Original Research

The Role of Akt2 and CA-125 Serum Levels as Predictors for Successful Cytoreduction in Epithelial Ovarian Cancer Surgery

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Summary

Ovarian cancer is one of the common causes of cancer deaths in gynecological malignancies in Indonesia, and indeed the world. Of all classifications of ovarian cancer, the epithelial subtype shows the highest incidence. Cytoreductive surgery is a determinant of prognosis for patients with advanced epithelial ovarian cancer. One possible way to predict the results of cytoreductive surgery is to measure preoperative tumor marker levels. This study aimed to assess the validity of serum levels of Protein kinase Bβ (Akt2) and cancer antigen-125 (CA-125) as outcome predictors for cytoreduction in epithelial ovarian cancer surgery. This was an observational, analytical, cross-sectional study. Akt2 and CA-125 serum levels were examined by enzyme-linked immunosorbent assay (ELISA) and immunoassay technique, respectively. Mean levels of Akt2 and CA-125 were significantly different between optimal and suboptimal cytoreduction groups ($p < 0.05$). The cut-off point (COP) value obtained for Akt2 was 1.20 U/mL with area under curve (AUC) value of 68.9%, while the COP for CA-125 was 222.50 U/mL with AUC value of 75.3 % ($p < 0.05$). If the preoperative Akt2 serum level was greater than 1.20 U/mL, and preoperative CA-125 level was greater than 222.5 U/mL, the probability of suboptimal cytoreduction was increased. Thus, our study highlights the possibility for Akt2 and CA-125 levels to be used as serum biomarkers in predicting the success of cytoreductive surgery.

Key words: Epithelial ovarian cancer; cytoreduction; Akt2; CA-125.

Introduction

Ovarian cancer is one of the leading causes of death from cancer in women worldwide. In 2012, there were almost 240,000 new cases of ovarian cancer, ranking it the seventh highest of all cancers in women. By 2018, this figure had risen to almost 300,000, making it the fourth most common cancer in women. Ovarian cancer was the cause of death in 151,917 cases and 184,799 cases worldwide in 2012 and 2018, respectively [1, 2].

Classification of malignant ovarian cancer consists of epithelial-, stromal sex-cordal and germ cell-type; 90% of malignant ovarian cancers are of the epithelial type [3, 4]. The standard management of epithelial ovarian cancer is surgical staging in early-stage (stage 1) cases and cytoreductive surgery in cases of advanced stage (stages 2, 3 and 4), followed by platinum-taxane based chemotherapy [5].

Cytoreductive surgery is performed on advanced stage epithelial ovarian cancer to remove as much of the tumor bulk as possible. Intraoperatively by gross examination, surgery is considered as optimal cytoreduction if residual tumor < 1 cm at greatest dimension, while cytoreduction is suboptimal if the residual tumor is > 1 cm [3, 5, 6]. Saitou *et al.* reported that patient prognosis only improved when residual tumor nodules were < 1 cm [7].

Measurement of tumor marker levels is among the outcome predictors of cytoreductive surgery. Cancer antigen-125 (CA125) serum level > 420 U/ml was a strong predictor of suboptimal cytoreduction surgery in patients with epithelial ovarian cancer [8]. The combination of CA-125 levels with other tumor markers may help determine management [9]. The increase in CA-125 causes an increase in Protein kinase B(AKT) expression [10]. AKT is a key signaling molecule that regulates cellular processes such as proliferation, cell growth and metabolism as well as serving as a tumor marker [11]. Of the three AKT isoforms, AKT2 expression is found elevated in ovarian cancer [12]. Overexpression of AKT2 leads to increased expression of pyruvate kinase (PKM2) in ovarian cancer cells in nude mice [13]. Elevation of AKT2 expression induced cell migration and invasion *in vitro*, as well as lung metastasis *in vivo*, while suppression of AKT2 blocked these effects. STAT3 expression was elevated and NF-κB p65 nuclear translocation was activated both *in vitro* and *in vivo* when AKT2 was overexpressed; these effects were inhibited when AKT2 expression was suppressed. AKT2 increases the migration, progression and invasion of ovarian cancer cells *in vitro* and in nude mice *in vivo* through PKM2-mediated elevation of STAT3 expression and NF-κB activation [13].

Preoperative combination of AKT2 and CA-125 levels may predict the outcome of cytoreductive surgery, which in turn may help clinicians determine the subsequent management of patients with advanced ovarian cancer.

Methods

This study was registered and approved by the Research Ethics Committee, Faculty of Medicine Padjadjaran University/Dr. Hasan Sadikin Hospital, Bandung, Indonesia, under trial registration number 36/UN6.KEP/EC/2018 on April 13th, 2018.

Study subjects

This study was a prospective, observational analysis with a cross-sectional design. The population included patients with a diagnosis of suspected advanced ovarian cancer who would undergo cytoreductive surgery at Dr. Hasan Sadikin General Hospital, Bandung. The inclusion criteria were new patients with suspected epithelial ovarian cancer undergoing cytoreductive surgery who were willing to give informed consent, and who were not suffering from chronic diseases or other tumors. Consecutive patients from the 2018-2019 period attending Dr. Hasan Sadikin General Hospital, Bandung were included.

Before surgery, blood samples were taken from the entire study population for the assessment of serum biomarker levels. Patients who were confirmed histopathologically to not suffer from epithelial ovarian cancer, or who only had stage I disease, were excluded from the study. Patients were also excluded if their histopathological preparations were damaged or could not be assessed or if they were not willing to provide informed consent.

Materials

AKT2 serum examination was performed by ELISA (Enzyme-Linked Immunosorbent Assay. Cloud-Clone Corp., USA). CA-125 examination was done by immunoassay technique analyzed by ADVIA Centaur® XP system (Siemens Healthcare Diagnostics Inc., USA). All techniques were done according to the manufacturer's instructions.

Statistical Analysis

All data were assessed statistically using SPSS® (24.0.0). For normally distributed data, a paired *t*-test analysis was used, while a Mann Whitney analysis was used for not normally distributed data. As for categorical data, *p*-values were analyzed using the Chi-Square test; if the Chi-Square requirements were not met, then Kolmogorov Smirnov and Exact Fisher tests were used. The cut-off point (COP) was made using receiver operating characteristic (ROC) curve 23 analysis.

Results

Fifty-three patients were included in this study, divided into suboptimal and optimal cytoreductive groups. Char-

acteristics of the subjects in the two groups were analyzed. There were no significant differences ($p > 0.05$) between the two groups regarding patients' age, parity, height, weight, body mass index, ascites, bleeding, staging, and histopathology (Table 1). Analysis of blood samples taken before surgery revealed the levels of serum AKT2 and CA-125 had a significant difference ($p < 0.05$) between that of suboptimal and optimal cytoreductive groups (Table 2).

The COP of AKT2 was 1.20 U/mL, with a significant p value ($p < 0.05$) between COP and results of cytoreduction (Table 3). The AUC value of AKT2 levels with ROC method was 68.9%, implying that 68.9% of patients with AKT2 serum levels greater than 1.20 U/mL would undergo suboptimal cytoreduction with 76.2% specificity, 65.6% sensitivity, and 69.8% accuracy (Figure 1, $p = 0.021$).
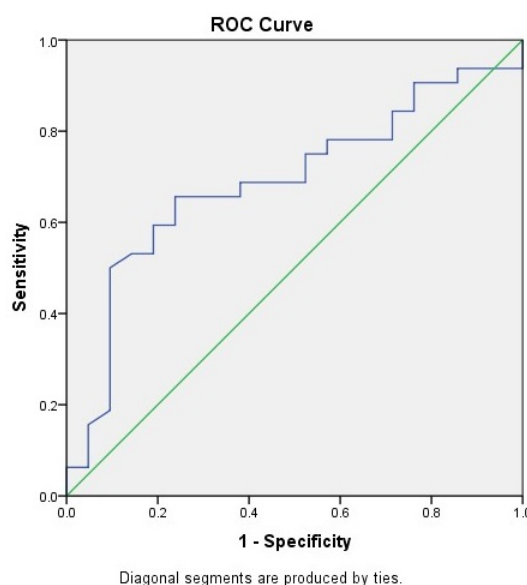

Figure 1. — Akt2 with Cytoreduction. The AUC value obtained from the ROC method was 68.9% ($p = 0.021$), meaning that Akt2 can predict cytoreduction correctly in 37 patients out of a total of 53 patients.

The COP of CA-125 obtained from this study was 222.5 U/mL, with a significant p value ($p < 0.05$) between COP and results of cytoreduction (Table 4). Based on the ROC method, the AUC value received was 77.5%, suggesting that 77.5% of patients with serum CA-125 levels exceeded 222.5 U/ml. Suboptimal cytoreduction was predicted with 61.9% specificity, 75% sensitivity and 69.8% accuracy (Figure 2, $p = 0.002$).

Multivariate analysis was obtained by logistic regression test to determine whether AKT2 or CA-125 was more closely related to the cytoreduction result. As Table 5 shows, AKT2 had a comparably smaller p value than CA-125 ($p = 0.003$ *vs.* $p = 0.005$, respectively), and higher odds ratio (OR = 12.404 *vs.* OR = 10.379, respectively). These data indicate that AKT2 measurement may be more likely

Table 1. — *Comparison of Characteristics of Patients in Optimal and Suboptimal Cytoreduction groups.*

Variable	Group		p Value
	Suboptimal cytoreduction n = 32	Optimal cytoreduction n = 21	
Age (years)			0.131
Mean ± SD	50.09 ± 9.686	45.23 ± 13.374	
Parity			0.979
0	7 (21.9%)	2 (9.5%)	
1	4 (12.5%)	8 (38.1%)	
2	8 (25.0%)	1 (4.8%)	
> 3	13 (40.6%)	10 (47.6%)	
Height (cm)			0.164
Mean ± SD	153.09 ± 5.348	150.80 ± 4.285	
Weight Preop (kg)			0.056
Mean ± SD	56.25 ± 8.925	51.19 ± 9.825	
Weight Postop			0.057
Mean ± SD	50.12 ± 9.317	45.26 ± 8.169	
BMI			0.175
Mean ± SD	21.44 ± 4.259	19.90 ± 3.501	
Ascites			0.195
Mean ± SD	1892.50 ± 3126.565	2281.90 ± 5117.13	
Bleeding Volume			0.114
Mean ± SD	1312.10 ± 920.868	1357.14 ± 1826.08	
Stage			0.149
II	5 (15.6%)	10 (47.6%)	
III	20 (62.5%)	11 (52.4%)	
IV	7 (21.9%)	0 (0.0%)	
Histopathology			0.873
Serous	13 (40.6%)	6 (28.6%)	
Mucinous	7 (21.9%)	10 (47.6%)	
Endometrioid	7 (21.9%)	2 (9.5%)	
Clear Cell	5 (15.6%)	3 (14.3%)	

Age, Weight PostOp (preoperative), and BMI were analyzed by Independent t-Test. Height, Weight PreOp (preoperative), Ascites, and Bleeding Volume were analyzed by Mann Whitney test. Parity, Stage, and Histopathology were analyzed by Kolmogorov Smirnov test.

Table 2. — *Comparison of Akt2 and CA-125 in the Suboptimal and Optimal Cytoreduction groups.*

Variable	Groups		p Value
	Suboptimal cytoreduction n = 32	Optimal cytoreduction n = 21	
Akt2			**0.021***
Mean ± SD	1.41 ± 0.555	1.12 ± 0.286	
Median	1.43	1.09	
Range	0.65 - 3.79	0.80 - 1.89	
CA-125			**0.002***
Mean ± SD	964.22 ± 1722.532	264.98 ± 251.883	
Median	600.00	132.70	
Range	4.29 - 9934.00	5.10 - 701.00	

$*p < 0.05$ (Mann Whitney Test)

to accurately predict optimal tumor resection probability.

Both AKT2 and CA-125 had *p*-value < 0.05 according to multivariate analysis, (table 6). The new cut-off point was generated by re-coding AKT2 value based on the orig-inal AKT2 COP 1.20. AKT2 values < 1.20 were re-coded to "1" and values > 1.20 were re-coded to "2". The re-coded values were multiplied by corresponding CA-125 to produce the combined variable. An ROC curve was plotted

Table 3. — *Comparison between Cut-Off Points of Akt2 in Suboptimal and Optimal Cytoreduction Groups.*

	Cytoreduction		
Variable	**Suboptimal n = 32**	**Optimal n = 21**	**p Value**
Akt2			**0.003***
> 1.20	21 (65.6%)	5 (23.8%)	
< 1.20	11 (34.4%)	16 (76.2%)	

*p < 0.05(chi-square test).

Table 4. — *Comparison between Cut-off Points of CA-125 in Suboptimal and Optimal.*

	Cytoreduction		
Variable	**Suboptimal n = 32**	**Optimal n = 21**	**p Value**
Ca-125			**0.007***
> 222.50	24 [75.0%]	8 [38.1%]	
< 222.50	8 [25.0%]	13 [61.9%]	

*p < 0.05(chi-square test).

from the combination variable, which resulted in the combination COP was 410.45 U/mL. The new COP had a 75% sensitivity, 61.9% specificity and 69.8% accuracy for predicting optimal cytoreduction (Figure 3, $p = 0.001$).
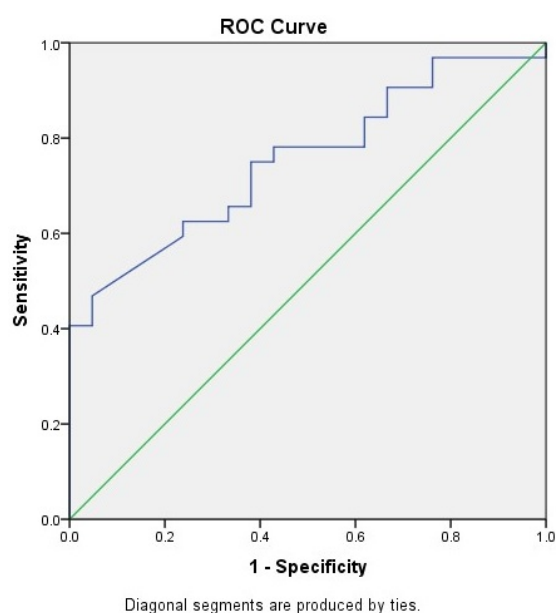

Figure 2. — CA-125 with Cytoreduction. The AUC value obtained from the ROC method was 75.3% ($p = 0.002$), meaning that CA-125 can predict cytoreduction correctly in 40 patients out of a total of 53 patients.
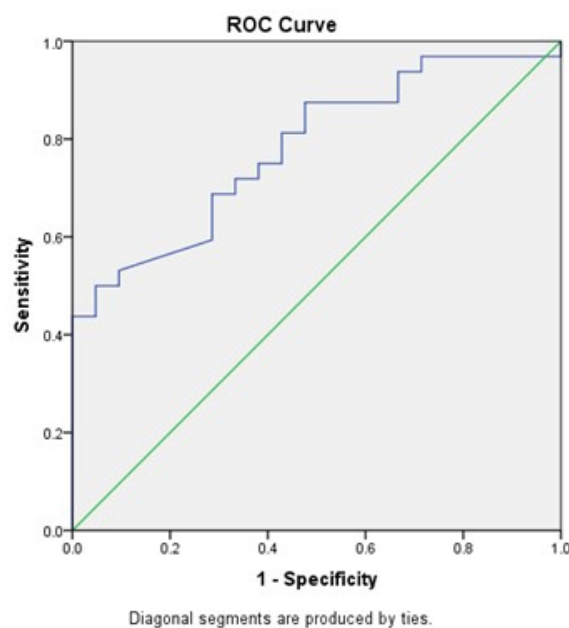

Diagonal segments are produced by ties.

Figure 3. — The combination of Akt2 and CA-125 with Cytoreduction. The AUC value obtained from the ROC method was 78.1% ($p = 0.001$), meaning that combination of Akt2 and CA-125 can predict cytoreduction correctly in 41 patients out of 53 patients.

Discussion

Cytoreductive surgery in epithelial ovarian cancer patients determines prognosis and subsequent therapy. Studies have shown that patients with optimal cytoreduction have a better prognosis. Optimal cytoreduction with a residual mass < 1 cm increases the survival rate by 22 months [14].

The AKT signaling pathway is key in mediating the survival of tumor cells and avoiding apoptosis [13]. A 2014 meta-analysis conducted by Cai *et al.* that reviewed 11 articles stated that a high expression of AKT was related to poor survival in patients with epithelial ovarian cancer. The authors concluded that only high expression of AKT was significantly related to a poor prognosis, reflecting its oncogenic nature [15].

In this study, the average serum level of AKT2 was statistically significantly different between the optimal and suboptimal cytoreductive group. The COP of AKT2 was 1.20 U/mL, with a significant p value between COP and results of cytoreduction. The AUC value of AKT2 levels with ROC method was 68.9%, implying that 68.9% of patients with AKT2 serum levels more than 1.20 U/mL would undergo suboptimal cytoreduction with 76.2% specificity, 65.6% sensitivity The results of this study indicate that an increase in AKT expression will make it more difficult to achieve optimal tumor cytoreduction. This is consistent with the theory that high AKT expression is associated with a worse prognosis since oncogenic activity in the Akt sig-

Table 5. — *Multivariate COP of Akt2 and CA-125 Analysis.*

		B	S.E.	p value	OR	Lower	95% C.I.for OR Upper
Step 1	CutoffAkt2	2.518	0.846	0.003*	12.404	2.365	65.070
	CutoffCA-125	2.340	0.837	0.005*	10.379	2.014	53.487

Cytoreduction Groups
*Note: *p < 0.05 (logistic regression test)*

Table 6. — *Comparison between Cut-off Points of CA-125 in Suboptimal and Optimal.*

	Cytoreduction		
Variable	Suboptimal n = 32	Optimal n = 21	**p Value**
Combinations CA-125 dan Akt2			0.006*
> 410.45	23 (71.9%)	7 (33.3%)	
< 410.45	9 (28.1%)	14 (66.7%)	

*Note: *p < 0.05(chi-square test)*

naling pathway is known to have an essential role in tumorigenesis by influencing the absorption of glucose, amino acids, and lipids [11]. Thus, AKT2 serum levels can be used to predict whether results of cytoreduction will be optimal or suboptimal.

CA-125 is one of the significant predictors for outcome of cytoreduction [16]. Other studies have suggested that the COP of CA 125 > 100 U/ml increases the occurrence of suboptimal cytoreduction [17]. Feng *et al.* stated that CA-125 could predict optimal or suboptimal cytoreduction. A pre-operative COP of CA-125 > 500 U/ml had a sensitivity of 78% and specificity of 73% for predicting suboptimal cytoreduction [18]. Another study stated that 912 U/ml was an optimal cut-off value of CA-125 in predicting optimal and suboptimal cytoreduction [19]. The COP of serum CA-125 levels still varies.

In our study, the COP of CA-125 was 222.5 U/mL; based on the ROC method, the AUC value received was 77.5%, suggesting that 77.5% of patients with serum CA-125 levels exceeded 222.5 U/ml. This was predictive of suboptimal cytoreduction with 61.9% specificity, 75% sensitivity, and 69.8% accuracy. The specificity value of AKT2 was higher than that of CA-125, matching the current theory that pre-operative CA-125 serum level is not a specific tumor marker to diagnose ovarian cancer [3]. CA-125 also has a low specificity for malignant ovarian cancer because it often increases in patients with benign endometriosis [15].

When CA-125 and AKT2 were combined, the new COP was 410.45 U/mL with a specificity value of 61.9%, sensitivity of 75%, and the same accuracy value of 69.8%. The AUC value obtained from the ROC method was 78.1%, meaning that as many as 78.1% of patients with a combination of CA-125 and AKT2 value more than 410.45 U/mL may experience suboptimal cytoreduction. Based on the confidence interval, the combination of AKT2 and CA-125 value ranged from 65.9% to 90.3%. Whether separate or

in combination, AKT2 and CA-125 had the same accuracy level.

Currently, there is insufficient evidence to recommend the use of AKT levels in clinical practice as a predictor of epithelial ovarian cancer prognosis [15]. Further research will be necessary to substantiate our present findings. However, as the combination of AKT2 and CA-125 has a higher AUC value, it can be concluded that the combination of both tumor markers is beneficial than either used alone.

Finally, the success of cytoreductive surgery still depends on the experience of the surgeon as well as other factors such as FIGO cancer stage, histopathological type, and body mass index [19-21]. Findings from this research may prove useful in helping to predict outcomes following cytoreduction and patient prognosis.

The major limitation of our study was insufficient patient cohort. Therefore, future studies should involve a larger number of patients to increase the power of the study and the validity of our findings.

Conclusions

AKT2 and CA-125 serum levels are significantly different between the patients in suboptimal and optimal cytoreduction groups. AKT2 or CA-125 can be used as single tumor markers to predict cytoreduction, wherein the COP of AKT is 1.20 U/mL and the COP of CA-125 is 222.5 U/mL. As both tumor markers are correlated, AKT2 and CA-125 can be used in combination to achieve a new COP of 410.45 U/mL, providing a better AUC value.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee, Faculty of Medicine Padjadjaran University/Dr. Hasan Sadikin Hospital, Bandung, Indonesia, under trial registration number 36/UN6.KEP/EC/2018 on April 13th, 2018. Suspected ovarian cancer patients were invited to

participate in this study. Patients who were willing to become participants in this study were asked to fill and sign an informed consent form.

Funding

Authors' Contributions

YMH, GNAW, and SRK designed the research study. YMH, GNAW, AK performed the research. MDLT, KIM, SRK provided help and advice on the experiments. YMH, MDLT, KIM analyzed the data. YMH, KIM, AK, SRK wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Availability of data and materials section

The authors declare that the data will not be shared due to issues of patient confidentiality.

Consent to Publish

All authors declare that consent was given for publication of this study and accompanying images to be published.

Acknowledgments

Conflict of interest

Authors have declared that no competing interests exist.

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