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The Ability Pre-operative Serum (Cancer Antigen-125, Fatty Acid Synthase, and Glucose Transporter) to Predict Primary Suboptimal Cytoreduction in Epithelial Ovarian Cancer

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ABSTRACT

BACKGROUND: The incidence of ovarian cancer ranks 8th in the world, with 295,414 cases and 184,799 death in 2018. Management in ovarian cancer is surgery and chemotherapy. Some studies state that patients who underwent optimal cytoreduction surgery have better survival rates than suboptimal cytoreduction surgery. The pre-operative serum assessed in this study was Cancer Antigen-125 (CA-125), Fatty Acid Synthase (FASN), and Glucose Transporter (GLUT) to predict suboptimal cytoreduction in epithelial ovarian cancer (EOC).

AIM: We aimed to use FASN and GLUT1 as other biomarkers, besides CA-125, to predict suboptimal cytoreduction surgery in epithelial ovarian cancer.

METHODS: This observational-analytic cross-sectional study included 109 women diagnosed with epithelial ovarian cancer (EOC) between 2017 and 2019, who had serum CA-125, FASN, and GLUT measured preoperatively and underwent cytoreductive surgery.

RESULTS: The results of the statistical analysis test in this study obtained p values at CA-125 (p = 0.0001), FASN (p = 0.017), and at GLUT (p = 0.013). While the cutoff point (COP) on CA-125 was 248.55, FASN was 0.445, and GLUT was 0.1980. The value of area under curve (AUC) obtained by the ROC method at CA-125 76.7%, FASN 65.3%, and GLUT 63.8%. The combination of CA-125 and FASN shows AUC value 76.9%, the combination of CA-125 and GLUT shows AUC value 72.2%, and the combination of the three shows AUC value 75.2%.

CONCLUSION: The use of CA-125 as a predictor of cytoreduction surgery is still considered to be the best predictor compared to serum biomarkers in this study.

Introduction

The number of new cases of ovarian cancer in 2018 is 295,414. When compared to 2012, this number has increased by 56414 new cases [1], [2]. Likewise, the mortality rate in ovarian cancer has increased from 152,000 in 2012 cases to 184,799 in 2018 [1], [2].

The standard of management of epithelial ovarian cancer is surgical staging in cases of early-stage (Stage 1) and cytoreduction surgery in cases of advanced stages (Stages 2, 3, and 4), which will be followed by adjuvant therapy of platinum-taksan class chemotherapy [3]. Cytoreduction surgery has aimed to remove all tumors. If this surgery leaves a tumor >1 cm called suboptimal cytoreduction surgery, if the remaining tumor <1 cm called optimal cytoreduction surgery [3], [4].

The success rate varies in cytoreduction surgery depending on many things, including the oncologist, completeness of the operating equipment in a hospital, degree of cancer based on the International Federation of Gynecology and Obstetrics (FIGO), the histopathological type of ovarian cancer, and body mass index [5], [6], [7]. A study assessed ovarian cancer patients, and 30% of samples underwent optimal cytoreduction surgery. In contrast, the others (70%) underwent suboptimal cytoreduction surgery. The high rate of suboptimal cytoreduction surgery makes management of ovarian cancer which has a low survival rate. The high rate of suboptimal cytoreduction surgery is due to the inability to predict the results of cytoreduction surgery well.

Cytoreduction surgery can be predicted in various ways; one of them is pre-operative assessment. The pre-operative assessment consists of clinical examinations, supporting examinations such as routine blood laboratory examinations, ultrasound examination (USG), X-rays, computed tomography scans (CT Scan), magnetic resonance imaging (MRI), positron emission tomography scan (PET Scan), and assessment of tumor markers [8], [9], [10], [11].

Tumor markers that have been investigated as predictors of cytoreduction surgery are Cancer Antigen-125 (CA-125), human epididymis 4 protein (HE4), caspase 3, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), vascular endothelial growth factor (VEGF) levels) serum-peritoneum-VEGF load, and a combination of CA 125 with HE4, YKL 40, BCL 2, cathepsin L [12], [13], [14], [15], [16], [17].

Uncontrolled proliferation is one of the main characteristics of cancer. Proliferating cancer cells require much energy. The sources of energy comes from glucose and the glucose metabolism needs a transporter called GLUT (Glucose Transport). It was happened because of the increasing glycolysis process up to 30 times faster in cancer cells [18]. One of the sources of energy is Glucose. Increased glucose metabolism increases glucose transport (GLUT). Previous studies had assessed that GLUT increased 20 times compared to healthy cells [19], [20], [21], [22], [23]. Glucose transporters typically found in ovarian cancer are GLUT1 (98.7%), GLUT3 (92.8%), and GLUT4 (84.4%) [24]. GLUT1 is the essential transporter in the absorption of glucose in tumor cells. The increase of GLUT1 levels has a relationship in worsening survival rates in ovarian cancer patients [24], [25]. Various studies have been conducted further to analyze the role of GLUT as a cancer predictor. Patients with advanced tumors are considered to have excessive GLUT1 expression, which will result in the possibility of suboptimal cytoreduction surgery [26]. This reason has led researchers to make GLUT1 one of the tumor markers assessed in this study.

Besides requiring glucose, cancer cells also need fatty acids. In cancer cells, the fatty acids needed come from food consumed (exogenous) or from the metabolism of fatty acids in the body (lipogenesis *de novo*) [27]. The primary source of fatty acids is from food consumed or exogenous, but the cancer cells will increase the production of fatty acids in the body or *de novo* lipogenesis. The synthesis of these fatty acids requires the activation of several enzymes; one of them is fatty acid synthase (FASN). FASN contributes to the process of fatty acid oxidation and biogenesis in cell membranes, which can thus divide rapidly [28]. Studies conducted by Cai *et al*. found that an increase of FASN was associated with the degree of cancer and the stage of cancer [28]. In stage IV, ovarian cancer has a higher FASN 94.1% compared to stage I ovarian cancer 1.25% [29], [30].

Due to the perceived strong relationship between FASN and GLUT1, the researchers will use FASN and GLUT1 as other biomarkers assessed in this study besides CA-125 to predict suboptimal cytoreduction surgery in epithelial ovarian cancer.

Methods

The design of this study was a prospective observational analytic with a cross-sectional study design. In this study, researchers will look for a relationship between the independent variables (risk factor) with the dependent variable (effect). The population in this study was patients with a diagnosis of suspected ovarian malignant tumors who would undergo cytoreduction surgery at RSUP Dr. Hasan Sadikin. The inclusion criteria in this study were all new patients with epithelial ovarian cancer, underwent cytoreduction surgery techniques, willing to follow the study after giving informed consent, and not suffering from chronic diseases or other tumors. A consecutive sampling made the selection of subjects of the population in the 2017–2019 period in Dr. Hasan Sadikin Hospital Bandung.

Before surgery, the entire population in this study will take blood to assess serum biomarker levels. Serum examination by Enzyme-Linked Immunosorbent Assay technique was carried out at the Eyckman Laboratory, Faculty of Medicine, Padjadjaran University. In patients who were confirmed histopathologically, not epithelial ovarian cancer or stage I patients would be exclusion criteria in this study. In addition, if the histopathological preparations are damaged or cannot be assessed, did not undergo cytoreduction surgery, and did not willing to be sampled in the study will be excluded from this study.

Serum biomarkers CA-125, FASN, and GLUT are independent variables, and the dependent variable in this study is optimal and suboptimal cytoreduction surgery. All data will be assessed statistically using SPSS™ (24.0.0). If the data are normally distributed, it will use paired t-test analysis, whereas if it is not normally distributed, it will use Mann–Whitney analysis. As for categorical data, p-values will be analyzed using the Chi-Square test, and if the Chi-Square requirements are not met, we will use the Kolmogorov–Smirnov, and exact Fisher tests. The cut off point (COP) was made using receiver operating characteristic (ROC) curve 23 analysis.

Results

There were 304 patients for the population in this study for the period 2017–2019. A total of 195 patients did not meet the inclusion criteria, so there were 109 patients sampled in this study. There were 56 patients underwent suboptimal cytoreduction surgery, while 53 others underwent optimal cytoreduction surgery (Table 1). The youngest sample is 17 years old, while the oldest is 75 years old (Table 1). There were 28 (25.7%) samples with parity 0, 16 (14.7%) samples with parity 1, 23 (21.1%) samples with parity 2, and 42 (38.5%) samples with parity> 3 (Table 1).

A total of 57 samples were patients with Stage III malignancy, 42 samples were patients with Stage II malignancy, and 10 samples were patients with Stage IV malignancy. The most histopathological types in this

study were the mucinous type with 38 patients (34.9%), the serous with 27 patients (24.8%), the endometrioid with 21 patients (19.3%), the clear cell with 16 patients (14.7%), and others with 7 patients (6.4%) (Table 1). There were no differences between the variables of age, parity, BMI (Body Mass Index), stage and histopathology with p values greater than 0.05 (Table 1). The stage variable has a p < 0.05 (p = 0.0001), so there is a difference between the suboptimal and optimal cytoreduction groups (Table 1).

Table 1: Background characteristics of the study population

Variable	N=109	Group		p value
		Suboptimal cytoreduction n = 56	Optimal cytoreduction n = 53	
Age (years)				0.269
Mean ± Std	47.48 ± 11.347	48.66 ± 9.648	46.24 ± 12.880	
Median	47.00	47.00	47.00	
Range (min-max)	17/00–75.00	26.00–64.00	17.00–75.00	
Parity				0.261
0	28 (25.7%)	16 (28.6%)	12 (22.6%)	
1	16 (14.7%)	6 (10.7%)	10 (18.9%)	
2	23 (21.1%)	15 (26.8%)	8 (15.1%)	
>3	42 (38.5%)	19 (33.9%)	23 (43.4%)	
Body Mass Index				0.353
Mean ± Std	21.30 ± 3.907	20.96 ± 3.675	21.66 ± 4.143	
Median	21.30	21.25	21.40	
Ascites				0.089
Mean ± Std	1652.56 ± 3664.119	1703.75 ± 3393.296	1598.49 ± 3962.289	
Median	300.00	400.00	300.00	
Stage				0.0001
II	42 (38.5%)	8 (14.3%)	34 (64.2%)	
III	57 (52.3%)	38 (67.9%)	19 (35.8%)	
IV	10 (9.2%)	10 (17.9%)	0 (0.0%)	
Histopathology				0.559
Serous	27 (24.8%)	18 (32.1%)	9 (17.0%)	
Mucinous	38 (34.9%)	12 (21.4%)	26 (49.1%)	
Endometrioid	21 (19.3%)	14 (25.0%)	7 (13.2%)	
Clear cell	16 (14.7%)	8 (14.3%)	8 (15.1%)	
Others	7 (6.4%)	4 (7.1%)	3 (5.7%)	

Serum CA-125 values in the suboptimal cytoreduction group (1157.62 ± 2105.195) were higher than those in the optimal cytoreduction group (237.52 ± 319.431), as well as the values on the FASN, GLUT, FASN + CA-125 combination, GLUT + CA-125 combination, and the combination of GLUT + FASN + CA-125 have higher values in patients with suboptimal cytoreduction group than patients with optimal cytoreduction group (Table 2). Based on P-value analysis of CA-125 (p = 0.0001), FASN (p = 0.006), GLUT (p = 0.013), FASN + CA-125 combination (p = 0.0001), GLUT + CA-125 combination (p = 0.0001), and GLUT + FASN + CA-125 combination (p = 0.0001), p values in serum biomarkers have a value of less than 0.05 which means that there are significant differences in the suboptimal and optimal cytoreduction group patient variables (Table 2).

The subsequent analysis is to analyze how the cutoff point for each biomarker. In Table 3 described the cutoff value for each serum biomarker. CA-125 has the cutoff point 248.55 (p = 0.0001) with a sensitivity value (73.2%), specificity (73.6%), and an accuracy value (73.3%) (Table 3). Whereas the FASN did not appear to have a sensitivity value (62.5%), specificity (60.4%), and an accuracy value (61.4%), which was better than CA-125 (Table 3). The cut off value for FASN serum biomarkers is 0.445, which means if the patient has a serum value > 0.445. has 65.3% (AUC value) is likely to undergo suboptimal cytoreduction surgery. It seems that GLUT also does not provide better results than CA-125 and FASN. Patients who have a GLUT serum biomarker > 0.1980 have 63.8% (AUC value) chance of having suboptimal cytoreduction surgery. The sensitivity value of this biomarker is 75%, and its specificity is 56.6% (Table 3).

Table 2: Comparison between CA-125, FASN, and GLS serums level in the suboptimal sitoreduction and optimal sitoreduction groups

Variable	Group		p value
	Suboptimal cytoreduction n = 56	Optimal cytoreduction n = 53	
CA-125			0.0001
Mean ± Std	1157.62 ± 2105.195	237.52 ± 319.431	
Median	600.00	120.30	
Range (min-max)	4.29–9934.00	5.10–1941.90	
FASN			0.006
Mean ± Std	0.58 ± 0.271	0.46 ± 0.288	
Median	0.50	0.37	
Range (min-max)	0.11–1.59	0.03–1.19	
GLUT			0.013**
Mean ± Std	0.41 ± 0.337	0.33 ± 0.298	
Median	0.28	0.19	
Range (min-max)	0.11–1.47	0.04–1.42	
Combination FASN + CA-125			0.0001**
Mean ± Std	1.02 ± 0.581	0.55 ± 0.314	
Median	0.93	0.49	
Range (min-max)	0.21–3.18	0.03–1.58	
Combination GLUT + CA-125			0.0001
> 0.3793	38 (67.9%)	18 (34.0%)	
< 0.3793	18 (32.1%)	35 (66.0%)	
Combination GLUT+FASN+CA-125			0.0001**
Mean ± Std	1.18 ± 1.212	0.54 ± 0.483	
Median	0.79	0.35	
Range (min-max)	0.16–5.88	0.08–1.86	

In addition to using biomarker values as a single predictor, this study is also using a combination of biomarker values as predictors of suboptimal cytoreduction surgery. This combination value uses CA-125 as a categorical value where if the patient has a value > 248.55 is 2, and if the patient has a value < 248.55 is 1. The formula for three combination biomarker used two variables CA-125 and FASN as the categorical value based on each cut off point, where the value of CA-125 was > 248.55 = 2 and < 248.55 = 1 or FASN level was > 0.445 = 2 and <0.445 =1, while for the combination of CA-125 + FASN and CA-125 + GLUT used CA-125 as categorical value. This categorical value will then be multiplied by the value of each pair of combinations.

The combination value of CA-125 and FASN has a cutoff value of 0.69 (p = 0.0001) with a sensitivity value of 71.4%, specificity of 71.7%, and an accuracy value of 71.6% (Table 3). While the combination of CA-125 and GLUT has a cutoff point of 0.3793 (p = 0.0001) with a sensitivity of 67.9%, specificity 66%, and an accuracy value of 67% (Table 3). The combination of CA-125 + FASN + GLUT with a cutoff value of 0.5150 has sensitivity 71.4%, a specificity 71.7%, and an accuracy value of 71.6% (Table 3).

Furthermore, each biomarker will be analyzed using ROC curve 23 analysis to illustrate in what direction the curve will move from the 50% line. The CA-125 is depicted in Figure 1. The curves in the ROC analysis move away from the 50% line and approach 100%, with a value of 76.7% (p = 0.000), which can illustrate that the CA-125 can predict 84 patients correctly from a total of 109 patient (Figure 1). Figure 2 illustrates FASN as a predictor of cytoreduction surgery with an area under

Table 3: Sensitivity and specificity of predictor cytoreduction scoring of epithelial ovarian cancer

Variable	Cutoff	Sensitivity %	Specificity %	AC %	PPV %	NPV %	p Value
CA-125	248.55	73.2	73.6	73.3	74.5	72.2	0.0001
FASN	0.445	62.5	60.4	61.4	62.5	60.4	0.017
GLUT	0.1980	75	56.6	66.1	64.6	68.2	0.001
Combination CA-125 and FASN	0.69	71.4	71.7	71.6	72.7	70.4	0.0001
Combination CA-125 and GLUT	0.3793	67.9	66	67	71.7	66	0.0001
Combination CA-125, FASN, and GLUT	0.5150	71.4	71.7	71.6	72.7	70.4	0.0001

AC: Accuracy classification, PPV: Positive predictive value, NPV: Negative predictive value

curve (AUC) value of 65.3% (p = 0.006). This AUC FASN value was described as being able to predict 71 patients correctly from a total of 109 patients. Not much different from GLUT can only predict 70 patients correctly from 109 patients (AUC value 63.8% p = 0.0013) (Figure 3). AUC value of a combination of FASN + GLUT + CA-125 is 75.2% (p = 0.000), this value can correctly predict 82 patients out of 109 patients (Figure 4).

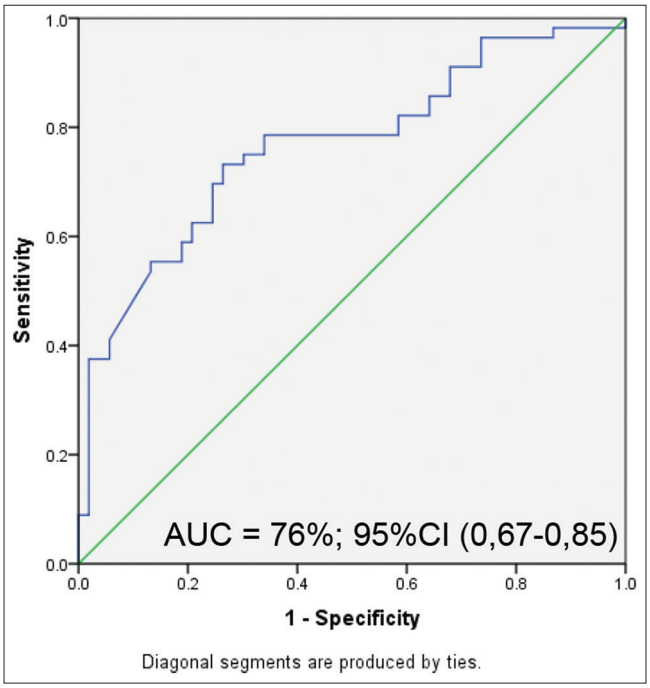

Figure 1: ROC curve showing the value of CA-125 with cytoreduction. Area under curve value was 76.7% CI 67.8%-85.6% (p = 0.000), implicating that CA-125 can predict cytoreduction correctly in 84 patients out of a total of 109 patients

Discussion

Cytoreduction surgery plays an essential role in the management of epithelial ovarian cancer. Tumor residues are considered to be a prognostic factor of the survival rate of patients. The standard management of epithelial ovarian cancer management is surgical therapy and followed by platinum therapy and taksan for advanced stage [31]. Based on the GOG Guideline, the main goal for cytoreduction procedures is to take all parts of the tumor or leave the tumor part with size <1 cm (optimal cytoreduction) [32]. Based on research conducted by Bacalbasa in 2014, he collected 338 patients who were willing to be the subjects in his study. He found that 242 patients who underwent optimal cytoreduction had an increase in survival compared to patients who underwent suboptimal cytoreduction [33].

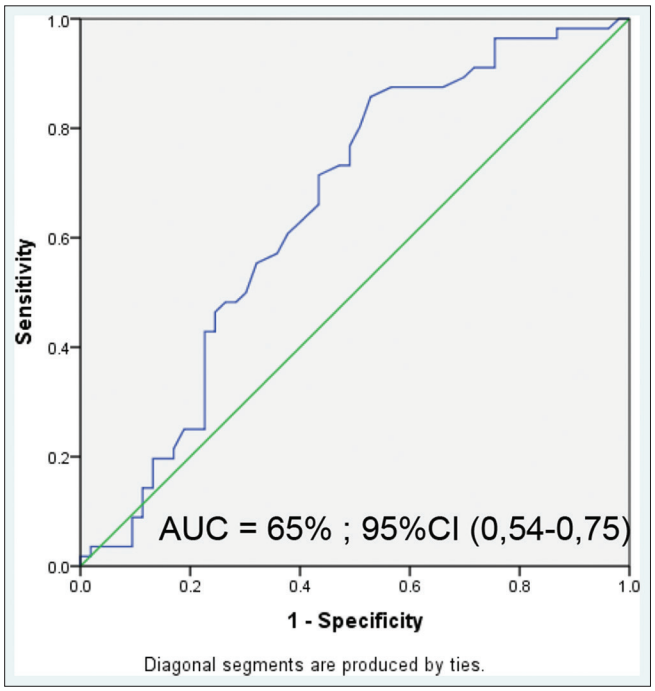

Figure 2: ROC curve showing the value of FASN with cytoreduction. Area under curve value was 65.3% CI 54.8%-75.8% (p = 0.006), implicating that FASN can predict cytoreduction correctly in 71 patients out of a total of 109 patients

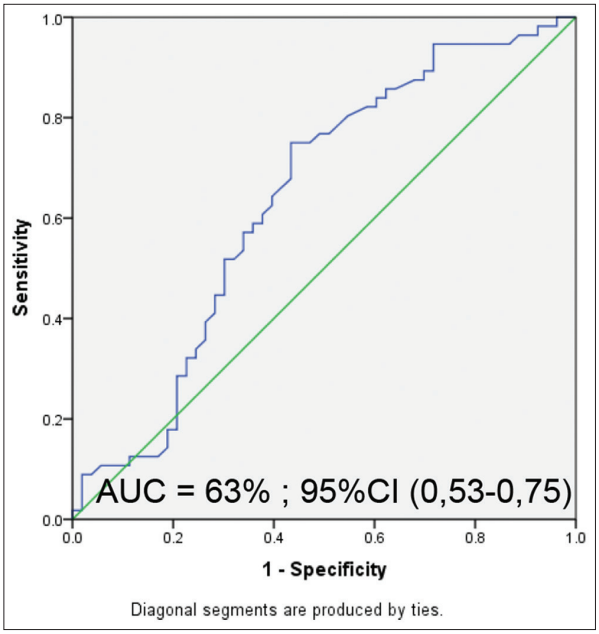

Figure 3: ROC curve showing the value of GLUT with cytoreduction. Area under curve value was 63.8% CI 53.2% sampai 74.4% (p = 0.0013), implicating that GLUT can predict cytoreduction correctly in 70 patients out of a total of 109 patients

An appropriate predictor tool is needed to assess whether the patient can do optimal cytoreduction or not. Several methods have been used to predict the results of cytoreduction surgery such as physical examination, ultrasound examination, CT scan, and laboratory examination. However, it seems that the predictor tool still has many shortcomings. Tumor markers that have been investigated as predictors of cytoreduction surgery are CA-125, human epididymis 4 protein (HE4), Caspase 3, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), vascular endothelial growth factor (VEGF) levels serum-peritoneum-VEGF load, and a combination of CA 125 with HE4, YKL 40, BCL 2, and cathepsin L [12], [13], [14], [15], [16], [17]. Therefore, in this study researchers are trying to find alternative examinations that are expected to be other predictors than CA-125, namely, FASN and GLUT.

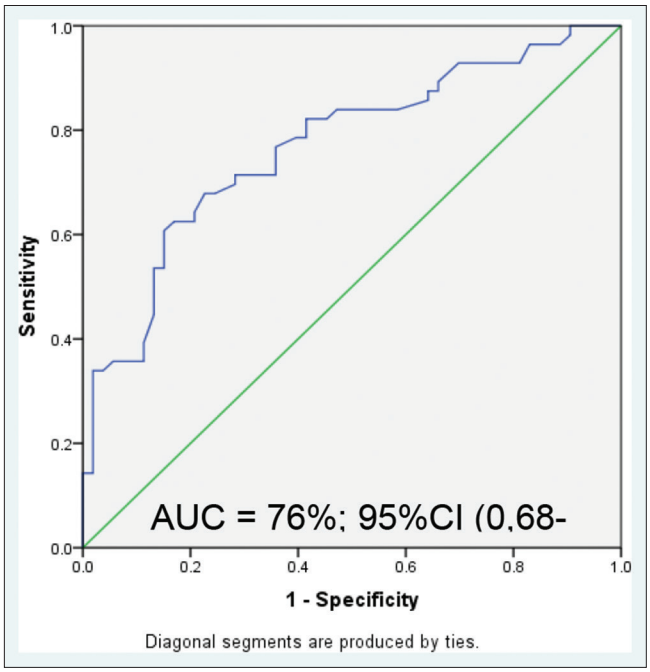

Figure 4: ROC curve showing the value of combination FASN and CA-125 with cytoreduction. Area under curve value was 76.9% CI 68.1%-85.8% (p = 0.0000), implicating that FASN and CA-125 can predict cytoreduction correctly in 84 patients out of a total of 109 patients

CA-125 or commonly referred to as CA-125 is the most studied serum biomarker as a predictor of cytoreduction surgery. Vorgias et al. in their study entitled "Can the pre-operative Ca-125 predict optimal levels of cytoreduction in patients with advanced ovarian carcinoma? A single institution cohort study" examining 426 patients with stage III/IV ovarian cancer stated that CA-125 is a good predictor for predicting optimal cytoreduction. Furthermore, Vorgias said that the cutoff point of CA-125 is 500 IU/mL with the sensitivity 78.5%, the specificity 89.6%, positive predictive value 84.2%, negative predictive value 85.4%, and the accuracy rate 85% [34]. Based on the recommendations of The Society of Gynecologic Oncology and the American Society of Clinical Oncology Clinical Practice Guideline that every patient who has a low likelihood of optimal cytoreduction, then it is better to receive NACT therapy first [35]. Even the study from Canada stated that the reduction in CA-125 during chemotherapy was related to the success rate of cytoreduction surgery [36].

In this study was found that there were significant differences in CA-125 as a predictor of cytoreduction surgery (p = 0.0001). The cutoff point of CA-125 as a predictor was 248.55 U/mL, with a sensitivity 73.2%, a specificity 73.6%, and an accuracy rate 73.3% (Table 3). Figure 1 shows ROC curve of CA-125 with cytoreduction with AUC value that was 76.7% CI 67.8%-85.6% (p = 0.000), implicating that CA-125 can predict cytoreduction correctly in 84 patients out of a total of 109 patients.

In normal biological systems, levels of CA-125 or Mucin 16 (MUC-16) are expressed in several epithelial layers of organs such as the mouth, esophagus, lungs, breast, large intestine, ovary, and cervix. CA-125 has the function of hydration and lubrication to maintain the mucosal layer of epithelial cells and protect the cell surface from pathogen attack [37]. Regulatory errors in CA-125 play a role in cancer pathogenesis [13], [37]. In ovarian cancer, MUC16 will interact with NK cells through the Siglec receptor-9 and cause immunosuppression. This MUC16 will interact with galectin 1 and 3 in cancer cells, which will cause an increase in cancer progressivity [37].

Various evidence has been found about changes in several branches of metabolism that support the transformation of malignancy. Changes in metabolism that occurs in cancer are associated with activation of proto-oncogenes and inactivation of tumor suppressor genes. Various oncogenic signaling pathways are needed in tumor cell metabolism to support cell growth and resistance. Various cellular metabolic changes to support the three basic need of cells that are dividing; the formation of adenosine triphosphate (ATP) increase macromolecular biosynthesis and monitor redox conditions. Cancer cells require changes in all significant macromolecular metabolic pathways: Carbohydrates, proteins, lipids, and nucleic acids [27].

FASN and GLUT play an essential role in the metabolic changes that exist in cancer cells. FASN plays a role in lipogenesis *de novo*, a mechanism of synthesis of fatty acids in the body. The rapid proliferation of cancer cells requires large amounts of fatty acids [38]. The lipogenesis *de novo* process will produce saturated fatty acids and monounsaturated fatty acids. These types of fatty acids make cancer cells survive from oxidative stress, which will cause cell death. Besides, fatty acids in large quantities can also reduce the absorption of drugs by cancer cells which will cause resistance to therapy [39].

Increased synthesis of fatty acids in tumor cells will increase the activation of several enzymes in the lipogenic pathway. Increased FASN activity found

in early oncogenesis, which would correlate with the pathogenesis of cancer. Therefore, an increase in FASN expression can indicate a more aggressive type of cancer cell [28].

Until now, there have been no studies using serum FASN as a predictor of suboptimal surgery in ovarian cancer. Stefanie et al. said in their study that benign ovarian tumors have low FASN numbers when compared to malignant ovarian tumors. In FASN staining, high-grade serous carcinoma has a higher score compared to low-grade serous carcinoma [29].

There was a significant difference in FASN as a predictor of cytoreduction surgery (p = 0.006). The cutoff point of FASN as a predictor was 0.445, with a sensitivity 62.5%, a specificity 60.4%, and an accuracy rate 61.4% (Table 3). Figure 2 shows ROC curve of FASN with cytoreduction with AUC value was 65.3% CI 54.8%-75.8% (p = 0.006), implicating that FASN can predict cytoreduction correctly in 71 patients out of a total of 109 patients.

The next biomarker serum is GLUT, one of the proteins that play a role in transporting glucose. Glucose is a source of fuel for almost all body cells, including cancer cells. Glucose will go through processes glycolysis, the Krebs cycle, and oxidative phosphorylation to supply energy in the form of ATP. Malignant cells will tend to metabolize through the process of glycolysis, and it will require faster glucose absorption [18]. The glucose demand will increase GLUT expression.

Based on Table 2, GLUT has a significant difference as a predictor of cytoreduction surgery (p = 0.013). The use of GLUT as a predictor of cytoreduction surgery resulted in a sensitivity of 75% and specificity 56.6%, with a cutoff point of 0.1980 (Table 2). Figure 2 shows the ROC curve of GLUT with cytoreduction with AUC value that was 63.8% CI 53.2–74.4% (p = 0.0013), implicating that GLUT can predict cytoreduction correctly in 70 patients out of a total of 109 patients.

The combination of CA-125 + FASN produces a cutoff point of 0.69 with CA-125 as a categorical group (1; ≦ 248.55, 2> 248.55). The use of this combination has a sensitivity rate of 71.4%, a specificity of 71.7%, and an accuracy rate of 71.6% (p = 0.0001). While the combination of CA-125 + GLUT produces a cutoff point of 0.3793 with CA-125 as a categorical group (1; ≦ 248.55, 2> 248.55). The use of this combination has a sensitivity rate of 67.9%, a specificity of 66%, and an accuracy value of 67% (p = 0.0001).

The combination of the three namely CA-125 + FASN + GLUT can correctly predict 82 patients out of 109 patients (Figure 6) using CA-125 (1; ≦ 248.55, 2> 248.55) and FASN (1; ≦ 0.445, 2 > 0.445) as a categorical group. All three have a cutoff point of 0.5150 (table 3.) with a sensitivity value of 71.4%, specificity of 71.7%, and an accuracy value of 71.6%.

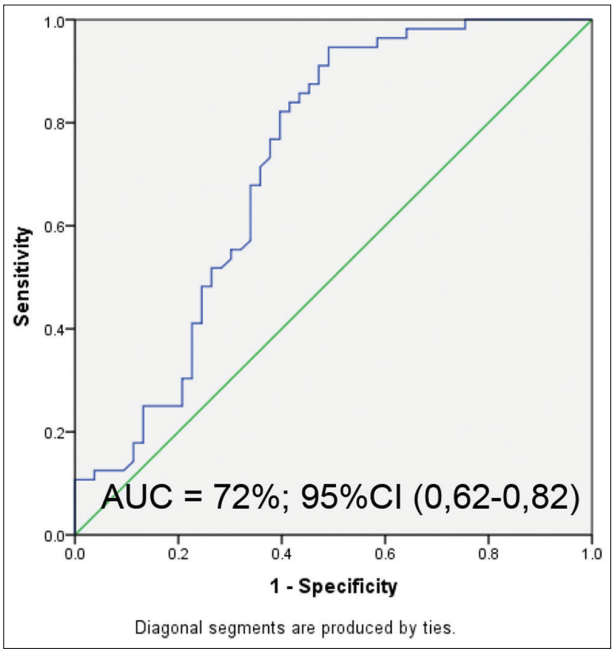

Figure 5: ROC curve showing the value of combination GLUT and CA-125 with cytoreduction. Area under curve value was 72.2% CI 62.3%-82.1% (p = 0.000), implicating that GLUT and CA-125 can predict cytoreduction correctly in 79 patients out of a total of 109 patients

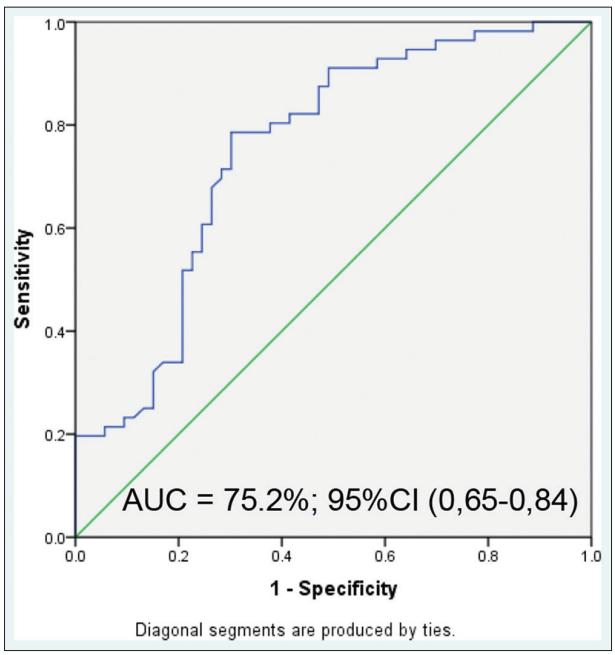

Figure 6: ROC curve showing the value of combination CA-125, FASN, and GLUT with cytoreduction. Area under curve value was 75.2% CI 65.9–84.5%. (p = 0.000), implicating that CA-125, FASN, and GLUT can predict cytoreduction correctly in 82 patients out of a total of 109 patients

Conclusion

Although the use of CA-125 has not been proven to be specific as a predictor of cytoreduction surgery, it seems that GLS and FASN are no better than the use of CA-125. Neither the combination nor the value of the biomarker singly does not have better

results than the use of CA-125. It is hoped that this research can provide an overview of other biomarkers for their use as predictors of cytoreduction surgery.

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Ethical approval and consent to participate

The study was approved by Research Ethics Committee, Faculty of Medicine Padjadjaran University/ Dr. Hasan Sadikin Hospital, Bandung, Indonesia, No. Ref 0518010184. "The Research Ethic Committee Universitas Padjadjaran Bandung, to protect the rights and welfare of the research subject, and to guaranty that the research using survey questionnaire/registry/ surveillance/epidemiology/humaniora/social-cultural/ archieved biological materials/stem cell/other non-clinical material, will carried out according to ethical, legal, social implications, and other applicable regulations, has been thoroughly reviewed the proposal entitled The Ability Pre-operative Serum (CA-125, FASN, and GLUT) to Predict Primary Suboptimal Cytoreduction in Epithelial Ovarian Cancer".

The suspected ovarian cancer patient was invited to participate this study. The patient who was willing to be participants in this study will be asked to fill and sign an informed consent form. They were told that all data concerning of self-sample would be handled with full confidentiality.

Declarations

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

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