RESEARCH ARTICLE

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Ovarian Cancer-Self Assessment: An Innovation for Early Detection and Risk Assessment of Ovarian Cancer

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Abstract

Objective: The modality to detect ovarian cancer at an early stage is very limited. Early diagnosis determines the prognosis. This study aimed to develop a risk assessment tool for early detection of ovarian cancer using artificial intelligence. To accomplish this, the presence of ten signs and symptoms reported by patients with ovarian cancer was assessed. **Methods:** This study was carried out as a cohort study of patients diagnosed with suspected ovarian tumors undergoing cytoreduction operation at Hasan Sadikin Hospital, Bandung, from December 2019 to September 2020. Compared to ovarian cancer self-assessment through questionnaire, postoperative histopathology in patients with suspected ovarian tumors. The questionnaire proceeded by artificial intelligence is grouped into risk and no risk. Statistical analyses were done using Chi-Square and Exact Fisher Test. **Result:** In total, 115 patients included in this study. The differences were statistically significant in terms of the six variables (abdominal bloating, nausea/vomiting, decreased of appetite, fullness, menstrual disturbance, and weight loss) ovarian cancer self-assessment compared to postoperative histopathology with a tendency towards benign ovarian tumors ($p<0.05$), while there was no statistically significant difference in the four variables (abdominal enlargement, abdominal pain, urinating disturbance, and defecation disturbance) ($p>0.05$). According to the artificial intelligence grouping, fifty-five patients were at risk, and sixty patients were not at risk. The Fifty-five risk patients were related with postoperative histopathology diagnosis (with RR 0.682 and CI 95% 0.519-0.895). **Conclusion:** Risk assessments based on ovarian cancer self-assessment unfortunately were not comparable to postoperative histopathology as a single predictor. Ten variables in ovarian cancer artificial intelligence self-assessment for early detection needs improvement in adding another variable like tumor marker and ultrasonography assessment.

Keywords: Artificial intelligence- malignancy- ovarian cancer- screening- self-assessment

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Introduction

Ovarian cancer is the third most common gynecological cancer globally after cervical cancer and endometrial cancer. The prevalence of five years of ovarian cancer globally is 823,315 cases, with an incidence of 313,959 cases and 207,252 deaths. In Indonesia 13,310 of new cases ovarian cancer with total death of 7,842 occurred in year 2018 (Jasen, 2009; Doubeni et al., 2016). Ovarian cancer is one of the deadliest cancers. Only 45% of sufferers survive after five years. Diagnosis at an early stage determines the prognosis of this disease (Doubeni, 2016).

There are many blood markers examination modalities for early diagnosis of ovarian cancer, for example, tumor markers (HE4, CA-125) or an algorithm of RMI (Risk of Malignancy Index) and ROMA (Risk of Ovarian Malignancy Algorithm). The CA-125 is a frequently assessed tumor marker for ovarian cancer; however, it has a low sensitivity in predicting malignancy at an early stage. The increased sensitivity and specificity of CA-125 in all epithelial ovarian cancers (EOC) is approximately 80%; however, only 50% are in stage I EOC. The CA-125 is rarely used to predict malignancy because this serum may increase in value in the setting of menstruation, fibroids, endometriosis, and pelvic infection (Zurawski, 1988; Zurawski, 1988). The HE4 levels are overexpressed in ovarian tumors, especially ovarian tumors that do not express CA-125 (Schummer, 1999; Moore et al., 2008). Moore et al., (2008) reported that HE4 had a high sensitivity of 72.9% (95% specificity) in detecting stage I ovarian cancer. The combination of HE4 and CA-125 may increase the sensitivity to 76.4% (and specificity to 95%). Though variations in HE4 may occur due to smoking or

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estrogen and progestin contraceptives (Moore et al., 2008).

The Royal College of Obstetricians and Gynecologists' guidelines recommend the use of an RMI algorithm that uses menopausal conditions, imaging, and tumor markers to predict suspected ovarian masses with a sensitivity of 78% and a specificity of 87% (Geomini, 2009).

On the other hand, the ROMA algorithm assessing the CA-125 and HE4 markers has an accuracy of up to 83% in pre-menopausal women in diagnosing malignancy at early stages (Momenimovahed, 2019). In addition, there is also an ultrasound examination modality based on the examiner's subjective impressions, namely, pattern recognition using the simple rules International Ovarian Tumor Analysis (SR-IOTA). Kaijser et al., (2013) performed a meta-analysis on 19 studies and showed the superiority of SR-IOTA with a sensitivity of 93% and a specificity of 81% (DiSaia, 2018). Many modalities do not have satisfactory results in predicting malignancy compared to post operative surgery and histopathological examination of the surgical removed tissue (Matulonis, 2016; Siegel, 2016). The symptoms of ovarian cancer at early stage can be difficult to detect because the symptoms are believed to be due to other causes. Thus, the early stage can be evaluated if the patient is aware of and understands the symptoms and signs of ovarian cancer and seeks medical attention to detect ovarian cancer at an early stage.

In recent years, the role of artificial intelligence in the health sector has grown widely, including for screening, diagnosing, therapeutics, and monitoring purposes. Artificial intelligence (AI) has the potential to store large amounts of data and exploit it with exponential learning capabilities and high computing power (big data analysis). In this study, AI was used to find patterns of ten answers to the questionnaire about the possible symptoms of ovarian cancer. Each combination of patient's answers was directed at two conclusions, namely at risk of cancer and not at risk. Artificial intelligence in this study used a machine learning platform based on the decision tree classification method to determine the rules for determining the label. The data processing with AI was aimed at processing a combination of ten patient answers, which were then calculated for entropy and information gain. The entropy and information gain values were then used as parameters to predict the results of the answers of patients with the possibility of being at risk or not at risk of ovarian cancer with the rule model system formed by the decision tree classification. Research on cancer prediction with AI using the decision tree method has widely been used for breast cancer prediction with data in the form of x-ray images (predicting the parameters that can affect the mortality rate) (Timmerman, 2000; Berek, 2012; Rossing, 2010). In gynecological oncology, AI is expected to play a bigger role in detecting signs and symptoms of ovarian cancer at an early stage, which can assist physicians in diagnosing and administering therapy as early as possible. This study aimed to develop early detection and risk assessment based on ovarian cancer self-assessment that compiles signs and symptoms of ovarian cancer.

Materials and Methods

Data collection

A cohort study was done on all women with suspected ovarian tumors undergoing cytoreduction operation at Hasan Sadikin Hospital, Bandung, from December 2019 to September 2020. Women with postoperative histopathology that could not be assessed were excluded from this study. The sampling was done using a consecutive sampling method, and all participants provided a written informed consent. The ten signs and symptoms of ovarian tumor-self assessment questionnaire consisted of abdominal enlargement, abdominal bloating, abdominal pain, nausea/vomiting, decreased of appetite, fullness, urinating disturbance, defecation disturbance, menstrual disturbance, and weight loss. All the question were examined in a pilot study on 30 respondents to assesed the validity and reliability.

Development of artificial intelligence

Ten validated and reliable questions were processed in the artificial intelligence procedure. Artificial intelligence was used to find the patterns of ten answers to the questionnaire about the possible symptoms of ovarian cancer. Each combination of patient answers is directed at two conclusions namely at risk of cancer and not at risk. Artificial intelligence in this study used a machine learning platform using the decision tree classification method to determine the rules for determining the label. The formation of the rules began with inputting the data from the questionnaire. All data were calculated for entropy and information gain. These calculations were carried out to reduce uncertainty while looking for data attributes as parameters for determining the root or node in the decision tree. The root of the decision tree was determined based on the largest gain value from the data attribute based on the calculation of entropy and information gain. Next, a tree was made as a system rule model with a decision tree to predict risk and no risk labels. The combination of ten patient answer was calculated for entropy and information gain. The entropy and information gain values were then used as parameters to predict the results of the answers by patients with the possibility of being at risk or not at risk of ovarian cancer with the rule model system formed by the decision tree classification.

Histopathological evaluation

Ovarian tumors removed from cytoreduction surgery were sent to be evaluated by Anatomical Pathology Hasan Sadikin Hospital, Bandung for histopathological examination. The histopathological results of the samples were collected and classified as malignant or benign tumors.

Statistical analysis

The collected data were analyzed using SPSS for Windows (v24.0). Characteristics of subjects and examination results were analyzed using descriptive tools. Statistical analysis was done using Chi-Square and using Kolmogorov Smirnov and Fisher's Exact if the requirements of the Chi-Square were not met. Analysis

of categorical data on abdominal bloating, abdominal pain, nausea/vomiting, decreased of appetite, fullness, menstrual disturbance, and weight loss were done using the Chi-Square test and in the case of abdominal enlargement, urinating disturbance, and defecation disturbance Fisher's Exact was used. The risk variables were tested using the Chi-Square test (p-value <0.05).

Ethical approval

This study was approved by Research Ethics Committee Hasan Sadikin Hospital, Bandung with approval number LB.02.01/X.6.5/148/2021.

Results

A total of 115 womens who met the inclusion criteria were included in this study. The following sysmptoms were assessd and analyzed including abdominal enlargement, abdominal bloating, abdominal pain, nausea/vomiting, decreased of appetite, fullness, urinating disturbance, defecation dirturbance, menstrual disturbance, and weight loss. Table 1 lists the frequency of the symptoms ovarian cancer subjects.

Table 1. The Frequency of the Symptom Ovarian Cancer Subjects at Hasan Sadikin Hospital

Variable	N=115
Abdominal enlargement	
Yes	102 (88.7%)
No	13 (11.3%)
Abdominal bloating	
Yes	60 (52.2%)
No	55 (47.8%)
Abdominal pain	
Yes	57 (49.6%)
No	58 (50.4%)
Nausea/vomiting	
Yes	52 (45.2%)
No	63 (54.8%)
Decreased of appetite	
Yes	67 (58.3%)
No	48 (41.7%)
Fullness	
Yes	63 (54.8%)
No	52 (45.2%)
Urinating disturbance	
Yes	7 (6.1%)
No	108 (93.9%)
Defecation disturbance	
Yes	15 (13.0%)
No	100 (87.0%)
Menstrual disturbance	
Yes	52 (45.2%)
No	64 (54.8%)
Weight loss	
Yes	68 (59.1%)
No	47 (40.9%)

The most common symptoms were abdominal enlargement (88.7%), weight loss (59.1%), and decreased of appetite (58.3%). On the other hand, the least common symptoms were defecation disturbance (13.0%) and the disturbance of urination (6.1%). Table 2 shows the comparison of ovarian cancer self-assessment with postoperative histopathology classified as malignant and benign.

According to the results in Table 2, the common symptoms in malignant group are abdominal enlargement (84.6%), abdominal bloating (44.9%), and weight loss (44.9%); in the case of benign group, these symptoms are abdominal enlargement (97.3%), decreased appetite (89.2%), and weight loss (89.2%). Several symptoms (abdominal enlargement, abdominal pain, urinating disturbance, and defecation disturbance) did not show

Table 2. Comparison of Sign and Symptoms with Malignant and Benign Groups at Hasan Sadikin Hospital

Variable	Group		P value
	Malignant	Benign	
	N=78	N=37	
Abdominal enlargement			0.058
Yes	66 (84.6%)	36 (97.3%)	
No	12 (15.4%)	1 (2.7%)	
Abdominal pain			0.063
Yes	34 (43.6%)	23 (62.2%)	
No	44 (56.4%)	14 (37.8%)	
Urinating disturbance			0.145
Yes	3 (3.8%)	4 (10.8%)	
No	75 (96.2%)	33 (89.2%)	
Defecation disturbance			0.077
Yes	7 (9.0%)	8 (21.6%)	
No	71 (91.0%)	29 (78.4%)	
Abdominal bloating			0.023*
Yes	35 (44.9%)	25 (67.6%)	
No	43 (55.1%)	12 (32.4%)	
Nausea/ vomiting			0.012*
Yes	29 (37.2%)	23 (62.2%)	
No	49 (62.8%)	14 (37.8%)	
Decreased of appetite			0.0001**
Yes	34 (43.6%)	33 (89.2%)	
No	44 (56.4%)	10.8%)	
Fullness			0.0001**
Yes	31 (39.7%)	32 (86.5%)	
No	47 (60.3%)	5 (13.5%)	
Menstrual disturbance			0.035*
Yes	30 (38.5%)	22 (59.5%)	
No	48 (61.5%)	15 (40.5%)	
Weight loss			0.0001**
Yes	35 (44.9%)	33 (89.2%)	
No	43 (55.1%)	4 (10.8%)	

Table 3. Relationship between Risk Variable and Tumor Histopathology Group at Hasan Sadikin Hospital

Variable	Group		RR Cl	P value
	Malignant (N=78)	Benign (N=37)	95%	
Risk				0.004*
Risk	30 (54.5%)	25 (45.5%)	0.682 (0.519-0.895)	
No-risk	48 (80.0%)	12 (20.0%)		

statistically ($p<0.05$) significant differences between the malignant and benign groups. There were significant differences in several symptoms between malignant and benign group including abdominal bloating, nausea/vomiting, decreased of appetite, fullness, menstrual disturbance, and weight loss ($p<0.05$) with a tendency towards benign ovarian tumors.

There were 55 samples in the risk group and 60 samples in the no-risk group based on the AI processes. All of the samples underwent surgery, and the specimen was examined histopathologically. The histopathology results indicated 78 samples malignant and 37 samples benign. The relationship between ovarian cancer self-assessment using AI processes and postoperative histopathology in malignant and benign groups is presented in Table 3.

Based on the statistical analysis, in malignant group, 30 patients (54.5%) were at risk and 48 (80.0%) were at no risk group. In addition, there were 25 patients at risk (45.5%) in benign group and 12 patients at no risk group (20.0%). The risk variables were compared to postoperative histopathology with RR ratio equal to 0.682 (95% CI; 0.519-0.895, $p<0.05$).

Discussion

The associations between ovarian cancer self-assessment ad postoperative histopathology patients with suspected malignant ovarian tumors were examined. Ovarian cancer self-assessment consists of 10 ovarian cancer risk symptoms. However, in this study, six out of ten questions were statistically significant between benign and malignant groups with a tendency towards benign ovarian tumors. It might be because symptoms are not enough for diagnosing ovarian cancer and there is a need for additional examination to support the diagnosis of ovarian cancer, such as ultrasound and tumor markers (Doubeni, 2016; Menon, 2014). Ovarian cancer is detected based on a simple descriptor and simple IOTA rules. It could be done step by step to conclude malignant or benign characteristics and will be evaluated by an oncologist (Timmerman, 2000).

Tumor marker was an additional exam that supported ovarian cancer. It was a molecule produced to respond to neoplastic proliferation, which entered circulation with a detectable amount. It showed cancer potential or information related to its effectiveness. Screening is related to sensitivity and specificity. The CA-125 is one of the tumor markers which can be used in screening, assessing the response of therapy, assessing the recurrence of cancer, or predicting the prognosis of the disease. The CA-125 is primarily used as a tumour marker in epithelial ovarian cancer during chemotherapy, 50% increase in ovarian cancer stage I and 80-90% in advanced-stage ovarian cancer (Jasen, 2009; Doubeni, 2016)

As can be seen in Table 3, the risk patients were 55 (30 patients in malign and 25 on benign group), while in no-risk category there were 60 patients (48 patients on malign and 12 patients on benign). We hypothesize the risk factor as the malign patient but it was non appropriate with the result of this study. So that we conclude that another aspect such as the family history of cancer should be added in the quosionnare. Another aspect that should be added to the questions is a family history of cancer. It could be due to other factors affecting diagnostic accuracy, whether sign and symptom or additional examination. Epithelial ovarian cancer is a primarily sporadic event; however, a quarter of cases are related to germline mutation at specific genes and hereditary. Hereditary ovarian cancer, primarily due to BRCA1 mutation, occurs at a younger age and ten years earlier than sporadic ovarian cancer. Most hereditary ovarian cancer results from germline mutation or genes *BRCA 1* and *BRCA2*. Mutation inherited by autosomal dominant, thus the history of cancer in the family, including breast and ovarian cancer from paternal and maternal family, should be evaluated, especially at epithelial ovarian cancer, fallopian tube and peritoneal cancers (Matulonis, 2016; Menon, 2014)

We still need more improvement in our application trial with more numbers of sample. The results showed us that ovarian cancer is not that easy to predict. Family history of cancer and additional examination such as ultrasonography examination or tumor marker may improve early diagnosis and risk assessment of ovarian cancer.

In conclusion, the ovarian cancer-self assessment based on artificial intelligence was an innovative trial for early detection and risk assessment of ovarian cancer even though it needed more improvement for clinical application. As a screening tool innovation, it needs additional examinations such as ultrasound and tumor marker for a better result. Improvement in the questionnaire and the number of samples will yield more reliable results.

Author Contribution Statement

SS, AR, ABH, FE did the conception and design of the study, acquisition of data, analysis and interpretation of the data, drafting the manuscript and revising the manuscript critically for important intellectual content; HF did the the conception and design of the study, analysis and interpretation of the data; HP, RN did the acquisition of data, drafting the manuscript, and revising the manuscript critically for important intellectual content.

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General

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Approval

All authors have read and approved the final manuscript

Etical Declaration

All study participants provided written informed consent prior to engaging in any study-related procedures. This study was approved by Research Ethics Committee Hasan Sadikin Hospital, Bandung with approval number LB.02.01/X.6.5/148/2021. All authors here by declare that all patients have been examined in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Data Availability

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

Conflict of Interest

The authors declare that they have no conflict of interest.

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