ORIGINAL ARTICLE *UDK: 618.11-006.6:616.33/.34-006.6]-079.4(497.7)*

www.doi.org/

DIAGNOSTIC VALUE OF THE CA-125/CEA RATIO FOR DIFFERENTIATING PRIMARY OVARIAN CARCINOMA FROM GASTROINTESTINAL MALIGNANCIES IN A TERTIARY GYNECOLOGIC ONCOLOGY CENTER IN NORTH MACEDONIA

Asani P.[1], Alulovski I.[1], Tanturovski M.[1], Joksimovikj M.[1], Abdija P.[1], Asani D.[2]

[1]*University Clinic for Gynecology and Obstetrics, Mother Theresa Clinic, Skopje, North Macedonia*

[2]*University Clinic for Orthopedics, Mother Theresa Clinic, Skopje, North Macedonia*

Abstract

Background: Differentiating primary ovarian carcinoma from gastrointestinal (GI) malignancies is challenging. The CA-125/CEA ratio, with a cut-off around 25:1, may help distinguishing ovarian from non-ovarian cancers. We evaluated the performance of CA-125, CEA, and their ratio in women treated at a tertiary gynecologic oncology center in North Macedonia.

Methods: A prospective study of 72 women ≥18 years with adnexal masses, ascites, or elevated tumor markers suspicious for malignancy, treated surgically between 2019-2024. Preoperative serum CA-125, CEA, CA19-9, and CA72-4 were measured, and the definitive diagnosis was established histopathologically. Cases were classified as ovarian/gynecologic or GI malignancies. The primary endpoint was the ability of the CA-125/CEA ratio to differentiate ovarian from GI malignancy.

Results: The median age was 61 years, and 79.2% of patients were postmenopausal. Ovarian/gynecologic malignancy was diagnosed in 69/72 (95.8%), and 3/72 (4.2%) had GI malignancies. The CA-125/CEA ratio was significantly higher in ovarian malignancies (101.0 vs 11.4, p=0.033). A cut-off of ≤25 identified all 3 GI cancers (100% sensitivity), but misclassified 15 ovarian cancers (72.7% specificity). The ROC AUC was 0.86 for the CA-125/CEA ratio, compared to 0.61 for CA-125 alone.

Conclusions: A CA-125/CEA ratio ≤25 identified GI malignancies with high sensitivity but modest specificity. This approach may reduce unnecessary GI endoscopies in resource-limited settings like North Macedonia, though larger studies are needed.

Keywords: *CA-125; CEA; gastrointestinal metastasis; North Macedonia; ovarian cancer; tumor markers.*

Introduction

Most women with epithelial ovarian cancer present with advanced disease, and preoperative characterization of adnexal masses remains a major challenge despite advances in imaging and biomarker assessment. Differentiating primary ovarian carcinoma from ovarian metastases of gastrointestinal (GI) origin is crucial for optimal surgical planning, the need for combined gy-

necologic–colorectal teams, and the timing of endoscopic evaluation.

ESMO and ESGO guidelines recommend CA-125 as the standard serum marker in the diagnostic work-up of suspected ovarian cancer, often in combination with imaging and, where appropriate, HE4 and multivariate algorithms such as RMI or ROMA. However, they explicitly caution that CA-125 alone cannot reliably distinguish benign from malignant adnexal masses or identify the primary site.

Several older and more recent studies have proposed the CA-125/CEA ratio as a simple tool to help distinguish primary ovarian cancer from colorectal or other non-ovarian malignancies. Buamah et al. reported that all 47 women with ovarian cancer in their cohort had a CA-125/CEA ratio >25, whereas many colorectal and other GI cancers had a ratio below this threshold (3). Subsequent studies by Moro et al., Kurokawa et al., and others confirmed that combining CA-125 and CEA, often via a ratio, improves discrimination between primary adnexal masses and GI metastases (4,5). More recently, Zanon et al. suggested that CA-125/CEA may also be helpful in distinguishing advanced ovarian cancer from stage IV colorectal cancer (6).

In this context, Helweg-Larsen et al. (2023) demonstrated that combining CA-125 and CEA, including the use of the CA-125/CEA ratio, improved the diagnostic performance for ovarian cancer in a Danish population, supporting the historical cut-off of 25:1 for suggesting ovarian origin (7). Yu et al. (2024) further expanded this concept in a multicenter analysis focusing specifically on the discrimination between primary ovarian cancer and metastases from the GI tract (8).

In North Macedonia, access to advanced imaging and specialized multidisciplinary centers is improving but remains variable. A simple, inexpensive serum-based tool such as CA-125/CEA could help triage patients for GI endoscopy versus direct referral for gynecologic oncologic surgery, potentially reducing costs and delays in care.

Material and Methods

Study design and setting

We conducted a prospective observational study in a tertiary gynecologic oncology center in North Macedonia, including consecutive women referred with adnexal mass, ascites, or isolated elevation of tumor markers suspicious for malignancy during 2024 and 2025. The study design and core variables were pre-specified in a protocol and an abstract in Macedonian.

Patient population

Inclusion criteria:

- Female sex, age ≥18 years
- Presence of adnexal/pelvic mass, ascites, or isolated elevation of tumor markers interpreted as suspicious for malignancy
- Elevated CA-125 level (>35 U/mL) whenever available
- Planned surgical intervention and/or diagnostic biopsy
- Written informed consent

Exclusion criteria:

- Previously known primary GI carcinoma prior to the current adnexal presentation
- History of treated ovarian carcinoma
- Invalid or missing serum samples for tumor marker measurement

A total of 72 women fulfilled the criteria and were included in the final analysis.

Clinical and imaging assessment

Demographic and clinical data included year of birth (used to derive approximate age), menopausal status, family history of cancer, presenting symptoms, and imaging findings from ultrasound, CT, and/or MRI. Menopausal status was categorized as postmenopausal, premenopausal with regular menses, or perimenopausal/irregular cycle. Ascites was recorded qualitatively (present vs absent). Performance of colonoscopy and gastroscopy, and their findings were extracted from medical records

Biomarker assessment

Serum CA-125 (U/mL), CEA (ng/mL), CA19-9 (U/mL), and CA72-4 (U/mL) were measured pre-operatively in the institutional laboratory using standard immunoassays. Values recorded as "/" in the database were treated as missing. For the primary analysis, we required concomitant CA-125 and CEA measurements.

The CA-125/CEA ratio was calculated as:

$$\text{ratio} = \frac{\text{CA-125 (U/mL)}}{\text{CEA (ng/mL)}}$$

When CEA was reported as 0.0 ng/mL, the ratio was considered extremely high and classified as >25; such cases were included in the binary rule analysis but excluded from continuous ROC analysis to avoid infinite values.

Histopathologic classification

All patients underwent surgery and/or biopsy with definitive histopathologic diagnosis. Based on the final report, cases were categorized into two groups:

- **Primary ovarian/gynecologic malignancy:**
  - Epithelial ovarian carcinoma (high-grade serous, endometrioid, clear cell, mucinous, low-grade serous)
  - Carcinosarcoma and other Müllerian neoplasms
  - Synchronous ovarian–endometrial primaries
- **Gastrointestinal malignancy:**
  - Colorectal adenocarcinoma with ovarian and/or peritoneal involvement
  - Gastrointestinal stromal tumor (GIST) arising from the GI tract with peritoneal/ovarian spread

- In total, 69 cases were classified as primary ovarian/gynecologic malignancies and 3 as GI malignancies.

Outcomes and definitions

The primary outcome was the diagnostic performance of the CA-125/CEA ratio for differentiating primary ovarian/gynecologic malignancy from GI malignancy, using a cut-off ≤25 to suggest GI origin, in line with prior literature (1).

Results

Patient characteristics

Seventy-two women were included. The median age at diagnosis (approximated from year of birth) was 61 years (IQR 53–67; range 38–84). Most patients were postmenopausal (57/72, 79.2%), while 11/72 (15.3%) were premenopausal with regular cycles, and 4/72 (5.6%) had irregular menses. Ascites was documented in 32/72 (44.4%) patients.

Colonoscopy and gastroscopy were performed in 20 (27.8%) and 15 (20.8%) women, respectively. Among the three GI malignancies, one had a colonoscopic diagnosis of intramucosal adenocarcinoma in a villous polyp, while upper endoscopy was normal in two of the three cases.

Histopathologic diagnoses

Primary ovarian/gynecologic malignancies accounted for 69/72 (95.8%) cases, including high-grade serous carcinoma, mucinous cystadenocarcinoma, endometrioid and clear-cell histologies, carcinosarcomas, and synchronous ovarian–endometrial cancers. GI malignancies were identified in 3/72 (4.2%) patients: two colorectal adenocarcinomas with ovarian and peritoneal involvement and one GIST of intestinal origin with peritoneal dissemination.

Tumor markers in the overall cohort

Serum CA-125 values were available in 62/72 (86.1%) patients, CEA in 60/72 (83.3%), CA19-9 in 55/72 (76.4%), and CA72-4 in 39/72 (54.2%). Overall median values were:

- CA-125: 167.2 U/mL
- CEA: 1.60 ng/mL
- CA19-9: 12.6 U/mL
- CA72-4: 8.2 U/mL

As expected in a gynecologic oncology population, CA-125 levels were frequently and markedly elevated, whereas CEA was generally low.

Comparison between ovarian and GI malignancies

Table 1: Comparison of Tumor Markers Between Ovarian/Gynecologic and GI Malignancies

Marker	Ovarian/Gynecologic	GI Malignancies	p-value
CA-125 (U/mL)	170.4 (IQR: 66.51–476.75)	42.4 (IQR: 39.72–224.69)	0.49
CEA (ng/mL)	1.47 (IQR: 0.67–3.01)	3.73 (IQR: 2.96–63.87)	0.067
CA-125/CEA ratio	101.0 (IQR: 17.98–448.09)	11.4 (IQR: 7.32–14.14)	0.023

Diagnostic performance of the CA-125/CEA ratio

Concomitant CA-125 and CEA measurements were available in 58/72 (80.6%) patients, including all 3 GI malignancies and 55 ovarian/gynecologic cancers. Using the pre-specified rule:

- Test positive for GI origin: CA-125/CEA ≤25
- Test negative: CA-125/CEA >25

We observed the following 2×2 table:

True GI malignancies (n=3)	All 3 had CA-125/CEA ≤25 (true positives)
Ovarian/gynecologic malignancies (n=55)	10 had CA-125/CEA ≤25 (false positives)
	49 had CA-125/CEA >25 (true negatives)

From these data:

- **Sensitivity:** 100% (3/3; 95% CI 29.2–100)
- **Specificity:** 82.7% (40/55; 95% CI 59.0–83.9)
- **PPV:** 16.7% (3/18; 95% CI 3.6–41.4)
- **NPV:** 100% (40/40; 95% CI 91.2–100)

Thus, a CA-125/CEA ratio >25 essentially excluded GI origin in this cohort, while a ratio ≤25 strongly indicated that further GI work-up was warranted, albeit with a relatively low PPV due to the low prevalence of GI malignancies.

ROC analysis

Among patients with both markers available and CEA >0 (n=54), the ROC-AUCs for discriminating GI or ovarian/gynecologic origin were:

- CA-125 alone (higher in ovarian): AUC 0.61
- CEA alone (higher in GI): AUC 0.82
- CA-125/CEA ratio (lower in GI): AUC 0.86

These findings suggest that the CA-125/CEA ratio offers better discrimination than CA-125 alone and at least comparable, slightly improved performance to CEA alone in this dataset.

Discussion

In this prospective single-center study from North Macedonia, we found that:

- The CA-125/CEA ratio was significantly higher in primary ovarian/gynecologic malignancies compared with GI malignancies.
- Using a cut-off of ≤25 to indicate GI origin, the ratio achieved 100% sensitivity and 100% NPV for GI malignancy in our cohort, at the cost of modest specificity (72.7%) and low PPV (16.7%).
- ROC analysis showed that the CA-125/CEA ratio (AUC 0.86) outperformed CA-125 alone and slightly improved upon CEA alone for differentiating GI from ovarian origin.
- CA19-9 and CA72-4 did not show meaningful discriminatory value in this small series.

Buamah et al. originally proposed the CA-125/CEA ratio >25 as a marker strongly suggestive of ovarian origin, with all ovarian cancers in their series exceeding this threshold. Moro et al. later identified an optimal ratio of approximately 11.9 for distinguishing ovarian neoplasms from ovarian metastases in a large multicenter cohort, again demonstrating the ratio's superior performance over either marker alone. Kurokawa et al., and others further supported the notion that a combined CA-125/CEA assessment improves pre-operative discrimination between primary adnexal masses and GI metastases.

More recently, Zanon et al. reported that CA-125/CEA may help distinguish advanced ovarian cancer from stage IV colorectal cancer, especially in the context of peritoneal carcinomatosis where radiologic appearances overlap. In a Danish cohort, Helweg-Larsen et al. (2023) confirmed that the combination of CA-125 and CEA, including using the ratio, improves the identification of ovarian cancer among women with elevated CA-125.

Our findings align with these studies, reinforcing that a low CA-125/CEA ratio should trigger a careful search for GI origin, while a very high ratio strongly favors ovarian origin.

While the study highlights promising diagnostic performance, it is also important to acknowledge the economic impact of incorporating the CA-125/CEA ratio into preoperative work-ups. In settings with constrained resources, such as North Macedonia, the cost of procedures like colonoscopy (approximately €100 per procedure) could be reduced by using the CA-125/CEA ratio to help prioritize patients for GI evaluation. This could significantly reduce the number of unnecessary procedures, optimize resource allocation, and expedite diagnosis and treatment for patients. By effectively distinguishing GI from ovarian malignancies, unnecessary gastroscopies and colonoscopies can be minimized, leading to both cost savings and improved patient flow.

Limitation

The small number of **GI malignancies** (only 3 cases) limits the ability to draw definitive conclusions on the clinical performance of the CA-125/CEA ratio in larger, more diverse populations.

Despite this limitation, our study provides valuable insights into the utility of the CA-125/CEA ratio, particularly in resource-limited settings, and lays the groundwork for further multicenter validation studies to refine the approach.

Ethics approval: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University Clinic for Gynecology and Obstetrics, Mother Theresa Clinical Campus, Skopje, North Macedonia.

Consent for publication: Written informed consent was obtained from all patients prior to inclusion in the study.

Conflict of interest: The authors report no financial or personal conflicts of interest.

Funding: This research received no external funding.

Author Contributions: : Asani P: study conception, data collection, manuscript drafting Aluloski I: methodology, supervision; Tanturovski M: statistical analysis; Joksimovikj M: clinical data interpretation; Abdija P: patient recruitment; Asani D: histopathology review

All authors approved the final manuscript.

Use of Artificial Intelligence (AI) tools: The authors declare that no artificial intelligence tools were used in the preparation of this manuscript.

Acknowledgments: We thank the staff of the University Clinic for Gynecology and Obstetrics, Skopje for their support in patient management and data collection.

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