Original Article

Pleural pro-gastrin releasing peptide is a potential diagnostic marker for malignant pleural effusion induced by small-cell lung cancer

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Background: Serum pro-gastrin releasing peptide (proGRP) is a well-recognized diagnostic marker for small cell lung cancer (SCLC). Pleural effusion is common in patients with advanced SCLC. The diagnostic accuracy of pleural proGRP for malignant pleural effusion (MPE) has not yet been established. This study aimed to evaluate the diagnostic accuracy of pleural proGRP for MPE.

Methods: We prospectively recruited patients with undiagnosed pleural effusions from two centers (Hohhot and Changshu). An electrochemiluminescence immunoassay was used to detect pleural fluid proGRP. The diagnostic accuracy of proGRP for MPE was evaluated using a receiver operating characteristic (ROC) curve.

Results: In both the Hohhot (n=153) and Changshu (n=58) cohorts, pleural proGRP in MPE patients did not significantly differ from that in patients with benign pleural effusions (BPEs) (Hohhot, P=0.91; Changshu, P=0.12). In the Hohhot and Changshu cohorts, the areas under the curves (AUCs) of proGRP were 0.51 [95% confidence interval (CI): 0.41–0.60] and 0.62 (95% CI: 0.47–0.77), respectively. However, patients with SCLC-induced MPE had significantly higher proGRP levels than those with BPE and other types of MPE (P=0.001 for both). In the pooled cohort, the AUC of proGRP for SCLC-induced MPE was 0.90 (95% CI: 0.78–1.00, P=0.001). At a threshold of 40 pg/mL, proGRP had a sensitivity of 1.00 (95% CI: 0.61–1.00) and specificity of 0.59 (95% CI: 0.52–0.66). The positive likelihood ratio was 2.61 (95% CI: 1.99–3.41), and the negative likelihood ratio was 0.

Conclusions: Pleural proGRP has no diagnostic value for MPE, but has high diagnostic accuracy for SCLC-induced MPE. In patients with proGRP levels <40 pg/mL, MPE secondary to SCLC can be excluded.

Keywords: Diagnostic accuracy; malignant pleural effusion (MPE); pro-gastrin releasing peptide (proGRP); small cell lung cancer (SCLC)

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Introduction

Pleural effusion (PE) can result from a range of pathological conditions (1-3). PEs are classically categorized into malignant pleural effusion (MPE) and benign pleural effusion (BPE), and the former accounts for approximately 20–30% of cases (2,3). The most common cause of MPE is lung cancer, followed by breast cancer and lymphoma (3,4). MPE is an indicator of advanced cancer with a median survival of 3–12 months (5). Therefore, the suspicion of MPE must be confirmed, as misdiagnosis can cause heavy psychological and economic burden on patients.

The gold standards for MPE are effusion cytology, image-guided pleural biopsy or thoracoscopy (1,6-8). The specificity of effusion cytology is 100%, but its sensitivity is only around 50% (9,10). Image-guided pleural biopsy and thoracoscopy have high diagnostic yields, but they are invasive and operation-related complications are problematic (11-13). In addition, thoracoscopy requires special equipment and training, which limits its use in remote areas. Therefore, less invasive and objective tools are attractive for diagnosing MPE. Tumor markers in pleural fluid may represent alternative diagnostic methods for MPE, particularly for deciding whether subsequent invasive procedures are required to confirm malignancy. Compared to effusion cytology, biopsy or thoracoscopy, tumor markers have the advantages of minimal invasiveness, objectiveness, and low cost (14,15).

Pro-gastrin releasing peptide (proGRP) is a well-recognized tumor marker that is highly expressed in embryonic and placental tissues, but rarely expressed in healthy adult tissues (16). Serum proGRP is a useful diagnostic marker for small cell lung cancer (SCLC), with a sensitivity of 0.72 and specificity of 0.92 (17). Given that serum proGRP exhibits moderate diagnostic accuracy for SCLC, and SCLC is a contributing factor to MPE (18), we speculated that pleural proGRP could serve as an additional diagnostic marker for MPE. This study aimed to investigate the diagnostic accuracy of pleural fluid proGRP for MPE. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-278/rc) (19,20).

Highlight box

Key findings

- Pleural pro-gastrin releasing peptide (proGRP) level does not significantly differ between malignant and benign pleural effusions. However, patients with small cell lung cancer (SCLC) had significantly higher proGRP levels than those with other types of malignant pleural effusion (MPE). The area under the curve of proGRP for SCLC-induced MPE was 0.90, indicating a high diagnostic accuracy.

What is known and what is new?

- Serum proGRP is a well-recognized diagnostic marker for lung cancer, and lung cancer accounts for approximately half of MPE. It is reasonable to hypothesize that proGRP in pleural fluid helps the diagnosis of MPE.
- We evaluated the diagnostic accuracy of pleural fluid proGRP for MPE and found that it has limited diagnostic utility for MPE. However, it helps the diagnosis of SCLC.

What is the implication, and what should change now?

- High pleural fluid proGRP is indicative of MPE. Patients with proGRP level >40 pg/mL had a high probability of SCLC-associated MPE.

Methods

Participants

The participants were recruited from the SIMPLE (No. ChiCTR1800017449), a pre-registered, double-blind, prospective diagnostic test accuracy study (21,22). We prospectively recruited patients who visited the Affiliated Hospital of Inner Mongolia Medical University (September 2018 to July 2021; Hohhot cohort) and Affiliated Changshu Hospital of Nantong University (June 2020 to July 2021; Changshu cohort). The inclusion criteria for both the Hohhot and Changshu cohorts were as follows: (I) patients with PE of unknown etiology and (II) patients who underwent thoracocentesis. PE was confirmed

using ultrasonography, chest radiography, or computed tomography (CT). The exclusion criteria were as follows: (I) patients with PE of known etiology during the past three months; (II) patients aged <18 years, (III) pregnant, (IV) patients with insufficient pleural fluid specimens for research aims, (V) patients who developed PE during hospitalization, and (VI) PE caused by trauma or surgery.

This study was approved by the Ethics Committees of the Affiliated Hospital of Inner Mongolia Medical University (No. 2018011) and Affiliated Changshu Hospital of Nantong University (No. KY2021014). All the participants provided written informed consent. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013).

Diagnostic criteria

After admission, the participants underwent microbiological cultures, thoracoscopy, pleural biopsy, effusion cytology, and serum and pleural fluid biochemistries, as appropriate. These investigations were ordered by the attending physicians based on the clinical pictures of the patients. The diagnostic criteria for MPE were positive effusion cytology, pleural biopsy, or the presence of a primary tumor and the exclusion of other causes. The diagnostic criteria for tuberculous pleural effusion (TPE) were positive pleural fluid *Mycobacterium tuberculosis* culture, acid-fast staining, pleural biopsy, and response to anti-tuberculosis treatment. The diagnostic criteria for parapneumonic pleural effusion (PPE) were positive pleural fluid bacterial culture, pleural biopsy, imaging characteristics (loculation), or response to antibiotic treatment. The diagnostic criteria for PE caused by heart failure (HF) were the presence of a transudate, biochemical tests (e.g., elevated serum natriuretic peptides), imaging features, and response to diuretic treatment. Patients with PE caused by non-malignant diseases (e.g., TPE, PPE, and HF) were categorized as having BPE. In both cohorts, pleural proGRP was masked to the clinicians who made the diagnosis.

ProGRP and pleural biochemistry

After enrollment, a pleural fluid specimen was obtained and placed in an anticoagulant-free tube for each patient. After centrifugation, the supernatant was obtained, aliquoted, and stored at −80 to −70 ℃ until analysis. Pleural proGRP was measured by electrochemiluminescence immunoassay using a Roche E602 analyzer. The limits of blank (LOB), limit of detection (LoD), and limit of quantification (LoQ) were 2, 3, and 7 pg/mL (≤30% total error), respectively, as claimed by the manufacturer. The coefficient of variance (CV) of proGRP was 2.16% at 100.30 pg/mL in our laboratory. The technicians who conducted the proGRP testing were not provided with any clinical details. In addition, we collected clinicopathological data from participants' medical records. The extracted clinicopathological data included pleural glucose, adenosine deaminase (ADA), white blood cells (WBCs), lactate dehydrogenase (LDH), and total protein concentration. LDH, ADA, total protein, and glucose levels were measured using Beckman AU5831 (Brea, CA, USA; Hohhot cohort) and Siemens ADVIA 2400 (Berlin, Germany; Changshu cohort) analyzers.

Statistical analysis

We used median and interquartile intervals (IQR) to describe continuous variables and the Kolmogorov-Smirnov test to determine their distribution. For normally distributed data, an independent Student's *t*-test and one-way ANOVA were used for comparison. Otherwise, the Mann-Whitney *U* test or Kruskal-Wallis *H* test was performed. The Chi-square test was used to compare categorical variables. A receiver operating characteristic (ROC) curve was used to analyze the diagnostic accuracy of ProGRP, and the overall diagnostic accuracy was measured by the area under the ROC curve (AUC). All statistical analyses were performed using SPSS (version 26), R (version 4.0.5) and GraphPad Prism (version 9.4.1). Statistical significance was set at $P<0.05$.

Results

Characteristics of the participants

A total of 153 participants were enrolled in the Hohhot center (66 MPEs and 87 BPEs), and 58 participants were enrolled (26 MPEs and 32 BPEs) in the Changshu cohort. *Table 1* presents the characteristics of the participants.

Pleural ProGRP in MPE and BPE

Figure 1 shows the pleural proGRP levels in MPE and BPE. The median (IQR) proGRP levels in patients with MPE and BPE were 38 pg/mL (30–50 pg/mL) and 39 pg/mL (27–52 pg/mL), respectively, in the Hohhot cohort (P=0.91). In the Changshu cohort, the median (IQR)

Table 1 Characteristics of the participants

Variables	Hohhot cohort (n=153)			Changshu cohort (n=58)		
	MPE (n=66)	BPE (n=87)	P	MPE (n=26)	BPE (n=32)	P
Age (years)	72 [65–78]	72 [64–80]	0.75	76 [72–81]	69 [47–76]	<0.01
Male	41 [62]	60 [69]	0.48	14 [54]	20 [63]	0.70
WBC (10^6/mL)	942 [625–1,472]	737 [340–2,005]	0.21	909 [722–1,709]	1,781 [705–3,834]	0.17
LDH (U/L)	231 [176–447]	171 [94–385]	0.004	344 [243–539]	316 [188–644]	0.98
ADA (U/L)	8 [6–12]	10 [4–25]	0.38	12 [9–16]	26 [15–54]	<0.01
Glucose (mmol/L)	5.6 [4.4–6.6]	5.7 [4.7–7.0]	0.47	6.4 [5.8–8.0]	5.8 [4.7–7.0]	0.051
Protein (g/L)	37 [31–43]	30 [17–41]	<0.01	42 [38–46]	46 [36–50]	0.13
Type of MPE						
Lung cancer	55			21		
SCLC	5			1		
NSCLC	50			20		
Mesothelioma	5			1		
Others	6			4		

Continuous data with skewed distribution were expressed as median [interquartile range]. Categorical data were expressed as n [%] or n. MPE, malignant pleural effusion; BPE, benign pleural effusion; WBC, white blood cell; LDH, lactate dehydrogenase; ADA, adenosine deaminase; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

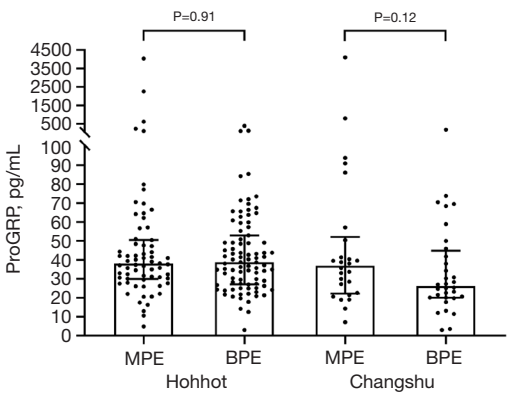

Figure 1 Comparison of pleural proGRP levels between MPE and BPE. ProGRP, pro-gastrin releasing peptide; MPE, malignant pleural effusion; BPE, benign pleural effusion.

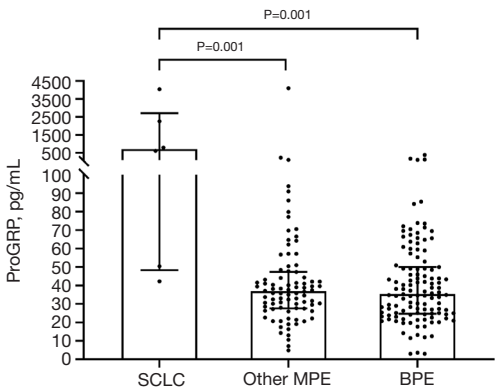

Figure 2 Pleural proGRP in patients with various types of pleural effusion. ProGRP, pro-gastrin releasing peptide; SCLC, small cell lung cancer; MPE, malignant pleural effusion; BPE, benign pleural effusion.

proGRP levels in the MPE and BPE groups were 37 pg/mL (24–48 pg/mL) and 26 pg/mL (20–43 pg/mL), respectively (P=0.12).

Next, we analyzed whether pleural proGRP levels were elevated in MPE secondary to SCLC. Since there was only one SCLC in the Changshu cohort, the two cohorts were combined as a pool. *Figure 2* shows the proGRP levels in the different types of PE. Patients with SCLC-induced MPE had significantly higher proGRP levels than those

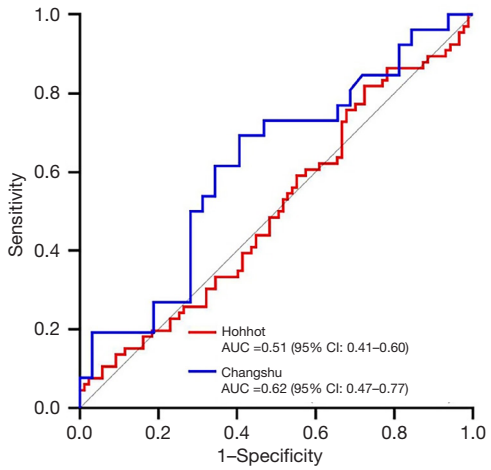

Figure 3 Receiver operating characteristic curve of proGRP for malignant pleural effusion. AUC, area under the curve; CI, confidence interval; proGRP, pro-gastrin releasing peptide.

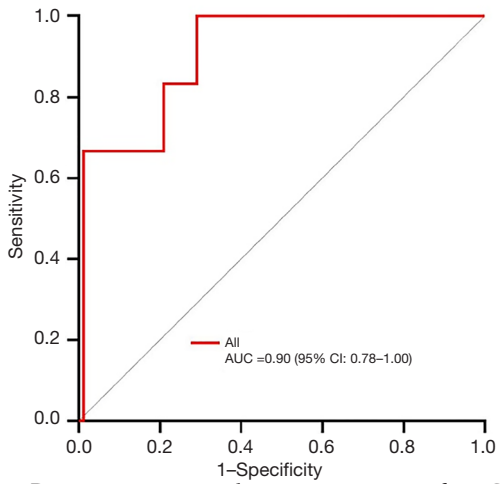

Figure 4 Receiver operating characteristic curve of proGRP for SCLC-induced malignant pleural effusion. AUC, area under the curve; proGRP, pro-gastrin releasing peptide; SCLC, small cell lung cancer; CI, confidence interval.

with other types of MPE, as well as BPE (P=0.001 for both).

Diagnostic accuracy of proGRP

Figure 3 shows the ROC curves of proGRP for MPE in both cohorts. The areas under the ROC curves (AUCs) of proGRP in the Hohhot and Changshu cohorts were 0.51 [95% confidence interval (CI): 0.41–0.60, P=0.91] and 0.62 (95% CI: 0.47–0.77, P=0.12), respectively.

Figure 4 shows the ROC curve of proGRP in SCLC. In the pooled cohort, the AUC of proGRP for SCLC-induced MPE was 0.90 (95% CI: 0.78–1.00). At a threshold of 40 pg/mL, the sensitivity and specificity were 1.00 (95% CI: 0.61–1.00; 6/6) and 0.59 (95% CI: 0.52–0.66, 121/205), respectively. The positive likelihood ratio was 2.61 (95% CI: 1.99–3.41) and the negative likelihood ratio was 0.

Discussion

In this study, we evaluated the diagnostic accuracy of pleural proGRP for MPE in two independent cohorts. We found that pleural proGRP levels in MPE and BPE patients were not significantly different, suggesting that proGRP has limited diagnostic value for MPE-BPE differentiation. Indeed, ROC curve analysis revealed that the AUC of proGRP was near 0.5, indicating that proGRP has limited discriminatory ability to differentiate between MPE and BPE. Considering that proGRP has a high specificity for SCLC, we tested whether proGRP can assist in the diagnosis of SCLC-induced MPE. We found that SCLC patients had significantly higher proGRP than those with other types of MPE, as well as BPE (P=0.001 for both). The AUC of proGRP for SCLC-induced MPE was 0.90. Taken together, these results indicate that pleural proGRP is not a useful diagnostic marker for MPE, but has a high diagnostic value for excluding SCLC-induced MPE.

To date, only one study has analyzed the diagnostic accuracy of pleural proGRP for MPE in patients with undiagnosed PE (23). This study found that patients with SCLC-induced MPE had significantly higher proGRP levels than those with other types of MPE and pleural infections, but the levels of proGRP in lung adenocarcinoma and squamous cell carcinoma were similar to those in patients with pleural infection. However, the diagnostic accuracy of proGRP for SCLC-induced MPE was not analyzed. Compared to the previous study, our study has some strengths. First, we analyzed the diagnostic accuracy of proGRP using an ROC curve and found that the diagnostic value of proGRP for MPE was limited. Second, we found that proGRP had high diagnostic accuracy for SCLC-induced MPE, as indicated by the AUC. At a threshold of 40 pg/mL, the sensitivity and specificity were 1.00 (95% CI: 0.61–1.00) and 0.59 (95% CI: 0.52–0.66), respectively. In addition, proGRP had a positive likelihood ratio of 2.61 (95% CI: 1.99–3.41) and a negative likelihood ratio of 0. These results indicate that SCLC can be excluded in patients with proGRP levels <40 pg/mL.

Our results showed that proGRP has limited value in differentiating between MPE and BPE. A possible reason for this is that proGRP is secreted and released mainly by SCLC cells and is rarely secreted and released by other types of cancer cells. Therefore, serum proGRP is a relatively specific diagnostic marker for SCLC and does not increase in other types of lung cancer (24). A large-scale study (n=11,206) showed that serum proGRP levels for SCLC were significantly higher than those for non-SCLC (NSCLC), and serum proGRP levels in NSCLC patients were similar to those of benign diseases (25). In PE induced by SCLC, proGRP in the pleural fluid may be derived from SCLC cells in pleural metastasis. Therefore, it is reasonable to conclude that proGRP is a relatively specific diagnostic marker for MPE in SCLC.

Our study had some limitations. First, although the total sample size of our study was relatively large, only six SCLC patients were enrolled. This is because SCLC occurs at a frequency of approximately 10% in MPE (3). Second, we measured proGRP in frozen stored pleural fluid specimens; however, the long-term stability of proGRP in pleural fluid remains unknown.

Conclusions

In conclusion, our study shows that pleural proGRP has low diagnostic accuracy for MPE but high diagnostic accuracy for SCLC-induced MPE. SCLC can be effectively ruled out in patients with proGRP levels <40 pg/mL. Despite this, it is essential to recognize that any tumor marker assessed in the pleural fluid serves only as a potential indicator of the malignant nature of effusion, but does not preclude the need to demonstrate this possibility through cytohistological means. Nevertheless, in an infrequent situation in which a patient with a lung tumor with an associated PE is in a life-threatening condition and a definitive etiology has not yet been established, the detection of a pleural fluid proGRP level of <40 pg/mL would support the administration of empirical systemic oncologic therapy targeting NSCLC rather than SCLC.

Given the relatively small sample size of this study, our findings need to be validated in future studies with large sample sizes.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-278/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-278/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-278/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-278/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. This study was approved by the Ethics Committees of the Affiliated Hospital of Inner Mongolia Medical University (No. 2018011) and Affiliated Changshu Hospital of Nantong University (No. KY2021014). All the participants provided written informed consent. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013).

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