PHAL and SII: Innovative Biomarkers for Diagnosing Ovarian Cancer in Both Epithelial and Non-Epithelial Subtypes

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Abstract

Objective: To evaluate the diagnostic utility of PHAL (Platelet, Hemoglobin, Albumin, and Lymphocyte), SII (Systemic Immune Inflammation Index), and SIRI (Systemic Inflammatory Response Index) for both epithelial and non-epithelial ovarian cancer.

Methods: A cross-sectional study of 156 patients with ovarian masses was conducted using preoperative laboratory data to calculate PHAL, SII, and SIRI scores. Histopathology confirmed diagnoses. Population I included all ovarian cancer types and benign tumors, while Population II included only non-epithelial ovarian cancer and benign tumors. Statistical analysis using SPSS 25.0, involved ROC curve and validity testing to assess diagnostic performance.

Result: SII showed the best performance in the overall population (AUC 0.738; sensitivity 71.25%; specificity 72.37%; accuracy 71.79%; LR+ 2.58; LR– 0.40). In the subgroup of non-epithelial ovarian cancer versus benign tumors, PHAL had the highest diagnostic accuracy (AUC 0.819; sensitivity 81.81%; specificity 73.68%; accuracy 75.51%; LR+ 3.11; LR– 0.25).

Conclusion: PHAL and SII are effective, accessible, and low-cost biomarkers that can support ovarian cancer diagnosis through routine blood tests.

Key words: Ovarian cancer, Platelet-Hemoglobin-Albumin-Lymphocyte (PHAL) score, Systemic Immune-Inflammation Index, Systemic Inflammatory Response Index

PHAL dan SII: Biomarker Inovatif untuk Diagnosis Kanker Ovarium Subtipe Epitel dan Non-Epitel

Abstrak

Tujuan: Penelitian ini bertujuan untuk mengevaluasi nilai diagnostik dari PHAL (Platelet, Haemoglobin, Albumin, dan Limfosit), SII (*Systemic Immune Inflammation Index*), dan SIRI (*Systemic Inflammatory Response Index*) pada kanker ovarium epitelial dan non-epitelial.

Metode: Penelitian dengan metode potong lintang ini melibatkan 156 pasien dengan massa ovarium. Data laboratorium pra-operatif digunakan untuk menghitung skor PHAL, SII, dan SIRI. Diagnosis ditegakkan melalui pemeriksaan histopatologi. Populasi I mencakup semua jenis kanker ovarium dan tumor jinak, sedangkan Populasi II hanya mencakup kanker ovarium non-epitelial dan tumor jinak. Analisis statistik dilakukan menggunakan SPSS 25.0, termasuk analisis kurva ROC dan uji validitas untuk menilai kinerja diagnostik.

Hasil: Hasil penelitian menyimpulkan bahwa SII memiliki performa terbaik pada seluruh populasi (AUC 0,738; sensitivitas 71,25%; spesifisitas 72,37%; akurasi 71,79%; LR+ 2,58; LR– 0,40). Pada subkelompok kanker ovarium non-epitelial dibandingkan dengan tumor jinak, PHAL menunjukkan akurasi diagnostik tertinggi (AUC 0,819; sensitivitas 81,81%; spesifisitas 73,68%; akurasi 75,51%; LR+ 3,11; LR– 0,25).

Kesimpulan: PHAL dan SII merupakan biomarker yang efektif, mudah diakses, dan berbiaya rendah yang dapat mendukung diagnosis kanker ovarium melalui pemeriksaan darah rutin.

Kata kunci: Kanker ovarium, Skor PHAL (Platelet-Hemoglobin-Albumin-Limfosit), Systemic Immune-Inflammation Index, Systemic Inflammatory Response Index

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Introduction

Ovarian cancer still remains the most lethal gynecologic malignancy. Ovarian cancer accounts for 2.5% of cancers in women, making it the 11th most common cancer and the 5th leading cause of cancer death among women in the US, with an estimated 19,680 new cases and 12,740 deaths projected in 2024.1 Globally, its incidence is higher in developed countries.2 In Indonesia, the prevalence of ovarian cancer was reported to be 48.74% at Dr. Cipto Mangunkusumo National Central General Hospital (RSCM), Jakarta and 48.7% at Dr. Hasan Sadikin General Hospital, Bandung in 2016.3–5 The high mortality rate is primarily due to delayed diagnosis, with 70% of cases identified at advanced stages. The 5-year survival rate for ovarian cancer is around 48% compared to 90% if detected early.[6,7]

Most ovarian cancers are of the epithelial type, while about 10% are non-epithelial, such as germ cell tumors and sex cord-stromal tumors (SCST).8 CA-125 is widely used for epithelial ovarian cancer, while markers for non-epithelial ovarian cancer include lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and inhibin, among others. These advanced tumor marker tests are often expensive or unavailable in low-resource settings. Hence, accessible and affordable alternatives are needed.[9,10]

Several mechanisms may explain the influence of nutritional and inflammatory status on cancer prognosis. In chronic inflammatory conditions, various cytokines in the body, such as NF-ƙB, p53, HIF-α, and VEGF, become dysregulated. This dysregulation can lead to the disruption of apoptosis, inhibition of cancer suppression, and promotion of neovascularization. Additionally, inflammation causes a shortening of erythrocyte lifespan, suppression of bone marrow function, and hypoferremia, resulting in decreased blood hemoglobin levels. Moreover, certain pro-inflammatory cytokines, such as thrombopoietin and IL-6, stimulate platelet production, leading to a condition known as reactive thrombocytosis. Reactive thrombocytosis is associated with poor survival and prognosis of cancer patients.[8,11,12]

Furthermore, malnutrition which is commonly occurs in cancer may lead to reduced albumin and lymphocyte levels due to cancer-related metabolic changes. This is also known as the Reverse Warburg Effect, which shifts energy from healthy cells to cancer cells, thereby facilitating tumor growth and tissue damage.[11,13]

Recent studies suggest immuno-nutritional and inflammatory biomarkers derived from routine blood tests, such as Hemoglobin, Albumin, Lymphocyte Platelet (HALP), Platelet, Hemoglobin, Albumin, Lymphocyte (PHAL), Systemic Immune-Inflammation Index (SII), and Systemic Inflammatory Response Index (SIRI) may aid in early detection.[12,14–17]

To date, the HALP score has been widely implemented in various cancer studies, including gynecologic types to predict outcomes.18–22 Njoku et al. reported that HALP correlated with FIGO staging, histology, grading, lympho-vascular space invasion (LVSI), and myometrial invasion in endometrial cancer.19–21 HALP components are affected by cancer-related inflammatory and metabolic changes, including cytokine dysregulation, anemia, thrombocytosis, and cancer-induced malnutrition.[11,19]

Systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) are emerging markers of inflammatory status that have been widely studied. SII reflects the balance between inflammation and immunity, while SIRI indicates inflammation linked to carcinogenesis. Studies suggest these markers may aid early cancer detection, with

elevated SIRI linked to poor prognosis and SII associated with disease progression and overall prognosis in ovarian cancer.[14,15,23,24]

PHAL was originally introduced by Chen et al. in 2015 as the HALP score for prognostic assessment in gastric carcinoma. HALP score was subsequently modified into the PHAL score to retain a positive correlation with ovarian cancer diagnosis and improve statistical applicability.[25]

With the growing need for accessible and cost-effective diagnostic tools, this study investigates the utility of PHAL, SII, and SIRI as alternative biomarkers for detecting both epithelial and non-epithelial cancer.

Method

This study was conducted to evaluate the utility of an immune-nutritional biomarker (PHAL) and systemic inflammatory biomarkers (SII and SIRI) for the diagnosis of ovarian cancer in both epithelial and non-epithelial subtypes. For this purpose, the study population consisted of cases of benign ovarian tumors and ovarian cancer of both epithelial and non-epithelial subtypes (referred to as Population I). Subsequently, the authors aimed to evaluate the diagnostic performance of PHAL, SII, and SIRI specifically for non-epithelial ovarian cancer. To achieve this, epithelial ovarian cancers were excluded, resulting in a study population comprising benign ovarian tumors and non-epithelial malignant ovarian tumors (hereafter referred to as Population II).

An analytic observational study with a cross-sectional design was implemented. The data were obtained from medical records of patients treated at Dr. Hasan Sadikin General Hospital, Bandung.
The study protocol adhered to all legal and ethical standards and the ethical approval was obtained from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia No. D4.04.03/D.XIV.6.5/90/2024. The medical records of 156 subjects presenting with ovarian masseswere consecutively enrolled at Dr. Hasan Sadikin General Hospital, Bandung, from February 2024 to January 2025. Subjects with a history of other malignancies, prior chemotherapy, bone marrow or hematological disorders, acute or chronic inflammatory conditions, or steroid hormone use within the past threemonths were excluded from the study.

Laboratory data prior to surgery were obtained, and biomarker values were calculated using specific formulas. The formulas for PHAL, SII and SIRI were defined as.[9,21,22]

$$\text{PHAL} = \frac{\text{Platelet}}{\text{Hemoglobin x Albumin x Lymphocyte}}$$

$$\text{SII} = \frac{\text{Platelet x Neutrophil}}{\text{Lymphocyte}}$$

$$\text{SIRI} = \frac{\text{Neutrophil x Monocyte}}{}$$

All ovarian masses were examined for their histopathology, and the results were considered the final diagnosis. In accordance with the objectives of this study, the study population was categorized into two datasets: Population I and Population II. Population I comprises the entire study cohort, including cases of ovarian cancer of both epithelial and non-epithelial subtypes, as well as benign ovarian tumors, while Population II consists solely of non-epithelial ovarian cancer cases and benign ovarian tumors. Statistical analyses were performed using IBM SPSS Statistics version 25.0 for Windows. Receiver Operating Characteristic (ROC) curve analysis was employed to determine the area under the curve (AUC) and the optimal cutoff values for each biomarker

in both Population I and Population II. Subsequent analysis included validity testing to determine sensitivity, specificity, likelihood ratio positive, likelihood ratio negative, and overall accuracy.

Result

Table 1 Subject's characteristic features of Population I

Characteristic	Population I (n=156)
Malignancy status (n=156)	
Malignant	80/156 (51.28%)
Benign	76/156 (48.72%)
Types of histopathology	
Malignant (n=80)	58/80 (72.5%)
Epithelial (n=58)	20/58 (34.48%)
Serous carcinoma	19/58 (32.76%)
Mucinous carcinoma	9/58 (15.52%)
Clear cell carcinoma	7/58 (12.07%)
Endometrioid carcinoma	3/58 (5.17%)
Other	22/80 (27.5%)
Non-epithelial (n=22)	10/22 (45.45%)
Adult granulosa cell tumor	5/22 (22.72%)
Yolk sac tumor	2/22 (9.09%)
Dysgerminoma	5/22 (22.72%)
Other	
Benign (n=76)	13/76 (17.10%)
Teratoma	23/76 (30.26%)
Endometrioma	20/76 (26.31%)
Mucinous cystadenoma	16/76 (21.05%)
Serous cystadenoma	4/76 (5.26%)
Other	
Extend of the disease (malignant group; n=80)	
Advance stage	48/80 (60%)
Early-stage	32/80 (40%)

Medical records from 156 women diagnosed with an ovarian mass who were scheduled for surgery were reviewed. Among these patients, 80 (51.28%) were confirmed to have ovarian cancer, indicating a prevalence of 51.28% at our Gynecology-Oncology center. Of the ovarian cancer cases, 48 (60%) were diagnosed as advanced-stage and 32 (40%) as early-stage. Histopathological evaluation revealed that 58 cases (72.5%) were of the epithelial type, while 22 cases (27.5%) were non-epithelial. Notably, serous carcinoma was the most common epithelial subtype, and Adult Granulosa Cell Tumor was the most frequently observed non-epithelial type (Table 1).

Population II comprised a total of 98 subjects, including 76 benign ovarian tumors and 22 non-epithelial ovarian cancers. Among the cancer cases, 59.09% were diagnosed at an advanced stage, while 40.91% were diagnosed at an early-stage. The most common non-epithelial ovarian cancer was Adult Granulosa Cell Tumor, whereas the most frequent benign ovarian tumor was teratoma (Table 2).

Table 2 Subject's characteristic features of Population II

Characteristic	Population II (n=98)
Malignancy status (n=98)	
Malignant	22/98 (22.45%)
Benign	76/98 (77.55%)
Types of histopathology	
Malignant	
Non-epithelial (n=22)	10/22 (45.45%)
Adult granulosa cell tumor	5/22 (22.72%)
Yolk sac tumor	2/22 (9.09%)
Dysgerminoma	5/22 (22.72%)
Other	
Benign (n=76)	13/76 (17.10%)
Teratoma	23/76 (30.26%)
Endometrioma	20/76 (26.31%)
Mucinous cystadenoma	16/76 (21.05%)
Serous cystadenoma	4/76 (5.26%)
Other	
Extend of the disease (malignant non-epithelial; n=80)	
Advance stage	13/22 (59.09%)
Early-stage	9/22 (40.91%)

Population I includes benign ovarian tumors, epithelial ovarian cancer, and non-epithelial ovarian cancer. Subsequently, data were analyzed using Receiver Operating Characteristic (ROC) analysis and graphical methods to determine the AUC, significance, sensitivity, and specificity of PHAL, SII, and SIRI. It was observed that all variables exhibited statistically significant values ($p < 0.001$), with PHAL showing the highest AUC of 0.740. (Table 3, Fig 1)

Population II refers to the study population comprising only benign ovarian tumors and non-epithelial ovarian cancer. Data from Population II were analyzed using ROC curves to determine the optimal cutoff points and diagnostic values of PHAL, SII, and SIRI in the subgroup of non-epithelial ovarian cancer. PHAL demonstrated the highest diagnostic performance for non-epithelial ovarian cancer, with an optimal cutoff of 3.920, a significance level of $p < 0.001$, an AUC of 0.819, sensitivity of 81.8%, and specificity of 73.7%. SII and SIRI also showed good diagnostic values, with optimal cutoffs of 779.468 and 1.331, significance levels of $p = 0.001$ and $p = 0.003$, AUCs of 0.743 and 0.707, sensitivities of 81.8% and

63.6%, and specificities of 65.8% and 68.4%, respectively (Table 4 and Fig.2).

Table 5 displays the diagnostic performance of the three biomarkers for both the overall ovarian cancer population (Population I), which includes epithelial and non-epithelial subtypes, and the non-epithelial ovarian cancer population (Population II). In Population I, SII demonstrated the best diagnostic performance, with a sensitivity of 71.25%, specificity of 72.37%, accuracy of 71.79%, a positive likelihood ratio (LR+) of 2.58, and a negative likelihood ratio (LR-) of 0.4. In Population II, the best diagnostic performance was observed with PHAL, exhibiting a sensitivity of 81.81%, specificity of 73.68%, accuracy of 75.51%, an LR+ of 3.11, and an LR- of 0.25.

Discussion

PHAL, an immune-nutritional biomarker, can be utilized as a diagnostic tool for ovarian malignancy in both epithelial and non-epithelial subtypes, with an AUC of 0.740, a sensitivity of 70.0%, and a specificity of 69.73%. Similarly, the Systemic Immune-Inflammation Index (SII) demonstrated comparable diagnostic performance, with an AUC of 0.738, a sensitivity of 71.25%, and a specificity of 72.37%. In contrast, SIRI exhibited a diagnostic AUC of 0.718, with a sensitivity of 70% and a specificity of 67.1%, indicating that its diagnostic performance is inferior to that of PHAL and SII. These parameters can be compared to the well-established tumor marker CA-125; for example, Kim et al. (2019) reported an AUC of 0.811 for CA-125, while Zheng et al. reported a sensitivity of 75.97% and a specificity of 79.59%.[26,27]

As biomarkers of immune-nutrition and systemic inflammation, PHAL, SIRI, and SII remain imperfect for diagnosing ovarian

Table 3 ROC analysis and optimal cutoff of PHAL, SII, and SIRI of Population I

Biomarker	AUC	95%CI	p	Cutoff	Sensitivity	Specificity
PHAL	0.740	0.661-0.819	<0.001	3.816	70.0%	69.7%
SII	0.738	0.660-0.816	<0.001	890.255	71.3%	72.4%
SIRI	0.718	0.638-0.798	<0.001	1.289	70.0%	67.1%

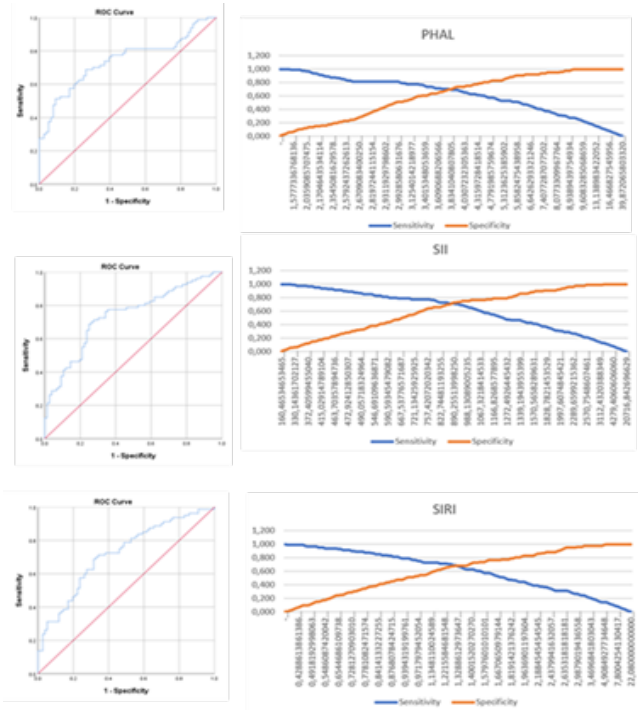

Figure 1 ROC curve and optimal cutoff of PHAL, SII and SIRI of Population I

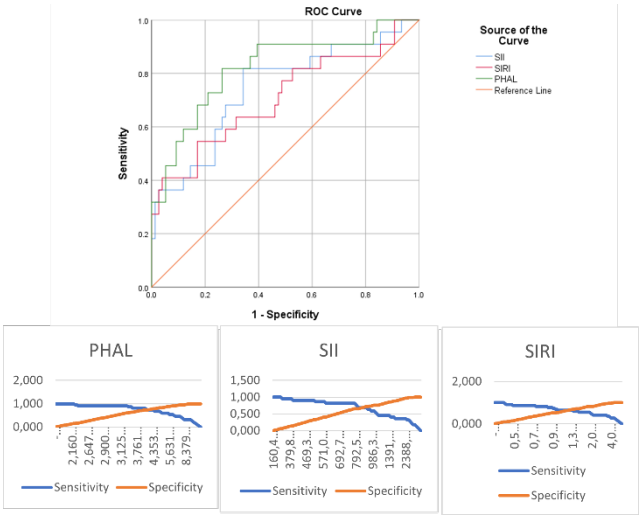

Figure 2. ROC curve and optimal cutoff of PHAL, SII and SIRI in Population II

Table 4 ROC analysis and optimal cutoff of PHAL, SII, and SIRI of Population II

Biomarker	AUC	95%CI	p	Cutoff	Sensitivity	Specificity
PHAL	0.819	0.711-0.928	<0.001	3.920	81.8%	73.7%
SII	0.743	0.618-0.868	0.001	779.468	81.8%	65.8%
SIRI	0.707	0.570-0.844	0.003	1.331	63.6%	68.4%

Table 5 Validity test (diagnostic performance) of biomarkers

	Population I			Population II		
	PHAL	**SII**	**SIRI**	**PHAL**	**SII**	**SIRI**
Sensitivity	70%	71.25%	70%	81.81%	81.81%	63.63%
Specificity	69.73%	72.37%	67.10%	73.68%	65.79%	68.42%
Accuracy	69.87%	71.79%	68.59%	75.51%	69.39%	67.35%
Likelihood ratio positive (LR+)	2.31	2.58	2.128	3.11	2.39	2.01
Likelihood ratio negative (LR-)	0.43	0.40	0.45	0.25	0.28	0.53

malignancy. Their diagnostic performance is influenced by various factors, including infections, chronic inflammatory conditions, patients' nutritional status and diet, conditions that may lead to malnutrition, and the presence or absence of blood transfusions. In contrast, CA-125, although a well-established tumor marker, also has several limitations. Its diagnostic value is affected by menopausal status, with higher levels typically observed in healthy premenopausal women. CA-125 levels are also elevated in several benign conditions, such as endometriosis—which induces chronic inflammation in the pelvic cavity and abdominal wall—leading to false positives. Furthermore, CA-125 can increase during menstruation, pregnancy, and childbirth, as well as in individuals with a high body mass index, where exces adipose tissue contributes to higher CA-125 levels. Ethnicity also plays a role; African and Asian women tend to have lower CA- 125 levels compared to Caucasian women. Additionally, some studies have reported that CA-125 is expressed in only 80% of ovarian cancer cases, with elevated levels observed in just 70% of early-stage cases.[28,29]

To minimize bias, it is reasonable to compare the diagnostic performance of PHAL, SII, and CA-125 within the same racial group—in this case, the Indonesian population. Winarto and Feharsal from Indonesia have previously reported on the diagnostic value of CA-125 for ovarian malignancy.4,5 The sensitivity of PHAL, SII, and CA-125 were 70.0%, 71.3%, and 67.2%, respectively, while their specificities were 69.7%, 72.4%, and 75.4%. These comparisons indicate that PHAL, SII, and CA-125 have nearly comparable diagnostic performance, suggesting that they can complement each other in the diagnosis of ovarian malignancy. To address the potential use of PHAL,

SII, and SIRI in diagnosing non-epithelial ovarian cancer, we refer to Tables 4 and 5. In these analyses, PHAL, SII, and SIRI demonstrated AUC values of 0.819, 0.743, and 0.707, respectively, with corresponding sensitivities of 81.81%, 81.81%, and 63.63%, and Specificities of 73.68%, 65.79%, and 68.42%. These results clearly indicate that PHAL is the most robust biomarker for the diagnosis of non-epithelial ovarian cancer.

Furthermore, when evaluating diagnostic accuracy, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) in Table 5, the optimal biomarker for ovarian cancer diagnosis can be identified—bearing in mind that a superior test exhibits higher accuracy and LR+ values coupled with a lower LR- value. In the overall population of ovarian masses (without confirmed epithelial versus non-epithelial subtypes), SII demonstrated the best performance, with an accuracy of 71.79%, an LR+ of 2.58, and an LR- of 0.40. Conversely, in the subgroup of ovarian masses suspected to be non-epithelial, PHAL exhibited excellent diagnostic performance, with an accuracy of 75.51%, an LR+ of 3.11, and an LR- of 0.25.

Conclusion

Both PHAL and SII are effective biomarkers

that can complement existing diagnostic methods for ovarian cancer across both epithelial and non-epithelial subtypes. In particular, in low-resource settings where established tumor marker testing (e.g., CA-125, AFP, LDH, or HCG) is unavailable, PHAL or SII may serve as viable alternative diagnostic modalities. Moreover, these biomarkers offer additional advantages, including greater accessibility, lower cost, and shorter assay times, as they require only routine blood tests.

Conflict of Interest

The authors report no conflicts of interest in this work.

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