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C-REACTIVE PROTEIN/ALBUMIN (CRP/ALB) RATIO AS A PREDICTOR OF OVARIAN CANCER

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ABSTRACT
Ovarian cancer is a type of cancer with a high incidence and mortality rate in Indonesia and worldwide. C-reactive protein (CRP) is an inflammatory marker meanwhile albumin is an indicator of nutritional deficiencies in ovarian cancer. This study is a diagnostic test for ovarian cancer in women aged >18 years and without previous history of ovarian cancer who underwent laparotomy or laparoscopy at Prof. Ngoerah General Hospital, Denpasar. Samples were taken by consecutive sampling. CRP examination was carried out in the laboratory by immunoturbidimetry method using the CRP Latex Kit (Roche) and measured using a Cobas integra 501 at a wavelength of 552 nm. The gold standard to diagnosed ovarian cancer was according to histopathological examination. A total of 69 women with ovarian tumors were recruited into the study which consisted of 40 ovarian cancers and 29 benign ovarian tumors. A significantly higher median CRP/Albumin ratio was found in ovarian cancer patients compared to benign ovarian tumors (6.9 vs 0.45; p=0.001). The optimal CRP/albumin ratio cut-off value was 1.34. The diagnostic capability of the CRP/Albumin ratio was found to be the best in diagnosing cancer at an advanced stage with a sensitivity of 86.9%, specificity of 68.9%, PPV of 68.9%, NPV of 86.9%, accuracy of 76.9%, positive likelihood ratio 2.8 and negative likelihood ratio 0.2. CRP/Albumin ratio can a potential diagnostic tool for ovarian cancer especially in advanced stage.

Info Article

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INTRODUCTION

Ovarian cancer is one of the most common gynecological cancers with a high mortality rate (Qaseem et al., 2014). The global incidence of ovarian cancer (185 countries in the world) based on Global Cancer Statistics (GLOBOCAN) data for 2018 was 295,414 cases with 184,799 deaths (Bray et al., 2018). The new cases reached 13,310 with 7,842 mortality in 2018 (Cancer, 2018). The incidence of ovarian cancer in the national central general hospital Dr. Cipto Mangunkusumo Jakarta from 2002 to 2006 also showed the highest proportion of gynecological cancers. Its mortality rate from 2002 to 2006 was also quite high, namely 34.1% of the 327 cases of death from gynecological cancer (Surbakti, 2004). Our institute, Prof. IGNG Ngoerah General Hospital, had 73 (15.33%) ovarian cancer patients out of 476 cases of gynecological cancer during the period July 2013-June 2014 (Dhitayoni & Budiana, 2017).

Chronic inflammation plays an important role in ovarian cancer. Several conditions such as endometriosis and pelvic inflammatory disease increase the risk of ovarian cancer, whereas exposure to anti-inflammatories reduces it (Browning et al., 2018). Ovarian cancer can produce cytokines which trigger inflammatory processes in the body. One of the most common marker of inflammatory process is C-reactive protein (CRP). It can be produced in the carcinogenesis process, either in the stage of tumor cell production or as a result of the reaction defense system against malignant cells (Hefler et al., 2008). Secretion of CRP is triggered by interleukin-1 (IL-1), IL-6, and Tumor Necrosis Factor (TNF). As an inflammatory marker, CRP is more stable than pro-inflammatory cytokines which have a short half-life (Shrotriya et al., 2015).

Ovarian cancer also often occurs in a state of hypoalbuminemia which can be caused by poor nutrition, obstruction of the small intestine, ascites, effects of tumor metabolism and inflammatory processes. Hypoalbuminemia can be an indicator of ongoing inflammatory condition in the body (Ataseven et al., 2015). Previous study (Kelly et al., 2015). revealed that ovarian cancer has lower serum albumin than benign tumors in pelvic area. The CRP/albumin ratio obtained from the combination of CRP and albumin may reflect inflammation and nutritional status in ovarian cancer patients. Therefore, the chronic systemic inflammatory response and progressive nutritional decline are reflected as an increased CRP/albumin ratio, which can consequently reduce the survival of patients with ovarian cancer (Liu et al., 2017). Stated that the preoperative CRP/albumin ratio correlated significantly with advanced tumor stage, residual tumor, increased CA 125 and the presence of ascites. So, an increase in the CRP/albumin ratio correlates with the level of malignancy in ovarian cancer.

One of the main problems in treating ovarian cancer is the difficulty in detecting ovarian cancer at an early stage. For now, there is no single diagnostic modality with sufficient sensitivity and specificity to meet these criteria (Qaseem et al., 2014). The ratio of CRP/albumin is a promising predictor of malignancy in pelvic area, especially ovarium. Study of CRP/albumin ratio to predict ovarian cancer is still very limited, therefore we aimed to know the accuracy of the CRP/albumin ratio as a predictor of ovarian cancer at Sanglah Central General Hospital, Denpasar.

METHODS

The design of this study was a diagnostic test. This research has received approval for ethical feasibility from the research ethics commission of the Faculty of Medicine, Udayana University/Prof. IGNG Ngoerah General Hospital Denpasar dated July 22 2021, Number 1951/UN14.2.2.VII.14/LT/2021 and obtained a research permit from the education and research division of Prof. IGNG Ngoerah Hospital dated August 20, 2021, Number LB.02.01/XIV.2.2.1/30558/2021.

This research was conducted at the Obstetrics and Gynecology Polyclinic and Clinical Pathology Laboratory, Prof. IGNG Ngoerah General Hospital Denpasar from September 2021 to May 2022. The sample was collected from the population by consecutive sampling. The inclusion criteria for this study were: 1) women aged ≥18 years with a diagnosis of ovarian tumor who underwent laparotomy or laparoscopy at Prof. IGNG Ngoerah General Hospital Denpasar with anatomical pathology results of benign tumors or malignant ovarian tumors; 2) no history of previous ovarian cancer treatment; 3) signing a written informed consent. Exclusion criteria in this study were women with ovarian tumors accompanied by primary malignancy in other organs, obesity, autoimmune disease, sepsis, or liver disease.

RESULTS AND DISCUSSION

Characteristics of the Research Sample

A total of 69 women with ovarian tumors were enrolled during the study period, consisting of 40 ovarian cancers and 29 ovarian benign tumors. The most common histopathological type was epithelial (69.9%). Among the epithelial subtypes, 30% (n=12) were serous high grade, 2.5% (n=1) were serous low grade, 22.5% (n=9) were mucinous, 12.5% (n=5) endometrioid, 10% (n=4) clear cells, and 2.5% (n=1) mixed epithelial. Median age and parity were not significantly different between ovarian cancer and benign ovarian tumor groups ($p>0.05$). The proportion of postmenopausal patients and epithelial-type tumors was significantly higher in the ovarian cancer group than in the benign ovarian tumors.

Table 1. Characteristics of the study population

Variable	Total (n=69)	Ovarian Cancer (n=40)	Benign Ovarian Tumor (n=29)	P-value
Age (years), median (IQR)	50 (15.5)	51.5 (9.75)	46 (17.5)	0.144
Parity, median (IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (1.0)	0.477
Menopause, n (%)				
Yes	32 (44.9)	23 (57.5)	9 (27.6)	0.014
No	37 (55.1)	17 (42.5)	20 (72.4)	
Histopathological type, n (%)	48 (69.6)	32 (80)	16 (55.2)	0.000
Epithelial	10 (14.5)	8 (20)	2 (6.9)	
Non-epithelial	11 (15.9)	0 (0)	11 (37.9)	
Others				
FIGO stage, n (%)				
I		13 (32.5)		
II		4 (10)		
III		22 (55)		
IV		1 (2.5)		
CA125 level (ng/ml), median (IQR)	128 (407.3)	225.9 (429.1)	67.2 (141.4)	0.009
RMI score, median (IQR)	582.3 (2450.2)	985.8 (4092.8)	249.6 (917.4)	0.001
	7.5 (35.4)	23.3 (55.5)	2.1 (7.3)	0.001
CRP level (mg/l), median (IQR)	3.96 (301.4)	3.9 (16.2)	4.2 (376.6)	0.015
Albumin level (g/dl), median (IQR)				
CRP:Albumin ration, median (IQR)	1.9 (12.1)	6.9 (16.9)	0.45 (1.82)	0.001
Post Menopause	8.66 (14.81)			0.001
Pre Menopause	2.38 (18.16)			
Early stage		1.92 (6.52)		0.000
Advance stage		11.0 (23.8)		

CRP/Albumin Ratio Comparison

Median CA125 levels, RMI scores, and CRP levels were significantly higher in ovarian cancer group. A significantly higher median CRP/Albumin ratio was found in ovarian cancer patients compared to benign ovarian tumors (6.9 vs 0.45; p=0.001). Based on menopausal status and ovarian cancer stage, the median CRP/Albumin ratio was significantly higher in the postmenopausal (8.66 vs 2.38; p = 0.001) and advanced cancer stages (11.0 vs 1.92; p = 0.000).

Diagnostic ability of CRP/Albumin ratio

The cut-off value of the CRP/albumin ratio used in this study was 1.34 which was obtained from the ROC curve (Figure 1) with area under the curve (AUC) 0.728, p=0.045; 95% CI 0.528 – 0.927). The AUC values for the stage, menopausal status and histopathological type subgroups are shown in Table 2. The diagnostic capability of the CRP/Albumin ratio was found to be the best in diagnosing cancer at an advanced stage with a sensitivity of 86.9%, specificity of 68.9%, PPV of 68.9%, NPV of 86.9%, accuracy of 76.9%, positive likelihood ratio 2.8, and negative likelihood ratio 0.2 (Table 3). The specificity, PPV and likelihood ratio positive of the CRP/albumin ratio also improved when combined with CA125 levels.

Figure 1. The ROC Curve

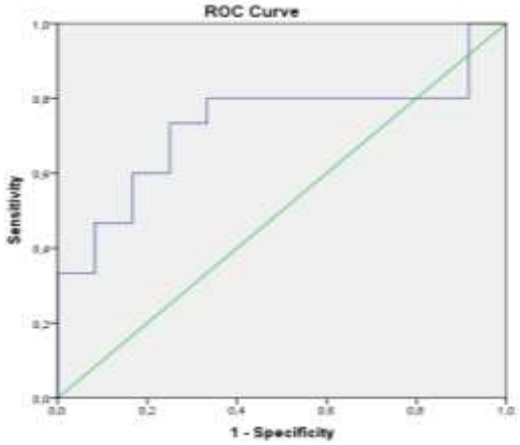

Table 2. Subgroup Analysis of the AUC

Subgroup	N	AUC	95% CI	P-value
Stage				
Early stage	17	0.636	0.466 – 0.806	0.127
Advance stage	23	0.826	0.705 – 0.947	0.000
Menopausal status				
Pre-menopausal	37	0.732	0.567 – 0.898	0.016
Post-menopausal	32	0.715	0.495 – 0.935	0.062
Histopathology				
Epithelial	32	0.729	0.596 – 0.862	0.002
Non-epithelial	8	0.810	0.665 – 0.956	0.008

Table 3. Diagnostic Performance

	N	Sen	Spe	PPV	NPV	Accuracy	LR+	LR-	DOR (95% CI)
All patients	69	72.5	68.9	76.3	64.5	71.0	2.3	0.4	5.859 (2.052 – 16.727)
Stage									
Early	17	52.9	68.9	50.0	71.4	63.0	1.7	0.7	2.500 (0.727 –
Advance	23	86.9	68.9	68.9	86.9	76.9	2.8	0.2	8.598) 5.287 (1.790 – 15.618)
Menopausal status									
Pre-menopausal	37	58.8	75.0	66.7	68.1	67.6	2.3	0.5	4.286 (1.058 –
Post-menopausal	32	82.6	55.5	82.6	55.5	75.0	1.8	0.3	17.363) 5.938 (1.084 – 32.513)
Histopathology									
Epithelial	32	71.8	68.9	71.8	68.9	70.5	2.3	0.4	5.679 (1.888 –
Non-epithelial	8	-	-	-	-	-	-	-	17.082) 4.400 (1.022 – 18.938)
Combined marker +CA125 (≥35 U/ml)	69	65	79.3	81.8	63.8	72.4	3.1	0.4	7.962 (2.609 – 24.299)

In this study, the mean age and proportion of postmenopausal women were not significantly different between subjects with ovarian cancer and benign ovarian tumors. Globally, the median age at diagnosis of ovarian cancer is 50-79 years, with a significantly increased incidence of ovarian cancer in women over the age of 65 years (Bray et al., 2018). The proportion of subjects with postmenopausal ovarian cancer is higher than pre-menopausal and this is consistent with the trend globally where the peak incidence of ovarian cancer is in the postmenopausal group (Momenimovahed et al., 2019). The risk of ovarian cancer decreases with an increase in the number of live births. An increasing number of pregnancies is associated with a consistently reduced relative risk of invasive ovarian cancer, epithelial cancer, stromal cancer, and germ-cell cancer (Razi et al., 2016). Pregnancy causes anovulation and suppresses gonadotropin secretion from the pituitary gland. It is consistent with the "incessant ovulation" and gonadotropin hypothesis. The proportion of epithelial type was significantly higher in the ovarian cancer group. Approximately 80% of ovarian cancers in this study were of the epithelial type. This is consistent with the global epidemiology of ovarian cancer where up to 90% of ovarian cancers were the epithelial type (Reid et al., 2017).

Accuracy of the CRP/Albumin Ratio as a Predictor of Ovarian Cancer

C-reactive protein (CRP) and albumin are widely-used indicators to assess the condition and prognosis of cancer (Hefler et al., 2008). The inflammatory response may promote tumorigenesis through its effect on the microenvironment, especially in gynecological cancer. Tumor growth, invasion, necrosis and hypoxia initiate an immune response in the tumor microenvironment thereby promoting the formation of various

inflammatory cytokines (Fang et al., 2021). CRP secretion is triggered by the release of other inflammatory mediators such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) which can occur in ovarian cancer. Compared to other inflammatory markers, CRP has better stability, resulting in a longer half-life (Qaseem et al., 2014).

Serum albumin levels may also be used as an indicator of the prognosis of cancer patients. Albumin plays a role in maintaining blood vessel oncotic pressure, transportation of various endogenous substances and drugs in the body, and has an antioxidant effect (Gupta & Lis, 2010). A decrease in serum albumin levels can be an indicator of inflammation in the body and a predictor of worsening or postoperative complications of various types of cancer.9 Hypoalbuminemia is a physiological response due to the presence of cancer or chronic disease that causes increased permeability and volume of interstitial fluid. In inflammatory conditions, there is an increase in transmembrane flux which causes albumin to return to the plasma and only a small amount enters the cells. Albumin that enters the plasma is usually degraded in the liver after undergoing oxidation or transporting residue from cells (Soeters et al., 2019).

This study showed that the median serum CRP levels were significantly higher in the ovarian cancer group, whereas albumin levels were significantly lower in the ovarian cancer group than in the benign ovarian tumors. A study by Liu et al in ovarian cancer patients set a cut off CRP/albumin ratio of 0.68 and 34.5% of the sample had a high CRP/albumin ratio, while 65.5% had a low CRP/albumin ratio. An increased CRP/albumin ratio is associated with more advanced tumor stage and the presence of ascites. The increased CRP/albumin ratio is also a consistent factor for worse overall survival (OS) in ovarian cancer patients (Liu et al., 2017).

This study also demonstrated that the median CRP/albumin ratio was significantly higher in advanced stage patients. Increased levels of CRP and decreased serum albumin correlate with the level of malignancy in ovarian cancer. Decreased serum albumin levels can also occur in malnutrition. Malnutrition causes a systemic inflammatory response in the body which can increase the use of albumin in the body. Malnutrition occurs in about 20% of gynecological cancer patients and is most common in ovarian cancer patients. Frequently, malnutrition become a response to tumors or as a result of side effects of chemotherapy in cancer patient.9,18 A meta-analysis assessed seven studies with a total of 1,847 gynecological cancer patients found that a high CRP/albumin ratio was associated with an almost three times higher risk of having stage III-IV cancer according to the International Federation of Gynecology and Obstetrics classification (Fang et al., 2021).

Research on the respective roles of CRP or albumin in the diagnosis of cancer has been carried out quite a lot. Level of CRP serum was reported to be able to predict the presence of malignant tumor with a sensitivity of 49.8% and a specificity of 84.1% (Hefler et al., 2008). Another study (Toriola et al., 2011), found that women with an increase of CRP level >100% of baseline had nearly twice the risk of ovarian cancer compared to a lower change in CRP concentration (Kennelly et al., 2016). A study (Miyamoto et al., 2019). reported that women with ovarian cancer had lower serum albumin levels than those with benign tumors. Another study (Kim et al., 2015), also found that preoperative

hypoalbuminemia was a significant risk factor for complications of gynecological malignancies 30 days postoperatively.

Epithelial type is the most common histopathological type of ovarian cancer in this study. The CRP/albumin ratio also showed good results in predicting epithelial-type ovarian cancer. These results were quite similar to the accuracy for predicting ovarian cancer in general. Another study on epithelial-type ovarian cancer showed that serum CRP levels did not have a significant correlation with histological type (Hefler et al., 2008). Other studies showed that CRP levels >10 mg/l were positively associated with a 10 times higher risk of mucinous carcinoma and 3.4 times higher risk of endometrioid carcinoma than CRP levels <1mg/l (Peres et al., 2019).

The median CRP/albumin ratio was also found to be higher in postmenopausal patients. Menopausal status is a risk factor for ovarian cancer and most ovarian cancers in Caucasians occur after menopause. Study in China showed that about 58% of epithelial ovarian cancer patients were diagnosed after menopause, while 58% of sex-cord tumors and 95% of germ cell tumors were diagnosed before menopause (Bray et al., 2018). The prospective cohort study by Lundin et al.24 demonstrated that CRP levels >10 mg/l were associated with an almost eight times higher risk of developing ovarian cancer than CRP levels <10 mg/l in postmenopausal women. Study (Peres et al., 2019) found that there was a strong association between CRP increases in premenopausal and postmenopausal women who used hormone-replacement therapy (HRT) compared with who did not use HRT.

There are significant changes in CRP levels throughout the menstrual cycle. A 10-fold increase in estradiol is associated with a 24.3% decrease in CRP levels, while a 10-fold increase in luteal progesterone is associated with a 19.4% increase in CRP. These results support the hypothesis that endogenous estrogen has an anti-inflammatory effect. Estrogen is able to reduce TNF-α levels which reduces the synthesis and release of chemokines such as interleukin-8 and platelet activating factor and then reduce CRP levels. The relationship between progesterone and CRP is controversial because progesterone can promote neutrophil chemotaxis and increase the production of inflammatory mediators such as interleukin-6. Besides, progesterone may also reduce the activity of natural killer cells, macrophage tumor necrosis factor and nitric oxide synthase production (Gaskins et al., 2012).

Uninterrupted ovulation is known to be one of the main etiologies of ovarian cancer. The incessant ovulation hypothesis suggests that uninterrupted ovulation may contribute to ovarian cancer by damaging the ovarian epithelium. Various factors that reduce ovulation may have a protective effect against ovarian cancer, such as use of oral contraceptives and pregnancy. In addition, premenopausal women are more exposed to ovarian cancer protective factors such as oral contraceptives and pregnancy than postmenopausal women (Moorman et al., 2008).

Combination of CRP/Albumin Ratio and CA125 as a Predictor of Ovarian Cancer

Serum level of carbohydrate antigen 125 (CA125) is a serum tumor marker for ovarian cancer that has been widely used, but has low specificity for ovarian cancer (Sastra

et al., 2022). Both ovarian cancer, benign gynecological tumors and other types of cancer can increase serum CA125 levels (Wang et al., 2021). The combination of CRP/albumin ratio and CA125 levels for predicting ovarian cancer revealed a good result. This combined results in higher specificity, positive predictive value and positive likelihood ratio than the CRP/albumin ratio alone, but with lower sensitivity and negative predictive value.

Lu et al (Lu et al., 2015). found a significant positive correlation between CRP expression and CA125 levels. The results of this study were also supported by the research of Wang et al.27 which suggests that the combination of a plasma protein biomarker with CA125 can be used to diagnose ovarian cancer earlier. The combination of plasma CRP and CA125 (>35 U/ml) was able to improve the prediction of ovarian cancer compared to CA125 levels alone. This study also used a combination of plasma CRP, CA125 and Rho guanine nucleotide exchange factor 11 (ARHGEF 11) in predicting ovarian cancer with a sensitivity of 94%, specificity of 97%, positive predictive value of 94% and negative predictive value of 97% (Lu et al., 2015).

This research has several limitations. First, the number of samples that do not cover all histopathological types of ovarian cancer causes these results to be less representative of various types of ovarian cancer. Second, various other ovarian cancer risk factors that might influence the predictive effect of CRP/albumin ratio such as history of hormonal contraceptive use and history of previous disease were not analyzed in this study. Third, this study did not perform a comparative test between the CRP/albumin ratio and other cancer markers, so the statistical significance could not be explained.

CONCLUSION

The median CRP/Albumin ratio was significantly higher in ovarian cancer than in benign ovarian tumors. This ratio is higher in postmenopausal and advanced cancer. The optimal cut-off ratio of CRP/Albumin is 1.34. The specificity, PPV and positive likelihood ratio of the CRP/albumin ratio also improved when combined with CA125 levels.

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