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Investigating the Relationship Between Immunohistochemical Expression of CA 125 in Ovarian Epithelial Tumors and Serum Levels as Diagnostic Indicators

Fianda Restalia[1]* , Dwi Andhika Panjarwanto[2], Johannes Sudarwantono[3], Daniel Alexander Suseno[4], I Wayan Agung Indrawan[5]
[1,2]Universitas Brawijaya, Indonesia
[3]Rumah Sakit Umum Pindad Turen, Indonesia
[4]Rumah Sakit Umum Soebandi, Indonesia
[5]Rumah Sakit Umum Daerah Saiful Anwar, Indonesia
Email: fiandarestalia55@gmail.com*, dwiandhikapanjarwanto@gmail.com, jsudarwantono@gmail.com, dr.danielsuseno@gmail.com, iwa_obg@yahoo.com

Abstract

This systematic literature review evaluates the relationship between CA-125 immunohistochemical expression in ovarian epithelial tumors and serum CA-125 levels as diagnostic indicators. Five studies meeting inclusion criteria from 20,500 initially identified articles consistently demonstrated significant positive correlations between tissue expression intensity and serum concentrations. Key findings reveal that elevated preoperative serum levels correspond directly with increased tissue expression intensity, while combined assessment improves diagnostic accuracy. Both parameters effectively predict early recurrence in advanced-stage (III/IV) disease and show distinct variation across histological subtypes, with mucinous carcinomas exhibiting the lowest expression levels. However, methodological limitations, including heterogeneous study designs, varying immunohistochemical techniques, and restricted sample sizes, affect generalizability. Clinical implications support integrating tissue immunohistochemistry with serum measurements and complementary biomarkers like HE4 for enhanced subtype differentiation. Future multicenter prospective studies with standardized protocols are recommended to establish definitive cut-off values and long-term prognostic significance. These findings underscore CA-125's enduring clinical value while emphasizing that optimal diagnostic performance requires contextual interpretation alongside other markers, histological classification, and comprehensive patient assessment. The systematic PRISMA-guided approach ensured rigorous evidence synthesis, highlighting CA-125's crucial role in addressing ovarian cancer's significant global burden through improved early detection strategies.

Keywords: CA-125; Ovarian Epithelial Tumor; Immunohistochemistry; Serum Levels; Diagnostic Indicators.

INTRODUCTION

Ovarian cancer is a condition caused by the abnormal growth of tissue in the mother's egg (ovary). The ovary is a pair of reproductive organs in women where egg cells are produced. There are three types of ovarian cancer, classified as epithelial tumors that develop on the surface (epithelium) of the ovary, germ cell tumors that originate from cells that produce eggs and are found mostly in young women, and stromal tumors originating from cells that secrete female hormones, namely estrogen and progesterone (Rahayu et al., 2022).

Ovarian cancer is one of the most aggressive diseases with a high death rate worldwide. It ranks as the eighth leading cause of cancer-related death among women globally and is the seventh most common cancer in women (Rahayu et al., 2022). According to data from the Global Burden of Cancer, the incidence rates of reproductive cancers are led by breast cancer

with new cases reaching 24.2% and 15% of deaths, cervical cancer with 6.6% new cases and 7.5% mortality, and ovarian cancer with new cases reaching 4.4% and deaths also 4.4% (International Agency for Research on Cancer, 2018). Data from the World Cancer Research Fund (2018) showed new ovarian cancer cases reached 300,000 globally. Indonesia is among countries with the highest numbers of ovarian cancer patients, reporting 13,310 (7.1%) new cases and 7,842 (4.4%) deaths (International Agency for Research on Cancer, 2018).

In general, ovarian cancer is found in women over the age of 55. In women younger than 20 years, germ cell tumors are most common, whereas in older women (more than 50 years), epithelial tumors are frequently diagnosed. Because ovarian cancer is a silent disease with few specific symptoms, about 70% of ovarian cancer cases are already diagnosed at an advanced stage, where the 5-year survival rate falls below 30%. Conversely, if diagnosed at stage I, the 5-year survival rate increases dramatically to about 90% (Sabaruddin & Ferry, 2018).

Early diagnosis and a deeper understanding of the biological characteristics of ovarian tumors are crucial for improving prognosis and developing more effective treatment strategies. Diagnosis of ovarian cancer requires anamnesis, physical/gynecological examination, abdominal ultrasound, biopsy, routine blood tests, and tumor markers, one of which is CA-125 (Sabaruddin & Ferry, 2018). In this context, CA 125 (cancer antigen 125) has become a focus of study as a potential biomarker for diagnosis and monitoring of ovarian cancer.

Anamnesis and physical examination are procedures generally performed in hospitals. Abdominal ultrasound is an important tool to detect masses or tumors in the abdomen, though it cannot differentiate between benign and malignant tumors (Abramowicz & Timmerman, 2017; Pelayo et al., 2023). Biopsy examination is also a crucial diagnostic support for ovarian cancer; however, if biopsy is not followed by appropriate care and treatment, it may worsen disease prognosis due to wound sites potentially accelerating tumor growth (Molla & Bitew, 2025; Neagu et al., 2025; Uchikov et al., 2024). CA-125, also called Cancer Antigen 125 or Carbohydrate Antigen 125, was first discovered by Bast et al. in 1981. CA-125 is found in all originating tissues derived from mesothelial and coelomic epithelial cells, including pleura, pericardium, peritoneum, fallopian tubes, endometrium, and endocervix (Sabaruddin & Ferry, 2018). CA-125 is the most commonly used tumor marker in ovarian cancer, often referred to as the "Gold Standard" for the diagnosis of ovarian cancer (Wijaya et al., 2017).

CA 125, a glycoprotein generally expressed by ovarian epithelial cells, has attracted interest as a potential diagnostic marker (Giamougiannis, Martin‐Hirsch, & Martin, 2021; Liberto et al., 2022). According to (Gomes et al., 2020), CA 125 expression can be observed not only on the surface of cells but also detected in patient serum levels. Approximately 80% of patients with ovarian epithelial carcinoma show elevated serum levels of CA125, and more than 90% exhibit correlated serum CA125 levels with disease severity (Qing et al., 2022). CA125 expression is associated with various systemic tumors (such as ovarian cancer, digestive system malignancies, tongue cancer, breast cancer, and lung cancer). Several studies report that serum CA125 levels vary according to different types and pathological stages of ovarian cancer, with a diagnostic cutoff value of CA125 > 35 U/mL (Israilov et al., 2022; Björkman et al., 2021). Research shows that serum CA125 is higher in patients with ovarian epithelial cancer than in those with germ cell or sex cord stromal tumors (Gomes et al., 2020; Nasioudis, Wilson, Mastroyannis, & Latif, 2019; Rao et al., 2021). In particular, CA125 is

significantly higher in serous cystadenocarcinoma than in mucinous cystadenocarcinoma and clear cell carcinoma (Qing et al., 2022).

With advances in immunohistochemistry, analysis of CA 125 expression at the cellular level has become more precise, providing deeper insight into tumor biology. Although CA 125 has been identified as a promising marker for ovarian cancer, its use as a diagnostic indicator remains a subject of intensive research. Therefore, investigating the relationship between CA 125 immunohistochemical expression in ovarian epithelial tumors and serum CA 125 levels as diagnostic indicators requires a systematic review of existing scientific literature.

The novelty of this study lies in its comprehensive approach synthesizing evidence on the correlation between CA-125 immunohistochemical expression and serum levels specifically in the Indonesian context, where diagnostic challenges and late-stage presentations are prevalent. Unlike previous studies focusing separately on serum or tissue expression, this research integrates both aspects to provide a holistic diagnostic perspective, addressing the unique epidemiological and clinical landscape of ovarian cancer in Indonesia.

This study aims to investigate empirical evidence supporting the relationship between CA 125 immunohistochemical expression at the cellular level with serum CA 125 levels as diagnostic indicators of ovarian cancer. By conducting a systematic review of relevant literature, trends of consistency, differences, and knowledge gaps can be identified to guide further research and improve development of more accurate and efficient diagnostic strategies. This study hopes to provide a deeper understanding of the role of CA 125 in diagnosing ovarian cancer, paving the way for improved diagnostic methods and ultimately enhancing prognosis and quality of life for affected patients.

METHOD

This study was conducted using a literature review method, where researchers surveyed various sources, including reputable journals, books, documentation, internet resources, and libraries. Literature review involves reading materials specifically related to the object of ongoing research being reviewed (Prastowo, 2016). Data used for the search focused on journals selected using the PICOT framework and published in international online journals. The PICOT framework stands for P = population/problem, referring to the population or problem analyzed in accordance with predetermined themes; I = intervention/indicator, referring to the action or indicator related to the problem based on the theme; C = comparison, which is the intervention used as a comparator; O = outcome, which is the results or outcomes obtained in the selected studies; and T = time, which is the duration over which the research was conducted. The authors browsed journals through Google Scholar, Science Direct, and PubMed using keywords: *Immunohistochemical Expression of CA 125*, *Serum Levels*, *Diagnostic Indicators*, and *Ovarian Epithelial Tumors*.

Table 1. PICOT Framework Literature Review Format

Criteria	Inclusion	Exclusion
Population	Patients who suffer tumor ovarian epithelium	Patient with type non- epithelial ovarian tumor
Intervention	Patients undergoing inspection expression CA 125 immunohistochemistry in ovarian tumors	Studies that do not take into account expression CA 125

Criteria	Inclusion	Exclusion
		immunohistochemistry in ovarian tumors
Comparison	Patients who have measured serum CA 125 levels in a way simultaneously	Studies that do not covers measurement serum CA 125 levels simultaneously
Outcomes	Patients who have outcome data diagnostic based on expression CA 125 immunohistochemistry and serum CA 125 levels	Studies that do not report results related diagnostics with expression CA 125 immunohistochemistry and serum CA 125 levels
Time	n't any limitation time certain	Study with information that is not relevant or No covers sufficient time For analysis connection
Publication Years	Range time publisher journals used 2003-2023	Under 2003

Source: Compiled by researchers based on Prastowo (2016), 2024

Based on a search of journals on Google Scholar, Science Direct, and PubMed with the keywords *Immunohistochemical Expression of CA 125*, *Serum Levels*, *Diagnostic Indicators*, and *Ovarian Epithelial Tumors*, 20,500 suitable journals were initially identified through the keywords. Screening was then performed. From the screening results of journals published in the last 5 years, 145 complete-text journals were assessed for eligibility. After the eligibility assessment, 57 journals were found suitable for the research objectives; among these, 27 journals were excluded because they were duplicates, and 25 journals were excluded due to lack of full text or non-publication. Consequently, 5 journals with full texts were obtained and reviewed.

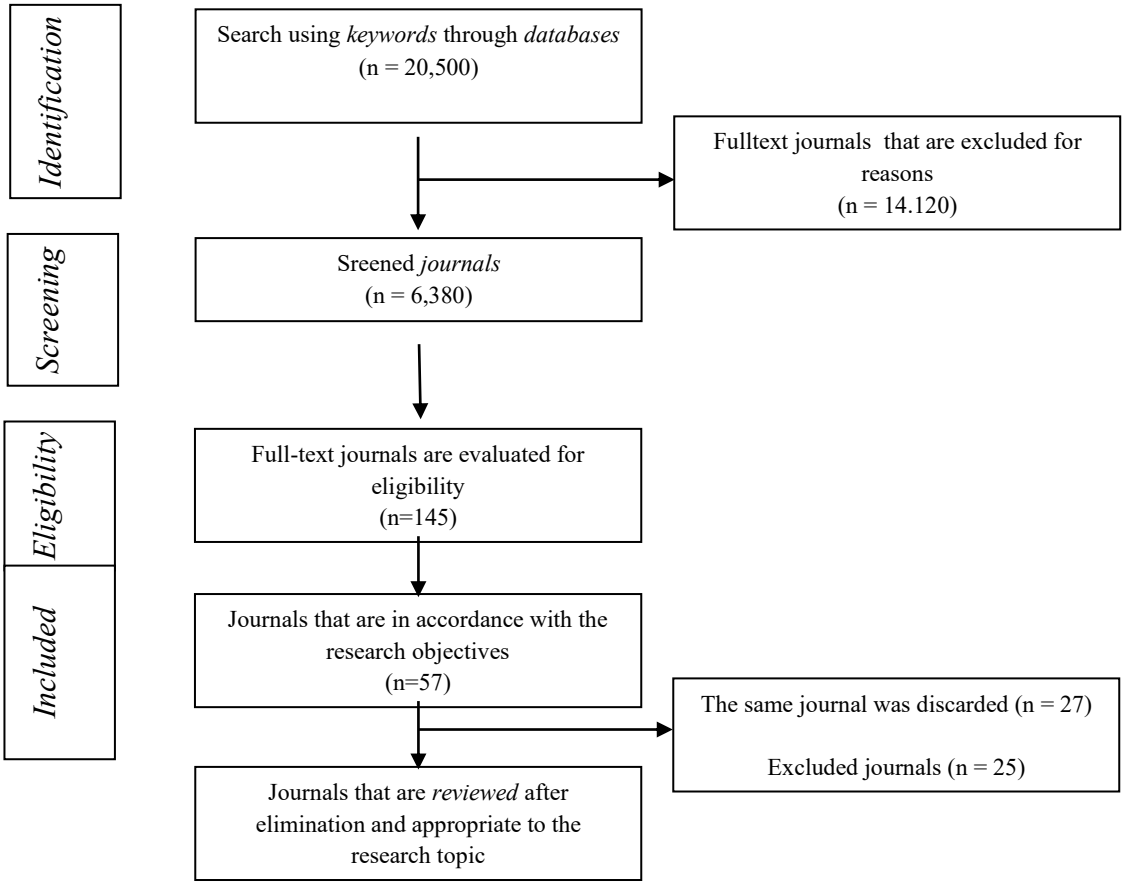

Figure 1. PRISMA Literature Review diagram

Source: Processed by researchers based on PRISMA guidelines, 2024

Table 2. Search Results Literature Review

No	Researcher Name	Year	Journal Name	Title	Summary of Research Results
1.	Daniel G. Rosen, Lin Wang, J. Neeley Atkinson, Yinhua Yu, Karen H. Lu, Eleftherios P. Diamandis, Ingegerd Hellstrom, Samuel C. Mok, Jinsong Liu & Robert C. Bast Jr	2005	*Gynecologic oncology*	*Potential markers that complement expression of CA125 in epithelial ovarian cancer*	Results: Low CA125 expression or No present in the specimen surgery epithelial ovarian cancer associated with low serum CA125 levels in pre-operative serum specimen . In ovarian cancer that is not have CA125, all specimens (100%) expressed human kallikrein 10 (HK10), human kallikrein 6 (HK6), osteopontin (OPN), and claudin 3. A small proportion CA125-deficient ovarian cancers express DF3 (95%), a factor growth endothelium vascular (VEGF) (81%), MUC1 (62%), mesothelin (MES) (34%), HE4 (32%), and CA19-9 (29%). When reactivity with normal tissue is considered , MES

No	Researcher Name	Year	Journal Name	Title	Summary of Research Results
					and HE4 show specificity biggest . Expression differentials were also found for HK10, OPN, DF3, and MUC1.
2.	Fatih Gundogdu, Ferit Soylu, Levent Erkan, Orkan Tatli, Sadiye Mavi & Ali Yavuzcan	2011	*Archives of Gynecology and Obstetrics*	*The role of serum CA-125 levels and CA-125 tissue expression positivity in the prediction of the recurrence of stage III and IV epithelial ovarian tumors (CA-125 levels and tissue CA-125 in ovarian tumors)*	Results. Relationship between CA-125 values and recurrence significant in stage III/IV patients (p = 0.041/ p = 0.006). The relationship between CA-125 values and recurrence significant in patients with serous tumors , endometrioid tumors , tumors cell clear , and tumors that are not differentiated tumor (p = 0.034 / p = 0.044 / p = 0.039 / p = 0.043 respectively, p \ 0.05). It was not significant in tumors mucinous (p = 0.667). Connection between CA-125 expression network positive and developmental relapse significant in stage III/IV patients (p = 0.041 / p = 0.029). This correlated significant with relapse in patients with serous tumors , endometrioid tumors , tumors cell clear , tumor mukin , and tumors that are not differentiated (p = 0.034 / p = 0.044 /). p = 0.047 / p = 0.036 / p = 0.043 respectively, p \ 0.05).
3.	Estrid VS Høgdall, Lise Christensen, Susanne K. Kjaer, Jan Blaakaer, Anette Kjærbye-Thygesen, Simon Gayther, Ian J. Jacobs & Claus K. Høgdall	2007	*Gynecologic oncology*	*CA125 expression pattern, prognosis and correlation with serum CA125 in ovarian tumor patients From The Danish "MALOVA" Ovarian Cancer Study*	Results. In general significant more Lots tumor positive CA125 expression (no There is expression vs expression) was found in the serous subtype compared with percentage tumor positive on subtype mucinous , endometrioid and subtypes other For patient with borderline ovarian tumors and with OC (p<0.00001, p<0.00001). Similarly , the correlation significant positive found between improvement serum CA125 levels and increases level of expression CA125 tissue (N= 382 stage I-IV OC,

No	Researcher Name	Year	Journal Name	Title	Summary of Research Results
					Spearman ρ= 0.31, p<0.0001) (N= 206 stage III OC, Spearman ρ= 0.30, p<0.0001). We found out continuity life that is significant more short For stage III/IV OC patients without expression CA125 network compared with OC stage III/IV patients with expression CA125 positive tissue (p= 0.0003).
4.	Chhanda Das, Madhumita Mukhopadhyay, Tarun Ghosh, Ashis Kumar Saha & Moumita Sengupta	2014	*Journal of clinical and Diagnostic Research: JCDR*	*Correlation of Cytohistlogical Expression and Serum Level of Ca125 in Ovarian Neoplasm*	Results. Correlation significant positive found between improvement serum CA125 levels and expression cytohistology from CA125. Sensitivity overall is 100%, specificity 86%, value predictive positive is 74% and predictive negative 100% accuracy value diagnostic is 90% with statistics tall significance (p < 0.001).
5.	Ji Hui Choi, Geum Seon Sohn, Doo Byung Chay, Han Byoul Cho, Jae-Hoon Kim	2018	*Obstetrics & gynecology science*	*Preoperative serum levels of cancer antigen 125 and carcinoembryonic antigen ratio can improve differentiation between mucinous ovarian carcinoma and other epithelial ovarian carcinomas*	CCR in carcinoma mucus (average 32.1) in significant more low compared to with cell clear (mean 235.0) and endometrioid carcinoma (mean 427.0) in stage I (all P<0.05). In stages II-IV, CCR in endometrioid carcinoma mucus (average 37.6) in significant more low than serous carcinoma (mean 148.0) (P<0.01). Sensitivity and specificity of CCR in detect carcinoma mucinose from other types of EOC were 75.0% and 77.5%, respectively in stage I and 100.0% and 84.4%, respectively in stage II-IV (both cut-off value <90.7).

Source: Results of researcher analysis from Google Scholar, Science Direct, and PubMed databases, 2024

RESULT AND DISCUSSION

This review already includes five original articles about diagnostic indicators in ovarian epithelial tumors. Rosen et al. (2005) found that serum CA125 levels before operation correlated with CA125 expression in ovarian tumor tissues. The correlation was significant between serum CA125 levels and CA125 expression in ovarian tumor tissues (Spearman rank correlation 0.28; $P \leq 0.0005$). Additionally, median serum CA125 levels significantly increased from cancers not expressing CA125 (151 U/mL) to cancers expressing CA125 with low

intensity (878 U/mL), and further to cancers expressing CA125 with high intensity (1223 U/mL).

Meanwhile, Gundogdu et al. (2011) showed that serum CA-125 values and CA-125 expression networks can be used as markers to predict the risk of relapse in early-stage ovarian cancer. The relationship between serum CA-125 and recurrence was significant in patients with serous tumors, endometrioid tumors, clear cell tumors, and undifferentiated tumors ($p = 0.034$, $p = 0.044$, $p = 0.047$, $p = 0.036$, $p = 0.043$ respectively, all $p < 0.05$). In addition, positive CA-125 tissue expression was also significantly correlated with relapse development in patients with these tumor types ($p = 0.041$, $p = 0.044$, $p = 0.039$, $p = 0.043$ respectively, all $p < 0.05$).

Høgdall et al. (2007) used tissue array (TA) analysis to determine CA125 expression in ovarian tumor tissues and correlated it with clinicopathological parameters and serum CA125 levels. Their results showed a significant correlation between high serum CA125 levels and CA125 expression in ovarian tumor tissues. CA125 expression in tissues also served as a prognostic marker in ovarian cancer, especially in patients with advanced-stage disease. This study demonstrated that CA125 expression in ovarian tumor tissues can be a determinant factor for selecting customized treatment for patients.

Das et al. (2014) showed a significant positive correlation between high serum CA125 levels and CA125 cytohistological expression. Overall sensitivity was 100%, specificity was 86%, positive predictive value was 74%, and negative predictive value was 100%. Diagnostic accuracy was 90% with high statistical significance ($p < 0.001$). Their results indicate that high serum CA125 levels correspond to strong cytohistological expression, with high sensitivity and adequate specificity, supporting the use of serum CA125 as a diagnostic indicator for ovarian cancer.

Choi et al. (2018) demonstrated that CA125, the most common marker for epithelial ovarian cancer (EOC), has varying expression depending on the histological type of ovarian tumors. CA125 was increased in 85% of serous carcinomas, 65% of endometrioid tumors, 40% of clear cell tumors, and 36% of undifferentiated tumors, but only increased in 12% of mucinous ovarian carcinomas. This highlights the importance of finding additional markers to differentiate ovarian pelvic masses preoperatively, especially to distinguish mucinous tumors from other types of EOC.

Various studies, including those by Rosen et al. (2005), found a significant correlation between preoperative serum CA125 levels and tissue CA125 expression in ovarian tumors. This was supported by Gundogdu et al. (2011), who showed that serum CA-125 and CA-125 expression networks can predict relapse risk in early-stage ovarian cancer, particularly in certain tumor types. Høgdall et al. (2007) confirmed a positive correlation between high serum CA125 levels and tissue expression and highlighted CA125's prognostic value in advanced ovarian cancer. Das et al. (2014) found a significant positive correlation between high serum CA125 and cytohistological expression, endorsing CA125 as a sensitive and specific diagnostic marker. Finally, Choi et al.'s (2018) work showed that CA125 expression varies by histological tumor type, enhancing understanding of CA125's role as an ovarian cancer marker. Overall, these findings provide a basis to consider CA125 an important marker in diagnosis, prognosis, and treatment selection for ovarian cancer patients.

CONCLUSION

Serum CA125 levels demonstrate a significant relationship with CA125 expression in ovarian tumors, highlighting CA125 as a crucial marker for diagnosis, prognosis, and treatment of ovarian cancer. The marker's connection with early relapse risk, prognostic value in advanced stages, and correlation with cytohistological expression confirms its clinical relevance. These findings support integrating tissue CA125 expression with serum levels to improve diagnostic accuracy, especially in resource-limited settings such as Indonesia. For future research, there is a need to standardize immunohistochemical techniques, establish population-specific serum cut-off values, and investigate complementary biomarkers like HE4 and the CA-125/CEA ratio for better subtype differentiation. Multicenter prospective studies with long-term follow-up are recommended to validate these approaches and explore combined CA125 assessment's prognostic value across diverse populations, ultimately enhancing early detection and personalized treatment strategies for ovarian cancer patients.

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