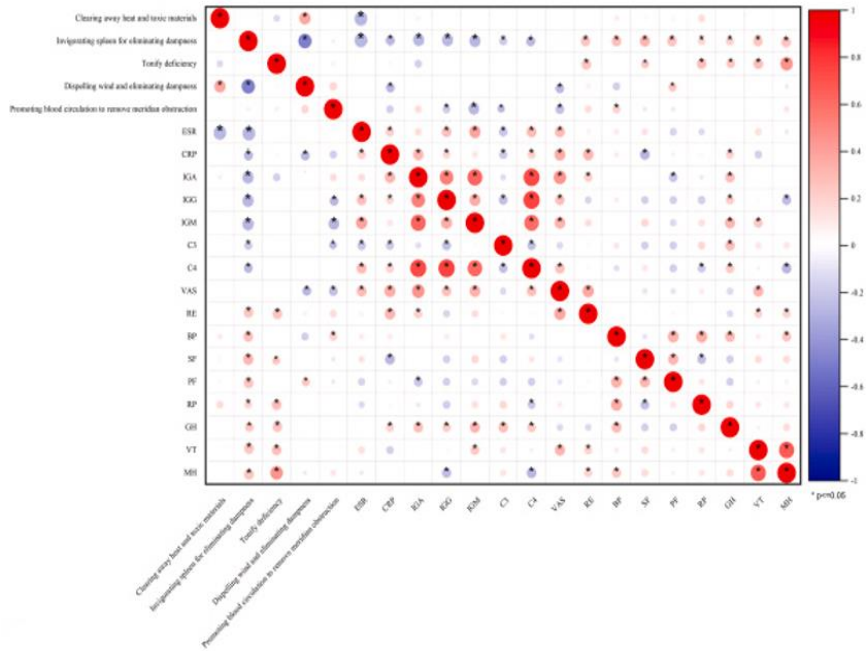
Table 7. Analysis of association rules between CHM and patient outcomes.

LHS	RHS	Support (%)	Confidence (%)	Rule support (%)	Lift
Herba Taraxaci Mongolici, Radix Achyranthis Bidentatae	No pain worsening	56.843	81.470	41.867	1.017
Flos Carthami, Poria	No re-admission	59.773	88.953	53.171	1.012
Radix Angelicae Biserratae, Flos Carthami	No joint replacement	50.432	98.780	41.915	1.005

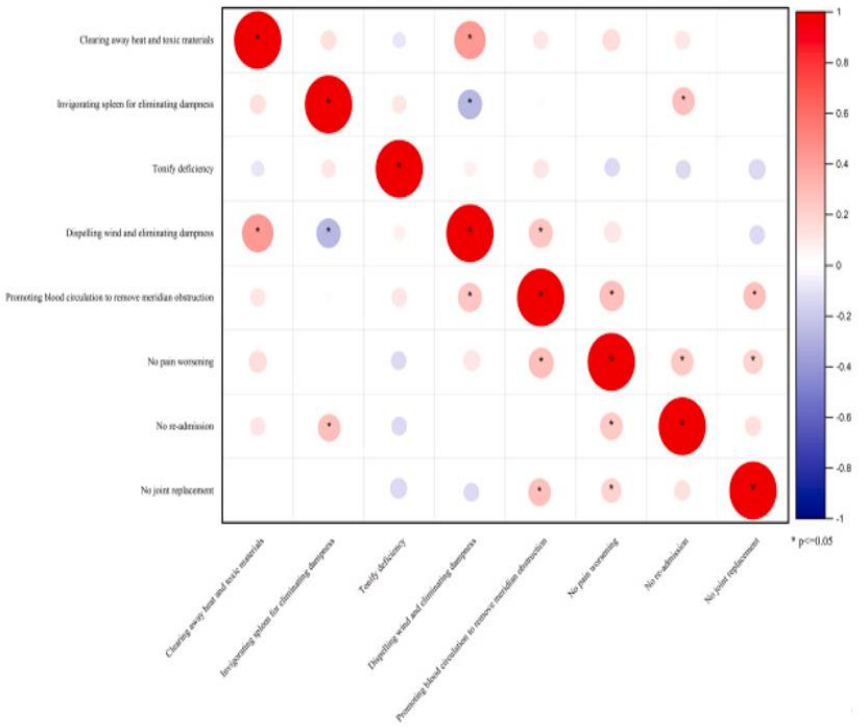
Analysis of herbal categories in relation to immune-inflammatory markers and patient outcomes in TCM users

We investigated how different classes of Chinese herbs relate to both immune-inflammatory markers and clinical improvements. Herbs aimed at strengthening the spleen and eliminating dampness were consistently central in the treatment formulations. Herbs that enhance blood circulation and clear meridians were particularly influential in reducing inflammatory markers, as well as in improving pain perception (VAS) and bodily pain scores (BP) **(Figure 8a)**. Additionally, herbs categorized as tonifying deficiencies showed strong associations with better scores across emotional, social, physical, role, general health, and mental health measures (RE, SF, PF, RP, GH, and MH).

Interestingly, herbs that stimulate circulation and clear meridians were also linked to fewer pain events and a lower probability of requiring joint replacement. In contrast, herbs that focus on spleen strengthening and dampness elimination were tied to a reduced risk of hospital readmission **(Figure 8b).**



a)



b)

Figure 8. Correlation heatmaps of CHM categories with immune-inflammatory markers (a) and patient outcomes (b). Note: Blue indicates a negative correlation, red indicates a positive correlation, and the size of each colored square reflects the correlation strength. (For interpretation of the colors in this figure, readers are referred to the Web version of this article.)

Our findings indicate that TCM therapy may help reduce the incidence of pain, hospital readmission, and joint replacement events, suggesting that CHM as an adjunctive treatment could offer clinical benefits in osteoarthritis management. Compared with prior research, this cohort study employs more extensive and diverse data-mining approaches, enhancing its depth and reliability. By utilizing association rules, cluster analysis, network diagrams, and random walk models, we analyzed all TCM prescriptions, laboratory indicators, PROs, and outcome events

in this cohort to identify key relationships between TCM interventions and OA patient outcomes. In addition, we developed a nomogram to predict patient prognosis, demonstrating greater clinical applicability and utility.

Among the 3,747 OA patients included in this study, 2,511 (67.01%) had received CHM at some point **(Table 1).** Compared to non-TCM users, patients receiving TCM showed a significant reduction in the risk of pain, readmission, and joint replacement events ($p < 0.001$, **Table 1**). Multivariate Cox proportional hazards analysis and survival curve evaluation revealed that TCM use was associated with lower risks of pain (HR = 0.416, 95% CI = 0.402–0.954, p = 0.025), readmission (HR = 0.489, 95% CI = 0.133–0.967, p = 0.022), and joint replacement (HR = 0.580, 95% CI = 0.135–0.982, p = 0.021) compared to non-TCM users **(Table 2; Figure 4)**, with the greatest benefits observed in patients receiving TCM for more than 24 months **(Figure 5)**. Specifically, TCM users experienced 58.4% lower pain incidence, 51.1% fewer readmissions, and 42% fewer joint replacements than non-users **(Table 2, Figure 2).**

Nomogram-based risk stratification demonstrated strong predictive performance for survival outcomes in both development and validation cohorts, allowing more precise assessment of patient risk. The nomogram validation confirmed excellent discrimination and calibration **(Figure 3)**. Age, osteoporosis, and diabetes emerged as consistent risk factors for pain, joint replacement, and readmission **(Table 2)**. Diabetes contributes to OA progression, exacerbates clinical symptoms, and promotes structural joint changes [30], primarily through chronic low-grade inflammation and oxidative stress caused by insulin resistance and prolonged hyperglycemia [31]. Women, particularly post-menopause, are at higher risk for knee osteoarthritis, likely due to the effects of estrogen [32]. Osteoporosis also increases OA susceptibility and can accelerate disease progression, with OA severity worsening as osteoporosis advances [33].

According to TCM theory, osteoarthritis is classified under bi-syndromes, which arise from a decline in the body's protective energy. External pathogenic factors such as wind, cold, dampness, and heat invade the body, obstruct meridians, and deplete primordial Qi and blood, resulting in joint pain, swelling, stiffness, and, in severe cases, deformity [10]. Herbal therapy in TCM is guided by syndrome differentiation to tailor treatments to individual patient needs. Chinese herbal medicine, a key component of TCM, is widely used for managing OA in China [34], with recent studies demonstrating its safety and efficacy in alleviating pain, improving function, and enhancing overall wellness in knee OA [35]. Customized TCM prescriptions offer distinct clinical advantages. In this study, 20 CHM herbs commonly used by OA patients were categorized into five groups: clearing heat and toxins, invigorating the spleen to remove dampness, tonifying deficiencies, dispelling wind and dampness, and promoting blood circulation to unblock meridians **(Figure 6a)**. Cluster and network analyses further identified characteristic CHM combinations, reflecting synergistic interactions among herbs. Frequently used combinations included blood circulation-promoting and stasis-removing herbs (Flos Carthami, Radix Salviae Miltiorrhizae, Semen Persicae) and spleen-strengthening, dampness-eliminating herbs (Pericarpium Citri Reticulatae, Poria) **(Figures 6b and 6c).**

Inflammation is central to OA pathogenesis, contributing to pain, swelling, and joint dysfunction [36]. CRP [37] and ESR [38] serve as widely used, cost-effective, noninvasive markers for initial diagnosis and monitoring treatment response. Activation of the innate immune system plays a crucial role in initiating and sustaining inflammation, thereby influencing OA pathology and pain [39]. Our findings demonstrated that TCM treatment significantly reduced ESR, CRP, IgA, and C4 levels, decreased VAS scores, and improved SF-36 outcomes in OA patients **(Table 4)**, with no observed liver or kidney abnormalities **(Table 5)**. To assess the long-term impact of TCM interventions, a random walk model was applied, revealing sustained correlations between TCM treatment and comprehensive patient indices, including immune-inflammatory markers, SF-36 scores, and VAS scores **(Figure 7).**

Association rule analysis, which identifies relationships and hidden patterns within data [40], showed that Herba Taraxaci Mongolici, Semen Coicis, and Rhizoma Chuanxiong were strongly linked to reductions in inflammatory markers such as ESR and CRP. Flos Carthami, Poria, and Radix Salviae Miltiorrhizae were associated with improvements in immune indices including IgG, IgM, IgA, C3, and C4 **(Table 6)**. Patient-reported outcomes, including the VAS [41] and SF-36 scales [42], confirmed that Radix Salviae Miltiorrhizae and Radix et Rhizoma Clematidis were key for improving VAS and BP scores, while Semen Coicis, Radix Angelicae Sinensis, and Poria contributed to improvements in other SF-36 domains. Interestingly, Herba Taraxaci Mongolici and Radix Achyranthis Bidentatae were strongly associated with pain exacerbation **(Table 3)**, Flos Carthami and Poria with readmission events, and Radix Angelicae Biserratae and Flos Carthami with joint replacement events **(Table 7).**

We further examined the relationships between different TCM herbal categories and their impact on immune-inflammatory markers and patient outcomes **(Figure 8)**. Herbs aimed at invigorating the spleen and eliminating dampness were central in treatment regimens, with Poria and Semen Coicis serving as the principal components. Herbs categorized as tonifying deficiencies, particularly Radix Angelicae Sinensis, were associated with improvements in SF, RE, MH, PF, RP, and GH scores. Herbs promoting blood circulation and unblocking meridians, including Radix et Rhizoma Clematidis Chinensis, Flos Carthami, and Radix Salviae Miltiorrhizae, contributed significantly to reductions in inflammatory markers, VAS scores, BP, and VT scores.

Regarding clinical outcomes, blood circulation-promoting herbs were linked to lower pain levels and a reduced likelihood of joint replacement, with Radix Achyranthis Bidentatae, Flos Carthami, and Radix Salviae Miltiorrhizae leading these effects. Herbs focused on spleen strengthening and dampness removal, primarily Poria, were associated with decreased readmission risk. Pharmacological studies show that Poria exerts antioxidant, anti-inflammatory, and immunomodulatory effects [43], while Semen Coicis demonstrates anti-inflammatory, analgesic, and immune-enhancing properties [44]. Radix Salviae Miltiorrhizae can mitigate cartilage damage by modulating JAK2/STAT3 and AKT signaling pathways [45], and Flos Carthami reduces cartilage destruction through inhibition of MMPs and ADAMTS5 [46]. Traditional texts describe Radix Achyranthis Bidentatae as nourishing the liver and kidneys, strengthening bones and muscles, and enhancing circulation [47], and modern research highlights its immune, bone metabolism, and joint protective effects. Radix Angelicae Biserratae possesses anti-inflammatory and anti-apoptotic properties in chondrocytes, which is crucial in OA progression [48]. Collectively, these herbs and their combinations were strongly associated with reductions in pain, readmission, and joint replacement, likely mediated through improvements in immune-inflammatory markers and patient-reported outcomes. Different herbal subgroups displayed varying therapeutic effects, offering guidance for clinical OA management.

Strengths and limitations

This study has several notable strengths. First, it is a large-sample, real-world, retrospective cohort study, providing insights into a broader, more heterogeneous patient population than typical clinical trials, which may enhance generalizability. Second, our prognostic model incorporated bootstrap and cross-validation techniques to calculate C-indices, time-dependent AUCs, and calibration curves, with robust replication in the validation cohort. Patients were grouped by therapy regimen rather than randomly, which may improve internal validation and applicability to diverse treatment strategies. Third, patient-reported VAS and SF-36 outcomes were thoroughly analyzed, highlighting the potential of CHM in improving quality of life for OA patients.

However, the study has limitations. Key factors such as smoking, diet, exercise, and stress were not available in the dataset. Being a single-center, retrospective cohort study, incomplete or unquantifiable hospitalization records limited validation of treatment effects. Further experimental studies are needed to clarify the mechanisms of herbal effects in OA. Finally, while internal validation confirmed strong discriminative performance, external validation is lacking due to patient confidentiality constraints; future multi-center studies are needed to confirm model generalizability.

Conclusion

Our findings indicate that TCM use is associated with reduced risk of pain progression, readmission, and joint replacement in OA patients, particularly among those receiving TCM for over 24 months. Herbs that promote blood circulation and unblock meridians, such as Radix Achyranthis Bidentatae, Flos Carthami, and Radix Salviae Miltiorrhizae, may lower the risk of pain and joint replacement, while herbs that invigorate the spleen and remove dampness, including Poria, may reduce the risk of readmission. Future randomized controlled trials are warranted to clarify causality and further substantiate these associations.

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Conflict of Interest: None

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