

Research Article

## Mesothelin versus Ca-125 in Screening the Ovarian Malignancy

### *Mesothelin dan Ca-125 dalam Memprediksi Keganasan Ovarium*

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#### Abstract

**Objective:** To determine the sensitivity and specificity of mesothelin compared with Ca-125 as a tumor marker in predicting ovarian malignancy.

**Method:** The cross sectional study design with diagnostic tests was conducted in 30 samples of patients undergoing elective laparotomy due to ovarian tumor. We compared the sensitivity and specificity between mesothelin and Ca-125, then the data were analyzed using SPSS software version 22.0.

**Result:** According to the ROC curve analysis, optimal sensitivity and specificity value of mesothelin was 63.2% and 54.5% at a cut-off point of 0.45 pg/ml; or 42.1% and 72.7% at a cut-off point of 0.55 pg/ml. While the value of both optimal sensitivity and specificity of Ca-125 was 73.7% and 63.6% at a cut-off point of 46.63 U/ml.

**Conclusion:** Mesothelin and Ca-125 are not different significantly for the AUC value of 50%. Due to higher sensitivity and specificity of Ca-125 than mesothelin, Ca-125 is still used as tumor marker for screening the ovarian malignancy.

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**Keywords:** Ca-125, mesothelin, ovarian malignancy

#### Abstrak

**Tujuan:** Untuk menentukan sensitivitas dan spesifisitas mesothelin dibandingkan dengan antigen Ca-125 sebagai penanda tumor dalam memprediksi keganasan ovarium.

**Metode:** Studi potong lintang dengan uji diagnostic dilakukan pada 30 pasien yang akan menjalankan laparotomy elektif karena tumor ovarium. Kami akan membandingkan sensitivitas dan spesifisitas antara mesotelin dan Ca-125. Data yang diperoleh kemudian dianalisis dengan menggunakan SPSS versi 22.0 dan dilakukan pembahasan sesuai literatur yang ada.

**Hasil:** Berdasarkan analisis kurva ROC, sensitivitas dan spesifisitas yang optimal pada mesothelin adalah 63,2% dan 54,5% dengan nilai cut-off 0,45 pg/ml dan 42,1% dan 72,7% dengan nilai cut off 0,55 pg/ml. Sedangkan, nilai sensitivitas optimal dan spesifisitas Ca-125 adalah 73,7% dan 63,3% dengan nilai cut-off 46,6 U/ml.

**Kesimpulan:** Mesotelin dan Ca-125 tidak berbeda bermakna pada nilai kurva AUC 50%. Ca-125 memberikan nilai sensitivitas dan spesifisitas lebih tinggi dari mesotelin sehingga Ca-125 masih digunakan sebagai alat skrining keganasan ovarium.

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**Kata kunci:** Ca-125, keganasan ovarium, mesotelin

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## INTRODUCTION

Ovarian carcinoma as a malignant tumor in women after cervical and endometrial carcinoma has the prevalence rate of 2.4-5.6%. This carcinoma causes mortality higher than other malignant tumors. It is because 70% of the cases is diagnosed in advanced stage (between stage III and IV) so that it has spread far beyond the ovary. Therefore, there is a need to find a highly effective screening tools in ovarian malignant tumor to reduce the morbidity and mortality of this disease.<sup>1,2</sup> Excellent screening tools has high both sensitivity and specificity.<sup>1</sup> One of the antigens released from the malignancy of the epithelial ovarian cells is Ca-125.<sup>1</sup>

Approximately, 83% of patients with ovarian malignant tumor had a high level of Ca-125, which

showing the value more than 35 U/ml.<sup>1,3</sup> A study conducted in Sweden stated that the specificity of Ca-125 in ovarian malignant tumor was 97% and the positive predictive value (PPV) was 4.6%. The low level of PPV was caused by the elevation of Ca-125 happened in several condition such as other malignant tumors like breast, pancreas, bladder, lung and liver cancer; as well as in other benign abnormalities including endometriosis, myoma uteri, tuba-ovarian abscess, benign ovarian cyst, ectopic pregnancy, diverticulitis; even in physiological conditions for example pregnancy and menstruation. Meanwhile, other tumor markers that could be detected in ovarian malignancies including Ca-19-9, Ca 15-3, Ca 72-4, LSA (lipid-associated sialic acid), LPA (lysophosphatide acid), osteopontin, and mesothelin.<sup>2,3</sup>

Mesothelin as a 40-kDa glycoprotein is bound to glucosylphosphatidylinositol. In normal tissues, the expression of mesothelin can be found on the mesothelial cells (cells that border the pleura, peritoneum and pericardium) and also epithelial cells of the trachea, tonsils, fallopian tubes, and kidneys.<sup>4</sup> According to study by Hough, et al. in 2000, mesothelin was also expressed in ovarian carcinoma. Thus, it usually used as a screening tool in ovarian carcinoma.<sup>5</sup> Lowe, et al. in their study stated that increased levels of mesothelin were higher in patients who had undergone optimal debulking compared with those with advanced ovarian cancer.<sup>6,7</sup> In addition, 42% of patients who were at an early-stage of ovarian cancer also had elevated levels of mesothelin in the urine compared with only 12% of patients who had elevated in mesothelin serum. This proved that mesothelin had the potency as a screening tool to detect the ovarian carcinoma.<sup>8</sup>

Based on recent literatures, we would like to determine the relationship between mesothelin and Ca-125 as screening tools for ovarian malignant tumor.

## METHODS

This cross sectional study to determine the diagnostic test was carried out in ovarian carcinoma patients who were registered at the gynecology out patient polyclinic in Prof. Dr. R. D. Kandou hospital. The inclusion criterias were the patients diagnosed as ovarian tumor, they would undergo the elective laparotomy, also they did not suffer from other malignancies. If they would like to participate, they had to sign the informed consent form. We excluded the patients who could not do the laparotomy. Besides, the result of biopsy showed the tumor not original from the ovary was excluded. The patients were checked the blood samples to show the level of mesothelin. This examination was sent to Prodia laboratory, Manado. This study was conducted from June to August 2015.

By calculating using the formula, we had to full-fill minimally 30 samples of ovarian carcinoma. Data were analyzed by the ROC to calculate sensitivity and specificity levels of mesothelin to the histopathology samples of ovarian carcinoma. The data were processed using the software program of Statistical Product and Service Solutions (SPSS) for Windows version 22.0.

## RESULTS

Of 30 patients included in this study, most of them (18/50) were 40-59 years old and more than half of patients (18/30) were multi parity (Table 1). The histopathology characteristic of ovarian tumors showed that 2 samples were serous cystadenoma and 10 samples were mucinous cystadenoma as the benign ovary tumors. Meanwhile, ovarian serous cystadenocarcinoma was on 3 patients and the remaining was mucinous cystadenocarcinoma (15 samples) as malignant ovary tumors. This examination was done at the Laboratory of Pathology Anatomy Faculty of Medicine Universitas Sam Ratulangi, Manado.

**Table 1.** Characteristics of Respondents

Characteristics	N (30)	
Age	<20	1
	20-39	5
	40-59	18
	≥60	6
Parity	0	3
	1-2	9
	3-5	16
	>5	2
BMI	≤18	3
	18-24	14
	≥25	13

Based on the statistical group, Ca-125 levels had an average value of 412.0 U/dl with a standard deviation of 963.9. On the other hand, mesothelin levels showed an average value of 1.5 pg/ml with a standard deviation of 3.7 (figure 1). There was not correlation between mesothelin and ovarian malignant tumor ( $p=0.15$ ;  $r=0.15$ ).

From the ROC method above, we obtained 59.8% (95% CI 39.3-80.3%) for AUC values of mesothelin. It meant that mesothelin levels were not significantly different to the 50% value of AUC. While, the AUC values of Ca-125 was 60.5% (95% CI 38.3-80.3%) which meant that Ca-125 levels were not significantly different from AUC value of 50%.

From the table of coordinates, sensitivity and specificity for mesothelin levels with a "cut off point" of 0.45 pg/ml were 63.2% and 54.5%;

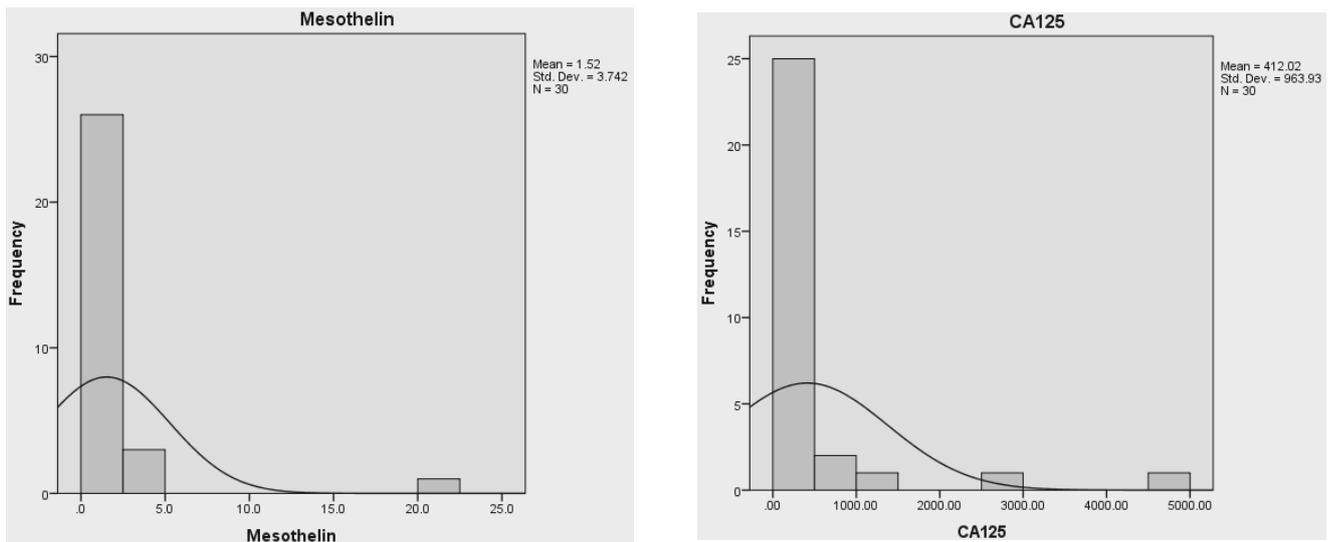


Figure 1. The Graphs of Mesothelin and Ca-125 Level.

meanwhile, if we set up the "cut off point" of mesothelin levels at 0.55 pg/ml, the sensitivity and specificity would be 42.1% and 72.7%. The interpretation was that 63.2% sensitivity values obtained from this study was valid if mesothelin levels of 0.45 pg/ml were used in 100 patients and 63 patients had mesothelin levels greater than or equal to 0.45 pg/ml, they had epithelial ovarian malignant tumor which confirmed through histopathology examination as a gold standard. This was implied vice versa for the specificity.

## DISCUSSION

Until 2010, ovarian cancer was still the third malignant diseases in women. According to study conducted by Jemal, et al. in the United States, there were an estimated of 21,880 new cases, whereas 13,850 patients passed away due to this disease. In Indonesia itself, the ovarian cancer was ranked the second after cervical cancer as the cause of gynecological cancer death. Nearly 70% of women with ovarian cancer were diagnosed in advanced stage so that the five-year survival rate was only 30%.<sup>2</sup>

In this study, the majority of patients were 40-59 years old and most of them had three to five children. According to another study, it was found that the population of patients with ovarian tumors were between 20 and 65 years old. This statement

was supported through study by Boy B et al and Diana HF et al where they said that the ovarian malignant tumor was rare under 40 years old.<sup>9,10</sup> A little bit different result by Martin Siregar, et al, they found that the distribution of patients with ovarian malignant tumor were mostly in the age group of 41 to 50 years old.<sup>11</sup>

Hala Abdel-Azeez, et al in their study reported that the cut-off value for mesothelin was 1.4nM, which meant that it had a lower sensitivity when compared with Ca-125 in detecting ovarian malignancies. Increased mesothelin levels in serum was ranged from 60% to 77% in women with ovarian cancer.<sup>12</sup> Several studies investigated the use of Ca-125 and mesothelin as single also combined markers in patients with ovarian malignancy. As a single marker, Ca-125 had higher sensitivity than mesothelin itself.<sup>14</sup> Although mesothelin could not be used as a single marker to detect ovarian cancer, when combined with Ca-125, it resulted high sensitivity. Serum mesothelin increased at a fraction of patients with normal Ca-125 serum. The combination of Ca-125 and mesothelin would rise the sensitivity compared with a single use of Ca-125 in detecting the ovarian malignancy. According to study by Badgwell, et al. in 2007, mesothelin in the urine acted more sensitive marker than mesothelin serum in the blood to differentiate patients with early-stage of ovarian malignancy.<sup>7</sup>

## CONCLUSION

We conclude that mesothelin and Ca-125 are not significantly different to the AUC value of 50%. The optimal sensitivity and specificity for mesothelin was lower than the results shown by Ca-125. Therefore, Ca-125 is still used as a tumor marker for screening the ovarian malignancy.

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