Review Article

Pleural fluid biomarkers: a narrative review

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Contributions: (I) Conception and design: C Chan; (II) Administrative support: Both authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: C Chan; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Background and Objective: Pleural fluid is a source from which various biomarkers can be obtained and measured to facilitate the management and prognostication of various conditions. This narrative review aims to summarise a few selected applications of pleural fluid biomarker analysis based on the latest literature.

Methods: A literature search for articles published in English regarding human subjects from the period January 2000 to December 2023 was performed through PubMed. Publications considered by the authors to be relevant were included in this review, with additional references added based on the authors' judgement. This review considered both prospective and retrospective cohort studies analysing the clinical value of a range of pleural fluid biomarkers.

Key Content and Findings: The biomarkers selected in this narrative review have either established clinical applicability or promising initial results which require further research. Pleural fluid adenosine deaminase, mesothelin and N-terminal pro-B-type natriuretic peptide can optimize the diagnosis of tuberculous pleuritis, malignant mesothelioma and heart failure-related pleural effusion respectively. The detection rate for epidermal growth factor receptor mutations for lung cancer is higher in the pleural fluid than in the pleural tissue or plasma. Suitable targeted therapy in patients with detectable mutations can offer survival benefits. The pleural fluid neutrophil-lymphocyte ratio, soluble urokinase plasminogen activator receptor and plasminogen activator inhibitor 1 carry prognostic implications and can potentially guide subsequent treatment decisions. These biomarkers used individually, or in conjunction with other clinical parameters, should only be utilised in pre-defined, appropriate clinical conditions to maximize their clinical value.

Conclusions: A great variety of different biomarkers are available for analysis in pleural fluid. Further research and development are necessary to widen the spectrum and enhance the clinical utility of pleural fluid biomarkers. Comparison with the diagnostic utilities of serum biomarkers and other investigation parameters, such as radiological findings, could be considered when evaluating the performance of pleural fluid biomarkers.

Keywords: Pleural effusion; biomarkers; malignant pleural effusion (MPE); pleural infection; heart failure; tuberculous pleuritis

Submitted Mar 21, 2024. Accepted for publication Jun 14, 2024. Published online Jul 18, 2024.
doi: 10.21037/jtd-24-467
View this article at: https://dx.doi.org/10.21037/jtd-24-467

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Introduction

A biomarker is defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention" (1). Common examples of biomarkers in blood include C-reactive protein (CRP), cardiac troponins, and carcinoembryonic antigen (CEA) (2-4). Similarly, different biomarkers in pleural fluid have been explored with varying degrees of clinical significance and applicability.

Rationale and knowledge gap

The analysis of biomarkers is widely employed in various fields of clinical medicine, and pleural fluid represents a valuable source from which a range of biomarkers can be found. Whilst there has been previous literature reviewing the application of pleural fluid biomarkers, much of the focus of discussion was regarding the diagnostic capabilities of tumour markers in suspected malignant pleural effusion (MPE) (5). However, the prognostic capabilities of pleural fluid biomarkers should also not be overlooked.

Objective

This article aims to review the diagnostic and prognostic capabilities of pleural fluid biomarkers in a range of malignant, infectious and cardiovascular conditions, and highlight possible areas in which the analysis of such biomarkers may bridge current unmet needs in clinical practice. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-467/rc).

Methods

This review summarises currently available literature regarding the clinical applications of biomarkers found in the pleural effusions of patients with a range of conditions encompassing malignant, infectious, and cardiovascular causes, and provides an overview of clinical conditions in which the analysis of pleural fluid biomarkers may be helpful. A systematic online literature search via PubMed database was conducted for the period from January 2000 to December 2023 for English-language articles published using the keywords "pleural fluid", "biomarkers" with "malignancy", "malignant pleural effusion" or "tuberculosis", "tuberculous pleurisy", "tuberculous pleural effusion" or "pleural infection", "parapneumonic effusion", "empyema" or "heart failure". The search strategy is summarised in *Table 1*.

MPE

MPE is a common affliction affecting up to 15% of patients with cancer. It is more commonly seen in patients afflicted with cancers of the lung, breast, gynaecological system, lymphoma, and malignant mesothelioma (6). Pleural fluid biomarkers can provide important information to facilitate the diagnostic process, guide treatment decisions and gauge prognoses. In contrast, the diagnostic yield of pleural tissue can sometimes be jeopardised by inadequate tissue, limiting options for molecular testing for targetable mutations.

Epidermal growth factor receptor (EGFR) mutation

EGFR mutations in advanced non-small cell lung cancer (NSCLC) are clinically significant, as tyrosine kinase inhibitors (TKIs) targeting these mutations can offer survival benefits (7). In patients with MPE, pleural fluid samples are often more easily obtained than tissue samples or biopsies of the primary tumour. In up to 80% of cases, pleural fluid and small tissue biopsies may be the only specimens available for pathological diagnosis (7).

Pleural fluid can provide more clinical information than pleural tissue. In a review of 5,504 EGFR testing results on pathology specimens at a tertiary referral centre in Hong Kong, the rates of detection and cellular adequacy were higher in pleural fluid (59.3% and 81.5% respectively) than sputum, bronchial cytology and fine-needle aspiration specimens, and the detection rate of EGFR in pleural fluid also surpassed that of pleural biopsy (59.8% *vs.* 50.7%) (8). This may be due to the nature of sporadic pleural involvement in pleural metastases, and inadequacy of tumour tissue on pleural biopsies, but nevertheless reflects the utility of testing for EGFR mutations in pleural fluid specimens.

The advancement of liquid biopsy also complements tumour genotyping for detecting EGFR variants in NSCLC. There was high concordance between pleural fluid cell-free DNA (cfDNA) and tissue captured by tumour biopsy or pleural fluid cell block samples in detecting EGFR-variant and acquired EGFR T790M mutation in EGFR-TKI naïve, and EGFR-TKI treated but osimertinib-naïve patients with NSCLC respectively. The pleural

Table 1 The search strategy summary

Item	Specification
Date of search	1 February, 2024
Database	PubMed
Search terms	"Pleural fluid" AND "biomarkers" AND ("malignancy" OR "malignant pleural effusion")
	"Pleural fluid" AND "biomarkers" AND ("pleural infection" OR "parapneumonic effusion" OR "empyema")
	"Pleural fluid" AND "biomarkers" AND ("tuberculosis" OR "tuberculous pleurisy" OR "tuberculous pleural effusion")
	"Pleural fluid" AND "biomarkers" AND "heart failure"
Timeframe	From January 2000 to December 2023
Inclusion and exclusion criteria	Inclusion criteria: human-based studies with full paper available, English language
	Exclusion criteria: animal-based studies
Selection process	The selection process was conducted by C.C. and K.K.P.C. individually. Duplicate results were removed. Additional articles not seen in the initial search results were included after consensus was reached by discussion. Review of the final list of references was done by both authors

fluid cfDNA was more sensitive than plasma in detecting sensitising EGFR variants (97% *vs.* 74%) in TKI-naïve patients. More EGFR T790M mutations were detected in pleural fluid cfDNA than in guideline-recommended pleural fluid cell block preparations (51% *vs.* 25%) (9).

The results from these studies suggest that pleural fluid is an invaluable source of material to be used for EGFR testing. Pleural fluid obtained from patients with suspected or confirmed lung cancer should be considered for EGFR testing, via cell block analysis and cfDNA, to derive earlier benefit from treatment with TKIs (5).

Malignant mesothelioma

Mesothelin is a biomarker found in serum as well as in pleural fluid which has received Food and Drug Administration approval for clinical use in diagnosis of mesothelioma. It has been found to have greater sensitivity in diagnosing malignant mesothelioma when measured in pleural fluid as opposed to serum, with sensitivities of up to 79% compared to 61% respectively. Specificities are similar, with pooled estimates ranging from 85% to 87% (10). An optimal cutoff value of 3.0 nmol/L was suggested by Ashour *et al.* which yielded a sensitivity of 73% and specificity of 82% (11). The specificity of mesothelin testing could be limited by other conditions associated with mesothelin expression, such as pancreatic and ovarian cancers (10). Given the low sensitivity (around 30%) of pleural fluid cytology in diagnosing mesothelioma (5), it may be reasonable to test for pleural fluid mesothelin in addition to biopsy in the diagnostic workup of patients with suspected mesothelioma in prevalent regions to maximize the diagnostic yield. Patients who have significantly elevated mesothelin levels in pleural fluid may be indicated for more extensive workup, including thoracic imaging and thoracoscopy, even in the absence of negative pleural fluid cytology. The turnaround time of such testing, which has not been widely reported in current literature, may be an important factor to consider when evaluating its potential for more widespread use.

Pleural fluid neutrophil-lymphocyte ratio (NLR)

Predicting the prognosis in patients with MPE is crucial. NLR in blood is a recognised biomarker index associated with inflammation and immune response. Similarly, a high pleural fluid NLR was found to be an independent predictor of mortality in MPE (12). Popowicz *et al.* investigated the prognostic values of serum and pleural fluid NLR in patients with MPE. They confirmed that pleural fluid NLR was an independent predictor of survival, with a level of >0.745 associated with a shorter median survival of 130 days compared to 312 days for patients with pleural fluid NLR <0.745 (13). The NLR in blood was also predictive of poorer survival in MPE patients but it only had moderate correlation with the pleural fluid NLR (13). Further analysis revealed that patients with a greater proportion of pleural fluid neutrophils in the total white cell count (>4.74%) had

Table 2 LENT score (12)

Variables	Score
LDH in pleural fluid (IU/L)	
<1,500	0
≥1,500	1
ECOG performance status	
0	0
1	1
2	2
3–4	3
Pleural fluid neutrophil-lymphocyte ratio	
<9	0
≥9	1
Tumour type	
Mesothelioma, haematological malignancies	0
Breast cancer, gynaecological cancers, renal cell carcinoma	1
Lung cancer and other tumours	2

LENT, pleural fluid LDH, ECOG performance status, neutrophil/lymphocyte ratio in pleural fluid, tumour type; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

Table 3 LENT score interpretation

Risk categories	Score
Low risk	0–1
Moderate risk	2–4
High risk	5–7

LENT, pleural fluid LDH, ECOG performance status, neutrophil/lymphocyte ratio in pleural fluid, tumour type; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

a poorer median survival of 216 days compared to 552 days for patients in the low neutrophil group. On the contrary, the proportion of pleural fluid lymphocytes was not associated with mortality (13).

The LENT score is a composite clinical assessment tool composed of pleural fluid lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status (PS), neutrophil-lymphocyte ratio in pleural fluid, and primary tumour type to estimate survival in patients with MPE based on risk stratification (*Tables 2,3*). All four components are independently predictive of survival (12). The LENT score was superior in predicting survival compared with ECOG PS at 1, 3 and 6 months. Although other prognostic scores have been developed that some also include previous treatment status (PROMISE score) and tumour genotype [SELECT (SEX, ECOG PS, Leukocyte count, EGFR mutation, Chemotherapy, primary Tumour type) and EGFR-LENT scores], the LENT score has an advantage of easy calculation as pleural fluid white cell differential count and LDH are routinely ordered in clinical practice (14). It is therefore a useful prognostic tool to inform prognosis and guide treatment aggressiveness. Specific prognostic scores with local applicability should be considered in suitable clinical contexts.

Parapneumonic effusions

Parapneumonic effusions are common among patients presenting with chest infection (15). Patients with pleural infection often require additional intervention to ensure early clearance of loculated pleural effusion and sepsis control, including repeated pleural drainage, intrapleural fibrinolytics and surgery (16). The availability of biomarkers to stratify patients based on severity of parapneumonic effusions would, therefore, potentially allow clinicians to formulate appropriate management at an earlier stage. Newer biomarkers currently under research that have yet to be adopted into widespread clinical use include soluble urokinase plasminogen activator receptor (suPAR) and plasminogen activator inhibitor 1 (PAI1) (17,18).

suPAR

suPAR is an activator receptor of urokinase which accelerates the conversion of plasminogen into plasmin once bound, promoting fibrinolysis. Its level is elevated in pleural fluid with pleural infection, compared with MPE or transudative effusions (17). At a cutoff of 35 ng/mL, pleural fluid suPAR had a 100% sensitivity and 91% specificity in predicting the presence of pleural fluid loculations, and was superior to conventional markers, including pleural fluid pH <7.2, glucose ≤3 mmol/L or LDH ≥1,000 IU/L, in predicting the need for rescue therapies such as intrapleural fibrinolytics or surgery [area under receiver operating characteristic curve (AUROC) of 0.92 with cutoff 65 ng/mL *vs.* AUROC of 0.76 for pleural fluid meeting any of the above biochemical criteria of pH, glucose or LDH] (19). It is also predictive of developing pleural fluid loculations in

early stage of parapneumonic effusion when septation has not yet developed.

PAI1

PAI1 is a naturally occurring inhibitor of plasminogen, which has a physiological role in fibrinolysis. Pleural injury is characterized by fibrin accumulation and suppression of fibrinolysis, at least in part due to the presence of PAI1 in the pleural fluid, which leads to the formation of pleural loculations or septations. Bedawi *et al.* analyzed 166 patients from the PILOT study and found that increasing levels of PAI1 in pleural fluid were associated with an increasing degree of septations. Semiquantitative septation severity scores determined through ultrasonography were compared against the concentration of various pleural fluid proteins. PAI1 concentrations in pleural fluid could independently discriminate between patients with septated (median 1,104.1, 1,464.9, and 1,573.7 ng/mL in mild, moderate, and severely septated effusions respectively) and nonseptated effusions (median 725.2 ng/mL) (18). Moreover, higher levels of PAI1 were also associated with a longer length of stay (18).

Whilst testing for suPAR and PAI1 is not yet part of routine clinical practice, these biomarkers are promising for their ability to estimate the risk of developing loculated pleural effusion, need for more intensive treatment and earlier intrapleural fibrinolysis. Further prospective, multicenter studies are needed to determine the clinical applicability of these findings to a wider population.

Tuberculous pleuritis

Infection by *Mycobacterium tuberculosis* (MTB) was one of the leading infectious diseases with high mortality in 2022, second only to coronavirus disease 2019 (COVID-19) (20). Tuberculous pleuritis is the most prevalent common form of extrapulmonary tuberculosis in two large-scale retrospective studies in China (21,22).

Diagnosis of tuberculous pleuritis is often limited by the long turnaround time (4 to 6 weeks for solid culture media and 2 weeks for liquid culture media) and low sensitivity of pleural fluid MTB culture (varying from 7% to 63%) (23). MTB polymerase chain reaction (PCR) techniques may represent a complementary means of diagnosis, yet studies have shown that the sensitivity of PCR testing by commercially available GeneXpert MTB/RIF (rifampicin resistance) is still only around 50% when compared against pleural fluid MTB culture, or only 18.4% when compared against a clinical composite as the gold standard (23,24). Even with the latest version, Xpert Ultra, the diagnostic sensitivity is still suboptimal at 44.2% amongst cases of probable tuberculous pleurisy and 83.6% amongst patients with MTB culture positive tuberculous pleuritis (25).

Differences in the quoted sensitivities of the above diagnostic tests could partly be related to the use of a composite of clinical parameters to define probable tuberculous pleurisy, including granulomatous inflammation on pleural biopsy (while negative MTB culture), lymphocyte predominant exudative effusion, or clinical response to anti-tuberculous treatment in the absence of other likely aetiologies (23,25). Regardless of which reference is used as the gold standard, it remains clear that there is room for improvement in the diagnostic capabilities for tuberculous pleurisy of these tests. Pleural fluid biomarkers that may facilitate earlier and more effective diagnosis include adenosine deaminase (ADA) and unstimulated interferon-gamma (IFN-gamma). Nevertheless, the inability to evaluate anti-TB drug sensitivity by pleural fluid biomarkers is a major drawback in regions with high incidence of drug resistant tuberculosis, where early initiation of suitable anti-TB treatment remains critical in-patient treatment and infection control.

ADA

ADA is an enzyme predominantly produced by T-lymphocytes and is elevated in the pleural fluid of patients afflicted by tuberculous pleuritis, but may also be increased in patients with pleural infection, malignancy or autoimmune pleuritis (26). Variable cut-off levels have been reported, although commonly a level of ≥40 U/L with lymphocytic exudative pleural effusion in areas with high TB burden is sufficient to initiate empirical anti-TB treatment, provided that alternative diagnoses have been adequately excluded (27). Its reported sensitivities and specificities vary; a meta-analysis pooling 44 publications estimated that the sensitivity and specificity for ADA at a cutoff level of ≥40 U/L for diagnosing tuberculous pleurisy were 0.88 [95% confidence interval (CI): 0.85–0.91] and 0.91 (95% CI: 0.89–0.92) respectively (28,29), yet more recently published data suggest that specificities may be lower, in the range of 0.58 to 0.78 amongst paediatric and adult populations respectively (30,31).

Unstimulated IFN-gamma

IFN-gamma is a cytokine involved in the activation of

macrophages in tuberculous pleuritis (5). It shows slightly higher sensitivity and specificity than ADA in diagnosing tuberculous pleuritis in a meta-analysis, at 93–95% and 96% respectively (5,32). It is important to note that unstimulated IFN-gamma differs from interferon gamma release assay, which has poor diagnostic capabilities for tuberculous pleuritis (33). Limitations and barriers to the use of unstimulated IFN-gamma include the lack of widely accepted cut-offs for interpretation, as well as high costs of testing (5). Given the relatively lower cost of ADA and comparable sensitivity and specificity (5), ADA is more commonly adopted in a public healthcare system owing to cost constraints.

Heart failure

The classification of new-onset pleural effusion into effusions of transudative or exudative nature is fundamental in formulating subsequent investigation and management plan (7). This is typically done using Light's criteria, and less commonly serum-pleural effusion protein gradient (SPPG) or serum-pleural effusion albumin gradient (SPAG). However, Light's criteria and SPPG may also fail to correctly identify transudative effusions in some cases, especially after the use of diuretics (34). Pleural fluid N-terminal pro-B-type natriuretic peptide (NT-proBNP) and SPAG have both shown improved ability to classify effusions previously mislabelled as exudates by Light's criteria or SPPG, with some studies even suggesting that pleural fluid NT-proBNP could have greater diagnostic accuracy (35). The use of pleural fluid NT-proBNP could therefore represent newer diagnostic methods which could be employed to reduce the chances of misdiagnosis and subsequent unnecessary investigations (35). The latest British Thoracic Society (BTS) Guideline suggested a sensitivity of 93% and specificity of 93% could be achieved by using pleural fluid NT-proBNP levels to diagnose unilateral pleural effusion due to heart failure in a combined analysis of five studies (28,34,36-38).

Barriers against the routine implementation of testing for pleural fluid NT-proBNP include the relative invasiveness of obtaining a pleural fluid sample, and a high degree of correlation between pleural and serum NT-proBNP reported in current literature (35). As such, although the BTS guidelines acknowledge the utility of pleural fluid NT-proBNP, its routine use is not as of yet recommended by current guidelines as serum NT-proBNP is thought to be at least equally efficacious.

There are some limitations with the current available literature and guidelines. Firstly, there is a lack of data from Chinese patients, and scarce data on patients of Asian descent. Moreover, many studies had stringent exclusion criteria, or focused only on specific subgroups of patients, such as those with heart failure with reduced ejection fraction (34). Lastly, the pleural fluid NT-proBNP level has not previously been correlated with the advanced classification of heart failure with preserved and reduced ejection fraction. As such, these unmet needs limit the global applicability of recommendations on interpreting pleural fluid NT-proBNP level outside the studied regions.

Conclusions

A variety of pleural fluid biomarkers have been validated to aid the diagnosis and treatment decisions for different types of pleural effusion. Many more pleural fluid biomarkers exist, some of which currently only have academic applications due to inconclusive results or have economic barriers to their widespread implementation due to costs of testing. There are many more opportunities for research into this aspect of pleural medicine, which remains a treasure trove of untapped potential. Nevertheless, it is important to remember that the analysis of pleural biomarkers is only one aspect of pleural medicine. An armamentarium of tools including radiological imaging, medical thoracoscopy, video-assisted thoracoscopic surgery, and pleural biopsies are available, and a carefully selected combination of any of the above modalities of diagnostic and therapeutic techniques can be utilised to great effectiveness in the management of different pleural conditions.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-467/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-467/prf

Conflicts of Interest: Both authors have completed the ICMJE

uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-467/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Chan C, Chan KKP. Pleural fluid biomarkers: a narrative review. J Thorac Dis 2024;16(7):4764-4771. doi: 10.21037/jtd-24-467