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Longitudinal Pathogenesis Reconstruction and Staged Treatment of Mild Cognitive Impairment Characterized Based on the Holistic Concept of Five Zang-Organss

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Abstract: ***Mild Cognitive Impairment (MCI) represents an intermediate clinical state between physiological aging and dementia, serving as a critical intervention window to block the progression of cognitive decline toward dementia. Most existing studies treat the pathogenesis of "essence depletion and marrow reduction combined with phlegm-stasis intermingling" as a static cross-sectional consensus, which fails to capture the stage-specific pathogenetic features of MCI. Furthermore, clinical therapeutic strategies are often limited to isolated kidney-tonifying or phlegm-stasis resolving approaches, lacking systematic coordination guided by the holistic concept of five zang-organs. Based on a systematic review of contemporary traditional Chinese medicine (TCM) theories for differentiating and treating MCI and dementia, this study incorporates a temporal dimension and the holistic five zang-organ framework. Using multi-center clinical survey data, binary logistic regression was performed to verify the independent effects of "essence depletion and marrow reduction combined with phlegm-stasis intermingling" during the MCI stage and quantify their contribution magnitudes. A longitudinal pathogenesis model covering the full spectrum of cognitive impairment and a corresponding staged syndrome differentiation-treatment system were subsequently constructed. After adjusting for confounders including age and years of education, multivariate analyses identified phlegm turbidity syndrome (odds ratio [OR]=2.56, P<0.001) and marrow reduction syndrome (OR=2.52, P<0.001) as independent risk factors for MCI onset; these associations remained statistically significant in high-risk subgroups complicated with cerebrovascular disease and hypertension. These findings demonstrate that the core pathogenesis of MCI is characterized by predominant root deficiency (marrow reduction) accompanied by latent branch excess (phlegm turbidity). A staged diagnosis-treatment framework centered on the Kidney–Essence–Marrow–Brain axis with synergistic regulation of the heart, spleen, liver, and lung was established accordingly. A data-driven diagnostic criterion for the marrow depletion and phlegm obscuration syndrome was developed, alongside the therapeutic principle of "reinforcing the spleen to resolve phlegm, tonifying qi, and resuscitating orifices" exemplified by Xixin Decoction, bridging theoretical deductions and clinical empirical evidence.***

Keywords: Mild Cognitive Impairment, Five zang-organ holistic concept, Longitudinal pathogenesis model, Marrow depletion and phlegm obscuration, Essence depletion and marrow reduction, Logistic regression, Clinical empirical research**.**

1. Introduction

Mild Cognitive Impairment (MCI) is defined as mild deterioration of cognitive function that does not meet the diagnostic threshold for dementia. Epidemiological evidence confirms MCI as a pivotal transition point from quantitative to qualitative cognitive decline, with substantially elevated risk of conversion to dementia [1]. Clarifying the stage-specific core pathogenesis of MCI and developing operable early intervention protocols is critical for delaying cognitive deterioration and alleviating long-term care burdens in aging populations.

From a public health perspective, MCI is not merely mild age-related forgetfulness but a major contributor to chronic disease burden in aging societies. The prevalence of MCI among older Chinese adults remains high [1]. Within the dementia spectrum, Alzheimer's disease (AD) accounts for 60%–80% of all dementia subtypes. A meta-analysis covering 1990–2016 reported a pooled AD prevalence of 4.9%, with prevalence rising sharply with age and higher incidence in females than males [16]. Amnestic MCI (aMCI) carries the highest risk of progression to AD; without targeted intervention during the MCI phase, patients face increased risk of permanent functional dependence and excessive medical resource consumption.

The selection of cognitive screening scales directly affects case identification and subsequent syndrome stratification in the "early screening–early differentiation–early treatment" workflow. The Mini-Mental State Examination (MMSE) is suitable for preliminary MCI screening, while the Montreal Cognitive Assessment Beijing Version (MoCA-BJ) demonstrates superior sensitivity for detecting deficits in executive function, attention, and delayed recall—core cognitive domains impaired in MCI. Community-based cohort studies report a strong correlation between total MoCA-BJ and MMSE scores (r=0.791), with education-stratified cut-off values: 19 points for illiterate participants,21 points for primary school education, and 25 points for junior high school education or above [17]. Failure to calibrate screening thresholds for educational attainment causes systematic false-negative and false-positive diagnoses, distorting the true correlation between TCM syndrome elements and cognitive impairment domains. Therefore, scale threshold stratification and education bias correction were integrated as core methodological prerequisites for constructing the longitudinal pathogenesis model, alongside quantitative assessment of TCM syndrome elements.

No direct nomenclature equivalent to MCI exists in classical

TCM literature; its clinical manifestations are categorized under amnesia and dementia. Plain Questions · Treatise on the Natural Truth in Ancient Times states that "yin essence diminishes by half after the age of forty", establishing kidney essence consumption as an initiating factor for cognitive decline. Spiritual Pivot · Treatise on the Sea notes that "insufficiency of the marrow sea causes vertigo and tinnitus", further validating the causal link between essence depletion, marrow hypoplasia, and mental dysfunction. Contemporary TCM scholars uniformly summarize the core pathogenesis of dementia-spectrum disorders as "essence depletion and marrow reduction, phlegm-stasis obstructing cerebral orifices" [2], encapsulating the root deficiency–branch excess pathological framework and guiding clinical formula development.

Two critical gaps persist in current MCI TCM management:(1) Pathogenesis interpretations are often static, applying consensus theories for end-stage dementia to the distinct MCI phase, resulting in ambiguous early intervention targets;(2) Therapeutic approaches frequently rely on isolated kidney-tonifying or phlegm-stasis resolving regimens without holistic five zang-organ coordination, leading to clinical pitfalls including tonification-induced stagnation and purgation-induced depletion of healthy qi. This study combines theoretical inference with testable clinical empirical analyses to address three core research questions:

1) After adjusting for age, education, and other confounders, which TCM syndrome elements exert the strongest predictive effect on MCI incidence?

2) Do these predictive associations remain robust in high-risk subgroups complicated with cerebrovascular disease and hypertension?

3) Can a quantifiable syndrome diagnostic scale be developed to support disease staging and personalized medication regimens?

Addressing these questions refines the generalized consensus of "kidney deficiency as root, phlegm-stasis as branch" into a stage-specific MCI pathological profile of "predominant root deficiency with latent branch excess", enabling earlier, targeted therapeutic intervention [1,3,6].

This multi-center cross-sectional clinical survey enrolled MCI patients and age-matched healthy controls, collecting demographic covariates (age, sex, years of education, comorbidities) and quantitative TCM syndrome element evaluations. Binary logistic regression served as the primary statistical model, with receiver operating characteristic (ROC) curve analysis used to quantify model discriminative performance. The total sample size was N=1855. ROC analysis yielded an area under the curve (AUC) of 0.722 (95% confidence interval [CI] 0.698–0.746), with an optimal diagnostic threshold of 0.336, corresponding to a sensitivity of 0.645 and specificity of 0.698; these values provided empirical evidence for scale cut-off calibration.

Syndrome elements were selected via a triple screening framework integrating classical TCM theories, contemporary clinical consensus, and data-driven empirical evidence: 1) The Kidney–Essence–Marrow–Brain physiological axis documented in the Internal Classic and modern studies on kidney-based cognitive disorder interventions [3,7]; 2) Syndrome differentiation literature focused on phlegm-stasis pathology, highlighting phlegm turbidity obscuring cerebral orifices and blood stasis blocking intracranial collaterals as primary branch excess manifestations [5,6]; 3) Pre-established item pools for quantitative evaluation of marrow depletion and phlegm obscuration syndrome developed by the research team [4].

The present analysis prioritizes marrow reduction and phlegm turbidity as core pathogenic elements, with kidney deficiency and blood stasis treated as secondary accompanying dimensions to reflect authentic MCI clinical phenotypes. Syndrome elements do not exhibit one-to-one correspondence with cognitive impairment domains but interact through complex network pathways. Population-based research identifies kidney deficiency and marrow reduction as dominant deficiency patterns, while phlegm turbidity, internal heat, and blood stasis constitute major excess patterns; MMSE and MoCA capture distinct profiles of cognitive domain impairment [18]. Spearman correlation analyses further report negative associations between immediate memory and phlegm turbidity, as well as delayed recall and marrow reduction [18]. These external cohort data validate the focus on the marrow reduction–phlegm turbidity (accompanied by blood stasis) pathological axis: marrow reduction primarily drives deficits in delayed recall and high-order cognitive processing, whereas phlegm turbidity and blood stasis exacerbate cognitive lability via disrupted attention and executive function pathways.

2. Theoretical Review and Critical Appraisal of Contemporary TCM MCI Therapeutic Frameworks

Current TCM research on MCI and dementia is categorized into three dominant therapeutic paradigms: kidney-tonifying therapy, phlegm-stasis resolving therapy, and five zang-organ correlative therapy. A critical synthesis of their respective strengths and limitations supports the development of integrated, stage-specific MCI intervention protocols.

2.1 Kidney-Tonifying Therapy: Theoretical Merits and Clinical Limitations

The theoretical foundation of kidney-tonifying intervention rests on the TCM axiom that "the kidney stores essence, governs bone, generates marrow, and connects with the brain". Most scholars identify progressive kidney essence depletion as the fundamental driver of cognitive dysfunction [3]: physiological aging gradually consumes congenital essence, failing to nourish the marrow sea and cerebral mansion, manifesting as forgetfulness and bradyphrenia. This paradigm accurately captures the root deficiency component of cognitive decline and improves long-term prognostic outcomes.

However, MCI rarely presents as pure deficiency syndrome. Clinical manifestations including heavy-headedness, epigastric distension, anorexia, and thick greasy tongue coating confirm concurrent excess pathogenic accumulation.

Exclusive essence-filling and kidney-tonifying regimens ignore fluid metabolism dysfunction-induced phlegm-stasis deposition, failing to restore cerebral lucidity; additionally, cloying tonic herbs impair spleen transportation and exacerbate damp-phlegm generation, limiting therapeutic efficacy.

2.2 Phlegm-Stasis Resolving Therapy: Targeted Advantages and Therapeutic Risks

Classical doctrines that "intractable disorders originate primarily from phlegm" and "blood stasis obstructs collaterals" emphasize the central pathogenic role of phlegm turbidity obscuring cerebral orifices and blood stasis blocking intracranial collaterals in cognitive impairment [6]. Modern pathological findings including amyloid protein deposition and cerebral microcirculatory dysfunction provide objective mechanistic support for phlegm-stasis resolving interventions. The core strength of this paradigm is its focus on eliminating pathological metabolic waste to restore mental clarity.

Nevertheless, most MCI patients are middle-aged or older adults with progressive depletion of healthy qi; phlegm-stasis pathology arises secondarily to underlying visceral qi transformation dysfunction. Prioritizing drastic phlegm-eliminating and blood-breaking medicinals without addressing the root visceral deficiency risks the therapeutic error of reinforcing excess and purging deficiency, further depleting healthy qi and impeding long-term disease control.

2.3 Five Zang-Organ Correlative Therapy: Multidimensional Expansion and Demand for Integrated Axis-Based Regulation

Existing studies investigating heart-, spleen-, liver-, and lung-centered interventions expand the understanding of cognitive disorder pathogenesis [7–12], confirming cerebral spirit function is modulated by coordinated qi, blood, and fluid metabolism across all five zang-organs. However, current literature predominantly examines single-viscus pathology in isolation, lacking a unifying framework linking multi-viscus dysregulation to the core "essence depletion and marrow reduction combined with phlegm-stasis intermingling" pathogenesis via a central physiological axis, resulting in fragmented, uncoordinated multi-herb therapeutic combinations. Reconstructing a longitudinal disease evolution model integrating synergistic five zang-organ regulation anchored on the Kidney–Essence–Marrow–Brain axis is therefore clinically necessary.

3. Pathogenesis Reconstruction: Longitudinal Evolution Model of "Essence Depletion and Marrow Reduction Combined with Phlegm-Stasis Intermingling"

This study posits that "essence depletion and marrow reduction combined with phlegm-stasis intermingling" constitutes a dynamic progressive pathological cascade rather than a static diagnostic label. Integrating a temporal dimension reconstructs this pathogenesis as the unifying longitudinal thread spanning the full dementia disease spectrum.

3.1 Core Concept Definitions

1) Marrow depletion with phlegm turbidity (pathogenesis): Root deficiency originates from kidney essence exhaustion leading to an underfilled marrow sea; branch excess arises from disordered visceral qi transformation disrupting fluid metabolism, generating damp-phlegm that ascends to obscure clear cerebral orifices. The two pathological states reciprocally exacerbate one another: marrow hypoplasia deprives the brain of nourishment, while phlegm turbidity veils mental lucidity.

2) Marrow depletion and phlegm obscuration (syndrome): The standardized clinical manifestation cluster corresponding to the above pathogenesis, characterized by recent memory loss, persistent heavy-headedness, lumbago and knee weakness, pale enlarged tongue with greasy coating, and thin slippery pulse.

3.2 Staged Pathological Progression Across the Cognitive Impairment Spectrum

Stage 1: Early Phase (MCI Stage) – Predominant Root Deficiency, Latent Branch Excess

Driven by congenital endowment limitations or physiological senescence, kidney essence is gradually consumed, resulting in marrow undernourishment and cardinal manifestations of recent memory loss. Concurrently, spleen qi function declines, impairing transportation and transformation and generating latent damp-phlegm that has not yet fully occluded cerebral orifices. The defining pathological signature—predominant root deficiency with latent branch excess—marks the optimal therapeutic window to interrupt disease progression.

Stage 2: Middle Phase (Mild to Moderate Dementia) – Intermingled Deficiency and Excess, Cemented Phlegm-Stasis Pathology

Kidney essence depletion advances further; spleen deficiency drives sustained phlegm generation, while qi stagnation induces blood stasis. Phlegm and stasis interlock to obstruct intracranial collaterals, severely disrupting cerebral spirit function. The marrow depletion with phlegm turbidity theoretical framework [10] fully explains the bidirectional exacerbation of deficiency and excess during this phase: marrow hypoplasia inhibits clear yang ascent and promotes phlegm accumulation, while persistent phlegm turbidity gradually consumes marrow qi and worsens cerebral emptiness.

Stage 3: Advanced Phase (Severe Dementia) – Exhausted Essence and Marrow, Global Five Zang-Organ Collapse, Complete Orifice Obstruction by Dense Pathogens

Severe depletion of visceral qi, blood, yin, and yang occurs, accompanied by total exhaustion of essence and marrow and irreversible cerebral atrophy. Phlegm-stasis deposits solidify into refractory pathological masses deeply lodged within intracranial collaterals. Although excess pathogens fully obscure cerebral orifices, healthy qi is irreparably depleted, and mental vitality cannot be restored.

4. Pathological Mechanism Analysis Under the Five Zang-Organ Holistic Concept

Along the longitudinal disease progression axis, the five zang-organs collectively modulate cerebral spirit function via coordinated circulation of qi, blood, and body fluids, with spleen-kidney interaction serving as the central regulatory pivot:

- Kidney: The congenital visceral foundation governing bone development and marrow generation, functioning as the initiating node of cognitive decline pathogenesis. Progressive kidney essence depletion and marrow hypoplasia constitute the root etiology of memory impairment during MCI.

- Spleen: The acquired visceral root and core hub of transportation and transformation. (1) Impaired qi-blood biosynthesis eliminates postnatal nourishment for congenital kidney essence, exacerbating marrow depletion; (2) disordered fluid metabolism generates phlegm—the primary source of turbid cerebral pathogens. This dual pathological role provides robust theoretical support for prioritizing spleen-reinforcing phlegm-resolving therapy in MCI management.

- Heart: Governs mental consciousness and systemic blood circulation. Heart-kidney disharmony disrupts water-fire balance and impairs mental lucidity; insufficient heart blood and sluggish circulatory flow induce intracranial blood stasis.

- Liver: Regulates global qi dynamic function as the visceral pivot of qi movement. Qi stagnation drives fluid retention into phlegm and blood stagnation into stasis; emotional lability frequently presents as a comorbid clinical feature of MCI.

- Lung: Governs qi regulation and fluid conveyance. Lung qi deficiency obstructs upward ascent of clear yang; disrupted diffusion-descent function impairs systemic fluid circulation, facilitating damp-phlegm accumulation within cerebral collaterals.

5. Empirical Statistical Analysis and Diagnostic Scale Validation: Confirming Marrow Reduction–Phlegm Turbidity as the Core MCI Pathological Signature

Binary logistic regression quantified the independent predictive contribution of TCM syndrome elements to MCI onset risk, with ROC curve analysis validating discriminative performance of the Marrow Depletion and Phlegm Obscuration Syndrome Diagnostic Scale.

Consistent with international cognitive disorder research standards, heterogeneous results frequently arise from inconsistent syndrome differentiation criteria and divergent disease staging frameworks. Ni et al. proposed synchronized disease staging and syndrome differentiation protocols for TCM clinical trials, recommending the Dementia Syndrome Element Scale (PES-D/11) and tripartite disease stratification: plateau phase, fluctuation phase, and progressive decline phase, with syndrome profiles shifting from dominant deficiency to prominent phlegm turbidity, blood stasis, and internal heat [19]. This staging framework aligns with the MCI "predominant root deficiency, latent branch excess" profile and progressive phlegm-stasis aggravation model proposed herein, enhancing translational compatibility between study results, clinical trials, and real-world clinical practice.

5.1 Full Cohort Multivariate Regression Analysis: Independent Risk Effects of Phlegm Turbidity and Marrow Reduction

Multivariate logistic regression adjusted for age, sex, hypertension, and other cardiovascular comorbidities identified phlegm turbidity syndrome (OR=2.556, P<0.001) and marrow reduction syndrome (OR=2.517, P<0.001) as independent MCI risk factors; kidney deficiency syndrome (OR=1.629, P<0.001) and blood stasis syndrome (OR=1.702, P=0.001) also demonstrated statistically significant predictive associations. These results confirm MCI is not a pure deficiency disorder: phlegm turbidity exerts potent pathogenic effects from the earliest disease stage, forming the core clinical pathological signature of predominant root deficiency with latent branch excess alongside marrow reduction.

5.2 High-Risk Subgroup Sensitivity Analysis: Pathway Robustness Under Complex Comorbidity Profiles

Within participants diagnosed with cerebrovascular disease, phlegm turbidity syndrome retained statistical significance (OR=2.376, P=0.0035), while the pathogenic contribution of blood stasis syndrome increased markedly (OR=2.749, P=0.0039), confirming vascular-origin MCI exhibits prominent intermingled phlegm-stasis pathology. Among participants with concurrent cerebrovascular disease and hypertension, marrow reduction syndrome (OR=2.457, P=0.015) and phlegm turbidity syndrome (OR=2.213, P=0.029) remained independent MCI risk factors. These subgroup analyses verify the marrow depletion–phlegm turbidity pathological axis represents a universal core signature across heterogeneous patient populations, supporting strong external validity and statistical stability of the diagnostic scale.

5.3 Development of the MCI Marrow Depletion and Phlegm Obscuration Syndrome Diagnostic Scale

Scale items were dual-screened based on statistically significant elevated OR values in multivariate regression models and high clinical prevalence rates of associated manifestations (dizziness: 81.25%; greasy tongue coating: 90.48%). ROC curve analysis established a total score cut-off of >15 points for definitive diagnosis of marrow depletion and phlegm obscuration syndrome. The scale functions as an auxiliary quantitative tool for syndrome differentiation and patient risk stratification and does not replace comprehensive four-diagnosis clinical evaluation. For patients complicated by depression, sleep disturbance, or other neuropsychiatric comorbidities, integrated assessment of emotional and sleep domains is required for holistic syndrome differentiation.

6. Staged Syndrome Differentiation and Therapeutic Strategies: Prioritizing Healthy Qi Reinforcement with Concurrent Phlegm Resolution for the MCI Phase

Based on the longitudinal pathogenesis model and empirical statistical evidence, a full-spectrum staged therapeutic framework is proposed to facilitate early, targeted disease intervention.

6.1 Early Phase (MCI Stage): Tonify Kidney to Fill Marrow, Reinforce Spleen to Resolve Phlegm (Prevent Progressive Deterioration)

Pathogenetic core signature: Marrow depletion as root, incipient latent damp-phlegm as branch excess.

Therapeutic principle: Prioritize reinforcement of healthy visceral qi, concurrent activation of spleen transportation and dampness elimination to block disease progression at the pre-dementia stage.

Representative formula: Xixin Decoction

Formula composition analysis: Ginseng, Atractylodis Macrocephalae Rhizoma, Poria cocos, and Glycyrrhizae Radix et Rhizoma are heavily dosed to tonify the middle jiao, embodying the spleen-reinforcing essence-generating doctrine: robust postnatal qi-blood biosynthesis nourishes congenital kidney essence. Pinelliae Rhizoma and Citri Reticulatae Pericarpium descend turbid qi and resolve phlegm; Acori Tatarinowii Rhizoma and Polygalae Radix resuscitate cerebral spirit and unblock orifices. The complete formula achieves tonification without cloying stagnation and pathogen elimination without drastic purgation, fulfilling the therapeutic objective of sufficient essence replenishing marrow and resolved phlegm unblocking cerebral orifices to interrupt disease progression at its source.

Modification guidelines: Add Pogostemonis Herba, Magnoliae Officinalis Cortex, and Perillae Folium for severe damp-phlegm accumulation; supplement Ziziphi Spinosae Semen and Platycladi Semen for palpitations, amnesia, and insomnia; integrate Bupleuri Radix and Curcumae Radix for prominent liver qi stagnation and emotional depression [13,14].

6.2 Middle Phase (Mild to Moderate Cognitive Impairment): Reinforce Spleen to Resolve Phlegm, Soothe Liver to Activate Blood, Resuscitate Spirit and Unblock Orifices (Treat Established Disease Pathology)

This phase is defined by intermingled deficiency and excess, with severe cemented phlegm-stasis pathology as the dominant clinical feature.

Therapeutic principle: Concurrent tonification and purgation; prioritize drying dampness to resolve phlegm, soothing liver qi stagnation, and activating collateral blood circulation.

Representative modified formulas: Wendan Decoction combined with Xiaoyao San or Xuefu Zhuyu Decoction. Escalate doses of processed Pinelliae Rhizoma, Arisaema Erubescens, and Acori Tatarinowii Rhizoma for severe phlegm obscuration; add Salviae Miltiorrhizae Radix et Rhizoma, Chuanxiong Rhizoma, and Pheretima for marked intracranial blood stasis. Medicinal agents are selected to activate circulation without breaking blood and resolve phlegm without drying visceral yin, avoiding healthy qi depletion or liver wind agitation. For vascular-origin MCI or patients with hypertension, additional therapeutic emphasis is placed on unobstructing cerebral collaterals and harmonizing systemic qi-blood circulation [8].

6.3 Advanced Phase (Severe Dementia): Reinforce Healthy Qi to Consolidate the Root, Harmonize Five Zang-Organs, Mildly Eliminate Branch Excess (Preserve Vital Functional Status)

This phase presents global depletion of healthy visceral qi with dense pathogens fully occluding cerebral orifices.

Therapeutic principle: Aggressively tonify original qi and harmonize five zang-organ function, prioritizing improvement of patient quality of life; drastic purgative therapies targeting excess pathogens are contraindicated.

Representative modified formulas: Zuogui Wan or Yougui Wan, with high-dose Rehmanniae Radix Preparata, Corni Fructus, and ginseng for intensive root tonification. Low-dose Notoginseng Radix et Rhizoma and Curcumae Radix are supplemented to regulate qi and activate blood circulation, ensuring tonification without visceral stagnation and mild circulatory modulation without drastic purgation. Multimodal supportive interventions including structured cognitive training, standardized daily routines, and emotional counseling are integrated; concurrent sleep disorders and neuropsychiatric manifestations require targeted syndrome differentiation treatment [13,14].

7. Discussion

7.1 Stage-Specific MCI Pathogenetic Localization: From Generalized Consensus to Phase-Specific Pathological Profiling

Prior literature uniformly summarizes the full-spectrum dementia pathogenesis as “essence depletion and marrow reduction combined with phlegm-stasis intermingling” [5,6], yet MCI cannot be simplified as an attenuated precursor of moderate-severe dementia. Multivariate regression results demonstrate phlegm turbidity and marrow reduction exert the strongest predictive risk effects for MCI (both OR>2.5), confirming branch excess pathogens obscuring cerebral orifices are already active during the MCI phase, while marrow hypoplasia constitutes the foundational underlying pathological driver. Balancing the dual pathological components of predominant root deficiency and latent branch excess is the core therapeutic priority for MCI management: exclusive tonification exacerbates damp-phlegm accumulation, while drastic purgation depletes healthy qi; both strategies deviate from optimal early intervention protocols for this pre-dementia stage.

7.2 Holistic Five Zang-Organ Synergy: Defined Central

Axis with Dynamically Modulated Visceral Therapeutic Weight Across Disease Stages

All therapeutic interventions are anchored on the Kidney–Essence–Marrow–Brain central physiological axis, with the spleen as the primary regulatory pivot and coordinated modulation of heart, liver, and lung function integrated as secondary therapeutic targets. Spleen deficiency drives dual pathological cascades: impaired qi-blood biosynthesis worsens marrow depletion, while disordered fluid transportation generates phlegm that ascends to obscure cerebral lucidity [9,15]. Insufficient heart blood disrupts mental consciousness and executive cognitive function; liver qi stagnation accelerates phlegm-stasis cementation and correlates with comorbid emotional disturbance [8,10]. Lung dysfunction in diffusion-descent and fluid conveyance inhibits clear yang ascent and promotes systemic damp-phlegm retention [11,12]. Staged therapy does not involve indiscriminate multi-viscus regulation but dynamically adjusts the therapeutic weighting of each zang-organ pathway based on disease progression, anchored to a unified core pathological axis.

Evidence from randomized controlled clinical trials supports measurable cognitive benefits of integrated kidney-tonifying, spleen-reinforcing, and phlegm-resolving therapy for MCI. A randomized double-blind controlled trial conducted by Wu et al. reported that a kidney-tonifying, spleen-reinforcing, phlegm-resolving herbal formula administered for 12 weeks reduced ADAS-Cog scores, improved verbal fluency, and decreased PES-D-11 subscores for kidney deficiency, spleen deficiency, and phlegm turbidity with favorable safety profiles [20]. These findings confirm that targeting spleen transportation function and resolving phlegm to resuscitate cerebral orifices during the MCI therapeutic window improves cognitive phenotypes without excessive cloying tonic burden. Future research may integrate the marrow depletion and phlegm obscuration diagnostic scale with MoCA and ADAS-Cog to standardize clinical outcome indicators and unify syndrome differentiation criteria for cross-study comparability.

7.3 Clinical Utility and Limitations of the Quantitative Diagnostic Scale

The Marrow Depletion and Phlegm Obscuration Syndrome Diagnostic Scale develops core items from syndrome elements demonstrating the highest multivariate regression risk contribution, with diagnostic thresholds calibrated via ROC curve analysis. This framework enhances quantifiability and clinical operability of MCI syndrome differentiation, supporting rapid screening and risk stratification in primary care settings: patients with elevated total scale scores exhibit the combined pathological profile of predominant marrow depletion (root deficiency) and latent phlegm turbidity/blood stasis (branch excess), requiring immediate systematic intervention. For high-risk vascular-origin MCI populations, weighting of blood stasis-associated scale items can be increased during stratification assessments to align with disease-specific pathological phenotypes. Critical limitations include the scale's role as an auxiliary differentiation tool—designed to improve diagnostic consistency and stratification efficiency—and its inability to replace comprehensive four-diagnosis clinical evaluation. Complex comorbid cases with depression, sleep disturbance, and neuropsychiatric dysfunction require integrated multi-domain assessment for holistic syndrome differentiation and treatment [13,14].

To further validate scale and threshold rationality, syndrome construction protocols reference the 2017 clinical guideline Correlation Between Dementia Syndrome Changes and Cognitive Outcomes, which outlines diagnostic criteria for spleen-kidney deficiency with phlegm-turbidity obstructed collaterals [1]. Combined with the core pathogenesis theory of marrow depletion as root and phlegm turbidity as branch, standardized quantitative TCM diagnostic criteria were formulated for marrow depletion-phlegm turbidity aMCI. Eligible patients must meet Western diagnostic criteria for aMCI and present memory loss as a mandatory primary symptom, with quantitative scoring of four core syndrome elements (marrow reduction, kidney deficiency, spleen deficiency, phlegm turbidity) following the Alzheimer's Disease Syndrome Element Scale (AD-PES-11).

Definitive diagnosis of marrow depletion-phlegm turbidity syndrome requires all four syndrome element subscores >7 points, accompanied by tongue manifestations of enlarged pale tongue with dental impressions and thick white greasy coating, plus pulse presentations including sunken slippery, sunken slow, thin slippery, or sunken cubital pulse.

7.4 Study Limitations and Future Research Directions

First, the present analysis relies exclusively on cross-sectional clinical data; the longitudinal pathogenesis model is derived from theoretical inference, requiring prospective long-term cohort follow-up to validate dynamic syndrome element trajectories across disease stages and their predictive validity for AD conversion. Second, scale diagnostic thresholds and statistical regression parameters may be biased by regional population demographics and comorbidity prevalence, necessitating multi-center external cohort validation and threshold recalibration. Third, integrated translational research combining peripheral biological biomarkers and cerebral neuroimaging may identify objective mechanistic correlations between phlegm turbidity and inflammatory-metabo8 Conclusionlic dysfunction, as well as blood stasis and cerebral microcirculatory impairment, bridging TCM syndrome theory and modern pathological mechanisms [2,6].

Building on the universal consensus of "essence depletion and marrow reduction combined with phlegm-stasis intermingling" for cognitive impairment disorders, this study integrates a temporal disease progression dimension and the five zang-organ holistic TCM framework to reconstruct a unified longitudinal pathogenesis model and comprehensive staged syndrome differentiation-treatment system. Three core contributions are summarized below:

1) Theoretical Innovation: A full-spectrum longitudinal pathogenesis model for cognitive impairment disorders is proposed, establishing the unique stage-specific pathological signature of MCI as predominant root deficiency (essence depletion and marrow reduction) accompanied by latent

branch excess (phlegm turbidity and phlegm-stasis intermingling), correcting the oversimplified clinical framing of MCI as isolated kidney deficiency syndrome.

2) Clinical Empirical Evidence: Multivariate logistic regression analyses across the full study cohort and high-risk comorbidity subgroups validate marrow reduction and phlegm turbidity as independent risk factors for MCI onset (both OR>2.0), providing objective clinical empirical support for the marrow depletion-phlegm turbidity pathogenesis theory.

3) Translational Clinical Application: A tiered dynamic therapeutic regimen was developed: spleen-reinforcing phlegm-resolving qi-tonifying orifice-resuscitating intervention for the MCI pre-dementia phase, concurrent tonification-purgation therapy for mild-moderate dementia, and root-consolidating visceral harmonizing tonification for severe dementia. The quantitative Marrow Depletion and Phlegm Obscuration Syndrome Diagnostic Scale is introduced, supplying standardized quantitative tools and structured clinical workflows for precision TCM prevention and management of MCI.

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