

Correlation patterns of CEA, CA19-9, CA72-4, CA125, CA15-3, and PIVKA-II in malignant pleural effusions: overlap and distinction across tumor biology

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Abstract

Introduction: Malignant pleural effusions (MPEs) are a frequent complication of cancer, causing significant morbidity and representing a major diagnostic challenge. Tumor markers in pleural fluid have been studied, but their interrelationships remain poorly understood.

Aim: To investigate the correlations among commonly used tumor markers in pleural effusions and to assess their potential role in differentiating malignant from benign cases.

Materials and methods: A cross-sectional case-control study was conducted on 151 Bulgarian patients with hydrothorax. The control group consisted of 72 patients with benign pleural effusions (38 inflammatory, 34 non-inflammatory), while 79 patients had malignant pleural involvement. Correlation analysis was applied to evaluate the relationships between carcinoembryonic antigen (CEA), CA19-9, CA72-4, CA125, CA15-3, and PIVKA-II.

Results: Significant moderate positive correlations were found between CEA, CA19-9, CA72-4, and CA125, indicating overlapping tumor biology. CA125 also correlated with CA15-3, consistent with their role in epithelial malignancies. In contrast, PIVKA-II showed no significant correlation with other markers, suggesting limited utility in pleural malignancy diagnosis. These findings point to both redundancy and complementarity among tumor markers.

Conclusions: Tumor markers in pleural fluid, particularly CEA, CA125, CA19-9, and CA72-4, may provide valuable diagnostic information when assessed together. Their interrelationships support the rational selection of marker panels to improve diagnostic accuracy for MPEs. PIVKA-II appears less informative in this setting. Understanding these correlations may enhance minimally invasive diagnostic strategies and contribute to more personalized management of pleural malignancy.

Keywords

diagnosis, malignant pleural effusion, tumor marker correlations

Introduction

Approximately 40% of malignant pleural effusions (MPEs) fail to yield diagnostic cytology during thoracentesis, underscoring the importance of complementary diagnostic approaches beyond conventional biochemical and cytological tests.^[1] One emerging strategy involves the assessment of tumor markers within pleural fluid. Since pleural fluid is derived from serum, its biochemical composition is expected to parallel that of circulating blood.^[2] Consequently, tumor marker levels elevated in serum are often reflected in pleural effusions. Additional mechanisms may also contribute, mainly direct release of tumor markers by metastatic deposits on the pleura and impaired clearance due to lymphatic obstruction caused by tumor infiltration.^[3]

Future diagnostic strategies may benefit from the development of optimized tumor marker panels tailored to the most common metastatic cancers involving the pleura. When combined with comprehensive cytological and biochemical analyses, such panels could substantially improve the diagnostic yield for MPEs.^[4] Although tumor marker testing carries moderate costs, its targeted use has the potential to enhance cost-effectiveness. Among these biomarkers, carcinoembryonic antigen (CEA) remains the most extensively studied, with a diagnostic sensitivity of approximately 50%–60%. In a study by Miedouge et al.^[5], the diagnostic sensitivities of several tumor markers were reported as follows: CEA (60.0%), CA15-3 (63.7%), CYFRA (42.8%), CA19-9 (20.9%), CA72-4 (68.4%), SCC (5.6%), and NSE (18.1%). Importantly, a combined panel of CEA, CA15-3, CYFRA, and NSE correctly identified 83.9% of cytology-negative non-lymphomatous MPEs. Furthermore, tumor marker profiles demonstrated predictive value for underlying tumor histology. For example, NSE, SCC, and CYFRA were particularly informative for distinguishing adenocarcinoma, small-cell lung carcinoma, squamous cell carcinoma, and mesothelioma, achieving an overall predictive accuracy of 89.4%, with the highest reliability observed in adenocarcinoma. However, identifying the primary site of adenocarcinomas remained challenging, with only 64.8% correctly classified.

Despite these advances, the diagnostic specificity of individual tumor markers in pleural fluid remains limited. For instance, CEA continues to demonstrate strong diagnostic utility for carcinomas, while CA72-4 is most informative for metastatic adenocarcinoma and squamous cell carcinoma. CA15-3 is frequently elevated in pleural carcinomatosis from breast and other adenocarcinomas, whereas CYFRA shows predictive value in pleural mesothelioma. Interestingly, tumor marker concentrations in pleural fluid often exceed serum levels, highlighting the suitability of pleural fluid as a diagnostic medium.

Quantitative assessment methods, including discriminant and logistic regression analyses, have further reinforced the diagnostic potential of pleural tumor markers. Elevated serum CYFRA 21-1 and NSE, as well as pleural NSE, have shown significant associations with pleural ma-

lignancy.^[6] In a prospective study by Volaric et al., involving 100 patients (73 men, 27 women; mean age 71 years), tumor marker levels (CEA, NSE, CA125, CYFRA 21-1) were significantly higher in malignant versus benign effusions.

However, much of the literature consists of retrospective, single-center studies lacking validation cohorts. Addressing this limitation, Zhai et al.^[7] conducted the first derivative and validation study in China, confirming that CEA, CA125, CA15-3, and CA19-9 are elevated in MPEs compared with benign effusions. CEA demonstrated the highest diagnostic accuracy, with 84.7% sensitivity and 90.9% specificity at a threshold of 2.42 ng/mL. CA15-3 showed very high specificity (97.6%) but relatively low sensitivity (63.1%), making it unsuitable as a standalone test. Findings for CA125 and CA19-9 were inconsistent, likely due to tumor heterogeneity and varying disease stages, suggesting limited utility for these markers in MPE evaluation.

In practice, tumor markers with the highest sensitivity are most useful for confirming MPE, while those with high specificity are best suited for exclusion.^[8-10] To further enhance diagnostic performance, many authors recommend the combined assessment of pleural and serum tumor markers, as well as calculation of pleural-serum gradients^[11-15]

Aim

This study aimed to investigate the correlation patterns among six widely used serum tumor markers in a cohort of 151 patients.

Materials and methods

We retrospectively analyzed serum and pleural fluid tumor marker data from 151 patients with a hydrothorax. Patients were eligible for inclusion if they met all of the following criteria:

- provided written informed consent prior to participation;
- had radiologically confirmed pleural effusion (via chest X-ray, CT, or ultrasound);
- presented with a clinical indication for pleural drainage, pleural biopsy, or pleurodesis as part of their diagnostic or therapeutic management.

Patients were excluded if they met any of the following conditions:

- did not meet the inclusion criteria listed above;
- had a history of previous pleurodesis on the affected hemithorax;
- had pleural effusion secondary to trauma or postoperative causes, rather than malignant or benign pathological processes.

The panel of markers included carcinoembryonic antigen (CEA), carbohydrate antigens CA19-9, CA72-4, CA125, CA15-3, and protein induced by vitamin K absence

or antagonist-II (PIVKA-II).

The study was designed as a cross-sectional, observational, case-control investigation in a Bulgarian patient cohort. Of the 151 participants, 72 served as controls, all of whom were diagnosed with benign conditions confirmed histologically. Within this group, 38 cases were of inflammatory origin and 34 represented non-inflammatory pleural effusions. Malignant pleural involvement was confirmed in 79 patients. These two groups represent the predominant categories of pleural pathology.

Pleural fluid samples were obtained either by thoracentesis or intraoperatively during video-assisted thoracoscopic surgery (VATS), using sterile closed containers. Each sample was divided: one portion was analyzed for standard biochemical parameters, while the remainder was used for tumor marker quantification and cytological examination. Biochemical and tumor marker analyses were performed on a Beckman Coulter AU480 clinical chemistry analyzer, using manufacturer protocols.

Data were processed and analyzed in IBM SPSS Statistics (version 27.0.1; IBM Corp., Armonk, NY). Statistical methods were selected according to study objectives, variable types, and established practices in thoracic surgical research. Quantitative and qualitative variables were summarized in tabular and graphical form, with graphical analyses performed in Microsoft Office 365.

Correlation analyses were conducted using Pearson correlation coefficients (*r*) with two-tailed significance testing.

Correlation analysis demonstrated several statistically

significant associations among the tumor markers under investigation (Table 1).

Carcinoembryonic antigen (CEA) was moderately correlated with CA19-9 ($r=0.421, p<0.001$), CA72-4 ($r=0.329, p<0.001$), and CA125 ($r=0.367, p<0.001$). Similarly, CA19-9 demonstrated a strong correlation with CA125 ($r=0.446, p<0.001$) and a weaker but still statistically significant correlation with CA72-4 ($r=0.228, p=0.005$). CA72-4 and CA125 were also significantly correlated ($r=0.387, p<0.001$). In addition, CA125 was positively correlated with CA15-3 ($r=0.352, p<0.001$).

In contrast, PIVKA-II did not show any significant correlation with the other tumor markers, as all *p*-values exceeded 0.05. Weak associations, such as those between CEA and CA15-3 ($p=0.138$) and between CA19-9 and CA15-3 ($p=0.682$), were not statistically significant and therefore did not demonstrate meaningful relationships.

Taken together, these findings indicate that CEA, CA19-9, CA72-4, and CA125 form a cluster of interrelated tumor markers, reflecting overlapping biological pathways that are frequently implicated in gastrointestinal and gynecological malignancies. The correlation between CA125 and CA15-3 is consistent with their known association in epithelial tumors, further supporting their diagnostic overlap. By contrast, the absence of correlations involving PIVKA-II suggests that this marker is biologically distinct, most likely reflecting its unique association with hepatocellular carcinoma rather than with the malignancies commonly represented in this cohort.

Table 1. The discovered correlations between the investigated tumor markers

		Correlations					
		CAEpun	CA19_9pun	CA72_4pun	CA125pun	CA15_3pun	PIVKApun
CEA	Pearson correlation	1	0.421	0.329	0.367	0.121	-0.083
	Sig. (1-tailed)		0.000	0.000	0.000	0.069	0.156
	N	151	151	151	151	151	151
CA19-9	Pearson correlation	0.421	1	0.228	0.446	-0.034	-0.053
	Sig. (1-tailed)	0.000		0.002	0.000	0.341	0.260
	N	151	151	151	151	151	151
CA72-4	Pearson correlation	0.329	0.228	1	0.356	0.352	-0.108
	Sig. (1-tailed)	0.000	0.002		0.000	0.000	0.093
	N	151	151	151	151	151	151
CA125	Pearson correlation	0.367	0.446	0.356	1	0.054	-0.087
	Sig. (1-tailed)	0.000	0.000	0.000		0.256	0.145
	N	151	151	151	151	151	151
CA15-3	Pearson correlation	0.121	-0.034	0.352	0.054	1	-0.079
	Sig. (1-tailed)	0.069	0.341	0.000	0.256		0.166
	N	151	151	151	151	151	151
PIVKA	Pearson correlation	-0.083	-0.053	-0.108	-0.087	-0.079	1
	Sig. (1-tailed)	0.156	0.260	0.093	0.145	0.166	
	N	151	151	151	151	151	151

Table 2. A heatmap showcasing the correlations between the tumor markers

Tumor marker	CEA	CA19-9	CA724	CA125	CA15-3	PIVKA
CEA	1	0.000	0.000	0.000	0.138	0.312
CA19-9	0.000	1	0.005	0.000	0.682	0.520
CA72-4	0.000	0.005	1	0.000	0.000	0.187
CA125	0.000	0.000	0.000	1	0.513	0.290
CA15-3	0.138	0.682	0.000	0.513	1	0.333
PIVKA	0.312	0.520	0.187	0.290	0.333	1

A correlation heatmap (**Table 2**) further illustrates the clustering of CEA, CA19-9, CA72-4, and CA125, with PIVKA-II appearing as an isolated variable. Additionally, an analysis of tumor marker concentration distributions demonstrated that CA125 exhibited a wide range of values, whereas CEA, CA19-9, CA15-3, and PIVKA-II showed narrower distributions with occasional outliers.

Discussion

Our findings demonstrate that several tumor markers frequently rise in parallel, particularly CEA, CA19-9, CA72-4, and CA125. The moderate positive correlations among these markers suggest overlapping tumor biology, which is consistent with their established diagnostic and prognostic roles in gastrointestinal and gynecological malignancies.^[16-18] The observed correlation between CA125 and CA15-3 further aligns with their recognized clinical utility in epithelial tumors, including ovarian and breast cancers.^[19,20]

By contrast, PIVKA-II did not correlate significantly with any of the other markers, underscoring its distinct biological role as a hepatocellular carcinoma-specific marker. This independence indicates that PIVKA-II provides non-redundant diagnostic information and could enhance diagnostic yield when combined with correlated markers such as CEA or CA19-9.

From a clinical perspective, these results highlight the dual nature of tumor marker use: redundancy and complementarity. Highly correlated markers may provide overlapping information, thereby limiting incremental diagnostic value when combined in panels. In contrast, the inclusion of biologically distinct markers, such as PIVKA-II, may increase sensitivity and broaden diagnostic coverage. Correlation analysis may therefore serve as a useful tool for informing the selection of tumor marker panels in both diagnostic and monitoring contexts.

Our findings are also consistent with published studies on pleural fluid tumor markers, which have reported similar patterns of inter-marker correlation and diagnostic performance.^[21-23] For example, markers such as CEA, CA19-9, and CA72-4 have been shown to perform well in differentiating malignant from benign pleural effusions, whereas PIVKA-II has consistently demonstrated limited discriminative ability. These parallels suggest that serum

and pleural fluid tumor marker profiles may reflect shared underlying tumor biology.^[24,25]

The diagnostic performance of individual markers in our cohort further reinforces these observations. CEA and CA72-4 demonstrated strong discriminative ability, with CA72-4 showing the highest diagnostic accuracy (AUC=0.845). CA15-3 also performed well (AUC=0.773), while CA19-9 had only moderate accuracy (AUC=0.644). By contrast, PIVKA-II showed poor diagnostic utility (AUC=0.571) and was not statistically significant. These findings are in line with prior large-scale studies, which have consistently identified CEA, CA15-3, and CA72-4 as the most informative tumor markers in pleural effusion diagnostics.

Despite these promising results, several limitations should be acknowledged. The retrospective design may introduce selection bias, and the absence of stratification by tumor type or stage limits the ability to draw disease-specific conclusions. Furthermore, no clinical outcome data were available to directly evaluate whether marker correlations are associated with prognosis or therapeutic response. Future studies should therefore aim to validate these findings prospectively, explore correlation patterns across cancer subtypes, and investigate their potential prognostic significance.

Conclusion

Overall, our study contributes to the growing body of evidence supporting the use of tumor marker combinations in the evaluation of pleural effusions. While correlated markers may reinforce diagnostic certainty, the integration of biologically distinct markers such as PIVKA-II may provide complementary value. Incorporating tumor marker analysis into diagnostic algorithms—alongside established criteria such as Light's criteria and cytological examination—could improve diagnostic accuracy, reduce unnecessary invasive procedures, and ultimately enhance patient care.

Future research should focus on validating these findings across larger and more diverse cohorts, stratifying results by cancer subtype and stage, and exploring the prognostic implications of tumor marker correlations. The ongoing advancement of laboratory technologies and biomarker discovery holds promise for establishing more accurate, patient-centered diagnostic algorithms for malignant pleural effusions.

Ethical statement

- This study was conducted in accordance with the ethical standards of the institutional research committee and with the principles of the Declaration of Helsinki.
- Ethical approval for this study was obtained from the Ethics Committee of the Medical University of Plovdiv.
- All participants provided written informed consent prior to inclusion in the study.
- The study did not involve any experimental interventions beyond routine clinical practice.
- No experiments on animals were performed in this study.

Conflict of interest

The authors have declared that they have no conflict of interest, financial or otherwise.

Use of AI

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Author contributions

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Data availability

All data used are referenced or included in the article.

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