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Changes in CA 125 Level Pre and Post Ovarian Cancer Surgery

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ABSTRACT

Background: Ovarian cancer is one of the gynecological cancers that has a fairly high mortality rate and has a poor prognosis. In 2018, the global incidence of ovarian cancer was 4.4% which is 184,799 of all cancer deaths in women and is expected to increase significantly by 2040. Ovarian cancer management includes optimal surgery followed by chemotherapy, which at follow up will have an effect on decreasing CA 125 levels. But in fact there are several studies showing increased CA
125. Given these differences in findings, this study attempted to evaluate the pre and post surgery changes in CA 125 levels in ovarian cancer patients.
Objective: This study aims to determine the changes in CA 125 levels pre and post surgery in ovarian cancer patients. And to determine the relation between optimal surgery and postoperative CA 125 levels.
Methods: The type of research is an analytic study with a prospective cohort design. The data source taken from the SIMETRIS Dr. Sardjito Hospital within 6 months in 2021.
Results and Discussion: The distribution of the age < 40 years was 11 and 19 were 40 years old. There was a significant change in pre surgery log CA 125 levels (mean = 2,53 or 902,03U/ml) and post surgery log CA 125 levels (mean = 1,92 or 406,23 U/ml). With a difference or delta mean of 0,61 or 495,80 U/ml and p value = 0.001. There was a significant difference in post surgery log CA 125 levels between optimal and non optimal surgery. Based on data analysis on the table above, there was no significant difference in log CA 125 levels pre or post in each risk factor.
Conclusion: There was a significant decrease in log CA 125 levels pre and post surgery in patients with ovarian cancer who underwent surgery. The post surgery log CA 125 level in optimal surgery is lower than in non-optimal surgery**.**

Keywords: CA 125; Ovarian Cancer; Surgery; Optimal.

ABSTRAK

Latar Belakang: Kanker ovarium merupakan salah satu kanker ginekologi yang memiliki angka kematian yang cukup tinggi dan memiliki prognosis yang buruk. Pada tahun 2018, kejadian kanker ovarium di dunia sebanyak 4,4% yaitu 184.799 dari seluruh kematian akibat kanker pada wanita dan diperkirakan angka kematiannya akan meningkat signifikan pada tahun 2040. Manajemen kanker ovarium meliputi operasi secara optimal diikuti kemoterapi, yang pada follow up nya akan berpengaruh pada penurunan kadar CA 125. Namun pada kenyataannya ada beberapa penelitian yang menunjukkan peningkatan kadar CA 125. Dengan ada nya perbedaan temuan tersebut, penelitian ini berusaha untuk mengevaluasi perubahan kadar CA 125 *pre* dan *post* operasi pada pasien kanker ovarium.
Tujuan: Untuk mengetahui perubahan kadar CA 125 *pre* dan *post* operasi pada pasien kanker ovarium. Dan untuk mengetahui hubungan operasi yang optimal dengan kadar CA 125 *post* operasi
Metode: Jenis penelitian ini adalah penelitian analitik dengan rancangan *cohort* prospektif. Sumber berasal dari data sekunder yang diambil dari simetris RSUP Dr. Sardjito dalam kurun waktu 6 bulan pada tahun 2021.
Hasil dan Pembahasan: Distribusi usia < 40 tahun sebanyak 11 dan 19 ≥ 40 tahun. Terdapat perubahan yang bermakna log kadar CA 125 *pre* operasi (rerata = 2,53 atau 902,03 U/ml) dan log kadar CA 125 post operasi (rerata = 1,92 atau 406,23 U/ml). Dengan selisih atau delta mean sebesar 0,61 atau 495,80 U/ml dan nilai p = 0,001. Penderita dengan operasi optimal terdapat perubahan yang signifikan log kadar CA 125 *pre* dan *post* operasi dibandingkan dengan operasi tidak optimal. Berdasarkan hasil analisa data, tidak terdapat perbedaan yg signifikan log kadar CA 125 *pre* maupun *post* operasi.
Kesimpulan: Terdapat penurunan yang signifikan pada log kadar CA 125 *pre* dan *post* operasi pada penderita kanker ovarium yang dilakukan operasi. Log kadar CA 125 post operasi pada tindakan operasi yang optimal lebih rendah dibandingkan pada tindakan operasi yang tidak optimal

Kata Kunci: CA 125; Kanker Ovarium; Operasi; Optimal.

BACKGROUND

Ovarian cancer is gynecological cancer that has high mortality and a poor prognosis. In 2018, ovarian cancer incident is 4.4% with around 184,799 death in women. It is estimated that in 2040, the death caused by this cancer will significantly increase. The high rate of death caused by ovary cancer is caused by asymptomatic growth, the onset of delayed symptoms, and lack proper of screening which resulted in the diagnosis of advanced stage.[1,2]

Management of ovarian cancer includes optimal surgery followed by chemotherapy, which in follow up will affect the decrease in CA 125 levels. Several studies have shown that perisurgery CA 125 levels are the initial biomarker predicting survival in patients undergoing surgery. Perisurgery changes in CA125 may be a better marker of residual tumor volume after suboptimal surgery. But in fact, there are several studies that show an increase in CA 125 levels reported in some post surgery patients.[3,4]

With these differences in findings, this study attempted to evaluate changes in pre surgery and post surgery CA 125 levels in ovarian cancer patients.

METHODS

This research uses analytic research with a prospective cohort design. The source comes from secondary data taken from the symmetrical Sardjito Hospital in 2021. The inclusion criteria used in this study were patients with ovarian cancer who underwent surgery at Sardjito Hospital. The exclusion criteria used in this study were women with non epithelial ovarian cancer and incomplete medical record data.

Data analysis used the statistical test of normality test with Shapiro Wilk, the data were not normally distributed, then a log10 transformation was performed and the normality test was repeated to show that the transformed data were normally distributed.

Independent variables and external variables with a p value < 0.25 followed by multivariate analysis with the Logistic Regression test then the stratification test and the Paired T-Test.

RESULTS AND DISCUSSION

1. Characteristic of research subjects

Tabel 1. Characteristic of research subjects

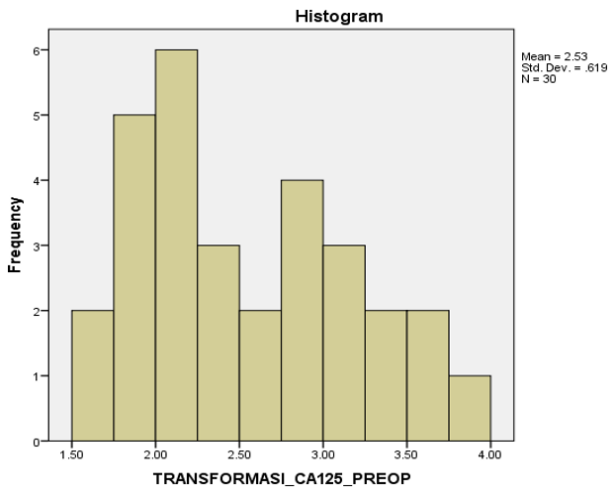
	Surgery				Total	*p*
	Optimal	%	Non Optimal	%		
Age						
< 40 years old	7	46,67	4	26,67	11	0,256
≥ 40 years old	8	53,33	11	73,33	19	
Total	15	100,00	15	100,00	30	
Parity						
Nulipara	8	53,33	4	26,67	12	0,136
Multipara	7	46,67	11	73,33	18	
Total	15	100,00	15	100,00	30	
Menopause Status						
Yes	15	100,00	7	46,67	22	0,002
No	0	0,00	8	53,33	8	
Total	15	100,00	15	100,00	30	

	Surgery				Total	p
	Optimal	%	Non Optimal	%		
Contraception history						
Hormonal	6	40,00	2	13,33	8	0,288
Non Hormonal	2	13,33	5	33,33	7	
No contraception	7	46,67	8	53,33	15	
Total	15	100,00	15	100,00	30	
Histophatology						
Type 1	12	80,00	9	60,00	21	0,427
Type 2	3	20,00	6	40,00	9	
Total	15	100,00	15	100,00	30	
Stadium						
Early	8	53,33	2	13,33	10	0,020
Advanced	7	46,67	13	86,67	20	
Total	15	100,00	15	100,00	30	

2. Changes in Log CA 125 Levels Pre and Post surgery in Ovarian Cancer Patient

Based on the results of the normality test with Shapiro Wilk, the results of the normality test on data on pre surgery and post surgery CA 125 levels have a p-value < 0.05 which indicates that the CA 125 level data is not normally distributed but after transformation with log10 and re-testing normality for both of these data yields a p value > 0.05 which indicates that the transformation data for CA 125 levels pre surgery (p = 0.201) and post surgery (p = 0.272) are normally distributed. Furthermore, the data analyzed were data on CA 125 levels pre and post surgery results of the transformation. The log10 mean pre surgery CA 125 level was 2.53 while the log10 mean post surgery CA 125 level was 1.92.

	Shapiro-Wilk		
	Statistic	df	Sig.
TRANSFORMATION_ CA125_PREOP	.953	30	.201
TRANSFORMASI_CA12_ POSTOP	.958	30	.272



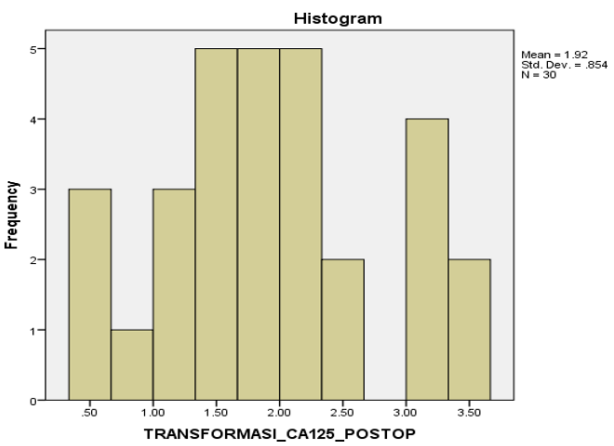


Table 2. Changes in Pre and Post Surgery Log Levels of CA 125in Ovarian Cancer Patients

CA Level 125	Mean ± SD	p
Pre surgery (n = 30)	2,53 ± 0,62	
Post surgery (n = 30)	1,92 ± 0,85	0,001
Δ mean	0,61	

Paired T-Test test

There was a significant change in the log pre surgery mean CA 125 levels ± SD = 2.53 ± 0.62 (902.03 U/ml ± 1447.12 U/ml) and log levels of CA 125.

Post surgery mean ± SD = 1.92 ± 0.85 (406.23 U/ml ± 697.73 U/ml). With a mean difference or delta of 0.61 or 495.80 U/ml and p value = 0.001.

3. Comparison of Log Levels of CA 125 Pre and Post Surgery in Optimal and non optimal Groups

In patients with optimal surgery, there was a significant change in log CA 125 levels pre surgery, mean ± SD = 2.36 ± 0.60 (611.78 U/ml ± 1018.17 U/ml) and post surgery, mean ± SD = 1.42 ± 0.69 (122.57 U/ml ± 341.54 U/ml) with delta 0.94 or 489.21 U/ml compared to patients with non-optimal surgery log CA 125 levels pre surgery, mean ± SD = 2.71 ± 0.60 (1192.29 U/ml ± 1766.55 U/ml) and post surgery, mean ± SD = 2.42 ± 0.70 (689.90 U/ml ± 848.14 U/ml) with delta 0.29 or 502.4 U/ml (see Table. 3).

Table 3. Comparison of Log Levels of CA 125 Pre and Post surgery in Optimal and non optimal Groups

Optimalisation Surgery	Log Level of CA 125		*p**	Δ	*p***
	Pre surgery Mean ± SD	Post surgery Mean ± SD			
Optimal (n=15)	2,36 ± 0,60	1,42 ± 0,69	0,001	0,94	0,008
Non Optimal (n=15)	2,71 ± 0,60	2,42 ± 0,70	0,092	0,29	

*Paired T-Test test, **Independent T-Test test

Table 4. Comparison of Log Levels of CA 125 Pre and Post Surgery Based on Risk Factors

	n	Log Level of CA 125		*p**	Δ	*p***
		Pre surgery Mean ± SD	Post surgery Mean ± SD			
Age						
< 40 years old	11	2,46 ± 0,54	1,67 ± 0,70	0,001	0,79	0,292
≥ 40 years old	19	2,57 ±0,67	2,07 ± 0,92	0,010	0,51	
Parity						
Nulipara	12	2,42 ± 0,61	1,58 ± 0,78	0,003	0,84	0,148
Multipara	18	2,61 ± 0,63	2,15 ± 0,85	0,006	0,46	
Menopause Status						
Yes	22	2,57 ± 0,67	1,88 ± 0,92	0,001	0,70	0,280
No	8	2,44 ± 0,50	2,06 ± 0,66	0,064	0,38	
Contraception history						
Hormonal	8	2,60 ± 0,69	1,95 ± 0,86	0,034	0,65	0,232
Non-Hormonal	7	2,47 ± 0,44	2,24 ± 0,84	0,381	0,23	
No contraception	15	2,53 ± 0,69	1,75 ± 0,87	0,001	0,78	

	n	Log Level of CA 125		p*	Δ	p**
		Pre surgery Mean ± SD	Post surgery Mean ± SD			
Histopathology						
Type 1	21	2,29 ± 0,49	1,78 ± 0,84	0,004	0,51	0,226
Type 2	9	3,10 ± 0,53	2,25 ± 0,72	0,003	0,85	
Stadium						
Early	10	2,19 ± 0,40	1,35 ± 0,56	0,004	0,85	0,202
Advanced	20	2,70 ± 0,65	2,21 ± 0,84	0,004	0,50	

*Paired T-Test test, **Independent T-Test test

4. Comparison of Log levels of CA 125 Pre and Post surgery based on Risk Factors

Based on data analysis on the Table 4, there was no significant difference in log CA 125 levels pre or post in each risk factor.

5. Multivariate Relationship between Risk Factors and Post Surgery Log Levels of CA 125

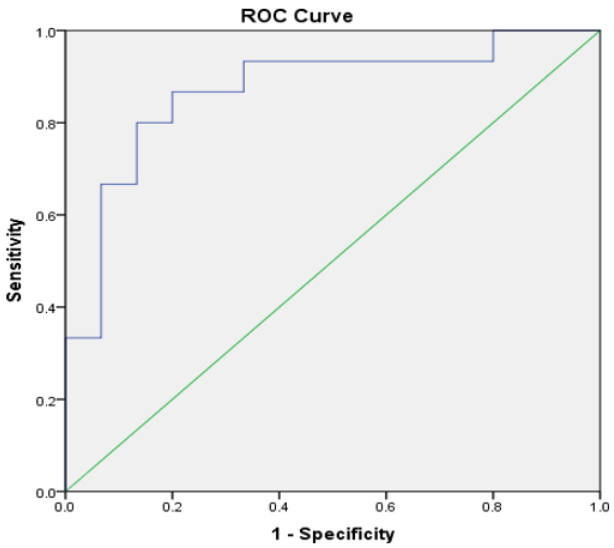
Independent variables and external variables with a p value <0.25 were subjected to multivariate analysis using the Logistic Regression test to assess the association between the independent variables and external variables simultaneously with log postoperative CA 125 levels. The OR value of the Logistic Regression test results is converted to the RR value with the following formula :

$$RR = \frac{OR}{(1-p0)+(p0 \times OR)}$$

$$CI = RR \pm 1{,}96 \times SE$$

The previous post-surgery log level of CA 125 was converted into a nominal categorical scale by determining the cut of point. Cut of point from ROC Curve results for post surgery CA 125 levels ≤ 80 or post surgery log level of CA 125 values ≤ 1.9 with sensitivity 86.7%, specifity 80 %, Youden index 0.667 AUC values AUC value 0.871 and p = 0.001, 95% CI = 0.737-1.

The AUC ROC score demonstrate that optimal ovarian cancer surgery had positive result to predict the changes in ca 125 level pre and post surgery.



Picture 1. ROC Curve CA125 Log Levels Post Surgery

Table 5. Multivariate Relationship between Risk Factors and Post Surgery Log level of CA 125

		Log Levels of CA 125				Total	*p*	RR	CI 95%
Optimization Surgery	Optimal	13	86,67	2	13,32	15	0,009	4,595	1,735 – 7,456
	Non Optimal	3	20,00	12	80,00	15		1	
Age	< 40 years old	9	81,82	2	18,18	11	0,064	2,440	0,481 – 5,360
	≥ 40 years old	7	36,84	12	63,16	19		1	
Parity	Nulipara	8	66,67	4	33,33	12	0,681	1,278	0,071 – 3,628
	Multipara	8	44,44	10	55,56	18		1	
Histophatology	Type 1	12	57,14	9	42,86	21	0,588	0,582	0,401 – 3,566
	Type 2	4	44,44	5	55,56	9		1	
Stadium	Early	8	80,00	2	20,00	10	0,928	1,074	0,586 – 3,734
	Advanced	8	40,00	12	60,00	20		1	

Table 6. Comparative Stratification of Changes in CA125 Levels Pre and Post Surgery between Optimal and Non Optimal Surgery Subjects based on Risk Factors

	Variable	Log Levels of CA 125 Pre surgery Mean ± SD	Post surgery Mean ± SD	*p**	Δ	*p***
Age	< 40 years old					
	Optimal (n=7)	2,38 ± 0,58	1,43 ± 0,39	0,003	0,95	0,233
	Non Optimal (n=4)	2,61 ± 0,48	2,09 ± 1	0,138	0,53	
	≥ 40 years					
	Optimal (n=8)	2,34 ± 0,66	1,40 ± 0,91	0,010	0,94	0,035
	Non optimal (n=11)	2,75 ± 0,66	2,55 ± 0,57	0,331	0,20	
Parity	Nulipara					
	Optimal (n=8)	2,35 ± 0,66	1,18 ± 0,54			
	Non Optimal (n=4)	2,56 ± 0,54	2,39 ± 0,49	0,002	1,18	0,027
	Multipara			0,571	0,18	
	Optimal (n=7)	2,37 ± 0,58	1,69 ± 0,78			
	Non optimal (n=11)	2,76 ± 0,64	2,44 ± 0,78	0,016	0,68	0,254
Histophatology	Type 1					
	Optimal (n=12)	2,19 ± 0,52	1,35 ± 0,76			
	Non Optimal (n=9)	2,42 ± 0,44	2,35 ± 0,73	0,001	0,84	0,011
	Type 2			0,716	0,07	
	Optimal (n=3)	3,02 ± 0,51	1,68 ± 0,29			
	Non Optimal (n=6)	3,14 ± 0,57	2,53 ± 0,70	0,027	1,35	0,089
Stadium	Early					
	Optimal (n=8)	2,15 ± 0,42	1,26 ± 0,50			
	Non Optimal (n=2)	2,39 ± 0,34	1,71 ± 0,87	0,013	0,89	0,738
	Advanced			0,319	0,69	
	Optimal (n=7)	2, 60 ± 0,72	1,60 ± 0,87			
	Non Optimal (n=13)	2,76 ± 0,63	2,53 ± 0,64	0,002	1	0,011

*Paired T-test test, **Independent T-Test tes

The results of the stratification test showed that only patients with optimal surgery experienced a significant log change in pre and post surgery CA 125 levels in both age groups, parity, histopathology, and stages, whereas, in patients with non optimal surgery, there are no significant changes of CA 125 log levels both pre and post surgeries. Patients with surgeries that are non optimal, at age ≥ 40 years old, nulliparous, histopathological type 1, and advanced stage experienced a log decrease in CA 125 levels less than patients aged < 40 years, multiparous, histopathological type 2, and early stage. In patients with optimal surgery, both aged < 40 years and ≥ 40 years experienced a significant change in log CA 125 levels pre and post surgeries ($p < 0.05$), with a difference of 0.95 U/ml and 0.94 U/ml . But in patients who were non optimal for surgery, there was no significant change in log CA 125 levels pre- and post-surgery ($p > 0.05$) in both age groups with a difference of 0.53 U/ml and 0.20 U/ml. In subjects aged ≥ 40 years, the difference in log CA 125 levels pre and post surgery was significantly different between patients who were optimal and non optimal ($p = 0.035$), this indicated that the age factor (≥ 40 years) in patients with suboptimal surgery inhibited decreased log CA125 levels.

Likewise in the age group, patients with optimal surgery both nulliparous parity (Δ = 1.18 U/ml) and multiparas (Δ = 0.68 U/ml) experienced a significant log change in pre and post- surgery CA 125 levels ($p <0.05$) whereas in non-optimal patients there was no significant change between nulliparous patients (Δ = 0.18 U/ml) and multiparas (Δ = 0.33 U/ml). In patients with suboptimal surgery, nulliparas experienced a log decrease in CA 125 levels less than multiparas. Based on histopathology, patients with surgery were non optimal with type 1 histopathology (Δ = 0.07 U/ml) experienced a log decrease in pre and post-surgery CA 125 levels less than that of type 2 histopathology (Δ = 0.61 U/ml). Subjects with advanced stages with non-optimal surgery experienced a log decrease in CA 125 levels less (Δ = 0.22 U/ml) than those with early stages (Δ = 0.69 U/ml).

DISCUSSION

The risk of developing ovarian cancer increases with age. Ovarian cancer is rare in women under 40 years of age. Most ovarian cancers develop after menopause. This is consistent with the data obtained in this study, namely that there were 11 subjects aged less than 40 years and 19 subjects more than 40 years of age. 22 patients had experienced menopause and 8 patients had not yet experienced menopause. Nulliparas with no risk factors for family disease with cancer have a lower risk of developing ovarian cancer.[5] This was found in the results of studies with a greater number of multiparous patients than nulliparas. The use of oral contraceptives also has reduced the risk of developing ovarian cancer.[6] While in the data presented, 6 subjects used hormonal contraception, 2 subjects used non hormonal contraception and 7 subjects did not use contraception.

Type I histopathology is the most common group found in Ovarian cancer with the highest proportion in the Asian continent. Ovarian cancer is often asymptomatic in its early stages and therefore most patients present at an advanced stage.[7] In accordance with the data that most ovarian cancer patients are found to have type 1 histopathology compared to type 2 histopathology. And there are a large proportion of ovarian cancer patients at an advanced stage.

In research conducted by Zwakman et al (2017) with ovarian cancer patients undergoing optimal surgery, CA 125 levels decreased by ⍰ 80%. In the statistical test, it was found that the CA level was 125 pre surgery (mean = 6.41) and post surgery (mean = 5.14) whereas in this study there was a significant change in pre surgery CA 125 levels (mean = 2.53 or 902.03U/ml) and post surgery CA 125 levels (mean = 1.92 or 406.23 U/ml). With a mean difference or delta of 0.61 or 495.80 U/ml and a p value = 0.001. In patients with optimal surgery, there was a significant change in log CA 125 levels pre and post surgeries compared to patients with suboptimal surgery.

Based on the stratification results, there was a significant change/decrease in log CA 125 levels pre and post optimal surgery in all risk factors studied. While in non-optimal surgery there was no significant change in log CA 125 levels. And there was a significant difference in log CA 125 levels pre and post optimal or non-optimal surgery in several groups with a p value <0.05.

A significant decrease in CA 125 in the first postoperative week was seen in the majority of

ovarian cancers that underwent optimal surgery, which was attributed to the maximum amount of tumor volume removed compared to non-optimal surgery. It is considered optimal surgery if the residual tumor is <1 cm in size, while it is not optimal if the residual tumor is >1cm.

CONCLUSION

The conclusion from the results of this study are:

1. There was a significant reduction in log CA 125 levels pre and post surgery in ovarian cancer patients who underwent surgery.
2. Changes/ decreases in log levels of CA

125 post surgeryly in patients who underwent optimal surgery were more numerous than those with non-optimal surgeries.

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