

Diagnostic Performance of the Cancer Ratio in Malignant Pleural Effusion in Combination with the Light's Criteria

Desempenho Diagnóstico do Rácio de Cancro no Derrame Pleural Maligno em Combinação com os Critérios de Light

Maria João CAVACO ^{✉1}, Sofia FONTÃO ALVES ¹, Catarina SILVA ¹, Sofia PIMENTEL ¹, Luís MATEUS ¹, Carina RÔLO SILVESTRE ¹, Joana FERRA ¹, Daniel DUARTE ¹, Carla CARDOSO ¹, Paula RAIMUNDO ¹, Teresa FALCÃO ¹
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ABSTRACT

The cancer ratio (CR), defined as serum lactate dehydrogenase to pleural fluid adenosine deaminase ratio (sLDH/pADA), has emerged as a diagnostic marker for malignant pleural effusion (MPE). However, previous studies have primarily compared MPE with exudative effusions, excluding transudates. The aim of this study was to determine the diagnostic accuracy of CR in differentiating MPE from benign pleural effusions (BPE), including both exudates and transudates. An observational analysis was conducted on patients with pleural effusion (PE) evaluated in a Portuguese center between January 2017 and August 2025. Diagnostic accuracy was assessed using receiver operating characteristic curves and area under the curve (AUC) analysis. Of the 423 PE evaluated, 154 (36.4%) were MPE and 269 (63.6%) were BPE, including 82 transudates, 159 true benign exudates (TBEPE) and 28 PE misclassified as exudates. Significantly higher CR levels were observed in MPE than in BPE ($p < 0.001$). When comparing MPE with TBEPE, a CR threshold of 20 yielded an AUC of 0.90, with 76.0% sensitivity and 93.1% specificity. The inclusion of misclassified exudative BPE and transudates reduced diagnostic accuracy (AUC 0.86/0.73, respectively). In conclusion, a CR > 20 is highly predictive of malignancy etiology. Accurate pre-classification according to the Light's criteria is essential to preserve the diagnostic validity of this biomarker.

Keywords: Biomarkers; Exudates and Transudates; Pleural Effusion, Malignant/diagnosis

RESUMO

O *cancer ratio* (CR), definido como o rácio entre a lactato desidrogenase sérica e a adenosina desaminase pleural (sLDH/pADA), tem emergido como marcador diagnóstico de derrame pleural maligno (DPM). No entanto, estudos anteriores compararam principalmente o DPM com derrames exsudativos, excluindo os transudatos. Este estudo teve como objetivo determinar o valor diagnóstico do CR na diferenciação entre DPM e derrames pleurais benignos (DPB), incluindo exsudatos e transudatos, através da análise observacional de doentes com derrame pleural avaliados num centro português entre janeiro de 2017 e agosto de 2025. A precisão diagnóstica foi definida através de curvas ROC e análise da área sob a curva (AUC). Dos 423 derrames estudados, 154 (36,4%) eram malignos e 269 (63,6%) eram benignos, incluindo 82 transudatos, 159 exsudatos verdadeiramente benignos (EVB) e 28 exsudatos mal classificados. Observaram-se níveis de CR mais elevados nos DPM do que nos DPB ($p < 0,001$). Comparando DPM com EVB, um CR > 20 apresentou AUC de 0,90, sensibilidade de 76,0% e especificidade de 93,1%. A inclusão de DPB exsudativos mal classificados e transudatos reduziu a precisão diagnóstica (AUC 0,86/0,73, respetivamente). Em conclusão, um CR > 20 é altamente preditivo de etiologia maligna. A pré-classificação correta segundo os critérios de Light é essencial para preservar a validade diagnóstica deste biomarcador.

Palavras-chave: Biomarcadores; Derrame Pleural Maligno/diagnóstico; Exsudatos e Transudatos

Pleural effusion (PE) is associated with more than sixty-five recognized causes, including malignant (MPE) and benign (BPE) diseases.¹ Management of PE is usually initiated after determining its transudative or exudative nature according to the Light's criteria.² Misclassification of transudates can occur in 20% of these cases, namely in heart failure after diuretic therapy.³ Although cytology of PE and pleural biopsy remain the gold standards for diagnosing MPE, their diagnostic accuracy is limited by factors such as low sensitivity, inter-observer variability, procedural invasiveness, and prolonged turnaround times.⁴ In recent years, efforts have been made to find practical, inexpensive and universally applicable biomarkers to aid in the diagnosis of MPE.

In 2016, Vera *et al* proposed the cancer ratio (CR), defined as serum lactate dehydrogenase (sLDH) to pleural fluid adenosine deaminase ratio (pADA), as a useful diagnos-

tic marker for MPE, with a sensitivity of 98% and specificity of 94% at a cut-off level of > 20.⁵ Two meta-analyses have confirmed that CR possesses high diagnostic accuracy for MPE; however, the optimal cut-off values reported varied, and the control groups typically comprised of tuberculous and parapneumonic PE, with transudates and other benign exudative PE (BEPE) were usually excluded.^{6,7} The aim of this study was to assess the diagnostic accuracy of the CR in the diagnosis of MPE when compared with true benign exudative PE (TBEPE) and to evaluate the effect of including misclassified exudative PE and transudates in its accuracy.

This is an observational study of adult patients with PE who underwent thoracentesis at Unidade Local de Saúde do Oeste (ULSO) between January 2017 and August 2025. Until December 2020, the study was retrospective and included patients (35%) who had complete data including

1. Center of Integrated Responsibility for Pneumology. Hospital de Torres Vedras. Unidade Local de Saúde do Oeste. Torres Vedras. Portugal.

✉ **Autor correspondente:** Maria João Cavaco. mj.cavaco@hotmail.com

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sLDH and pADA. Patients with an inconclusive final diagnosis ($n = 5$) or incomplete laboratory data ($n = 7$) were excluded. From 2021, the study was prospective and all patients were consecutively recruited (65%). Written informed consent was obtained from all patients for the analysis and publication of their anonymized data in scientific research. This study was approved by ULSO's Ethics Committee (No. 28/CES/2021).

Plural effusions were classified as transudates or exudates according to the Light's criteria. Exudative effusions were considered misclassified transudates when the difference between serum and PE protein concentrations exceeded 3.1 g/dL and the serum to PE albumin gradient was greater than 1.2 g/dL, provided that the clinical etiology was concordant.

Statistical analysis was performed using SPSS Statistics®, Version 29. A p -value below 0.05 was considered statistically significant. The Mann-Whitney test was used for comparison of the CR between groups. The diagnostic performance of CR was analyzed using the receiver operating characteristic (ROC) curves and the area under the curve (AUC) as a measure of accuracy. The best cut-off values were found using the Youden index.

Of the 423 patients evaluated, the majority were male ($n = 253$, 59.8%), with a mean age of 70.1 ± 17.0 years. About one third of the PE were malignant ($n = 154$, 36.4%, Fig. 1). The remaining benign PE included 82 transudates (19.4%), 159 true exudates (37.6%, TBEPE) and 28 transudates misclassified as exudates (6.6%) (Appendix 1: <https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24234/15964>). Cancer ratio levels were significantly higher in patients with MPE than in patients with BPE (U 11028, $Z = -8.0$, $p < 0.001$), BEPE (U 3987, $Z = -11.5$, $p < 0.001$) and TBEPE (U 2577, $Z = -12.1$, $p < 0.001$).

The best cut-off value found was > 20 , with an AUC of 0.90 [95% CI 0.86 - 0.93 (Fig. 2)], a sensitivity of 76.0% and a specificity of 93.1% when comparing MPE to TBEPE [Appendix 1, Table 1 (Appendix 1: <https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24234/15964>)].

When misclassified exudative benign pleural effusions (BEPE) and transudative benign pleural effusions (BPE) were included, the optimal cut-off value remained unchanged; however, diagnostic accuracy declined, with lower AUC values (0.86 and 0.73, respectively) and reduced specificity (88.2% and 68.9%, respectively). No significant differences were found between the results of the patients whose data was retrospective or prospectively collected.

There is a clear need for non-invasive, rapid, and cost-effective biomarkers to support the diagnosis of MPE. In patients with undiagnosed effusions, routine blood and PE biochemical tests, including measurements of pADA and

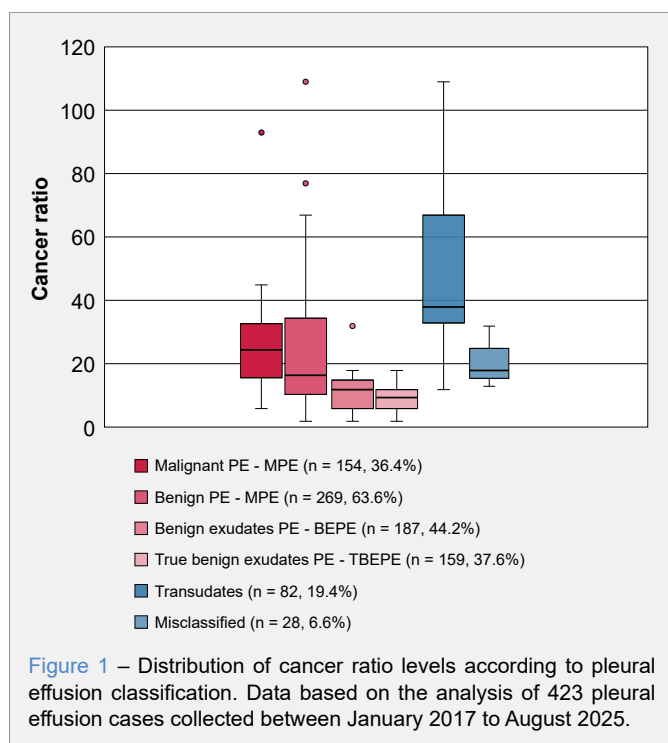


Figure 1 – Distribution of cancer ratio levels according to pleural effusion classification. Data based on the analysis of 423 pleural effusion cases collected between January 2017 to August 2025.

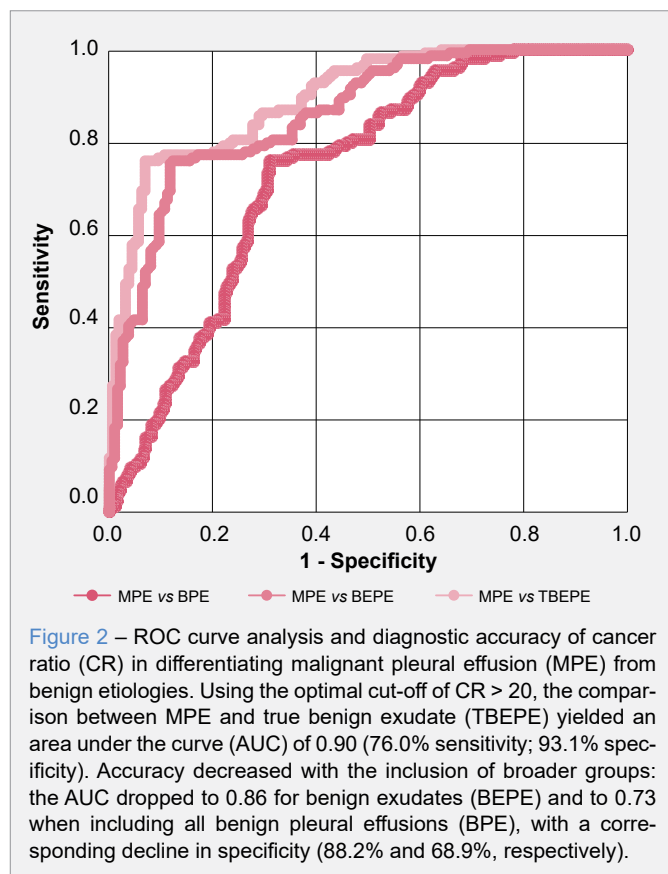


Figure 2 – ROC curve analysis and diagnostic accuracy of cancer ratio (CR) in differentiating malignant pleural effusion (MPE) from benign etiologies. Using the optimal cut-off of CR > 20 , the comparison between MPE and true benign exudate (TBEPE) yielded an area under the curve (AUC) of 0.90 (76.0% sensitivity; 93.1% specificity). Accuracy decreased with the inclusion of broader groups: the AUC dropped to 0.86 for benign exudates (BEPE) and to 0.73 when including all benign pleural effusions (BPE), with a corresponding decline in specificity (88.2% and 68.9%, respectively).

sLDH, are already widely available. Our findings suggest that the CR is a valuable biomarker for differentiating MPE from other forms of PE, achieving an AUC of 0.90, and may therefore contribute to earlier diagnosis and management.

A key strength of this study is its real-world design. Unlike many previous analyses, this dataset represents an unselected cohort of patients evaluated in routine clinical practice, including both transudates and exudates misclassified by the Light's criteria. Moreover, no restrictions were applied regarding the underlying benign exudative etiologies, enhancing the generalizability of these findings.

The sensitivity observed in our cohort was lower than that reported in previous studies. This discrepancy may be partly explained by the lower cut-off values adopted in some studies. Nonetheless, several pathophysiological mechanisms may also contribute to this finding. On the one hand, concomitant or recent inflammatory processes can result in modest elevations of pADA, thereby reducing the CR and falsely suggesting a BPE. Conversely, sLDH may be only modestly elevated in patients with a limited tumour burden or indolent malignancies, in whom systemic inflammation and tissue turnover remain minimal. Collectively, these factors emphasize the need for cautious, context-dependent interpretation of CR values and their integration into the broader clinical and biochemical assessment.

This study has several limitations. First, it was conducted at a single center, which may limit the external validity of the findings. Second, in order to maximize sample size, a proportion of retrospectively enrolled patients was included; although no statistically significant differences were identified in this subgroup, the possibility of selection bias cannot be fully excluded. Third, the analysis considered MPE as a single entity, without subgroup-analyses according to tumor etiology or stage, which may have obscured important biological variations. Further validation in larger, preferably multicenter, prospective studies is therefore required.

In conclusion, a CR > 20 seems to be a practical and accessible biomarker for MPE, reaching its full diagnostic

potential when integrated with the Light's criteria in the differentiation of purely exudative effusions. These findings support the CR as a valuable adjunct to standard biochemical evaluation in the diagnostic assessment of PE.

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The authors declare that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

MJC, SFA, CS, SP, LM, CRS: Study conception and design, data acquisition, analysis and interpretation, writing and critical review of the manuscript.

JF, DD: Data acquisition, analysis and interpretation, writing and critical review of the manuscript.

CC, PR, TF: Study conception and design, data interpretation, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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