JOURNAL OF INNOVATIONS IN MEDICAL RESEARCH

ISSN 2788-7022 MAR. 2026 VOL. 5, NO. 1

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Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
MAR. 2026 VOL.5, NO.1

Predictive Value of CCL3 Expression Levels for Therapeutic Response in Patients with Locally Advanced Cervical Cancer

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doi:10.63593/JIMR.2788-7022.2026.03.001

Abstract

Rationale: Locally advanced cervical cancer (LACC) exhibits profound therapeutic heterogeneity, with therapy resistance heavily influenced by the immunosuppressive tumor microenvironment. The myeloid compartment, particularly tumor-associated macrophages (TAMs), serves as a key mediator of this therapeutic resistance, yet the precise molecular hubs for predicting neoadjuvant chemotherapy (NACT) sensitivity remain insufficiently characterized. ***Objectives:*** This study aims to decipher the myeloid-driven mechanisms of chemoresistance and validate the clinical utility of the chemokine CCL3 as a predictive and prognostic biomarker in LACC patients to optimize personalized treatment strategies. ***Methods:*** We integrated single-cell transcriptomics (GSE236738) from six LACC patients with high-dimensional Weighted Gene Co-expression Network Analysis (hdWGCNA) to identify macrophage-specific functional modules and hub genes. Subsequent retrospective clinical validation was conducted via immunohistochemistry (IHC) on pre-treatment primary tumor biopsies from a cohort of 33 LACC patients receiving NACT, correlating CCL3 protein expression with RECIST outcomes and survival trajectories. ***Measurements and Main Results:*** Single-cell analysis revealed a substantial expansion of macrophages, accounting for approximately 35% of the immune infiltrate. hdWGCNA pinpointed the chemokine CCL3 as the central hub gene driving this macrophage functional polarization. In the clinical cohort, elevated CCL3 expression was significantly linked to diminished chemosensitivity and a poor pathological response, characterized by higher median Tumor regression rate (based on RECIST 1.1)s (0.31 vs. 0.57; $P = 0.001$). Furthermore, univariate Cox regression and Kaplan-Meier analyses confirmed that high CCL3 expression shows potential as a reliable prognostic factor for both reduced progression-free survival (HR = 1.190; $P = 0.004$) and overall survival (HR = 1.278; $P < 0.001$). ***Conclusions:*** CCL3 is a pivotal orchestrator of macrophage-mediated immune exclusion and chemoresistance in LACC. Assessing CCL3 expression levels provides a promising predictive tool for NACT sensitivity and a vital prognostic indicator, offering actionable insights for developing targeted immunotherapies and advancing precision oncology for LACC management.

Keywords: cervical cancer, CCL3, immunohistochemistry, neoadjuvant chemotherapy, prognosis

1. Introduction

Locally advanced cervical cancer (LACC) constitutes approximately 37% of all cervical carcinoma cases globally (Roberta Massobrio *et al.*, 2024; Carlo Ronsini *et al.*, 2024) and continues to pose a significant major clinical challenge due to its high propensity for recurrence and distant metastasis. Although definitive concurrent

chemoradiotherapy (CCRT) is established as the gold standard of care (Roberta Massobrio *et al.*, 2024; Carlo Ronsini *et al.*, 2024), neoadjuvant chemotherapy (NACT) is increasingly utilized as a strategic intervention to reduce tumor volume, improve operability, and eradicate occult micrometastases (Patricia Pautier, 2024; Malede Birara, Tadesse Urgie & Abraham Fessehaye Sium, 2024; Liang-Chih Liu *et al.*, 2024; Sudeep Gupta *et al.*, 2023; Vanita Noronha *et al.*, 2023; Mei Feng *et al.*, 2023; Young Ju Suh *et al*., 2025; Zi-Tong Zhang *et al.*, 2024; Jing Li *et al.*, 2023; Jing Chen *et al.*, 2023; Hitomi Sakaguchi-Mukaida *et al*., 2023). High-level clinical evidence, notably from the INTERLACE trial, indicates that induction chemotherapy prior to standard CCRT provides significant survival advantages, particularly when utilizing dose-dense weekly platinum-paclitaxel regimens (Mary McCormack *et al.*, 2024; Matheus de Oliveira Andrade *et al.*, 2025). The therapeutic landscape is further evolving with the introduction of neoadjuvant chemo-immunotherapy, which has demonstrated objective response rates as high as 98%, suggesting a powerful synergistic effect in enhancing clinical outcomes (Chen, Z. *et al.*, 2024). Despite these advancements, a striking heterogeneity in therapeutic response persists among LACC patients; for example, while approximately 72.4% of patients may achieve a good pathological response, a significant minority experiences poor outcomes and disease progression (Lijun Wei *et al.*, 2024). This efficacy variance is closely linked to the diverse immune landscapes within the tumor microenvironment and specific clinical-pathological factors such as baseline tumor size and histological grade (Lijun Wei *et al.*, 2024; Antonino Ditto *et al.*, 2024). Consequently, while NACT remains a critical life-saving alternative in settings with limited radiotherapy access (Malede Birara, Tadesse Urgie & Abraham Fessehaye Sium, 2024; Irene Alinafe Chidothe-Chisale *et al.*, 2025), identifying reliable molecular biomarkers is essential to pre-emptively determine therapeutic sensitivity and personalize treatment strategies (Pankaj Garg *et al.*, 2024; Wang, Z. *et al.*, 2023).

The tumor microenvironment (TME) is a complex and dynamic ecosystem where the myeloid compartment, particularly tumor-associated macrophages (TAMs), serves as a key mediator of therapeutic resistance (Arian Jahandideh *et al.*, 2023; Belén Toledo *et al.*, 2024; Bartosz Wilczyński *et al.*, 2024). These highly plastic cells frequently undergo polarization towards a pro-tumorigenic M2-like phenotype, which actively dampens anti-tumor immune responses and creates an immunosuppressive niche conducive to tumor survival (Belén Toledo *et al.*, 2024; Zhang, B. *et al.*, 2023; Liu, C. *et al.*, 2025). This M2-mediated resistance is orchestrated through diverse molecular mechanisms, including the secretion of pro-tumor factors and the modulation of drug metabolism, which collectively shield malignant cells from cytotoxic agents (Belén Toledo *et al.*, 2024; Liu, C. *et al.*, 2025). Furthermore, intercellular communication via extracellular vesicles and cytokines between TAMs and other stromal components facilitates the transport of drug efflux pumps and signaling molecules that enhance chemoresistance (Bartosz Wilczyński *et al.*, 2024). Recent evidence also highlights the role of specific macrophage subsets, such as C1q-expressing populations, in fostering resistance to modern therapies and promoting disease relapse (Caleb K. Stein *et al.*, 2024). Beyond direct biochemical interference, TAMs significantly impact treatment outcomes by promoting angiogenesis and remodeling the extracellular matrix, which can physically impair drug penetration into the tumor core (Arian Jahandideh *et al.*, 2023; Belén Toledo *et al.*, 2024). Consequently, reprogramming the myeloid landscape to favor anti-tumor M1 phenotypes represents a promising strategy to overcome these immunosuppressive barriers and restore therapeutic sensitivity in solid tumors (Zhou, S. *et al.*, 2025).

Among the myriad signaling molecules regulating this myeloid landscape, chemokine (C-C motif) ligand 3 (CCL3) has emerged as a key mediator of macrophage recruitment and functional polarization. Recent evidence underscores the diverse and context-dependent roles of CCL3 across various malignancies (Wang, Z. *et al.*, 2023; Zhou, S. *et al.*, 2025). For instance, in esophageal squamous cell carcinoma, radiotherapy induces CCL3 expression in infiltrating myeloid cells, driving a transition toward a pro-tumorigenic environment (Bryan Chee-chad Lung *et al.*, 2025). Similarly, dysbiosis-induced activation of the CCL3-CCR1 axis has been shown to foster immune evasion and correlates with poor overall survival (Teizo Yoshimura *et al.*, 2023), while myeloid-derived CCL3 recruits CCR1-high monocytes to establish robust immunosuppression under hyperglycemic conditions (Teizo Yoshimura *et al.*, 2023). Conversely, CCL3 can also exhibit anti-tumor properties by triggering pro-inflammatory M1-type polarization, thereby enhancing antigen presentation and the efficacy of both immune checkpoint blockade and chemotherapeutic agents like docetaxel (Yue, S. et al., 2023). Despite its recognized immunomodulatory roles, the specific impact of macrophage-derived CCL3 on NACT resistance in LACC remains poorly understood. To bridge this gap, we first integrated single-cell transcriptomics with high-dimensional network analysis to objectively identify key molecular hubs driving macrophage-mediated chemoresistance. Having pinpointed CCL3 as a central orchestrator in non-responding tumors, we subsequently validated its predictive and prognostic value in a clinical cohort of LACC patients receiving NACT. Ultimately, this study aims to establish CCL3 as a reliable biomarker to guide personalized precision oncology in cervical cancer.

2. Materials and Methods

2.1 Bioinformatics Analysis and Target Identification

Single-cell transcriptomic profiles of tumor samples from six cervical cancer patients (GSE236738) were analyzed using the Seurat package (v4.3.0) (Xiao Liang *et al.*, 2023; Juok Cho *et al.*, 2024; Qiqing Fu *et al.*, 2024; Yu Zhou *et al.*, 2024; Annekathrin Silvia Nedwed *et al.*, 2023). Quality control was performed by excluding cells with nFeature_RNA > 5,000 and a mitochondrial gene proportion (percent.mt) > 10%. After SCTransform normalization, the top 1,500 highly variable genes were selected for Principal Component Analysis (PCA). Batch effects across samples were mitigated using the Harmony algorithm (Sindri Emmanúel Antonsson & Páll Melsted, 2025; John Arévalo *et al.*, 2024). Unsupervised clustering was executed at a resolution of 1.0 using FindNeighbors and FindClusters functions. Cell clusters were visualized via UMAP dimensionality reduction and annotated based on canonical lineage markers. Differential expression patterns between chemo-responsive and non-responsive groups were evaluated using the Wilcoxon rank-sum test.

High-dimensional Weighted Gene Co-expression Network Analysis (hdWGCNA, v0.4.08) was applied to the processed single-cell data (Morabito, S. *et al.*, 2023). The analysis included genes expressed in at least 5% of the total cells. For the macrophage population, a co-expression network was constructed using an optimal soft-thresholding power of 16 (Mahsa Eshaghi & Sajad Rashidi Monfared, 2024; Jing Sui et al., 2025; Muhammad Farhan et al., 2025; Zahra Zinati & Leyla Nazari, 2024; Stephanie P. Klein et al., 2024). Gene modules were identified via hierarchical clustering and the dynamic tree-cut algorithm, visualized through dendrograms. Correlation analysis between gene modules and macrophage identity was conducted to pinpoint key modules. Intramodular connectivity was further calculated to identify central hub genes within these modules.

2.2 Patient Selection and Clinical Cohort

Clinical records of 33 patients with locally advanced cervical cancer (LACC) who received neoadjuvant chemotherapy (NACT) at Renmin Hospital of Wuhan University and Zhongnan Hospital of Wuhan University between 2021 and 2023 were retrospectively reviewed. The cohort comprised 33 female patients with ages ranging from 34 to 75 years. Significant therapeutic response was quantitatively assessed by the tumor regression rate, defined as the percentage decrease in the sum of the longest diameters of target lesions post-NACT compared to baseline, in accordance with RECIST 1.1 guidelines (Zhi-Hua Shi, 2022).

Inclusion criteria were: (1) primary squamous cell carcinoma of the cervix with a maximum tumor diameter > 4 cm; (2) administration of the NACT protocol (2-week Paclitaxel and Platinum-based regimen); (3) availability of comprehensive clinicopathological data. Exclusion criteria included patients with multiple primary malignancies or secondary cervical involvement originating from other metastatic sites. The study protocol was approved by the Medical Ethics Committee of the Medical College of Wuhan University (No: WHU2021-jchx001). Written informed consent for the academic use of clinical data and tissue samples was obtained from all participants prior to their inclusion in the study.

2.3 Immunohistochemistry (IHC) Staining

Immunohistochemical staining was performed to evaluate CCL3 expression in pre-treatment primary tumor biopsy specimens from patients with locally advanced cervical cancer (LACC). Tissue samples were fixed in 4% paraformaldehyde and embedded in paraffin. Serial sections were cut at a thickness of 3–4 μm, baked, deparaffinized, and rehydrated through graded alcohols. Heat-induced epitope retrieval (HIER) was executed in Tris-EDTA buffer (pH 9.0). Slides were then incubated with primary antibody (anti-CCL3, Affinity, DF8572; 1:100 dilution) for 60 minutes. A prediluted horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG polyclonal antibody was employed as the secondary antibody. The procedure was carried out strictly according to the manufacturer's instructions. Visualization was achieved using 3,3'-diaminobenzidine (DAB), followed by counterstaining with Mayer's hematoxylin.

2.4 Evaluation of IHC Staining

Immunohistochemical (IHC) slides were independently reviewed by two senior pathologists blinded to the clinical outcomes. The expression of CCL3 within the peritumoral stroma was assessed using a semi-quantitative scoring system based on both staining intensity and the percentage of positive cells. The proportion of positive cells was scored as: 0 (<5%), 1 (5%–25%), 2 (26%–50%), 3 (51%–75%), and 4 (>75%). Staining intensity was categorized as: 0 (no staining), 1 (light yellow), 2 (brownish-yellow), and 3 (dark brown). The total IHC score was evaluated by multiplying the staining intensity score (0–3) by the percentage of positive cells score (0–4), resulting in a final score ranging from 0 to 12. For all subsequent statistical analyses, patients were dichotomized into two groups based on the median total score (median = 1.0). Specifically, a total score of ≤ 1 was defined as low CCL3 expression (n = 18), and a total score > 1 was defined as high CCL3 expression (n = 15).

2.5 Patient Follow-up and Survival Definitions

The 33 patients were followed up through a combination of clinical record reviews and telephone interviews. The follow-up period spanned from December 1, 2021, to March 5, 2026, with a median follow-up duration of

35.3 months. Progression-free survival (PFS) was defined as the interval from the initiation of neoadjuvant chemotherapy (NACT) to either the first documentation of disease progression or the date of the last follow-up. Overall survival (OS) was calculated as the time from NACT initiation to death from any cause or the last follow-up.

2.6 Statistical Analysis

Bioinformatics was performed using R (v4.5.0), while clinical data were analyzed via Python (v3.14.0). Survival analysis, including Kaplan-Meier survival curves and Cox proportional hazards regression models, was conducted using the lifelines package (version 0.27.1). Continuous variables were assessed for normality using the Shapiro-Wilk test and compared using independent t-tests or Mann-Whitney U tests. Categorical data were analyzed using Chi-square or Fisher's exact tests. Survival curves for PFS and OS were estimated by the Kaplan-Meier method and compared via log-rank tests. Significant prognostic factors were identified using univariate and multivariate Cox proportional hazards regression models. A two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1 Single-Cell Landscape of Cervical Cancer Tissues

To elucidate the cellular determinants of therapeutic efficacy, we characterized the single-cell transcriptional landscapes of patients stratified by their response to NACT. Initial quality control assessments confirmed high data fidelity across all samples, characterized by consistent gene detection frequencies and minimal mitochondrial contamination (Figure 1A-B). Unsupervised clustering partitioned the integrated dataset into 18 distinct clusters (Figure 1C), which were subsequently annotated into nine major cell lineages—including macrophages, epithelial/tumor cells, and various stromal and lymphoid populations (Figure 1D). This annotation was based on the expression of canonical markers, such as TREM2 and APOE for macrophages, and EPCAM and KRT19 for tumor cells (Figure 1E). Quantitative compositional analysis revealed a distinct divergence in the tumor microenvironment (TME) between the two groups. Specifically, non-responding samples were characterized by an extensive presence of tumor cells and a concomitant expansion of the macrophage compartment, which accounted for approximately 35% of the immune infiltrate (Figure 1F). In contrast, responding patients exhibited a higher prevalence of endothelial cells and tumor-infiltrating T and NK cells. The marked accumulation of TREM2+/APOE+ macrophages in non-responders suggests that a polarized, pro-tumorigenic niche contributes to therapeutic resistance, underscoring the potential role of myeloid-driven immune exclusion in dictating clinical outcomes.

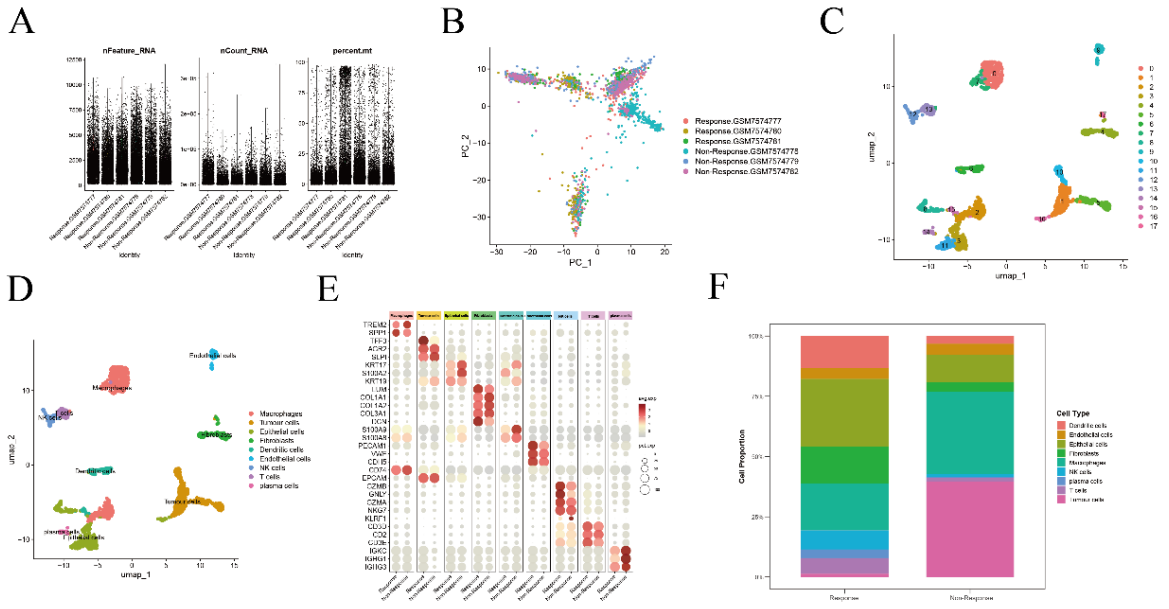

Figure 1. Single-cell Transcriptomic Landscape of Clinical Samples Categorized by Therapeutic Response

(A) Quality control metrics across all sequenced samples, including the number of detected genes (nFeature_RNA), total UMI counts (nCount_RNA), and the percentage of mitochondrial gene expression (percent.mt).

(B) Principal Component Analysis (PCA) plot demonstrating the effective integration of samples from both Response and Non-Response groups, indicating the absence of significant batch effects.

(C) UMAP visualization of 18 transcriptionally distinct cell clusters (Clusters 0–17) identified by unsupervised clustering.

(D) UMAP plot annotated by nine major cell lineages, including Epithelial/Tumor cells, Macrophages, T cells, NK cells, and Fibroblasts.

(E) Dot plot showing the expression of canonical marker genes used for lineage annotation (e.g., EPCAM/KRT19 for tumor cells, TREM2/APOE for macrophages, and CD3D/GZMB for lymphoid cells). The color intensity represents the average expression level, and the dot size indicates the percentage of cells expressing the marker.

(F) Bar plot quantifying the cellular proportions within the tumor microenvironment (TME) of Response and Non-Response groups, highlighting the enrichment of lymphoid populations in responders and tumor cells in non-responders.

3.2 Identification of Macrophage-Specific Hub Modules and CCL3 via hdWGCNA

To further delineate macrophage functional polarization, we applied hdWGCNA and identified 11 co-expression modules under a scale-free topology (R-squared > 0.8, soft-power = 16) (Figure 2A-C). Specificity scoring highlighted the M7 module as a key functional unit highly enriched within the macrophage compartment (Figure 2D-F). Within this regulatory network, the chemokine CCL3 emerged as a central hub gene, with its expression predominantly localized to the macrophage and NK cell lineages (Figure 3A-C). Notably, comparative analysis demonstrated that CCL3 expression was significantly elevated in macrophages derived from the non-response group compared to those from responders ($P < 0.05$; Figure 3D). These findings indicate that the macrophage-derived CCL3 axis may foster an immunosuppressive microenvironment that blunts therapeutic efficacy, positioning it as a key candidate driving treatment resistance.

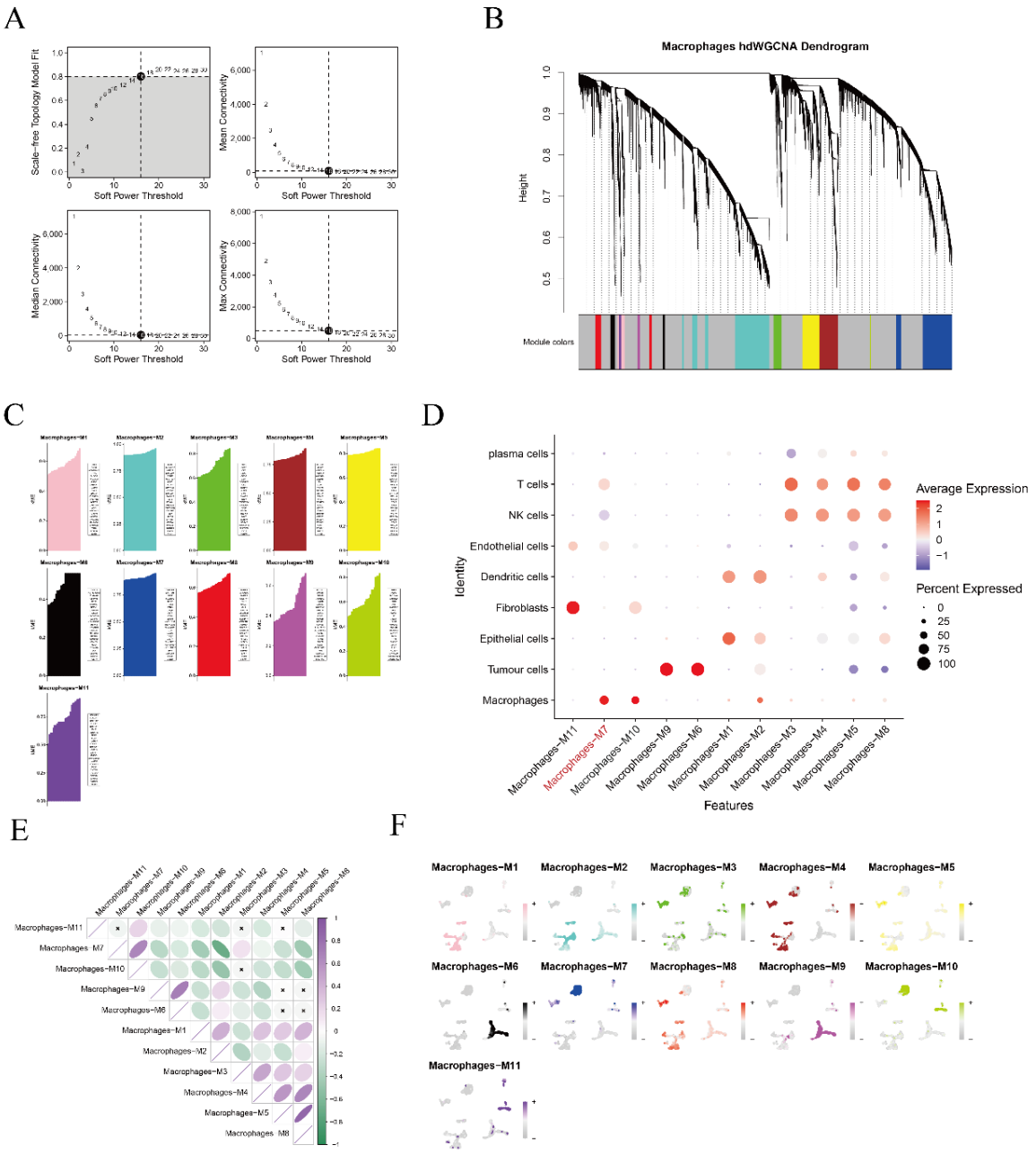

Figure 2. Modular Analysis of Macrophage Heterogeneity via High-Dimensional WGCNA (hdWGCNA)

(A) Selection of the soft-power threshold for network construction. Left: Scale-free topology model fit index (R-squared) as a function of soft-power (Power = 16 achieved R-squared > 0.8). Right: Mean connectivity across various soft-power thresholds.

(B) Gene dendrogram obtained by average linkage hierarchical clustering, with colors representing 11 identified co-expression modules (M1–M11).

(C) Distribution of module eigengenes (MEs) across individual cells within the macrophage compartment.

(D) Dot plot illustrating the specificity of the 11 modules across different cell lineages, identifying M7 as a macrophage-specific functional unit.

(E) Correlation heatmap showcasing the expression relationships and synergies among the identified co-expression modules.

(F) UMAP feature plots projecting the module scores of M1 through M11 onto the macrophage subpopulation, visualizing the spatial distribution of functional modules.

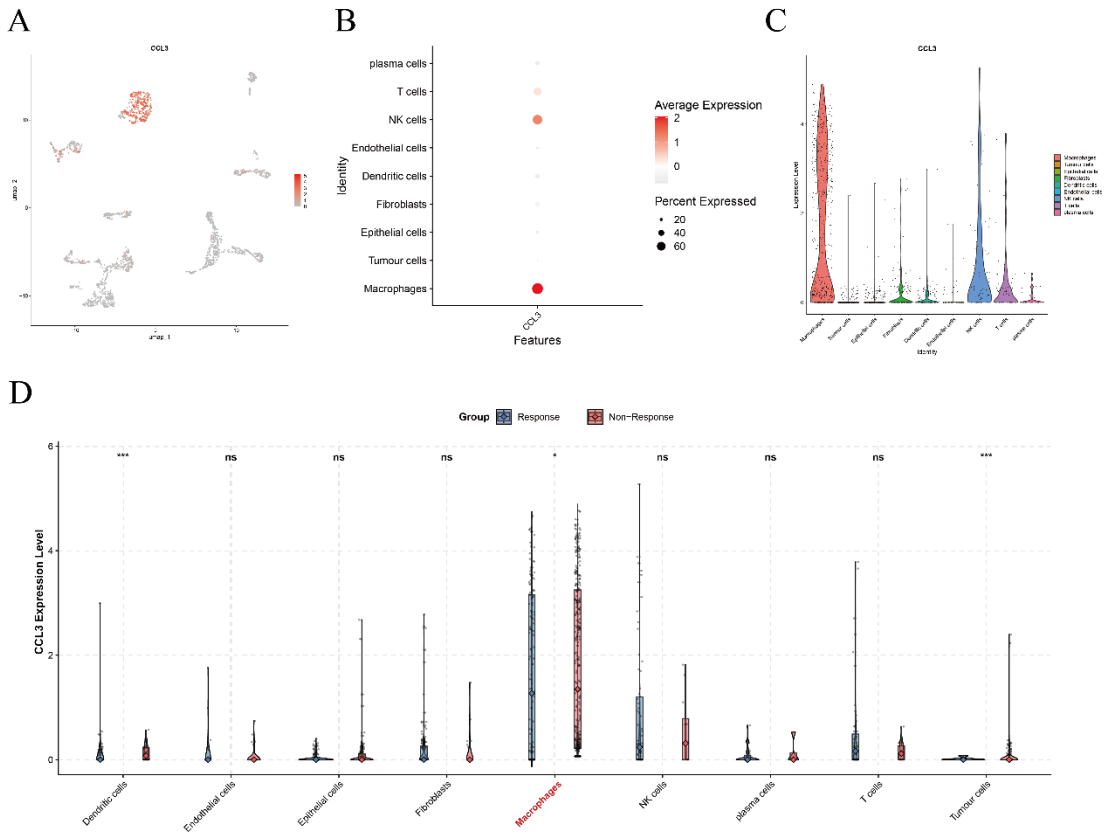

Figure 3. Identification of CCL3 as a Key Hub Gene Associated with Therapeutic Resistance

(A) UMAP feature plot visualizing the expression pattern of CCL3 across the entire single-cell dataset.

(B) Dot plot showing the expression frequency and intensity of CCL3 across major cell types, indicating its predominant origin from Macrophages and NK cells.

(C) Violin plot comparing the transcript levels of CCL3 among various cell lineages.

(D) Comparative analysis of CCL3 expression between Response (blue) and Non-Response (red) groups across identified cell types. Statistical significance was determined by the Wilcoxon rank-sum test (* $p < 0.05$, *** $p < 0.001$, ns: not significant). Note the significant upregulation of CCL3 in macrophages and tumor cells from the non-response cohort.

3.3 Validation of CCL3 Expression in LACC via Immunohistochemistry

To evaluate the clinical relevance of CCL3 in locally advanced cervical cancer (LACC), we performed immunohistochemical (IHC) profiling on 33 patient specimens. CCL3 protein was predominantly localized within the cytoplasm and the surrounding extracellular matrix, exhibiting a distinct expression gradient across the cohort (Figure 4). Quantitative assessment revealed that 36.4% of cases (n = 12) were negative (score 0), 45.5% (n = 15) were weakly positive (score 1–4), and 18.2% (n = 6) exhibited moderate-to-strong positivity (score ≥ 5). Following semi-quantitative scoring that integrated staining intensity and the percentage of positive cells, patients were stratified — based on the median total score (median = 1.0) — into a low-expression group (total score ≤ 1; n = 18, 54.5%) and a high-expression group (total score > 1; n = 15, 45.5%). This stratification served as the primary histological framework for correlating CCL3 abundance with therapeutic outcomes.

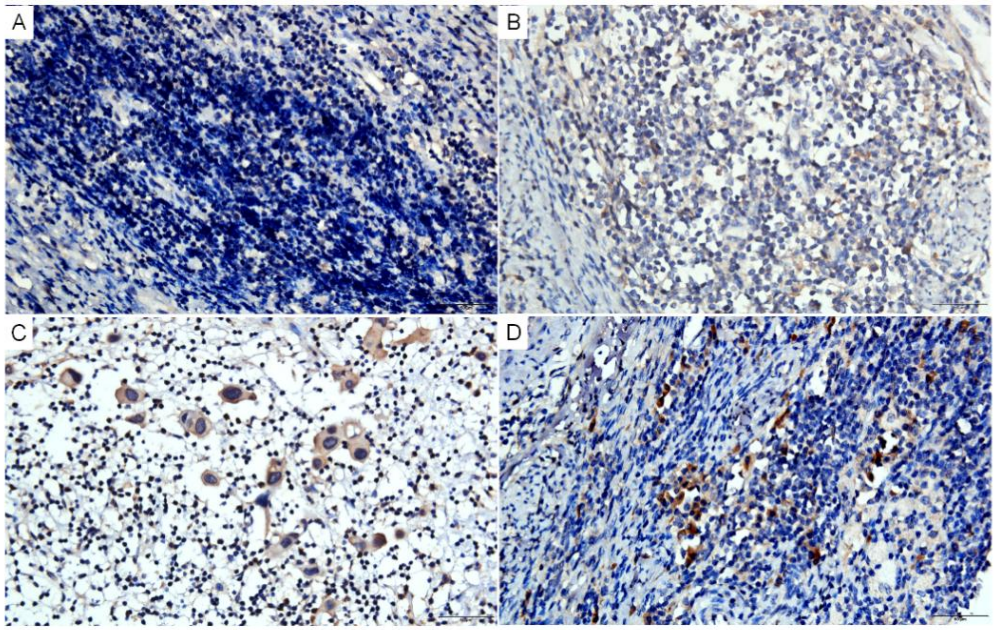

Figure 4. Immunohistochemical (IHC) characterization of CCL3 expression levels in LACC

(A-D) Representative images illustrating the CCL3 staining gradient: (A) negative (score 0), (B) weak (scores 1-4), (C) moderate (scores 5-8), and (D) strong (scores ≥ 9) positivity

Immunoreactivity is primarily concentrated in the cytoplasm. All slides were independently scored by two senior pathologists blinded to clinical data. Patients were dichotomized into low-expression (total score ≤ 1, n = 18) and high-expression (total score > 1, n = 15) cohorts based on the median IHC score. Scale bars = 50 μm.

3.4 Association of CCL3 with Clinicopathological Features and NACT Sensitivity

Analysis of the 33-patient locally advanced cervical cancer cohort established strong comparability between the good response and poor response groups, as baseline parameters—including mean age (57.03 ± 9.25 years) and FIGO stage (60.6% IIA2)—exhibited no statistical divergence (P > 0.05). While aggressive histological features such as nerve and vascular invasion were more frequent in non-responders (35.7% vs. 21.1%), these trends remained statistically non-significant (P = 0.442). Crucially, categorical stratification revealed a robust association between CCL3 levels and treatment efficacy, which was further corroborated by quantitative tumor regression metrics. Specifically, the CCL3-high cohort achieved a significantly lower median Tumor regression rate (based on RECIST 1.1) of 0.31 (IQR: 0.25–0.40) compared to 0.57 (IQR: 0.44–0.62) in the CCL3-low cohort (P = 0.001), indicating that elevated CCL3 levels in the tumor microenvironment are strongly linked to diminished chemosensitivity and a poor pathological response to NACT. Table 2 details the comparison between CCL3-low (n=18) and CCL3-high (n=15) patients, focusing on the substantial divergence in median Tumor regression rate (based on RECIST 1.1)s as a reliable metric for treatment sensitivity (Zhi-Hua Shi, 2022).

Table 1. Clinical characteristics and treatment outcomes of patients according to NACT response

Characteristics	Overall (n=33)	Good response (n=19)	Poor response (n=14)	P value
Age (years, mean ± SD)	57.03 ± 9.25	57.21 ± 10.88	56.79 ± 6.83	0.892
FIGO, No. (%)				
IB3	1 (3.0)	0 (0.0)	1 (7.1)	
IIA	7 (21.2)	3 (15.8)	4 (28.6)	0.139
IIA1	2 (6.1)	2 (10.5)	0 (0.0)	
IIA2	20 (60.6)	14 (73.7)	6 (42.9)	
IIB	3 (9.1)	0 (0.0)	3 (21.4)	
Nerve Invasion, No. (%)				0.442
Positive	9 (27.3)	4 (21.1)	5 (35.7)	

Negative	24 (72.7)	15 (78.9)	9 (64.3)	
Vascular Invasion, No. (%)				
Positive	9 (27.3)	4 (21.1)	5 (35.7)	0.442
Negative	24 (72.7)	15 (78.9)	9 (64.3)	
CCL3 Scores, median (IQR)				
Positive Cell Score	1.0 (0.0–2.0)	1.0 (0.0–2.5)	1.0 (0.0–2.0)	0.812
Intensity Score	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.724
Total Score	5.0 (2.0–8.0)	3.0 (1.0–4.0)	8.0 (5.0–10.0)	0.003
CCL3 Expression, No. (%)				
Low	18 (54.5)	7 (36.8)	11 (78.6)	**0.047**
High	15 (45.5)	12 (63.2)	3 (21.4)	

Note. Data are expressed as mean ± SD, median (IQR), or n (%). P values were calculated using Student's t-test, Mann-Whitney U test, Chi-square test, or Fisher's exact test, as appropriate. Good response: CR or PR; Poor response: SD or PD. CCL3 expression was dichotomized into low (total score ≤ 1) and high (total score > 1) groups based on the median IHC score. Bold P value indicates statistical significance ($P < 0.05$). Abbreviations: NACT, neoadjuvant chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; SD, standard deviation; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; CCL3, C-C motif chemokine ligand 3.

Table 2. Association of CCL3 expression with pathological characteristics in locally advanced cervical cancer

Characteristics	n (%)	CCL3 Expression		P value
		CCL3-High (n=15)	CCL3-Low (n=18)	
Age (years)				
< 60 years	22 (66.7)	8	14	0.162
≥ 60 years	11 (33.3)	7	4	
Clinical Stage				
IB/IIA	29 (87.9)	13	16	>0.999
IIB	4 (12.1)	2	2	
Nerve Invasion				
No	22 (66.7)	9	13	0.710
Yes	11 (33.3)	6	5	
Vascular Invasion				
No	23 (69.7)	9	14	0.447
Yes	10 (30.3)	6	4	
Treatment Regimen				
TP	29 (87.9)	13	16	
TP + Immunotherapy	2 (6.1)	2	0	0.253
TC	1 (3.0)	0	1	
LP+CDDP+Nida	1 (3.0)	0	1	
Tumor regression rate (based on RECIST 1.1) [Median (IQR)]	0.41 (0.26–0.58)	0.31 (0.25–0.40)	0.57 (0.44–0.62)	**0.001**

Note. CCL3 expression was dichotomized into low (total score ≤ 1) and high (total score > 1) groups based on the median IHC score. Clinical stage was determined according to FIGO 2018 criteria. Categorical data are presented as n (%), and continuous data as median (interquartile range [IQR]). P values were calculated using Fisher's exact test, Pearson chi-square test, or Mann-Whitney U test, as appropriate. Two-tailed $P < 0.05$ was considered statistically significant.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LP+CDDP+Nida, lobaplatin + cisplatin + nidaplatin; RECIST, Response Evaluation Criteria in Solid Tumors; TC, taxol + carboplatin; TP, taxol + cisplatin.

3.5 Prognostic Significance of CCL3 for Survival Outcomes in LACC Patients

To elucidate the impact of macrophage heterogeneity on therapeutic response, we constructed gene co-expression networks using hdWGCNA within the macrophage compartment. Applying a soft-threshold power of 16 to achieve a scale-free topology fit (R-squared > 0.8), we identified 11 distinct modules, among which M7 exhibited high macrophage specificity. The chemokine CCL3 emerged as a central hub gene within this regulatory network, with single-cell analysis localizing its expression primarily to macrophages and NK cells. We subsequently validated the clinical utility of CCL3 in a cohort of 33 patients with locally advanced cervical cancer (LACC) using immunohistochemistry. Categorical stratification revealed that high CCL3 expression was significantly enriched in the poor response group compared to good responders (P = 0.047). Crucially, longitudinal Kaplan-Meier survival analysis demonstrated inferior clinical outcomes for patients with elevated CCL3 levels, who exhibited significantly reduced overall survival (OS, P = 0.030) and progression-free survival (PFS, P = 0.004) compared to the low-expression cohort (Figure 5A-B). Collectively, these findings establish CCL3 as a promising predictive biomarker for NACT sensitivity in LACC management. Table 1 summarizes clinical characteristics stratified by NACT response, while Table 2 details the pathological outcomes based on CCL3 status. Representative IHC gradients are shown in Figure 4.

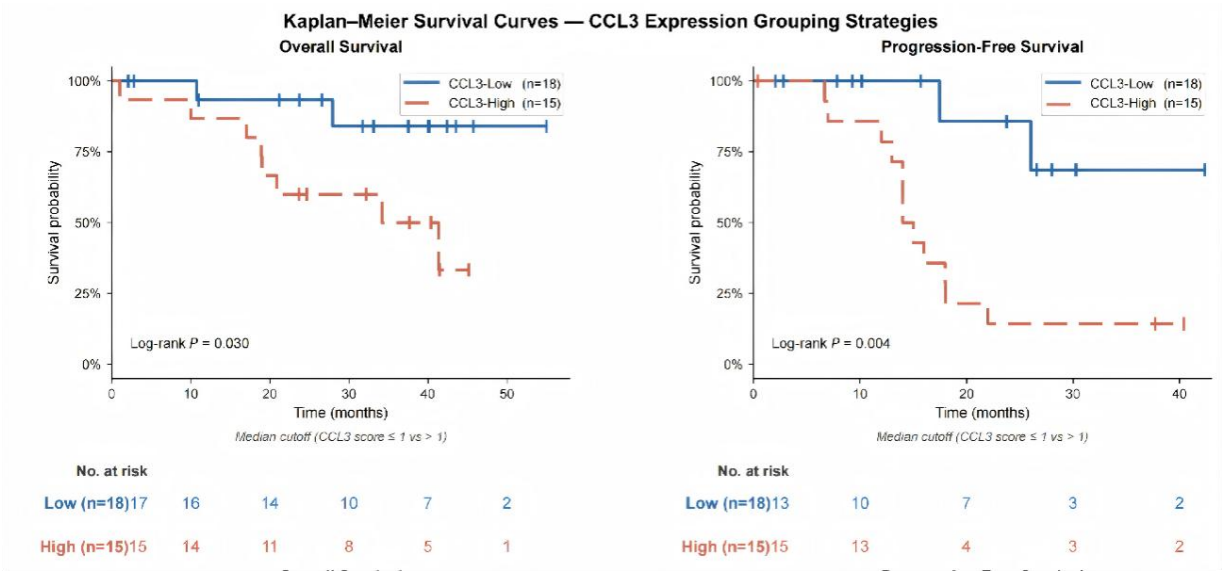

Figure 5. Kaplan-Meier survival analysis of patients stratified by high (total score > 1) versus low (total score ≤ 1) CCL3 expression

Note: (A) Overall survival (OS); (B) Progression-free survival (PFS).

Univariate Cox proportional hazards regression was performed to evaluate the prognostic impact of clinicopathological and molecular variables on progression-free survival (PFS) and overall survival (OS) in this cohort. As detailed in Table 3, conventional clinical parameters, including age, FIGO stage, nerve invasion, and vascular invasion, did not emerge as statistically significant predictors for either survival endpoint (P > 0.05). In contrast, clinical response indicators demonstrated robust prognostic value; a favorable treatment response was strongly associated with a diminished risk of progression (HR = 0.167, P = 0.002) and death (HR = 0.073, P < 0.001). Similarly, the Tumor regression rate (based on RECIST 1.1) served as a significant protective factor for both PFS (P = 0.007) and OS (P = 0.017). Notably, the CCL3 expression score was identified as a significant risk factor for poor prognosis. Higher CCL3 expression levels correlated significantly with an increased hazard of disease progression (HR = 1.190, 95% CI: 1.056–1.342, P = 0.004) and mortality (HR = 1.278, 95% CI: 1.112–1.470, P < 0.001). These findings suggest that while standard pathological features may have limited discriminatory power in this specific cohort, treatment-related responses and CCL3 expression levels offer substantial utility in the risk stratification of LACC patients.

Table 3. Univariate Cox Proportional Hazards Analysis of Prognostic Factors for PFS and OS in 33 Patients with Locally Advanced Cervical Cancer

Variable	PFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.016 (0.955–1.081)	0.612	1.075 (0.991–1.167)	0.082
FIGO	0.474 (0.104–2.149)	0.333	0.684 (0.085–5.474)	0.720
Nerve Invasion	1.393 (0.456–4.258)	0.561	0.643 (0.166–2.493)	0.523
Vascular Invasion	1.357 (0.454–4.058)	0.585	1.156 (0.324–4.125)	0.823
Treatment Response	0.167 (0.052–0.531)	0.002	0.073 (0.018–0.304)	< 0.001
Tumor regression rate (based on RECIST 1.1)	0.012 (0.000–0.297)	0.007	0.030 (0.002–0.530)	0.017
CCL3 Expression Score	1.190 (1.056–1.342)	0.004	1.278 (1.112–1.470)	< 0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumours; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TP, taxol + cisplatin. CCL3 High Expression defined as CCL3 Total Score > 1 (median, n = 15); CCL3 Low Expression: Score ≤ 1 (n = 18). Significant P values (< 0.05) shown in bold red. Cox proportional hazards model; HR > 1 indicates worse prognosis.

4. Discussion

The profound heterogeneity of the tumor immune microenvironment in locally advanced cervical cancer (LACC) remains a primary barrier to achieving consistent efficacy with neoadjuvant chemotherapy (NACT), frequently leading to variable treatment responses and disease relapse (Mary McCormack *et al.*, 2024; Lijun Wei *et al.*, 2024). While emerging evidence highlights the substantial role of tumor-associated macrophages in orchestrating chemoresistance across various malignancies (Belén Toledo *et al.*, 2024; Bo Yin *et al.*, 2025), precise molecular biomarkers capable of predicting this myeloid-driven resistance in LACC remain clinically elusive. By integrating single-cell transcriptomic profiling with high-dimensional weighted gene co-expression network analysis (hdWGCNA), our study identified the chemokine CCL3 as a central hub gene dictating the functional polarization of a distinct macrophage subpopulation. This initial finding was strictly substantiated in a reliable clinical validation cohort. Immunohistochemical assessments revealed that elevated CCL3 expression within the LACC microenvironment strongly correlates with inferior pathological responses and diminished sensitivity to NACT. Furthermore, longitudinal survival analyses confirmed that a high CCL3 burden serves as a significant prognostic factor for both shortened progression-free and overall survival. Together, these findings establish the clinical utility of CCL3 as a reliable predictive biomarker for treatment resistance and poor prognosis, offering a valuable molecular tool to guide personalized therapeutic interventions targeting the myeloid compartment in cervical cancer.

Our scRNA-seq analysis revealed a striking expansion of the macrophage population, which constituted approximately 35% of the immune infiltrate in the non-responder (NR) group following neoadjuvant chemotherapy. This pronounced accumulation aligns with clinical observations where CD68+ macrophages predominantly populate the tumor microenvironment (TME) of advanced cervical cancer patients failing to respond to standard therapies (Patrícia Rocha Martins *et al.*, 2023). The dramatic influx of macrophages can be attributed to the synergistic interplay between residual tumor cells and chemotherapeutic agents, which actively reshapes the myeloid compartment and promotes the survival and marker expression of M2-like phenotypes (Patrícia Rocha Martins *et al.*, 2023; Viktória Jenei *et al.*, 2025). Within this repopulated landscape, our data highlights a prominent subset of CCL3-expressing macrophages. Although the precise mechanisms of CCL3 in cervical cancer chemoresistance remain underexplored, tumor-associated macrophages (TAMs) are known to establish supportive niches for immune evasion and therapeutic resistance through complex cytokine and chemokine crosstalk (Yue, S. et al., 2023). We hypothesize that these CCL3+ macrophages act as central signaling hubs, secreting chemokines to recruit further immunosuppressive populations and impair T-cell function, mirroring the T-cell exhaustion and reduced cytotoxicity observed in SCCA-mediated macrophage polarization (Chen, Z. *et al.*, 2024). Consequently, this dynamic CCL3-driven network fortifies an immunosuppressive barrier within the TME, directly contributing to the refractory nature and poor prognosis of the NR cohort.

Building on current literature, we hypothesize that the expanded macrophages in the non-responder (NR) microenvironment drive cervical cancer immunosuppression and chemoresistance primarily via CCL3 secretion.

Mechanistically, CCL3 likely engages its receptors, CCR1 or CCR5, to recruit immunosuppressive populations such as regulatory T cells (Tregs) and monocytes into the tumor bed, thereby facilitating immune evasion (Zaineb Hassouneh *et al.*, 2024). Furthermore, the CCL3-CCR1 signaling axis can stabilize direct physical interactions between macrophages and tumor cells, a critical step for promoting metastasis and therapeutic resistance (Teizo Yoshimura *et al.*, 2023). Concurrently, this localized CCL3 overexpression — resembling the CCL3high PD-L1high super-immunosuppressive subsets observed in other malignancies — may exacerbate dysregulated inflammatory responses and subsequently impair the infiltration and cytotoxic efficacy of CD8+ T cells (Jing Li *et al.*, 2023; Liu, C. *et al.*, 2025). Beyond immune modulation, CCL3 might also directly fuel tumor progression by activating downstream epigenetic targets like m6A modifications (Zhou, S. *et al.*, 2025). Therefore, targeting this macrophage-driven CCL3 chemokine network holds promise for dismantling this multidimensional pro-tumorigenic cascade.

Given the critical role of CCL3 in macrophage-mediated chemoresistance, our findings demonstrate substantial clinical translational potential. Because patients with locally advanced cervical cancer exhibit significant heterogeneity in their responses to neoadjuvant chemotherapy (NACT) (Patricia Pautier, 2024), CCL3 emerges as a promising predictive biomarker within the precision medicine framework (Pankaj Garg *et al.*, 2024). Evaluating CCL3 expression and the histological distribution of specific macrophages in pre-treatment biopsies via routine immunohistochemistry (IHC) provides a cost-effective and intuitive method to profile the immunosuppressive microenvironment. For potential non-responders presenting with elevated CCL3 levels, clinicians might bypass standard NACT to prevent ineffective drug toxicity, opting instead for upfront concurrent chemoradiotherapy or alternative strategies involving immunotherapies. Integrating CCL3 assessment into standard pathological screening protocols will strongly facilitate personalized therapeutic stratification, optimize clinical decision-making, and ultimately improve survival benefits in cervical cancer management.

While our findings highlight the critical role of macrophage-derived CCL3 in cervical cancer chemoresistance — suggesting it shows potential as a reliable prognostic factor—certain limitations exist (Viktória Jenei *et al.*, 2025). Primarily, alongside the exploratory retrospective design, we must explicitly acknowledge that the small sample size intrinsically limits the statistical power of our Cox regression analyses. The single-center nature of the data also necessitates cautious interpretation regarding clinical generalizability. As advocated in recent oncology studies (Angela Collarino *et al.*, 2024), future validation across large-sample, multi-center prospective cohorts is strictly required to firmly establish the prognostic value of CCL3. Additionally, deeper mechanistic investigations are necessary to fully elucidate the immunosuppressive microenvironment reprogramming driven by these macrophages, ultimately bridging the gap toward effective clinical translation and personalized therapy. Finally, while our scRNA-seq analysis localized CCL3 expression predominantly to the macrophage compartment, our clinical validation relied on single-plex IHC. Future spatial transcriptomics or multiplex immunofluorescence (e.g., CCL3/CD68 co-staining) studies are warranted to precisely map the cellular origins and spatial interactions of CCL3 within the LACC microenvironment.

Data Availability Statement

The data are available upon reasonable request.

Competing Interests

The authors declare no competing interests.

Ethics Approval and Consent to Participate

This study was approved by the ethical standards of the Medical Ethics Committee of the Medical College of Wuhan University (No: WHU2021-jchx001). Written informed consent for the use of tissue samples in research was obtained from all participants.

Conceptualization

H.C. performed development of methodology and writing, review, revision of the paper, provided acquisition, analysis, and interpretation of data; HL.C. statistical analysis provided technical and material support. All authors read and approved the final paper.

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Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
MAR. 2026 VOL.5, NO.1

Epidemiological Investigation of Hepatitis F Viruses (HFV)

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doi:10.63593/JIMR.2788-7022.2026.03.002

Abstract

The hepatitis is a liver inflammation that is related to hepatocellular necrosis. Viral hepatitis may be caused by various hepatitis viruses, such as A, B, C, D, E, F, and G. Hepatitis F is a hypothetical virus linked to viral hepatitis. Sporadic non-A, non-B hepatitis, such as hepatitis F is the most common, presumed viral that may cause acute liver failure. A novel agent called hepatitis French virus (HFV) was present as 27-37nm particles in the infectious stool extract of French patients. The virology, epidemiology, hepatotropism, and clinical importance of HFV are quite uncertain, and are not determined yet. This study tries to discuss the known structure and other clinical features of HFV.

Keywords: Hepatitis F virus, non-A-E hepatitis, liver failure, rhesus monkeys

1. Introduction

Hepatitis F is a hypothetical virus linked to viral hepatitis. At present seven viruses: A, B, C, D, E, F, and G have been described as agents of acute or chronic hepatitis infection. Of these five hepatitis viruses A, B, C, D, and E are all well-characterized (Yasmin et al., 1997). An enteric agent responsible for sporadic non-A, non-E hepatitis is tentatively called hepatitis F virus (HFV) or hepatitis French virus (HFV) and has been described by two groups. In 1992, the first group has realized that a toga virus like agent was visualized by electron microscopy from liver biopsies of patients with unexplained fulminant viral hepatitis (Fagan et al., 1992). In 1994, the second group has realized that a virus from the feces of a patient with hepatitis and was transmitted to primates. But the role of this virus remains unclear (Deka et al., 1994).

Some cases of hepatitis transmitted through contaminated food or water are attributed to the HFV, which was first reported in 1994. Several hepatitis F candidates emerged in the 1990s; however, none of these claims were substantiated. In December 1994, researchers published evidence for the transmission of the enteric agent responsible for sporadic non-A, non-E hepatitis to rhesus monkeys that measuring 27-37nm in diameter (Kim et al., 1995).

2. Literature Review

The literature review section is an introductory region of research, which shows the works of previous researchers in the same field within the existing knowledge (Polit & Hungler, 2013). Niren Deka and his coauthors have indicated that 27 to 37-nm virus like particles are responsible for sporadic non-A, non-B hepatitis in rhesus monkeys. They have shown that sporadic non-A, non-B hepatitis in humans is serially transmitted in rhesus monkeys by intravenous inoculation of the stool extract from a patient (Deka et al., 1994). Scott Bowden has found that the HFV has a high prevalence in cases of non-A-E hepatitis, it also has a high prevalence in the appropriate control groups and convincing evidence for its replication in the liver is lacking (Bowden, 2001).

Krisnan Rajeshwari has taken communication attempts to summarize the recent relevant information in relation to the newer discovered hepatitis viruses through the application of the latest molecular technology to the

primate model (Rajeshwari, 1997). Elizabeth Ann Fagan and Tim J. Harrison have determined whether HAV, HEV, HCV, or HBV were detectable in prospectively stored hepatectomies from seven British patients grafted for acute liver failure attributed to sporadic non-A, non-B hepatitis. They have considered it candidate hepatitis F virus (HFV) in sporadic non-A, non-B acute liver failure (Fagan & Harrison, 1995). W. Keith Paver and Philip P. Mortinzer have indicated that a 60-nm particle is seen in the livers of patients with fulminant hepatitis, aid in subsequent graft necrosis following liver transplantation, and is originally proposed as hepatitis F virus (Paver & Mortinzer, 1996).

3. Research Methodology of the Study

Research is an essential device to the academicians for the leading in academic area (Pandey & Pandey, 2015). Methodology provides the research design and analysis procedures to perform a good research (Hallberg, 2006). Hence, research methodology is the collection of a set of principles for organizing, planning, designing and conducting a good research (Legesse, 2014). In this paper, I have depended on the secondary data sources of optimization, such as journal articles, books of famous authors, conference papers, internet, websites, etc. (Mohajan, 2017, 2018, 2020, 2024a-l).

4. Objective of the Study

Main objective of this article is to discuss the basic concept of hepatitis F virus (HFV). The exact role of HFV in human disease is not clear and needs more exploration (Rajeshwari, 1997). Other minor objectives of the study are as follows:

- to focus on the historical background of HFV,
- to highlight virology and symptoms of HFV, and
- to show diagnosis and treatment of HFV.

5. Historical Background of HFV

The 1980s' investigators of England, Italy, France, the USA, and India have studied on the sporadic non-parenteral non-A, B, C, D, E hepatitis (Deka et al., 1994). In 1987, the disease was transmitted to cynomolgus macaques and tamarins, and 27-34nm viral-like particles that consist of double-stranded DNA of approximately 20kb were observed in stool samples by electron microscopy (Bradley et al., 1987). The HFV is substantially different from HAV and HEV, and both of which consist of single-stranded RNA of approximately 7.5kb (Bowden et al., 1996). In December 1994, a group from New Delhi, India claimed to have transmitted the enteric agent responsible for sporadic non-A, non-E hepatitis in humans to rhesus monkeys using a stool extract from a patient. They have reported that the viral particles represented a "novel agent" that they called HFV (Deka et al., 1994).

6. Virology of HFV

Hepatitis F virus (HFV) first appeared as togavirus-like 60-70nm enveloped particles that were recovered from the hepatocytes of a number of patients transplanted for fulminant hepatic failure (Kim et al., 1995). The HFV is a purified viral 27-37nm consists of a double-strand DNA of 20kb that is incongruous considering the size of the virion, and is detected in infected monkey liver (Deka et al., 1994).

7. Symptoms and Transmission of HFV

The liver morphology of HFV infected persons may be of an acute hepatitis, and 20% of the cases the fatality of the disease becomes sever. In infected animals viral antigens and elevation of transaminases appear in an average of 20 days (Deka et al., 1994). The infection was not only sporadic but also enterically transmitted (Bradley et al., 1987).

8. Diagnosis and Treatment of HFV

The HFV antigen has been detected by enzyme-linked immunosorbent assay (ELISA) in 66% of coded specimen (Deka et al., 1994). The first- and second- round primers in a polymerase chain reaction (PCR) to amplify conserved regions of HAV, HEV, and HCV; the E1/S (gp35) region of HCV, and surface and core regions of HBV (Fagan & Harrison, 1995).

9. Conclusions

From this study, I have realized that HFV is transmitted in humans through the rhesus monkeys. The HFV genome is 27-37nm in diameter about 20kilobases of double-stranded DNA. More epidemiological studies are required to determine the complete knowledge on HFV.

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Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
MAR. 2026 VOL.5, NO.1

The "Romance of the Three Kingdoms" of EGFR-TKI Combination Therapy: Relationships Among Efficacy, Toxicity, and Resistance Mechanisms

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doi:10.63593/JIMR.2788-7022.2026.03.003

Abstract

Epidermal growth factor receptor (EGFR) mutations is one of the most significant driver genes in non-small cell lung cancer (NSCLC), particularly exhibiting a higher incidence among East Asian non-smokers with adenocarcinoma. The successful research and development of Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has significantly improved the survival for this patient population. But primary and secondary resistance remain core challenges in clinical practice. To overcome drug resistance, enhance efficacy, and prolong patient survival, targeted combination therapy strategies have emerged and become a research focus. This review provides a systematic review of the latest clinical evidence for EGFR-TKI combination therapy with chemotherapy, anti-angiogenic agents, other signaling pathway inhibitors, immunotherapy, and emerging dual-target therapies (such as bispecific antibodies and antibody-drug conjugates). The results indicate that TKIs combined with chemotherapy or bispecific antibody drugs have become one of the key options for first-line treatment; Precision combinations targeting resistance mechanisms (such as MET) is the developmental direction for subsequent lines of therapy; while the combination of TKIs with immune checkpoint inhibitors requires cautious exploration. In the future, personalized combination strategies guided by dynamic molecular profiling, the development of novel drugs, and the optimization of treatment modalities will be key to further overcoming therapeutic bottlenecks.

Keywords: non-small cell lung cancer, EGFR, TKI, combination therapy, resistance, Amivantamab, ADC

1. Introduction

Lung cancer accounts for 18. 0% of all cancer deaths worldwide, ranking first; non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases (BRAY F, LAVERSANNE M, SUNG H, et al., 2024). Among these, epidermal growth factor receptor (EGFR) mutations are the most common driver mutations in Asian populations, observed in approximately 40–50% of patients with lung adenocarcinoma. The successful development of EGFR tyrosine kinase inhibitors (TKIs) marked the dawn of the era of precision targeted therapy for NSCLC. As EGFR-TKIs have evolved through successive generations, their efficacy has gradually improved while associated adverse reactions have decreased, extending patients' median progression-free survival (PFS) to over 16 months and overall survival (OS) to more than 3 years (SORIA J C, OHE Y, VANSTEENKISTE J, et al., 2018). However, monotherapy with GFR-TKIs has limitations, as the therapeutic response often fails to improve further due to the development of resistance. Resistance is primarily categorized as primary resistance: approximately 10–30% of patients with EGFR mutations do not respond to initial treatment (SORIA J C, OHE Y, VANSTEENKISTE J, et al., 2018). Acquired resistance: After approximately 9–16 months of treatment,

nearly all patients develop resistance. The mechanisms underlying this resistance are complex and varied, including secondary EGFR mutations (such as T790M), bypass activation (such as MET or HER2 amplification), and histological transformation (such as transformation to small cell lung cancer) (WESTOVER D, ZUGAZAGOITIA J, CHO B C, et al., 2018). Consequently, combination therapy strategies—which aim to enhance tumor control through synergistic mechanisms and multi-target approaches that delay the development of resistance—have become a focal point of current clinical and basic research. This article systematically reviews key clinical research findings on various combination therapy strategies and outlines future directions for development.

2. EGFR-TKI Combined with Chemotherapy

Chemotherapy kills rapidly proliferating cancer cells by interfering with key processes of cell division. Its core mechanisms involve cytotoxic effects such as disrupting DNA structure and function, inhibiting nucleic acid (DNA/RNA) synthesis, and affecting microtubule function; it primarily acts on the cell cycle (particularly during the DNA synthesis and mitosis phases). This enables a synergistic mechanism in combination therapy: EGFR-TKIs target tumor cells that depend on the EGFR signaling pathway, while chemotherapy kills tumor cells that are resistant to EGFR-TKIs, thereby overcoming primary resistance caused by tumor heterogeneity. Current Phase III studies are exploring the value of combination chemotherapy. Results from the NEJ009 study show that gefitinib combined with pemetrexed and carboplatin significantly prolonged PFS (20. 9 months vs. 11. 9 months) and OS (50. 9 months vs. 38. 8 months) compared to gefitinib monotherapy, however, the incidence of Grade 3 or higher treatment-related adverse events (such as hematological toxicity) was higher in the combination group than in the gefitinib group (65. 3% vs. 31. 0%) (HOSOMI Y, MORITA S, SUGAWARA S, et al., 2020). Results from the FLAURA2 study showed that osimertinib in combination with pemetrexed and platinum-based chemotherapy significantly extended the investigator-assessed median PFS from 16. 7 months to 25. 5 months compared with osimertinib monotherapy, reducing the risk of disease progression or death by 38%. A benefit in PFS was also observed among patients with CNS metastases at baseline (24. 9 months vs. 13. 8 months) (PLANCHARD D, JäNNE P A, CHENG Y, et al., 2023). In terms of survival, the median overall survival was 47. 5 months in the osimertinib plus pemetrexed and platinum-based therapy group, compared with 37. 6 months in the osimertinib monotherapy group (P = 0. 02), representing a statistically significant difference; the hazard ratios (HRs) for patients with and without brain metastases at baseline were 0. 72 and 0. 77, respectively (JäNNE P A, PLANCHARD D, KOBAYASHI K, et al., 2026). For patients with the 19del and 21L858R mutations, the hazard ratio (HR) was 0. 76 in both cases. The incidence of Grade 3 or higher adverse events with combination therapy was five times higher than with EGFR-TKI monotherapy, primarily involving hematological (anemia and neutropenia), gastrointestinal (loss of appetite, mucositis, nausea, and vomiting), and fatigue/weakness (LANDRE T, ASSIé J B, CHOUAHNIA K, et al., 2024). This makes the regimen one of the first-line treatment options for advanced NSCLC with EGFR mutations. This combination strategy overcomes primary resistance caused by tumor heterogeneity, particularly in patients requiring rapid symptom relief. Related studies have also confirmed significant benefits in terms of PFS and OS. However, combination chemotherapy inevitably leads to cumulative toxicities, such as myelosuppression, nausea and vomiting, and fatigue (HOSOMI Y, MORITA S, SUGAWARA S, et al., 2020; PLANCHARD D, JäNNE P A, CHENG Y, et al., 2023), which may affect patients' quality of life and treatment adherence.

3. EGFR-TKIs in Combination with Anti-Angiogenic Agents

The vascular endothelial growth factor (VEGF) pathway plays a key role in tumor angiogenesis (OLSSON A K, DIMBERG A, KREUGER J, et al., 2006). Anti-angiogenic drugs (such as bevacizumab and anlotinib) can normalize tumor vasculature, reduce interstitial pressure, and improve drug delivery of TKIs (WILLETT C G, BOUCHER Y, DI TOMASO E, et al., 2004; VIALLARD C, LARRIVéE B., 2017). Results from the FL-ALTER (ZHOU H-Q, ZHANG Y-X, CHEN G, et al., 2024) study showed that gefitinib plus anlotinib provided a significant PFS benefit compared with gefitinib monotherapy (14. 8 months vs. 11. 2 months); in patients with brain metastases, gefitinib plus anlotinib extended median PFS by 5. 5 months (13. 8 months vs. 8. 3 months) compared with gefitinib monotherapy, reducing the risk of progression by 53% (HR = 0. 47). The gefitinib plus anlotinib group had a higher rate of Grade 3 or more severe adverse events (50% vs. 31%) compared with the gefitinib monotherapy group. The NEJ026 (SAITO H, FUKUHARA T, FURUYA N, et al., 2019) study results also confirmed the PFS advantage of erlotinib in combination with bevacizumab (16. 9 vs. 13. 3 months). However, the median overall survival did not show a significant benefit with erlotinib combined with bevacizumab compared to the erlotinib monotherapy group (50. 7 months vs. 46. 2 months; p = 0. 97) (KAWASHIMA Y, FUKUHARA T, SAITO H, et al., 2022). Regarding third-generation EGFR-TKIs, results from the WJOG9717L (KENMOTSU H, WAKUDA K, MORI K, et al., 2022) study showed that osimertinib combined with bevacizumab provided a PFS benefit compared to osimertinib monotherapy, but the difference was not statistically significant (22. 1 months vs. 20. 2 months, p = 0. 213). Afatinib combined with bevacizumab demonstrates some efficacy in the treatment of advanced EGFR-mutated non-small cell lung

cancer following osimertinib resistance, with median progression-free survival and overall survival of 2. 7 months and 9. 3 months, respectively (HATA A, KATAKAMI N, TAKASE N, et al., 2024). Further large-scale RCT studies are needed to confirm its true efficacy and safety. The combination of EGFR-TKIs and anti-angiogenic agents has been shown to significantly prolong PFS and is currently one of the effective treatment options. However, it was associated with a higher rate of Grade 3 or more severe adverse events, including bleeding (RR 1. 22, 95% CI: 0. 53–2. 79; P = 0. 64), hypertension (RR 1. 82, 95% CI: 0. 81–4. 09; P = 0. 15), and dyspnea (RR 1. 11, 95% CI: 0. 58–2. 14; P = 0. 75), particularly in cases of proteinuria (RR 4. 83, 95% CI: 1. 63–14. 31; P=0. 004) and diarrhea (RR 2. 37, 95% CI: 1. 29–4. 35; P=0. 005) (CHEN Z, JIANG S, LI X, et al., 2021). Patients should be closely monitored.

4. EGFR-TKIs in Combination with Other Signaling Pathway Inhibitors (to Target Bypass Activation)

Combination MET inhibitors: MET amplification is one of the most common mechanisms of resistance to EGFR-TKIs, particularly osimertinib (approximately 15–20%) (LEONETTI A, SHARMA S, MINARI R, et al., 2019), this is targeted therapy following the resolution of acquired resistance. The SAVANNAH Phase II study demonstrated that, in patients with osimertinib resistance and high levels of MET amplification or overexpression, the objective response rate (ORR) for the combination of osimertinib and cevotinib reached 32%, with a median progression-free survival (PFS) of 5. 3 months (YANG J C, CHEN Y M, BATRA U, et al., 2025). Tepotinib in combination with gefitinib has also demonstrated activity in the first-line treatment of patients with MET-amplified EGFR mutations (WU Y L, CHENG Y, ZHOU J, et al., 2020), Median PFS: 16. 6 months vs. 4. 2 months; median OS: 37. 3 months vs. 13. 1 months. Several Phase III studies are currently underway to further evaluate the efficacy and safety of EGFR-TKIs in combination with MET inhibitors.

Combination with HER2 inhibitors: HER2 amplification or mutation is also one of the mechanisms of resistance (LEONETTI A, SHARMA S, MINARI R, et al., 2019). The antibody-drug conjugate (ADC) Trastuzumab Deruxtecan has demonstrated groundbreaking efficacy in patients with HER2-mutated non-small cell lung cancer (NSCLC), including those who have previously received EGFR-TKI therapy, with an objective response rate of 55%, a median progression-free survival of 8. 2 months, and a median overall survival of 17. 8 months (LI B T, SMIT E F, GOTO Y, et al., 2022), which offers a new treatment option for these drug-resistant patients. Combination therapy with MEK/AXL inhibitors: For cases involving persistent activation of the downstream RAS/RAF/MEK pathway or AXL activation associated with epithelial-mesenchymal transition (EMT) (TANIGUCHI H, YAMADA T, WANG R, et al., 2019), clinical trial results for combination therapy with trametinib and dabrafenib showed objective response rates and disease control rates of 61. 5% and 92. 3%, respectively. The median PFS was 13. 5 months (WENG C D, LIU K J, JIN S, et al., 2024), while this combination strategy demonstrated a favorable disease control rate, its true efficacy and safety still require further validation.

5. EGFR-TKI Combined with Immunotherapy

TKI-induced tumor cell death can release antigens and enhance immunogenicity, while immune checkpoint inhibitors (ICIs) can lift T-cell suppression; the two may act synergistically (CHEN G, HUANG A C, ZHANG W, et al., 2018). However, clinical practice faces serious challenges. A collaborative Phase 1 study, the CAURAL trial, reported an increased incidence of interstitial lung disease (ILD)-like events in the osimertinib plus durvalumab group in the independent Phase Ib TARTON trial (NCT02143466), with an overall incidence of ILD/pneumonitis as high as 38%, including 13% of Grade 3 or higher events. (OXNARD G R, YANG J C, YU H, et al., 2020) Recruitment for CAURAL has ended early (YANG J C, SHEPHERD F A, KIM D W, et al., 2019). The combination of EGFR-TKIs and ICIs (PD-1/PD-L1 inhibitors) carries a significant risk of additive toxicity; in particular, the incidence of interstitial pneumonia is significantly higher than with either agent alone. Five out of seven patients (71. 4%) receiving pembrolizumab plus gefitinib experienced Grade 3 or 4 hepatotoxicity, leading to permanent discontinuation of treatment in four patients. (YANG J C, GADGEEL S M, SEQUIST L V, et al., 2019) The final analysis of the IMpower150 (SOCINSKI M A, NISHIO M, JOTTE R M, et al., 2021) clinical trial showed that atezolizumab in combination with bevacizumab and chemotherapy (ABCP) continued to demonstrate an overall survival (OS) benefit in patients with EGFR-mutated NSCLC, with a median OS of 19.5 months—a significant improvement over chemotherapy alone. The first interim results from the ORIENT-31 (LU S, WU L, JIAN H, et al., 2022) trial further confirm that the combination of sintilimab with the bevacizumab biosimilar IBI305 and chemotherapy significantly improves PFS (6. 9 vs. 4. 3 months, HR 0. 46) in patients whose disease has progressed on EGFR-TKIs. However, it was associated with an increased incidence of immune-related adverse events (irAEs) (relative risk: 2. 02, 95% CI: 1. 45–2. 81, p < 0. 0001) and grade 3–5 adverse events (irAEs, RR: 2. 02, 95% CI: 1. 03–3. 98, p = 0. 04) (CHEN X, ZHAO J, ZHANG W, et al., 2025). The above clinical trials indicate that first-line concurrent combination therapy with EGFR-TKIs and ICIs does more harm than good in most patients. However, combination immunotherapy demonstrates some efficacy following resistance to EGFR-TKIs. Immunotherapy may be used as sequential therapy for

EGFR-mutated non-small cell lung cancer after resistance to EGFR-TKIs.

6. Dual-Target Combination Therapy

Amivantamab: A bispecific antibody whose core mechanism of action involves simultaneously targeting two key driver pathways: the epidermal growth factor receptor (EGFR) and the c-MET pathway. It exerts potent antitumor activity through a dual synergistic mechanism and has demonstrated unique advantages, particularly in overcoming resistance to EGFR-TKIs. The CHRYSALIS (PARK K, HAURA E B, LEIGHL N B, et al., 2021) study demonstrated sustained efficacy in patients who had developed resistance to osimertinib and whose disease had progressed despite chemotherapy. The Phase III MARIPOSA (ROSENFELD R., 2025) study demonstrated that, in first-line treatment, the combination of Amivantamab and the third-generation TKI lazertinib significantly prolonged PFS (23. 7 vs. 16. 6 months) compared to osimertinib monotherapy, and is expected to become a new option for first-line treatment. This drug also demonstrates some efficacy against EGFR exon 20 insertion mutations (YUN J, LEE S H, KIM S Y, et al., 2020), but it is associated with an increased incidence of adverse reactions; the combination group reported a higher rate of Grade 3 or higher adverse events (75% vs. 43%).

Ivonescimab: a bispecific antibody targeting PD-1 and VEGF. Results from the AK112-201 (ZHAO Y, CHEN G, CHEN J, et al., 2023) study demonstrate outstanding efficacy when combined with chemotherapy: an ORR as high as 50% and an mPFS of 8. 2 months, significantly outperforming historical controls treated with chemotherapy alone (ORR of approximately 20–30% and mPFS of approximately 4–5 months). Monotherapy demonstrated activity: the ORR reached 26. 7% and mPFS reached 7. 1 months, far exceeding the response rates of less than 10% observed with traditional PD-1 monotherapy in similar patient populations, confirming the advantages of its bispecific antibody design.

7. Challenges

EGFR-TKIs represent a major milestone in precision targeted therapy for non-small cell lung cancer (NSCLC). First-generation TKIs (gefitinib and erlotinib) effectively inhibit classic EGFR mutations, significantly improving objective response rates (60%–70%) and progression-free survival (PFS) compared to chemotherapy. Additionally, their side effects (such as rash and diarrhea) are generally easier to manage than those of chemotherapy, thereby improving patients' quality of life. With the continuous development and advancement of TKIs, disease control rates have steadily improved for patients with advanced EGFR-mutated NSCLC. However, most patients experience disease progression approximately 9–16 months after receiving monotherapy with an EGFR-TKI. The mechanisms of resistance are complex and diverse, including on-target mutations (such as the T790M mutation following TKI treatment), bypass activation (such as MET or HER2 amplification), and histological transformation (such as progression to small cell lung cancer). The shift from single-agent targeted therapy to combination targeted therapy aims to delay the development of drug resistance through the synergistic action of multiple mechanisms. To overcome the limitations of single-agent therapy, various combination strategies have been explored and have shown promise; however, significant challenges remain. Combination therapy is associated with a broader range of more severe adverse reactions and places higher demands on patients' physical condition. Tumor heterogeneity results in complex and variable mechanisms of drug resistance. The greatest challenge lies in using liquid biopsy (ctDNA) for real-time dynamic monitoring to identify the most effective combination therapy for patients at the optimal time, thereby avoiding "blind combination therapy." Financial burden and drug accessibility: Many novel combination therapies (particularly bispecific antibodies and ADCs) are prohibitively expensive, limiting their clinical application.

8. Future Research Approaches and Directions

Future breakthroughs will depend on a shift in treatment strategies toward "precision, personalization, and dynamism." Precision and personalized treatment are based on "one-to-one" therapy guided by dynamic molecular subtyping: Future treatment decisions will rely heavily on repeated biopsies (tissue or liquid biopsies) conducted "during treatment" and "after resistance develops." By monitoring for the early emergence of resistance via ctDNA, combination regimens can be adjusted in a timely manner. Optimizing treatment modalities and sequences: Exploring optimal treatment sequences (e. g., "first-line combination therapy" vs. "sequential monotherapy followed by precision combination therapy") to achieve the best balance between efficacy and toxicity. The revolution in novel drugs and exploration of mechanisms: In-depth exploration of bispecific antibodies and antibody-drug conjugates (ADCs): This is currently the most groundbreaking area of research. Future research will not be limited to new targets (such as TROP2 and B7-H3); it will also need to explore combinations of novel ADCs and bispecific antibodies, as well as how to shift the timing of treatment to the first-line setting or even the adjuvant/neoadjuvant stages. Drug development to overcome specific resistance mechanisms: Development of fourth-generation EGFR-TKIs targeting grade 3 mutations, such as C797S, that arise following resistance to osimertinib. In summary, the treatment of EGFR-mutated NSCLC has evolved from an era of precise but short-lived efficacy with single-agent TKIs to a new era of long-term disease control

centered on combination therapy. Through the continuous emergence of innovative drugs and optimized treatment strategies, the ultimate goal is to transform advanced EGFR-mutated NSCLC into a chronic disease that can be effectively managed over the long term.

9. Conclusion

Targeted therapy for EGFR-mutated NSCLC has evolved from the era of monotherapy to a new era of combination therapy. Currently, TKI-chemotherapy combinations or TKI-bispecific antibody combinations have become standard options in first-line treatment. Precision combination therapies targeting mechanisms of acquired resistance (such as those targeting MET), as well as novel dual-target therapies represented by bispecific antibodies and ADCs, show great potential for breaking through the bottlenecks in second-line treatment. However, the combination of TKIs and immunotherapy must be approached with extreme caution. Individualized combination therapy strategies guided by real-time molecular monitoring, combined with a growing number of innovative drugs, are expected to further prolong survival in patients with EGFR-mutated NSCLC and ultimately achieve the goal of long-term disease control.

Table 1.

Strategy	Advantages/Mechanism of Action	Side Effects and Adverse Reactions	Representative research/evidence
TKI+ chemotherapy	Chemotherapy kills tumor cells that are resistant to EGFR-TKIs	Cumulative toxicity: Myelosuppression, nausea and vomiting, and fatigue are significantly increased, affecting quality of life and treatment adherence.	FLAURA2 Study: Median PFS of 25. 5 months with osimertinib plus chemotherapy versus 19. 0 months with osimertinib monotherapy; median OS extended from 37. 6 months to 47. 5 months.
TKI+ anti-angiogenic agents	Inhibit the VEGF pathway, normalize tumor vasculature, and improve drug delivery.	Specific toxicities: hypertension, proteinuria, risk of bleeding (hemoptysis), thromboembolic events, gastrointestinal perforation.	RELAY Study: Median PFS was 19. 4 months for erlotinib plus ramucirumab versus 12. 4 months for erlotinib monotherapy.
TKI+ other targeted therapies (to address bypass pathways)	Overcoming acquired resistance, such as that associated with specific resistance mechanisms like MET amplification	Therapeutic efficacy is highly dependent on precise biomarkers; new mechanisms of resistance may emerge.	MET amplification: Osimertinib + Sevotinib, ORR 32%.
Bispecific antibody	Simultaneously block multiple targets or signaling pathways	such as rash, hypoalbuminemia, risk of venous thromboembolism, and high cost associated with Amivantamab	MARIPOSA: Amivantamab (EGFR/MET bispecific antibody) + lazertinib vs osimertinib demonstrated a significant prolongation of PFS (23. 7 vs 16. 6 months) and reduced the risk of acquired C797S mutations and MET amplification by 5-fold and 4-fold, respectively.
TKI+ immunotherapy	Boost the immune system	The incidence of serious adverse reactions, such as interstitial pneumonia and hepatotoxicity, increased significantly, leading to the early termination of several studies. The efficacy remains unclear.	TATTON and CAURAL, and the incidence of Grade 3–5 adverse events was higher in the combined group.

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Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
MAR. 2026 VOL.5, NO.1

The "Triangle Operation" in Pancreatic Cancer: Toward Optimizing Oncological Radicality After Neoadjuvant Therapy

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doi:10.63593/JIMR.2788-7022.2026.03.004

Abstract

Recent advances in pancreatic cancer management, particularly with the introduction of intensive neoadjuvant chemotherapy regimens, have significantly reshaped surgical indications and objectives. In this context, the "Triangle Operation," described by Thomas Hackert, has emerged as an innovative approach aimed at improving R0 resection rates without systematically resorting to arterial resections. This technique is based on an extensive dissection of the peri-arterial compartment located between the superior mesenteric artery, the celiac trunk, and the porto-mesenteric axis. Its primary goal is to eradicate areas of potential microscopic tumor spread, particularly after neoadjuvant therapy. Through a detailed analysis of anatomical foundations, technical principles, and clinical outcomes, this article highlights both the benefits and limitations of this strategy in the management of borderline resectable and locally advanced pancreatic tumors.

Keywords: superior mesenteric artery, superior mesenteric vein, celiac trunk, mesopancreas, retroportal lamina, unresectable adenocarcinoma

1. Introduction

Pancreatic cancer remains one of the most aggressive solid malignancies, with a five-year overall survival rate below 10% in most contemporary series, largely due to late diagnosis and a strong tendency for both locoregional and systemic spread (Siegel RL et al., 2023; Sung H et al., 2021). Surgery remains the only potentially curative treatment; however, it is limited by a high rate of positive resection margins, particularly at the retroportal margin and around peri-arterial structures (Verbeke CS et al., 2006; Esposito I et al., 2008).

The introduction of neoadjuvant chemotherapy protocols, especially FOLFIRINOX and gemcitabine-based combinations, has increased the number of patients eligible for secondary resection by reducing tumor burden and enabling better biological selection (Conroy T et al., 2018; Suker M et al., 2016; Janssen QP et al., 2019). However, after neoadjuvant therapy, evaluating tumor–vascular relationships remains challenging due to persistent dense fibrosis, making it difficult to distinguish residual viable tumor from post-treatment scarring (Ferrone CR et al., 2015; Cassinotto C et al., 2014).

In this setting, the need for systematic arterial resection has been questioned, given the significant morbidity associated with such procedures (Mollberg N et al., 2011). The "Triangle Operation" was therefore developed to achieve maximal oncological radicality through extensive peri-arterial dissection without arterial reconstruction (Hackert T et al., 2016; Hackert, T. et al., 2017).

2. Anatomical Basis and Oncological Rationale

Tumor spread in pancreatic cancer preferentially occurs along neural sheaths and vascular structures, particularly

around the superior mesenteric artery and the celiac trunk (Bapat AA et al., 2011; Ceyhan GO et al., 2009). Perineural invasion is observed in more than 70% of cases and represents a major predictor of local recurrence (Liebig C et al., 2009).

The anatomical compartment targeted by the "Triangle Operation" corresponds to a three-dimensional space bounded by the superior mesenteric artery, the celiac trunk, and the portal vein. This region includes the retroportal lamina, peri-arterial nerve plexuses, and deep lymphatic pathways, which are the primary sites of positive margins following standard pancreaticoduodenectomy (Hartwig W et al., 2013; Nagakawa T et al., 1996; Pedrazzoli S et al., 1998).

After neoadjuvant therapy, these structures frequently exhibit reactive fibrosis that may conceal residual viable tumor, thereby justifying systematic resection of this compartment to improve local disease control (Strobel O et al., 2019; Truty MJ et al., 2020).

3. Surgical Technique

The "Triangle Operation" involves a systematic and extensive dissection of the peri-arterial compartment. Following thorough exploration to exclude metastatic disease, the procedure begins with mobilization of the porto-mesenteric axis, followed by complete skeletonization of the superior mesenteric artery and the celiac trunk. This step requires a circumferential 360-degree dissection, allowing en bloc removal of all peri-arterial fibro-neural tissue (Hackert T et al., 2016; Inoue Y et al., 2015).

Pancreatic resection is subsequently performed according to tumor location, either as pancreaticoduodenectomy or distal pancreatectomy. The primary objective is to achieve a negative retroportal margin by removing all tissues at risk of microscopic invasion (Hackert T, Werner J & Büchler MW., 2018).

4. Oncological and Clinical Outcomes

Initial series reported by Hackert et al. demonstrated that the "Triangle Operation" could achieve R0 resection rates of up to 80–90% in selected patients following neoadjuvant therapy (Hackert T et al., 2016; Hackert T et al., 2017). These findings have been supported by subsequent multicenter studies, which also reported improved overall survival compared with conventional surgical approaches (Kandel P et al., 2018; Michelakos T et al., 2019).

In terms of morbidity, this technique does not appear to significantly increase major postoperative complications compared to standard surgery, although functional disorders related to denervation, particularly postoperative diarrhea, are commonly observed (Addeo P et al., 2020; Welsch T et al., 2011).

Furthermore, several studies suggest that this approach reduces the need for arterial resections without compromising oncological outcomes, representing a major advantage in terms of morbidity and mortality (Klompmaker S et al., 2018; Del Chiaro M et al., 2019).

5. Limitations and Controversies

Despite its promising results, the "Triangle Operation" raises several concerns. The main limitation lies in the difficulty of distinguishing post-treatment fibrosis from residual tumor, both preoperatively and intraoperatively, which may lead to incomplete resection (Katz MH et al., 2012).

Additionally, this technique is highly dependent on surgical expertise and requires advanced skills in vascular dissection, thereby limiting its application to high-volume specialized centers (Birkmeyer JD et al., 2002). The lack of standardization in both technique and indications further restricts its widespread adoption (Asbun HJ et al., 2014).

Finally, patient selection remains critical, as the "Triangle Operation" is primarily indicated in patients demonstrating a favorable response to neoadjuvant chemotherapy without disease progression (Tempero MA et al., 2021).

6. Discussion

The "Triangle Operation" represents a major paradigm shift in pancreatic surgery, moving from a purely anatomical approach toward a strategy focused on controlling the tumor microenvironment. It is based on the concept that peri-arterial structures serve as a sanctuary for tumor dissemination and must therefore be systematically resected to improve oncological outcomes (Strobel O et al., 2019; Neoptolemos JP et al., 2018).

This approach is closely linked to advances in medical oncology, particularly neoadjuvant chemotherapy, which enables better patient selection for radical surgery (Sohal DPS et al., 2021; Menoura R et al., 2025). It is thus part of a comprehensive multimodal strategy combining systemic therapy and targeted surgical intervention.

7. Conclusion

The "Triangle Operation" constitutes a significant advancement in the surgical management of borderline

resectable and locally advanced pancreatic cancer. By enabling complete dissection of the peri-arterial compartment, it improves R0 resection rates while avoiding complex arterial reconstruction. However, its indication must remain cautious and restricted to carefully selected patients, and it should be performed in specialized centers with advanced expertise in pancreatic surgery.

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Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
MAR. 2026 VOL.5, NO.1

Research Progress on the Effects of Immunonutrition on Oral Mucositis and Nutritional Status in Patients with Head and Neck Cancer Undergoing Radiotherapy

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doi:10.63593/JIMR.2788-7022.2026.03.005

Abstract

Patients with head and neck cancer (HNC) undergoing radiation therapy (RT) frequently face oral mucositis (OM), a challenging and highly prevalent acute toxic reaction. OM not only causes severe pain, dysphagia, and impaired nutritional intake but also intertwines with malnutrition to form a vicious cycle that is difficult to break, thereby significantly compromising treatment efficacy and patients' quality of life. While traditional nutritional support can barely maintain basic energy supply, it proves inadequate in modulating the cytokine storm and immune response. In contrast, immunonutrition, as an emerging therapeutic paradigm, attempts to exert "pharmacological-level" regulatory effects by precisely incorporating specific components such as arginine, ω-3 polyunsaturated fatty acids (EPA, DHA), and nucleotides into standard formulas, aiming to suppress inflammation and oxidative stress while providing nutrients. In recent years, the academic community has focused on immunonutritional formulations represented by IMPACT®, deeply exploring their clinical value in the HNC radiotherapy population. This review aims to systematically organize and analyze relevant evidence to discuss how immunonutrition intervenes in the prevention and management of oral mucositis and improves patients' nutritional status. Existing data suggest that immunonutritional intervention can not only effectively reduce the incidence of severe (grade ≥3) oral mucositis and alleviate its severity and progression but also demonstrate unique advantages in stabilizing patient body weight, lean body mass (muscle mass), and plasma protein levels (albumin, prealbumin), holding promise for breaking the causal chain between malnutrition and mucositis. Its underlying mechanisms may stem from recalibrating the balance of pro-inflammatory/anti-inflammatory cytokines (e.g., downregulating IL-6 and TNF-α while upregulating IL-10), reinforcing the body's antioxidant defenses, and maintaining lymphocyte count and function. Certainly, existing research results still exhibit heterogeneity, often involving multiple variables such as timing of intervention, dosage range, duration of treatment, subject characteristics, and control settings. Looking ahead, there is an urgent need for more rigorously designed, large-sample multicenter randomized controlled trials, supplemented by in-depth mechanistic exploration and long-term follow-up, to clarify the optimal strategies, cost-effectiveness, and true impact on long-term prognosis of immunonutrition in supportive care for HNC radiotherapy.

Keywords: head and neck cancer, immunonutrition, radiotherapy, oral mucositis, nutritional status

1. Introduction

Head and neck cancer (HNC) is one of the common malignant tumors worldwide, and radiotherapy (RT) serves as a core modality for both curative treatment and postoperative adjuvant therapy (Yang, T. T., Chen, Y., Hu, J.

J., et al., 2025). While radiation precisely targets tumor cells, it inevitably damages the rapidly proliferating normal mucosal epithelium in the oral cavity and pharynx, leading to oral mucositis (OM) (Liang, L. F., Song, Z. X., & Wang, R. S., 2024). OM is among the most common and distressing dose-limiting toxicities encountered during RT for HNC, clinically manifesting as mucosal erythema, edema, erosion, and ulceration, accompanied by severe pain, dysphagia, taste alterations, and reduced salivary secretion (Liang, L. F., Song, Z. X., & Wang, R. S., 2024; De Sanctis V, Bossi P, Sanguineti G, et al., 2016). Statistics indicate that over 80% of HNC patients undergoing curative radiotherapy develop oral mucositis (OM) of varying severity, with approximately 30–50% progressing to severe (grade 3–4) OM. This condition often renders patients unable to eat orally, causes rapid weight loss, and drastically reduces quality of life, frequently resulting in interruptions to radiotherapy or reductions in treatment dosage, thereby compromising local tumor control rates and long-term patient survival (Trotti A, Bellm L A, Epstein J B, et al., 2003; Qin, X. J., & Qin, W. Y., 2023).

Malnutrition is a prominent clinical issue throughout the diagnosis and treatment of patients with head and neck cancer (HNC). The tumor itself causes mechanical obstruction, altered taste, and anorexia, while treatment-induced side effects such as oral mucositis (OM), xerostomia, nausea, and vomiting collectively lead to severe deficiencies in energy and protein intake (Bossola M., 2015). Studies indicate that approximately 20–40% of HNC patients present with malnutrition at diagnosis, with both the prevalence and severity worsening during radiotherapy (De Pasquale G, Mancin S, Matteucci S, et al., 2023). A vicious cycle of mutual exacerbation exists between malnutrition and OM: severe OM directly impedes oral intake, thereby aggravating malnutrition; conversely, the state of malnutrition impairs mucosal epithelial repair capacity and reduces immune function, rendering the mucosa more susceptible to radiation injury, intensifying inflammatory responses, and thus worsening the severity and persistence of OM (Wu, J. Y., Wang, A. H., & Zou, J., 2022).

Conventional nutritional support therapy, including oral dietary guidance, enteral nutrition (oral nutritional supplementation and tube feeding), and parenteral nutrition, primarily aims to correct energy-protein deficiency. Although foundational, it constitutes a “passive supplementation” approach with limited efficacy in modulating the core pathological processes of excessive inflammation and immune dysregulation induced by radiotherapy (Krzywon A, Kotylak A & Rutkowski T., 2025; Gu Y, Lu W, Mao Y, et al., 2025). Therefore, there is a clinical need for a novel nutritional strategy capable of actively intervening in this vicious cycle.

Against this backdrop, immunonutrition has emerged as a research hotspot in the field of supportive cancer care. Immunonutrition is not merely an accumulation of nutrients; rather, it involves adding specific pharmacologically active nutrients—such as arginine, ω-3 polyunsaturated fatty acids, nucleotides, and glutamine—to standard nutritional formulas (Wu, J. F., Gao, T., & Sun, X. J., 2023; Liu, X. R., & Liu, Y. H., 2024). These components aim to modulate the body’s pathophysiological responses at their root by regulating immune cell activity, influencing the production of inflammatory mediators, and enhancing antioxidant defenses. Thus, while providing nutritional substrates, they also exert therapeutic effects as “nutritional drugs” (Liu, X. R., & Liu, Y. H., 2024; He, J., Li, J., & Ma, J., et al., 2020). In recent years, numerous clinical studies have focused on the application of immunonutrition in patients with head and neck cancer (HNC) undergoing chemoradiotherapy. This review aims to systematically summarize and analyze current clinical evidence regarding immunonutrition interventions for preventing and treating oral mucositis and improving nutritional status in HNC patients receiving radiotherapy, and to explore their potential mechanisms of action, thereby providing references for clinical practice and future research directions.

2. Core Components of Immunonutrition and Their Potential Mechanisms of Action

The efficacy of immunonutritional formulations stems from the synergistic effects of their core components; understanding the biological characteristics of these components is fundamental to elucidating their clinical outcomes.

2.1 L-Arginine

L-Arginine is a conditionally essential amino acid with significantly increased demand under stress conditions, serving as the direct precursor for nitric oxide (NO) synthesis. NO plays a dual role in immune regulation: appropriate levels of NO promote vasodilation, improve microcirculation in mucosa and tissues, facilitate injury repair, enhance macrophage phagocytic function, promote T-lymphocyte proliferation and activity, and strengthen cellular immune responses. In the context of mucositis, arginine promotes mucosal healing by supporting immune cell function and improving local blood flow (Liu, X. R., & Liu, Y. H., 2024; Molendijk E B D & Blijlevens N M A., 2021; Gogoi M, Datey A, Wilson K T, et al., 2016).

2.2 ω-3 Polyunsaturated Fatty Acids (ω-3 PUFAs)

The primary ω-3 polyunsaturated fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Their core mechanism involves competitively inhibiting the synthesis of potent pro-inflammatory mediators—specifically prostaglandin E2 [PGE2] and leukotriene B4 [LTB4]—derived from the metabolism of

ω-6 PUFAs (arachidonic acid). Simultaneously, EPA and DHA serve as substrates for generating lipid mediators such as Resolvins and Protectins, which possess active anti-inflammatory and pro-repair properties. ω-3 PUFAs can be incorporated into the phospholipids of immune cell membranes, influencing membrane fluidity and signal transduction, regulating immune function, and exhibiting certain antioxidant properties (Calder P C., 2015). In radiotherapy scenarios, ω-3 PUFAs are believed to mitigate excessive inflammatory responses and oxidative stress induced by radiation (Zhang Y, Zhang B, Dong L, et al., 2019).

2.3 Nucleotides

As the basic units of DNA and RNA, nucleotides are essential substances for cell proliferation and protein synthesis. Within the immune system, rapidly proliferating immune cells (lymphocytes, intestinal mucosal epithelial cells) have a high demand for nucleotides (Raczyńska A, Leszczyńska T, Skotnicki P, et al., 2025). Exogenous supplementation of nucleotides is considered to support lymphocyte proliferation and differentiation, particularly when endogenous synthesis is insufficient due to high metabolic stress states, thereby helping to maintain the integrity of immune system function (Raczyńska A, Leszczyńska T, Skotnicki P, et al., 2025; Gil A., 2002).

2.4 Synergistic Effects and Comprehensive Mechanisms

The aforementioned components do not act in isolation but produce synergistic effects. Immunonutritional intervention influences OM and nutritional status through the following comprehensive pathways: (1) Anti-inflammatory and immunomodulatory effects: Downregulating pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), upregulating anti-inflammatory cytokines (IL-10), balancing Th1/Th2 responses, and maintaining immune homeostasis. (2) Antioxidant protection: Enhancing the body's ability to scavenge free radicals, reducing oxidative damage caused directly or indirectly by radiation, and protecting normal cells. (3) Improvement of anabolism and nutrient utilization: Based on the provision of high-quality protein and energy, reducing muscle protein breakdown and promoting the preservation of lean body mass through an anti-inflammatory and pro-anabolic environment. (4) Maintenance of gut barrier function and microecology: Some evidence suggests that immunonutrition benefits intestinal mucosal health, and gut-axis communication may indirectly influence systemic inflammatory status (Raczyńska A, Leszczyńska T, Skotnicki P, et al., 2025; Howes N, Atkinson C, Thomas S, et al., 2018).

3. Analysis of Clinical Evidence for Immunonutrition in the Prevention and Treatment of Oral Mucositis

3.1 Early Exploration and Positive Signals

Early prospective studies and Phase II clinical trials have provided preliminary evidence for the application of immunonutrition. Some studies observed that among patients with head and neck cancer (HNC) receiving concurrent chemoradiotherapy, those who regularly took oral immunonutritional formulas (IMPACT®) showed a trend of lower-than-expected or lower-than-historical-control incidence rates of grade 3-4 severe oral mucositis (OM) (Assenat E, Latournerie M, Thézenas S, et al., 2011). Another Phase II study indicated that immunonutritional support helps improve the inflammatory status of patients with head and neck squamous cell carcinoma during chemoradiotherapy, thereby preventing severe acute oral mucositis (Machon C, Thezenas S, Dupuy A M, et al., 2012). Although these studies had limited sample sizes, they stimulated the conduct of larger-scale research.

3.2 Evidence from Randomized Controlled Trials

Subsequent multiple randomized controlled trials (RCTs) have provided high-level evidence. A double-blind RCT focusing on patients with locally advanced HNC receiving chemoradiotherapy found that, compared to patients receiving isonitrogenous and isocaloric standard enteral nutrition, those receiving immunonutrition had a reduced risk of developing ≥ grade 3 OM. Furthermore, in the immunonutrition group, the time to first onset of mucositis was delayed until the 5th week (compared to the 3rd week in the control group), and both the analgesic usage rate (18.5% vs. 93.8%) and the requirement for nasogastric tube insertion (0% vs. 8.5%) were significantly reduced. This indicates that immunonutritional intervention can effectively delay the progression of mucosal injury and mitigate its severity (Pattanayak L, Panda N, Dash M K, et al., 2016). Other studies have reported similar results, showing that patients in the immunonutrition group had a lower incidence of severe OM, with the peak severity occurring later and lasting for a shorter duration, suggesting an effect in delaying and alleviating the process of mucosal injury (Tan S E, Abdul Satar N F & Majid H A., 2022).

3.3 Pivotal Phase III Trials and Controversies

The results of the largest Phase III double-blind trial (the IMPATOX study) have sparked extensive discussion. In this study involving HNC patients receiving postoperative adjuvant chemoradiotherapy, the intention-to-treat analysis showed no statistically significant difference between the immunonutrition group and the standard nutrition group regarding the primary endpoint of severe OM incidence. This negative result suggests that the

efficacy of immunonutrition may be influenced by the study population (postoperative status), timing of intervention (adjuvant therapy phase), and other confounding factors. Meanwhile, subgroup analysis of this study revealed that among patients with good compliance (taking ≥ 75% of the planned dose), the immunonutrition group showed a trend toward prolonged progression-free survival and overall survival, implying potential long-term benefits (Boisselier P, Kaminsky M C, Thézenas S, et al., 2020).

3.4 Comprehensive Conclusions from Meta-Analyses

To integrate findings from different studies, several systematic reviews and meta-analyses have been published. One meta-analysis, including 27 studies and nearly 1,500 patients, provided relatively clear conclusions: although immunonutrition did not reduce the overall incidence of OM of all grades, it could lower the risk of developing ≥ grade 3 severe OM, with a pooled relative risk (RR) of approximately 0.45–0.65. This indicates that the core value of immunonutrition lies in preventing or mitigating "severe" mucositis, which most significantly affects treatment progress and quality of life. Comprehensive analysis suggests that immunonutrition has definite clinical value in preventing and treating severe OM associated with radiotherapy in HNC, with its effects achieved through modulating local and systemic inflammatory responses. The heterogeneity in efficacy is closely related to factors such as the timing of intervention initiation (prophylactic use is superior to therapeutic use), duration of intervention, specific formulations of the preparations, and the baseline nutritional and immune status of patients (Zheng X, Yu K, Wang G, et al., 2020).

4. Clinical Observation of the Impact of Immunonutrition on the Nutritional Status of Radiotherapy Patients

4.1 Maintenance of Body Weight and Body Composition

Multiple studies consistently report that patients receiving immunonutrition intervention experience less weight loss during and after radiotherapy compared to those receiving standard nutritional support. Body composition analysis reveals that immunonutrition is particularly effective in reducing the loss of lean body mass (muscle mass). For instance, studies utilizing bioelectrical impedance analysis (BIA) or CT imaging have found that patients in the immunonutrition group exhibit a smaller decline in the skeletal muscle index (SMI). Maintaining lean body mass is crucial for preserving patient physical strength, immune function, treatment tolerance, and long-term prognosis (Cuesta-Sancho S, Gomez J J L, García-Luna P P, et al., 2025; Vasson M P, Talvas J, Perche O, et al., 2014).

4.2 Improvement of Hematological Nutritional Indicators

Plasma protein levels are sensitive indicators reflecting nutritional status and anabolic state. Clinical observations indicate that the decline in serum albumin and prealbumin (which has a shorter half-life and is more sensitive) levels during radiotherapy is less pronounced in the immunonutrition group compared to the control group (Yang, Q., Chai, H. Y., & Guo, L., et al., 2021). This suggests that immunonutrition provides raw materials (amino acids) for protein synthesis and, through its anti-inflammatory effects, reduces inflammation-induced protein catabolism and vascular leakage, thereby better maintaining visceral protein reserves. Comprehensive scores such as the Nutritional Risk Index (NRI) are typically better maintained in the immunonutrition group (Chao P C & Lin F C F., 2020).

4.3 Reduction in the Need for Escalated Nutritional Support

Due to better maintenance of oral intake capacity and nutritional status, patients receiving immunonutrition require escalation from oral nutritional supplements to full-volume tube feeding enteral nutrition or parenteral nutrition at a later time point and in lower proportions compared to the standard nutrition group (Kiss N, Findlay M, Frowen J, et al., 2026). This indicates that immunonutrition delays or reduces the need for higher-level nutritional support, indirectly reflecting its effectiveness in maintaining patients' inherent eating ability.

5. Considerations on Clinical Application, Existing Issues, and Future Prospects

5.1 Current Considerations on Clinical Application

Based on existing evidence, immunonutrition should be regarded as an integral component of comprehensive supportive care for patients with head and neck cancer (HNC) undergoing radiotherapy, rather than a substitute. The recommended application strategies are as follows: (1) Early intervention: Initiate before or at the onset of radiotherapy to exert a preventive effect. (2) Adequate dosage and duration: Ensure sufficient dosing and coverage throughout the period of acute toxicity risk (typically extending several weeks post-radiotherapy). (3) Individualized selection: Patients with high nutritional risk or those planned for high-intensity chemoradiotherapy (concurrent chemotherapy) stand to benefit more. (4) Multidisciplinary collaboration: Implement under the joint management of medical oncology, radiation oncology, and nutrition departments, integrating it into standard protocols for pain management, oral care, and nutritional support.

5.2 Existing Issues and Challenges

Currently, there is no globally unified standard regarding the optimal regimen for immunonutrition. Specifically, variations exist among different studies concerning formula composition, recommended daily dosage, timing of initiation, and duration of treatment, which may contribute to inconsistent results across clinical trials. In terms of cost-effectiveness, immunonutrition formulations are generally more expensive than conventional nutritional support products. Although they may reduce overall healthcare expenditures by lowering the incidence of severe complications, shortening hospital stays, and minimizing treatment interruptions, further economic evaluation data based on different healthcare systems are required for validation. Existing evidence predominantly focuses on Western populations, while large-scale, high-quality clinical studies targeting Chinese patients with head and neck cancer remain relatively insufficient. Given that differences in genetic background, dietary habits, and spectra of underlying diseases among ethnic groups may influence intervention outcomes, there is an urgent need to conduct clinical studies tailored to local population characteristics to provide more direct evidence. Although immunonutrition has demonstrated certain efficacy in clinical practice, its specific mechanisms of action at the molecular, cellular, and systemic levels, particularly the biological pathways involved in the specific context of head and neck cancer radiotherapy, still require further elucidation through deeper translational medical research.

5.3 Future Research Directions

Conducting large-scale, multicenter randomized controlled trials is crucial for clarifying the specific role of immunonutrition in tumor therapy. Such studies should focus on specific patient subgroups—for instance, those with different tumor sites or receiving different treatment regimens—and explore the practical value of combining immunonutrition with emerging radiotherapy technologies (such as proton therapy). While accumulating evidence on efficacy, future research must strive to identify biomarkers capable of predicting responses to immunonutrition, including baseline inflammatory markers and gene polymorphisms, thereby promoting the development of “precision nutrition” interventions and ensuring that medical resources serve patients likely to benefit more precisely. Beyond focusing on short-term toxicities, attention should also be paid to the impact of immunonutrition on long-term patient outcomes. This includes quality of life, functional recovery, late complications (such as trismus and swallowing dysfunction), and overall survival rates; these endpoint indicators can more comprehensively reflect the integrated value of the intervention. On this basis, innovative formulations and combination strategies hold promise for further enhancing efficacy. For example, developing novel immunonutrition formulas or exploring their combined application with other approaches such as mucosal protectants (e.g., epithelial growth factor, stem cell therapy) and probiotics/prebiotics may generate synergistic effects, bringing greater clinical benefits to patients.

6. Conclusion

In summary, current clinical evidence strongly supports the value of immunonutrition interventions in the management of patients with head and neck cancer undergoing radiotherapy. As a strategy combining nutritional support and pharmacological modulation, immunonutrition effectively reduces the risk and severity of severe oral mucositis and demonstrates significant advantages in maintaining body weight, preserving lean body mass, and improving plasma protein levels. Its benefits are primarily attributed to the synergistic anti-inflammatory, immunomodulatory, antioxidant, and anabolic effects of its core components (arginine, ω-3 fatty acids, and nucleotides). While further exploration is needed regarding optimal application protocols and cost-effectiveness, integrating immunonutrition into standard supportive care regimens for HNC radiotherapy patients is undoubtedly a rational and effective clinical choice that can improve treatment tolerance, enhance quality of life, and potentially influence prognosis. Future in-depth basic and clinical research holds promise for further optimizing application strategies to benefit more patients.

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Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
MAR. 2026 VOL.5, NO.1

Challenges and Optimization Strategies for School-Based Health Interventions in Adolescent Myopia Prevention and Control

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doi:10.63593/JIMR.2788-7022.2026.03.006

Abstract

Adolescent myopia has become a major visual health concern closely related to daily learning routines, prolonged near work, limited outdoor activity, and increasing screen use. Schools are an important setting for myopia prevention because they can organize regular screening, provide health education, manage classroom conditions, and influence students' everyday eye-use behavior. However, the effectiveness of school-based health interventions is often limited by several practical problems. Academic pressure may reduce outdoor activity and prolong continuous near work. Vision screening may not be followed by timely referral and sustained follow-up. Health education may improve awareness but fail to change daily behavior. Uneven resources and weak cooperation among schools, families, and medical institutions may also weaken intervention outcomes. This paper analyzes the main forms and challenges of school-based health interventions in adolescent myopia prevention and control, and proposes optimization strategies from the perspectives of routine school governance, closed-loop screening and follow-up, behavior-oriented health education, school-family-medical collaboration, and improvement of outdoor activity and classroom visual environment. The paper argues that school-based myopia prevention should not rely on isolated campaigns or periodic screening alone. More attention should be paid to connecting existing measures with students' daily school life, so that prevention becomes a continuous and practical part of visual health management.

Keywords: adolescent myopia, myopia prevention and control, school-based health intervention, visual health, health education, school-family-medical collaboration

1. Introduction

Myopia has become one of the most common visual health problems among adolescents. Its significance does not lie only in blurred distance vision or the inconvenience of wearing spectacles. When myopia occurs early and progresses rapidly, it increases the possibility of high myopia in later life, which may further raise the risk of serious ocular complications. For school-aged children and adolescents, myopia is also closely connected with daily learning routines, prolonged near work, insufficient outdoor exposure, and the growing use of digital devices. In this sense, adolescent myopia is not simply an individual clinical problem. It is also a public health issue shaped by school schedules, family supervision, learning habits, and access to eye-care services.

Schools occupy a central position in myopia prevention and control. Adolescents spend a large part of their day in classrooms, and many risk-related behaviors occur during school time, such as continuous reading, writing, screen-based learning, and limited outdoor activity. Compared with interventions carried out only by families or medical institutions, school-based health interventions have a clear practical advantage: they can reach students regularly and organize preventive measures in a relatively stable environment. Vision screening, health education, outdoor activity arrangements, classroom lighting improvement, and follow-up communication with parents can all be integrated into school routines.

However, the existence of school-based measures does not necessarily mean that they work well in practice. Many schools are able to arrange vision screening or health education activities, but the more difficult part lies in whether abnormal screening results are followed by timely referral, whether students change their daily eye-use behavior, and whether outdoor activity time can be protected under academic pressure. In some cases, myopia prevention becomes a periodic campaign rather than a part of ordinary school management. Students may understand the basic rules of eye protection, yet still return to long periods of near work, poor posture, short recess, and heavy screen use.

This paper focuses on the challenges and optimization strategies of school-based health interventions in adolescent myopia prevention and control. It does not aim to conduct an empirical investigation. Instead, it analyzes the main forms of current school-based interventions, identifies the practical barriers that limit their effectiveness, and proposes possible ways to improve school-based prevention through routine governance, closed-loop screening and follow-up, behavior-oriented health education, school-family-medical collaboration, and the optimization of outdoor activity and visual environment. The central argument is that the key to school-based myopia prevention is not only to introduce more intervention measures, but to make existing measures more continuous, behavior-focused, and closely connected with students' everyday school life.

2. Necessity of School-Based Health Interventions in Adolescent Myopia Prevention and Control

School-based health interventions are necessary because adolescent myopia is closely tied to the ordinary conditions of school life. The development and progression of myopia are affected by repeated daily behaviors, including long periods of near work, insufficient breaks, limited outdoor exposure, and inappropriate reading or writing posture. These behaviors do not occur only at home. For most adolescents, they are embedded in lessons, homework, examinations, digital learning, and classroom routines. If prevention is left only to families or medical institutions, many risk factors during the school day may remain unchanged.

The school setting also provides a relatively stable space for early detection and continuous prevention. Regular vision screening can help identify students with declining visual acuity before the problem becomes more serious. Health education can remind students of proper eye-use habits, while teachers can observe whether these habits are actually followed in daily learning. Outdoor activities and physical education can reduce prolonged near work and increase exposure to natural light. Classroom environment management, including lighting, desk-chair matching, and screen-use arrangements, can also reduce avoidable visual strain. These measures are difficult to achieve through one-time clinical advice alone, but they can be repeatedly reinforced in schools.

Another reason for emphasizing school-based intervention is that adolescents are still in the process of forming health behaviors. Many students know that they should protect their eyesight, but this knowledge is easily weakened by academic pressure, peer habits, and convenience. A school can shape the environment in which these choices are made. For example, if recess is protected, outdoor activity is encouraged, and teachers pay attention to reading distance and posture during class, eye protection becomes part of daily routine rather than a slogan on a poster. In this sense, the school is not merely a place for delivering health knowledge. It is a place where visual health behaviors can be practiced, corrected, and gradually stabilized.

School-based intervention is also important for connecting families and medical services. Parents may notice vision problems late, or they may not fully understand the meaning of screening results. Medical institutions can provide professional diagnosis and treatment, but they usually have limited access to students' everyday learning environment. Schools can serve as an intermediate link. They can organize screening, inform parents of abnormal findings, guide students to seek timely medical evaluation, and cooperate with health professionals in follow-up management. Without this connection, myopia prevention may become fragmented: schools screen, parents worry, hospitals diagnose, but no one follows whether the student's daily habits have actually changed.

For these reasons, school-based health interventions are not optional additions to adolescent myopia prevention. They are a practical necessity. The effectiveness of myopia control depends not only on medical correction after vision decline has occurred, but also on whether preventable risks in everyday school life can be reduced. A well-functioning school-based intervention system can turn prevention from occasional publicity into a continuous process that combines screening, education, environmental improvement, outdoor activity, and coordinated follow-up.

3. Main Forms of School-Based Health Interventions

3.1 Vision Screening and Health Monitoring

Vision screening is usually the most direct form of school-based myopia prevention. Compared with waiting for students or parents to notice blurred vision, regular screening allows schools to identify visual decline at an earlier stage. This is particularly important for adolescents because myopia may progress quietly. Some students may adapt to unclear distance vision, sit closer to the blackboard, or rely on classmates' notes without immediately reporting the problem. School-based screening can make these changes visible before they lead to

more serious visual impairment.

In practice, vision screening should not be understood as a simple measurement of visual acuity. Its value depends on whether the results are recorded, interpreted, communicated, and followed up. A student with abnormal screening results needs more than a notification slip. The school should be able to inform parents clearly, remind them of the need for professional eye examination when necessary, and keep track of whether further assessment has been completed. Without this process, screening may become a routine administrative task: data are collected, but the student's visual health risk is not truly managed.

Health monitoring also helps schools observe changes over time. A single screening result can only show the student's current visual status, while repeated records can reveal whether visual acuity is stable, declining slowly, or worsening rapidly. This distinction matters because students with rapid progression may need closer attention, more timely referral, and stronger behavioral guidance. For schools, maintaining visual health records can also help identify class-level or grade-level problems, such as heavy near-work pressure, inadequate outdoor time, or poor classroom lighting.

At the same time, school-based monitoring should avoid becoming merely a numerical exercise. The purpose is not to rank students by visual acuity, nor to place pressure on teachers or parents through simple indicators. Its real function is to support early warning and timely intervention. Screening data should be connected with health education, classroom management, parental communication, and medical referral. Only when these links are in place can vision screening become the starting point of prevention rather than the endpoint of school responsibility.

3.2 Health Education and Daily Behavior Guidance

Health education is another basic component of school-based myopia prevention, but its effect depends on whether it can move beyond general reminders. In many schools, students are repeatedly told to protect their eyesight, reduce screen time, maintain a proper reading distance, and take breaks after prolonged near work. These messages are necessary, yet they may have limited influence if they remain at the level of slogans or occasional lectures. Adolescents often know the basic rules of eye protection, but knowledge alone does not always lead to stable behavior.

Daily behavior guidance should therefore be built into ordinary learning situations. Teachers can remind students to keep an appropriate reading and writing distance during class, adjust poor posture when it appears, and encourage short visual breaks after continuous near work. These small interventions may seem less formal than a health education lecture, but they are closer to the moments when visual strain actually occurs. For adolescents, behavior is often shaped by repeated correction in familiar settings rather than by one-time information delivery.

Screen use also needs more specific guidance. With the expansion of digital learning, electronic devices have become part of school life. The problem is not simply whether screens are used, but how long they are used, under what lighting conditions, at what distance, and whether breaks are arranged. Schools should avoid treating digital teaching as automatically harmful or automatically efficient. A more practical approach is to set clear rules for screen-based learning, reduce unnecessary continuous screen exposure, and help students recognize symptoms such as eye fatigue, dryness, blurred vision, or headache.

Health education should also pay attention to students' ability to manage their own eye-use behavior. Adolescents cannot rely only on teachers' reminders. They need to understand when to stop near work, when to look into the distance, when to report visual discomfort, and why early correction matters. In this sense, daily behavior guidance is not only about preventing wrong posture or excessive screen time. It is also about helping students develop a basic awareness of visual health and a more responsible attitude toward their own eye-use habits.

3.3 Outdoor Activity and Classroom Environment Improvement

Outdoor activity is one of the most practical measures that schools can use in myopia prevention. Its value is not limited to physical exercise. For students who spend long hours reading, writing, and looking at screens, outdoor time helps interrupt continuous near work and increases exposure to natural light. These two conditions are closely related to visual health. In school practice, however, outdoor activity should not be understood only as formal physical education classes. Recess, morning exercises, extracurricular sports, and outdoor class activities can all become part of myopia prevention if they are protected in the daily timetable.

The difficulty is that outdoor activity is often the first part of the school day to be reduced when academic tasks increase. Recess may be used for homework correction, test preparation, or extra exercises. Physical education may also be affected by examination pressure, safety concerns, weather, or limited campus space. Once this happens, myopia prevention loses an important daily mechanism. For this reason, schools need to treat outdoor activity as a health requirement rather than a flexible arrangement that can be easily replaced by classroom study.

Classroom environment improvement is another important form of intervention. Poor lighting, unsuitable desk and chair height, unclear blackboard writing, unreasonable seating arrangements, and prolonged use of multimedia screens may all increase visual strain. These factors are not always noticed by students themselves, but they shape eye-use conditions throughout the school day. Regular checks of classroom lighting, desk-chair matching, screen brightness, and viewing distance can help reduce avoidable risks. This is especially important for younger adolescents, who may not yet have stable reading posture or enough awareness of visual fatigue.

Outdoor activity and classroom environment improvement should be considered together because both concern the conditions in which students use their eyes every day. Health education tells students what they should do, but the school environment determines whether those behaviors are realistic. If students are asked to protect their eyesight while recess is shortened, classrooms are poorly lit, and screen-based teaching is used without breaks, the message becomes difficult to follow. A more effective school-based intervention should therefore combine behavioral guidance with changes in the physical and organizational environment of the school.

4. Challenges in School-Based Health Interventions

4.1 Tension Between Academic Pressure and Visual Health Protection

One of the most persistent challenges in school-based myopia prevention is the tension between academic pressure and visual health protection. Most preventive measures require time and space: students need breaks after near work, enough outdoor activity, appropriate reading distance, and reduced continuous screen exposure. These requirements are reasonable from a health perspective, but they may conflict with the actual rhythm of school learning. When class schedules are tight and academic performance remains a major concern for schools and families, visual health measures can easily be pushed aside.

This tension is especially clear in the use of recess and after-class time. In principle, recess should allow students to rest their eyes, move around, and look into the distance. In practice, it may be occupied by homework, test preparation, unfinished classroom tasks, or quiet indoor activities. Even when schools formally arrange physical education or outdoor activity, these activities may be shortened or weakened during examination periods. As a result, myopia prevention exists in policy and school notices, but the daily routine still encourages long periods of near work.

Homework and digital learning further complicate this problem. Students may spend many hours on reading and written assignments after school, while online learning platforms and electronic devices add another layer of visual burden. Schools may emphasize eye protection during the day, but the total amount of near work often extends beyond school hours. If academic tasks are not coordinated with visual health requirements, school-based intervention can only reduce part of the risk, while the broader learning environment continues to promote myopia progression.

The difficulty is not that schools are unaware of myopia prevention. Many schools already organize screening, eye exercises, health education, and outdoor activities. The problem is that these measures compete with academic demands that are seen as more urgent. Under this pressure, eye health is sometimes treated as an additional responsibility rather than a condition for students' long-term development. This makes the effectiveness of intervention unstable. When prevention depends mainly on campaigns or reminders, it is likely to weaken whenever academic pressure increases.

For school-based intervention to work, visual health protection must be placed within the structure of daily teaching rather than outside it. The key challenge is therefore not only how to persuade students to protect their eyes, but how to adjust school routines so that healthy eye-use behavior becomes possible. Without this adjustment, health education may remain correct in principle but difficult to practice in students' real learning life.

4.2 Weak Continuity of Screening, Referral, and Follow-Up

Another major weakness lies in the discontinuity between screening, referral, and follow-up. Vision screening is relatively easy for schools to organize because it can be arranged at a fixed time and completed for many students within a short period. The more difficult work begins after the screening. Once a student is found to have declining visual acuity or suspected myopia, the result needs to be explained to parents, followed by professional examination when necessary, and connected with later behavioral guidance. In many cases, this chain is not strong enough.

A common problem is that screening results are communicated, but not truly managed. Parents may receive a notice from the school, yet the notice may not clearly explain the seriousness of the result or the need for timely ophthalmic assessment. Some parents may assume that a slight decline in vision is not urgent, especially if the student can still manage daily learning. Others may delay medical consultation because of time, cost, or limited awareness of myopia progression. When this happens, school screening identifies risk but does not necessarily

lead to intervention.

Follow-up is even harder to sustain. Schools may know which students have abnormal screening results, but they may not have enough staff, professional knowledge, or time to track whether each student has received further examination or whether the recommended measures have been followed. Medical institutions, on the other hand, can provide diagnosis and advice, but they usually do not see how the student uses their eyes in school every day. As a result, responsibility is easily divided: schools complete screening, parents arrange treatment if they choose to, and hospitals provide clinical advice, but no actor fully oversees the whole process.

This weak continuity reduces the value of early detection. Myopia prevention depends not only on finding problems early, but also on acting early. If abnormal results are not followed by timely referral, corrected optical management, daily behavior adjustment, and repeated monitoring, screening becomes a record of decline rather than a starting point for prevention. For students whose myopia progresses quickly, delayed follow-up may mean losing an important window for control.

The issue is therefore not simply a technical problem of screening frequency. It is a problem of connection. A more effective school-based system needs to make each step lead naturally to the next: screening should trigger clear feedback, feedback should guide medical referral when needed, referral results should inform school and family management, and later monitoring should check whether the student's visual risk is changing. Without this continuity, even regular screening may have limited practical effect.

4.3 Limited Transformation from Health Knowledge to Daily Behavior

A further challenge is that health knowledge does not always become daily behavior. In school-based myopia prevention, students are often familiar with basic advice: keep a proper reading distance, sit upright, avoid using screens for too long, take breaks during near work, and spend more time outdoors. These messages are not difficult to understand. The problem is that they are easy to forget or ignore when students return to ordinary learning situations.

This gap is especially visible in classroom behavior. A student may know the correct reading posture, but still lower the head when writing for a long time. A student may understand the need for visual breaks, but continue reading or using a device because the task has not been finished. Some students notice eye fatigue but do not report it, either because they think it is normal or because they do not want to interrupt their study. In these situations, the obstacle is not lack of information. It is the weak conversion of information into repeated, stable habits.

Health education can also lose its effect when it is delivered in a general and detached way. Posters, lectures, and short campaigns may raise awareness for a period of time, but they do not necessarily change how students behave during class, homework, recess, and screen-based learning. Myopia prevention requires small actions repeated every day. If education is not connected with these specific moments, it may remain a form of correct knowledge rather than practical guidance.

Another reason for the weak transformation is that adolescents are not always able to manage visual health risks on their own. Their behavior is influenced by teachers' expectations, peer habits, academic tasks, family supervision, and the design of the school environment. Asking students to "protect their eyes" is not enough if the surrounding routine still encourages long periods of near work and limited outdoor activity. In this sense, behavior change cannot rely only on individual self-discipline.

School-based intervention therefore needs to pay more attention to the process of habit formation. The aim of health education should not be merely to make students know what myopia prevention means, but to help them practice it in ordinary situations. This requires reminders during learning activities, correction of poor posture, protected breaks, reasonable screen-use rules, and cooperation from teachers and parents. Only when health knowledge is repeatedly linked to daily behavior can it become part of students' visual health protection.

4.4 Uneven Resources and Insufficient Collaborative Support

Uneven resources also limit the quality of school-based myopia prevention. Different schools may face very different conditions in terms of classroom lighting, desk and chair equipment, campus space, health personnel, and access to professional eye-care services. Some schools can organize regular screening, maintain visual health records, and invite medical professionals to provide guidance. Others may only be able to complete basic vision checks, with limited capacity for follow-up or individualized advice. These differences make school-based intervention uneven in practice.

The gap is more obvious when professional support is needed. Myopia prevention is not only a matter of school management. It involves visual acuity screening, refractive assessment, risk identification, optical correction, and advice on myopia control. Teachers and school health workers can play an important role in daily supervision, but they cannot replace professional eye-care services. When schools lack stable cooperation with

medical institutions, screening results may not be interpreted accurately, and students with visual decline may not receive timely guidance.

Family support is another unstable link. Some parents pay close attention to their children's vision and respond quickly to school notices. Others may not recognize the importance of early intervention, or may focus only on whether the child needs glasses. At home, students' eye-use habits are also shaped by homework time, screen use, lighting conditions, and parental supervision. If families do not cooperate with schools, the effect of school-based intervention is easily weakened after students leave the campus.

Collaboration among schools, families, and medical institutions often remains loose. Each side may take some responsibility, but the responsibilities are not always clearly connected. Schools may screen and notify, parents may decide whether to seek medical care, and hospitals may provide diagnosis and advice. Yet the information does not always return to the school, and the student's daily habits may not be adjusted accordingly. In this situation, prevention becomes fragmented rather than continuous.

For this reason, resource gaps and weak collaboration should be considered together. Even when a school is willing to carry out myopia prevention, its effectiveness depends on whether it has the material conditions, professional support, parental cooperation, and communication channels needed to sustain the work. Without these supports, school-based health interventions may remain formal and uneven, with stronger effects in some schools and much weaker effects in others.

5. Optimization Strategies for School-Based Myopia Prevention and Control

5.1 Integrating Myopia Prevention into Routine School Governance

Myopia prevention should be built into routine school governance rather than treated as a temporary health campaign. In many schools, eye health work is most visible during screening periods, health education weeks, or special inspection activities. These arrangements are useful, but they cannot replace daily management. The risks that contribute to myopia are repeated every day through reading, writing, homework, screen use, classroom lighting, and limited outdoor activity. If prevention is only activated at certain moments, it is difficult to influence the routines in which visual strain actually occurs.

A more effective approach is to make myopia prevention part of ordinary school organization. This means that visual health should be considered when schools arrange timetables, recess, homework, physical education, classroom seating, and the use of digital teaching equipment. For example, recess should not be easily occupied by extra academic tasks, and long periods of continuous near work should be avoided where possible. When screen-based teaching is used, teachers should also consider viewing distance, brightness, duration, and breaks. These details may seem small, but they determine whether students can practice healthy eye-use behavior during the school day.

Routine governance also requires clearer responsibilities within the school. Myopia prevention cannot rely only on school doctors or health teachers. Class teachers, subject teachers, physical education teachers, and school administrators all affect students' visual health in different ways. Class teachers may notice changes in students' vision or posture. Subject teachers can adjust classroom rhythm and remind students to rest their eyes. Physical education teachers help protect outdoor activity time. Administrators are responsible for resources, schedules, and environmental improvement. When these responsibilities are distributed clearly, myopia prevention becomes a shared part of school management rather than a task assigned to one department.

At the same time, schools should avoid turning myopia prevention into another form of paperwork. The aim is not to produce more records or formal reports, but to change the conditions of daily learning. A practical governance system should focus on whether students receive timely screening feedback, whether outdoor activity is actually protected, whether poor classroom conditions are corrected, and whether teachers can integrate eye-health reminders into ordinary teaching. In this way, myopia prevention can become more stable and less dependent on short-term campaigns.

Integrating myopia prevention into routine school governance does not mean weakening academic work. Rather, it recognizes that visual health is part of students' long-term learning capacity. A school routine that ignores eye health may support short-term academic intensity, but it also increases the risk of visual problems that can affect students for years. The purpose of governance optimization is therefore to make health protection compatible with daily teaching, so that myopia prevention is not an extra burden, but a basic condition of a healthier learning environment.

5.2 Building a Closed-Loop System for Screening, Referral, and Follow-Up

A closed-loop system is needed to prevent vision screening from becoming a one-time administrative task. In school-based myopia prevention, screening is only the first step. Its real value depends on what happens after abnormal results are found. If students with declining visual acuity are only recorded or briefly notified to

parents, the opportunity for early intervention may be missed. Screening should therefore be connected with referral, medical assessment, behavior guidance, and later monitoring.

The first step is to make feedback more understandable and actionable. Parents should not receive only a simple statement that the child's vision is below standard. The school should explain what the result may indicate, why further assessment may be needed, and what steps parents are expected to take. For students with suspected myopia or rapid decline, the notice should clearly recommend timely examination by professional eye-care services. This kind of feedback can reduce parental delay and help families understand that myopia control is not limited to buying glasses.

Referral should also be more organized. Schools do not need to replace medical institutions, but they can guide families toward appropriate professional assessment. After referral, the results should be brought back into school health management where possible. For example, if a student is diagnosed with myopia or advised to reduce near-work strain, the school can pay closer attention to seating, classroom posture, screen exposure, and outdoor activity participation. This does not require teachers to provide medical treatment. It means that clinical advice should have a place in the student's daily learning environment.

Follow-up is the part most likely to be neglected, but it is also the part that gives screening long-term meaning. Schools can establish simple visual health records to track students with abnormal results, repeated decline, or high risk of progression. These records should not be used to label students. They should help teachers and school health workers know who needs closer attention and whether previous advice has been acted on. For students whose vision continues to worsen, parents should be reminded again, and health professionals should be consulted when necessary.

A closed-loop system also requires clear communication among schools, families, and medical institutions. Screening data, parental response, referral results, and later observation should not remain isolated. When these links are connected, prevention becomes more continuous: schools identify risks, parents arrange professional assessment and support home management, medical institutions provide diagnosis and guidance, and schools continue to observe daily eye-use behavior. This process is more useful than repeated screening alone, because it turns early detection into actual intervention.

The purpose of building such a system is not to make school health work more complicated. It is to ensure that each step has a clear next step. Screening should lead to feedback, feedback should lead to referral when needed, referral should guide daily management, and follow-up should check whether the student's visual health risk has changed. Only in this way can school-based myopia prevention move from periodic measurement to continuous protection.

5.3 Strengthening Behavior-Oriented Health Education

Health education should be directed more clearly toward behavior change. In myopia prevention, students usually do not lack basic information. Many of them have heard that they should keep a proper reading distance, take breaks after near work, reduce unnecessary screen time, and spend more time outdoors. The difficulty is that these rules are easily separated from actual school life. Once students return to homework, examinations, classroom tasks, or digital learning, correct knowledge may quickly give way to convenience and academic pressure.

For this reason, school health education should be less like occasional publicity and more like daily behavioral guidance. Instead of only telling students that myopia is harmful, teachers can help them notice concrete moments of risk: lowering the head too close to the desk, reading continuously without rest, using a screen for a long time, or staying indoors during breaks. These moments are where intervention is most needed. A short reminder during class or after a period of near work may have more practical value than a formal lecture that students listen to once and then forget.

Behavior-oriented education also requires clear and simple rules that students can actually follow. For example, schools may guide students to keep an appropriate distance when reading and writing, look into the distance during recess, avoid using electronic devices in dim light, and report symptoms such as eye fatigue, blurred distance vision, or frequent squinting. These rules should not be presented as abstract health slogans. They should be connected with ordinary learning scenes, so that students know what to do during class, while doing homework, when using a tablet, and after noticing visual discomfort.

Teachers play an important role in this process. They do not need to become eye-care specialists, but they can help turn health advice into classroom habits. Subject teachers can arrange brief visual breaks after intensive reading or writing. Class teachers can observe posture and remind students who often squint or move too close to the blackboard. Physical education teachers can encourage outdoor participation rather than allowing recess and activity time to become passive indoor rest. When different teachers give consistent guidance, students are more likely to treat eye protection as part of school routine.

Health education should also avoid placing all responsibility on students. Adolescents' behavior is shaped by the environment around them. If homework remains excessive, recess is shortened, and screen-based learning has no clear limits, students will find it difficult to maintain healthy eye-use habits even when they understand the risks. Behavior-oriented education therefore needs support from school management, family supervision, and classroom organization. Its goal is not only to make students "know more," but to make healthy choices easier to practice in daily life.

5.4 Improving School-Family-Medical Collaboration

School-family-medical collaboration should be built around clear responsibilities rather than general calls for cooperation. In myopia prevention, each side has a different role. Schools are closest to students' daily learning routines. Families influence homework habits, screen use, sleep, and after-school activities. Medical institutions provide professional diagnosis, correction, and guidance on myopia control. If these roles are not connected, prevention easily becomes fragmented: schools screen, parents receive notices, hospitals give advice, but the student's daily behavior may remain unchanged.

Schools should act as the organizer of daily prevention. They can arrange vision screening, maintain visual health records, observe changes in students' learning behavior, and communicate abnormal results to parents in a timely way. For students who show repeated vision decline, schools should not stop at a single reminder. They can encourage parents to seek professional assessment and pay closer attention to the student's classroom seating, reading posture, outdoor activity, and screen exposure. This kind of management does not mean that schools take over medical responsibility. It means that schools help connect clinical advice with ordinary school life.

Families are responsible for the part of eye-use behavior that schools cannot fully control. Much near work occurs after school, especially homework, extracurricular study, and recreational screen use. Even if schools protect outdoor activity during the day, the effect may be weakened if students spend long hours on digital devices at night or study under poor lighting. Parents therefore need to understand screening results, arrange timely eye examinations when necessary, and supervise home-based eye-use habits. Their role is not only to decide whether a child should wear glasses, but to support long-term visual health management.

Medical institutions provide the professional basis for prevention and control. Screening results from schools can indicate possible risk, but diagnosis and individualized guidance require professional evaluation. Ophthalmologists and optometrists can help distinguish between simple visual acuity decline and clinically significant myopia, assess progression risk, and give advice on correction and control measures. When medical advice is communicated back to schools and families in an understandable way, it becomes easier to translate professional recommendations into daily management.

The key is to create a communication mechanism that allows information to move between these three sides. Schools should inform parents clearly, parents should report relevant examination results when appropriate, and medical institutions can provide guidance that is practical for school and home settings. For example, a student with rapid progression may need not only optical correction, but also closer attention to outdoor time, near-work duration, and regular review. Without communication, these recommendations may stay within the clinic and fail to affect daily habits.

Improving collaboration does not require a complicated system at the beginning. A workable model may start with a few concrete tasks: clear feedback after screening, referral reminders for students at risk, parental confirmation of follow-up, and basic guidance from medical professionals for schools. Over time, these tasks can form a more stable prevention network. The purpose is to make sure that no single actor is left to handle myopia prevention alone, and that students receive consistent support across school, home, and medical settings.

5.5 Optimizing Outdoor Activity and Visual Environment

Outdoor activity should be treated as a regular part of myopia prevention, not as an activity that can be reduced whenever academic tasks become heavier. For adolescents, outdoor time helps break long periods of near work and provides exposure to natural light. These conditions cannot be replaced by eye exercises or classroom reminders alone. Schools therefore need to protect recess, physical education, and other outdoor activities in the daily timetable. When possible, short outdoor breaks and outdoor class activities can also be arranged, especially after periods of intensive reading, writing, or screen use.

The key is not only to increase the number of outdoor activities on paper, but to make sure they actually happen. In some schools, outdoor time may be formally arranged but weakened in practice because students stay indoors, teachers use breaks for unfinished teaching tasks, or activity time is occupied by test preparation. To avoid this, schools should set clearer rules for protecting recess and physical education. Teachers also need to share the understanding that outdoor activity is not unrelated to learning. It supports students' long-term visual health and helps reduce the risks created by prolonged classroom study.

The classroom visual environment also needs regular improvement. Students spend many hours in classrooms, so small environmental problems may accumulate into continuous visual strain. Lighting should be sufficient and stable, desks and chairs should match students' height as much as possible, and blackboards or screens should be clear from different seating positions. When multimedia equipment is used, schools should pay attention to screen brightness, viewing distance, font size, and the duration of continuous use. These details are easy to overlook, but they directly affect students' daily eye-use conditions.

Seating arrangements should also be managed with visual health in mind. Students with visual decline should not simply be moved closer to the blackboard without further attention. A change of seat may help them see temporarily, but it does not address the underlying need for professional assessment or myopia control. Schools can rotate seats reasonably, observe whether students often squint or lean forward, and remind parents when such behaviors appear. In this way, classroom management can become an early warning point rather than a passive response to poor vision.

Outdoor activity and environmental optimization should work together. If students are told to protect their eyesight but remain in poorly lit classrooms, use screens for long periods, and lose recess time to academic tasks, health education will be difficult to translate into behavior. A healthier school environment gives students a real chance to follow visual health guidance. For this reason, optimizing outdoor activity and classroom conditions is not only a logistical issue. It is part of the basic support system that makes school-based myopia prevention possible.

6. Discussion

School-based myopia prevention should be understood as a long-term public health practice rather than a collection of isolated school activities. Vision screening, health education, outdoor activity, classroom environment improvement, and parental communication are all necessary, but none of them can work well on their own. The real difficulty lies in whether these measures can be connected with students' everyday learning routines. If screening is not followed by referral and management, if health education does not change daily behavior, or if outdoor activity is repeatedly sacrificed to academic tasks, the intervention may exist in form but remain weak in effect.

A key issue is the gap between knowing and doing. Most schools and families already recognize that myopia prevention is important. Students also know many basic rules of eye protection. The problem is that visual health behaviors are often fragile in the face of school routines. Long periods of reading and writing, examination pressure, homework, digital learning, and indoor recess all make unhealthy eye-use habits easier to continue. This means that myopia prevention cannot rely only on awareness raising. It has to enter the ordinary structure of teaching, homework, breaks, classroom management, and family supervision.

Another point worth stressing is that schools should not be asked to solve the problem alone. Schools are important because they can organize students and influence daily routines, but they cannot replace families or medical institutions. Parents determine much of what happens after school, including homework habits, recreational screen use, sleep, and lighting conditions at home. Medical institutions provide diagnosis, correction, and professional advice that schools cannot provide by themselves. A more realistic prevention model should therefore treat schools as the coordinating setting, while families and medical institutions provide support on the parts that schools cannot cover.

The discussion also shows that myopia prevention needs to shift from periodic intervention to continuous management. Many measures are easier to carry out as campaigns: a screening week, a health lecture, a poster display, or a short-term outdoor activity requirement. These activities can raise attention, but adolescent myopia develops through repeated exposure to daily risks. Prevention should therefore be judged not only by whether activities are carried out, but by whether they change daily patterns of eye use. The more important questions are whether students have enough outdoor time, whether screen-based teaching is controlled, whether abnormal screening results lead to follow-up, and whether parents respond to school feedback.

In this sense, the optimization of school-based interventions is not simply about adding more measures. It is about making existing measures more connected and more practical. A school may already have screening, health education, physical education, and classroom management, but these components may remain separate. When they are linked into a routine system, their value becomes stronger. Screening can identify risk, health education can guide behavior, outdoor activity can reduce near-work pressure, classroom improvement can lower environmental strain, and collaboration with families and medical institutions can support follow-up. The effectiveness of prevention depends on this connection.

Future school-based myopia prevention should therefore pay more attention to implementation quality. Measures that appear sound in principle may fail if they are too general, too temporary, or too detached from students' actual school life. The practical direction is to make prevention visible in daily routines: protected recess,

reasonable homework arrangements, timely feedback after screening, behavior-oriented health education, regular classroom environment checks, and clear communication with parents. These are not dramatic reforms, but they are the kinds of changes that can make prevention more stable and less dependent on short-term attention.

7. Conclusion

School-based health interventions play an important role in adolescent myopia prevention and control because many risk factors are embedded in students' daily learning routines. Vision screening, health education, outdoor activity, classroom environment improvement, and school-family-medical communication can all contribute to visual health protection. Their value, however, depends on whether they are carried out as continuous practices rather than occasional activities.

The main challenge is not the complete absence of intervention measures, but the weak connection between them. Academic pressure may reduce outdoor activity and prolong near work. Screening may identify visual decline but fail to lead to timely referral and follow-up. Health education may improve awareness but not change daily behavior. Resource gaps and insufficient collaboration may also weaken the support that schools can provide. These problems show that adolescent myopia prevention cannot rely only on reminders, publicity, or periodic screening.

To improve school-based myopia prevention, schools need to integrate visual health protection into routine governance. Screening should be connected with feedback, referral, and follow-up. Health education should focus on concrete behaviors in daily learning. Outdoor activity and classroom visual conditions should be protected and regularly improved. Schools, families, and medical institutions also need clearer division of responsibilities and more stable communication.

In general, effective myopia prevention requires a shift from isolated measures to a connected system of daily management. Only when preventive actions are built into students' ordinary school and home life can school-based health interventions better support adolescent visual health and reduce the risk of myopia progression.

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Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
MAR. 2026 VOL.5, NO.1

Research on the Construction of a Screening and Intervention Service System for Postpartum Depression

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doi:10.63593/JIMR.2788-7022.2026.03.007

Abstract

Postpartum depression is a common but easily overlooked mental health problem in maternal care. Many women do not actively describe themselves as depressed, and their symptoms may be hidden behind sleep loss, childcare pressure, breastfeeding difficulties, irritability, guilt, or fatigue after delivery. At present, postpartum health services still tend to focus more on physical recovery and infant health, while psychological screening, referral, intervention, and follow-up are not always well connected. This paper discusses the construction of a screening and intervention service system for postpartum depression. It analyzes the service needs of postpartum women, the current gaps in screening and intervention, the design of a screening pathway, the construction of an intervention service pathway, coordination among maternal care, community health, and mental health services, and the supporting mechanisms needed for implementation. The paper argues that postpartum depression care should not stop at one-time screening or general advice. A more effective service system should combine routine screening, risk classification, graded intervention, referral collaboration, family support, privacy protection, and continuous follow-up, so that women at risk can receive timely and appropriate help within the maternal and child health service process.

Keywords: postpartum depression, screening, intervention service system

1. Introduction

Postpartum depression is one of the mental health problems that can easily be overlooked in maternal care. The World Health Organization has estimated that about 13% of women who have just given birth experience a mental disorder, primarily depression, and the proportion may be higher in developing countries. A global review also reported that postpartum depression affected about 17.22% of postpartum women, although prevalence varies across regions and assessment methods. These figures suggest that postpartum depression is not a rare or marginal condition, but a common maternal health issue that requires regular attention in postpartum care.

After childbirth, many women experience changes in sleep, physical strength, family roles, feeding pressure, and emotional regulation. Some emotional fluctuations may be temporary, but when persistent low mood, anxiety, irritability, guilt, loss of interest, or feelings of helplessness continue, they may indicate a more serious depressive state. The difficulty is that these symptoms are often hidden behind the ordinary language of “being tired after delivery” or “not yet adapting to motherhood,” so they may not receive timely attention.

The influence of postpartum depression is not limited to the mother’s emotional state. It may affect breastfeeding, mother-infant bonding, infant care, marital communication, and the wider family atmosphere. In more serious situations, it can also be associated with self-harm risk or thoughts of harming the infant. For this reason, postpartum depression should not be treated as a private emotional problem that women must endure by themselves. It is a maternal and child health issue that requires early identification and appropriate service support.

At present, maternal health services still tend to pay more attention to physical recovery after childbirth. Uterine involution, wound healing, lactation, contraception, and infant growth are usually easier to observe and manage. Psychological symptoms, by contrast, are less visible and may not be actively reported by women. Some mothers worry that admitting emotional distress will make them seem weak or unqualified as mothers. Family members may also misread depressive symptoms as bad temper, lack of patience, or normal postpartum fatigue. These misunderstandings can delay screening and intervention.

A screening and intervention service system is therefore needed. Screening alone is not enough. If a woman is identified as being at risk but no one explains the result, follows up her condition, offers basic psychological support, or refers her to professional services when necessary, the screening process loses much of its value. In the same way, intervention cannot depend only on specialist hospitals, because many women first appear in obstetric clinics, maternal and child health institutions, community health services, or child health visits. These service points need to be connected.

This paper discusses the construction of a screening and intervention service system for postpartum depression. The focus is not on evaluating a single scale or proving the effect of one intervention method. Instead, it considers how postpartum depression can be identified earlier, how risk can be classified, how different levels of intervention can be arranged, and how maternal care, community health services, mental health professionals, and families can work within the same care pathway. A more useful system should make psychological care a regular part of postpartum health services, rather than an emergency response after symptoms have already become severe.

2. Service Needs of Women with Postpartum Depression

Women with postpartum depression often need more than a diagnosis. What they face is usually mixed with emotional distress, physical exhaustion, childcare pressure, and changes in family relationships. Some mothers may not describe themselves as “depressed” at first. They may only say that they cannot sleep even when the baby is asleep, that they cry more easily than before, that they feel guilty for not being a good mother, or that they have lost interest in things they used to care about. These expressions may sound ordinary in postpartum life, but they can also indicate that the woman is already under considerable psychological strain.

In routine maternal care, emotional distress can be difficult to notice. A postpartum visit may confirm that the wound is healing well, lactation is normal, and the baby is growing as expected, while the mother’s mood is still unstable. She may look calm during the consultation, especially when family members are present. She may also avoid speaking directly about sadness, fear, anger, or hopelessness because she worries that these feelings will be judged. For this reason, postpartum care needs to leave room for emotional expression, not only physical examination.

Many women at this stage need practical psychological support rather than immediate specialist treatment. Timely listening, reassurance, and basic guidance may help them understand that emotional difficulty after childbirth is not a personal failure. Some women need advice on sleep, feeding pressure, role adaptation, and communication with family members. Some need short-term counseling. Others may need more structured psychological intervention. If early distress is simply dismissed as normal postpartum fatigue, symptoms may become harder to manage later.

Family support is closely tied to these service needs. After childbirth, the mother’s mental state is often affected by how childcare responsibilities are shared at home. Lack of sleep, pressure around breastfeeding, disagreement over infant care, conflict with elders, or limited support from the spouse can all worsen emotional distress. In some families, the mother is expected to recover quickly and take care of the baby as a matter of course. Such expectations leave little space for her fatigue and vulnerability. A service system for postpartum depression therefore needs to involve family members, helping them understand what kind of support is actually useful.

For women with more serious symptoms, accessible referral and treatment are essential. Comfort and encouragement are not enough when there is persistent depression, obvious functional impairment, self-harm thoughts, or possible risk to the infant. These women may need professional assessment by mental health specialists, psychotherapy, medication evaluation, or crisis intervention. The difficulty is that many mothers do not know where to seek help, or they hesitate because of stigma, cost, time, and concern about breastfeeding or medication. If the referral channel is unclear, they may move between obstetric care, community services, and mental health departments without receiving continuous support.

Postpartum depression also requires follow-up over time. It does not always appear immediately after delivery, and it does not necessarily end after the routine postpartum check-up. Some women develop symptoms gradually as childcare pressure accumulates. Others experience repeated emotional fluctuations over several months. A single screening or one brief consultation cannot fully capture these changes. Follow-up should pay attention not only to mood, but also to sleep, family support, parenting stress, and whether the woman has

actually received the help she was advised to seek.

The service needs of women with postpartum depression are therefore broader than symptom identification. They include being heard, receiving practical psychological help, gaining family support, finding professional care when necessary, and being followed up after the first contact with health services. This is why postpartum depression care is better organized as a continuous service process rather than a single clinical encounter.

3. Current Gaps in Postpartum Depression Screening and Intervention

Postpartum depression has received more attention in recent years, but the service response is still not very stable. A recent review reported that the prevalence of postpartum depression in China was about 21.4%, suggesting that this is not a marginal problem in maternal health care. Even so, postpartum services often remain centered on physical recovery and infant health. During a postpartum visit, medical workers may ask carefully about breastfeeding, lochia, wound healing, contraception, and the baby's growth, while the mother's emotional state is touched on only briefly. If she does not say directly that she feels depressed or anxious, her condition may be missed.

Part of the difficulty comes from the way postpartum distress is understood. Some women do not recognize their own symptoms as something that needs help. Crying often, sleeping poorly, losing interest, feeling guilty, or becoming unusually irritable may be explained as the normal cost of becoming a mother. Family members may use similar explanations, seeing these changes as tiredness, bad temper, or lack of patience. In this kind of atmosphere, a mother may learn to hide her feelings, or give safer answers when asked about her mood. The problem is not only that screening is absent, but that women may not feel able to speak honestly when screening does occur.

The use of screening tools is also uneven. The Edinburgh Postnatal Depression Scale can help health workers identify women who may be at risk, but it is not used consistently across hospitals, maternal and child health institutions, and community services. Some institutions screen regularly, while others depend more on clinical impression or the mother's own complaint. Even when the scale is used, the process can become too procedural. A woman may fill in the form, receive a score, and leave without being told clearly what the result means or what she should do next. Under these conditions, screening finds a risk on paper, but does not necessarily lead to care.

The link between screening and intervention is still weak. Some institutions can identify possible depressive symptoms, yet lack a clear referral or follow-up pathway. Mild symptoms may be put aside because they do not look urgent. Moderate symptoms may be left to the woman and her family to "adjust slowly." More serious symptoms may also be referred late if obstetric, community, and mental health services are not connected. One study of 429 postpartum women in China reported a postpartum depression prevalence of 22.14%, which again suggests that a noticeable proportion of mothers may need more than a single score or a brief reminder.

Professional support is limited in many frontline settings. Obstetricians, midwives, nurses, and community health workers are often the first to meet postpartum women, but not all of them have enough training in mental health assessment or psychological communication. They may know that postpartum depression exists, yet still feel unsure about how to ask sensitive questions, how to respond when a woman cries during consultation, or when referral should be made. Without training and backup from mental health professionals, some frontline workers may avoid going deeper, not because they are indifferent, but because they do not know how to manage what may come next.

Family participation is another weak part of current services. Screening and intervention are often directed at the mother alone, while the family environment around her is left outside the process. This is a problem because postpartum women rely heavily on family members for rest, childcare, medical visits, and emotional support. If the spouse or other caregivers do not understand postpartum depression, they may increase pressure without realizing it. They may tell the mother to "think less," criticize her feeding choices, or treat her symptoms as a bad attitude. These responses can make her less willing to talk about her condition the next time she meets a health worker.

Privacy and stigma also affect whether women accept screening and follow-up. Some mothers worry that a depression label will be written into their record, judged by relatives, or interpreted as evidence that they are unable to care for the baby. Others fear that psychiatric treatment may affect breastfeeding, work, or family reputation. These concerns are not always expressed openly. They may appear as refusal to complete a scale, denial of symptoms, vague answers, or failure to return after a positive screening result.

4. Design of the Screening Pathway

The screening pathway for postpartum depression should be embedded in the ordinary contacts between postpartum women and the health service system. Many women will not go directly to a psychiatric clinic, even

when they are already distressed. They are more likely to appear in antenatal care, delivery hospitalization, postpartum visits, the 42-day postpartum review, vaccination appointments, or child health clinics. These routine contacts are often the first chance to notice emotional changes. If screening is left only to mental health departments, a large number of women with early symptoms may never enter the service pathway.

Screening also needs to follow the actual course of postpartum psychological changes. Some women begin to show anxiety or depressive symptoms before delivery, especially when there is a history of mental disorder, poor family support, pregnancy complications, or a difficult childbirth experience. For these women, risk identification can start in late pregnancy. After delivery, the first few weeks are often unstable. Pain, feeding problems, sleep loss, and the sudden change of family roles may all affect mood. A woman who seems calm before discharge may feel much worse after returning home. The 42-day postpartum visit and later community follow-up should therefore not be treated as routine physical checks only; they are also useful points for mental health screening.

Screening tools can help, but they should not dominate the whole process. The Edinburgh Postnatal Depression Scale is widely used and is suitable for initial screening in maternal care settings. Still, a scale score is not the same as a diagnosis. A high score needs further conversation and, when necessary, professional assessment. A low score should not automatically end concern if the woman is crying repeatedly, sleeping very little, expressing strong guilt, or saying that she cannot cope. In real clinical work, the scale is only one part of judgment. The health worker's observation and the woman's own description are just as important.

The way screening is carried out will affect whether women are willing to speak honestly. Some mothers may avoid telling the truth if their spouse, parents, or parents-in-law are sitting beside them. This is especially likely when the distress is related to family conflict, childcare burden, or lack of support. Screening should, as far as possible, give the woman a short private space. The language used by health workers also matters. If the questions sound like criticism, the woman may protect herself by denying symptoms. If screening is explained as a normal part of postpartum care, it is easier for her to talk about sadness, anxiety, anger, or exhaustion without feeling that she is being judged.

After screening, the result needs to lead somewhere. Women with no obvious depressive symptoms can still receive brief mental health education, because mood problems may appear later. Women with mild symptoms may need advice on rest, feeding pressure, family communication, and a planned follow-up. Those with more persistent or moderate symptoms should be linked with psychological counseling or community follow-up. For women who express self-harm thoughts, thoughts of harming the infant, psychotic symptoms, or severe functional impairment, referral to mental health professionals should be immediate rather than delayed until the next routine visit.

Records are also necessary, but they should serve care rather than paperwork. A useful record should show when the woman was screened, what level of risk was identified, whether referral was advised, and whether follow-up has taken place. This is important because postpartum women may move between obstetric clinics, maternal and child health institutions, community health services, and child health clinics. Without a shared or at least continuous record, each setting may see only one fragment of the problem. The woman may then be screened repeatedly, but not actually helped.

A workable screening pathway does not have to be complicated. It should make use of the service contacts that already exist, protect the woman's privacy, combine scale results with clinical judgment, classify risk in a practical way, and connect positive screening results with follow-up or referral. Otherwise, screening may remain a form filled out during postpartum care, rather than the beginning of real support.

5. Construction of the Intervention Service Pathway

After screening, the real question is whether the woman can receive help that matches her situation. A high score or a suspected risk is only a signal. If the service ends with "pay more attention to your mood" or "go to a specialist hospital if necessary," the mother may still be left to handle the problem by herself. For many women, especially those who are tired, ashamed, or unsure whether their symptoms are serious, this kind of vague advice is not enough.

For women with mild symptoms, intervention does not have to begin with specialist treatment. Some mothers mainly need someone to explain that emotional distress after childbirth is not a personal failure. They may also need practical advice on sleep, feeding pressure, physical recovery, and how to ask family members for help. A short conversation can be useful if it is specific. For example, telling a mother to "relax" is not very helpful, but discussing who can take one night feeding shift, how to arrange rest after breastfeeding, or when to return for another mood check is much more concrete.

When symptoms last longer or begin to affect daily function, the service response should become more active. A mother who keeps crying, feels hopeless, loses interest in caring for herself, or cannot manage basic childcare

should not simply be told to adjust slowly. At this point, follow-up needs to be planned, not left to chance. Community health workers, maternal health staff, or psychological counselors can keep contact with her, check whether symptoms are improving, and decide whether professional mental health care is needed. The pathway should allow the level of support to rise when the woman's condition does not improve.

High-risk cases need a much clearer route. If a woman mentions self-harm, thoughts of harming the infant, severe insomnia, psychotic symptoms, or obvious inability to care for herself or the baby, referral should not wait until the next routine visit. Obstetric and community services should know whom to contact and how to respond. In these cases, the aim is not only emotional comfort. Safety assessment, family notification when appropriate, urgent specialist care, and crisis management may all be necessary.

Family involvement should be part of the pathway, but it should not be treated as a simple instruction to "give more care." Some families do not know what care means in practice. They may offer advice, criticism, or pressure while believing that they are helping. Health workers can explain to family members that postpartum depression may appear as sadness, irritability, withdrawal, guilt, or loss of confidence. More importantly, they can tell the family what to do: reduce blame, share childcare, protect the mother's sleep, accompany her to medical visits, and avoid treating her symptoms as laziness or bad temper.

Follow-up is what keeps the intervention from breaking off after one contact. A woman referred for counseling may not go. A woman advised to rest may still have no one to help at home. A woman who seemed better at the first visit may worsen after several weeks of poor sleep. For this reason, the intervention pathway should include a return point. Health workers need to know whether the mother received the suggested service, whether her mood changed, whether family support improved, and whether risk signs appeared later.

The pathway does not need to be overly complicated. Mild distress can be supported through explanation, listening, practical guidance, and planned observation. More persistent symptoms need counseling and closer follow-up. Severe symptoms require urgent referral and safety management. What matters is that screening should lead to a response, and that response should not depend entirely on whether the mother has the energy and courage to seek help on her own.

6. Coordination Among Maternal Care, Community Health, and Mental Health Services

Postpartum depression care cannot be handled by one service setting alone. Many women first appear in obstetric clinics, maternal and child health institutions, or community health services, not in psychiatric departments. This means that the first opportunity for identification often belongs to workers who are not mental health specialists. If these services are not connected, a woman may be screened in one place, advised to seek help in another, and then lost before any real intervention begins.

Maternal care services should take the first step in recognition. Obstetricians, midwives, and nurses are familiar with the woman's pregnancy, delivery process, physical recovery, and breastfeeding problems. These details are often related to her emotional state. A difficult delivery, poor lactation, wound pain, or repeated concern about the baby may all increase psychological pressure. Maternal care workers do not need to provide full psychiatric treatment, but they should be able to notice risk signs, ask basic questions about mood and sleep, and explain why further support may be necessary.

Community health services are important because postpartum life mostly happens after the woman leaves the hospital. Emotional symptoms may become clearer at home, when sleep loss, childcare pressure, and family conflict begin to accumulate. Community health workers can provide follow-up during home visits, postpartum reviews, vaccination appointments, or child health services. Their advantage is continuity. They may see the mother more than once and may understand something about her family situation. This makes them suitable for checking whether symptoms are improving, whether referral advice has been followed, and whether the family is giving enough support.

Mental health services should provide professional assessment and intervention for women whose symptoms go beyond basic support. This includes women with persistent depressive symptoms, serious anxiety, self-harm thoughts, psychotic symptoms, or obvious impairment in daily functioning. The problem is that referral to mental health services is often not easy for postpartum women. Some are afraid of being labeled. Some worry about medication and breastfeeding. Some do not know which department to visit. If referral only means telling the woman to "go to psychiatry when you have time," many cases will not be followed through.

A more workable model is to create a clear connection between these services. Maternal care workers can identify risk and explain the need for help. Community health workers can keep contact after discharge and support follow-up. Mental health professionals can provide diagnosis, counseling, medication assessment, or crisis management when needed. The connection does not have to be complicated, but it should be specific. For example, a positive screening result should indicate who informs the mother, who contacts the family, who arranges referral, and who checks whether the referral was completed.

Information sharing is also part of coordination, but it has to be handled carefully. Postpartum depression involves privacy, and some women may be sensitive about who can see their mental health information. A basic record system can help different service points understand the woman's risk level and follow-up needs, but access should be limited to relevant health workers. The aim is not to circulate private information widely. It is to avoid the situation in which the woman has to repeat her distress at every visit while no one takes continuous responsibility.

Family members can also be included in coordination when the woman agrees and when safety allows. In many cases, the family decides whether the mother can rest, attend follow-up, receive counseling, or seek specialist care. If the family does not understand the seriousness of postpartum depression, referral advice may not be carried out. Health workers can explain the situation in practical terms: what symptoms need attention, what kind of support is useful, and when urgent help is needed. This is more useful than simply telling the family to be considerate.

The coordination among maternal care, community health, and mental health services should finally make the care pathway less dependent on the woman's own initiative. A mother with postpartum depression may not have the energy to find the right department, explain her condition repeatedly, and insist on getting help. The service system should reduce this burden. Once risk is identified, the next contact point should already be clear. This is the basic meaning of coordination in postpartum depression care.

7. Supporting Mechanisms for System Implementation

A screening and intervention system for postpartum depression will not work only because a pathway has been written down. It needs several forms of support in daily practice. The first is training. Obstetricians, midwives, nurses, maternal and child health workers, and community health workers are often close to postpartum women, but many of them have not received enough training in mental health communication. They may know the name of postpartum depression, yet feel unsure about how to ask about sadness, anxiety, guilt, self-harm thoughts, or family conflict. Training should therefore be practical. It should help frontline workers recognize warning signs, use screening tools properly, respond to emotional disclosure, and decide when referral is needed.

Another support is a clear working procedure. If a woman screens positive, health workers should know what to do next. Who explains the result to her? Who contacts the family if family support is needed? Which department receives referral? Who follows up if she does not attend the referral appointment? These details may look small, but they decide whether the system can really operate. Without a procedure, screening may depend too much on individual responsibility. Some health workers may handle the case carefully, while others may simply record the score and move on to the next patient.

Privacy protection is also important. Postpartum depression is still surrounded by misunderstanding and stigma. Some women are afraid that their emotional problems will be known by relatives, employers, or people outside the clinic. If they do not trust the service, they may refuse screening or hide their symptoms. Health institutions should make it clear that mental health information will be used only for care and follow-up. Conversations about mood should be arranged as privately as possible, especially when family conflict or self-harm thoughts may be involved.

Family education is another necessary mechanism. The family is often the place where postpartum depression becomes better or worse. A mother may receive good advice from a doctor, but if she returns home to constant criticism, poor sleep, and little childcare support, the advice may not help much. Health services can provide simple guidance to spouses and other caregivers: postpartum depression is not laziness or weakness; the mother needs rest, emotional support, and help with infant care; blame and pressure usually make symptoms worse. These messages do not need to be complicated, but they need to be repeated in different service contacts.

Digital tools can support the system, but they should be used carefully. Electronic health records, online follow-up, appointment reminders, psychological hotlines, and internet hospital services may make postpartum care more continuous. They can help health workers track screening results and remind women to attend follow-up. Still, digital follow-up cannot replace face-to-face assessment when symptoms are serious. It also cannot solve the problem of stigma or family pressure by itself. Its value lies in making contact easier, not in replacing professional judgment.

The system also needs evaluation, but evaluation should not become empty paperwork. It is useful to know whether women at risk are actually followed up, whether referrals are completed, whether health workers receive training, and whether families understand basic warning signs. These indicators are more meaningful than simply counting how many screening forms were collected. A service system should be judged by whether it helps women receive care after risk is identified, not only by whether screening has been performed.

8. Conclusion

Postpartum depression care should not depend only on whether a mother has the courage to ask for help. Many women may not recognize their symptoms at first, or they may hide their distress because they fear being judged. This makes active screening and a clear intervention pathway necessary in postpartum health services.

The construction of a screening and intervention service system should begin with routine maternal and child health contacts. Screening can be placed in antenatal care, postpartum visits, the 42-day review, community follow-up, and child health services. The result should not stop at a score. It should lead to risk classification, explanation, follow-up, psychological support, family involvement, or referral when needed.

A workable system also depends on coordination. Maternal care services can identify early risk, community health services can provide continuing contact, and mental health professionals can take over more serious cases. Families should also be included, because the mother's recovery is closely related to sleep, childcare support, communication, and the emotional atmosphere at home.

The main purpose of this system is not to make postpartum care more complicated. It is to prevent women with depressive symptoms from being seen once and then forgotten. When screening, intervention, referral, and follow-up are connected, postpartum mental health can become a regular part of maternal care rather than a problem addressed only after symptoms become severe.

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