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CONTENTS

RESEARCH

Differences of Plasma Interleukin-6 and Tumor Necrosis Factor-A Levels in Healthy People, Rifampicin Resistant and Sensitive Pulmonary Tuberculosis Patients
Wahyu Setiani Wibowo, Jusak Nugraha, Soedarsono ..... 129 - 134

Association between Specific Enolase Serum Levels and Outcome Acute Ischemic Stroke One Month After Onset
Yuri Haiga, Darwin Amir, Yuliarni Syafrita ..... 135 - 139

Analysis of Hemoglobin Levels And Leukocyte Count in Neonates with Hyperbilirubinemia
Dewi Suharti, Sulina Yanti Wibawa, Muthmainnah ..... 140 - 144

Diagnostic Value of Ca-125 in Patients with Epithelial Ovarian Cancer at the Dr. Soetomo General Hospital Surabaya in 2016
Kintan P. R. Kania, Betty A. Tambunan, Willy Sandhika ..... 145 - 149

Analysis of Vitamin D in Patients with Type 2 Diabetes Mellitus
Arfandhy Sanda, Uleng Bahrun, Ruland DN. Pakasi, Andi Makbul Aman ..... 150 - 154

Proportion of Rhesus Blood Phenotypes at the Blood Donor Unit in Bandung City
Ivana Dewi, Nadjwa Zamalek Dalimoenthe, Anna Tjandrawati, Nida Suraya ..... 155 - 160

Correlation of Total Lymphocyte Count with CD4 Count in HIV/TB Coinfected Patients
Herniaty Rampo, Uleng Bahrun, Mansyur Arif ..... 161 - 164

Using Six Sigma to Evaluate Analytical Performance of Hematology Analyzer
Robiul Fuadi ..... 165 - 169

Correlation of AA Index with Degree of Liver Fibrosis in Chronic Hepatitis B Patients
Rika Andriany, Ibrahim Abdul Samad, Mansyur Arif ..... 170 - 173

Difference in HbA1c Level between Boronate Affinity and Ion Exchange-High Performance Liquid Chromatography Method in Diabetic Patient
Tuti Asryani, Ellyza Nasrul, Rikarni, Tutty Prihandani ..... 174 - 179

Diagnostic Value of Neutrophil Lymphocyte Ratio to Differentiate Ischemic and Hemorrhagic Stroke
Martina Rentauli Sihombing, Liong Boy Kurniawan, Darwati Muhadi ..... 180 - 183

D-Dimer and Fibrinogen in Patients Underwent Surgery in Malignant and Benign Ovarian Tumor
Ismail Aswin, Herman Hariman, Fauzie Sahil ..... 184 - 190

Relationship between Specific Gravity of Cupric Sulfate and Saturation of Blood Droplets During Donor's Hemoglobin Screening
Resna Hermawati, Solichul Hadi ..... 191 - 193

Vancomycin-Resistant *Staphylococcus aureus* at the Dr. Wahidin Sudirohusodo Hospital Makassar
Fatmawaty Ahmad, Nurhayana Sennang, Benny Rusli ..... 194 - 198

The Levels of Interleucin-6 (Il-6) and Tumor Necrosis Factor Alpha (TNF-ALFA) in Preeclampsia Patient and Normal Pregnancy
Mawardi, Ratna Akbari Ganie, Sarma N. Lumbanraja ..... 199 - 201

Analysis of Platelet Volume Mean, Platelet Distribution Width, and Platelet Count in Hemorrhagic and Non-Hemorrhagic Stroke
Gita Medita Sunusi, Darwati Muhadi, Mansyur Arif ..... 202 - 206

High Fluorescent Lymphocyte Count Examination in Dengue Hemorrhagic Patients with Sysmex Xn-1000 Hematology Analyzer
Budiono Raharjo, Solichul Hadi ..... 207 -210

Prevalence and Characteristics of Multidrug-Resistant *Acinetobacter baumannii* Cases at the Dr. Wahidin Sudirohusodo General Hospital in Makassar
Dewi Kartika Tungadi, Nurhayana Sennang, Benny Rusli ..... 211 - 217

The Correlation of Anemia and Hepcidin Serum Levels in Regular Hemodialysis Patients with Chronic Hepatitis C
Wingsar Indrawanto, Adi Koesoema Aman, Alwi Thamrin ..... 218 - 223

The Comparison between HbA1c and Glycated Albumin Level Patient with Type II Diabetes Mellitus with or without CKD
M. Rusli, Zulfikar, Santi Syafril ..... 224 - 227

Differentiation of Tγδ Lymphocyte Cells Expressing Interleukin-17 on Healthy Persons and Adult Acute Myeloid Leukemia Patients
Elvan Dwi Widyadi, Yetti Hernaningsih, Endang Retnowati, Ugroseno, Ryzky Widi Atmaja ..... 228 - 232

LITERATURE REVIEW

Hormone Examination in Menopause
Ferdy Royland Marpaung, Trieva Verawaty Butarbutar, Sidarti Soehita ..... 233 - 239

CASE REPORT

Chronic Myelogeneous Leukemia Transformation into Acute Lymphoblastic Leukemia
Endah Indriastuti, Arifoel Hajat ..... 240 - 245

Rapid Progression of Clavicular Solitary Plasmacytoma to Multiple Myeloma
Hantoro Gunawan, **Paulus Budiono Notopuro** ..... 246 - 249

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DIAGNOSTIC VALUE OF CA-125 IN PATIENTS WITH EPITHELIAL OVARIAN CANCER AT THE DR. SOETOMO GENERAL HOSPITAL SURABAYA IN 2016

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ABSTRACT

Ovarian cancer is fourth leading cancer. The incidence in Indonesian females was 10,238 cases in 2014. Tumor marker CA-125 is associated with ovarian cancer, especially epithelial ovarian cancer. This study aimed to find out diagnostic value (sensitivity, specificity, positive predictive value, negative predictive value) of CA-125 among patients with epithelial ovarian cancer in the Dr. Soetomo Hospital Surabaya in 2016. This study used a cross-sectional analytic method and was performed by evaluating medical records of patients suspected of ovarian malignancy in the Dr. Soetomo Hospital Surabaya in 2016. Total of 97 patients were had met the criteria of inclusion in this study. Tissue histopathological examination confirmed that 66 patients had ovarian epithelial malignancy and 31 patients did not. Samples distributed showed CA-125 upper limit of 35 U/mL, TP: 54.64%, FP: 19.59%, FN: 13.40%, and TN: 12.37%. The diagnostic values obtained as follows: sensitivity 80.30%, specificity 38.71%, positive predictive value 73.61%, negative predictive value 48%, and accuracy 67.01%. Tumor marker associated with ovarian cancer CA-125 was found high in sensitivity but low in specificity among patients with ovarian epithelial cancer in the Dr. Soetomo Hospital Surabaya in 2016.

Key words: Tumor marker CA-125, diagnostic value of CA-125, ovarian epithelial cancer

INTRODUCTION

Ovarian cancer is cancer with the highest prevalence in the females. National The Institutes of Health (NIH) National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) in 2016 found that 22,280 new cases of ovarian cancer happened in the USA.[1,2] Cancer Country Profiles found that ovarian cancer was fourth cancer with the most incidence in Indonesian females with 10,238 cases in 2014. Epithelial ovarian cancer takes up to 65-70% of all ovarian cancer incidence and 90% of all ovarian cancer malignancy.[3]

Ovary epithelial cells take part in ovulation, causing injury followed by inflammation and resolution.[4] Repeated ovulation and ovary injury will cause surface epithelial cells entrapped in the ovary cortex and form small epithelial cysts. This process could change into ovarian epithelial malignancy.[3] It means that the more ovulation happens, the higher risk for ovarian epithelial malignancy. Risk factors include early menarche, late menopause, nulliparity, obese, estrogen hormone therapy, and family history of an ovary or breast cancer involving the BRCA gene. Protective factors include oral contraception, breast feeding, tubal ligation, and hysterectomy.[5] Screening for ovarian cancer is done using ultrasound or by determining tumor marker CA-125.[6] It is not recommended for a population with no symptoms but strongly recommended for post-menopausal and older females, as more than 80% of ovarian cancer is found in females aged more than 50.[7]

CA-125 is used as a tumor marker for ovarian cancer. Use for tumor markers includes early detection and screening, diagnostic confirmation, prognosis, a prediction for therapy and disease monitoring and recurrence.[8] The rise in CA-125 level is related to malignancy such as in epithelial ovarian cancer in which 80%-85% of all cases are found with an increase of CA-125 level.[9] A physiological condition such as menstruation and pregnancy or non malignancy condition such as endometriosis, acute pancreatitis, cirrhosis, peritonitis, and pelvic inflammatory disease could also cause arise in CA-125 level.[10] Reference values mostly used for CA-125, in general, is below 35 U/mL. It is important to note that in healthy conditions, the level of CA-125 in post-menopausal females is significantly lower than those in pre-menopausal females.[11]

The use of diagnostic test is the ability to detect

someone with a specific disease or to exclude someone without the disease, usually described by sensitivity, specificity, positive predictive value, and negative predictive value. Sensitivity and specificity are essential in measuring diagnostic test accuracy but cannot determine the probability of disease in an individual. Predictive values, on the other hand, can be used to determine the likelihood of disease in an individual, but it may vary according to disease prevalence in the population, so it is population specific.[12] This study aimed to find out the diagnostic value (sensitivity, specificity, positive predictive value, negative predictive value) of CA-125 among patients with epithelial ovarian cancer in Indonesia specifically in the Dr. Soetomo Hospital Surabaya in 2016.

METHODS

This study was conducted in the Installation of Communication and Information Technology Dr. Soetomo Hospital Surabaya from April 2017 to November 2017. This study used a cross-sectional analytic method and was performed by evaluating medical records of patients suspected of ovarian malignancy in the Dr. Soetomo Hospital Surabaya in 2016. Inclusion criteria for the sample are females, who had ovary tissue histopathological examination done with an ovarian epithelial cancer diagnosis and had CA-125 examination before surgery. Patients who performed ovary tissue histopathological examination outside the Dr. Soetomo Hospital, diagnosed with ovarian cancer other than epithelial type and had CA-125 examination with a value that is not round numbers (example >600) are excluded.

Tissue histopathological examination was performed by the Anatomical Pathology Department, Dr. Soetomo Hospital Surabaya. Examination of CA-125 in the Dr. Soetomo Hospital Surabaya was performed by the Immunology Division of Clinical Pathology Department using a quantitative method and chemiluminescence technique. The reference value for serum CA-125 level was 35 U/mL. Diagnostic value included sensitivity, specificity, positive predictive values, negative predictive values, and accuracy.

RESULTS AND DISCUSSION

As seen in Table 1, the age group of 20-54 years consisted of the most patients in this study 67.01% (65/97). Sattar, said that most serious or mucinous benign ovarian tumor was found in patients age 30-40 years old, meanwhile malignant ovarian tumor

Table 1. Patients distribution according to age group

Age group	Patient(s)	Percentage (%)
<20	1	1.03%
20-54	65	67.01%
55-84	31	31.96%
>84	0	0.00%
Total	97	100.00%
Median	50	

was found in patients aged 45-65 years old.[3] SEER 18 2009-2013 found that the most distribution of age group was 55-64 years old (24.3%) in first place, followed by 65-74 years old (21.7%) in second place and 45-54 years old (18.5%) in the third group with a median of age 63 when diagnosed.[2] The median of age between patients in this study was 50 meaning that half of the population was diagnosed before reaching 50 years of age and the other half was diagnosed after reaching 50 years of age.

Table 2. Histopathological findings of epithelial ovarian cancer according to malignancy attribute

	Patient(s)	Percentage (%)
Benign	31	31.96%
Borderline	6	6.19%
Malignant	60	61.86%
Total	97	100.00%

Majority of patients in this study had a malignant ovarian tumor with 61.86% (60/97), as shown in Table 2. Only 31.96% (31/97) had a benign ovarian tumor and 6.19% (6/97) with a borderline tumor. Lack of numbers of patients with a benign tumor to those with malignant tumor could be related to unspecific symptoms of ovary tumor, especially in the early stage, so it was hard for patients to notice.[13]

This condition could result in a patient delay to see a doctor. Symptoms will be noticeable in a more advanced grade such as urinary or bowel problems, pain during intercourse (dyspareunia), bleeding, and if it has spread to other organs the patient may feel shortness of breath and weakness.[13] Goff, Mandel, and Melancon found in their study that almost half of ovarian cancer patients waited three months to obtain the right diagnosis even 95% of them had felt symptoms before.[14] Benign and borderline ovary tumors can develop slowly and gradually into invasive malignancies.[3] Delays in patients to see a doctor or delays in making the right diagnosis could explain why the numbers of benign histopathological findings were less than malignant ones.

Table 3, 4, and 5 shows that the most histopathological types were endometriosis ovarii in

Table 3. Distribution of epithelial ovarian cancer histological types in benign findings

Histological type	Patient(s)	Percentage (%)
Fibroma ovarii	2	6.45%
Benign Brenner tumor	2	6.45%
Endometriosis ovarii	10	32.26%
Mucinous cystadenoma	6	19.35%
Serous cystadenoma	2	6.45%
Seromucinouscystadenoma	2	6.45%
Abcess	1	3.23%
Bleeding	1	3.23%
Inflammation	2	6.45%
No tumor cells were found	3	9.68%
Total	31	100.00%

Table 4. Distribution of epithelial ovarian cancer histological types of borderline types findings

Histological type	Patient(s)	Percentage (%)
Mucinous cystadenoma	4	66.67%
Seromucinouscystadenoma	1	16.67%
Endometrioid	1	16.67%
Total	6	100.00%

Table 5. Distribution of epithelial ovarian cancer histological types of malignant types

Histological type	Patient(s)	Percentage (%)
Mucinous adenocarcinoma	16	26.67%
Serous adenocarcinoma	14	23.33%
Seromucinous adenocarcinoma	1	1.67%
Endometrioid carcinoma	12	20.00%
Clear cell carcinoma	10	16.67%
Squamous cell carcinoma	1	1.67%
Adenocarcinoma	5	8.33%
Signet ring cell carcinoma	1	1.67%
Total	60	100.00%

benign findings (32.26%, 10/31), mucinous cystadenoma in borderline findings (66.67%, 4/6), and mucinous adenocarcinoma in malignant findings (26.67%, 16/60). These were different than Sattar who said that serious type was the most common type in ovarian tumor cases.[3] Distribution of histological types in benign findings showed that more endometriosis patients came to see a doctor than other types of benign tumors. Endometriosis symptoms include chronic pelvic pain, menstruation pain, pain during intercourse, and infertility.[14] Patients with chronic pelvic pain experience decreased in productivity leading to a material loss.[15] Endometriosis may also be a contributor in marital distress due to infertility problem. Main problems of endometriosis such as pain and infertility may cause more patients to see a doctor. Sattar stated that borderline and malignant serous types were the most common type of ovarian malignancy with 60% of all ovarian malignancy.[3] This study showed more patients with mucinous type than serous type. Mucinous tumors tend to be larger and multicystic than serous types.[3] The recorded average size of mucinous tumors is 16-20 cm and can be very large causing urinary tract obstruction to abdominal compartment syndrome.[16] This condition may cause more severe symptoms in mucinous type than serious type resulting in patients seeing a doctor.

Table 6 showed that 74.23% (72/97) patients in this study presented with CA-125 serum level above 35 U/mL, amongst them 54.64% (53/97) had malignant histopathological findings while 19.59% (19/97) had benign histopathological findings. About 25.77% (25/97) patients in this study presented with CA-125 serum level equal to or below 35 U/mL, amongst them 13.40% (13/97) had malignant histopathological findings while 12.37% (12/97) patients had benign histopathological findings. Patients with malignant histopathological findings in this study were 68.04% (66/97) while 31.96% (31/97) patients had benign histopathological findings.

Table 6. Distribution of epithelial ovarian cancer histopathological findings according to CA-125 serum level

CA-125 serum level (U/mL)	Histopathological findings		Total
	Malignant	Benign	
>35	53 (54.64%)	19 (19.59%)	72 (74.23%)
≤35	13 (13.40%)	12 (12.37%)	25 (25.77%)
Total	66 (68.04%)	31 (31.96%)	97 (100%)

Table 7. Diagnostic value of CA-125

Sensitivity	Specificity	Diagnostic value of CA -125		Accuracy
		Positive predictive value	Negative predictive value	
53/(53+13) (80.30%)	12/(12+19) (38.71%)	53/(53+19) (73.61%)	12/(12+13) (48.00%)	53+12/(53+19+13+12) (67.01%)

Sensitivity in diagnostic test measures the ability to identify subjects correctly with a specific condition.[17] As seen in Table 7, the sensitivity of CA-125 in this study was 80.30% meaning that of ovarian malignancy cases in this study, 80.30% of were found with arise in CA-125 level above 35 U/mL. Sensitivity 80.30% was between sensitivity in studies conducted by Meier *et al.* (75%) and Zanaboni *et al*. (85%), both using second look laparotomy as the gold standard and taken from a literature review by Jacobs and Bast.[18] Specificity showed a normal level of CA-125 in those without ovarian malignancy. It measured the test ability to identify subjects correctly without certain conditions.[17] Specificity of 38.71% meant that in those without malignancy, only 38.71% had a CA-125 level below or equal to 35 U/mL, while more than 60% of them had a CA-125 level above 35 U/mL. This finding might be connected with the majority of endometriosis in benign findings with 32.26%. Several studies found that some patients with endometriosis had elevated levels of CA-125 which also correlated to the severity of the disease.[18] Menstruation and pregnancy also could cause CA-125 elevation. Haga, Sakamoto, Egami, Yoshimura, and Akagi found that CA-125 was elevated significantly in healthy females under 49 years old than in healthy females older than 49 years.[18]

Positive predictive value and negative predictive value are two primary measures to determine diagnostic accuracy. Positive predictive value is the probability that there is a disease condition in a positive result.[17] Positive predictive value of 73.61% showed that of all patients in this study with CA-125 level above 35 U/mL, 73.61% of them had ovarian epithelial malignancy. Research conducted by Einhorn *et al*. found a positive predictive value of 82%.[18] The low positive predictive value in this study correlated to high false positive in this study (19.59%) due to patients without malignancy but had CA-125 levels above 35 U/mL. Negative predictive value was the probability that there was not a disease in a negative result.[17] Negative predictive value of 48% showed that in patients with CA-125 level under or equal to 35 U/mL, only 48% of them did not have ovarian malignancy. High false negative and low true negative in this study could cause low negative predictive level. False negative in CA-125 in most cases attributed to the small volume of tumors, therefore minimal tumor volume is needed to obtain CA-125 level elevation.[18] Diagnostic method centers in concepts that the tumor will release a certain specific cell surface antigen determinant.[4] Small volume tumors with fewer cells will express less CA-125 than tumors with larger volume. Criteria of samples in this study were not explicit in stage, grade, or size of the tumor so findings may vary in patients in this study. Diagnostic accuracy correlated with test ability to distinguish between target conditions, in this study, it was between ovarian epithelial malignancy and without one. The discriminatory potential of accuracy can be measured by sensitivity, specificity, predictive value, and area under the ROC curve.[19] The accuracy of CA-125 in this study is 67.01%, almost equal to the overall accuracy of 67% in al iterature review by Jacobs and Bast.[18]

CONCLUSION AND SUGGESTION

This study found CA-125 diagnostic value as follows: sensitivity of 80.30%, specificity of 38.71%, the positive predictive value of 73.61%, the negative predictive value of 48%, and accuracy of 67.01%. CA-125 is high in sensitivity but low in specificity among epithelial ovarian cancer patients in the Dr. Soetomo Hospital Surabaya in 2016. A similar study in the future is suggested to use cohort design with the primary data source.

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