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Predictive Value of Symptom Index for Early Detection of Ovarian Cancer

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ABSTRACT

Objective: Although symptom-based screening has a positive role in identifying women at risk, it's yet to be validated as screening tool. The present study aimed to validate the ovarian cancer symptom index in Pakistani population.
Methods: From June 2019-December 2020, presenting symptoms were prospectively recorded in patients with ovarian cancer (n=70) and benign ovarian tumor (n=140) using Goff's questionnaire.
Results: Symptoms such as unable to eat normally, feeling full quickly, weight loss, increased abdomen size and postmenopausal bleeding were reported more frequently among the cancer group ($p<0.05$). Symptoms including feeling full quickly, increased abdominal size and patients' age were independent predictors of cancer. The sensitivity, specificity, positive and negative predictive value, of symptom index were found to be 31.43%, 79.29%, 43.13%, and 69.81%, respectively.
Conclusion: This study confirms that specific symptoms were useful in diagnosing women with ovarian cancer. Low sensitivity and specificity of the symptom index limit its use as an independent screening method. Nonetheless, with further validation it can be included for screening in clinical settings.

Keywords: ovarian cancer, symptom index, diagnosis, predictive value

INTRODUCTION

Amongst the many gynecological malignancies reported worldwide, ovarian cancer is the most noxious one causing at least 140,000 deaths annually (1). In Pakistan, it is the second most common female cancer with a prevalence of 13.6% (2, 3). Five-year survival rate of cancers confined only to the ovaries is 70% to 90% compared to advanced disease (15–30%). Unfortunately, due to the deeper anatomic location, most cancers (60%-70%) are detected at a later stage, and only 19% of ovarian cancer cases are diagnosed in the initial stages (4-8). Although previously regarded as a "silent killer "due to its insidious nature and late diagnosis, the results of several case studies have proven otherwise. These studies infer that ovarian cancer causes a distinct pattern and timing of symptoms. Given the deeper anatomic locations, overlapping symptoms, and absence of high-quality, standard screening techniques, ovarian cancer remains a diagnostic challenge (4, 5, 8).

With limited available data on the efficacy or potential morbidity of ovarian cancer screening tools in the asymptomatic general population, currently, routine screening is not recommended. Amongst many screening approaches, ovarian symptom index is currently the most commonly used

index to detect ovarian cancer in low to moderate risk patients (9). It was developed by Goff and colleagues in 2007, based on the results of a case-control study carried out to assess the frequency, severity, and duration of symptoms in women with ovarian cancer (10). The symptom index is considered to be positive if a woman reports either pain in the abdomen or pelvis, feeling full quickly or inability to eat normally and abdominal bloating, or increased abdominal size within the last year with a frequency of more than 12 times per month.

Although few researchers have evaluated the predictive value of the symptom index (6, 11, 12), there is a paucity of comparable data in our local setting to prove and validate the above-mentioned research outcomes. Hence, the present study was carried out with an objective to determine the predictive value of ovarian cancer symptom index in high-risk women with suspicion of ovarian cancer and to determine its effective role as a screening tool for early diagnosis. Results of this study may aid in apprising the institutional screening policy to triage women who might need detailed screening workup.

MATERIAL AND METHODS

A case-control study was conducted among 210 patients diagnosed with an adnexal mass in the Department of Obstetrics and Gynecology at Aga Khan University Hospital, Karachi, from June 2019 to December 2020. Institution ethics approval (Ref No. 2019-1038-3586 dated-14-May-2019) and copyright permission to use the Goff et al.-ovarian cancer symptom index tool from the publishing copyright holder were obtained. Based on Department's statistics, a sample size of 70 cases and 140 controls was considered appropriate for the study.

Using purposive sampling, women aged 19-years and above referred for clinical evaluation and surgical management of the adnexal mass with either confirmed or suspected malignancy were included in the study. Patients with a previous history of ovarian, fallopian tube or peritoneal cancer and those with a history of bilateral salpingo-oophorectomy (BSO) were excluded. Informed consent was obtained from all patients.

Based on the histopathologic diagnosis, patients were divided into two groups. The test group (n=70) consisted of patients diagnosed with a malignant ovarian tumor, while those diagnosed with benign ovarian tumors were considered controls (n=140). After recording the patient demographics (age, parity, body mass index) and history (menstrual history, family history of ovarian, breast, endometrial, and colorectal carcinoma), individual patients were interviewed by the investigators about symptoms based on the ovarian cancer symptom index tool consisting of 23 symptoms specific to ovarian cancer. The interviews were carried out before the histopathological diagnosis to avoid interviewer bias. Presentation of either pain in abdomen or pelvis, feeling full quickly or inability to eat normally, abdominal bloating, or increased abdominal size for a period of ≥2 weeks but ≤ 1 year, with a recurrent incidence of >12 times per month was indicative of positive symptom index (12, 13).

Statistical analysis

The data was compiled and entered in IBM SPSS version 22.0 software for analysis. Comparison of frequency of symptoms was performed using chi-square test, and quantitative variables were compared using independent t-test. Logistic regression analysis was applied with an ovarian cancer diagnosis as the dependent variable, and the variables found significant in the bivariate analysis as independent variables. Sensitivity analysis was conducted to assess the sensitivity, specificity, positive predictive value, and negative predictive value of symptom index. For all tests, confidence interval and p-value were set at 95% and ≤ 0.05, respectively.

RESULTS

Of the total of 210 patients included in the study, test group comprised of 70 cancer patients while 140 patients with benign tumors belonged to the control group. The demographic characteristics revealed that the mean age of patients was significantly higher in the test group as compared to the control group (47.83 ± 15.34 vs. 36.99 ± 12.02 years, p=0.000). Similarly, mean parity was also higher among cases than controls (p=0.009); however, no difference in body mass index was observed between the two groups (p=0.685).

In patients with ovarian cancer, lower abdominal pain (57.1%) and increased abdomen size (50%) were the commonest symptoms reported. While lower abdominal pain (64.3%) followed by backache (27.1%) were the most common reported symptoms in the control group. Analysis with chi-square test showed that symptoms such as unable to eat normally (11.4% vs 2.9%; p=0.023), feeling full quickly (27.1% vs 5%; p=0.000), weight loss (18.6% vs 2.1%; p=0.000), increased abdomen size (15.7% vs 18.6%; p=0.000), bleeding after menopause (5.7% vs. 0%;p=0.012), breathing difficulty (5.7% vs 0%;p=0.012) were reported to occur more frequently among the patients in test group in comparison to the control group (Table 1).

Table 1: Comparative assessment of presence of symptoms among cases and controls

Symptoms	Cases (n=70)	Controls (n=140)	p-value	Total (n=210)
Lower abdominal pain	40 (57.1%)	90 (64.3%)	0.366	130 (61.9%)
Whole abdominal pain	12 (17.1%)	29 (20.7%)	0.584	41 (19.5%)
Backache	17 (24.3%)	38 (27.1%)	0.740	55 (26.2%)
Indigestion	13 (18.6%)	14 (10%)	0.086	27 (12.9%)
Unable to eat normally	8 (11.4%)	4 (2.9%)	0.023*	12 (5.7%)
Feeling full quickly	19 (27.1%)	7 (5%)	0.000*	26 (12.4%)
Nausea or vomiting	14 (20%)	21 (15%)	0.432	35 (16.7%)
Weight loss	13 (18.6%)	3 (2.1%)	0.000*	16 (7.6%)
Abdominal bloating	10 (14.3%)	14 (10%)	0.365	24 (11.4%)
Increased abdomen size	35 (50%)	26 (18.6%)	0.000*	61 (29%)
Able to feel abdominal mass	11 (15.7%)	12 (8.6%)	0.158	23 (11%)
Urinary urgency	8 (11.4%)	8 (5.7%)	0.170	16 (7.6%)
Frequent urination	10 (14.3%)	13 (9.3%)	0.348	23 (11%)
Constipation	12 (17.1%)	13 (9.3%)	0.115	25 (11.9%)
Diarrhea	2 (2.9%)	2 (1.4%)	0.602	4 (1.9%)
Menstrual irregularities	5 (7.1%)	19 (13.6%)	0.249	24 (11.4%)
Bleeding after menopause	4 (5.7%)	0	0.012*	4 (1.9%)
Pain during intercourse	5 (7.1%)	9 (6.4%)	1.000	14 (6.7%)
Bleeding with intercourse	1 (1.4%)	4 (2.9%)	0.667	5 (2.4%)
Fatigue	6 (8.6%)	8 (5.7%)	0.558	14 (6.7%)
Leg swelling	3 (4.3%)	1 (0.7%)	0.109	4 (1.9%)
Difficulty breathing	4 (5.7%)	0	0.012*	4 (1.9%)
Others	12 (17.1%)	49 (35%)	0.009*	61 (29%)

Test applied: Chi-square test, *indicates statistically significant difference

Table 2: Binary Logistic Regression analysis with ovarian cancer as the dependent variable

	Odds ratio	Confidence Interval	p-value
Unable to eat normally	2.619	0.373-18.399	0.333
Feeling full quickly	0.280	0.087-0.904	0.033*
Weight loss	0.136	0.023-0.821	0.03*
Increased abdomen size	0.386	0.187-0.795	0.01*
Other symptoms	1.487	0.670-3.301	0.330
Age	1.051	1.020-1.083	0.001*
Parity	0.994	0.647-1.527	0.979

Demographics and symptoms with a significant difference between the two groups were subjected to binary logistic regression analysis (Table 2). In our study, age was also an independent predictor of ovarian cancer. With one unit increase in age, the odds of ovarian cancer increase by 1.051 units (p=0.001). Symptoms including feeling full quickly, weight loss, and increased abdominal size were independent predictors of ovarian cancer. Those who had the symptom of feeling full quickly had 0.28 times lesser odds of ovarian cancer than those without the symptom (p=0.033). Those who had the symptom of weight loss had 0.136 times lesser odds of ovarian cancer than those without the symptom (p=0.03). Those who had the symptom of increased abdomen size had 0.386 times

lesser odds of ovarian cancer than those without the symptom (p=0.01).

Table 3: Sensitivity and specificity of Symptom index among cases and controls

True positive	22 (10.48%)
True negative	111 (52.86%)
False positive	29(13.81%)
False negative	48(22.86%)
Sensitivity	31.43%
Specificity	79.29%
Positive predictive value	43.13%
Negative predictive value	69.81%

Table 3 shows the sensitivity and specificity of the symptom index. In the test group, the symptom index was positive in 22 (31.43%) and negative in 48 (68.57%) patients. While in the control group, it was positive and negative in 29 (20.71%) and 111 (79.29%) patients. In the study while 22 (10.48%) cases were true positive, 29(13.81%) were false positive. Similarly, 111 (52.86%) and 48 (22.86%) patients were true negative and false negative, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value were found to be 31.43%, 79.29%, 43.13%, and 69.81%, respectively.

DISCUSSION

Raising awareness of cancer symptoms will benefit the early recognition of cancer and improve cancer outcomes by initiating treatment at the early stages. Although previously considered a silent killer, reports of many case-control studies in the last decade have proven otherwise (6, 14, 15). Since symptoms of cancer are often non-specific and overlap with symptoms of much more common disorders affecting the nearby organs, women and physicians tend to underestimate their importance (16, 17). Ebell et al. in their systematic review suggested that the presence of symptoms like abdominal distension, abdominal or pelvic bloating, abdominal mass, loss of appetite, and abdominal or pelvic pain significantly increases the likelihood of ovarian cancer. Goff proposed the Ovarian Cancer Symptom Index by combining few of the most common symptoms, including abdominal & pelvic pain, bloating, increased abdominal size, difficulty in eating, and fullness in stomach to aid in early diagnosis (10). The clinical utility of this index has been tested by previous researchers (6, 18-22). To the best of our knowledge, the present study is the first of its kind carried out to assess the predictive value of ovarian cancer symptom index in Pakistan.

In a study by Goff et al., sensitivity of symptom index in women aged 50 years and above was found to be 66.7% (10). Subsequent studies carried out by Andersen (2008) (64%), Rossing (67.5%), Andersen, 2010 (63.5%), Lim, 2012 (61.4%) found similar sensitivity ((6, 18-22). Similarly, these studies validated the specificity of 86.7-90% reported by Goff et al. On the other hand, higher sensitivity was reported by Macuks (83.3%) and Jain (77.8%) ((6, 18-22). Likewise, this symptom index was an effective first-line screening method for detecting ovarian malignancies in the study of Korea (6, 18-22)) and India (1, 23). However, the sensitivity and specificity predicted in our study are 31.43% and 79.29%, respectively, much lower as compared to previous studies. The sensitivity of symptom index could also be affected by concomitant chronic illness, especially in patients with multiple symptoms (24). Specificity of symptom index depends on women's symptom reports, which are dependent on the ability of the patient to recall symptoms. This recall bias is believed to affect the sensitivity and specificity of the index to a greater extent. To avoid this, we used the symptom index in women already diagnosed with an adnexal mass and aimed at discriminating those with malignancy from the rest. This study cohort of high-risk symptomatic women forms a valuable control as compared to the general population without symptoms (6, 18-22)). Only 10.48% of cases were true positive in the study.

One of the main drawbacks of the symptom index is the false-positive results. An increased number of false-positive results would lead to unnecessary surgery (16, 17).

In a prospective symptom-based diagnostic study by Andresen et al., only 4.8% of patients had positive symptom index and rate of false-positive surgery was only 0.008% (12, 13). In our study 13.81% of patients were false positive. Additionally, the positive predictive value is an important parameter to assess the utility of any new tool. It predicts the diagnostic ability of the tool to be used as an independent aid (25). In a study by Urban, negative predictive value and positive predictive value were 82.1% and 70.2%, respectively (26). Rossing in their study estimated the overall positive predictive value of symptom index to be 0.6-1.1% (22). In our study, positive predictive value and negative predictive value were found to be 43.13% and 69.81%, respectively.

In a case-control study by Kim, the symptom index was positive in 65.5% and 31.1% of women with ovarian cancer and benign cysts, respectively (6, 18-22)). However, the proposed ovarian cancer symptoms were significantly higher in ovarian cancer patients as compared with the control group. In addition to the six symptoms suggested by Goff et al., Shetty et al. found that loss of appetite or loss of weight were significantly associated with ovarian cancer (1, 23). Similarly, weight loss was found to be an independent predictor of ovarian cancer in our study. Clinical staging of ovarian cancer is directly correlated to the symptom index results. There is an increase in the positive rates of the index with advanced cancer (70.7%-80%) compared to early-stage ovarian cancer (57%-62.3%) (27). However, we did not categorize the cancer patients in our study.

The low specificity of the ovarian cancer symptom poses a great challenge while using a symptom-based diagnostic modality for screening (9). Moreover, according to a National Ovarian Cancer Coalition study, only 15% of women are familiar with specific symptoms associated with this cancer. Moreover, around 82% never discuss the symptoms and risk factors with their physicians during the regular scheduled appointments (28). Nevertheless, the usage of symptom-based diagnostic approach as the first line of screening method is widely encouraged, especially in women at high risk for ovarian cancer (9), including women with possible BRCA1/2 mutation and a family history of cancer (16, 17). Moreover, the current advised screening methods, including CA125, transvaginal ultrasonography, or symptom-based screening though are effective; however, it has less sensitivity when used alone ((6, 18-22). By increasing the frequency of screening or adding another screening method such as biomarker, the symptom index can be effectively incorporated in a clinical setting. A study by Andreasen et al. reported that aggressive evaluation of patients with positive symptoms results in the increased diagnosis of ovarian cancer, suggesting a better prognosis (12, 13). Additionally, studies by Andreasen et al., Kim et al., and Goff et al. highlight the potential benefits of using a combination of biomarker and symptom index as a first-line of a screening method to improve the sensitivity of screening tool to aid in better cancer detection (6, 18-22)).

Despite its limitations, the symptom index provides more objective clinical input from the patient, which further enhances the diagnostic acumen. Also, mere participation in the screening studies increases the knowledge of these high-risk cancers. Moreover, due to its cost-effectiveness, symptom index is a feasible alternative compared to the previously used screening methods. Although low sensitivity and specificity were observed in our study, with further validation, the index can be included as a part of the current primary care strategies for screening low to moderate risk women. The prospective nature of the study was one of the main strengths of our study. Also, using the predefined index and direct questioning enhanced patient engagement and patient-centered care. A relatively small sample size obtained from single hospital-

based setting limits the generalizability of the results.

CONCLUSION

The symptom index tool dictates whether further investigations need to be sought to reduce the incidence of unwanted surgeries. However, since the sensitivity of the symptom index is not very promising, it is not advisable to be recommended as an independent screening tool. In view of this, larger prospective trials are warranted to assess the cost-effectiveness, acceptability and impact on clinical outcomes of symptom index. Meanwhile, the combination of symptom index and biomarkers followed by transvaginal ultrasonography can be used as a primary screening tool.

Declaration by Authors

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