Review

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Pleural fluid biochemical analysis: the past, present and future

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Abstract: Identifying the cause of pleural effusion is challenging for pulmonologists. Imaging, biopsy, microbiology and biochemical analyses are routinely used for diagnosing pleural effusion. Among these diagnostic tools, biochemical analyses are promising because they have the advantages of low cost, minimal invasiveness, observer independence and short turn-around time. Here, we reviewed the past, present and future of pleural fluid biochemical analysis. We reviewed the history of Light's criteria and its modifications and the current status of biomarkers for heart failure, malignant pleural effusion, tuberculosis pleural effusion and parapneumonic pleural effusion. In addition, we anticipate the future of pleural fluid biochemical analysis, including the utility of machine learning, molecular diagnosis and high-throughput technologies. *Clinical Chemistry and Laboratory Medicine* (*CCLM*) should address the topic of pleural fluid biochemical analysis in the future to promote specific knowledge in the laboratory professional community.

Keywords: biochemical analysis; biomarker; diagnosis; pleural effusion.

Introduction

Pleural effusion is a common sign that is associated with various disorders. It can cause symptoms such as cough, dyspnea and chest pain. Because these symptoms are not specific to a given disease, the differential diagnosis of pleural effusion is challenging for clinicians. The causes of pleural effusion vary across different countries and regions. Pneumonia, cancer, tuberculosis and heart failure (HF) are four frequent causes of pleural effusion [1, 2]. The first step in pleural effusion management is identifying its cause. Currently, several diagnostic tools are available for differentiating pleural effusion, including pleural fluid cytology, Ziehl–Neelsen staining and bacterial culture, biochemical analyses and biopsy. However, these tools have limitations. For example, pleural fluid cytology has high specificity for malignant pleural effusion (MPE), but its sensitivity is only 46% [3]. Pleural fluid culture is the gold standard for parapneumonic pleural effusion (PPE) but has low sensitivity and a long turn-around time. Pleural biopsy guided by imaging (e.g., CT or ultrasound) or thoracoscopy has a high diagnostic yield for pleural effusion. Nevertheless, it is an invasive tool, and operation-related complications are problematic [4]. In addition, special training and equipment are needed for biopsy, limiting its application in remote areas.

Pleural fluid biochemical analyses are promising diagnostic tools for pleural effusion because they have the advantages of low cost, short turn-around time, and objectivity. Some review articles have been published to summarize the diagnostic and prognostic value of pleural fluid biomarkers for specific etiologies, such as MPE [5–7], PPE [8], tuberculosis pleural effusion (TPE) [9, 10] and HF [11], including two reviews from our team [5, 10]. However, reviews on the history, current status and future of pleural fluid biochemical analyses are rare. Here, we performed a review to summarize the history of pleural fluid biochemical analyses. We also reviewed the current status and anticipated the future of pleural fluid biochemical analysis.

The past

Pleural effusion can be categorized into exudate and transudate based on the cause and underlying pathophysiology. Transudates arise from increased hydrostatic pressure or decreased oncotic pressure [12]. In a few cases, it can also be caused by the passage of ascitic fluid from the peritoneal cavity to the pleural surface via

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transdiaphragmatic lymphatics (hepatic hydrothorax) or low pressure in the pleural cavity (atelectasis) [13]. In contrast, exudates develop due to inflammation in the pleural cavity. Inflammation can be caused by metastatic pleural tumors or infectious pathogens (e.g., *Mycobacterium tuberculosis* (*Mtb*) *and Streptococcus pneumoniae*) [12]. Inflammation increases capillary permeability and allows serum proteins to enter the pleural cavity. The management of a transudate requires clinicians to treat the underlying condition with specific therapies (e.g., diuretics), and further investigations are unnecessary. In contrast, additional examinations and even invasive procedures are needed to elucidate the etiology of an exudate [14]. Therefore, identification of the exudative or transudative nature of the pleural fluid is the initial step in the diagnostic work-up of pleural effusion [15]. Notably, the appearance of pleural fluid does not help differentiate pleural effusion and thus should not be overemphasized [16]. Biochemical analyses of pleural fluid are of great value for differentiating between exudates and transudates.

History of Light's criteria

The earliest studies revealed that pleural fluid protein [17, 18], lactate dehydrogenase (LDH) [18], and the pleural fluid to serum LDH ratio were useful markers for differentiating exudates and transudates. These findings promote the proposition of Light's criteria in 1972 [19]. According to Light's criteria, pleural effusion should be categorized as an exudate if it meets one or more of the following items: (i) A pleural fluid to serum protein ratio >0.5; (ii) A pleural fluid to serum LDH >0.6; (iii) A pleural fluid LDH activity >2/3 the upper limit of serum LDH's reference interval. The original aim of Light's criteria was to maximize the identification of exudates; thus, the items are combined in a parallel "or" rule. Light's criteria have high diagnostic sensitivity (99%) and specificity (98%) for an exudate [19]. However, subsequent studies did not obtain such a high diagnostic accuracy [20–22]. All these studies revealed that the sensitivity of Light's criteria is near 100%, but its specificity is approximately 70% [23]. Light's criteria are more accurate than clinical judgment for differentiating pleural transudates and exudates (84% vs. 93%) [24]. Notably, more than 50% of the misclassified transudates only met one item of Light's criteria, and the values of LDH and protein were near the established threshold [25]. In patients who meet both a pleural fluid-to-serum total protein ratio >0.5 and LDH >2/3 of its reference interval, the presence of an exudate effusion is conclusive [26]. Inadequate specificity is partially caused by diuretics [27, 28]. Under such conditions, an albumin gradient >12 g/L or a protein gradient >31 g/L is recommended [12, 25, 28]. Pleural fluid N-terminal pro-brain natriuretic peptide (NT-proBNP) >1,500 pg/mL is also an alternative tool with high accuracy in misclassified cardiac effusions [29–32]. Notably, the sensitivity of an albumin gradient >12 g/L for identifying an exudate is only 67% [12], indicating that 33% of the exudates will be misidentified as transudates. Therefore, the albumin gradient should be used only in patients with marginal exudative effusions with suspected HF [12].

Modified Light's criteria

In addition to LDH and protein in pleural fluid and serum, some biomarkers have been proposed as alternative diagnostic tools, such as cholesterol [33], NT-proBNP [34], C-reactive protein (CRP) [35], bilirubin [36], cholinesterase [37], albumin and protein gradients [24]. Among the reported markers, cholesterol is the most widely investigated. A meta-analysis revealed that it has a sensitivity of 88% and specificity of 96% [33], which is comparable to those of pleural fluid LDH, the serum-to-pleural fluid LDH ratio and the pleural fluid-to-serum protein ratio [38]. Therefore, adding cholesterol is a potential modification of Light's criteria.

Table 1 lists some of the modifications for Light's criteria. Some modifications were made by adjusting the threshold of protein, LDH or their ratios [39, 40], while others introduced pleural fluid cholesterol into their criteria [41, 42]. Notably, pleural fluid LDH is highly correlated with the serum-to-pleural fluid LDH ratio [38], so it is reasonable to hypothesize that one of them can be moved from Light's criteria. Two simplified Light's criteria, which contain only pleural fluid cholesterol and LDH, have been proposed [41, 42]. These criteria have comparable, but not superior, diagnostic accuracy with Light's criteria. Nevertheless, it should be noted that Light's criteria are near perfect for discriminating between transudates and exudates. Although clinical diagnosis is the gold standard for defining transudates and exudates, it has a small but definite error rate. Although superior diagnostic criteria were theoretically possible, at least 13,000 subjects are needed to prove the superiority of any newly proposed criteria over Light's criteria [43].

Perspective from laboratory medicine

Light's criteria are undoubtedly the milestone in pleural fluid biochemical analyses. From the perspective of

Table 1: Light's criteria and its modifications.

Light's criteria and its modifications	Criteria	Sensitivity	Specificity
Light's criteria [19]	Pleural fluid to serum protein ratio >0.5; Pleural fluid to serum LDH ratio >0.6; Pleural fluid LDH >2/3 the upper limit of normal serum LDH	98%	70%
Modifications			
Romero's criteria [39]	Pleural fluid to serum protein ratio >0.6; Pleural fluid to serum LDH ratio >0.9; Pleural fluid LDH >280 IU/L	94%	93%
Costa's criteria [41]	Pleural fluid LDH >200 IU/L; Pleural fluid cholesterol >1.16 mmol/L	99%	98%
Lepine's criteria [42]	Pleural fluid LDH >0.6 the upper limit of normal serum LDH; Pleural fluid cholesterol >1.04 mmol/L	98%	71%
Vives' criteria [40]	Pleural fluid to serum protein ratio >0.5; Pleural fluid to serum LDH ratio >0.9; Pleural fluid LDH >380 IU/L	96%	81%

LDH, lactate dehydrogenase.

laboratory medicine, some issues should be strengthened. First, analytical platforms for LDH and protein analyses can affect the accuracy of Light's criteria, and there is a 10% discrepancy among different platforms [44]. The discrepancy increases to 18% in patients with a pleural fluid protein level between 25 and 35 g/L [45]. Second, preanalytical errors should be considered [46]. Pleural fluid protein and LDH are stable at room temperature for 6 h [47], but the long-term stability of LDH and protein remains unknown. Third, in Light's work, the time interval between serum and pleural fluid specimen collection was within 30 min [19]. However, it has been reported that the time interval between serum and pleural fluid specimen collection did not significantly affect the accuracy of Light's criteria [48]. Fourth, pleural erythrocyte count positively correlates with LDH activity, and the specificity of Light's criteria decreased in patients with high pleural erythrocyte count [49, 50]. It is widely accepted that hemolysis can increase serum LDH [51]. Therefore, it seems that increased LDH in pleural fluid specimens with high erythrocyte counts is associated with hemolysis. Indeed, a high prevalence of hemolysis can be observed in pleural fluid specimens [52]. A formula proposed to correct LDH can increase the specificity of Light's criteria [49]. Fifth, although the biochemical analyzers used to measure pleural fluid LDH and protein have only validated their assays for serum or plasma, the recovery rates of LDH and protein are near 100%, indicating that there is no "matrix effect" for pleural fluid LDH and protein [53–55]. In addition, the intra-assay and interassay precisions of pleural fluid LDH and protein are comparable to their serum partners [54].

The present

The proposition of Light's criteria is a landmark work in differentiating pleural effusion; however, additional procedures are needed to define the etiology of pleural effusion. As mentioned above, tuberculosis, HF, malignancy, and pneumonia are four primary causes of pleural effusion, accounting for 75% of pleural effusion [1, 2]. Many studies investigating the diagnostic role of pleural fluid biochemical analyses focus on these four causes. Here, we summarize the current status of pleural fluid biochemical analyses in these four disorders.

Biochemical analyses for HF

HF is the primary cause of transudates, accounting for 85% of the transudates [1, 2]. Nevertheless, Light's criteria have low diagnostic accuracy for HF [56]. Currently, circulating brain natriuretic peptide (BNP) and NT-proBNP are two guideline-endorsed diagnostic biomarkers for HF [57]. In patients with pleural effusion, both BNP and NT-proBNP, either in the blood or pleural fluid, have high diagnostic accuracy for HF-induced pleural effusion, also termed cardiac effusion [58]. Evidence from systematic reviews and meta-analyses indicates that pleural fluid NT-proBNP has high diagnostic accuracy for HF in patients with undiagnosed pleural effusion, with both a sensitivity and a specificity higher than 90% [59–61]. The diagnostic accuracy of pleural fluid BNP is slightly inferior to that of NT-proBNP, with a sensitivity of 92% and a specificity of 88% [59]. The recommended threshold of pleural fluid

NT-proBNP for HF is 1,500 ng/L [62]. Notably, blood NT-proBNP is highly correlated with pleural fluid NT-proBNP, with a coefficient >0.95 [63]. Therefore, both blood and pleural fluid NT-proBNP are useful diagnostic biomarkers for HF in undiagnosed pleural effusion, and their diagnostic accuracy is comparable. Because thoracocentesis can be avoided, blood NT-proBNP is more suitable than pleural fluid in patients who cannot tolerate thoracocentesis. The diagnostic accuracy of pleural fluid NT-proBNP is affected by age and estimated glomerular filtration rate (eGFR). A higher threshold should be adopted in patients with old age or decreased eGFR [29]. The specificity of pleural fluid NT-proBNP for HF decreases because septic shock and acute kidney injury can elevate pleural fluid NT-proBNP. These two disorders are common in critical care settings [64]. In cases when NT-proBNP is unavailable, a simple scoring system based on albumin gradient, age, pleural fluid LDH, bilateral effusion on CXR and protein gradient can assist clinicians in accurately identifying HF [65].

Serum mid-regional pro-atrial natriuretic peptide (MR-proANP) is a promising diagnostic marker for HF in patients admitted to the emergency department with dyspnea [66, 67]. Pleural fluid MR-proANP is also increased in pleural effusion patients with HF [29]. Its diagnostic accuracy is comparable to that of pleural fluid NT-proBNP [29]. The coefficient between MR-proANP and NT-proBNP is 0.79, indicating that combinational use of MR-proANP and NT-proBNP cannot improve the diagnostic yield for HF [29]. The diagnostic accuracy of serum MR-proANP for HF patients with pleural effusion remains unknown.

Two studies revealed that serum soluble CD146 (sCD146) is a promising diagnostic marker for HF [68, 69]. Unlike NT-proBNP and MR-proANP, which are released by ventricular or atrial cardiomyocytes in response to stress, sCD146 is primarily released by vascular endothelial cells [68]. The diagnostic accuracy of blood sCD146 and NT-proBNP is comparable [69]. It remains unknown whether pleural fluid sCD146 is a promising diagnostic marker for HF. In addition, some other biomarkers have been proposed as diagnostic markers for HF in undiagnosed pleural effusion patients, such as ischemia-modified albumin [70, 71]. However, further studies are needed to validate the findings of the initial studies.

Biochemical analyses for MPE

Diagnosing MPE is a challenge for pulmonologists and laboratory clinicians. Numerous studies have investigated the diagnostic accuracy of serum or pleural fluid tumor markers for MPE, including neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 19-9 (CA19-9), and a fragment of cytokeratin 19 (CYFRA 21-1) [5]. Evidence from meta-analyses indicates that the specificities of these tumor markers are >90%, but their sensitivities are only approximately 50% [72–74]. Notably, in diagnostic test accuracy studies, the sensitivity and specificity are threshold-dependent [75, 76], and the thresholds of tumor markers used in previous studies vary. Theoretically, higher sensitivity can be obtained by decreasing the threshold of the tumor marker, but the high sensitivity is at the expense of a lower specificity. To date, there is no uniform threshold used for pleural fluid tumor markers. However, an extremely high tumor marker value has 100% specificity for MPE. For example, CEA (>45 ng/mL) or CA 15-3 (>77 UI/l) can be used to confirm MPE because of their 100% specificities [56, 77].

Combinations of these tumor markers can slightly increase the diagnostic sensitivity, especially the combinations of CEA+CYFRA 21-1 and CA15-3+CYFRA 21-1 [6]. A nomogram is a novel method to investigate the combination of these tumor markers and other biochemical analyses (e.g., erythrocyte sedimentation rate, LDH, ADA). Two previous studies have constructed nomograms to investigate the diagnostic accuracy of multiple tumor markers, and the AUCs of the nomograms in the studies were >0.90 [78, 79].

Serum tumor markers also increased in MPE patients, but their diagnostic accuracy was inferior to that of their pleural fluid partners [80–83]. The pleural fluid to serum ratios of tumor markers have been proposed to increase the diagnostic accuracy of MPE. Nevertheless, these ratios do not significantly increase the diagnostic accuracy of MPE [80–85]. With rigorous statistical methods such as net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [86], we found that the CEA ratio did not provide added diagnostic value over pleural fluid CEA (our unpublished data). In addition to the pleural fluid to serum ratio, the tumor marker gradient has also been investigated in several studies. Nevertheless, their gradients do not show superior diagnostic accuracy over pleural fluid tumor markers [83]. Therefore, the current evidence does not support determining serum and pleural fluid tumor markers simultaneously when pleural fluid tumor markers are available.

In addition to conventional tumor markers, some novel markers have been reported to be promising in diagnosing MPE, such as endostatin [87], vascular endothelial growth factor (VEGF) [88, 89], apolipoprotein

E (Apo-E) [90], tumor-associated macrophages (TAMs) in pleural fluid [91], cancer ratio [92, 93] and cancer ratio plus [94, 95]. TAM ($CD14^+CD206^+$, $CD14^+CD163^+$) has exceptionally high diagnostic accuracy among these markers. However, TAM is determined by flow cytometry, which lacks standardization and thus limits its clinical implications. The cancer ratio is defined as the ratio of serum LDH to pleural fluid ADA and has high diagnostic accuracy for MPE (97% sensitivity and 89% specificity), as indicated by meta-analyses [92, 96]. The strength of the cancer ratio is low cost, easy to obtain, and well-standardized. However, our recent study indicated that the diagnostic accuracy of the cancer ratio decreased with age (unpublished data).

Biochemical analyses for TPE

TPE is one of the most common extrapulmonary tuberculosis forms in adults [97]. The diagnosis of TPE is often challenging because the gold standards (e.g., Ziehl–Neelsen staining, pleural fluid *Mtb* culture, and biopsy) are time-consuming, invasive and have low sensitivity [98]. The diagnostic value of many pleural fluid biomarkers for TPE has been investigated [10]. Among the investigated biomarkers, adenosine deaminase (ADA) [99], interferon-gamma (IFN-γ) [100], and interleukin 27 (IL-27) [101] are the most promising.

ADA is an enzyme produced by many types of lymphocytes and is involved in the metabolism of purines. It has consistently demonstrated high accuracy for TPE since it was first reported in 1978 [102]. Evidence from meta-analyses indicates that pleural fluid ADA has a sensitivity range between 86 and 93%, and the specificity varies between 88 and 93% [99, 103–105]. The ADA threshold used in most published studies ranges between 35 U/L and 60 U/L [99, 103]. Some meta-analyses from specific countries (e.g., Spain [106], Brazil [107] and India [108]) showed that the diagnostic accuracy of ADA is similar across different regions. Notably, in areas with low tuberculosis prevalence, pleural fluid ADA ≥15 U/L has a sensitivity of 100% and a negative predictive value (NPV) of 100% [109]. Extremely high pleural fluid ADA (>100 IU/L) is frequently observed in patients with empyema or lymphoma rather than TPE [110]. The pleural fluid ADA level is negatively correlated with age [111, 112]. However, findings from studies with age stratification designs are not always consistent [111, 113, 114], and further studies are needed to address the effect of age on the diagnostic accuracy of ADA. In addition, pleural fluid ADA has no diagnostic value in pediatrics [115].

IFN-γ is a cytokine produced by activated $CD4^+$ T helper cells in the pleural compartment and can increase the mycobactericidal activity of macrophages [116]. Many studies have investigated the diagnostic value of pleural fluid IFN-γ for TPE since the first report, which was published in 1988 [117]. Three meta-analyses summarized the diagnostic accuracy of pleural fluid IFN-γ for TPE [100, 104, 118]. All these meta-analyses indicated that the sensitivity and specificity of IFN-γ were >90%. Similar to ADA, the diagnostic accuracy of IFN-γ is also affected by age [113, 114].

The diagnostic value of pleural fluid IL-27 was first reported by Shi et al. in 2012 [119]. To date, four meta-analyses have reported the diagnostic value of pleural fluid IL-27 for TPE [101, 120–122]. The most recent and comprehensive study, which included eleven studies with 1,454 patients in the analysis, showed that pleural fluid IL-27 had a sensitivity of 95% and specificity of 91% [101]. These results indicate that IL-27 has extremely high diagnostic accuracy for TPE. Although IL-27, IFN-γ and ADA have comparable and extremely high diagnostic accuracy for TPE, ADA is preferred because of its low cost. In addition, the ADA assay is well standardized, and the results from different laboratories are comparable. In contrast, IL-27 and IFN-γ were measured by enzyme-linked immunosorbent assays (ELISAs), which are expensive and lack standardization [123].

Notably, interferon-gamma release assays (IGRAs) have been proposed as a potential diagnostic tool for TPE. There are two types of IGRAs, named T-SPOT. TB (Oxford Immunotec) and QuantiFERON-TB Gold (QIAGEN). In both IGRAs, antigens from *Mtb* were used to stimulate lymphocytes from the patient's blood or pleural fluid. IFN-γ in the culture media was determined by ELISA or enzyme-linked immunospot (ELISPOT) assay. The diagnostic accuracy of IGRAs for TPE is insufficient, as indicated by meta-analyses [124–126]. According to the most recently published meta-analysis, the sensitivity and specificity of IGRA are 88 and 79%, respectively [126], which are obviously lower than those of ADA, IFN-γ and IL-27. In addition to its low diagnostic accuracy, other disadvantages, including high cost, long turn-around time, and labor consumption, limit its utility in diagnosing TPE.

Other biomarkers have been proposed as potential diagnostic markers for TPE, such as interleukin 32 (IL-32) [127], C1q [128], C-X-C motif chemokine receptor 3 (CXCR3)

ligands (e.g., CXCL9, CXCL10, CXCL11) [129, 130] and soluble interleukin-2 receptor (sIL-2R) [131]. The initial studies revealed that the diagnostic accuracy of these biomarkers is promising; however, further studies are needed to validate the findings reported in these studies. In addition, nucleic acid amplification tests (NAATs) are also promising diagnostic tools for TPE. Its specificity is close to 100%, but its sensitivity is only approximately 30% [132].

Biochemical analyses for PPE

PPE is a common complication associated with pneumonia [133]. Approximately 18% of community-acquired pneumonia (CAP) patients will develop PPE during their disease courses [134]. The in-hospital mortality rate of PPE is approximately 10% [134, 135]. There are three types of or progression phases of PPE: uncomplicated parapneumonic effusion (UPPE), complicated parapneumonic effusion (CPPE) and empyema [136, 137]. In UPPE, the pleural cavity is free of infection, and approximate antibiotic treatment can cure it [136]. In CPPE and empyema, pathogens translocate from the lung to the pleural cavity, and drainage or surgery is needed because antibiotics alone are insufficient [136]. Empyema is characterized by the presence of frank pus in the pleural cavity. Typically, CPPE is described as high LDH activity (>1000 U/L), decreased pleural fluid glucose (<2.2 mmol/L), low pleural fluid pH (<7.2) and positive pleural fluid bacterial culture [136]. The diagnosis and stratification of PPE are two major roles of biochemical analysis in PPE.

Pleural fluid pH is the most accurate indicator of CPPE, as indicated by a meta-analysis [138]. It is also endorsed by the guidelines released by the British Society of Chest Physicians [62], the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) [139]. Pleural fluid pH should be measured by blood gas analyzer rather than pH meter or indicator strip [140, 141]. There is no need to measure pH in purulent samples because it has the potential to damage the blood gas analyzer [141, 142]. Several factors can affect the value of pleural fluid pH, including the presence of air and residual lidocaine or heparin in the collection syringe [143]. Notably, pleural fluid pH is unstable after collection. Pleural fluid specimens stored at room temperature should be analyzed within an hour after collection [143, 144]. When stored in slushed ice, samples should be analyzed within 2 h and 15 min [144].

As shown in studies since 1988, serum and pleural fluid C-reactive protein (CRP) have potential diagnostic value for PPE [145–147]. However, the evidence from a meta-analysis published in 2012 revealed that the pooled sensitivity and specificity of serum CRP were 54% and 77%, respectively [148]. A recently published meta-analysis showed that the sensitivity and specificity were 77% and 71%, respectively [149]. These results suggest that serum CRP is not a good diagnostic marker for PPE. The diagnostic accuracy of pleural fluid CRP seems to be higher than that of serum CRP (80% sensitivity and 82% specificity) [149]. In addition, pleural fluid CRP has moderate accuracy for discriminating UPPE from CPPE [150, 151]. A recent meta-analysis showed that the pooled sensitivity and specificity of pleural fluid CRP for distinguishing uncomplicated from complicated PPE were 65% and 85%, respectively [149]. Serum CRP can also distinguish UPPE from CPPE, but its performance varies across available studies [150, 152, 153].

Procalcitonin (PCT) is the precursor of calcitonin, which is mainly synthesized by thyroid C cells [154]. During the development of infectious disease, pathogens and inflammatory factors can induce the expression of PCT in thyroid C cells and other cells, which results in high blood PCT [155]. Therefore, blood PCT is a promising diagnostic marker for bacterial infectious diseases, such as sepsis and pneumonia [156, 157]. PPE is caused by pneumonia, and blood PCT theoretically has diagnostic value for PPE. The diagnostic value of blood PCT for PPE has been investigated by many studies [158–160]. The pooled sensitivity and specificity of blood PCT for PPE were 78% and 74%, respectively [161], indicating the unsatisfactory diagnostic value of PCT for PPE. Pleural fluid PCT has also been proposed as a diagnostic marker for PPE, but its pooled sensitivity and specificity are only 62% and 71%, respectively, as revealed by meta-analysis [161]. Therefore, the diagnostic value of pleural fluid PCT is inferior to that of serum PCT. This conclusion is also supported by findings from head-to-head comparison studies [159, 160, 162]. Blood PCT is positively correlated with pleural fluid PCT [160], suggesting that pleural fluid PCT is derived from blood PCT, and pleural fluid PCT does not provide additional diagnostic value beyond serum PCT. The diagnostic accuracy of serum and pleural fluid PCT does not outperform CRP, as indicated by a head-to-head comparison study [159]. Some studies showed that pleural fluid and serum PCT levels in UPPE, CPPE and empyema were similar [146, 163], indicating that PCT cannot be used for PPE stratification.

Other parameters, including soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) [164], IL-6 [165, 166], IL-8 [151], presepsin [167], lipopolysaccharide-binding protein (LBP) [146], serum amyloid A (SAA)

[168], pentraxin-3 (PTX3) [169], and soluble urokinase plasminogen activator receptor (suPAR) [170], are potential biomarkers for PPE diagnosis or stratification. Among those biomarkers, sTREM-1 in the pleural fluid has moderate diagnostic accuracy for PPE. The pooled sensitivity and specificity of pleural fluid sTREM-1 were 78% and 84%, respectively [164]. However, no evidence suggests that pleural fluid sTREM-1 is beneficial for the stratification of PPE. In addition, whether serum sTREM-1 contributes to the diagnosis and stratification of PPE is unknown.

The future

Machine learning

Machine learning is a subset of artificial intelligence. It enables the computer to have intelligence by creating algorithms with large and complex data [171]. Machine learning has shown promising value in clinical diagnostics [172]. The clinical utility of machine learning in patients with undiagnosed pleural effusion has been investigated in some studies, such as treatment selection [173] and imaging [174]. Using machine learning algorithms with conventional biomarkers and other clinical characteristics (e.g., imaging, symptoms, signs, history, demography) can significantly improve the diagnostic accuracy of biomarkers in undiagnosed pleural effusion patients [175–178]. For example, in a study that investigated the diagnostic markers for TPE, the clinical characteristics of patients were incorporated into machine learning algorithms, including a logistic regression model, support vector machine (SVM), random forest (RF), and k-nearest neighbor (KNN). The AUC of the RF was 0.97, which is significantly higher than that of pleural fluid ADA (0.89) [175].

Molecular diagnosis

Currently, most pleural fluid biomarkers are protein, enzyme or cancer antigens. Recently, the diagnostic accuracy of cell-free nucleic acids in undiagnosed pleural effusion patients has attracted much attention [179]. Serum or pleural fluid cell-free microRNAs, mRNAs, and long noncoding RNAs (lncRNAs) are the primary cell-free nucleic acids investigated. By using microarray or sequencing, several molecular markers have been identified [180, 181]. Some pilot studies with small sample sizes have revealed that these molecular markers represent promising diagnostic markers for pleural effusion [182, 183]. Further studies are needed to validate their diagnostic accuracy.

High-throughput technologies

As mentioned above, a single biomarker is insufficient for differentiating the causes of pleural effusion. Therefore, high-throughput technologies are promising. First, high-throughput technologies generate significant opportunities for identifying novel biomarkers for differentiating pleural effusion. Second, high-throughput data can be incorporated into mathematical models, which yields good diagnostic accuracy for a given disease. Genomics, transcriptomics, proteomics, and metabolomics are the most popular high-throughput technologies. These technologies can generate massive data in a short period of time with a small volume of the specimen. The primary studies indicated that these technologies have high diagnostic accuracy in differencing pleural effusion. Here, we introduced several examples.

By comparing the protein profile of CPPE and UPPE with isobaric tags for relative and absolute quantification

Table 2: Diagnostic accuracy of biomarkers in undiagnosed pleural effusion: evidence from meta-analyses.

Biomarker	Disease	Sensitivity, %	Specificity, %	Reference
Pleural fluid NT-proBNP	HF	94–95	91–94	[59–61]
Blood NT-proBNP	HF	92	88	[59]
ADA	TPE	65–94	89–92	[99, 105, 106, 108, 126, 188]
Interferon-γ	TPE	89–93	96–97	[118, 188, 189]
Interleukin-27	TPE	92–94	90–92	[120, 122]
IGRA, pleural fluid	TPE	72–90	78–87	[124–126, 190]
IGRA, blood	TPE	77–80	71–72	[124, 125]
CEA	MPE	46–55	94–97	[72, 73, 191]
CA15-3	MPE	51–58	93–98	[72, 192, 193]
CA 19-9	MPE	25–38	96–98	[72, 192]
NSE	MPE	53–61	85–88	[72, 74]
CA 125	MPE	48–58	85–93	[72, 192]
CYFRA 21-1	MPE	47–63	92–93	[72, 191, 192]
Cancer ratio	MPE	91–97	67–89	[92, 96]
Pleural fluid CRP	PPE	80	82	[149]
Blood CRP	PPE	54–77	71–77	[148, 149]
Pleural fluid procalcitonin	PPE	62–67	70–71	[148, 161]
Blood procalcitonin	PPE	65–78	68–74	[148, 161]

reagents (iTRAQ)-based mass spectrometry analysis, four useful biomarkers (bactericidal permeability-increasing protein, neutrophil gelatinase-associated lipocalin, azurocidin and calprotectin) for differentiating CPPE and UPPE were identified. These biomarkers are promising for differentiating between UPPE and CPPE, with AUCs >0.90 when used alone [184]. With high-resolution nuclear magnetic resonance (NMR) spectrometry, lipoprotein was highly accurate for distinguishing exudates from transudates, with an AUC of 0.96 [185]. In addition, label-free surface-enhanced Raman spectroscopy (SERS) has also been suggested to be a promising diagnostic tool for MPE, with an AUC of 0.99 [186]. Next-generation sequencing (NGS) analysis can identify pathogens more accurately than pleural fluid culture and thus serves as a valuable tool that could facilitate the treatment of PPE with antibiotics [187].

Conclusions

To date, numerous diagnostic markers have been investigated. Table 2 summarizes the evidence from systematic reviews and meta-analyses. Generally, pleural fluid NT-proBNP and ADA have high diagnostic accuracy for HF and TPE, respectively. These two biomarkers have been endorsed by the guidelines released by the British Thoracic Society [62]. However, the diagnostic markers for PPE and MPE are far from perfect. Therefore, novel biomarkers and analytical methods are needed to improve the diagnostic yield of undiagnosed pleural effusion. *Clinical Chemistry and Laboratory Medicine* (*CCLM*) should address the topic of pleural fluid biochemical analysis in the future to promote specific knowledge in the laboratory professional community.

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