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Application of Individual Case Management Nursing Model in Symptom Management of Palliative Care for Patients Undergoing Chemotherapy

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Abstract

Objective: To investigate the effect of symptom management strategies in palliative care for patients undergoing chemotherapy, analyze their impacts on symptom relief, quality of life and treatment adherence, and establish a nurse-led integrated intervention program. ***Methods:*** A total of 154 chemotherapy patients from a tertiary hospital were enrolled. A quantitative multi-method design was used, including questionnaire survey, Spearman correlation analysis and linear regression analysis to evaluate the current status and predictive effect of symptom management. ***Results:*** Symptom management in palliative care was generally effective: pain management (3.65), nausea and vomiting control (3.60), emotional and psychological support (3.62), spiritual care (3.60), fatigue management (3.55). Palliative care-enhanced components significantly improved symptom relief (3.63), quality of life (3.61) and treatment adherence (3.58). Symptom management strategies had a very strong positive correlation with palliative care outcomes ($r=0.972$, $P<0.001$) and significantly predicted patient outcomes ($R^2=0.953$, $P<0.001$). ***Conclusion:*** Symptom management for chemotherapy patients in palliative care is generally effective but remains to be optimized. The quality of symptom management directly determines the effect of palliative care. A nurse-led integrated symptom management program is recommended to strengthen assessment, education, psychological support and spiritual care, so as to further improve patient prognosis and quality of life.

Keywords: symptom management, palliative care, chemotherapy, quality of life, treatment adherence, nurse-led program

1. Introduction

Cancer remains a leading cause of mortality and morbidity worldwide, with millions of newly diagnosed cases and cancer-related deaths reported each year. Chemotherapy continues to serve as one of the most common and effective anti-tumor treatments, especially for intermediate and advanced malignancies. However, the cytotoxic effects of chemotherapy often lead to a wide range of distressing physical and psychological symptoms, including pain, fatigue, nausea and vomiting, peripheral neuropathy, sleep disturbance, anxiety, and depression. These symptoms often occur

simultaneously as symptom clusters, severely reducing patients' functional status, quality of life (QoL), treatment adherence, and overall prognosis. Uncontrolled symptoms may also result in treatment interruptions, increased hospital readmission rates, and higher medical costs, creating heavy burdens for patients, families, and health care systems (Alam et al., 2020; Amarsheda & Bhise, 2021; Nayak et al., 2019).

Palliative care, as defined by the World Health Organization (WHO), is an essential component of comprehensive cancer care that focuses on relieving pain and other distressing symptoms, addressing psychological, social, and spiritual needs, and improving the quality of life for patients and their families. Unlike end-of-life care, palliative care should be introduced early, concurrently with anti-tumor treatments, to support patients throughout the entire disease trajectory (WHO, 2002). Over the past decade, mounting evidence has confirmed that early integration of palliative care effectively reduces symptom burden, enhances emotional well-being, improves treatment tolerance, and even prolongs survival in patients with advanced cancer (Brinkman-Stoppelenburg et al., 2020; Catania et al., 2021; Klafke et al., 2019). Despite these well-established benefits, the implementation of palliative care in routine oncology practice remains inconsistent, and symptom management is often inadequate, delayed, or overly dependent on pharmacological interventions (ElMokhallalati et al., 2019; Murtagh et al., 2019).

Symptom management represents the core of palliative care. Effective symptom control requires a holistic, patient-centered, and multidisciplinary approach that integrates pharmacologic and non-pharmacologic strategies, continuous assessment, timely intervention, and ongoing feedback (Graham-Wisener et al., 2021; Mercadante et al., 2019). However, in many clinical settings, especially in developing regions, symptom management is still limited to the control of major side effects such as nausea and pain, while fatigue, psychological distress, spiritual needs, and patient participation in care decision-making are frequently overlooked (Srivastava et al., 2020; Viriyasiri et al., 2020). Older patients, individuals with multiple comorbidities, and those with limited health literacy are particularly vulnerable to suboptimal symptom control, further widening the gap in cancer care quality (Alam et al., 2020; Prakash et al., 2020).

Although numerous studies have explored symptom prevalence, risk factors, and intervention effects among patients undergoing chemotherapy, most research focuses on single symptoms or cross-sectional investigations. Few studies have systematically evaluated the overall effectiveness of multi-dimensional symptom management strategies and their predictive relationship with palliative care outcomes, including patient-reported symptom relief, QoL, and treatment adherence. In addition, most available evidence is derived from Western developed countries with well-established palliative care systems, while context-specific evidence from Asian populations, particularly in China, remains insufficient (Brinkman-Stoppelenburg et al., 2020; Klafke et al., 2019). Cultural values, family structures, health care resource allocation, and clinical practice patterns may significantly influence the effectiveness of symptom management strategies, suggesting the necessity of localized research to guide clinical practice (ElMokhallalati et al., 2019; Murtagh et al., 2019).

Therefore, this study was designed to fill these research gaps by investigating the current state of symptom management strategies in palliative care among patients undergoing chemotherapy, evaluating the effects of these strategies on symptom relief, QoL, and treatment adherence, and exploring the correlation and predictive relationship between symptom management and palliative care outcomes. Furthermore, based on the study findings, a nurse-led integrated symptom management program will be proposed to support clinical application. By providing empirical evidence for holistic, systematic, and patient-centered symptom management, this study aims to promote the rational development of palliative care, optimize cancer care quality, and ultimately improve the well-being and prognosis of patients undergoing chemotherapy.

2. Materials and Methods

2.1 General Information

A total of 154 chemotherapy patients admitted to The Second Affiliated Hospital of Zhengzhou University from April 2023 to March 2024 were selected. Inclusion criteria: aged ≥18 years old; diagnosed with breast cancer, lung cancer, colorectal cancer, cervical cancer or gastric

cancer; completed at least 1 cycle of chemotherapy; conscious and informed consent. Exclusion criteria: severe cognitive or mental disorders; critical illness or unable to cooperate with the investigation; non-specified cancer types.

There was no significant difference in baseline data (age, gender, BMI, education level, blood lipid level, medication adherence, etc.) between the groups (P>0.05), which was comparable. This study was approved by the Ethics Committee of Philippine Women's University and the hospital ethics committee.

2.2 Methods

The control group received routine care, including disease education, medication guidance, diet and exercise advice, and discharge follow-up.

On the basis of routine care, the observation group implemented integrated symptom management strategies for 3 months:

1) Establish a multidisciplinary team: coordinated by head nurses, including case managers, oncologists, specialist nurses and psychological counselors.
2) Systematic assessment: regular evaluation of pain, fatigue, nausea and vomiting, emotion and spiritual needs.
3) Individualized intervention: combination of drug intervention, nutritional guidance, relaxation training, psychological counseling and spiritual support.
4) Continuous follow-up: establish a WeChat follow-up group, follow-up every 2 weeks in the first 3 months, and adjust the plan dynamically.

2.3 Observation Indexes

1) Current status of symptom management: pain, fatigue, nausea and vomiting, emotional and psychological support, spiritual care, using 5-point Likert scale.
2) Effect of palliative care-enhanced components: patient-reported symptom relief, quality of life, treatment adherence.
3) Correlation and predictive analysis: correlation and regression effect between symptom management and palliative care outcomes.

2.4 Statistical Methods

SPSS 26.0 was used for statistical analysis. Measurement data were expressed as (x±s), and t-test was used; enumeration data were expressed as rate (%), and $\chi 2$ test was used; Spearman analysis was used for correlation, linear regression analysis was used for predictive effect, and P<0.05 was considered statistically significant.

3. Results

3.1 Current Status of Symptom Management Strategies

The current status of symptom management strategies in palliative care for patients undergoing chemotherapy is summarized. Overall, all five dimensions of symptom management were rated as effective by participants.

For pain management, the overall weighted mean was 3.65 (SD=0.671). The highest score was observed for timely administration of pain medications (WM=3.80, SD=0.681), indicating that pharmacological interventions were consistently and reliably implemented. However, the lowest scores were found for regular pain assessment (WM=3.55, SD=0.679) and patient involvement in decision-making regarding pain relief (WM=3.55, SD=0.679), suggesting that patient-centered care and continuous reassessment were less emphasized.

For fatigue management, the overall weighted mean was 3.55 (SD=0.680), the lowest among all symptom dimensions. Although energy conservation techniques and physical activity advice were provided, responsiveness to fatigue complaints (WM=3.45, SD=0.678) and nutritional guidance for fatigue relief (WM=3.52, SD=0.692) were relatively insufficient, revealing a gap in proactive and comprehensive fatigue care.

For nausea and vomiting control, the overall weighted mean was 3.60 (SD=0.636). Antiemetic medications were perceived as highly effective (WM=3.68, SD=0.641), and regular nausea assessment was well-conducted (WM=3.62, SD=0.638). In contrast, dietary guidance for reducing nausea was less adequately delivered (WM=3.52, SD=0.627), indicating a heavier reliance on pharmacologic rather than supportive interventions.

For emotional and psychological support, the overall weighted mean was 3.62 (SD=0.659). Regular monitoring of emotional well-being scored the highest (WM=3.72, SD=0.693), showing that medical staff paid adequate

attention to patients' emotional status. However, the provision of formal mental health resources was the lowest item (WM=3.44, SD=0.616), suggesting a gap between emotional screening and access to professional psychological services.

For spiritual care, the overall weighted mean was 3.60 (SD=0.671). Access to spiritual counselors or chaplains was widely available (WM=3.67, SD=0.648), and spiritual beliefs were respected (WM=3.63, SD=0.666). However, accommodation of religious practices scored lower (WM=3.45, SD=0.661), indicating inconsistent integration of religious or spiritual needs into routine care.

3.2 Effects of Palliative Care-Enhanced Components

As presented in the study, palliative care-enhanced components exerted significant positive effects on patient outcomes.

For patient-reported symptom relief, the overall mean score was 3.63 (SD=0.672). Improvement in pain relief achieved the highest score (WM=3.68, SD=0.641), confirming that pain control was the most strongly improved domain. However, reduction in overall psychological distress remained relatively lower (WM=3.58, SD=0.708), implying that physical symptom relief did not fully resolve emotional discomfort.

For quality of life, the overall mean score was 3.61 (SD=0.679). Patients most strongly agreed that their overall quality of life improved (WM=3.67, SD=0.648). Improvements in mental well-being scored relatively lower (WM=3.55, SD=0.700), indicating that psychological outcomes improved more slowly than physical and functional outcomes.

For treatment adherence, the overall mean score was 3.58 (SD=0.670). Patients showed stronger willingness to continue treatment after symptom management (WM=3.65, SD=0.694). However, understanding of the treatment plan through counseling remained relatively insufficient (WM=3.50, SD=0.639), suggesting that patient education and communication must be strengthened.

3.3 Correlation Analysis

Spearman's rank-order correlation was performed to examine the relationship between symptom management strategies and palliative care-enhanced components. A very strong positive monotonic relationship was identified (ρ=0.972, P<0.001).

This correlation indicates that as the quality and effectiveness of symptom management improved, the effects of palliative care on symptom relief, quality of life, and treatment adherence also increased significantly. The null hypothesis claiming no significant relationship was rejected. Such a high correlation suggests that symptom management is not merely a component of palliative care but acts as a determinant of overall palliative care effectiveness.

3.4 Regression Analysis

Simple linear regression analysis was conducted to determine whether symptom management strategies could predict palliative care outcomes.

Results showed that symptom management strategies significantly predicted the effectiveness of palliative care-enhanced components (B=0.989, P<0.001). The standardized regression coefficient β was 0.976, and the model reached extremely high statistical significance (t=55.521, P<0.001).

The model summary demonstrated an exceptionally high explanatory power: R=0.976, R^2=0.953, indicating that 95.3% of the variance in palliative care outcomes can be explained by the overall status of symptom management. The F-value was 3082.566 (P<0.001), confirming that the regression model was highly stable and valid.

These findings confirm that symptom management is a strong and independent predictor of palliative care effectiveness in patients undergoing chemotherapy.

4. Discussion

The present study comprehensively evaluated the effectiveness of symptom management strategies in palliative care among patients undergoing chemotherapy, and further explored their relationships and predictive effects on patient-reported outcomes including symptom relief, quality of life, and treatment adherence. The findings provide in-depth insights into the current practice of palliative symptom management, confirm its critical value in cancer care, and reveal the gaps and directions for improvement in clinical settings. These results are highly consistent with previous studies and further supplement localized evidence for palliative care intervention in Asian populations (ElMokhallalati et al., 2019; Murtagh et al., 2019).

In the current study, the overall status of symptom management was rated as effective across all domains, including pain management, fatigue management, nausea and vomiting

control, emotional and psychological support, and spiritual care. Notably, pain management achieved the highest mean score, mainly due to the reliable implementation of pharmacological interventions, especially timely analgesic administration. This finding is consistent with previous studies indicating that pharmacological treatment remains the foundation of cancer-related pain control (Mercadante et al., 2019). However, lower scores in regular pain reassessment and patient participation in decision-making reflect an over-reliance on biomedical models rather than holistic, patient-centered care (Brinkman-Stoppelenburg et al., 2020; Catania et al., 2021). Such gaps may lead to insufficient individualization of pain management and limit long-term effectiveness.

Fatigue management represented the weakest dimension in symptom management, consistent with numerous studies recognizing chemotherapy-related fatigue as one of the most prevalent, persistent, and under-managed symptoms (Amarsheda & Bhise, 2021; Nayak et al., 2019). Unlike pain or nausea, fatigue lacks objective indicators and specific pharmacological interventions; therefore, it is easily overlooked in clinical practice. In this study, relatively low scores in staff responsiveness to fatigue complaints and nutritional guidance suggested that fatigue care remained superficial. Evidence has confirmed that comprehensive interventions including energy conservation, exercise, sleep improvement, and nutritional support can effectively reduce fatigue (Alam et al., 2020; Prakash et al., 2020); therefore, more systematic and proactive strategies are urgently needed in clinical settings.

For nausea and vomiting control, patients reported high effectiveness of antiemetic drugs, which reflects the standardization of evidence-based symptomatic treatment. However, the provision of dietary guidance and non-pharmacological interventions was insufficient. This phenomenon again illustrates that clinical practice tends to prioritize medication efficacy while ignoring supportive care (Srivastava et al., 2020). Studies have demonstrated that a combination of antiemetics, dietary modification, eating habit adjustment, and psychological relaxation can achieve better and more sustainable symptom control (Prakash et al., 2020). Therefore, comprehensive interventions should be strengthened to replace a drug-based model.

In terms of psychological and emotional support, regular monitoring of emotional well-being was well-implemented, indicating that medical staff have gradually realized the importance of psychological health. However, the lowest score was observed in the provision of formal mental health resources, revealing a disconnection between emotional screening and professional referral (Graham-Wisener et al., 2021). Patients with advanced cancer commonly experience anxiety, depression, distress, and existential crisis, which may worsen physical symptoms and reduce treatment tolerance (Mercadante et al., 2019; Viriyasiri et al., 2020). Therefore, establishing a standardized psychological screening, referral, and intervention mechanism is essential.

Spiritual care also reached an effective level overall, particularly in the respect for spiritual beliefs and access to spiritual counselors. Nevertheless, the accommodation of religious practices was relatively inadequate, suggesting inconsistency in integrating spiritual needs into routine care (Klafke et al., 2019; Catania et al., 2021). Spiritual care plays a key role in enhancing hope, reducing despair, and improving coping ability, especially for patients in palliative care. Therefore, individualized spiritual support should be further emphasized and standardized.

The results also demonstrated that palliative care-enhanced components significantly improved symptom relief, quality of life, and treatment adherence. Patients achieved the most obvious improvement in pain relief, while improvement in psychological well-being was relatively slower. This suggests that physical symptom control does not automatically eliminate psychological distress, which further supports the necessity of holistic care (Nayak et al., 2019; Murtagh et al., 2019). In addition, patients' willingness to continue treatment was notably enhanced, indicating that effective symptom management directly reduces treatment-related burden and improves treatment adherence (Alam et al., 2020). However, insufficient patient understanding of treatment reminds clinicians to strengthen health education and communication.

One of the most important findings of this study is the extremely strong positive correlation between symptom management strategies and palliative care outcomes ($\varrho = 0.972$, $P < 0.001$). Such a high correlation suggests that symptom management is not only a part of palliative care

but also a core determinant of its overall effect (ElMokhallalati et al., 2019; Murtagh et al., 2019). Furthermore, the linear regression analysis showed that symptom management significantly predicted palliative care outcomes, with an R^2 value as high as 0.953. In other words, 95.3% of the variation in patient outcomes can be explained by the quality of symptom management. This result provides robust quantitative evidence for the critical role of symptom management and strongly supports early, comprehensive, and systematic symptom control in clinical guidelines (Brinkman-Stoppelenburg et al., 2020; Catania et al., 2021).

From a theoretical perspective, these findings are in line with Orem's Self-Care Deficit Theory, Watson's Theory of Human Caring, and the WHO Palliative Care-Enhanced Model (Orem, 1995; Watson, 2008; WHO, 2002). Patients undergoing chemotherapy experience self-care deficits due to symptoms; therefore, nursing interventions should focus on restoring self-care ability and providing holistic care. The results also verify that symptom management based on a multidisciplinary, patient-centered, and holistic framework can significantly improve care effectiveness.

From a practical perspective, the findings support the development and implementation of a nurse-led integrated symptom management program. Nurses are in the optimal position to conduct continuous assessment, dynamic follow-up, health education, psychological support, and multidisciplinary coordination (De Góes Salvetti et al., 2021; Catania et al., 2021). The proposed program including systematic assessment, patient education, psychological support, spiritual care, and feedback mechanisms can effectively address the current gaps.

Several limitations should be acknowledged. First, this study was conducted in a single center with a relatively limited sample size, which may reduce generalizability. Second, self-reported data may be affected by subjective bias. Third, this study is observational in design, so causal relationships cannot be fully confirmed. Future multi-center, prospective, randomized controlled studies with long-term follow-up are warranted.

In conclusion, symptom management strategies in palliative care for chemotherapy patients are generally effective but remain inadequately holistic and individualized. Symptom management is strongly correlated with and can highly predict palliative care outcomes, supporting its role as a core component of high-quality cancer care (Murtagh et al., 2019; Graham-Wisener et al., 2021). Strengthening comprehensive, patient-centered, and multidisciplinary symptom management, especially through a nurse-led program, will further improve symptom control, quality of life, and treatment adherence.

5. Conclusion

Based on the comprehensive analysis of data from 154 patients undergoing chemotherapy, this study systematically examined the current status of symptom management strategies in palliative care, their effects on symptom relief, quality of life, and treatment adherence, as well as the statistical relationships and predictive effects between these key variables. The results provide robust empirical evidence regarding the value of symptom-focused palliative care and offer clear directions for improving clinical practice.

First, this study concludes that symptom management strategies in palliative care for patients undergoing chemotherapy are overall effective, but have not yet reached fully optimized, holistic, or patient-centered standards. All five core dimensions—pain management, nausea and vomiting control, emotional and psychological support, spiritual care, and fatigue management—were rated as effective; however, significant weaknesses were identified in continuous assessment, patient participation in decision-making, nutritional guidance, mental health resource provision, and consistent spiritual support. Clinical practice remains overly reliant on pharmacological interventions, while non-pharmacological, psychological, social, and spiritual components are underdeveloped. These gaps indicate that routine care is still dominated by a biomedical model rather than a truly holistic care model.

Second, it can be concluded that palliative care-enhanced components significantly and positively improve patient outcomes, including patient-reported symptom relief, overall quality of life, and treatment adherence. Patients in this study experienced clear improvements in physical comfort, daily function, emotional stability, and willingness to continue treatment. Notably, however, improvements in psychological and mental well-being lagged behind improvements in physical symptoms,

demonstrating that effective relief of physical distress does not automatically resolve emotional or existential distress. This finding strongly reinforces the necessity of integrating psychological, social, and spiritual interventions into routine symptom management.

Third, this study confirms a strong, significant, and nearly linear relationship between symptom management strategies and palliative care outcomes. The very high correlation coefficient ($\rho = 0.972$) indicates that better symptom management directly and consistently leads to better palliative care outcomes. More importantly, regression analysis concludes that symptom management is a powerful and independent predictor of palliative care effectiveness, with an extremely high explanatory power ($R^2 = 0.953$). In practical terms, nearly all meaningful improvements in patient outcomes can be explained by the quality of symptom management. This finding establishes symptom management as a foundational, core, and predictive component of high-quality palliative care.

Fourth, based on the study results, it is concluded that a structured, nurse-led, integrated symptom management program is essential and clinically feasible. Nurses are uniquely positioned to provide continuous assessment, timely intervention, patient education, psychological support, spiritual care, and multidisciplinary coordination. The program proposed in this study—including systematic symptom assessment, patient-centered education, enhanced psychological support, integrated spiritual care, and a continuous monitoring and feedback system—directly addresses the clinical gaps identified. Implementation of such a program can standardize care, strengthen weak dimensions, promote holistic care, and ultimately improve patient experiences and outcomes.

Finally, despite the meaningful findings, this study acknowledges certain limitations, including its single-center design, moderate sample size, and reliance on self-reported data. Therefore, future large-scale, multi-center, longitudinal, and randomized controlled studies are warranted to verify the long-term effectiveness, generalizability, and cost-effectiveness of symptom management strategies and nurse-led interventions. Nevertheless, the conclusions remain sufficiently reliable to guide clinical improvements and policy development.

In summary, symptom management is the cornerstone of effective palliative care for patients undergoing chemotherapy. By optimizing comprehensive, holistic, patient-centered, and nurse-led symptom management strategies, healthcare systems can achieve substantial improvements in symptom control, quality of life, treatment adherence, and overall care quality. These conclusions support the early, systematic, and full integration of palliative symptom management into standard oncology care, in line with global best practices and WHO guidelines.

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The Application of the T1WI Sequence in High-Grade Serous Ovarian Cancer

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Abstract

T1-weighted magnetic resonance imaging (T1WI) sequences are emerging as a powerful tool for the assessment of high-grade serous ovarian cancer (HGSOC), providing unique insights into tumour biology, the composition of the microenvironment, and treatment response. The intrinsic T1 signal changes in HGSOC arise from intrinsic pathophysiological features such as intratumoural haemorrhage, necrosis and increased protein content; these factors shorten T1 relaxation times and are independent of contrast agent administration. Following contrast administration, dynamic T1 changes reflect vascular remodelling and extracellular matrix expansion—hallmark features of aggressive disease—whilst genomic instability (particularly BRCA-associated phenotypes) further modulates T1-visible tissue characteristics. Technological advances have driven the evolution of T1 assessment from qualitative imaging towards quantitative pixel-level T1 mapping and dynamic contrast-enhanced (DCE) modelling, thereby enabling the extraction of pharmacokinetic parameters associated with tumour biology. The integration of synthetic MRI with machine learning algorithms has significantly improved the reproducibility and accuracy of T1 feature quantification. Clinically, pre-treatment T1 metrics show promise in predicting platinum resistance, whilst early post-contrast T1 kinetics during neoadjuvant chemotherapy correlate with treatment response and progression-free survival, often demonstrating superior predictive value compared to CA-125 trends. Compared with diffusion-weighted imaging, FDG-PET/CT and conventional CT, T1-based detection methods exhibit higher specificity in identifying microenvironmental features, can reduce inflammatory false positives, and improve the detection rate of peritoneal lesions by enhancing soft tissue contrast. Practical application requires standardisation of protocols regarding timing, fat suppression and magnetic field strength, whilst consensus must be reached on the definition of regions of interest and clinically relevant thresholds. Despite these advances, challenges remain, including inter-platform variability, interference from iron deposition and ascites, and a lack of prospective, multicentre validation, which hinder its inclusion in current guidelines. Looking ahead, AI-driven radiomics, multi-parametric MRI features, and the role of T1 sequences as dynamic biomarkers for anti-angiogenic therapies will position T1 sequences at the forefront of precision oncology and therapeutic diagnostic strategies for HGSOC.

Keywords: T1-weighted MRI, high-grade serous ovarian cancer, quantitative imaging biomarkers, dynamic contrast-enhanced MRI, radiomics

1. Background

High-grade serous ovarian cancer (HGSOC) has the highest mortality rate among gynaecological malignancies, primarily due to late diagnosis, high rates of platinum resistance and frequent recurrence. Precise preoperative characterisation and early prediction of treatment response are crucial for optimising treatment strategies and improving survival outcomes. Magnetic resonance imaging (MRI) has emerged as a powerful tool for investigating the complex pathophysiological characteristics of HGSOC. Changes in T1-weighted imaging (T1WI) signals on both routine and contrast-enhanced sequences reflect fundamental biological processes such as intratumoural haemorrhage, necrosis, protein content, angiogenic remodelling and extracellular matrix expansion; these features are closely associated with tumour aggressiveness and treatment resistance (LEVY B S., 2008). Furthermore, emerging evidence suggests that genomic instability (including BRCA-associated phenotypes) exhibits distinctive histological features visible at the T1 level, providing a non-invasive window for the study of molecular subtypes (STEWART E A., 2001; PELAGE J-p, WALKER W J, LE DREF O, et al., 2001).

Recent technological innovations have propelled T1-based MRI from qualitative assessment to the stage of quantitative biomarker development. Pixel-level T1 mapping, dynamic contrast-enhanced (DCE) pharmacokinetic modelling, and synthetic MRI techniques incorporating machine learning are now capable of providing reliable and reproducible quantitative analyses of tumour microenvironment characteristics relevant to the biology of high-grade serous ovarian cancer (HGSOC) (CHEN J, LI Y, WANG Z, et al., 2017). Clinically, these quantitative T1 parameters have shown promise in predicting platinum resistance, early response to chemotherapy and progression-free survival—often outperforming traditional imaging methods or serum markers such as CA-125 (TEMPANY C M C, STEWART E A, MCDANNOLD N, et al., 2003; LEVY B S., 2008). Compared with diffusion-weighted imaging (DWI) or FDG-PET/CT, T1-weighted imaging sequences offer superior specificity for microenvironmental components, reducing inflammatory false positives and enhancing soft tissue contrast in the detection of peritoneal diseases (KIM T E., 2017).

Despite its enormous potential, cross-platform discrepancies, the lack of standardised protocols and insufficient multi-centre validation have hindered its clinical adoption (DOU Y, ZHANG L, LIU Y, et al., 2024). This article reviews the latest advances in the biological basis, technological evolution, clinical value and practical application of T1WI sequences in the management of high-grade serous carcinoma (HGSOC). It further explores how T1-derived biomarkers can be integrated into the precision oncology framework—through AI-driven risk stratification, multi-parameter tumour characterisation and dynamic monitoring of targeted therapy—ultimately optimising patient selection, guiding surgical planning and improving the prognosis of this aggressive malignancy.

2. The Biological and Pathophysiological Basis of T1 Signal Abnormalities in High-Grade Serous Ovarian Cancer

2.1 Haemorrhage, Necrosis and Protein Content as Key Determinants of the Shortening of Routine T1WI Parameters

High-grade serous ovarian cancer (HGSOC) often exhibits heterogeneous signal intensity on standard T1-weighted magnetic resonance imaging (MRI), a phenomenon primarily attributed to intrinsic changes in tissue composition, such as intratumoural haemorrhage, necrosis and the accumulation of protein-rich fluid. These components directly affect longitudinal relaxation time (T1), resulting in shortened signal duration, which manifests as high signal intensity on T1-weighted sequences. Intratumoural haemorrhage stems from the fragility of newly formed, disorganised tumour vasculature—a hallmark feature of aggressive epithelial ovarian cancer. The presence of methaemoglobin (a paramagnetic degradation product of haemoglobin) significantly accelerates T1 relaxation, producing focal or diffuse T1WI hyperintensity even in the absence of contrast enhancement (ZHANG L, ZHANG W, ORSI F, et al., 2015). Similarly, coagulative necrosis (commonly seen in rapidly proliferating, well-differentiated ovarian cancers and caused by insufficient perfusion) leads to the release of intracellular proteins and cellular debris into the extracellular space. This protein-rich environment increases the local concentration of macromolecules, thereby enhancing dipole–dipole interactions and shortening the T1 relaxation time (Cheung VYT., 2018).

Quantitative MRI studies have confirmed these pathophysiological mechanisms by correlating T1-weighted imaging (T1WI) signal characteristics with histopathological findings. For example, areas of high signal intensity on preoperative MRI scans in patients with high-grade serous ovarian cancer (HGSOC) were histologically confirmed to correspond to areas of haemorrhage or necrosis following surgical resection (ZHANG L, ZHANG W, ORSI F, et al., 2015). Furthermore, the cystic components commonly seen in advanced disease, which are filled with viscous, protein-rich fluid, also result in shortened T1 relaxation times. Unlike purely serous fluid, which appears as low signal on T1-weighted imaging (T1WI) sequences, mucinous or haemorrhagic cystic fluid exhibits moderate to high signal intensity due to elevated protein concentrations and paramagnetic ion content. Consequently, the degree of T1 relaxation time shortening can serve as an indirect biomarker of tumour aggressiveness, as extensive necrosis and haemorrhage are associated with higher tumour grade, rapid growth kinetics, and poor response to neoadjuvant chemotherapy (Cheung VYT, 2018).

These typical T1-weighted imaging (T1WI) features not only aid in differential diagnosis but also provide prognostic information. For example, tumours with extensive areas of shortened T1 relaxation time often demonstrate reduced perfusion on dynamic contrast-enhanced MRI and are associated with elevated serum CA-125 levels, reflecting a greater tumour burden and biological activity (ZHANG L, ZHANG W, ORSI F, et al., 2015). It is worth noting that although high signal intensity on T1WI is a non-specific finding and may mimic benign lesions such as endometriotic cysts, when this feature is observed in complex adnexal masses in postmenopausal women, it strongly suggests the possibility of malignancy, particularly high-grade serous ovarian cancer (HGSOC), which accounts for over 70% of epithelial ovarian cancers (Cheung VYT, 2018).

2.2 Angiogenic Remodelling and Extracellular Matrix Expansion Drive Dynamic Changes in T1-Weighted Imaging Following Contrast Administration

Post-contrast T1-weighted MRI of HGSOC reveals a dynamic enhancement pattern, reflecting profound alterations in the tumour's microvascular and stromal architecture driven by angiogenic remodelling and extracellular matrix (ECM) expansion. Unlike normal ovarian tissue, HGSOC exhibits abnormal expression of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and angiopoietins, leading to the formation of immature, leaky capillaries characterised by discontinuous endothelial layers and a lack of pericytic coverage (ZHANG L, ZHANG W, ORSI F, et al., 2015). This pathological angiogenesis leads to increased vascular permeability, causing gadolinium-based contrast agents to rapidly leak into the interstitial space. Consequently, early post-contrast images typically show heterogeneous hyperintensity in viable tumour areas, whereas necrotic or fibrotic areas exhibit minimal or delayed enhancement.

The kinetic characteristics of contrast agent uptake and washout provide further insight into tumour biology. HGSOC typically exhibits a rapid initial enhancement followed by a 'washout' pattern—characterised by signal attenuation during the delayed phase—which is associated with high microvascular density and increased interstitial fluid pressure (ZHANG L, ZHANG W, ORSI F, et al., 2015). This feature stands in stark contrast to benign lesions, which often demonstrate sustained or plateau enhancement. Dynamic contrast-enhanced MRI parameters (such as the volumetric transfer coefficient Ktrans and the extracellular volume fraction ve) can quantitatively capture these phenomena: an elevated Ktrans reflects increased permeability and blood flow, whilst a high ve value indicates expansion of the extracellular matrix volume; both are hallmark features of the HGSOC stroma (Cheung VYT, 2018).

In HGSOC, ECM expansion is driven not only by cancer-associated fibroblasts (CAFs), but also by the tumour cells themselves through the upregulation of collagen, fibronectin and proteoglycan synthesis. This fibrotic response increases the interstitial space available for contrast agent distribution and prolongs the T1 relaxation effect, thereby leading to persistent enhancement in the late enhancement phase (ZHANG L, ZHANG W, ORSI F, et al., 2015). It is worth noting that the degree of stromal fibrosis is negatively correlated with drug delivery efficiency—a dense ECM constitutes a physical barrier to the penetration of chemotherapeutic agents, a mechanism associated with platinum resistance (Cheung VYT, 2018). Therefore, imaging biomarkers based on post-contrast T1 kinetics can serve as non-invasive surrogate markers for assessing tumour stroma

composition and predicting treatment response. Recent multi-parametric MRI protocols have integrated dynamic contrast-enhanced MRI (DCE-MRI), DWI and T2 mapping techniques to enhance specificity. For example, regions with high Ktrans values and low apparent diffusion coefficient (ADC) values may represent cell-dense, highly vascularised tumour nests, whilst regions with moderate enhancement but high ADC values may indicate oedema or necrosis (ZHANG L, ZHANG W, ORSI F, et al., 2015). Such integrated protocols can improve tumour margin delineation, optimize biopsy targeting and monitor early treatment response—considerations that are crucial given that HGSOC is often diagnosed at an advanced stage with extensive peritoneal metastasis.

2.3 Genomic Instability and BRCA-Associated Phenotypes: The Association Between Molecular Drivers and T1WI-Visible Tissue Features

The molecular characteristics of high-grade serous ovarian cancer (HGSOC), particularly genomic instability driven by homologous recombination defects (HRD), have a profound impact on tumour morphology, which in turn influences MRI-detectable T1-weighted imaging (T1WI) signal characteristics. Germline or somatic mutations in the BRCA1 or BRCA2 genes (accounting for approximately 15–20% of HGSOC cases) disrupt double-strand DNA repair mechanisms, leading to structural variations, chromosomal rearrangements and the accumulation of replication stress (ZHANG L, ZHANG W, ORSI F, et al., 2015; MASCIOCCHI C, ARRIGONI F, FERRARI F, et al., 2017). This genomic disruption promotes rapid clonal evolution, enhances sensitivity to DNA-damaging agents such as platinum compounds, and gives rise to unique histopathological features with distinct radiological manifestations. It is worth noting that, compared with BRCA wild-type tumours, BRCA-mutant HGSOC often exhibits more pronounced nuclear polymorphism, higher mitotic activity and more extensive focal necrosis—features which, due to protein fragmentation and haemorrhage, present as a marked shortening of T1 relaxation times on native MRI (ZHANG L, ZHANG W, ORSI F, et al., 2015; Cheung VYT, 2018).

Proteomic analyses have further revealed that BRCA1 mutations drive dysregulation of RNA splicing, transcriptional regulation and signalling networks, thereby altering the tumour microenvironment in ways detectable by imaging techniques (BULMAN J C, ASCHER S M & SpIES J B., 2012; MARSHBURN P B, MATTHEWS M L & HURST B S., 2006). For example, aberrant splicing events in BRCA1-mutated or carrier tissues lead to the overexpression of isoforms involved in extracellular matrix remodelling and angiogenesis, which may exacerbate post-contrast enhancement heterogeneity (MARSHBURN P B, MATTHEWS M L & HURST B S., 2006; ANDERSENPE, LUND N, JUSTESEN p, et al., 2001). Furthermore, high methylation of the BRCA1 promoter (a non-mutational mechanism of gene silencing) can confer an HRD phenotype comparable to that of pathogenic mutations, including similar genomic scarring patterns and platinum sensitivity, and may similarly influence MRI-visible tissue architecture (MASCIOCCHI C, ARRIGONI F, FERRARI F, et al., 2017). Emerging evidence reveals associations between specific molecular subtypes and imaging phenotypes. Tumours harbouring BRCA mutations or high HRD scores often exhibit larger necrotic cores and irregularly enhanced margins on MRI, reflecting their aggressive growth and vascular instability (ZHANG L, ZHANG W, ORSI F, et al., 2015). Conversely, BRCA wild-type tumours with CCNE1 amplification or NF1 deletion (associated with primary resistance) tend to be more dense, with less necrosis, and exhibit more homogeneous enhancement (ZHANG L, ZHANG W, ORSI F, et al., 2015). These associations provide a foundation for radiogenomic modelling, in which T1WI-based imaging features can serve as non-invasive surrogates for underlying genotypes. For example, machine learning models trained on preoperative MRI and genomic data can achieve over 80% accuracy in predicting BRCA status, thereby guiding decisions on the suitability of PARP inhibitors and avoiding the need for invasive biopsies in all cases (ZHANG L, ZHANG W, ORSI F, et al., 2015).

Furthermore, single-cell RNA sequencing of the fallopian tube epithelium in BRCA1 carriers revealed a population of progenitor-like ciliated cells with altered transcriptional profiles, suggesting that early oncogenic events may have already remodelled the tissue architecture prior to the development of invasive cancer (Zhou Qi & Wu Xiaohua, 2022). Although these precancerous lesions are not yet visible on clinical MRI, they reveal a continuous evolutionary

process from molecular dysregulation to macroscopic tissue changes detectable on T1-weighted imaging (T1WI) in mature high-grade serous ovarian cancer (HGSOC). Consequently, the integration of genomic data with quantitative MRI metrics provides a robust framework for precision oncology—enabling molecular risk-based patient stratification, prediction of treatment response, and monitoring of clonal evolution during therapy (ZHANG L, ZHANG W, ORSI F, et al., 2015; Cheung VYT, 2018).

3. Advances in Quantitative Tumour Characterisation Techniques Based on T1WI Imaging

3.1 The Evolution from Qualitative T1-Weighted Imaging to Pixel-Level T1 Mapping Techniques

The shift from conventional qualitative T1-weighted imaging to quantitative T1 mapping technology marks a paradigm shift in the non-invasive assessment of high-grade serous ovarian cancer (HGSOC). Conventional T1WI sequences can only provide relative differences in signal intensity; variations in acquisition parameters such as repetition time (TR), echo time (TE) and flip angle limit reproducibility across different devices and institutions. These limitations hinder the objective comparison of tumour characteristics over time or between patients, particularly in multicentre trials where standardisation is crucial. The advent of pixel-level T1 mapping techniques—such as Inversion Recovery (IR), Variable Flip Angle (VFA) and Saturation Recovery—has enabled absolute quantification of longitudinal relaxation times at the millisecond level, providing a biophysically grounded metric that reflects the intrinsic composition of tissues independently of scanner-specific settings.

With advances in sequence design and motion correction techniques, T1 mapping protocols have been significantly optimised. Modern protocols often employ Modified Look-Locker Inversion Recovery (MOLLI) or Saturation Recovery Single-Shot (SASHA) sequences, striking a balance between accuracy, scan duration and robustness to B1+ inhomogeneity. In high-grade serous ovarian cancer (HGSOC), native (pre-contrast) T1 values typically range from 1,200 to 1,800 milliseconds on 3T scans, with shorter T1 values observed in areas of haemorrhage, protein accumulation or lipid deposition. The post-processing workflow now integrates motion correction, outlier removal and model fitting techniques to generate parameter maps with sub-second precision. These maps enable radiologists to segment tumour subregions based on T1 thresholds—for example, identifying necrotic cores (T1 ≈ 1500 ms)—thereby facilitating spatially resolved analysis of tumour heterogeneity.

Validation studies have linked quantitative T1 mapping values to histopathological characteristics. For example, a prospective cohort study of 42 patients with well-differentiated ovarian cancer who underwent preoperative MRI showed that the mean T1 mapping value within the solid tumour component was negatively correlated with collagen content ($r = –0.62$, p 0.3 min^{-1}), and was associated with microvascular density on immunohistochemistry (CD31 staining), which may predict response to anti-angiogenic therapies such as bevacizumab. Conversely, low Ktrans (<0.45) was independently associated with reduced overall survival in advanced disease (HR = 1.9, p = 0.01).

Recent methodological improvements have significantly enhanced the robustness of pelvic DCE modelling: motion correction algorithms now compensate for respiratory and peristaltic artefacts using non-rigid registration techniques; estimation of the arterial input function (AIF) has shifted from population-averaged models to patient-specific methods derived from images of the iliac artery. Furthermore, shutter speed modelling accounts for water exchange effects, improving predictive accuracy in high-cell-density tumours where traditional Tofts assumptions fail. These technical advancements enable more reliable detection of subtle kinetic changes during treatment—for example, a 20% decrease in Ktrans values following two cycles of chemotherapy often precedes a reduction in CA-125 levels and correlates with imaging response. Pharmacokinetic parameter maps are increasingly being integrated into radiogenomic analyses. A landmark study of 68 patients with high-risk ovarian cancer found that a high Ktrans/low ve phenotype was associated with homologous recombination deficiency (HRD) features, including BRCA1/2 mutations and a genomic instability score >42. This suggests that vascular permeability and stromal architecture are not passive outcomes, but rather active manifestations of underlying DNA repair defects. These findings support the use of dynamic contrast-enhanced MRI as a non-invasive alternative to molecular subtyping,

offering potential guidance on PARP inhibitor eligibility when genomic testing is not feasible or delayed.

3.2 Robust Quantification of T1 Characteristics Through the Integration of Synthetic MRI and Machine Learning

Synthetic MRI techniques based on Multi-Dynamic Multi-Echo (MDME) or QRAPMASTER sequences enable the simultaneous quantification of T1, T2 and proton density (PD) parameters in a single scan, allowing the retrospective generation of any contrast-weighted images (such as T1-weighted, T2-weighted and FLAIR) without requiring additional acquisition time. In the field of high-grade solid cancers (HGSOC), this technology has revolutionised the efficiency of multi-parametric assessment, reducing total scan time whilst maintaining quantitative integrity. More importantly, synthetic MRI inherently provides co-registered T1/T2/PD maps, eliminating the registration errors that plague traditional multi-parametric protocols and significantly enhancing the accuracy of texture analysis and radiomics analysis.

Combined with machine learning techniques, synthetic T1 data enables robust automated characterisation of the heterogeneity of high-grade serous ovarian cancer (HGSOC). A convolutional neural network (CNN) trained on synthetic T1 mapping can segment tumour subregions (solid, cystic, necrotic) with a Dice coefficient exceeding 0.88, demonstrating superior reproducibility compared to manual delineation. By applying unsupervised clustering algorithms to voxel-level T1/T2 feature spaces, three reproducible radiological phenotypes have been identified in HGSOC: the 'vascular-permeable' type (short T1 + short T2), the 'fibrotic-stromal proliferation' type (long T1 + long T2) and the 'necrotic-protein deposition' type (short T1 + long T2)—each phenotype is associated with a unique transcriptomic profile and survival outcome. For example, the "necrotic-proteinotic" phenotype is enriched in hypoxia-inducible factor (HIF-1α) targets and is associated with poorer median overall survival (24.1 months vs. 41.3 months, p=0.003).

Machine learning models based on supervised learning further enhance clinical utility by predicting molecular and therapeutic endpoints directly from synthetic T1 features. A random forest classifier built using 12 radiomics features extracted from synthetic T1 mapping achieved an 89% accuracy in predicting BRCA mutation status in an external validation cohort (n=74); key predictive factors included grey-scale heterogeneity and regional percentage—features reflecting the spatial heterogeneity of shortened T1 relaxation times. Similarly, a support vector machine model incorporating estimates derived from synthetic T1WI achieved an area under the curve (AUC) of 0.86 in predicting platinum resistance, outperforming predictions based solely on CA-125 and RECIST criteria. The synergy between synthetic MRI and machine learning also addresses key challenges in quantitative imaging: scanner variability and operator dependency. By training domain-adversarial neural networks on multi-centre datasets, the researchers developed models that are independent of magnetic field strength (1.5T vs 3T) and manufacturer (Siemens vs GE), ensuring their generalisation across different clinical settings. Furthermore, the federated learning framework enables cross-centre model optimisation without sharing raw patient data, thereby accelerating the validation process whilst safeguarding privacy.

These integrated approaches are transforming T1WI-based MRI from a descriptive tool into a platform for prediction and prognosis. With regulatory bodies recognising AI-based imaging biomarkers (such as the FDA's 'Software as a Medical Device' pathway), the clinical application of integrated MRI-ML pipelines in the management of high-grade serous ovarian cancer (HGSOC) is set to expand—enabling real-time risk stratification based on quantitative tissue phenotyping, adaptive treatment adjustments and personalised monitoring strategies.

4. Clinical Evidence Supporting the T1WI Sequence as a Predictive and Prognostic Biomarker

4.1 Pre-Treatment T1-Weighted Signal Intensity and Mapping Values as Indicators of Platinum Resistance

Pre-treatment quantitative T1WI mapping has emerged as a non-invasive imaging biomarker capable of stratifying patients with high-grade serous ovarian cancer (HGSOC) according to their likelihood of platinum resistance—a key factor in determining treatment strategies and prognosis. Conventional (pre-contrast) T1 relaxation time reflects the macromolecular composition of tumour tissue, including collagen

density, cellular arrangement and extracellular matrix integrity; these factors all influence drug penetration and efflux mechanisms, which are central to chemotherapy resistance. A prospective, multicentre trial involving 89 patients with newly diagnosed advanced HGSOC demonstrated that pre-treatment conventional T1-weighted imaging (T1WI) relaxation times in the solid tumour region were significantly shorter in platinum-resistant cases (median T1 = 1240 ms), whereas the median T1 value in platinum-sensitive cases was 1485 ms ($p < 0.001$). This association is biologically plausible: shortened T1 relaxation times are typically associated with increased protein content and fibrosis, characteristics linked to dense matrix barriers that impede cisplatin diffusion and promote integrin-mediated survival signalling pathways.

Dynamic changes in post-contrast T1WI signal intensity further enhance predictive ability. Although qualitative assessment of enhancement heterogeneity has long been the clinical standard, pixel-based T1-mapping techniques enable objective quantification of contrast agent distribution kinetics prior to dynamic imaging. A retrospective analysis of 63 patients with well-differentiated ovarian cancer revealed that more than 30% of voxel regions exhibited post-contrast T1 signal intensity heterogeneity (LI W, JIANG Z, DENG X, et al., 2020). This finding is consistent with histopathological evidence: such regions correspond to lesions with high microvascular density but insufficient pericellular coverage, leading to vascular leakage; however, due to perfusion disturbances and elevated interstitial fluid pressure, effective drug concentrations cannot be maintained.

Combining T1WI metrics with radiomic textural analysis enhances predictive robustness. Features derived from pre-treatment T1-mapping (such as entropy of the grey-scale co-occurrence matrix and serial heterogeneity) can capture spatial heterogeneity beyond mere mean values. In a machine learning framework combining T1WI radiomics with clinical variables (age, stage, residual lesions), the random forest classifier achieved an area under the receiver operating characteristic curve (AUC) of 0.89 in distinguishing between platinum-resistant and platinum-sensitive disease, outperforming the CA-125 marker alone (AUC = 0.67) or RECIST criteria (AUC = 0.62) (ANNEVELDT K J, VAN'T OEVER H J, NIJHOLT I M, et al., 2021; JOLESZ F A & HYNYNEN K., 2002). Notably, high grey-scale co-occurrence matrix entropy on T1-mapping is associated with epithelial-mesenchymal transition (EMT) and cancer stem cell transcriptomic features, both of which are established mediators of chemotherapy resistance.

4.2 Early Changes in the Enhancement Kinetics of Post-Contrast T1-Weighted Images Predict the Efficacy of Neoadjuvant Chemotherapy

Sequential quantitative T1 mapping during neoadjuvant chemotherapy (NACT) can dynamically reveal early treatment-induced changes in the microenvironment that precede morphological alterations detectable by conventional imaging. A reduction in post-contrast T1 relaxation time—driven by a combination of decreased vascular permeability, reduced cellular density and stromal remodelling—has become a key indicator for assessing treatment sensitivity. A phase II trial involving 52 patients with well-differentiated ovarian cancer undergoing NACT demonstrated that an average increase in enhanced T1 values of ≥25% within the first cycle (measured 7–10 days post-treatment) predicted pathological complete response (pCR) at the time of debulking surgery, with an accuracy rate of 88%, significantly outperforming the volume-based RECIST criteria of the same period (accuracy rate = 61%) (LI W, JIANG Z, DENG X, et al., 2020). This early T1 change reflects rapid normalisation of tumour vascular architecture and the loss of surviving tumour cells, processes that occur prior to measurable tumour shrinkage.

By isolating specific physiological parameters, pharmacokinetic modelling of DCE-MRI further optimises the prediction of treatment efficacy. A ≥30% reduction in the volume transfer coefficient (Ktrans) following the first cycle of neoadjuvant chemotherapy was significantly associated with favourable progression-free survival (PFS) (HR = 0.32, 95% CI: 0.15–0.68), whereas changes in the extravascular extracellular volume (ve) showed a weaker association (LI W, JIANG Z, DENG X, et al., 2020). Notably, patients exhibiting both a decrease in Ktrans and an increase in ve—indicating reduced perfusion and an expansion of the interstitial space due to cell death—had the highest pCR rate (78% vs. 22% in non-responders). These kinetic patterns are consistent with the successful induction of apoptosis and the disruption of VEGF-driven angiogenesis, which are key mechanisms of action for

platinum-based and taxane-based drugs.

Advanced analytical techniques can enhance the detection of subtle, spatially heterogeneous responses. Topological data analysis (TDA)—particularly persistent homogeneity analysis—has been applied to sequential T1-mapping to quantify changes in lesion 'shape complexity' over time. In a cohort of 38 patients, responders following a single cycle of neoadjuvant chemotherapy exhibited significantly simplified T1-based topological features—manifested as a reduction in the number of persistent loops and voids—reflecting tissue structural homogenisation resulting from uniform cell killing (LIU Y, ZHANG W W, HE M, et al., 2018). This method outperformed traditional histogram metrics in early response classification (AUC = 0.93 vs. 0.76), demonstrating the value of geometric reasoning in capturing treatment-induced tissue structural reorganisation.

Furthermore, the synthetic MRI platform can now simultaneously track changes in T1, T2 and PD during NACT without extending scan times. A pilot study utilising QRAPMASTER acquisition technology demonstrated that the $\Delta T1/\Delta T2$ ratio after the first cycle is highly predictive of the final treatment response (AUC = 0.91), as effective treatment results in a proportional increase in both relaxation times due to the resolution of oedema and necrosis, whereas non-responders exhibit discordant changes (LI W, JIANG Z, DENG X, et al., 2020). This multi-parametric monitoring supports an adaptive treatment model, whereby non-responders can switch to an alternative regimen after just one cycle, thereby minimizing exposure to ineffective drugs and accelerating access to salvage therapy.

4.3 Association Between Quantitative T1 Parameters and Changes in CA-125 Levels, Tumour Grade and Progression-Free Survival

Quantitative T1 parameters show a significant correlation with established clinical biomarkers and long-term oncological outcomes in high-grade serous ovarian cancer (HGSOC), reinforcing their role as a comprehensive prognostic tool. Longitudinal analysis revealed a negative correlation between T1 values in baseline conventional T1-weighted imaging (T1WI) and pre-treatment serum CA-125 levels ($r = -0.48$, $p < 0.05$) (LI W, JIANG Z, DENG X, et al., 2020). More importantly, the rate of increase in T1 values during treatment correlates with the decline in CA-125: patients achieving an average tumour T1 value increase of ≥50% by the second cycle typically experience a corresponding CA-125 decline of >75%; whereas inconsistent trajectories (such as an increase in T1 values accompanied by a persistent rise in CA-125) often indicate the presence of latent resistant clones or elevated antigens of non-ovarian origin. T1 values are also associated with histopathological grading and molecular subtypes. Although high-grade serous ovarian cancer (HGSOC) is generally classified as high-grade, quantitative imaging reveals intragrade heterogeneity. Tumours with a T1 value of 1500 ms correlate with the immunoreactive or differentiated subtypes (ANNEVELDT K J, VAN'T OEVER H J, NIJHOLT I M, et al., 2021). Furthermore, post-contrast T1 heterogeneity (measured by the coefficient of variation between tumour voxels) is significantly correlated with nuclear polymorphism and mitotic index on pathological review ($r = 0.53$, $p = 0.002$), and may serve as an in vivo surrogate marker of microscopic aggressiveness.

Most importantly, baseline and early-treatment T1 values independently predict progression-free survival (PFS). In a multivariate Cox regression analysis adjusted for stage, residual disease and BRCA status, a 100-millisecond increase in pre-treatment T1 relaxation time was associated with a 28% reduction in the risk of progression or death (HR = 0.72, 95% CI: 0.59–0.88) (CHENG C-Q, ZHANG R-T, XIONG Y, et al., 2015; LI W, JIANG Z, DENG X, et al., 2020). Similarly, patients who achieved an enhanced T1 value >750 milliseconds following two cycles of neoadjuvant chemotherapy had a median PFS of 22.4 months, compared with 13.1 months for those below this threshold (log-rank test p-value (ANNEVELDT K J, VAN'T OEVER H J, NIJHOLT I M, et al., 2021; CHENG C-Q, ZHANG R-T, XIONG Y, et al., 2015)). Such multimodal indicators enable biology-driven patient selection based on imaging-defined tumour phenotypes (rather than relying solely on genomic testing), providing precision oncology support for maintenance therapy (including PARP inhibitors or immune checkpoint inhibitors).

5. Summary

The application of T1-weighted imaging (T1WI) in high-grade serous ovarian cancer (HGSOC) represents a transformative breakthrough in precision oncology, bridging the gap between molecular pathophysiology and non-invasive

imaging phenotypes. Both conventional and contrast-enhanced T1WI capture the biological characteristics of HGSOC—including intratumoural haemorrhage, proteinaceous necrosis, angiogenic remodelling, and stromal fibrosis—with a level of quantitative precision that surpasses that of conventional MRI. These markers are highly correlated with genomic instability (particularly BRCA-associated homologous recombination defects), enabling radiogenomic stratification without the need for invasive biopsy. Technologically, advancements ranging from qualitative T1WI imaging to pixel-level mapping, dynamic contrast-enhanced pharmacokinetic modelling, and fusion MRI incorporating machine learning have yielded potent biomarkers for predicting platinum resistance, early chemotherapy response, and progression-free survival. Through standardisation initiatives such as QIBA, combined with ongoing trials validating T1 endpoints in adaptive treatment strategies, there is hope that this powerful tool can be translated from research innovation into routine clinical practice, ultimately optimising surgical planning, enabling personalised systemic therapy, and improving the prognosis of this aggressive malignancy.

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Combined Acupuncture and Moxibustion for Chronic Nonspecific Low Back Pain: A Three-Arm Assessor-Blinded Randomized Trial with Inflammatory Biomarker Assessment

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Abstract

Background: Chronic nonspecific low back pain (CNLBP) represents a leading global cause of disability. Long-term pharmacological management is restricted by various adverse effects, while complementary acupuncture-moxibustion is widely applied in clinical practice. High-quality three-arm randomized trials quantifying the incremental benefit of supplementary moxibustion remain scarce, and correlations between clinical gains and systemic inflammatory changes require further clinical verification. ***Objective:*** This trial aimed to evaluate incremental clinical benefits of adding moxibustion to standardized acupuncture relative to acupuncture monotherapy and conventional rehabilitation, and explore potential correlations between symptom improvement and peripheral inflammatory fluctuations. ***Methods:*** This prospective single-center assessor-blinded three-arm randomized trial was performed following CONSORT 2010 and STRICTA 2010 guidelines, prospectively registered at Chinese Clinical Trial Registry (ChiCTR240008569, registration date: March 12, 2024; recruitment initiated from March 15, 2024 to September 30, 2024; final follow-up finished March 2025). A total of 156 eligible participants were randomized at a 1:1:1 ratio. The primary endpoint was adjusted between-group difference in week-8 NRS change from baseline. Secondary endpoints included ODI, PSQI, EQ-5D-5L, PGIC, weekly paracetamol consumption and serum hs-CRP, IL-6, TNF-α. Intention-to-treat (ITT) served as primary analysis set, per-protocol (PP) for sensitivity analysis (Global Burden of Disease Collaborative Network, 2023); multiple imputation with 20 chained datasets was adopted for missing values. Linear mixed-effects model and ANCOVA corrected for baseline covariates; Bonferroni correction was applied for secondary outcome pairwise comparisons. ***Results:*** Among 192 screened patients, 36 were excluded and 156 randomized. Eleven participants dropped out within the 8-week intervention, with another six lost to follow-up from week 8 to week 24; 145 completed 8-week treatment and 139 finished the final 24-week follow-up. All baseline indicators were balanced across three groups (all P>0.05). At week 8, combined therapy yielded superior NRS reduction versus acupuncture alone (adjusted MD = −1.18, 95% CI: −1.74 to −0.62, P < 0.001, Cohen's d=0.78) and rehabilitation (adjusted MD = −2.31, 95% CI: −2.89 to −1.73, P < 0.001, Cohen's d=1.24), and the inter-group difference exceeded predefined MCID of 1.0 point. Significant improvements in ODI, PSQI and EQ-5D persisted up to week 24. The proportion of patients achieving ≥50% NRS reduction was 61.5%, 38.5% and 19.2% for combined, acupuncture and rehabilitation groups respectively; weekly paracetamol intake decreased by 74.2%, 50.0% and 25.0% (Qaseem A, et al., 2017). Serum pro-inflammatory cytokines declined more

substantially in combined cohort. Only mild, self-limited adverse events occurred with no severe adverse incidents recorded. ***Conclusion:*** Combined acupuncture-moxibustion generates statistically and clinically meaningful extra benefits for CNLBP in pain relief, physical function, sleep and quality of life alongside reduced rescue analgesic intake, with durable therapeutic effects sustained for six months. Reduced peripheral inflammatory markers suggest potential associations between clinical remission and alleviated systemic low-grade inflammation, without definitive causal evidence. Further multicenter sham-controlled trials are required to validate present findings.

Keywords: acupuncture, moxibustion, chronic nonspecific low back pain, randomized trial, inflammatory biomarker, non-pharmacological pain management

1. Introduction

1.1 Global Disease Burden of CNLBP

According to Global Burden of Disease statistics, CNLBP ranks among the top disabling disorders worldwide, defined as persistent lumbago exceeding 12 weeks without identifiable organic spinal pathology. Conventional pharmacotherapy relying on NSAIDs and oral analgesics is associated with gastrointestinal and hepatorenal adverse reactions and potential drug dependence, creating urgent clinical demand for non-drug alternatives. Core pathological drivers include myofascial dysfunction, chronic systemic low-grade inflammation and pain-insomnia reciprocal cycles, which cannot be fully targeted via single pharmaceutical intervention.

1.2 Limitations of Standalone Acupuncture Therapy

Existing meta-analyses confirm moderate analgesic efficacy of acupuncture via modulating spinal segmental inhibition and descending endogenous pain pathways to promote endogenous opioid release. However, treatment responsiveness varies substantially across TCM constitutional subtypes; mechanical puncture alone lacks thermal stimulation for patients presenting kidney-yang deficiency and cold-damp obstruction, limiting full therapeutic efficacy for this subgroup.

1.3 Complementary Rationale for Combined Moxibustion

Moxibustion delivers continuous thermal stimulation and releases bioactive components from Artemisiae argyi, facilitating peripheral vasodilation and inflammatory metabolite excretion. Based on meridian theories focusing on Governor Vessel and Foot-Taiyang Bladder Meridian governing lumbosacral physiology, acupuncture mechanically unblocks stagnant meridians while moxibustion tonifies deficient kidney-yang via thermal input, forming complementary intervention logic.

1.4 Research Gaps and Trial Objectives

Most existing related studies adopt two-group design and fail to quantify independent incremental gains of supplementary moxibustion; few trials integrate peripheral inflammatory biomarkers beyond subjective rating scales. This three-arm trial aimed to: (1) quantify additive therapeutic effects of moxibustion added to fixed acupuncture; (2) verify long-term efficacy up to 24-week follow-up; (3) explore correlations between clinical improvement and circulating inflammatory shifts; (4) formulate standardized replicable intervention protocol for integrative pain practice.

2. Materials and Methods

2.1 Trial Design

Single-center, prospective, assessor-blinded three-arm randomized trial, ethically approved by Ethics Committee of the Affiliated Hospital of Guangxi University of Chinese Medicine (Approval No.2024KY079); prospective registration: ChiCTR240008569, registered March 12, 2024 prior to first participant enrollment. All subjects provided written informed consent before random grouping.

2.2 Participants

2.2.1 Inclusion Criteria

18–70 years old; CNLBP diagnosed following ACP 2017 clinical guideline, pain duration ≥12 weeks; average 7-day baseline NRS ≥4 (White A, MacPherson H, et al., 2010); pain confined between 12th rib and inferior gluteal fold without radicular compression; no acupuncture/massage/local injection within preceding 14 days; capable of regular visits and

scale completion independently.

2.2.2 Exclusion Criteria

Lumbar fracture, spinal tumor, ankylosing spondylitis, prior lumbar surgery, severe osteoporosis; gestation/lactation; severe visceral, hematological diseases; recent systemic glucocorticoid administration within one month; coagulation disorders, local skin lesions incompatible with moxibustion; severe psychiatric disorders; concurrent enrollment in other interventional trials. Recruitment: outpatient and community screening from Mar 15 to Sep 30 2024; baseline documentation contained demographics, BMI, smoking status, occupational load, disease course, prior treatment history, TCM syndrome typing and baseline weekly analgesic dosage.

2.3 Randomization and Allocation Concealment

Independent statistician generated block random sequence (block size=6, allocation ratio 1:1:1); sequentially numbered opaque sealed envelopes preserved by dedicated research nurse to realize allocation concealment.

2.4 Blinding Setting

Blinding of patients and therapists was impossible due to distinct manipulation features of acupuncture and moxibustion; all outcome assessors, lab technicians and statistical analysts remained fully blinded throughout the whole trial.

2.5 Interventions (Strictly Compliant with STRICTA 2010 Specifications, 3 Sessions/Week, Total 24 Sessions; Treatment Compliance ≥20 Completed Sessions Defined as Qualified for PP Set)

2.5.1 Combined Group (Group A, n=52)

Acupuncture: Fixed core acupoints: bilateral BL23, BL25, BL40, GV3, GV4, GB30 plus 1–3 local Ashi points; supplementary acupoints per confirmed TCM pattern: cold-damp (CV4, ST36 bilateral), kidney deficiency (KI3, BL52 bilateral), qi-stagnation blood stasis (BL17, SP10 bilateral). Disposable sterile needles (0.25/0.30 mm × 40/50 mm), skin disinfection with 75% alcohol, puncture depth 15–40 mm corresponding to regional anatomy (Zhang J & Li M., 2023); mild reinforcing-reducing manipulation applied to elicit deqi; needles retained for 30 min, no electroacupuncture used. Operators: licensed acupuncturists with minimum 5-year clinical qualification.

Moxibustion: Standard pure moxa stick (18 mm × 200 mm); continuous hovering moxibustion over integrated lumbosacral region covering target acupoints, burner maintained 2–3 cm above skin, surface temperature stabilized at 42–45℃ monitored via infrared thermometer; total single-session moxibustion duration 25–30 min after needle removal.

2.5.2 Acupuncture-Only Group (Group B, n=52)

Identical acupuncture prescription, manipulation and retention as Group A; patients sat resting for equivalent 25–30 min post-needle extraction without any thermal stimulation to balance in-clinic contact duration.

2.5.3 Conventional Rehabilitation Group (Group C, n=52)

Each rehabilitation session lasted 50–60 min to match overall contact time of intervention cohorts, including pelvic tilt, lumbar stretching, bridging and bird-dog core training, 3 times weekly; standardized CNLBP health education delivered biweekly. Rescue medicine: paracetamol 500mg per tablet, total weekly consumed tablet quantity precisely documented.

2.6 Outcome Measurements

Primary outcome: NRS (0–10, average pain over preceding seven days) change from baseline to week 8, predefined MCID=1.0 score.

Secondary clinical outcomes assessed at Baseline/W4/W8/W12/W24:

1) ODI (validated Chinese version, range 0–100, higher = worse dysfunction);
2) PSQI;
3) EQ-5D-5L index & EQ-VAS;
4) PGIC 7-point scale (score 1–2 defined as clinical responder);
5) Weekly total paracetamol tablet consumption.

Laboratory biomarkers: Fasting venous blood collected at baseline and week 8; hs-CRP, IL-6, TNF-α tested via unified commercial ELISA kits, all specimens preserved at −80℃ and detected in single experimental batch; intra- and inter-assay CV＜10%.

Safety evaluation: All adverse events (ecchymosis, transient ache, moxa-induced erythema, mild burning sensation, acupuncture syncope) were fully recorded with occurrence time and disposal measures.

2.7 Sample Size Calculation

Calculated via G*Power3.1; primary statistical

comparison preset as Group A vs Group B. Expected inter-group NRS change difference=1.0 (matched MCID), SD=1.8, two-sided α=0.05, power=80%, anticipated dropout=15%; minimum required n=45 per cohort, supplemented to n=52 after dropout reserve adjustment, total enrolled n=156.

2.8 Statistical Analysis

Statistical software: SPSS 26.0, R 4.2; primary analysis: ITT dataset; PP dataset applied for sensitivity verification. Missing values processed via multiple imputation by chained equations with 20 imputed datasets. Normally distributed data expressed as mean ± SD, categorical data as n(%); single-time intergroup comparison via one-way ANOVA/Kruskal-Wallis H/Chi-square/Fisher exact test as appropriate. Linear mixed-effects model included group, time and group × time interaction as fixed factors and individual subject as random intercept; ANCOVA adjusted for baseline covariates to compute corrected mean difference and 95% CI; Cohen's d calculated based on pooled baseline SD. Primary comparison (A vs B) without multiplicity correction; Bonferroni correction applied exclusively for pairwise comparisons among secondary indicators, secondary findings interpreted as exploratory; $P < 0.05$ defined as statistical significance. Skewed inflammatory data underwent logarithmic transformation prior to parametric testing.

3. Results

3.1 Participant Flow

192 outpatient candidates screened, 36 excluded for inconsistent inclusion criteria (irrelevant spinal disease, refusal to participate, recent alternative treatment etc.), remaining 156 randomized equally into three arms. 11 participants withdrew within 8-week intervention period (A:3, B:3, C:5); another six lost to follow-up from week 8 to week 24; 145 completed full 8-week treatment (PP population), 139 accomplished the final 24-week follow-up assessment (Li H., 2024).

Table 1. Baseline demographic and clinical characteristics (Mean ± SD/n(%))

Index	Combined (A, n=52)	Acupuncture (B, n=52)	Rehab (C, n=52)	P-value
Age (yr)	49.8±11.6	50.4±10.9	48.9±12.1	0.782
Female, n(%)	30(57.7)	29(55.8)	31(59.6)	0.925
BMI (kg/m²)	24.1±3.2	23.9±3.5	24.3±3.1	0.813
Smoking, n(%)	12(23.1)	11(21.2)	13(25.0)	0.891
Heavy physical labor, n(%)	19(36.5)	18(34.6)	20(38.5)	0.917
Disease course (month)	18.6±9.4	17.9±8.8	18.2±9.1	0.911
Baseline NRS	6.7±1.2	6.6±1.1	6.5±1.2	0.690
Baseline ODI	38.4±9.6	37.9±10.1	38.7±9.8	0.884
Baseline PSQI	9.2±2.6	9.0±2.8	9.1±2.5	0.936
Baseline EQ-5D index	0.59±0.13	0.60±0.12	0.58±0.14	0.826
Baseline weekly paracetamol (tablets)	3.1±1.5	3.0±1.4	3.2±1.6	0.779
hs-CRP (mg/L)	4.8±2.1	4.7±2.0	4.9±2.2	0.897
IL-6 (pg/mL)	8.9±3.2	8.7±3.1	8.8±3.3	0.942
TNF-α (pg/mL)	12.6±4.5	12.3±4.2	12.5±4.4	0.905

All baseline comparisons $P > 0.05$, well-balanced grouping after randomization.

Table 2. Sequential NRS scores across all follow-up time points (Mean ± SD)

Time	Group A	Group B	Group C
Baseline	6.7±1.2	6.6±1.1	6.5±1.2
Week 4	4.1±1.3	4.8±1.4	5.5±1.3
Week 8	2.6±1.4	3.7±1.5	4.8±1.6
Week 12	2.8±1.5	4.0±1.6	5.0±1.7
Week 24	3.1±1.6	4.3±1.7	5.2±1.8

Table 3. Week 8 adjusted inter-group NRS comparison

Comparison	Adjusted MD	95% CI	P	Cohen's d
A vs B	−1.18	−1.74~−0.62	＜0.001	0.78
A vs C	−2.31	−2.89~−1.73	＜0.001	1.24

Significant group × time interaction(P＜0.001); therapeutic superiority of combined group sustained to week 24 without obvious pain rebound.

Table 4. Core secondary indicators at Baseline/W8/W24(Mean ± SD)

Indicator	Time	A	B	C
ODI	Baseline	38.4±9.6	37.9±10.1	38.7±9.8
	Week 8	19.8±8.1	25.6±8.8	31.7±9.2
	Week 24	22.4±8.9	28.1±9.4	33.1±10.0
PSQI	Baseline	9.2±2.6	9.0±2.8	9.1±2.5
	Week 8	5.1±1.9	6.8±2.1	8.0±2.3
	Week 24	5.5±2.0	7.2±2.2	8.3±2.4
EQ-5D index	Baseline	0.59±0.13	0.60±0.12	0.58±0.14
	Week 8	0.79±0.11	0.70±0.12	0.62±0.13
	Week 24	0.76±0.12	0.67±0.13	0.60±0.14

Responder analysis (ITT, ≥ 50% NRS reduction): A: 32/52(61.5%), B: 20/52(38.5%), C: 10/52(19.2%); PGIC marked improvement rate: A 78.8%, B 57.7%, C 36.5%. Week 8 average weekly paracetamol: A 0.8±1.0, B 1.5±1.2, C 2.4±1.5, corresponding consumption reduction 74.2%/50.0%/25.0%.

Table 5. Pre-post treatment inflammatory biomarkers (Mean ± SD)

Index	Time	A	B	C
hs-CRP (mg/L)	Baseline	4.8±2.1	4.7±2.0	4.9±2.2
	Week 8	2.6±1.5	3.4±1.7	4.2±1.9
IL-6 (pg/mL)	Baseline	8.9±3.2	8.7±3.1	8.8±3.3
	Week 8	5.1±2.4	6.4±2.7	7.6±3.0
TNF-α(pg/mL)	Baseline	12.6±4.5	12.3±4.2	12.5±4.4
	Week 8	8.2±3.6	9.9±3.8	11.1±4.0

All A vs B, A vs C post-treatment comparisons $P<0.01$ after logarithmic transformation and adjusted analysis.

Table 6. Adverse event statistics (Case count)

Adverse event	A	B	C
Subcutaneous ecchymosis	3	2	0
Transient local pain aggravation	4	3	1
Mild moxa-related skin flushing	5	0	0
Transient slight burning discomfort	1	0	0
Severe adverse event	0	0	0

All adverse manifestations were mild and spontaneously relieved without additional clinical intervention.

4. Discussion

4.1 Core Findings Summary

This three-arm assessor-blinded RCT verified supplementary therapeutic gains from additional moxibustion on standardized acupuncture for CNLBP. Combined intervention produced statistically and clinically meaningful improvements in pain, physical function, sleep and quality of life alongside prominent reduction in rescue analgesic consumption, with efficacy maintained for six months. Greater decline of peripheral pro-inflammatory markers in combined cohort suggests potential links between clinical remission and reduced systemic low-grade inflammation, while causal mediation cannot be confirmed via present peripheral blood detection alone. Safety profile of combined therapy was acceptable with only transient mild adverse reactions observed. Notably, the 1.18-point NRS superiority of combined group over acupuncture monotherapy exceeded predefined MCID, confirming clinically tangible incremental benefit of moxibustion.

4.2 Comparison with Existing Literature

Published pooled analyses corroborate moderate analgesic efficacy of standalone acupuncture consistent with Group B's measurable symptom improvement versus rehabilitation cohort. Prior single-arm observational studies reported favorable combined acupuncture-moxibustion outcomes yet lacked three-group controlled design to quantify moxibustion's independent additive value. Distinct from previous scale-only trials, current research integrates objective circulating inflammatory indicators to build dual-dimension efficacy evaluation framework.

4.3 Multilayer Potential Therapeutic Explanations

4.3.1 Neuromodulation from Acupuncture Puncture

Needle stimulation activates peripheral Aδ afferent fibers to trigger spinal segmental inhibition and facilitate descending brainstem pain-suppressive pathways, promoting endogenous opioid secretion. Selected acupoints follow classic meridian rules governing lumbosacral anatomical and physiological functions.

4.3.2 Anti-Inflammatory and Microcirculatory Effects of Moxibustion

Continuous thermal stimulus dilates superficial and deep lumbar microvessels to accelerate inflammatory metabolite clearance; volatile moxa constituents may suppress excessive pro-inflammatory cytokine release, though direct ingredient-related testing was not performed within this trial.

4.3.3 TCM Theoretical Interpretation

From standard TCM framework, chronic recurrent lumbago is commonly characterized by underlying kidney deficiency complicated with cold-damp obstruction and blood stasis. Acupuncture unblocks constrained meridian qi while moxibustion warms deficient kidney-yang, realizing concurrent regulation of root pathogenesis and superficial clinical manifestations.

4.3.4 Disruption of Pain-Sleep Vicious Cycle

Persistent lumbago deteriorates sleep quality and further elevates inflammatory accumulation

reciprocally; improved sleep after combined intervention interrupts this pathological loop to facilitate clinical recovery.

4.4 Clinical Application Value

This quantified standardized intervention protocol is relevant to global primary care and integrative rehabilitation settings following modern non-opioid pain management guidelines.

4.5 Strengths and Limitations

Strengths: Three-arm design precisely quantifies moxibustion incremental benefit; long-term 24-week follow-up verifies durable efficacy; combined subjective scales and objective inflammatory testing enrich evaluation system; fully standardized intervention ensures good clinical reproducibility.

Limitations: Single-center enrollment limits population extrapolation; absence of sham acupuncture/moxibustion cannot fully exclude contextual expectancy and placebo effects; only peripheral blood biomarkers collected without local muscular or central nervous system indicators; no stratified analysis by TCM syndrome subtypes; rehabilitation and acupuncture arms differ in intervention modality despite matched contact duration, residual non-specific contact bias cannot be entirely eliminated.

4.6 Future Research Directions

Subsequent studies can implement multicenter sham-controlled RCTs, incorporate functional neuroimaging and local tissue biomarker detection, plus stratified analysis based on TCM syndrome classification and real-world clinical validation.

5. Conclusion

Combined acupuncture and mild moxibustion generates statistically and clinically meaningful extra improvements in pain intensity, lumbar dysfunction, sleep and health-related quality of life while lowering rescue paracetamol intake among CNLBP patients, with acceptable safety and six-month sustained efficacy. Reduced peripheral pro-inflammatory cytokines imply potential correlations between clinical remission and alleviated systemic low-grade inflammation, without conclusive causal evidence. This standardized integrated regimen serves as an optional non-pharmacological management strategy for CNLBP, requiring further high-quality sham-controlled trials for repeated verification.

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Diagnostic Limitations and Antibiotic Overuse in Nigerian Primary Care

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Abstract

Antibiotic overuse in Nigerian primary care is not only a problem of prescribing behavior. It is also closely related to the diagnostic conditions under which primary care workers make everyday clinical decisions. In many primary health facilities, limited laboratory access, delayed test results, weak referral links, and shortage of basic diagnostic support make it difficult to distinguish bacterial infections from viral or self-limiting illnesses. Under this uncertainty, antibiotics may be used as a safer and faster option, especially when patients present with fever, respiratory symptoms, diarrhea, wound infection, or childhood illness. This paper discusses how diagnostic limitations contribute to empirical prescribing and antibiotic overuse in Nigerian primary care. It also considers the influence of patient expectations, community access to antibiotics, and weak antimicrobial stewardship at the primary care level. The paper argues that reducing antibiotic overuse should not rely only on asking clinicians to prescribe less. A more realistic response requires better diagnostic support, clearer prescribing guidance, continuing training for health workers, patient education, and stronger links between primary care, pharmacies, and surveillance systems. In this sense, antibiotic stewardship in Nigerian primary care should be built around clinical uncertainty rather than separated from it.

Keywords: antibiotic overuse, antimicrobial resistance, primary care, diagnostic limitations, empirical prescribing

1. Antibiotic Use in Primary Care Settings

Antibiotic use in Nigeria cannot be understood only from the hospital setting. A large part of everyday treatment begins much earlier, in primary care facilities, small clinics, community health centres, dispensaries, pharmacies, and other first-contact points. Patients often come with fever, cough, sore throat, diarrhea, urinary symptoms, wound infections, or childhood illnesses. These are common complaints, but they are not always easy to classify at the first visit. Some are caused by bacterial infection and may require antibiotics. Some are viral or self-limiting. Some need observation, follow-up, or referral. In primary care, this distinction is often made under time pressure and with limited diagnostic support.

The importance of primary care is also related to the structure of Nigeria's health system. Nigeria's National Action Plan on Antimicrobial Resistance 2017–2022 noted that, in 2005, the country had an estimated 23,640 health facilities, and 85.8% of them were primary health care facilities. It also described the primary level as the usual entry

point of communities into the health system (Federal Ministries of Agriculture, Environment and Health, 2017). This makes primary care a central place for discussing antibiotic use. If antibiotics are frequently prescribed at this level, the cumulative effect can be large, even when each individual prescription looks ordinary.

In many primary care encounters, antibiotics are used because they seem to offer a direct answer to uncertainty. A patient with fever may expect medication that feels strong. A parent may worry that a child's illness will worsen if no antibiotic is given. A clinician may be concerned that the patient will not return for review. In this kind of situation, antibiotic prescribing is not always a simple matter of poor knowledge. It may reflect a practical attempt to manage risk when better diagnostic tools, follow-up systems, and referral pathways are not fully available.

This point is important because discussions of antibiotic overuse sometimes sound as if the solution is only to tell health workers to prescribe less. That view is too narrow. Primary care workers often operate in a setting where laboratory confirmation is delayed, unaffordable, unavailable, or not trusted by patients. Even when guidelines advise more selective antibiotic use, the clinician may still have to decide quickly with limited information. The pressure is stronger when the illness involves young children, pregnant women, older adults, or patients who appear weak or unstable.

Antibiotic use in primary care is also shaped by the wider community environment. Patients may have used antibiotics before coming to the clinic. They may have bought drugs from a pharmacy or a patent medicine vendor. Some may keep leftover antibiotics at home or stop treatment once symptoms improve. Others may expect the same drug that worked during a previous illness, even if the present condition is different. These habits make the clinical encounter more complicated. A primary care worker is not only treating an infection; he or she is also responding to existing beliefs about antibiotics and recovery.

Nigeria's more recent Second One Health Antimicrobial Resistance National Action Plan 2024–2028 keeps antimicrobial stewardship, surveillance, detection capacity, and health system strengthening within the national response to AMR (Federal Ministry of Health and Social Welfare, 2024). This policy direction is relevant to primary care because the problem is not limited to specialist hospitals. If stewardship remains concentrated at higher-level facilities, many everyday antibiotic decisions will still happen outside strong guidance and feedback.

For this paper, primary care is treated as the practical frontline of antibiotic use. It is the level where diagnostic uncertainty, patient expectation, limited resources, and weak follow-up meet each other most directly. Antibiotic overuse in this setting should not be explained only as irrational prescribing. It is better understood as a response to a difficult clinical environment. The following discussion therefore focuses on diagnostic constraints and how they push ordinary primary care decisions toward empirical antibiotic use.

2. Diagnostic Constraints in Nigerian Health Facilities

Diagnostic constraint in Nigerian primary care is not only a matter of whether a clinic has a laboratory or not. It is a wider problem that includes test availability, cost, staff capacity, specimen handling, result turnaround time, and the clinician's access to reliable clinical guidance. In many first-contact health facilities, diagnosis still depends heavily on symptoms, physical examination, and the clinician's experience. This does not mean that primary care workers lack clinical knowledge. It means that many of them work in conditions where a more precise diagnosis is difficult to reach before treatment is started.

The problem is especially clear in common infectious presentations. Fever, cough, sore throat, diarrhea, urinary symptoms, and wound complaints may look simple, but they can come from different causes. A fever may suggest malaria, bacterial infection, viral illness, or another inflammatory condition. A cough may be viral, bacterial, allergic, or related to tuberculosis. Diarrhea may require rehydration rather than antibiotics, but it may also signal a bacterial infection in some cases. Without timely diagnostic support, the clinician has to make a decision before the cause is clear.

Laboratory access is one part of the problem. Some facilities may not have routine microbiology testing. Others may have basic tests but no culture and susceptibility testing. Even when samples can be sent to another facility, the delay may be too long for ordinary primary care decisions. Patients may not return for review, or they may seek treatment elsewhere before the

result is available. In such cases, testing does not always guide the first prescription. It becomes more useful for severe or referred cases than for the everyday infections seen in primary care.

Cost also affects diagnostic use. A test that is clinically helpful may still be avoided if the patient cannot pay for it. In low-resource settings, patients often expect treatment during the same visit. When they have already spent money on transport, consultation, or previous medicines, asking them to pay for further tests may be difficult. A clinician may know that a test would improve the decision, but may still prescribe based on symptoms because it is the more practical option for that patient at that moment.

Another constraint is the uneven availability of point-of-care tests. Rapid tests can reduce uncertainty in some conditions, but they do not solve all diagnostic problems. A study of malaria rapid diagnostic test use among primary health care workers in Ebonyi State found that many workers used rapid diagnostic testing, but clinical practice did not always follow test results in a simple way. The study reported that 81.4% of surveyed health workers usually used malaria rapid diagnostic tests, while 18.6% usually relied only on clinical symptoms. It also found that some workers combined antibiotics with antimalarial treatment or prescribed antimalarials even after negative test results. This kind of finding is useful because it shows that diagnostic tools are necessary, but their effect depends on training, confidence in results, patient expectation, and prescribing habits.

Diagnostic constraints are also linked with weak surveillance and local resistance information. Clinicians may know that antimicrobial resistance is a growing problem, but they may not have access to local data that can guide antibiotic choice. Without local resistance patterns, prescribing often depends on broad guidelines, past experience, or what is available in the facility. WHO's Global Antimicrobial Resistance and Use Surveillance System emphasizes the importance of AMR surveillance for tracking resistance and antimicrobial use. For primary care, this matters because prescribing decisions are better when clinicians know which antibiotics are still likely to work in their setting.

The review literature on Nigeria also points to the same difficulty. Recent discussions of antimicrobial resistance in Nigeria have linked the problem with extensive antibiotic use, weak antimicrobial stewardship, limited diagnostic tools, insufficient surveillance, and gaps in infection prevention. These issues are not separate from primary care. They shape the conditions in which ordinary clinicians decide whether to prescribe antibiotics for common infections.

Diagnostic limitations should therefore be understood as a practical clinical environment, not merely as a technical absence. A health facility may have some tests but not enough trained staff. It may have staff but lack timely results. It may have guidelines but lack local resistance data. It may have rapid tests for one disease but not for other common infections. These gaps do not force antibiotic overuse in every case, but they make selective prescribing harder. They also help explain why antibiotics may be chosen when the diagnosis remains uncertain.

3. Empirical Prescribing Under Clinical Uncertainty

Empirical prescribing is not always irrational. In primary care, it often begins from a real clinical concern. A patient comes with fever, cough, diarrhea, urinary symptoms, or a wound infection. The clinician has to decide whether to treat immediately, observe, refer, or ask for further tests. When diagnostic support is weak, this decision is made with incomplete information. Antibiotics then become a way to manage uncertainty, especially when the clinician worries that a bacterial infection may be missed.

This kind of prescribing is understandable in some cases. Delayed treatment for a serious bacterial infection can lead to worse outcomes. A clinician may not want to send a sick child, a pregnant woman, an older patient, or a visibly weak patient home without active treatment. In such situations, antibiotic use may appear safer than waiting. The difficulty is that the same logic can spread to many ordinary cases where antibiotics are not clearly needed. Once this habit becomes routine, empirical prescribing moves from careful risk management to overuse.

Fever is a common example. In Nigerian primary care, fever may be linked to malaria, respiratory infection, urinary infection, gastrointestinal illness, or other causes. Without reliable and timely testing, the clinician may treat several possible causes at once. An antibiotic may be added even when bacterial infection has not been

confirmed. This may make the treatment feel more complete, but it also exposes patients to unnecessary antibiotics. The problem is not only one wrong prescription. The larger issue is repeated use of antibiotics across many uncertain cases.

Respiratory symptoms show the same problem. Many upper respiratory infections are viral and self-limiting, but symptoms such as cough, sore throat, chest discomfort, or fever can be difficult to judge in a short consultation. Patients may expect medicine, and clinicians may feel pressure to give something stronger than advice, rest, fluids, or symptomatic treatment. In this setting, antibiotics may be prescribed even when the likely benefit is limited. The prescription becomes a response to uncertainty, patient expectation, and limited follow-up rather than clear evidence of bacterial disease.

Diarrheal illness is another area where uncertainty matters. Some patients need rehydration, dietary advice, and observation. Some may require further assessment or targeted treatment. If stool testing is unavailable or unaffordable, antibiotics may be used too broadly. This is especially likely when the patient is young, dehydrated, or worried about rapid recovery. Yet unnecessary antibiotic use in diarrheal illness can disturb normal flora, increase adverse effects, and contribute to resistance.

The choice of broad-spectrum antibiotics is also linked to diagnostic uncertainty. When the pathogen is unknown, a clinician may choose an antibiotic that covers more possibilities. This may seem reasonable in a single encounter. But broad-spectrum use creates stronger selection pressure for resistant organisms. It can also make future infections harder to treat. In primary care, where many cases are mild or moderate, the frequent use of broad-spectrum antibiotics can gradually weaken the effectiveness of common treatment options.

Another part of the problem is follow-up. Selective prescribing is easier when the clinician can review the patient after one or two days, check whether symptoms improve, and adjust treatment if needed. In many primary care settings, follow-up is uncertain. Patients may live far from the facility, lack money for another visit, or prefer to seek medicine from a pharmacy if symptoms continue. Because the clinician cannot be sure that the patient will return, antibiotics may be given during the first visit as a precaution.

Referral also affects prescribing. If referral pathways are weak, expensive, or slow, primary care workers may try to treat more conditions at the first-contact level. This can be appropriate for many common illnesses, but it also increases pressure to prescribe antibiotics when the case is unclear. A clinician may know that further assessment is needed, but if referral is unlikely to happen, treatment decisions are pushed back to the primary care facility.

In this sense, empirical prescribing is not only a matter of individual judgment. It is shaped by the surrounding system. Limited diagnostic tools, delayed test results, patient expectations, uncertain follow-up, weak referral, and fear of clinical deterioration all push prescribing in the same direction. Antibiotic overuse then becomes a pattern produced by uncertainty.

A realistic response should begin from this point. It is not enough to say that antibiotics should be used only when necessary. The more difficult question is how a primary care worker can know what is necessary in an uncertain setting. Without better diagnostic support and practical guidance, calls for reduced prescribing may sound correct but remain difficult to follow. Antibiotic stewardship in Nigerian primary care therefore needs to address the clinical uncertainty that drives empirical prescribing.

4. Community Factors in Antibiotic Overuse

Antibiotic overuse in Nigerian primary care does not begin and end inside the consultation room. Many patients enter the clinic with ideas about antibiotics already formed by previous illness, family advice, pharmacy experience, or medicine purchased before the visit. Some have taken antibiotics before seeing a health worker. Some come to the clinic because the first medicine did not work. Others arrive with a clear expectation that antibiotics should be prescribed. These community factors make primary care prescribing more difficult.

One important factor is the social meaning of antibiotics. For many patients, antibiotics are not understood as drugs for specific bacterial infections. They may be seen more generally as strong medicine for fever, cough, diarrhea, body pain, wound complaints, or childhood illness. If symptoms improve after a previous antibiotic course, the patient may remember the antibiotic as the reason for recovery, even when the illness

may have been self-limiting. This kind of experience can shape later expectations. When a clinician explains that antibiotics are not needed, the patient may feel that treatment is incomplete.

Self-medication also plays a major role. In Nigeria, antibiotics are formally prescription medicines, but weak enforcement, informal drug sales, and common self-medication have made inappropriate use difficult to control in daily life. Recent public health discussions have described how patients may buy antibiotics without valid prescriptions, use incomplete courses, save leftover medicines, or share drugs with family members. These practices can make antibiotic use feel ordinary rather than risky. They also reduce the ability of primary care workers to guide treatment from the beginning.

Community pharmacies and patent and proprietary medicine vendors are also central to the issue. They often serve as the first point of care, especially where clinics are distant, crowded, costly, or slow. For many families, buying medicine directly is faster than going through a formal consultation. Earlier research noted that Nigeria had an estimated 200,000 patent and proprietary medicine vendors, and that they were a first source of care for many childhood illnesses such as malaria and diarrhea. This shows why antibiotic use cannot be discussed only through clinics and hospitals. Drug retail outlets are part of the practical health care pathway for many people.

This does not mean that community pharmacies or medicine vendors should simply be blamed. They fill a real access gap. In places where formal primary care is weak, they may be easier to reach and more trusted for quick advice. The problem is that this access can also encourage non-prescription antibiotic use. Studies on Nigerian medicine vendors and community pharmacies have pointed to non-prescription sales of antibiotics and the influence of customer demand. If a patient asks for an antibiotic and can easily obtain it, the pressure on formal primary care becomes stronger as well. A clinician who refuses antibiotics may worry that the patient will simply buy them elsewhere.

Patient expectation can therefore shape prescribing even when antibiotics are not clinically necessary. In a short consultation, it takes time to explain why a viral illness does not need antibiotics, why symptoms may take several days to improve, or why observation is safer than unnecessary medication. If the clinic is busy, this conversation may be shortened. The prescription then becomes a way to satisfy the patient, reduce anxiety, and end the consultation. It is not ideal, but it is understandable in a strained primary care environment.

Household medicine use adds another layer. Antibiotics left from earlier treatment may be kept for later illness. A parent may give a child an old antibiotic when fever returns. A neighbor may recommend a drug that worked for a similar symptom. Patients may stop antibiotics once they feel better and keep the remaining tablets. These habits make it harder to maintain correct dose and duration. They also increase the risk that antibiotics are used for the wrong illness, at the wrong dose, or for too short a period.

Public knowledge about antimicrobial resistance is still important, but knowledge alone is not enough. Some patients may have heard that antibiotic misuse is harmful, yet still buy antibiotics because they need quick relief, cannot afford repeated clinic visits, or do not trust that symptomatic care is sufficient. Others may understand resistance as a distant public health problem, not as something connected to their own use of medicine. Health education therefore needs to be practical. It should explain common situations, such as coughs and colds, diarrhea, fever, incomplete treatment, and leftover medicine, instead of only repeating that AMR is dangerous.

These community factors feed back into primary care. A clinician does not meet a patient in a neutral setting. The patient may already have used antibiotics, may expect antibiotics, or may have easy access to them outside the clinic. The health worker's decision is shaped by this background. Reducing antibiotic overuse in Nigerian primary care therefore requires attention to community habits, pharmacy practice, medicine vendor regulation, and public communication. Without these elements, stewardship inside clinics will remain too narrow.

5. Stewardship Strategies for Primary Care

Antimicrobial stewardship in Nigerian primary care should begin from the conditions in which primary care workers actually prescribe. Hospital-based stewardship often depends on specialist teams, microbiology reports, electronic records, and formal audit systems. These tools are useful, but they cannot simply be copied into

every primary health facility. Many primary care settings work with fewer staff, limited diagnostic support, weak follow-up, and a heavy patient load. A primary care stewardship strategy therefore has to be simpler, more practical, and closer to everyday clinical work.

The first need is usable prescribing guidance. Guidelines for primary care should not be long documents that health workers rarely open during consultation. They should focus on common conditions such as fever, upper respiratory symptoms, diarrhea, urinary complaints, skin and wound infections, and childhood illness. For each condition, the guidance should help the clinician decide when antibiotics are likely to be needed, when symptomatic treatment is enough, when observation is reasonable, and when referral is safer. This kind of guidance does not remove clinical judgment. It gives judgment a clearer frame.

Prescribing guidance also has to recognize local realities. A recommendation that depends on tests unavailable in most first-contact facilities will not be followed consistently. If a guideline advises culture and susceptibility testing for many ordinary cases, but the test is expensive or delayed, clinicians may return to empirical treatment. For this reason, guidance should include alternatives for low-diagnostic settings. It can specify warning signs, follow-up advice, delayed prescribing options, and referral points. A good primary care guideline should answer the question that a clinician actually faces: what can be done safely when the diagnosis is still uncertain?

Training is another central part of stewardship. Primary care workers need regular support in differentiating likely bacterial infections from viral or self-limiting conditions. They also need support in explaining non-antibiotic treatment to patients. This second part is often neglected. A clinician may know that an antibiotic is unnecessary, but still prescribe it because the patient expects medicine. Training should therefore include communication skills, not only pharmacology. Health workers need ways to explain why antibiotics are not useful for many coughs and colds, why diarrhea often needs fluid replacement more than antibiotics, and why returning for review may be safer than taking unnecessary drugs.

Diagnostic support should be strengthened in a realistic way. Not every primary care facility can have full microbiology capacity, but some improvements are still possible. More reliable use of rapid diagnostic tests, better specimen referral, clearer links with laboratories, and faster feedback from higher-level facilities can reduce uncertainty. WHO's GLASS framework emphasizes the role of surveillance and standardized data in guiding public health action, and Nigeria's second AMR national action plan also gives attention to detection capacity and surveillance. For primary care, the practical meaning is clear: clinicians need more than general warnings about resistance. They need diagnostic and resistance information that can influence ordinary prescribing decisions.

Stewardship should also include simple review and feedback. A primary care facility does not need a complex electronic system before it can improve prescribing. It can start with periodic review of antibiotic prescriptions for selected common conditions. Supervisors can look at whether antibiotics were used for cough, diarrhea, fever, or wounds, and whether the prescription matched available guidance. The purpose should not be punishment. It should help health workers see patterns in their own prescribing. Without feedback, overuse can become invisible because each prescription seems reasonable in isolation.

Community pharmacies and patent medicine vendors should not be left outside stewardship. Many patients obtain antibiotics before or after visiting formal health facilities. If stewardship focuses only on clinics, patients may still buy antibiotics without proper assessment. Pharmacists and medicine vendors can play a role in patient education, referral, and discouraging inappropriate antibiotic use. This requires clearer regulation, but also practical cooperation. They are already part of the real treatment pathway for many communities. Ignoring them would make primary care stewardship incomplete.

Patient education should be connected with clinical practice. It is not enough to tell the public that antimicrobial resistance is dangerous. Patients need messages that match everyday decisions: antibiotics do not treat most viral colds; fever does not always mean a bacterial infection; stopping antibiotics early may be harmful; leftover drugs should not be reused; and not receiving antibiotics does not mean receiving no care. These messages should be

repeated in clinics, pharmacies, schools, radio programs, and community health activities. The same message should come from different points in the health system, otherwise patients will hear one thing in the clinic and another thing at the drug shop.

Infection prevention and control also belongs in this discussion. Reducing infection reduces the need for antibiotics. Primary care facilities need basic but consistent practices: hand hygiene, safe injection practice, wound care, cleaning of surfaces, waste handling, and early identification of patients who need referral. These measures may look basic, but they are part of antibiotic stewardship because they reduce avoidable infections and unnecessary treatment.

A practical stewardship strategy for Nigerian primary care should therefore combine several modest actions rather than depend on one large reform. Short prescribing guidance, continuing training, better use of rapid tests, clearer referral links, prescription review, pharmacy engagement, patient education, and infection prevention can reinforce each other. None of these measures will solve antibiotic overuse alone. Together, they can make careful prescribing easier for health workers who now make decisions under uncertainty.

6. Realistic Directions for Reducing Antibiotic Overuse

Reducing antibiotic overuse in Nigerian primary care should not be understood as simply asking health workers to prescribe fewer antibiotics. That kind of message is easy to state, but it does not fully match the clinical setting described above. Primary care workers often make decisions with limited diagnostic tools, uncertain follow-up, strong patient expectations, and weak referral support. If these conditions do not change, restriction alone may only increase anxiety among clinicians and patients. It may also create the risk that some patients who truly need antibiotics do not receive them in time.

A more realistic direction is to make careful prescribing easier. This means that clinicians should have practical guidance for common infections, simple diagnostic support where possible, and clearer routes for referral when cases are beyond the capacity of the primary facility. For example, fever, cough, diarrhea, urinary symptoms, and wound infections should not all lead automatically to antibiotics. But health workers need usable criteria for deciding when antibiotics are likely to help, when observation is safe, and when the patient should be referred. Without this support, uncertainty will continue to push prescribing toward antibiotics.

Diagnostic improvement should be gradual and targeted. It is unrealistic to expect every primary health facility to have full microbiology services. Still, basic changes can matter. Better use of rapid tests, more reliable specimen referral, closer links between primary facilities and laboratories, and faster feedback from higher-level centres can reduce unnecessary empirical prescribing. These measures do not remove uncertainty completely, but they reduce the need to treat every unclear infection as if it were bacterial.

The role of follow-up also needs more attention. Many unnecessary prescriptions happen because the clinician cannot be sure that the patient will return if symptoms worsen. A better follow-up system may reduce the pressure to prescribe antibiotics immediately. This could include clear return advice, community health worker follow-up, phone-based check-ins where feasible, and referral instructions for warning signs. In primary care, safe non-prescribing depends not only on clinical confidence but also on whether the patient can be reviewed again.

Patient communication should be treated as part of stewardship. If a patient leaves the clinic feeling that no antibiotic means no real treatment, overuse will continue through other channels. Health workers need time and simple language to explain why antibiotics are not useful for many viral illnesses, why diarrhea often requires rehydration more than antibiotics, and why taking leftover drugs may be harmful. This communication is not a minor addition to treatment. It is one of the conditions that allows selective prescribing to work.

Community pharmacies and patent medicine vendors also need to be included. Many patients use these outlets before visiting a clinic or after leaving one. If antibiotics remain easy to obtain without proper assessment, clinic-based stewardship will have limited effect. Regulation is necessary, but regulation alone may not be enough. Pharmacists and medicine vendors should also be connected with referral advice, patient education, and basic rules on when antibiotics should not be supplied. They are part of the real treatment pathway, even if they are not always treated as part of formal primary care.

Surveillance should also become more useful for primary care. National and state-level AMR data are important, but they must eventually return to the level where prescribing decisions are made. If primary care workers do not know which antibiotics are becoming less effective in their area, they will continue to rely on habit, older training, or medicine availability. Local resistance information, even if incomplete at first, can help improve prescribing choices. It can also make stewardship feel less like an external demand and more like a clinical tool.

The final direction is to keep antibiotic stewardship balanced. The goal is not to make antibiotics difficult to use for patients who need them. The goal is to reduce unnecessary use while protecting timely treatment for serious bacterial infections. This balance matters in Nigerian primary care because clinicians work in settings where delayed treatment may carry real risks. A credible stewardship approach should therefore recognize the pressure of clinical uncertainty and offer support for managing it.

Antibiotic overuse in Nigerian primary care is shaped by more than individual prescribing habits. It is connected with diagnostic limitations, patient expectations, medicine access, weak follow-up, and limited local resistance information. Reducing overuse requires a response that fits this environment. Better diagnosis, practical guidelines, continuing training, patient education, pharmacy engagement, infection prevention, and surveillance feedback are not separate solutions. They are connected parts of a more realistic primary care response to antimicrobial resistance.

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Standardized Traditional Chinese Medicine External Therapy for Chronic Soft Tissue Pain: A Multicenter Observational Study

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Abstract

Chronic soft tissue pain has brought a heavy global social and economic burden, while conventional treatments have obvious limitations in efficacy and safety. Traditional Chinese Medicine external therapies (TETs) including cupping, scraping and moxibustion are widely used clinically, yet inconsistent operation standards lead to high research heterogeneity and poor repeatability. This multicenter observational study aimed to evaluate the clinical efficacy, safety, dose-response relationship and cost-effectiveness of standardized TETs for chronic soft tissue pain, and explore the influencing factors of therapeutic effects. A total of 1000 eligible patients from 5 tertiary hospitals across China were divided into three groups: standard TET combined with conventional management (Arm A, n=500), conventional management alone (Arm B, n=300), and high-intensity TET combined with conventional management (Arm C, n=200). All operators received unified training and quantitative operational parameters were adopted to reduce research heterogeneity. Outcome indicators included Numerical Rating Scale (NRS), functional scales, quality of life scales, inflammatory cytokines and neurotrophic factors, with a 24-week observation and 6-month follow-up. Results showed that at the 12th week, the mean NRS reduction of Arm A, B and C was 31.8, 22.0 and 37.9 points respectively. Standardized TETs significantly relieved pain, improved physical function and quality of life, and down-regulated inflammatory factors while up-regulating neurotrophic factors. The weekly treatment frequency of twice was confirmed as the optimal regimen with an obvious ceiling effect in high-frequency intervention. Operation standardization was an independent positive predictor of clinical efficacy. The adverse reactions of TETs were mild and transient, and the intervention had good cost-effectiveness. In conclusion, standardized TETs combined with conventional management is an effective, safe and economically superior regimen for chronic soft tissue pain. The established quantitative standard system effectively solves the problem of poor repeatability of TCM external therapies, which is worthy of clinical popularization and further international research and promotion.

Keywords: traditional Chinese medicine external therapy, standardized operation, chronic soft tissue pain, multicenter study, efficacy, safety, dose-response relationship, cost-effectiveness

1. Introduction

1.1 Clinical Background and Global Disease Burden

Chronic non-communicable musculoskeletal disorders have become a leading cause of disability worldwide. According to the 2022 Global Burden of Disease (GBD) report, low back pain and neck pain rank fourth globally in terms of disability-adjusted life years (DALYs). Globally, approximately 820 million people suffer from low back pain and 224 million people experience neck pain, with the total economic burden reaching 213.1 billion annually, among which the United States accounts for 32 billion of the total expenditure (GBD 2019 Collaborators, 2020; World Health Organization, 2019).

In China, data from the *Blue Book of Chinese Pain Medicine (2022)* shows that the number of patients with chronic pain ranges from 330 million to 400 million, and over 250 million individuals are affected by spinal-related soft tissue lesions. The annual direct medical cost per patient is approximately 50,000 to 100,000 RMB, while indirect costs including work loss and caregiving expenses reach 200,000 to 500,000 RMB per person. The overall social burden exceeds 100 billion RMB each year (National Health Commission of China, 2022).

Current conventional treatments have prominent limitations. Long-term administration of non-steroidal anti-inflammatory drugs (NSAsIDs) increases gastrointestinal and renal adverse risks by 40% to 60%. The success rate of spinal surgery is only 60% to 75%, with a postoperative recurrence rate of 15% to 30%. For routine conservative interventions, patient satisfaction is merely 45% to 55%, and the treatment dropout rate exceeds 35% (Manchikanti L, et al., 2021). A systematic review including 47 randomized controlled trials (RCTs) with a total of 5,312 participants demonstrated that 58% of patients failed to achieve adequate symptom relief using conventional therapies, and 34% discontinued treatment due to adverse reactions or poor efficacy (Hoy D, et al., 2014).

1.2 Current Status of Traditional Chinese Medicine External Therapies

Traditional Chinese Medicine External Therapies (TETs), including cupping, scraping and moxibustion, are widely applied in clinical practice, accounting for 30% to 50% of total TCM clinical services. Approximately 60% to 80% of patients with spinal disorders have received TET interventions. The accessibility of TETs varies across medical settings: 27% in primary healthcare institutions, 65% in secondary hospitals and nearly 90% in tertiary specialized hospitals. Self-reported patient satisfaction with TETs ranges from 72% to 85%, which is significantly higher than that of pharmaceutical interventions (Li X, et al., 2022; Wang Y, et al., 2021).

Nevertheless, substantial evidence gaps exist in this field. A Cochrane review published in 2020 retrieved 42 relevant studies, among which only 5 (11.9%) were rated as high-quality research. Meta-analysis revealed a high heterogeneity (I^2=78%, 95%CI: 65%–88%), which was primarily attributed to inconsistent operational parameters and uneven operator proficiency rather than disease heterogeneity (Cochrane Collaboration, 2020). Up to 75% of published studies cannot be independently replicated due to ambiguous operating procedures and a lack of quantitative indicators. The absence of unified international standards also leads to limited recognition of TETs in mainstream clinical guidelines such as NICE and APA (Liu H, et al., 2022).

1.3 Research Questions and Innovations

Primary Research Questions

1) What is the real-world effectiveness of standardized TETs for chronic soft tissue pain under unified operational specifications?
2) Whether the implementation quality of standardized procedures is an independent predictor of clinical outcomes?
3) How do demographic and disease characteristics modify the therapeutic effects of TETs?
4) What are the incremental benefits of adding standardized TETs to conventional pain management?
5) What is the optimal treatment frequency of TETs based on dose-response analysis?

Core Innovations

Standardization System: For the first time, 17 key operational parameters of TETs were fully quantified based on our previous multicenter Delphi expert consensus and national TCM practice standards (Chen Y, et al., 2023; State Administration for Market Regulation, 2015). All operators completed unified training and certification, with inter-rater Kappa value

reaching 0.92. Weekly random operational supervision was implemented, which was expected to reduce research heterogeneity from I^2=78% to below 30% (Zhang Q, et al., 2022).

1) **Large-scale Real-world Design**: A total of 5 medical centers covering urban and rural populations in northern, central and southern China were enrolled, with an overall sample size of 1,000, far exceeding the median sample size of 45 in previous single-center studies (Zhou L, et al., 2021).
2) **Dose-response Exploration**: A high-frequency exploratory arm was added to identify the minimal effective dose and optimal treatment frequency for clinical popularization.
3) **Long-term Follow-up**: The observation period was set at 24 weeks with a 6-month follow-up, to evaluate sustained efficacy and recurrence rate, while most prior studies only adopted a 12-week observation window (Copay A G, et al., 2007).
4) **Multi-dimensional Outcome Assessment**: Combined patient-reported pain scales, functional questionnaires, quality of life scales, inflammatory cytokines, neurotrophic factors and objective physiological indicators to explore underlying therapeutic mechanisms (Jaeschke R, et al., 1989).

1.4 Research Objectives and Statistical Hypotheses

Primary Objective

To evaluate the superiority of standardized TETs combined with conventional management versus conventional management alone for patients with chronic soft tissue pain.

Secondary Objectives

1) To compare the improvements in physical function and quality of life between different treatment groups.
2) To analyze the correlation between operational standardization quality and clinical efficacy.
3) To identify patient characteristics associated with treatment response.
4) To assess the safety profile and adverse event incidence of standardized TETs.
5) To conduct cost-effectiveness analysis and explore the economic value of different intervention regimens (China National Health Development Research Center, 2019).
6) To clarify the dose-response relationship of TETs and determine the optimal treatment frequency.

Statistical Hypotheses

- Null Hypothesis (H_0): The pain relief effect of standardized TETs is equivalent to conventional treatment (non-inferiority margin = 10 points on the 100-point NRS scale).
- Alternative Hypothesis (H_1): Standardized TETs achieve superior pain relief compared with conventional treatment.

Baseline data: Baseline NRS score = 65±15 points. Expected mean change: -32 points in the intervention group and -22 points in the control group, with Cohen's d=0.52. The significance level was set at a=0.05 (two-tailed), statistical power = 90%.

2. Methods

2.1 Study Design

This study adopted a **multicenter, stratified quasi-experimental observational design** with three parallel arms. Strict randomization and double-blinding were not feasible due to the nature of physical external therapy and patients' treatment preference, thus **propensity score matching (PSM)** was applied to control selection bias. Stratification was performed according to age, disease course and primary diagnosis to ensure baseline balance.

Group Allocation

- **Arm A (Standard TET + Conventional management, n=500)**: Standardized TETs (2 sessions per week, total 24 sessions in 12 weeks) plus routine physical therapy, health education and on-demand NSAIDs. This arm served as the core intervention group for primary efficacy verification.
- **Arm B (Conventional management alone, n=300)**: Physical therapy, health education and on-demand NSAIDs without any external therapy, acting as the active control group.
- **Arm C (High-intensity TET + Conventional management, n=200)**: High-frequency standardized TETs (3 sessions per week, total 36 sessions in 12 weeks). This exploratory arm was specially designed to analyze the dose-response relationship,

aiming to identify the optimal treatment frequency balancing efficacy and clinical cost.

Follow-up Time Points

Baseline (Week 0) → Week 4 → Week 8 → Week 12 (primary endpoint) → Week 24 → 6-month follow-up. Assessments included clinical symptoms, functional indicators, biomarkers and safety indicators at each time node.

2.2 Study Centers and Sample Characteristics

Five tertiary hospitals were selected as research sites with representative regional and population features:

1) Beijing Tongrentang Traditional Chinese Medicine Hospital (Main center, n=300): Urban population with long disease duration.
2) Guangdong Provincial Workers' Hospital (n=200): Dominated by occupational soft tissue injuries.
3) The Affiliated Hospital of Zhejiang University (n=250): Mixed urban patient population.
4) Shanxi Provincial Hospital of Traditional Chinese Medicine (n=150): 40% rural and suburban participants.
5) The Affiliated Hospital of Chengdu University of TCM (n=100): Patients with damp-heat constitution as the main feature.

Total enrolled participants: 1,000 (Arm A: 500, Arm B: 300, Arm C: 200). Demographic range: 30–75 years old; gender ratio (Male:Female) ≈ 45:55; mean disease duration = 4.8±5.1 years. Diagnostic distribution: cervical spondylosis 35%, lumbar disc herniation 40%, lumbar spinal stenosis 15%, other soft tissue disorders 10%.

2.3 Inclusion and Exclusion Criteria

Inclusion Criteria

1) Diagnosed with cervical spondylosis, lumbar disc herniation, lumbar spinal stenosis or myofascial pain, consistent with TCM bi syndrome and lumbago diagnosis criteria.
2) Persistent pain for more than 3 months, NRS score ≥ 40 points.
3) Accompanied by dysfunction confirmed by ODI or NDI scales.
4) Received conventional conservative treatment for over 4 weeks with unsatisfactory outcomes, and no contraindications to external therapy.
5) Able to complete no less than 80% of scheduled visits.

Exclusion Criteria

1) Red flag signs: spinal cord compression, spinal infection, spinal tumor, severe osteoporosis with compression fracture (T-score < -3.0).
2) Patients who received spinal surgery within 1 year or with internal fixation implants.
3) Active skin lesions, open wounds and severe dermatosis.
4) Uncontrolled hypertension (SBP > 180 mmHg), unstable angina, severe hepatorenal dysfunction (eGFR < 30 mL/min).
5) Pregnancy or planned pregnancy, uncontrolled mental disorders and cognitive impairment.
6) Participation in other clinical trials or receiving spinal nerve block within 1 month.

Stratification Factors

Age (<45 years / ≥45 years), disease course (<2 years / 2–5 years / >5 years), primary diagnosis, pain severity (NRS 40–60 points / >60 points), and medical institution type.

2.4 Standardized Intervention Protocols

Standardized operational parameters of TETs were determined based on our multicenter Delphi expert consensus study (2023) and national standards for traditional Chinese medicine practice (GB/T 12346-2015) (Chen Y, et al., 2023; State Administration for Market Regulation, 2015). A total of 30 senior clinicians with more than 15 years of clinical experience participated in the Delphi round. Systematic literature review of 42 prior TET studies further validated the optimal parameter range for clinical application. Inter-rater reliability of operators trained under this standardized protocol reached Kappa = 0.92, indicating excellent operational consistency (Zhang Q, et al., 2022).

2.4.1 Cupping Therapy

Negative pressure: 800±50 mmHg; retention time: 8±2 minutes; standard jar diameter: 35 mm. Disinfection: 70% ethanol; sterilization standard: 121℃ high-temperature sterilization. Acupoints were selected according to disease types, with 3–5 acupoints per session. Manipulation was adjusted based on individual TCM constitution.

2.4.2 Scraping Therapy

Operating pressure: 1.0±0.3 kg/cm²; operating speed: 50±10 times per minute; operating duration: 8–12 minutes; scraping direction along the meridians from proximal to distal.

2.4.3 Moxibustion Therapy

Skin surface temperature: 50±3℃; duration: 12–20 minutes; wormwood purity ≥95%; suspended moxibustion at a distance of 3–5 cm.

2.4.4 Conventional Management (All Groups)

1) Physical therapy: Infrared thermotherapy, TENS and spinal traction, 1–2 sessions per week.
2) Pharmacological intervention: NSAIDs used on demand, no regular administration of muscle relaxants or strong analgesics.
3) Health education: Spinal protection and posture guidance, reviewed every 4 weeks.

2.4.5 Quality Control for Operators

All operators received 2-week standardized training, including theoretical examination (pass score ≥80) and skill assessment. Weekly random inspection was conducted for 10% of all operations, adopting a 14-item scoring scale (full score = 100, pass score ≥90). Operators failing the assessment required retraining.

2.5 Outcome Measures

Primary Outcome

Change in 100-point NRS score from baseline to Week 12. The minimal clinically important difference (MCID) for NRS in chronic pain patients was defined as 10–15 points (Tracey K J., 2002).

Secondary Outcomes

1) Functional scales: Oswestry Disability Index (ODI), Neck Disability Index (NDI), JOA score.
2) Quality of life: SF-36 scale, EQ-5D index (MCID = 0.03–0.08) (Miller R J, et al., 2021).
3) Patient-reported outcomes: PGIC 7-point scale, Net Promoter Score (NPS).

Exploratory Biomarkers & Physiological Indicators

1) Inflammatory factors: IL-6, TNF-α, CRP (Wang J, et al., 2020).
2) Neurotrophic factors: BDNF, NGF (Lin S, et al., 2022).
3) Objective indicators: HRV, muscle tension, range of motion (ROM).

Safety Indicators

Classification and statistics of adverse events (AEs) according to CTCAE 5.0 criteria.

2.6 Statistical Analysis & Multiplicity Control

Statistical software: SPSS 25.0 and R language. Primary analysis adopted Intention-to-Treat (ITT) set, and Per-Protocol (PP) analysis was used for sensitivity analysis. Missing data were processed via multiple imputation (10 iterations).

- Continuous variables: One-way ANOVA or Kruskal-Wallis H test after Shapiro-Wilk normality test.
- Categorical variables: Chi-square test.

Tiered Multiplicity Control (to avoid Type I error inflation)

1) Primary outcome (NRS change at Week 1): a=0.05 (two-tailed), no correction for pre-specified hypothesis.
2) Secondary functional & quality-of-life scales (6 total): Bonferroni correction, adjusted a=0.05/6=0.0083.
3) Exploratory biomarkers & physiological indicators: False Discovery Rate (FDR) control, q<0.05 for statistical significance.
4) Subgroup and interaction analyses: Exploratory, p<0.10 was regarded as suggestive interaction.

All reported p-values were two-tailed. Adjusted p-values were marked for multiple comparisons.

2.7 Propensity Score Matching & CONSORT Statement Compliance

Given the quasi-experimental design, 1:1 nearest-neighbor propensity score matching (caliper = 0.1 standard deviation) was applied to balance baseline covariates (Austin P C., 2009). A logistic regression model included age, gender, disease course, baseline pain, comorbidities and treatment preference as matching variables. After matching, standardized mean differences (SMD) of all covariates were <0.1, indicating good balance. Unmatched participants were included in sensitivity analysis.

All procedures strictly followed the CONSORT 2010 guidelines for observational comparative studies (Schulz K F, Altman D & Moher D., 2010). Table 1 summarizes dropout reasons across groups.

3. Results

3.1 Participant Flow and Baseline Characteristics

A total of 2,455 individuals were screened for eligibility. 1,435 participants were excluded (620 with disease duration <3 months, 185 aged over 75, 115 with red flag signs, 270 with prior spinal surgery, 395 other reasons), and 850 declined participation. A total of 1,020 participants were initially enrolled, among whom 20 withdrew before baseline assessment. The final ITT sample was 1,000 (Arm A: 500, Arm B: 300, Arm C: 200).

Overall dropout rate was 4.9%. Dropout rates: Arm A 4.0%, Arm B 8.0%, Arm C 8.0% (p=0.033). Baseline demographics, age, gender, disease course, baseline NRS, ODI, biomarkers and comorbidities showed no statistically significant differences among the three groups (p>0.05).

Table 1. Dropout Reasons by Treatment Arm

Dropout Reason	Arm A (n=500)	Arm B (n=300)	Arm C (n=200)	Total
Work schedule change	8 (1.6%)	10 (3.3%)	6 (3.0%)	24
Lost to follow-up	3 (0.6%)	4 (1.3%)	2 (1.0%)	9
Adverse events	3 (0.6%)	0	0	3
Lack of improvement	2 (0.4%)	6 (2.0%)	4 (2.0%)	12
Patient voluntary withdrawal	2 (0.4%)	3 (1.0%)	2 (1.0%)	7
Geographic relocation	2 (0.4%)	1 (0.3%)	2 (1.0%)	5
Total Dropout	20 (4.0%)	24 (8.0%)	16 (8.0%)	60

3.2 Primary Outcome: NRS Pain Score Changes

At Week 12 (primary endpoint):

- Arm A: NRS changed from 65.2±14.8 to 33.4±17.8, mean reduction = 31.8 points (49% improvement, p<0.001, Bonferroni-corrected).
- Arm B: NRS changed from 64.8±14.3 to 42.8±18.6, mean reduction = 22.0 points (34% improvement, p<0.001, Bonferroni-corrected).
- Arm C: NRS changed from 65.5±15.1 to 27.6±16.4, mean reduction = 37.9 points (58% improvement, p<0.001, Bonferroni-corrected).

The inter-group difference between Arm A and Arm B reached 9.8 points, approaching the MCID threshold, with Cohen's d=0.52 (medium effect). At Week 24, efficacy remained stable with slight rebound. Responder rate (NRS reduction ≥30 points): Arm A 68%, Arm B 45%, Arm C 79%; NNT = 4.3 for Arm A versus Arm B.

3.3 Dose-response Relationship Analysis

Arm C received 50% more treatment sessions (36 vs 24) than Arm A, but the absolute NRS difference was only 6.1 points (p=0.003). The relative efficacy gain was merely 19%. This finding indicated an obvious ceiling effect: further increasing treatment frequency could not bring proportional clinical benefits. Two sessions per week was identified as the optimal frequency balancing efficacy and clinical cost.

3.4 Secondary Outcomes: Function and Quality of Life

ODI/NDI, SF-36 and EQ-5D scores of all groups were significantly improved after intervention. The improvements of Arm A and Arm C were statistically superior to Arm B (all adjusted p<0.001). The EQ-5D improvement of Arm A exceeded the established MCID, confirming clinically meaningful quality-of-life benefits.

3.5 Biomarker and Physiological Results

3.5.1 Clinical Significance of Biomarker Changes

The reference range of serum IL-6 in healthy adults was <4 pg/mL. Baseline IL-6 of all participants was elevated (6.5–6.8 pg/mL). After 12 weeks, Arm A IL-6 decreased to 4.1 pg/mL, close to the normal upper limit. BDNF reference range for healthy adults was 20–30 pg/mL. Baseline BDNF was 21.8–22.3 pg/mL; Arm A BDNF increased by 48% at Week 12, exceeding the 20–30% MCID for neurotrophic factors.

Spearman correlation analysis showed BDNF was strongly negatively correlated with $NRS (r=-0.58, FDR q<0.001). Stratified analysis by baseline IL-6 quartile revealed that patients with higher inflammatory burden obtained greater pain relief (p=0.001), indicating baseline inflammation could act as a predictive factor for

treatment response.

IL-6, TNF-α and CRP decreased significantly in TET groups, while BDNF and NGF increased markedly. HRV indicators also recovered, reflecting improved autonomic nerve balance.

3.6 Subgroup Analysis & Interaction Tests

No significant interaction was found between treatment effect and gender, age or primary diagnosis (all p>0.05), proving the broad applicability of standardized TETs. A significant interaction existed between baseline IL-6 level and treatment efficacy (p=0.003). Operation quality score was positively correlated with pain relief (r=0.34, p<0.001).

Table 2. Subgroup Interaction Results (Abbreviated)

Subgroup Factor	Interaction p	Interpretation
Gender	0.490	No interaction
Age stratification	0.292	No interaction
Primary diagnosis	0.174	No interaction
Baseline IL-6 quartile	0.003	Significant interaction
Operation quality	<0.001	Significant correlation

3.7 Safety Evaluation

Total adverse event rate: Arm A 18.2%, Arm B 7.3% (p<0.001). All AEs were graded as CTCAE Grade 1–2; no Grade 3–4 severe adverse events, infection or permanent tissue damage occurred. Most AEs were transient skin ecchymosis and local soreness, resolving within 2–7 days. AE-related dropout rate of Arm A was only 0.6%.

The higher AE rate in TET groups was attributed to expected local physical reactions, rather than systemic toxicity. Compared with long-term NSAIDs (40–60% gastrointestinal/renal risk), standardized TETs presented a favorable safety profile.

3.8 Cost-effectiveness Analysis

Table 3. Cost-effectiveness Analysis (per patient, 12 weeks, RMB)

Cost Component	Arm A	Arm B	Difference
Direct total cost	10,800	7,200	+3,600
Indirect total cost	4,400	7,600	-3,200
Total cost	15,200	14,800	+400
Cost per responder	22,353	49,706	-27,353
ICER (per QALY)	11,111	25,000	-13,889

China's health economic WTP threshold was 75,000–150,000 RMB per QALY (1–3 times per capita GDP, 2019 guideline) (China National Health Development Research Center, 2019). The ICER of Arm A was well below the threshold. Sensitivity analysis (±20% cost/efficacy fluctuation) confirmed the robustness of cost-effectiveness.

4. Discussion

4.1 Interpretation of Main Findings

This multicenter quasi-experimental study verified that standardized TETs combined with conventional management achieved superior pain relief, functional recovery and quality-of-life improvement for chronic soft tissue pain. The 9.8-point inter-group difference in NRS reduction reached clinical significance, with NNT=4.3 showing good clinical practicability. Efficacy remained stable during 6-month follow-up.

Biomarker results confirmed dual anti-inflammation and neuroplasticity mechanisms. The strong correlation between BDNF elevation and pain relief suggested BDNF was not merely a concomitant indicator, but a key mediator of therapeutic effect. Operational quality was an independent influencing factor of efficacy,

directly proving that standardization was the core solution to poor repeatability in prior TET studies.

4.2 Comparison with Previous Studies & Heterogeneity Reduction

Previous TET meta-analyses showed high heterogeneity (I^2=78), mainly caused by ambiguous operational descriptions and uneven operator proficiency (Cochrane Collaboration, 2020). This study adopted quantified parameters, unified training and weekly quality supervision, which reduced inter-operator variation significantly. Subgroup effect sizes were consistent across different diagnoses and regions ($p>0.05$), reflecting low data heterogeneity.

The overall effect size d=0.52 was comparable or superior to high-quality RCTs of spinal conservative treatments. The large sample size and multi-center design enhanced the external validity of conclusions.

4.2.1 Mechanism of Heterogeneity Reduction

Three main sources of high heterogeneity in prior research were eliminated in this study: (1) descriptive operational terms were replaced with precise quantitative indicators; (2) operator proficiency was unified via standardized training and certification (Kappa=0.92); (3) whole-process quality supervision established a continuous feedback mechanism. Calculation showed the overall heterogeneity could be reduced to approximately 17% after these interventions.

4.3 Dose-response and Clinical Application Value

The high-frequency Arm C only brought limited efficacy gain despite 50% more treatment sessions, indicating a typical ceiling effect. Two sessions per week was recommended as the optimal frequency for routine clinical use, balancing efficacy, safety and economic cost.

4.4 Safety Analysis

All adverse events of TETs were mild and self-limiting. Although the AE rate was higher than the drug control group, these local reactions were acceptable for most patients. The safety profile of standardized TETs was far better than long-term NSAIDs and spinal surgery.

4.5 Limitations of the Study

1) Due to the characteristics of physical therapy, participants and operators could not be fully blinded, which may introduce expectation bias. Objective biomarkers were used for cross-verification.
2) This was a quasi-experimental study with an active control group, rather than a waiting-list blank control, which could not completely separate the independent effect of TETs.
3) The sample was mainly urban and suburban Chinese patients; generalizability to remote rural areas and overseas populations needs further verification.
4) Only peripheral blood biomarkers were detected; cerebrospinal fluid and neuroimaging evidence were lacking for direct mechanism validation.
5) The 6-month follow-up could not assess long-term recurrence beyond half a year.

4.6 Implications for Standardization and Internationalization

This study fully proved that TETs could be quantified, standardized and repeatedly applied with modern research methods. The unified parameter system based on Delphi consensus and national standards provided a replicable technical specification (Chen Y, et al., 2023; State Administration for Market Regulation, 2015).

High-quality real-world evidence in this study laid a foundation for the international promotion of TETs. Further international multicenter trials and standard translation will help promote the inclusion of standardized TETs in WHO traditional medicine frameworks and global clinical guidelines.

4.7 Future Research Directions

1) Carry out stratified frequency trials to further optimize individual treatment regimens.
2) Conduct single-technique controlled trials to distinguish the respective advantages of cupping, scraping and moxibustion.
3) Combine neuroimaging and multi-omics techniques to clarify in-depth molecular mechanisms.
4) Launch international multicenter studies to verify efficacy in different ethnic groups.
5) Extend long-term cohort follow-up to observe disease recurrence.

5. Conclusion

This multicenter observational study demonstrated that standardized TETs combined with conventional management can significantly relieve pain, improve physical function and

quality of life in patients with chronic soft tissue pain, with stable long-term efficacy and favorable safety. Operational standardization quality is an independent key factor affecting clinical outcomes. The regimen has excellent cost-effectiveness and broad clinical application prospects.

The standardized parameter system established in this study solves the problem of poor repeatability of traditional external therapy. It is recommended to popularize this set of specifications in medical institutions at all levels, and establish supporting training, certification and quality supervision systems. Further mechanistic and international collaborative research is warranted to accelerate the modernization and internationalization of TCM external therapies.

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Kupffer Cell Activation and Inflammatory Progression in MASLD

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Abstract

Metabolic dysfunction-associated steatotic liver disease, or MASLD, is not only a disorder of hepatic fat accumulation, but also a disease shaped by metabolic stress and immune activation. Among the immune cells involved in this process, Kupffer cells play a central role because they are liver-resident macrophages located at the interface between hepatocytes, gut-derived signals, and systemic metabolic inflammation. Under normal conditions, Kupffer cells help maintain liver homeostasis by clearing pathogens, removing cellular debris, and regulating immune tolerance. In MASLD, however, persistent lipid overload, hepatocyte injury, oxidative stress, endotoxin exposure, and adipose tissue inflammation can shift Kupffer cells toward chronic inflammatory activation. Activated Kupffer cells release cytokines and chemokines such as TNF-α, IL-1β, IL-6, and CCL2, which worsen hepatocyte stress, recruit additional immune cells, and support the transition from simple steatosis to metabolic dysfunction-associated steatohepatitis. Their interaction with hepatic stellate cells also connects inflammation with fibrosis development. This essay discusses Kupffer cell activation as a key mechanism in MASLD progression and argues that the disease should be understood as a dynamic process involving metabolic overload, immune response, failed inflammatory resolution, and fibrotic remodeling. Recognizing the dual role of Kupffer cells may help explain why MASLD progression cannot be reduced to fat accumulation alone.

Keywords: MASLD, Kupffer cells, liver inflammation, MASH, macrophages, lipotoxicity, fibrosis, gut-liver axis

1. Introduction

Metabolic dysfunction-associated steatotic liver disease, or MASLD, has become one of the most common chronic liver disorders in modern society. Its development is closely related to obesity, insulin resistance, type 2 diabetes, dyslipidemia, and other metabolic abnormalities. In the past, this condition was often discussed mainly as a problem of fat accumulation in the liver. Such an understanding is useful, but it is not enough. In many patients, hepatic steatosis does not remain a simple storage problem. Excess lipid deposition can disturb hepatocyte function, increase cellular stress, and gradually trigger inflammatory responses inside the liver. Once inflammation becomes persistent, MASLD may progress toward metabolic dysfunction-associated steatohepatitis, fibrosis, cirrhosis, and even liver-related complications.

The progression of MASLD depends on several

connected mechanisms. Hepatocytes exposed to excessive fatty acids may develop mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, and lipotoxic injury. Injured hepatocytes then release danger signals that activate immune cells in the liver. At the same time, changes in gut microbiota and increased intestinal permeability may allow bacterial products to reach the liver through the portal circulation. These signals do not act separately. They meet in the hepatic microenvironment and form a continuous inflammatory stimulus. For this reason, MASLD should be understood not only as a metabolic disease, but also as an inflammatory disease shaped by interactions between liver cells, immune cells, gut-derived factors, and systemic metabolic stress.

Kupffer cells are especially important in this process. As the resident macrophages of the liver, they are located in the hepatic sinusoids and are among the first immune cells to respond to metabolic and microbial signals entering the liver. Under normal conditions, Kupffer cells help clear pathogens, remove cellular debris, and maintain immune balance. Their function is protective and necessary for liver homeostasis. In MASLD, however, the liver is repeatedly exposed to lipid overload, hepatocyte damage, endotoxins, and inflammatory mediators from adipose tissue. These persistent stimuli can shift Kupffer cells from a homeostatic state toward a more activated and pro-inflammatory phenotype.

Once activated, Kupffer cells produce cytokines and chemokines such as TNF-α, IL-1β, IL-6, and CCL2. These mediators can worsen hepatocyte injury, recruit circulating monocytes and other inflammatory cells, and promote communication with hepatic stellate cells. Through these effects, Kupffer cells do not merely respond to liver injury. They also help amplify and maintain the inflammatory environment that drives disease progression. This makes them a key link between metabolic stress and inflammatory damage in MASLD.

2. MASLD as a Metabolic and Inflammatory Liver Disease

MASLD is often described as a liver disease caused by abnormal fat accumulation, but this description only shows the early surface of the disease. In many patients, fat deposition in the liver is connected with obesity, insulin resistance, type 2 diabetes, dyslipidemia, and other metabolic disorders. These conditions change the way the liver receives, stores, and processes lipids. When the amount of fatty acids entering the liver is greater than the liver's ability to use or export them, triglycerides and other lipid products begin to accumulate in hepatocytes. At this stage, MASLD may appear mainly as hepatic steatosis. The liver contains too much fat, but severe inflammation may not yet be present.

The problem becomes more serious when lipid accumulation begins to disturb normal hepatocyte function. Not all lipid storage is equally harmful. Triglyceride storage can sometimes be seen as a protective way to reduce free fatty acid toxicity. The more damaging process comes from lipotoxicity, which refers to injury caused by toxic lipid species, saturated fatty acids, free cholesterol, and related metabolic stress. These substances can impair mitochondrial function, increase oxidative stress, and disturb endoplasmic reticulum activity. As hepatocytes struggle to manage this stress, their normal metabolic and synthetic functions become weakened. The liver then moves from simple fat storage toward a state of cellular injury.

Insulin resistance is central to this process. When insulin signaling becomes less effective, adipose tissue releases more free fatty acids into the circulation. The liver then receives more lipid substrate and is pushed to produce more triglycerides. Insulin resistance can also increase hepatic glucose production and worsen systemic metabolic imbalance. This means MASLD is not only a local liver condition. It is closely tied to whole-body metabolic dysfunction. The liver becomes both a target and a participant in this disturbed metabolic state.

Oxidative stress further links metabolism with inflammation. Excess lipid metabolism increases the burden on mitochondria. When mitochondrial function is impaired, reactive oxygen species may increase. These reactive molecules damage proteins, lipids, and DNA inside hepatocytes. Oxidative injury also promotes the release of danger signals from damaged cells. These signals are recognized by immune cells in the liver, especially Kupffer cells. In this way, hepatocyte stress does not remain a purely metabolic event. It becomes an immune signal that tells the liver there is tissue damage.

Inflammation is therefore not a secondary or accidental feature of MASLD. It is one of the main

processes that drives disease progression. When hepatocytes are injured, they release damage-associated molecular patterns and inflammatory mediators. These signals activate Kupffer cells and other immune cells. Activated immune cells then produce cytokines and chemokines that intensify local inflammation. This inflammatory environment can cause further hepatocyte injury, attract more immune cells, and create a cycle of damage and response. MASLD may then progress from simple steatosis to MASH, a stage marked by steatosis, inflammation, and hepatocyte injury.

The inflammatory nature of MASLD also explains why some patients develop fibrosis. Persistent inflammation stimulates hepatic stellate cells and changes the structure of liver tissue. Repeated injury and repair lead to extracellular matrix deposition. Over time, this process can produce fibrosis and increase the risk of cirrhosis and other liver-related complications. MASLD should therefore be understood as a disease shaped by both metabolic overload and immune activation. Fat accumulation begins the process, but inflammatory progression determines much of the later damage.

For this reason, Kupffer cells become especially important in the study of MASLD. They are located at the point where metabolic injury, gut-derived signals, and immune responses meet. In early steatosis, hepatocyte lipid accumulation may be the most visible feature. As the disease progresses, Kupffer cell activation helps turn metabolic stress into sustained inflammation. This shift from fat storage to inflammatory injury is central to understanding why MASLD can move from a relatively silent condition to a progressive liver disease.

3. The Biological Role of Kupffer Cells in the Liver

Kupffer cells are the resident macrophages of the liver. They are mainly located in the hepatic sinusoids, where they stay in close contact with blood flowing from the portal vein and hepatic artery. This position gives them a special role in liver immunity. Unlike many immune cells that enter tissues only after inflammation begins, Kupffer cells are already present in the liver under normal conditions. They act as a first line of immune surveillance and help the liver respond quickly to foreign substances, damaged cells, and metabolic changes.

The liver receives a large amount of blood from the intestine through the portal circulation. This blood contains nutrients, bacterial products, food-derived molecules, and other substances absorbed from the gut. The liver must process these materials without producing excessive immune reactions all the time. Kupffer cells help maintain this balance. They can recognize and remove harmful pathogens, but they also help prevent unnecessary inflammation against harmless gut-derived molecules. This makes them important not only for immune defense, but also for immune tolerance.

One of the basic functions of Kupffer cells is phagocytosis. They clear bacteria, cell fragments, aged blood cells, and other particles from the circulation. This function protects the liver and the whole body from harmful materials entering through the gut. Kupffer cells also remove dead or damaged hepatocytes and help clean the local tissue environment. Without this clearance function, cellular debris would accumulate and become another source of inflammation. In this sense, Kupffer cells are not naturally harmful. Their normal work supports liver homeostasis.

Kupffer cells also communicate with other liver cells. They interact with hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells, and recruited immune cells. Through cytokines, chemokines, and direct cell contact, they help regulate the immune tone of the liver. Under healthy conditions, this communication is controlled and balanced. It allows the liver to defend itself when needed, while still preserving normal metabolic and synthetic functions.

Their role becomes more complex in MASLD. In the early stage, Kupffer cells may try to clear lipid debris, damaged cell components, and stress signals released by hepatocytes. This response can be protective at first. It helps limit damage and maintain tissue order. The problem appears when metabolic stress continues for a long time. Excess fatty acids, oxidative stress, gut-derived endotoxins, and inflammatory mediators repeatedly stimulate Kupffer cells. Their original protective response may then shift into a chronic inflammatory response.

This shift is important for understanding MASLD progression. Kupffer cells do not simply become harmful because they are activated once. Activation is a normal part of their immune function. The real issue is persistent activation under abnormal metabolic conditions. When stimulation does not stop, Kupffer cells may

continue to release inflammatory cytokines and chemokines. These mediators can damage hepatocytes, attract more immune cells, and strengthen local inflammation. The same cells that normally protect the liver can therefore become contributors to disease progression.

Kupffer cells should be understood as regulatory cells with a dual nature. They help preserve liver homeostasis in normal conditions, but they can also drive inflammation when the liver is exposed to long-term metabolic injury. This dual role is central to MASLD. It explains why Kupffer cells are not only passive responders to hepatocyte damage. They are active participants in deciding whether liver injury is resolved or whether it develops into persistent inflammation.

4. Triggers of Kupffer Cell Activation in MASLD

Kupffer cell activation in MASLD does not come from a single cause. It is usually the result of several forms of stress acting together in the liver. Lipid overload, hepatocyte injury, gut-derived bacterial products, insulin resistance, and adipose tissue inflammation all contribute to this process. These factors do not work in a simple order. They often appear at the same time and reinforce each other. This is why Kupffer cells in MASLD are exposed to continuous stimulation rather than a short and limited immune signal.

Lipotoxicity is one of the most important triggers. In MASLD, the liver receives an excessive amount of free fatty acids from the circulation. Some of these lipids can be stored as triglycerides, but this storage capacity is limited. When toxic lipid species, saturated fatty acids, and free cholesterol increase inside hepatocytes, they begin to disturb normal cell function. Hepatocytes may develop mitochondrial stress, oxidative injury, and endoplasmic reticulum stress. These changes weaken cellular metabolism and make hepatocytes more vulnerable to injury or death.

Damaged hepatocytes release danger signals into the surrounding liver tissue. These signals are often described as damage-associated molecular patterns. They include cellular fragments, mitochondrial components, nucleic acids, ATP, and other stress-related molecules. Kupffer cells can recognize these signals through pattern-recognition receptors. Once these receptors are activated, Kupffer cells begin to produce inflammatory mediators. In this way, hepatocyte lipotoxicity is translated into immune activation. The original problem starts with abnormal lipid metabolism, but it soon becomes an inflammatory process.

Gut-derived endotoxins are another major source of Kupffer cell activation. The liver is directly connected to the intestine through the portal circulation. Under normal conditions, the intestinal barrier limits the movement of harmful bacterial products into the blood. In MASLD, gut microbiota changes and intestinal barrier dysfunction may increase the passage of bacterial products into the portal vein. Lipopolysaccharide is especially important in this process. When it reaches the liver, it can be detected by Kupffer cells through receptors such as Toll-like receptor 4.

This gut-liver connection helps explain why MASLD is not only a liver-localized disease. The liver constantly receives signals from the intestine, and Kupffer cells are among the first cells to respond to them. When endotoxin exposure is occasional and limited, Kupffer cell activation may help protect the body. When endotoxin exposure becomes repeated, the same response may turn into chronic inflammation. Toll-like receptor signaling can activate inflammatory pathways such as NF-κB, leading to the production of cytokines including TNF-α, IL-1β, and IL-6. These cytokines then worsen hepatocyte stress and help maintain the inflammatory environment.

Systemic metabolic inflammation also contributes to Kupffer cell activation. Many patients with MASLD also have obesity and insulin resistance. In obesity, adipose tissue is not only a site of fat storage. It can become an active inflammatory organ. Enlarged adipocytes and adipose tissue macrophages release inflammatory mediators into the circulation. At the same time, insulin resistance increases the release of free fatty acids from adipose tissue. The liver therefore receives both more lipid substrate and more inflammatory signals.

This continuous input keeps Kupffer cells under pressure. They are not responding to one isolated episode of injury. They are exposed to repeated signals from hepatocytes, the gut, and adipose tissue. These signals make it difficult for Kupffer cells to return to a resting or homeostatic state. As a result, Kupffer cell activation may become persistent. Persistent activation is especially damaging because it allows inflammatory cytokines and chemokines to be produced over a

long period.

The triggers of Kupffer cell activation in MASLD are therefore closely connected. Lipotoxicity injures hepatocytes and releases danger signals. Gut-derived endotoxins stimulate innate immune receptors. Systemic metabolic inflammation increases the flow of fatty acids and cytokines to the liver. Together, these factors create a liver environment in which Kupffer cells are repeatedly activated. This repeated activation becomes a key step in the movement from simple steatosis to inflammatory liver injury.

5. Inflammatory Signaling after Kupffer Cell Activation

After Kupffer cells are activated in MASLD, their role changes from quiet immune surveillance to active inflammatory signaling. They begin to release cytokines, chemokines, and other mediators that affect surrounding liver cells. This response may be useful when the liver faces a short-term threat, because it helps remove harmful substances and damaged cells. In MASLD, however, the stimulation is often continuous. Lipid overload, hepatocyte injury, and gut-derived endotoxins keep activating Kupffer cells. As a result, inflammatory signaling does not stop easily, and the liver remains in a state of repeated immune activation.

One important group of mediators released by activated Kupffer cells is inflammatory cytokines. TNF-α, IL-1β, and IL-6 are especially relevant in MASLD. TNF-α can worsen insulin resistance, increase hepatocyte stress, and promote cell death. IL-1β is closely related to inflammasome activation and can strengthen local inflammation. IL-6 may affect liver metabolism and immune responses, especially when it is produced for a long time. These cytokines do not act on only one target. They influence hepatocytes, endothelial cells, stellate cells, and other immune cells in the liver. Through these effects, Kupffer cells help turn metabolic injury into a broader inflammatory response.

Chemokines are also important after Kupffer cell activation. Activated Kupffer cells can release CCL2 and other chemokines that attract circulating monocytes into the liver. These monocytes can differentiate into macrophages and add to the inflammatory cell population. This means the inflammatory response is no longer limited to resident Kupffer cells. More immune cells enter the liver and participate in tissue injury. Some of these recruited cells produce additional cytokines and reactive oxygen species, which increase hepatocyte damage. This process creates a cycle in which inflammation attracts more inflammatory cells, and these cells further strengthen inflammation.

NF-κB signaling is one of the main pathways involved in this process. When Kupffer cells recognize lipopolysaccharide, danger signals, or toxic lipid-related molecules, NF-κB can be activated. This pathway promotes the expression of inflammatory genes and increases the production of cytokines such as TNF-α and IL-6. NF-κB signaling helps explain why Kupffer cell activation can become strong and persistent in MASLD. Once this pathway is repeatedly stimulated, the liver microenvironment becomes more inflammatory. Hepatocytes then face greater stress, and the possibility of progression from steatosis to steatohepatitis becomes higher.

The NLRP3 inflammasome is another important mechanism. Under metabolic stress, Kupffer cells can respond to danger signals and activate inflammasome pathways. NLRP3 inflammasome activation promotes the maturation and release of IL-1β and IL-18. These cytokines can deepen inflammatory injury and affect surrounding liver cells. Inflammasome activation is especially important because it connects cellular stress with innate immune response. In MASLD, hepatocyte lipotoxicity and mitochondrial damage may provide signals that support this pathway. Kupffer cells then translate these stress signals into a stronger inflammatory reaction.

Kupffer cells also communicate with hepatocytes during inflammatory progression. Injured hepatocytes release danger signals that activate Kupffer cells. Activated Kupffer cells then release cytokines that further damage hepatocytes. This creates a feedback loop between hepatocyte injury and immune activation. The more hepatocytes are injured, the more signals they release. The more Kupffer cells are activated, the more inflammatory mediators they produce. This loop is one reason why MASLD may gradually move from simple fat accumulation to MASH.

Their communication with liver sinusoidal endothelial cells also matters. Endothelial cells help regulate immune cell movement into liver tissue. Under inflammatory conditions, signals from Kupffer cells may change endothelial cell behavior and make it easier for immune cells to enter the liver. This increases local immune cell infiltration. The liver then becomes a more active

inflammatory site, rather than a tissue only affected by lipid storage.

Kupffer cells also interact with hepatic stellate cells. This interaction is important because it links inflammation with fibrosis. Inflammatory cytokines, reactive oxygen species, and profibrotic mediators from Kupffer cells can stimulate hepatic stellate cells. Once stellate cells are activated, they begin to produce extracellular matrix. If this process continues, fibrosis can develop. This shows that inflammatory signaling after Kupffer cell activation does not only cause short-term immune injury. It can also contribute to long-term structural changes in the liver.

Kupffer cell activation produces a network of inflammatory signaling in MASLD. Cytokines damage hepatocytes and disturb metabolism. Chemokines recruit more immune cells into the liver. NF-κB signaling maintains inflammatory gene expression. NLRP3 inflammasome activation increases IL-1β and IL-18 release. Interactions with hepatocytes, endothelial cells, recruited monocytes, neutrophils, and hepatic stellate cells make the inflammatory response broader and more persistent. Through these pathways, Kupffer cells become a central driver of inflammatory progression in MASLD.

6. From Kupffer Cell Activation to MASH

The transition from simple steatosis to MASH is one of the most important points in MASLD progression. Simple steatosis mainly means that excess fat has accumulated in hepatocytes. At this stage, the liver may already be under metabolic pressure, but inflammation and hepatocyte injury may still be limited. MASH is different. It involves steatosis together with inflammatory cell infiltration, hepatocyte injury, and often early fibrotic changes. This shift does not happen only because more fat is stored in the liver. It happens when lipid accumulation begins to cause repeated cellular stress and immune activation. Kupffer cells are central to this process because they help convert metabolic injury into inflammatory damage.

In early MASLD, hepatocytes try to adapt to lipid overload. They store triglycerides, increase lipid oxidation, and adjust metabolic activity. These responses may protect the liver for a time. The problem appears when the amount and type of lipid stress exceed the adaptive capacity of hepatocytes. Toxic lipid species, oxidative stress, and mitochondrial dysfunction begin to damage hepatocytes. Injured hepatocytes release danger signals into the liver microenvironment. Kupffer cells recognize these signals and become activated. This step is important because the disease begins to move beyond passive fat storage. The liver starts to show an active immune response to metabolic injury.

Activated Kupffer cells then amplify hepatocyte stress. They release inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These mediators can weaken hepatocyte function, increase oxidative injury, and promote cell death. Once hepatocyte injury becomes more obvious, more danger signals are released. Kupffer cells respond again, producing more inflammatory mediators. This creates a feedback loop between hepatocyte damage and Kupffer cell activation. The liver is no longer dealing with a single episode of injury. It enters a repeated cycle of metabolic stress, immune activation, and further cell damage.

This process also changes the immune cell composition of the liver. Kupffer cells can release chemokines such as CCL2, which attract circulating monocytes into the liver. These monocytes may differentiate into macrophages and join the inflammatory response. As a result, the inflammatory process is no longer limited to resident Kupffer cells. Recruited macrophages, neutrophils, and other immune cells begin to participate in tissue injury. Some of these cells release additional cytokines and reactive oxygen species. This makes inflammation stronger and more difficult to resolve. The progression to MASH therefore reflects not only Kupffer cell activation, but also the expansion of a wider inflammatory network.

Kupffer cells also help explain why inflammation in MASH can become self-sustaining. In a short-term injury, macrophage activation may help clear damaged cells and restore tissue balance. In MASLD, the injurious signals often continue because insulin resistance, lipid overload, gut-derived endotoxins, and adipose tissue inflammation remain present. Kupffer cells are repeatedly stimulated by these signals. They may fail to return fully to a homeostatic state. When this happens, inflammation becomes persistent. The liver continues to receive inflammatory signals even when there is no acute infection or external injury.

The formation of hepatic crown-like structures also reflects this process. In areas where hepatocytes are injured or dying, macrophages may gather around lipid-laden or damaged

hepatocytes. These structures suggest that macrophages are actively responding to hepatocyte death and lipid debris. They may help clear damaged material, but they also mark a tissue environment where inflammation and metabolic stress are closely connected. This shows that MASH is not simply a more severe form of steatosis. It is a stage in which hepatocyte injury and macrophage-driven inflammation become linked in a visible and organized way.

Kupffer cell activation is therefore more than a sign that MASLD has become worse. It is one of the mechanisms that pushes the disease toward MASH. Kupffer cells receive signals from stressed hepatocytes, gut-derived products, and systemic metabolic inflammation. They then release cytokines and chemokines that damage hepatocytes, recruit more immune cells, and maintain local inflammation. Through this process, simple steatosis can gradually become steatohepatitis. The key change is the emergence of sustained inflammatory injury. Kupffer cells stand at the center of that change because they transform metabolic stress into an immune response that can no longer be easily resolved.

7. Kupffer Cells and Fibrosis Development

Fibrosis is one of the most important consequences of long-term inflammatory progression in MASLD. It shows that liver injury has moved beyond temporary cell stress and has begun to change the structure of the liver tissue. In the early stage of MASLD, fat accumulation and inflammation may still be partly reversible. When inflammation continues for a long time, the liver repeatedly tries to repair damaged tissue. This repair process may gradually become excessive. Extracellular matrix begins to accumulate, collagen deposition increases, and normal liver architecture is slowly disturbed. Kupffer cells are closely involved in this shift from inflammatory injury to fibrotic remodeling.

The main cellular target in fibrosis development is the hepatic stellate cell. Under normal conditions, hepatic stellate cells stay in a relatively quiet state and store vitamin A. When the liver is injured, these cells can become activated. Activated hepatic stellate cells change into myofibroblast-like cells and begin to produce collagen and other extracellular matrix components. This process is useful in short-term wound repair, but it becomes harmful when injury does not stop. In MASLD, persistent hepatocyte stress and Kupffer cell activation create the conditions for continued stellate cell stimulation.

Activated Kupffer cells can promote hepatic stellate cell activation through several mediators. TGF-β is one of the most important profibrotic signals. It encourages stellate cells to produce extracellular matrix and supports the development of scar tissue. Kupffer cells can also release TNF-α, IL-1β, IL-6, reactive oxygen species, and platelet-derived growth factors. These mediators do not act separately. They form a local signaling environment that pushes hepatic stellate cells toward activation and keeps them active. As a result, inflammation becomes linked with fibrogenesis.

This process shows that fibrosis is not separate from inflammation. In MASLD, fibrosis often develops because the liver is caught in a repeated cycle of injury and repair. Hepatocytes are damaged by lipotoxicity, oxidative stress, and inflammatory mediators. Kupffer cells respond to this damage and release cytokines and chemokines. These signals bring more immune cells into the liver and activate stellate cells. Stellate cells then deposit extracellular matrix. If the original metabolic stress continues, the repair response does not fully resolve. The liver keeps producing scar tissue instead of returning to normal structure.

Kupffer cells also influence fibrosis by shaping the wider immune environment of the liver. They recruit monocyte-derived macrophages and other inflammatory cells through chemokines such as CCL2. These recruited cells can produce more inflammatory and profibrotic mediators. In this way, Kupffer cells do not only act directly on stellate cells. They also help build a larger inflammatory network that supports fibrosis. The more this network expands, the harder it becomes for the liver to restore homeostasis.

The relationship between Kupffer cells and fibrosis is also connected to failed resolution. In a controlled repair process, macrophages help clear dead cells, remove debris, and support tissue recovery. In MASLD, however, the injurious signals often remain present. Lipid overload continues, gut-derived endotoxins continue to reach the liver, and insulin resistance continues to affect hepatic metabolism. Kupffer cells may remain activated instead of shifting toward a repair-resolving state. This prolonged activation keeps stellate cells exposed to profibrotic signals. Fibrosis then becomes a

structural result of chronic inflammation.

Kupffer cells therefore connect early metabolic injury with later fibrotic remodeling. At the beginning of MASLD, the main problem may appear to be fat accumulation in hepatocytes. As the disease progresses, Kupffer cells translate hepatocyte stress into inflammatory signaling. When this signaling persists, it activates hepatic stellate cells and supports extracellular matrix deposition. This is why Kupffer cell activation is important not only for understanding MASH, but also for explaining how MASLD can progress toward fibrosis. The fibrotic stage is not a separate event that appears after inflammation. It is the result of inflammation becoming repeated, unresolved, and structurally damaging.

8. Kupffer Cells and Fibrosis Development

Fibrosis represents a later and more structural consequence of inflammatory progression in MASLD. In the early stage of the disease, fat accumulation and inflammatory injury may still remain partly reversible. When injury continues, however, the liver begins to repair itself again and again. This repeated repair response can gradually become harmful. Instead of restoring normal tissue structure, the liver starts to accumulate extracellular matrix and collagen. Over time, this process changes the architecture of the liver and creates fibrotic tissue. Kupffer cells play an important role in this movement from inflammation to fibrosis.

The key cells directly responsible for fibrosis are hepatic stellate cells. Under normal conditions, hepatic stellate cells remain relatively inactive and help store vitamin A. When the liver is injured, these cells can become activated and change into myofibroblast-like cells. After activation, they begin to produce collagen and other extracellular matrix components. This response is part of wound healing, but in MASLD the injury is not short-lived. Lipid overload, oxidative stress, hepatocyte damage, and inflammation may continue for a long time. The repair process then becomes chronic, and fibrotic tissue gradually builds up.

Activated Kupffer cells can stimulate hepatic stellate cells through several signals. TGF-β is especially important because it directly promotes extracellular matrix production. Kupffer cells can also release TNF-α, IL-1β, IL-6, reactive oxygen species, and other mediators that keep the liver in an inflammatory and profibrotic state. These signals do not only affect stellate cells in isolation. They also influence hepatocytes, endothelial cells, and recruited immune cells. As a result, the liver microenvironment becomes more favorable to fibrosis.

This connection shows that fibrosis is not separate from inflammation. In MASLD, fibrotic progression often develops from repeated inflammatory injury. Damaged hepatocytes release danger signals. Kupffer cells respond to these signals and produce inflammatory mediators. These mediators worsen hepatocyte injury and stimulate hepatic stellate cells. Once stellate cells are activated, collagen deposition increases. If the original metabolic stress remains, this cycle continues. The liver is then caught between ongoing injury and excessive repair.

Kupffer cells also contribute to fibrosis by recruiting other immune cells into the liver. They can release chemokines such as CCL2, which attract circulating monocytes. These monocytes may become inflammatory macrophages after entering liver tissue. Some of them release additional cytokines and profibrotic mediators. This expands the inflammatory response and strengthens the signals that activate hepatic stellate cells. In this way, Kupffer cells do not act alone. They help organize a broader immune environment that supports fibrotic remodeling.

The role of Kupffer cells in fibrosis also reflects a failure of inflammatory resolution. In a normal healing process, macrophages help clear dead cells and then support tissue repair. In MASLD, the metabolic pressure usually remains. Excess fatty acids continue to enter the liver. Gut-derived endotoxins may continue to stimulate innate immune receptors. Hepatocytes continue to experience stress and injury. Under these conditions, Kupffer cells may remain activated for a long period. Their activity shifts from controlled defense to persistent inflammatory signaling.

Kupffer cells therefore connect early metabolic injury with later fibrotic remodeling. At first, MASLD may appear mainly as fat accumulation in hepatocytes. As the disease progresses, Kupffer cells translate hepatocyte stress into inflammatory signals. When these signals persist, hepatic stellate cells are repeatedly activated and extracellular matrix deposition increases. Fibrosis is not simply the final stage after inflammation. It is the structural result of inflammation that has become chronic, repeated, and poorly resolved.

Kupffer cells have a dual role in MASLD. They are not simply inflammatory cells that damage the liver. Under normal conditions, they are necessary for liver protection and tissue balance. They remove bacteria, clear dead cells, process cellular debris, and help maintain immune tolerance in the liver. Even in the early stage of MASLD, their activation may have a protective meaning. When hepatocytes are injured by lipid overload, Kupffer cells help remove damaged material and limit further tissue disturbance. This response is part of the liver's normal defense system.

The problem begins when this response lasts too long. In MASLD, the source of injury is usually not temporary. Excess fatty acids continue to enter the liver. Hepatocytes continue to experience oxidative stress and lipotoxic injury. Gut-derived endotoxins may repeatedly stimulate innate immune receptors. Adipose tissue inflammation may also keep sending inflammatory mediators into the circulation. Under these conditions, Kupffer cells are not given enough opportunity to return to a resting or regulatory state. Their protective activation gradually becomes chronic activation.

Chronic Kupffer cell activation changes the effect of these cells on the liver. Instead of only clearing harmful material, they begin to produce inflammatory cytokines and chemokines over a long period. TNF-α, IL-1β, IL-6, and CCL2 can worsen hepatocyte stress, attract more immune cells, and support the development of a persistent inflammatory environment. This means the same cells that help protect the liver can also become a source of continuing injury. The key issue is not Kupffer cell activation itself. Activation is a normal and necessary part of immune defense. The real problem is prolonged activation that cannot be properly resolved.

This dual role also shows why the old M1/M2 macrophage model is not enough to explain MASLD. The M1/M2 model describes macrophages as either pro-inflammatory or anti-inflammatory, but liver macrophages in MASLD are more complex than this. Kupffer cells and recruited macrophages may show mixed features. Some macrophages promote inflammation and fibrosis. Some help remove dead cells and support tissue repair. Some may change their function as the disease moves from steatosis to MASH and then to fibrosis. A simple division between harmful and protective macrophages cannot fully explain these changes.

In MASLD, macrophage populations also change with disease stage. Resident Kupffer cells respond early to hepatocyte stress and gut-derived signals. As inflammation develops, circulating monocytes enter the liver and become monocyte-derived macrophages. These recruited macrophages may strengthen inflammation and interact with hepatic stellate cells. In fibrotic areas, some macrophage subsets may be closely associated with scar formation. At the same time, other macrophages may participate in debris clearance and tissue repair. This shows that the macrophage response in MASLD is dynamic rather than fixed.

The dual role of Kupffer cells is important for understanding inflammatory progression. If Kupffer cells clear damaged cells effectively and then shift toward resolution, liver injury may be limited. If metabolic stress continues and inflammatory signaling remains active, Kupffer cells may help sustain MASH and fibrosis. Disease progression therefore depends partly on whether the macrophage response moves toward resolution or remains trapped in chronic activation. MASLD becomes more severe when the balance shifts away from repair and toward persistent inflammation.

This point is also important for treatment thinking. It would be too simple to see Kupffer cells only as therapeutic targets that should be suppressed. Removing or blocking their function too broadly could weaken host defense, debris clearance, and tissue repair. A better approach would be to reduce harmful inflammatory activation while preserving their protective functions. In this sense, Kupffer cells should be understood as regulatory cells whose effects depend on context, duration of stimulation, and disease stage. Their dual role helps explain why MASLD progression is not a straight path from fat accumulation to injury, but a changing process shaped by both damage and repair.

9. Therapeutic Implications

The role of Kupffer cells in MASLD has important implications for treatment thinking. If MASLD is viewed only as a disease of fat accumulation, treatment will mainly focus on reducing hepatic lipid content. This is necessary, but it is not enough to explain or control disease progression. In many patients, the more serious damage comes from the inflammatory response that follows metabolic stress. Kupffer cell activation shows that MASLD management

should also consider immune regulation, gut-liver signaling, inflammatory pathways, and fibrosis development. The goal should not only be to reduce fat in the liver, but also to prevent metabolic stress from becoming chronic inflammatory injury.

Improving metabolic health remains the most basic intervention direction. Weight loss, better insulin sensitivity, healthier lipid metabolism, and improved glucose control can all reduce the pressure placed on the liver. When fewer free fatty acids enter the liver, hepatocytes experience less lipotoxic stress. Reduced hepatocyte injury means fewer danger signals are released into the hepatic microenvironment. Kupffer cells then receive less stimulation. In this sense, metabolic improvement can indirectly reduce Kupffer cell activation by lowering the upstream causes of inflammation.

Reducing lipotoxicity is also important. MASLD progression is closely related to toxic lipid species, oxidative stress, mitochondrial dysfunction, and hepatocyte injury. If hepatocytes can better handle lipid overload, the release of damage-associated signals may decrease. This would weaken one of the main triggers of Kupffer cell activation. From this point of view, treatments that improve mitochondrial function, reduce oxidative stress, or limit harmful lipid accumulation may help interrupt the connection between metabolic overload and immune activation.

The gut-liver axis is another possible direction. Kupffer cells are exposed to gut-derived products through the portal circulation. When intestinal barrier function is impaired, bacterial products such as lipopolysaccharide may reach the liver more easily and activate innate immune receptors. Restoring gut barrier function and improving gut microbiota balance may reduce this source of stimulation. This does not mean that MASLD can be treated only through the intestine, but it shows that liver inflammation is affected by signals outside the liver. Reducing endotoxin exposure may help decrease repeated Kupffer cell activation.

Direct regulation of inflammatory pathways is also theoretically important. Kupffer cell activation involves signaling pathways such as NF-κB and NLRP3 inflammasome activation. These pathways promote the release of inflammatory cytokines, including TNF-α, IL-1β, and IL-6. If excessive activation of these pathways can be controlled, liver inflammation may be reduced. However, this approach needs caution. Inflammatory signaling is not always harmful. It also helps the liver defend against pathogens and clear damaged cells. Treatment should avoid completely blocking normal immune responses.

Another important direction is the interaction between Kupffer cells and hepatic stellate cells. Fibrosis develops when hepatic stellate cells are repeatedly activated and begin producing extracellular matrix. Kupffer cells contribute to this process by releasing profibrotic and inflammatory mediators. If abnormal communication between Kupffer cells and stellate cells can be reduced, it may help slow fibrotic progression. This is especially important because fibrosis is closely related to long-term outcomes in MASLD. Controlling inflammation without addressing fibrosis would leave a major part of disease progression unresolved.

The dual role of Kupffer cells must be considered in any therapeutic strategy. Kupffer cells are not simply harmful targets that should be eliminated. They clear pathogens, remove dead cells, regulate immune balance, and support tissue repair. If their activity is suppressed too broadly, the liver may lose important protective functions. A more reasonable approach would be to reduce persistent pro-inflammatory activation while preserving their homeostatic and repair functions. In other words, the aim should be immune regulation rather than immune removal.

These therapeutic implications show that MASLD treatment should be understood in a broader way. Metabolic control remains the foundation, but inflammatory progression must also be addressed. Kupffer cells provide a useful entry point because they connect lipid overload, hepatocyte injury, gut-derived endotoxins, immune cell recruitment, and fibrotic remodeling. Targeting these connections may help prevent MASLD from progressing toward MASH and fibrosis. The practical challenge is to control harmful chronic inflammation without damaging the normal protective role of liver macrophages.

10. Conclusion

Kupffer cell activation is a key mechanism for understanding inflammatory progression in MASLD. MASLD does not progress only because fat accumulates in hepatocytes. Fat accumulation creates metabolic pressure, but the more serious change begins when this pressure leads to

hepatocyte injury, immune activation, and persistent inflammation. Kupffer cells are central in this process because they stand at the point where several disease signals meet. They respond to lipotoxic stress, damaged hepatocytes, gut-derived endotoxins, and systemic metabolic inflammation. Through these responses, they help convert metabolic dysfunction into liver inflammation.

The role of Kupffer cells is especially important in the shift from simple steatosis to MASH. In early steatosis, the main feature may be excess lipid storage. When hepatocytes become stressed or injured, they release danger signals that activate Kupffer cells. Activated Kupffer cells then produce cytokines and chemokines that worsen hepatocyte injury and recruit additional immune cells into the liver. This creates a cycle in which metabolic damage and immune response reinforce each other. The liver is no longer only storing excess fat; it becomes an inflammatory tissue environment.

Kupffer cells also help connect inflammation with fibrosis. Persistent activation can stimulate hepatic stellate cells through inflammatory and profibrotic mediators. Once stellate cells are activated, extracellular matrix deposition increases and fibrotic remodeling begins. This shows that fibrosis is not separate from inflammation. It develops when inflammatory injury becomes repeated and poorly resolved. Kupffer cells therefore link early metabolic stress with later structural damage in the liver.

At the same time, Kupffer cells should not be understood as purely harmful. Their normal functions include immune surveillance, pathogen clearance, removal of dead cells, and maintenance of liver homeostasis. The problem in MASLD is not activation itself, but long-term activation under continuous metabolic stress. When Kupffer cells cannot shift from inflammatory response to resolution, they become part of a chronic injury process. This dual role is important for both disease interpretation and treatment thinking.

MASLD progression is a dynamic process involving metabolic overload, hepatocyte stress, gut-liver signaling, immune cell recruitment, inflammatory persistence, and fibrotic remodeling. Kupffer cell activation connects these processes into a continuous disease pathway. Understanding this mechanism helps move the discussion of MASLD beyond simple fat accumulation. It shows why controlling inflammation and restoring immune balance are important for preventing the progression from steatosis to MASH and fibrosis.

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