Advances in cerebrospinal fluid biomarkers for the diagnosis, treatment and monitoring of leptomeningeal metastases (Review)

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Abstract. Leptomeningeal metastasis (LM) is an aggressive complication characterized by the dissemination of malignant cells to the leptomeninges, typically resulting in rapid neurological deterioration and poor prognosis. Clinical diagnosis and management are impeded by non-specific symptoms and the limited sensitivity of conventional cerebrospinal fluid (CSF) cytology. Consequently, CSF biomarkers have emerged as critical tools for diagnosis, treatment monitoring and prognostic evaluation. The present review summarizes recent advancements in CSF biomarkers, categorizing them into proteins, nucleic acids and metabolites. These biomarkers enhance diagnostic accuracy, facilitate longitudinal disease tracking and assess therapeutic efficacy. Despite notable progress, challenges persist regarding biomarker sensitivity, specificity and standardization. Furthermore, the potential of multi-omics technologies and single-cell analysis is discussed as a pathway for discovering novel biomarkers to enable the precise stratification and personalized management of LM.

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Contents

1. Introduction

Leptomeningeal metastasis (LM) is a severe complication characterized by the dissemination of malignant cells to the leptomeninges and cerebrospinal fluid (CSF) (1). LM occurs in ~5% of patients with solid tumors, most commonly lung cancer, breast cancer and melanoma (1-3). Notably, biological behaviors and CSF biomarker profiles of LM may vary substantially depending on the primary tumor origin (4). The mechanisms of LM metastasis involve diverse pathways, including direct extension from the primary tumor, hematogenous dissemination, perineural and perivascular spread and iatrogenic introduction (5,6). Prognosis remains poor, with a median overall survival time of 3.6-12.0 months despite aggressive multimodal therapy (7). In untreated patients, the median overall survival time is limited to 4-6 weeks (8), underscoring the urgent need for effective diagnosis and management. Clinically, LM presents with non-specific neurological symptoms, such as headache, cognitive impairment, cranial nerve palsies and radiculopathy, which frequently lead to a delayed diagnosis.

CSF circulates within the central nervous system (CNS), providing mechanical protection and maintaining biochemical homeostasis. Secreted by the choroid plexus, CSF contains water, electrolytes, glucose and proteins; it facilitates nutrient transport and metabolic waste elimination, processes essential for normal CNS physiology. Additionally, CSF accumulates bioactive substances (such as proteins, metabolites and RNA) secreted by CNS cells, as well as small molecules diffused

from systemic circulation (9). Given the limitations of tissue biopsy in CNS disorders, CSF profiling represents a promising strategy for biomarker discovery (10). Consequently, identifying effective CSF biomarkers is critical for the diagnosis and therapeutic monitoring of LM.

Despite advancements in LM diagnosis using CSF, the existing methods lack sufficient sensitivity and specificity. CSF cytology remains the gold standard but has a limited sensitivity of 45-67% (11). Although circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) offer higher sensitivity, they are limited by potential false positives and false negatives (12,13). Standard magnetic resonance imaging often fails to detect early or small metastatic foci (14) and tissue biopsy is too invasive for routine monitoring. Considering these challenges, developing novel CSF-based detection techniques is of paramount importance. As CSF directly contacts the leptomeninges, it captures biomolecules released by tumor cells. These biomarkers offer critical insights for early diagnosis, precision treatment and longitudinal monitoring of LM, potentially improving patient outcomes.

2. Biomarkers for diagnosing LM based on CSF

Diagnostic performance and clinical relevance of CSF biomarkers vary depending on the primary tumor type (15). CSF biomarker detection is critical for the clinical diagnosis and management of LM. As shown in Fig. 1, these biomarkers are categorized into proteins, nucleic acids, metabolites and others. Each category utilizes distinct detection methodologies to support early diagnosis, disease monitoring and treatment evaluation. Numerous biomarkers have been identified through integrative multi-omics and single-cell analyses of CSF, which enable comprehensive profiling of tumor and microenvironmental components. Protein biomarkers, reflecting tumor biological activity, are typically detected via immunoassays such as ELISA and immunohistochemistry (16,17). Nucleic acid biomarkers, particularly ctDNA and microRNAs (miRNAs/miRs), reveal molecular characteristics and are quantified using PCR and high-throughput sequencing (18,19). Metabolic biomarkers indicate tumor metabolic reprogramming and are identified through gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry (20). Additionally, emerging biomarkers such as exosomes and cytokines are analyzed using flow cytometry (21). Integrating these diverse methodologies facilitates a comprehensive strategy for early detection and personalized treatment of LM. The major CSF biomarkers and their clinical relevance are summarized in Table I. At present, ctDNA and cell-free DNA (cfDNA) are the most widely applied and clinically validated CSF biomarkers, whereas most other markers listed in Table I remain investigational.

Protein biomarkers. Altered expression of specific protein biomarkers in CSF offers potential for the early detection and monitoring of LM. For example, carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) is a critical biomarker for diagnosing lung adenocarcinoma (LUAD)-related LM. Elevated CSF CEACAM6 levels correlate closely with LM incidence (22). Moreover, combined detection of human epididymis protein 4 (HE4) and CEACAM6 enhances diagnostic sensitivity and specificity for this subgroup. HE4, a secretory protein associated with LM progression in LUAD, serves as a promising adjunctive biomarker (16,23). Additionally, elevated levels of CEA, prostate-specific antigen, cancer antigen (CA)-153, CA-125, melanoma antigen recognized by T-cells 1 and melanoma-associated antigen 3 are frequently used to diagnose LM (16,24,25). Although CSF expression of these markers is increased, definitive diagnosis still requires corroboration via clinical and imaging assessments.

Secreted phosphoprotein 1 (SPP1) is another notable protein in LM pathology. Studies show that markedly elevated CSF SPP1 levels augment the migratory capacity of tissue-resident boundary-associated macrophages, thereby facilitating meningeal metastasis (26,27). Notably, SPP1 is associated with matrix metalloproteinase 14 in CSF, suggesting its potential as a therapeutic target. Furthermore, a panel of proteins, including α1-antichymotrypsin, apolipoprotein A-I, apolipoprotein E, haptoglobin, hemopexin, prostaglandin D2 synthase, transthyretin and serotransferrin, exhibits altered CSF profiles in patients with LM (28). These proteins are primarily involved in the immune response, inflammation and lipid metabolism. Their detection in CSF aids in identifying LM and provides insights into disease progression and immune dynamics.

LM diagnosis is further supported by immunohistochemical staining for cytokeratin 7 and AE1.3. Positive expression of these markers is linked to specific malignancies, notably cholangiocarcinoma-related meningeal metastasis (29). These biomarkers facilitate conclusive diagnosis via immunocytochemical analysis, particularly when conventional CSF cytology is indeterminate. Additionally, epithelial cell adhesion molecule (EpCAM), detected via flow cytometry, exhibits high sensitivity for breast cancer-derived LM (30). Efficient detection of EpCAM-positive cells improves early diagnostic capabilities, especially when imaging and traditional cytology are non-diagnostic.

CYFRA 21-1, a widely employed tumor marker, shows diagnostic utility in CSF for LM, particularly in lung cancer cases (22,31). Combined analysis of CSF CYFRA 21-1 and cytology markedly improves diagnostic accuracy, facilitating earlier identification and therapeutic assessment (32). Neurofilament light chain (NfL) is also elevated in patients with LM and correlates with disease onset and progression (33). As a marker of neuronal injury, NfL offers prognostic value, particularly for monitoring treatment response and drug resistance.

Cytokines, especially tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are central to LM initiation and progression. Elevated CSF concentrations of TNF-α and IL-6 reflect inflammatory responses and immune dysregulation within the tumor microenvironment (34). These cytokines stimulate tumor cell proliferation and metastasis and may participate in immune evasion. Monitoring CSF cytokine levels facilitates early diagnosis and provides information on immune status, making them useful biomarkers for assessing therapeutic response.

Alterations in non-specific biomarkers such as β-glucuronidase, lactate dehydrogenase (LDH) and β2-microglobulin can also observed in CSF. While their elevation is not specific to LM, they retain value for adjunctive diagnosis and monitoring (35,36). Using multiplex

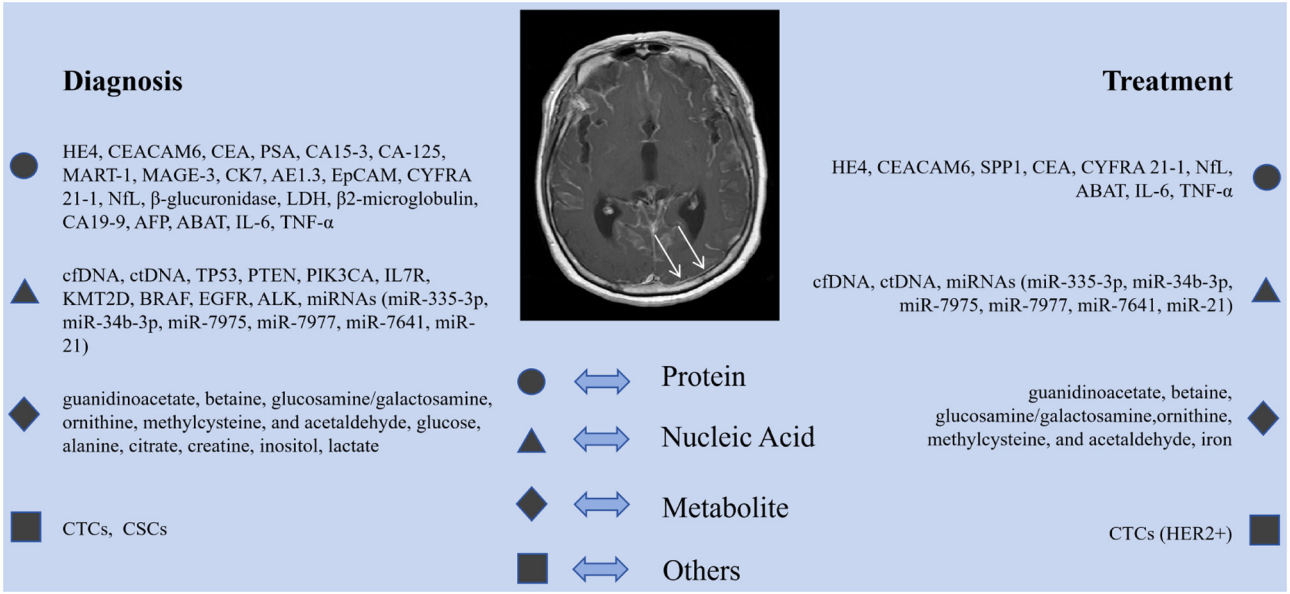

Figure 1. Cerebrospinal fluid biomarkers used for the diagnosis and treatment of LM. Biomarkers are arranged by clinical application (diagnosis vs. treatment monitoring) and by biomarker class (protein, nucleic acid, metabolite and cellular and other markers), as indicated by the symbols. The central panel shows a de-identified representative contrast-enhanced brain MRI of a patient with LM from the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital (Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China). The white arrows indicate leptomeningeal enhancement. LM, leptomeningeal metastasis; HE4, human epididymis protein 4; CEACAM6, carcinoembryonic antigen-related cell adhesion molecule 6; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen; CA-125/15-3/19-9, cancer antigen 125/15-3/19-9; MART1, melanoma antigen recognized by T cells 1; MAGE-3, melanoma-associated antigen 3; CK7, cytokeratin 7; EpCAM, epithelial cell adhesion molecule; NfL, neurofilament light chain; LDH, lactate dehydrogenase; AFP, α-fetoprotein; ABAT, 4-aminobutyrate aminotransferase; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; KMT2D, lysine methyltransferase 2D; ALK, anaplastic lymphoma kinase; miRNA/miR, microRNA; CTCs, circulating tumor cells; CSCs, cancer stem cells; SPP1, secreted phosphoprotein 1 (osteopontin).

immunoassay technology facilitates concurrent detection of these markers, augmenting diagnostic accuracy (37). Profiling CSF proteins via this approach yields broader biological insights and enhances the understanding of LM mechanisms.

Several candidate CSF biomarkers have been proposed for LM, including protein tyrosine phosphatase receptor C, serpin peptidase inhibitor clade C member 1, soluble CD44, soluble CD14, aminopeptidase, SPP1, Fc γ receptor 1A, complement component C9, soluble CD34 and soluble CD19. These biomarkers can be detected via multiplex immunoassay, furnishing information relevant to diagnosis and prognosis (36). Additionally, GABA transaminase (ABAT) has been identified as a key player in the CSF microenvironment. Elevated ABAT expression contributes to neuronal survival and promotes LM (38). ABAT upregulation may be linked to metabolic and epigenetic traits of tumor cells, presenting novel targets for intervention. Identifying these novel biomarkers expands the diagnostic toolkit for CSF analysis.

In summary, CSF protein biomarkers offer crucial biological insights for the management of LM. Concurrent detection of multiple biomarkers can improve diagnostic accuracy and sensitivity. While technological advancements will likely uncover additional biomarkers, it should be noted that most current protein biomarkers are supported by limited studies and require further validation in larger, prospective cohorts before routine clinical application.

Nucleic acid biomarkers. Liquid biopsy technologies focusing on nucleic acid detection have created new avenues for the early diagnosis and therapeutic monitoring of LM. Analysis of cfDNA, particularly its ctDNA fraction, has become a critical tool for tumor surveillance and efficacy evaluation (39,40). Compared with conventional cytology and neuroimaging, CSF-derived ctDNA offers superior sensitivity and specificity, particularly in early diagnosis, detection of resistance mutations and monitoring treatment response. Studies consistently demonstrate that CSF ctDNA outperforms peripheral blood ctDNA in identifying driver mutations in leptomeningeal metastases derived from non-small cell lung cancer (NSCLC), specifically for EGFR and ALK mutations (41,42). In patients with NSCLC-LM, the higher detection rate of driver mutations in CSF ctDNA compared with plasma provides critical molecular data for guiding precision therapy (43).

Exosomal miRNAs in CSF also represent a vital class of biomarkers with diagnostic promise. Specific miRNAs, such as miR-21, miR-483-5p and miR-342-5p, participate in the metastatic cascade by regulating proliferation, migration and drug resistance. Notably, miR-483-5p and miR-342-5p display differential expression patterns between the serum and CSF of patients with NSCLC with and without LM, suggesting their utility as targets for early diagnosis and monitoring (44). Additionally, CSF miR-21 levels are correlated with LM prognosis, particularly regarding drug resistance and therapeutic response (45). Liquid biopsy emphasizing miRNA analysis offers a sensitive, reproducible method for detecting tumor microenvironmental alterations to inform clinical decision-making.

Progress in molecular diagnostics has led to the identification of novel small non-coding RNAs, including PIWI-interacting RNA, Y RNA and small nucleolar RNA,

Table I. Summary of CSF biomarkers for the diagnosis of LM.

Biomarker	Category	Primary tumor type	Detection method	Clinical relevance	Evidence level
CEACAM6	Protein	LUAD	ELISA, immunoassay	Diagnostic marker for LUAD-related LM	Emerging
HE4	Protein	LUAD, breast cancer	ELISA	Improves the diagnostic sensitivity when combined with CEACAM6	Emerging
CEA	Protein	Lung cancer, breast cancer	Immunoassay	Auxiliary diagnostic marker in CSF	Exploratory
CA-125/CA15-3	Protein	Breast cancer	Immunoassay	Supportive diagnostic indicators	Exploratory
MART-1/MAGE-3	Protein	Melanoma	Immunocytochemistry	Tumor-specific markers for melanoma-related LM	Exploratory
SPP1	Protein	Multiple solid tumors	ELISA, proteomics	Associated with LM development and the immune microenvironment	Emerging
CK7/AE1.3	Protein	Cholangiocarcinoma	Immunocytochemistry	Improves diagnostic accuracy when cytology is inconclusive	Exploratory
EpCAM	Protein	Breast cancer	Flow cytometry	High sensitivity for detecting tumor cells in CSF	Emerging
CYFRA 21-1	Protein	Lung cancer	Immunoassay	Enhances diagnostic accuracy combined with cytology	Emerging
cfDNA/ctDNA	Nucleic acid	Lung cancer, breast cancer	PCR, NGS	High sensitivity for LM diagnosis and molecular profiling	Relatively established
Exosomal miRNAs (such as miR-21 and miR-483-5p)	Nucleic acid	NSCLC	Quantitative PCR, NGS	Potential early diagnostic biomarkers	Exploratory
Small non-coding RNAs	Nucleic acid	Multiple tumors	NGS	Emerging molecular diagnostic markers	Exploratory
Metabolite panels	Metabolite	Breast cancer, CNS tumors	GC-MS, LC-MS	Reflect tumor metabolic reprogramming in CSF	Exploratory
Iron ions	Metabolite	Multiple tumors	Biochemical assays	Associated with LM microenvironment alterations	Exploratory
Circulating tumor cells	Cellular	Breast cancer, lung cancer	Flow cytometry, immunostaining	Adjunct diagnostic tool	Emerging
Cancer stem cells	Cellular	Multiple tumors	Flow cytometry	Potential early diagnostic targets	Exploratory

CSF, cerebrospinal fluid; LM, leptomeningeal metastasis; LUAD, lung adenocarcinoma; CEACAM6, carcinoembryonic antigen-related cell adhesion molecule 6; HE4, human epididymis protein 4; CEA, carcinoembryonic antigen; CA-125/15-3, cancer antigen 125/15-3; MART-1, melanoma antigen recognized by T cells 1; MAGE-3, melanoma-associated antigen 3; SPP1, secreted phosphoprotein 1 (osteopontin); CK7, cytokeratin 7; EpCAM, epithelial cell adhesion molecule; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; NGS, next-generation sequencing; miRNA, microRNA; NSCLC, non-small cell lung cancer; GC-MS, gas chromatography-mass spectrometry; LC-MS, liquid chromatography-mass spectrometry.

as potential LM biomarkers (46). Using next-generation sequencing (NGS), researchers have delineated altered miRNA profiles in the CSF of patients with LM, including miR-335-3p and miR-34b-3p (9). These miRNAs, likely originating from CTCs, are linked to LM initiation and offer potential for early diagnosis and targeted therapy. Furthermore, upregulation of specific miRNAs, such as miR-7975, miR-7977 and miR-7641, shows diagnostic utility for monitoring LM (47). Longitudinal monitoring of these miRNA alterations allows clinicians to assess treatment response more precisely.

Beyond miRNAs and ctDNA, chromosomal aneuploidy in CSF is increasingly recognized as a biomarker (48,49). Aneuploidy, defined as an abnormal chromosome number, is associated with tumor malignancy, metastatic potential and prognosis (50). Angus *et al* (48) reported a strong correlation between CSF aneuploidy and both LM risk and overall survival in patients with NSCLC-LM. Detecting aneuploidy supports early diagnosis and aids in predicting treatment outcomes. NGS technology facilitates efficient aneuploidy detection, elucidating tumor genetic signatures to guide clinical management.

In conclusion, various nucleic acid biomarkers in CSF, including cfDNA, ctDNA, exosomal miRNAs and small non-coding RNAs, have shown promise for diagnosing, assessing prognosis and monitoring treatment responses in LM. Among these, ctDNA and cfDNA currently offer the most robust clinical utility, particularly for molecular profiling and resistance mutation detection. Other nucleic acid biomarkers remain investigational and require validation in large-scale studies before routine implementation.

Metabolite-based biomarkers. CSF metabolites are emerging as potential biomarkers for the diagnosis and monitoring of LM. Previous metabolomics studies have identified distinct metabolic profiles in the CSF of patients with LM. These metabolites reflect tumor-specific metabolic alterations and offer insights for early diagnosis and therapeutic strategy formulation. For example, metabolomic analysis of CSF from patients with breast cancer and CNS involvement revealed the upregulation of 20 metabolites in LM cases, including guanidinoacetate, betaine, glucosamine/galactosamine, ornithine, methylcysteine and acetaldehyde (51). These distinct metabolic deviations from normal cellular activity highlight metabolic reprogramming as a key characteristic of tumor survival and proliferation, providing a rationale for novel therapeutic interventions.

Reduced CSF glucose levels are consistently observed in patients with LM, a phenomenon common across diverse CNS malignancies (52-54). Notably, CSF glucose remains subnormal even after intravenous glucose administration (5). This persistent hypoglycemia suggests a hypoxic microenvironment, a hypothesis further supported by elevated CSF LDH levels (35,55). As an intracellular enzyme released upon membrane disruption, LDH facilitates anaerobic glycolysis under hypoxic conditions (56). Collectively, these alterations reflect the metabolic reprogramming inherent to LM and serve as supportive diagnostic evidence.

Further metabolomic analyses indicate that patients with LM exhibit significantly elevated CSF levels of lactate, alanine and citrate, alongside decreased creatine and myo-inositol (57). These profiles reflect tumor cell adaptation to the CSF environment. Specifically, elevated lactate is linked to anaerobic metabolism, while increased alanine and citrate suggest enhanced glycolysis and tricarboxylic acid cycle activity. Conversely, diminished creatine and myo-inositol may indicate altered energy metabolism and cell membrane perturbations (58,59). These metabolic shifts identify potential biomarkers and underscore the complexity of tumor metabolism in LM.

Metabolic alterations also offer new perspectives for immunotherapy. Chi *et al* (60) characterized the CSF microenvironment in LM, demonstrating that tumor cells compete with macrophages for essential trace elements, particularly iron, to gain a survival advantage. Therefore, iron metabolism plays a crucial role in LM progression. Studies show markedly elevated iron concentrations in the CSF of patients with LM compared with controls (60,61). In this iron-rich milieu, cancer cells meet metabolic demands through specific uptake mechanisms, such as the LCN2-SLC22A17 system. This finding has therapeutic implications: Preclinical studies indicate that the iron chelator deferoxamine effectively decreases CSF iron concentration, inhibiting LM growth and extending survival in mouse models (60,62). Thus, targeting iron metabolism represents a promising novel strategy for LM treatment.

In conclusion, CSF metabolite research provides a theoretical framework for improving LM management. Quantitative analysis of CSF metabolites elucidates tumor metabolic signatures and aids in identifying novel biomarkers to enhance diagnostic precision. While metabolomics technologies continue to advance, most current metabolite-based biomarkers remain exploratory and require clinical validation before routine application.

Other potential biomarkers. Beyond proteins, nucleic acids and metabolites, CTCs and cancer stem cells (CSCs) have emerging roles in LM diagnosis and monitoring. CTCs are valuable for early detection, prognosis and treatment response monitoring (63-66). In HER2-positive breast cancer with LM, CTCs serve as biomarkers to track therapeutic efficacy (63,65). Integrating CTC detection with liquid biopsy technologies, such as exosomal miRNA and ctDNA analysis, provides a comprehensive profile that enhances diagnostic sensitivity and specificity (21,67). Crucially, CTCs facilitate the identification of tumor-associated genetic abnormalities, including mutations in TP53, PTEN, PIK3CA, IL7R and KMT2D (68-70). These mutations correlate with LM pathogenesis, providing molecular insights to guide personalized treatment strategies.

CSCs are also implicated in LM initiation and progression. Possessing self-renewal and multipotent differentiation capabilities, CSCs drive tumor recurrence and metastasis. Evidence suggests the presence of CSCs in the CSF of patients with LM, presenting potential targets for early diagnosis and therapeutic intervention (71). Although detection technologies for CSCs remain developmental, their utility in LM is increasingly recognized. Identifying CSCs in CSF could support early diagnosis and inform personalized immunotherapy and targeted therapies. While methodology refinement is required, progress in this field supports the development of innovative diagnostic and therapeutic approaches. However, both CTC

and CSC analyses in CSF currently remain primarily research tools, with clinical application limited by technical challenges and the need for large-scale validation.

3. Application of biomarkers in treatment follow-up monitoring of LM

LM management necessitates a multidisciplinary approach combining systemic and local therapies. Systemic options include cytotoxic chemotherapy, targeted therapy and immunotherapy, selected based on primary tumor efficacy, molecular characteristics, CNS penetration, treatment history and patient factors (5). Intrathecal administration elevates CSF drug concentrations while minimizing systemic toxicity, although it is limited to agents capable of crossing the blood-brain barrier, such as methotrexate, cytarabine and thiotepa (72,73). For specific malignancies such as breast cancer and NSCLC, targeted agents (such as osimertinib) and immune checkpoint inhibitors (such as nivolumab) have shown efficacy (74,75). Radiotherapy, including stereotactic and focal techniques, is employed for symptom relief and CSF flow improvement, although survival benefits remain limited (76). Ultimately, LM treatment requires individualization guided by multidisciplinary evaluation and, where feasible, inclusion in clinical trials. Given the complexity of assessing therapeutic response, CSF biomarkers play a critical role in monitoring efficacy and prognosis. Key biomarkers for this purpose are summarized in Table II.

Evaluation of treatment efficacy. CSF biomarkers are critical for assessing therapeutic response in LM. ctDNA is widely utilized for monitoring tumor burden and efficacy (40,77). A post-treatment decrease in CSF ctDNA levels typically indicates tumor suppression. For example, in patients with NSCLC harboring EGFR mutations, reduced EGFR-mutant ctDNA in CSF following targeted therapy correlates with a positive response (78,79). Similarly, changes in CSF protein markers, such as CEA, reflect treatment outcomes: A decline in CEA levels signals reduced tumor burden (80,81). In breast cancer-associated LM, decreased CSF CEACAM6 levels also indicate therapeutic efficacy (22). Collectively, dynamic monitoring of these biomarkers allows clinicians to gauge treatment success promptly and adjust strategies as needed.

Advances in liquid biopsy enable the use of cfDNA methylation profiles and cell-free CSF cytological scoring (CNB) for efficacy assessment. CSF cfDNA methylation profiles provide molecular insights into disease progression (82,83), while CNB scoring offers an objective, efficient metric for diagnosing and evaluating LM status (84). These minimally invasive techniques facilitate real-time monitoring of therapeutic response. Consequently, CSF-based liquid biopsy, including methylation and CNB analysis, holds significant potential for optimizing therapeutic regimens (85,86).

Extracellular vesicle (EV)-derived miR-21 in CSF offers another novel metric for treatment evaluation. Research suggests that EV-mediated miR-21 modulates methotrexate resistance, particularly in patients with NSCLC-LM, identifying miR-21 as a potential target for overcoming resistance (45). Monitoring alterations in CSF EV miR-21 levels helps inform decisions regarding treatment continuation or modification. Furthermore, variations in EV concentration and miR-21 expression correlate with prognosis and serve as effective biomarkers for monitoring intrathecal chemotherapy response (87). These findings expand the repertoire of biomarkers available for precise patient assessment during LM follow-up.

Prediction of disease progression. Monitoring CSF biomarkers is critical for predicting disease relapse, which remains a risk despite initial clinical remission. Dynamic fluctuations in CSF ctDNA are key indicators of progression. Specifically, sustained low or undetectable post-treatment ctDNA levels suggest remission (88), whereas a resurgence in ctDNA indicates tumor reactivation and elevated relapse risk (89,90). For example, in breast cancer-LM, elevated post-treatment CEACAM6 levels strongly correlate with relapse (22). Detecting these biomarker changes prior to the onset of clinical symptoms provides an early warning system for disease progression.

Alterations in protein biomarkers such as SPP1 and HE4 are also linked to progression. Post-treatment elevations in these proteins frequently signal tumor cell reactivation (27). Specifically, in breast cancer LM, increased HE4 levels serve as a risk indicator for relapse (23). Consequently, longitudinal CSF biomarker monitoring facilitates the early detection of progression, enabling intervention before symptomatic deterioration, thereby potentially improving patient outcomes.

Guiding treatment plan adjustments. CSF biomarker monitoring allows clinicians to adjust treatment regimens based on therapeutic response and disease status. Persistently high or rebounding biomarker levels may necessitate treatment modification. For instance, in patients with EGFR-mutant NSCLC, failure of CSF EGFR-mutant ctDNA to decline during targeted therapy may indicate resistance to first-generation EGFR-tyrosine kinase inhibitors (TKIs). This finding supports transitioning to second- or third-generation EGFR-TKIs or incorporating chemotherapy or immunotherapy (91). This biomarker-guided strategy ensures patients receive optimal therapy.

Additionally, CSF biomarkers aid in assessing treatment tolerance and adverse effects. Abnormally elevated inflammatory markers or cytokines, accompanied by significant clinical toxicity, may suggest an exaggerated immune response or adverse reaction (92-94). In such scenarios, dose adjustment or temporary discontinuation may be required to mitigate side effects. Dynamic monitoring thus facilitates precise treatment customization.

In summary, CSF biomarkers are indispensable for assessing efficacy, predicting relapse and guiding therapeutic adjustments in LM. Integrating comprehensive biomarker monitoring into clinical practice enables precise management, ultimately aiming to improve patient survival and quality of life.

4. Conclusion and outlook

Despite notable progress in CSF biomarker research for LM, critical challenges persist. First, validating biomarkers with higher sensitivity and specificity is essential to enhancing diagnostic precision. Second, standardization of detection methodologies is a requisite to ensure clinical reproducibility.

Table II. CSF biomarkers for treatment monitoring and prognosis in LM.

Biomarker	Application	Dynamic change	Clinical implication	(Refs.)
ctDNA (EGFR and ALK mutations)	Treatment response monitoring	Decrease after effective therapy	Indicates therapeutic response and suppression of tumor burden	(39-41,74,75)
cfDNA methylation profile	Treatment efficacy assessment	Altered methylation patterns	Reflects disease progression and treatment response	(78,79)
CEA	Treatment monitoring	Decline after treatment	Indicates reduced tumor burden	(76,77)
CEACAM6	Prognosis/relapse prediction	Re-elevation post-treatment	Associated with disease recurrence	(20)
HE4	Prognosis	Increase during follow-up	Predicts relapse risk	(21)
SPP1	Disease progression	Elevated levels	Associated with LM progression and immune activation	(24,25)
Neurofilament light chain	Prognosis	Elevated levels	Reflects neuronal injury and disease severity	(31)
EV-associated miR-21	Drug resistance monitoring	Increased expression	Associated with methotrexate resistance	(43)
Cytokines (IL-6 and TNF-α)	Treatment tolerance/inflammation	Elevated levels	Reflect immune activation or adverse effects	(32,88-90)
Aneuploidy in CSF	Prognosis	Persistent chromosomal instability	Predicts poor survival	(46)
CSF cytological scoring	Treatment evaluation	Score reduction	Objective assessment of treatment response	(80)

CSF, cerebrospinal fluid; LM, leptomeningeal metastasis; ALK, anaplastic lymphoma kinase; ctDNA, circulating tumor DNA; cfDNA, cell-free DNA; CEA, carcinoembryonic antigen; CEACAM6, carcinoembryonic antigen-related cell adhesion molecule 6; HE4, human epididymis protein 4; SPP1, secreted phosphoprotein 1 (osteopontin); EV, extracellular vesicle; miR, microRNA; IL-6, interleukin-6; TNF-α, tumor necrosis factor-ss.

Third, further research must elucidate the biological mechanisms linking biomarker expression to LM pathogenesis. Notably, while ctDNA and cfDNA are clinically validated, most other biomarkers remain investigational.

Looking forward, advancements in multi-omics and single-cell sequencing will deepen the understanding of tumor heterogeneity and the CSF microenvironment. These technologies facilitate novel biomarker discovery and clarify tumor-immune interactions, enabling precision diagnosis and treatment stratification. Ultimately, enhanced clinical collaboration and data sharing are imperative for translating these findings into practice and improving patient outcomes.

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Authors' contributions

HC, JW and TX conceived and designed the review and revised the manuscript. HL, WF and FM drafted the manuscript. CF critically revised and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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