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ACCURACY OF CANCER ANTIGEN 125 AND ALBUMIN BEFORE OPERATION TO PREDICT THE OPERATION OUTCOME IN PATIENTS WITH ADVANCED STAGE EPITHELIAL TYPE OVARIAN CANCER

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ABSTRACT
Ovarian cancer is a malignancy that grows and develops in the ovaries with a high mortality rate. Primary debulking surgery (P.D.S.) is diagnostic and therapeutic and has become the standard option. CA-125 levels were increasing with the worsening disease conditions in ovarian cancer. In addition, preoperative albumin levels were strongly associated with worse ovarian cancer outcomes. This study assessed the prediction of CA-125 markers and albumin levels on P.D.S. outcomes. This research is a diagnostic test conducted at Prof. Dr I.G.N.G. Ngoerah Hospital. The study sample consisted of 50 women aged 18 and over who underwent P.D.S. from 2018 to 2020 with P.A. results of advanced stage (III-IV) epithelial-type ovarian cancer. CA-125 and albumin levels were assessed before surgery and compared with the findings of P.D.S., which were grouped into suboptimal debulking and optimal debulking. There were no significant differences in the characteristics of the two groups. The accuracy of CA-125 levels on the outcome of P.D.S. surgery with a sensitivity of 75.6%, specificity of 55.6%, PPV of 88.6%, N.P.V. of 35.3% and accuracy of 72%. While the accuracy of albumin levels on the outcome of P.D.S. surgery with a sensitivity of 55.6%, specificity of 51.2%, PPV of 20%, N.P.V. of 84% and accuracy of 52%. CA-125 levels were higher in the suboptimal group but not statistically significant, but the sensitivity (70%) and specificity (80%) were still high, so they still have diagnostic value for ovarian cancer. The relationship between albumin levels and ovarian cancer is multifactorial, so it cannot be used to predict surgical outcomes.

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INTRODUCTION

Ovarian cancer is a malignancy that grows and develops in the ovaries with a high mortality rate. Most patients are only diagnosed when they are at an advanced stage, where management in the form of primary cytoreductive surgery (debulking), which is both diagnostic and therapeutic, is the standard option. Debulking surgery has optimal and suboptimal clinical outcomes. If the surgery results are declared suboptimal, post-operative complications will also increase, leading to poor clinical prognosis. Therefore, a comprehensive clinical predictor must be obtained before debulking surgery to be an early detection tool for possible surgical outcomes and remain cost-effective.

Based on data from Global Cancer Statistics (GLOBOCAN), the incidence of ovarian cancer globally (185 countries in the world) in 2018 was 295,414 cases, with 184,799 cases of death (Bray et al., 2018). In Indonesia, in 2018, ovarian cancer was ranked third in women's highest incidence of cancer, reaching 13,310 new cases and mortality reaching 7,842 (Hutajulu et al., 2021). In an epidemiological study of ovarian cancer conducted at the Central General Hospital (R.S.U.P.) by Prof. Dr I.G.N.G. Ngoerah, there were 73 (15.33%) ovarian cancer patients from 476 cases of gynaecological cancer during the period July 2013-June 2014. Ovarian cancer at R.S.U.P. Prof. Dr I.G.N.G. Ngoerah mostly occurs in the age range of 41 – 50 years (38.4%), in stage I.I.I.C. (50.7%) with surface epithelial histopathology type (87.67%) (Dhitayoni & Budiana, 2017).

Most ovarian cancer patients are only diagnosed when they are at an advanced stage; there is the involvement of multiple tumour nodules in the parietal and visceral peritoneum in the pelvis, omentum and diaphragm, where more than 70% of patients with advanced cancer will experience disease recurrence (Romero & Bast Jr, 2012). This also results in poor prognosis of patients as a whole, where the survival rate for 5 years in advanced stages (III and IV based on F.I.G.O. classification) is only 10-30%, far different from the 5-year survival rate for early stages (I and II) (Wei et al., 2017).

Establishing the diagnosis (obtaining cancer cell material for histopathological examination) in advanced ovarian cancer and for this therapeutic purpose in primary debulking surgery (P.D.S.) (Karimi-Zarchi et al., 2015)v. The success of this surgery involves many factors, including patient selection, tumour location, and the expertise of each gynaecological surgeon operator/specialist (Schorge et al., 2010). The outcome of P.D.S. surgery greatly determines whether the surgical objectives can be carried out successfully, where the possibility of suboptimal debulking (residual tumour>1 cm) becomes a problem that causes complications in postoperative patients, delays in chemotherapy, which ultimately adversely affects the patient's clinical outcomes (Arab et al., 2018).

If there are modalities that can predict the occurrence of suboptimal P.D.S., then management options are neoadjuvant chemotherapy and interval debulking surgery (I.D.S.) (Arab et al., 2018). A study by (Fagotti et al., 2016) in advanced ovarian cancer patients with high tumour load (trial SCORPION) concluded that perioperative moderate morbidity and quality of life score (QoL) were better in patients receiving neoadjuvant

chemotherapy / I.D.S. than those undergoing primary debulking surgery (P.D.S.), where the percentage of optimal debulking results was higher in the group undergoing neoadjuvant chemotherapy / I.D.S. than directly P.D.S. (57.7% versus 45.5%).

CA-125 levels are stated to increase with the condition of the disease in ovarian cancer that is increasingly aggravating (Liao et al., 2014). In addition, albumin levels before surgery are strongly associated with worse ovarian cancer outcomes. In contrast, (Liao et al., 2014) have examined that low albumin levels are associated with an increased risk of surgical durante (blood loss), morbidity and mortality and are more advisable to consider neoadjuvant chemotherapy / I.D.S. management. This finding is usually obtained in cases of advanced malignancy, thus determining the right management options in patients (Balega, 2018) or deselecting primary surgery and giving more consideration to neoadjuvant chemotherapy in patients (Ibeanu & Bristow, 2010).

All tests that must be carried out to obtain data on the predictor factors above, namely albumin level examination and CA-125 examination, are standard procedures before P.D.S. surgery. Therefore, given the importance of studies that can determine the feasibility of P.D.S. in advanced ovarian cancer patients and cost-effective considerations, studies to determine the predicted value of CA 125 markers and albumin levels on P.D.S. output are needed.

METHODS

The research design used in this study is a diagnostic test. The research was conducted at the Obstetrics and Gynecology Polyclinic and at the Medical Records Installation of R.S.U.P. Prof. Dr I.G.N.G. Ngoerah Denpasar. This research was conducted from March 2021 to March 2022. The affordable population in this study is all women aged 18 years and over who underwent primary debulking (optimal and suboptimal debulking) in 2018-2021 at R.S.U.P. Prof. Dr I.G.N.G. Ngoerah with the results of a diagnosis of anatomical pathology confirmed by advanced epithelial type ovarian cancer (III-IV).

RESULTS AND DISCUSSION

Characteristics of the Research Subject

Of the total 148 cases of women with ovarian cancer diagnoses from 2018 – July 2021, 50 cases met the criteria of this study. This research has received ethical feasibility approval from the Research Ethics Commission of the Faculty of Medicine, Udayana University/R.S.U.P. Prof. Dr I.G.N.G. Ngoerah Denpasar dated July 29, 2021, Number 2001/UN14.2.2.VII.14/L.T./2021 and obtained a research permit from the Education and Research Section of R.S.U.P. Prof. Dr I.G.N.G. Ngoerah dated October 28, 2021, Number LB.02.01/XIV.2.2.1/41372/2021. The characteristics of the research sample are summarized in Table 1.

Table 1. Characteristics of the Research Subject

Variable	Total (n=50)	Optimal *Debulking* (n=9)	Suboptimal *Debulking* (n-41)	P value
Age (years), average±elementary school	49,8±9,15	48,7±7,05	50,0±9,61	0,715
Median parity (IQR)	2 (3)	2 (3)	2 (3)	0,823
Education, n (%)				0,715
Elementary/out-of-school	24 (48)	4 (44,4)	20 (48,8)	
Junior	17 (34)	4 (44,4)	13 (31,7)	
High school/college	9 (18)	1 (11,1)	8 (19,5)	
Occupation, n(%)				0,472
Does not work	19 (38)	4 (44,4)	15 (36,6)	
Self-employed	20 (40)	4 (44,4)	16 (39,0)	
Private employees	8 (16)	0 (0)	8 (19,5)	
Health workers	1 (2)	0 (0)	1 (2,4)	
Civil servants	2 (4)	1 (11,1)	1 (2,4)	
Menopausal Status, n (%)				1,000
Yes	30 (60)	5 (55,6)	25 (61,0)	
No	20 (40)	4 (44,4)	16 (39,0)	
Oral contraceptives, n (%)				1,000
Yes	2 (4)	0 (0)	2 (4,9)	
No	48 (96)	9 (100)	39 (95,1)	
BMI, n (%)				0,763
Low	2 (4)	0 (0)	2 (4,9)	
Usual	18 (26)	3 (33,3)	15 (36,6)	
Overweight/Obesity	30 (60)	6 (66,7)	24 (58,5)	
Epithelial Type, n(%)				0,843
Serous	23 (46)	3 (33,3)	20 (48,8)	
Mucinous	3 (6)	1 (11,1)	2 (4,9)	
Endometrioid	8 (16)	2 (22,2)	6 (14,6)	
Clear cell	11 (22)	2 (22,2)	9 (22,0)	
Mixed epistle	3 (6)	1 (11,1)	2 (4,9)	
Undifferentiated	2 (4)	0 (0)	2 (4,9)	
Stadium				0,000
IIIA1	2 (4)	2 (22,2)	0 (0)	
IIIA2	4 (8)	4 (44,4)	0 (0)	
IIIB	2 (4)	0 (0)	2 (4,9)	
IIIC	35 (70)	3 (33,3)	32 (78,0)	
IVB	7 (14)	0 (0)	7 (17,1)	
Bilaterality				0,271

Yes	21 (42)	2 (22,2)	19 (46,3)	
No	29 (58)	7 (77,8)	22 (53,7	
Mass Size, median (IQR)	15,5 (10,5)	10 (15)	16 (9)	0,356
Albumin levels, median (IQR)	3,5 (0,8)	4,4 (1,2)	3,5 (0,8)	0,119
CA-125 levels (ng/ml), Average±SD	2095,6 ±7394,61	1084,9 ±1602,0	2317,4 ±8135,7	0,378

There were no significant differences in the basic patient characteristics such as age, parity, education, occupation, menopausal Status, contraception, B.M.I., epithelial type, bilaterality and mass size in both groups. The median albumin level was lower in the suboptimal debulking group than in the optimal debulking group. The median CA-125 level was higher in the suboptimal debulking group than in the optimal debulking group. Of all the variables, only the stage variable had a significant value (p <0.000).

CA-125 Levels in Predicting P.D.S. Operating Outcomes

The CA-125 cut-off point value of 35 U/mL to determine normal and high CA-125 levels so that the accuracy of CA-125 levels is found as follows:

Table 2. CA-125 Content Accuracy in Predicting P.D.S. Operating Output

		Operating Outcomes	
		Optimal debulking	***Suboptimal debulking***
CA-125 levels	**High**	**4**	**31**
	Normal	**5**	**10**

Sensitivity : $\frac{A}{A+C} \times 100\%$ = 75,6%

Sensitivity : $\frac{D}{B+D} \times 100\%$ = 55,6%

PPV : $\frac{A}{A+B} \times 100\%$ = 88,6%

NPV : $\frac{D}{C+D} \times 100\%$ = 35,3%

Accuracy : $\frac{A+D}{A+B+C+D} \times 100\%$ = 72%

Albumin Levels in Predicting P.D.S. Operating Outcomes

The albumin cut-off point value of 3.5 g / dL to determine low and normal albumin levels so that the accuracy of albumin levels is found as follows:

Table 3. Accuracy of Albumin Levels in Predicting P.D.S. Operating Output

		Operating Outcomes	
		Optimal debulking	***Suboptimal debulking***
Albumin Levels	**Normal**	**5**	**20**

Low		**4**	**21**
Sensitivity	: $\frac{A}{A+C} \times 100\%$	= 55,6%	
Sensitivity	: $\frac{D}{B+D} \times 100\%$	= 51,2%	
PPV	: $\frac{A}{A+B} \times 100\%$	= 20%	
NPV	: $\frac{D}{C+D} \times 100\%$	= 84%	
Accuracy	: $\frac{A+D}{A+B+C+D} \times 100\%$	= 52%	

DISCUSSION

Characteristics of the Research Subject

In this study, the overall age of the study subjects was 49.8±9.15 years. The age between the group with optimal and sub-optimal results was not significantly different (p = 0.715), so it did not confuse the participant's study results. When compared to previous data, the age of the subjects in this study was much younger. According to previous data, the incidence of new ovarian cancer is most commonly found in the age range of 60 to 74 years, with the median age at diagnosis being 59. Research in Sweden found that the incidence of ovarian cancer increases with age, with most cases in the age range of 60 to 64 years (Granström et al., 2008). Research on serous epithelial type ovarian cancer gets the most optimal age as a cut-off to determine the difference in output (optimal or suboptimal) is 66 years of age (Kim et al., 2019). Age is one of the risk factors for ovarian cancer. The overall incidence of ovarian cancer increases until age 70, and then the cases decrease until over 80 years. In general, age allows a longer time for the body to accumulate genetic changes within the surface epithelium of the ovaries (Grossman et al., 2018).

Total parity negatively correlates with ovarian cancer (Bodelon et al., 2013). Nevertheless, at the age of more than 75 years, there was no significant association between the number of parties and the risk of ovarian cancer. The hypothesis that explains this protective factor of parity is the theory of anovulation during pregnancy and breastfeeding, which is lower so that the risk of ovarian epithelial cell mutation is lower. However, at an older age, over 75 years, there has been repeated somatic mitosis (normal cells) so that the risk of mutation remains high; thus, there is no difference between nullipara and multiparous (McGuire et al., 2016). In addition, other reports have also found that older first delivery age is associated with an increased risk of this cancer (Yang et al., 2007). Multiparity patients had a 78% lower risk of specific mortality than nulliparity. Research on advanced epithelial cell carcinoma also found a better prognosis in the group with multiparity than nulliparity (Khalafi-Nezhad et al., 2020). Thus, parity can potentially be a confounding factor for ovarian carcinoma output. However, in this study, there was no significant difference in the parity factor between the optimal and suboptimal groups. Hence, the risk of confusing the results of this study could have been bigger.

In this study, as many as 48% with primary education or no school, 34% with a recent high school education and only 18% with a high school education or above. This shows that the level of education in this study could be a lot higher. Previous research also

found that most with secondary (65%) and low (32.5%) education. The study also found a significant positive correlation between education level and ovarian cancer (Purwoko, 2018). In this study, the results of suboptimal surgery were higher at the lower education level, namely at the elementary level.

The most jobs obtained in this study were wiraswata (40%) and not working (38%). In the previous study, most ovarian cancer patients with non-working Status (57.8%). Similarly, other studies found that as many as 78.8% of homemakers, work did not have a significant correlation with ovarian cancer cases in the study conducted (Purwoko, 2018).

Most studies show that subjects develop ovarian cancer at a postmenopausal age. As explained earlier, most of these carcinomas occur in the age range of 60 to 74 years (Granström et al., 2008). Although post-menopause ovulation has not occurred, the theory underlying the increased risk of ovarian cancer at this age is somatic replication that occurs in higher frequency (McGuire et al., 2016). This study found that as many as 61% had experienced menopause. Research Trifanescu et al. (2018) found ovarian cancer outcomes were worse in postmenopausal subjects; the most important pathophysiological hypothesis for epithelial-type ovarian cancer is the "incessant ovulation" hypothesis which states that the rupture process and repeated proliferation of the ovarian surface epithelium that occurs during the ovulation process can cause malignant cell transformation in the ovarian epithelium. Comparable results were also found in our finding that the percentage of menopause was higher in the group with suboptimal outcomes.

Research shows that women without oral contraceptives have a greater risk of ovarian cancer. Rupture and proliferation of the surface epithelium of the ovary and ovulation lead to malignant transformation of the ovarian epithelium. Using oral contraceptives reduces the risk of ovarian cancer by reducing the number of ovulation cycles. However, this hypothesis is not entirely related to risk reduction. The second reason is that exposure to high levels of progestins, either through pregnancy or exogenous hormones, reduces the risk of ovarian cancer. This progestin regulates the expression of the tumour suppressor gene p53 and induces apoptosis. This may explain why we found that most subjects (95.1%) did not use oral contraceptives in this study.

Several studies have found a significant relationship between obesity and ovarian cancer risk. Meta-analysis showed a 16% increased risk of ovarian cancer in women with a B.M.I. of 25-29.9 kg/m2 and a 30% increased risk in women with a B.M.I. of 30 kg/m2 when compared to normal weight (18.5–24.9 kg/m2). The increased risk is hypothesized to result from the mitogenic effects of excess endogenous estrogen synthesized in adipose tissue via androgen aromatization. This may explain why this study found that as many as 60% are obese women.

Ovarian carcinoma can occur bilaterally or unilaterally. Bilaterality occurs through metastasis or does occur in both ovaries. Some studies even report that metastatic ovarian tumours are usually bilateral. Bilaterality is a good characteristic to distinguish primary tumours from metastatic ovarian tumours. However, other reports have had different results; common primary tumours, such as serous and undifferentiated metastatic ovarian tumours are also known to involve bilateral ovaries with a high proportion of cases

(Mukuda et al., 2018). In this study, we found that most cases (58%) were not bilateral cases. The non-optimal result group showed a greater proportion of bilateral tumours. This is only natural because bilateral tumours are certainly more difficult to eradicate tumours.

The size of the tumour does not always describe the severity (stage) of the disease. Previous research found that early-stage tumours (I and II) had a size of 10.7 cm, while advanced stages (III and IV) had a size of 4.8 cm. The same results also found that the tumour size in stage I was significantly larger than in stage III (Petru et al., 2018. This is because, at a higher stage, tumour cells can grow more optimally in the abdominal cavity. This may explain why there was no difference in tumour size between the two groups in this study. According to previous studies, tumours measuring more than 6 cm had a survival of 36 months, significantly higher compared to smaller tumours with a survival of 17 months. As explained earlier, smaller tumours are associated with higher stages. In this study, there was no difference in size between the two groups, but there was a tendency for the average size to be larger in the sub-optimal group. This may be caused by a higher stage (dominant stage III-IV in the sub-optimal group).

This study found that most of the subjects were stage I.I.I.C. (70%). In the optimal result group, most of them were in stage IIIA2 (44.4%), while in the sub-optimal group, most of the stage I.I.I.C. (78.9%) and there was stage I.V.B. (17.1%). Patients with suboptimal debulking outcomes have a higher stage than patients with optimal debulking outcomes ($p = 0.000$). In previous studies, 75% to 80% were diagnosed in stages II to IV. In all cancers, higher stages are associated with worse outcomes, including these cancers. Previous studies have found that higher stages have higher recurrence rates and a high frequency of recurrence in stage I ovarian cancer with spread to the peritoneum. Further clinical and baseline studies are needed to improve diagnostic methods and surgical procedures, and additional therapy may be required for patients with stage I ovarian cancer. Metastases and tumour invasions of surrounding organs may also affect the optimization of the outcome of this cancer surgery.

In this study, the most histological types were serious (46.0%) and clear cell (22.0%), followed by endometriosis (16%). This result is comparable to the results of previous studies that found the dominant histological types were high-grade serous (42%) and endometrioid (18%). Similarly, the CONCORD report found that the histological type of ovarian epithelial tumour was most often of the serous type.

CA-125 Levels in Predicting P.D.S. Operating Outcomes

In 2007, the American Congress of Obstetricians and Gynecologists (ACOG) published a practice bulletin for diagnosing adnexal masses. CA-125 assessment is one step that needs to be done. Elevated CA-125 levels are found in 80% of women with ovarian epithelial cancer, and ACOG recommends that postmenopausal women with adnexal masses with elevated CA-125 levels should receive further management by gynecologic oncologists. Some studies of increased levels of CA-125 can also be found in other malignant conditions such as breast, lung, and gastrointestinal cancer.

Several studies have proven the role of CA-125 in predicting therapeutic outcomes in ovarian cancer, including surgery. Research shows that 80% of patients with no residual disease results have CA-125 ≤100 IU / L, while in patients with optimal macroscopic disease, as much as 63.4% have CA-125 ≤100 IU / L. In this study, we found that the overall average CA-125 was 209.5 U/mL; the levels of this tumour marker were higher in the sub-optimal group but not statistically significant. The cut-off value in this study was 35 U/mL with a sensitivity of 75.6%, specificity of 55.6%, PPV of 88.6%, N.P.V. of 35.3% and accuracy of 72%.

Many studies have found that increasing or decreasing CA-125 levels are associated with disease progression and regression. Thus CA-125 is important for monitoring treatment response. In patients with ovarian carcinoma, tumour burden can be significantly reduced by tumour cytoreductive surgery and decreased serum CA-125 is associated with fewer tumour cells. Dynamic changes in serum CA-125 are associated with decreased CA-125 levels during treatment, and a rapid decrease predicts a favourable prognosis. Research shows that serum CA-125 concentrations are a strong independent predictor.

Most ovarian cancer patients are diagnosed at an advanced stage. Tumour biomarkers can be examined and used to diagnose and monitor therapeutic response in ovarian cancer. CA-125 is the most commonly used biomarker for ovarian cancer detection. In the meta-analysis study, CA-125 levels were evaluated as biomarkers for ovarian cancer diagnosis by assessing sensitivity (70%) and specificity (80%) where the A.U.C. value was 0.84 so that CA-125 levels, in general, were still feasible or had diagnostic value against ovarian cancer.

Albumin Levels in Predicting P.D.S. Operating Outcomes

Previous studies have found that low albumin levels are independently and significantly associated with patient outcomes. Similarly, previous meta-analyses obtained almost the same results. Another study found that the group with postoperative residual tumours had significantly lower preoperative albumin levels ($p<0.0001$). This study found that the average overall albumin was 3.5 g / dL. Albumin levels tended to be lower in the suboptimal group but were not statistically significant. Comparable results were also obtained in this study. Albumin content using the limitation of 3.55 g/dL as a predictor factor of P.D.S. operating output with a sensitivity of 55.6%, specificity of 51.2%, PPV 20%, N.P.V. 84% and accuracy of 52%.

A current systematic review and meta-analysis suggest that higher preoperative albumin levels are associated with better O.S. in epithelial-type ovarian cancer patients. Specifically, for every 1 g/dL increase in albumin levels before surgery, the O.S. of epithelial-type ovarian cancer patients will increase by 44%. Albumin levels are an important laboratory test to evaluate the nutritional Status of patients. Hypoalbuminemia in cancer patients can occur due to malnutrition, low appetite, weight loss and cachexia due to the body's acceptance of tumours and chemotherapy therapy. Amino acid intake, negative nitrogen balance, and degradation in albumin synthesis are determinants of albumin levels in the body.

It is reported that 24% of patients with gynecologic cancer have the highest malnutrition rate (67%). On the other hand, it is known that serum albumin levels are closely related to the inflammatory process, which is involved in all stages of ovarian cancer. Low albumin levels can result from poor nutrition, small intestinal obstruction, ascites, and metabolic effects of tumour mass. In normal women, albumin levels decrease slightly with age. Ovarian cancer is more common at an older age. Thus, albumin's association with ovarian cancer is multifactorial.

CONCLUSION

CA-125 levels were higher in the suboptimal group but not statistically significant, but the sensitivity (70%) and specificity (80%) were still high, so they still have diagnostic value for ovarian cancer. The relationship between albumin levels and ovarian cancer is multifactorial, so it cannot be used to predict surgical outcomes.

Preoperative CA-125 levels had a sensitivity of 75.6% and albumin of 55.6% in predicting surgical outcomes in patients with advanced epithelial-type ovarian cancer. Preoperative CA-125 levels had a specificity of 55.6% and albumin of 51.2% in predicting surgical outcomes in patients with advanced epithelial-type ovarian cancer.

CA-125 levels before surgery had a positive predictive value of 88.6% and albumin of 20% in predicting surgical outcomes in patients with advanced epithelial-type ovarian cancer. CA-125 levels before surgery had a negative predictive value of 35.3% and albumin of 84% in predicting the outcome of surgery in patients with advanced epithelial-type ovarian cancer. Preoperative CA-125 levels had 72% accuracy and albumin 52% in predicting surgical outcomes in patients with advanced epithelial-type ovarian cancer.

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