Short Communications

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Selenium Levels in Early and Advanced Stages of Epithelial Ovarian Cancer

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Abstract

Objective: This study aimed to explore selenium levels in patients with epithelial ovarian cancer and evaluate the role of this micronutrient in disease development. **Methods:** This analytical observational study employed a cross-sectional design and was conducted at the Cipto Mangunkusumo National Referral Hospital from March to August 2024. The study included patients with suspected ovarian malignancy undergoing oophorectomy, including conservative surgical staging, unilateral surgical staging, or debulking surgery. The primary outcome was the correlation between serum selenium levels and the staging of ovarian cancer. ANOVA or the Kruskal–Wallis test was used to examine relationships between variables. Receiver operating characteristic (ROC) curve analysis was also performed to determine the optimal cutoff value for serum selenium levels. **Result:** A total of sixty patients with ovarian cancer were studied, with 40% at stage I, 8.3% at stage II, 41.7% at stage III, and 10% at stage IV. Serum selenium levels varied significantly by tumor stage ($p < 0.05$), showing a negative correlation with tumor severity (Spearman's $r = -0.27$). Lower selenium levels were linked to higher cancer stages, with stage II exhibiting the highest levels and stage IV the lowest. ROC curve analysis demonstrated an area under the curve (AUC) of 0.648 (95% CI 0.503–0.794; $p < 0.05$), with a sensitivity of 65.5% and specificity of 61.3% at a cutoff value of selenium > 91.50 μg/L. Although patients with selenium levels ≤91.50 μg/L showed a higher proportion of advanced-stage disease, the difference was not statistically significant (OR 2.59, 95% CI 0.91–7.34; $p = 0.073$). **Conclusion:** Lower serum selenium levels were associated with more advanced stages of epithelial ovarian cancer, suggesting a potential relationship between selenium status and disease progression.

Keywords: antioxidants, adjuvant, micronutrients, ovarian neoplasms, selenium

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Introduction

Ovarian cancer (OC) is an aggressive gynaecological malignancy characterized by rapid progression, high metastatic potential, and poor prognosis. Globally, approximately 313,959 women are diagnosed with ovarian cancer each year, resulting in 207,252 cancer-related deaths. It ranks as the sixth leading cause of cancer mortality among women. In Indonesia, 14,896 new cases were reported in 2020, making ovarian cancer the third most common cancer among women after breast and cervical cancer, with 9,581 deaths [1]. Although less common than other gynaecologic malignancies, OC has the highest mortality rate, largely because more than two-thirds of cases are diagnosed at an advanced stage. Consequently, patients often require complex and intensive treatment with substantial physical and psychological burden [2-4]. Therefore, research on prevention, early detection, and effective therapeutic strategies remains essential to improve survival outcomes.

Micronutrients, including vitamins and minerals, are required in small amounts but play critical roles in growth, development, and disease prevention. However, the role of micronutrients in OC development remains unclear, with limited available evidence [5, 6]. Among micronutrients, vitamin D has been reported to contribute to ovarian cancer prevention through antitumor activity by regulating cellular proliferation and metabolism via genomic and non-genomic signalling pathways [7-9].

Other micronutrients, such as selenium, have demonstrated potential protective effects against several cancers, including prostate, colon, oesophageal, lung,

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and gastric cancers. Randomized controlled trials have suggested that selenium supplementation may reduce overall cancer morbidity by up to 50% [10]. Selenium functions as an antioxidant, anti-inflammatory agent, immune booster, and cancer risk reducer [11-13]. Selenium exerts antioxidant, anti-inflammatory, and immunomodulatory effects, and may inhibit tumour invasion and metastasis. It has also been used as an adjunct therapy in patients undergoing radiotherapy and chemotherapy [14]. Selenium supplementation during cancer treatment has been associated with increased plasma selenium levels, improved therapeutic response, reduced treatment-related side effects, and better quality of life [15].

To date, no studies have evaluated selenium levels in ovarian cancer patients in Indonesia. This study aims to investigate serum selenium levels in patients with epithelial OC at Cipto Mangunkusumo National Referral Hospital (RSCM), Jakarta, Indonesia. The findings may provide insight into the potential relevance of selenium in OC progression and management.

Materials and Methods

Study Design

This analytical observational study employed a cross-sectional design and was conducted at Cipto Mangunkusumo National Referral Hospital, Jakarta, from October 2023 to March 2024. Ethical approval was obtained from the Institutional Review Board of RSCM Faculty of Medicine Universitas Indonesia (No. KET-421/UN2.F1/ETIK/PPM.00.02/2024).

Study Population

This study includes patients diagnosed with epithelial ovarian (EOC) following surgery including oophorectomy, conservative surgical staging, unilateral surgical staging, or debulking surgery. Exclusion criteria were patients whose pathological examination did not confirm epithelial ovarian cancer, those who had received neoadjuvant chemotherapy, individuals with gastrointestinal or urinary disorders prior to study enrolment, and patients with a history of surgery involving the gastrointestinal or urinary tract. The sample size for this analytical cross-sectional study $[n1=n2=2([^{Z\alpha + Z\beta JS}) \chi_1 - \chi_2]$ calculated to be 44 patients [16, 17]; considering a potential dropout rate of 10%, the total sample size is determined to be 60 participants. Subjects were recruited using a consecutive sampling method.

Data Collection

Ovarian cancer staging in this study followed the FIGO 2014 classification system. Intraoperative histopathological examination was used to diagnose EOC, which comprises several histopathological subtypes, including serous carcinoma (high-grade and low-grade), endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma [18, 19].

Selenium is a chemical element with atomic number 34 that is primarily metabolized into selenocysteine (Sec). Serum selenium levels were measured from peripheral blood samples. Approximately 10 mL of blood was collected at hospital admission, one day prior to surgery, and analyzed in the laboratory. The normal reference range for serum selenium is 120–160 μg/L [20].

Study Outcome

The primary outcome of this study was to assess the association between serum selenium levels and the stage of EOC. The secondary outcome was to compare serum selenium levels among patients across different cancer stages.

Data Analysis

Statistical analysis was performed using SPSS version 25.0. Univariate analysis was conducted to describe the baseline characteristics of the study subjects. Categorical variables were presented as frequencies and percentages, while numerical variables were summarized using mean, median, standard deviation, minimum, and maximum values. To evaluate the relationship between selenium levels and ovarian cancer stage, ANOVA was used for normally distributed data, while the Kruskal–Wallis test was applied as a non-parametric alternative. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value for serum selenium levels.

Results

During the mentioned period, we included 60 patients with mean age of patients ranged from 44.5 to 54.1 years across stages. A total 24 were classified as stage I EOC (40%), 5 were staged II EOC (8.3%), 25 were staged III EOC (41.7%), and 6 were staged IV EOC (10%). The distribution of EOC histopathological subtypes varied across stages.

To differentiate between early-stage (FIGO stage I–II) and advanced-stage (FIGO stage III–IV) EOC, we divided the samples into two categories: early stage (n = 29, 48.3%) and advanced stage (n = 31, 51.7%). Serum selenium levels were evaluated as a potential indicator of disease severity in EOC based on tumor stage. As shown in Table 1, selenium levels differed significantly across tumor stages ($p < 0.05$) and demonstrated a significant negative correlation with stage (Spearman's $r = -0.27$, $p < 0.05$; Kendall's $\tau = -0.21$, $p < 0.05$). Lower selenium levels were associated with more advanced EOC stages, with stage II showing the highest median level and stage IV the lowest. Overall, a decreasing trend in selenium levels was observed with increasing cancer stage (Figure 1).

Receiver operating characteristic (ROC) analysis yielded an area under the curve (AUC) of 0.648 (95% CI 0.503–0.794; $p < 0.05$). A cutoff value of selenium >91.50 μg/L showed a sensitivity of 65.5% and specificity of 61.3%. However, this cutoff did not significantly differentiate the incidence of advanced-stage disease (OR 2.59, 95% CI 0.91–7.34; $p = 0.073$) (Figure 2).

Discussion

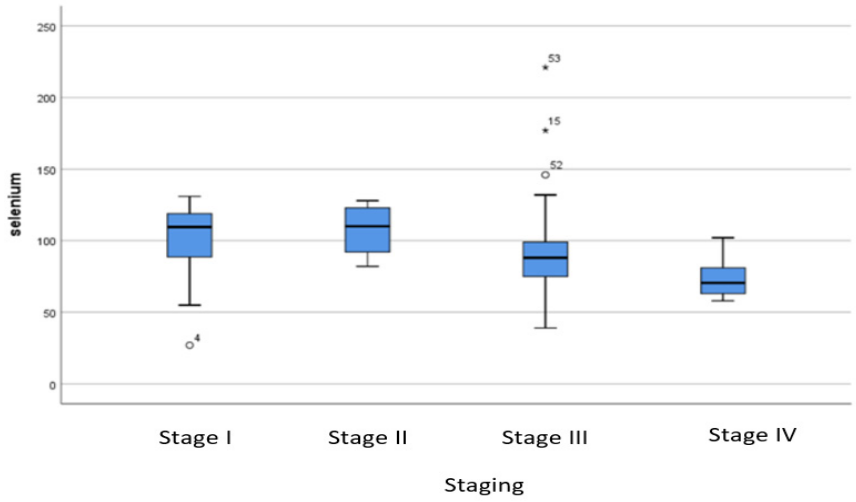

Figure 1. Selenium Levels Presented as Boxplot

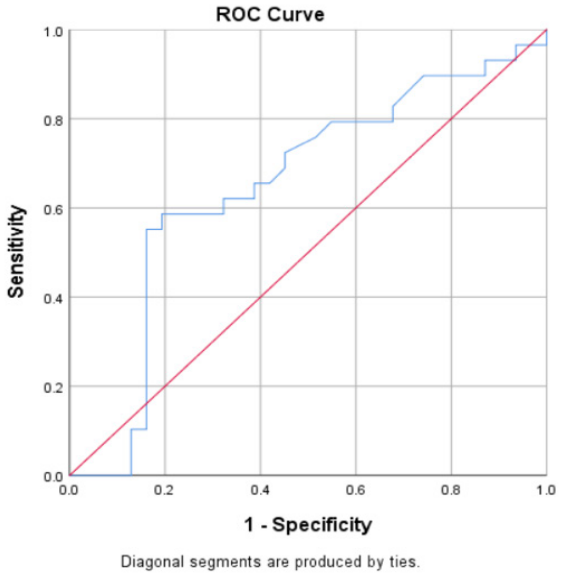

Figure 2. ROC for Selenium Levels

This study demonstrated a significant difference in serum selenium levels across FIGO stages I to IV with a negative correlation between selenium levels and cancer stage. These findings suggest that lower selenium levels are associated with more advanced disease. This result is consistent with previous studies reporting an inverse relationship between selenium concentration and cancer severity. Kluza et al. [16] involving a matched cohort of 314 women identified a significant inverse relationship between blood selenium levels and the presence of ovarian cancer across all cancer stages. This relationship aligns with the progression of the disease and the overall deterioration of the patients' conditions. Clear associations between low selenium concentrations and the incidence of ovarian cancer were found, with univariate analysis yielding an OR of 35.3 (95% CI: 11.2–111; $p < 0.001$) and multivariate analysis showing an OR of 45.8 (95% CI: 12.8–164; $p < 0.001$).

The role of selenium (Se) in cancer prevention and progression has been the subject of extensive research. The biological mechanisms behind selenium's potential protective effects against cancer are complex and not fully understood. Selenium plays a crucial role in cancer prevention by maintaining antioxidant defenses, stimulating immune function, regulating the cell cycle, inducing apoptosis, and inhibiting angiogenesis. It may also modulate the activity of tumor suppressor proteins like *p53* and influence DNA repair mechanisms. However, the specific ways selenium affects ovarian cancer development, especially at different stages, need further investigation [3, 21 , 22].

Selenium chemopreventive effects mainly involve maintaining redox homeostasis and preventing improper protein folding through selenoproteins such as glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs), and selenoprotein P (SelP), which help mitigate oxidative DNA damage. These selenoproteins play significant roles in inhibiting cell proliferation, promoting apoptosis, and reducing metastasis, primarily by halting the cell cycle at the G1 phase through redox modifications. Low selenium levels can disrupt these pathways, impairing selenoprotein synthesis and potentially leading to tumor initiation and progression, as observed in colorectal cancer (CRC). Moreover, certain single nucleotide polymorphisms that affect selenoproteins (GPX-1, GPX-2, SELENOP, TXNRD1) may also contribute to CRC development. Research indicates that sodium selenite can inhibit the growth of cancer cells, including those in prostate, liver, malignant melanoma, and various hematological

Table 1. Selenium Levels

Variables	FIGO Stage 2014				p-value[a]	r-value[b]
	Stage I (n=24)	Stage II (n=5)	Stage III (n=25)	Stage IV (n=6)		
Selenium (in blood; µg/L)	109.50 (27-131)	110 .00 (82-128)	88.00 (39-221)	70.50 (58-102)	0.035[a]*	-0.27; 0.05

Data are presented as Median (Min-max). [a], Kruskal-Walis; [b], Spearman. *significance ($p < 0.05$).

malignancies, by inducing apoptosis through mechanisms involving oxidative stress, mitogen-activated protein kinases, *p53*-dependent signaling, and mitochondrial pathways. Although some evidence suggests selective selenium toxicity against cancer cells, there is limited data on its specific cytotoxic effects and its supportive role during chemotherapy in epithelial ovarian cancer (EOC) [17, 23].

Several clinical trials have examined the effects of selenium supplementation during cancer chemotherapy. A clinical trial with 41 patients undergoing cisplatin chemotherapy for solid tumors found that those receiving selenium had significantly higher white blood cell counts on day 14 after treatment initiation. Additionally, the selenium group required notably less granulocyte colony-stimulating factor and had a reduced volume of blood transfusions. In a separate study involving 62 women with ovarian cancer receiving a combination of cisplatin and cyclophosphamide, those supplemented with selenium experienced significantly less neutropenia and increased leukocyte counts between the second and third chemotherapy cycles. The authors also reported a significant reduction in side effects, including nausea, vomiting, and hair loss. It also observed a slight increase in food intake in mice given selenium during chemotherapy, suggesting the need for further evaluation of these effects in human trials [17].

This study is the first to evaluate selenium levels in EOC patients in Indonesia. However, it has some limitations. First, the relatively small sample size, particularly in certain stages, may restrict the ability to detect significant differences. This issue is common in ovarian cancer research due to the challenges of early diagnosis and the tendency for the disease to be identified at more advanced stages. Second, selenium's protective effects may be more pronounced in individuals with low initial selenium levels, as observed in other cancers such as prostate and lung cancer. In populations with adequate or high initial selenium levels, increasing selenium intake or serum levels may not significantly influence cancer progression. Future research with larger sample sizes and more detailed analyses is needed to confirm these findings and improve our understanding of selenium's potential as a prognostic biomarker for ovarian cancer or as a therapeutic agent.

In conlusion, this study represents a significant step in understanding the relationship between selenium levels and EOC in Indonesia. The findings suggest that lower selenium levels may be associated with increased cancer risk and disease progression. While selenium supplementation during chemotherapy shows promise in improving patient outcomes, further research is essential to clarify its role as a protective agent.

Author Contribution Statement

Conceptualization: L., K.H.N., H.W., L.N.; Methodology: L., K.H.N., E.C., M.Y.Y.; Data Collection / Investigation: L., E.C., N.C., T.M.I., E.A., V.G.E.P.; Data Analysis: L., K.H.N., M.Y.Y.; Supervision: H.W., L.N., T.D.A.; Writing – Original Draft Preparation: L., M.Y.Y.; Writing – Review & Editing: K.H.N., H.W., L.N., T.D.A.

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Approval

This study has received ethical approval from RSCM-FKUI (No KET 421/UN2.F1/ETIK/PPM.00.02/2024).

Data Availability

Upon acceptance, the copyright will be transferred to the Asia Pacific Journal of Cancer.

Conflict of Interest

All authors declared no conflict of interest.

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