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Modified Goff Symptom Index

Simple triage tool for ovarian malignancy

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نسخة معدلة من مؤشر الأعراض جوف

أداة بسيطة لتصنيف حالات سرطان المبيض

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abstract: ***Objectives:*** Ovarian cancer often goes undiagnosed or misdiagnosed in the early stages. The present study aimed to validate a modified version of the Goff Symptom Index (GSI) in an Indian population. ***Methods:*** This prospective case-control study was conducted between July 2010 and June 2012 in a university hospital in Manipal, Karnataka, India. A total of 305 inpatients admitted for ovarian pathology investigations and outpatients undergoing routine gynaecological check-ups were included in the study. The modified GSI (MGSI) was used to investigate the presence, severity, frequency and duration of 10 ovarian cancer symptoms on a scale of 1–5. Four additional symptoms were included with those of the original GSI (two symptoms from a previous MGSI and two new symptoms). Patients were regarded as positive for ovarian cancer if symptoms occurred >12 times per month and time since onset was <1 year. Histopathology confirmed the diagnosis of ovarian tumours. ***Results:*** A total of 13 patients were excluded. The final sample (n = 292) was divided into a test group (n = 74) and a control group (n = 218) based on histopathology. Within the controls, 144 women were found to have benign tumours. The MGSI was positive in 71.6% of the test group as opposed to only 11.5% of the control group. The addition of two symptoms (loss of appetite and weight) to the GSI increased the test's sensitivity from 71.6% to 77% without compromising specificity (88.5%). ***Conclusion:*** Based on these findings, the addition of two new symptoms (loss of appetite and weight) to the GSI is proposed in order to increase the test's sensitivity. However, the addition of urinary symptoms to the GSI requires further validation.

Keywords: Ovarian Cancer; Diagnosis; Symptom Assessment; Triage; Algorithm; Reliability and Validity; India.

الملخص: الهدف: غالبا ما لا يتم تشخيص سرطان المبيض أو يشخص بشكل خاطئ في المراحل المبكرة. تهدف هذه الدراسة إلى التحقق من صحة استخدام نسخة معدلة من مؤشر الأعراض جوف (GSI) في السكان الهنود. **الطريقة:** أجريت هذه الدراسة على حالات مرضية وضوابط بين يوليو 2010 ويونيو 2012 في مستشفى الجامعة في مانيبال، كارناتاكا، الهند. أدرجت في هذه الدراسة 305 حالة من حالات أمراض المبيض المختلفة وضوابط تشمل نساء يأتين لفحوصات أمراض نساء روتينية في العيادات الخارجية. استخدمت نسخة معدلة من مؤشر الأعراض جوف (MGSI) للتأكد من وجود وشدة وتكرار ومدة 10 أعراض من سرطان المبيض على مقياس من 1-5. وأدرجت أربعة أعراض جديدة مع تلك المدرجة على مؤشر الأعراض جوف GSI. اعتبرت الحالات إيجابية لسرطان المبيض إذا حدثت الأعراض >12 مرة في الشهر منذ بداية الأعراض <1 سنة.وأكد التشخيص المجهري أورام المبيض. **النتائج:** تم استبعاد 13 مريضة من الدراسة ثم تقسيم العينة النهائية عدد 292 إلى مجموعة اختبار عدد 74 والمجموعة الضابطة عدد 218 على أساس التشخيص المجهري. ضمن الضوابط، تم العثور على 144 من النساء لديهم أورام حميدة. كان MGSI إيجابيا في 71.6% من مجموعة الاختبار في مقابل 11.5% فقط من المجموعة الضابطة. إضافة اثنين من الأعراض (فقدان الشهية والوزن) إلى GSI زادت حساسية الاختبار من 71.6% إلى 77% دون المساس بخصوصية الاختبار (88.5%). **الخلاصة:** استنادا إلى هذه النتائج، يقترح إضافة اثنين من الأعراض الجديدة وهي (فقدان الشهية والوزن) إلى GSI من أجل زيادة حساسية الاختبار. وإضافة الأعراض البولية لمؤشر الأعراض يتطلب مزيدا من التحقق من صحة الاختبار.

مفتاح الكلمات: سرطان المبيض؛ التشخيص؛ تقييم أعراض؛ تصنيف؛ النظم؛ الصحة والدقة؛ الهند.

Advances in Knowledge

- *Early-stage ovarian malignancies often go unnoticed or misdiagnosed. This study emphasises the importance of using a simple index based on the common non-specific symptoms of ovarian cancer.*
- *This study may be a platform for further population-based studies to determine the benefit of this simple index in screening women for early-stage ovarian malignancies.*

Applications to Patient Care

- *The modified symptom index was found to be helpful in identifying women with early-stage ovarian cancer among a sample in India.*
- *The identified clusters of non-specific symptoms in the proposed symptom index can assist women in self-screening and help family physicians to make timely patient referrals.*
- *Health workers and the general population should be made aware of the common non-specific symptoms of ovarian cancer in order to minimise delay in diagnosis.*

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Ovarian cancer remains a major health concern worldwide, with more than 225,000 new cases annually leading to 140,000 deaths.[1,2] Ovarian cancer often goes unnoticed or misdiagnosed in its early stages. Hence, many researchers have evaluated the predictive value of ovarian cancer symptoms.[3–5] Recent research has also emphasised the highly stressful effect of a late ovarian cancer diagnosis on quality of life.[6] Screening strategies like sonography and cancer antigen (CA) 125 tests have failed to prove their efficacy in early detection among the general population.[7]

The recognition of non-specific symptoms of the disease may minimise diagnostic delays, facilitate early management and improve survival rates. A thorough understanding of the spectrum of non-specific symptomatology in ovarian malignancies can help in making an early diagnosis. The other advantage of using a symptom-based screening tool is to create awareness among the general public. Thus, the potential utility of recognising unique patterns of non-specific symptoms is two-fold—such recognition can alert both patients and healthcare providers to potential ovarian malignancies.[8] The present study was conducted with the aim of validating Kim *et al*.'s modified version of the Goff Symptom Index (GSI) in an Indian population.[9,10] Furthermore, this study sought to validate the addition of two new symptoms to Kim *et al*.'s modified GSI (MGSI).[10]

Methods

This prospective case-control study was conducted between July 2010 and June 2012 in a university hospital in Manipal, Karnataka, India. A total of 305 women were enrolled in this study. This included both women who were admitted to the hospital for evaluation and management of ovarian tumour pathology and those with an intact uterus and at least one intact ovary who visited the outpatient department for a routine gynaecological check-up during the study period. The latter patients formed the control-clinic group.

All of the participants were given a survey to complete. The survey instrument was specifically designed for the current study and included questions eliciting demographic information, such as age, number of children and body mass index. The remainder of the survey investigated the presence, severity, frequency and duration of 10 ovarian cancer symptoms. These included six symptoms (pelvic pain, abdominal pain, increased abdominal size, bloating, difficulty in eating and a feeling of fullness) from the original symptom index proposed by Goff *et al*.[9] Two other symptoms (urinary urgency and frequency) were included, as proposed by Kim *et al*. in the MGSI.[10] Finally, two new symptoms (loss of weight and loss of appetite) were also included, based on the authors' past experience with ovarian cancer cases.

The participants were asked to rate the severity of each of these 10 symptoms on a scale of 1–5, with a score of 1 being mild and 5 being intolerable. Similar scales were used to determine the frequency and duration of each symptom. Eight symptoms, excluding the two new symptoms, were combined into four symptom clusters (abdominal/pelvic pain, increased abdominal size/bloating, difficulty in eating/feeling full and urinary frequency/urgency). The symptom index was considered to be positive for ovarian cancer if any of these symptoms occurred >12 times a month and the total duration since the onset of the symptom was <1 year. In order to avoid bias, the investigator involved with data collection remained unaware of the patients' diagnoses during the survey period.

Following their completion of the survey, all of the participants who presented with ovarian pathology underwent post-surgical histopathological assessment of their ovarian tumours. As the control-clinic group had no ovarian pathology, they did not undergo any histological assessment. If a post-surgical (following a cystectomy, ovariotomy or staging laparotomy) histopathology report revealed a borderline ovarian tumour, these patients were excluded from the final analysis. Participants with ovarian malignancies revealed by histopathology were assigned to the test group, while those with benign ovarian neoplasms or endometriomas were classified as the control-benign group. Participants were therefore assigned to one of two groups (test group or control group), with those in the control group further classified according to two subgroups (control-benign and control-clinic groups). The inclusion of a control-clinic group helped ensure the test and control-benign groups were comparable.

A comparative analysis was performed between the results of the survey and the final diagnoses for all participants. As no histological examinations were performed for the control-clinic group, transvaginal sonography suggestive of a normal ovarian architecture was taken to indicate no pathology. Statistical analysis was performed using the Statistical Package for the Social Sciences, Version 16.0 (IBM Corp., Chicago, Illinois, USA). Symptoms were compared using a Chi-squared test. The odds ratio of each symptom was calculated by logistic regression analysis. A multivariate logistic regression was performed to determine which of the four symptom clusters remained independently significant. For all analyses, P <0.05 was considered statistically significant.

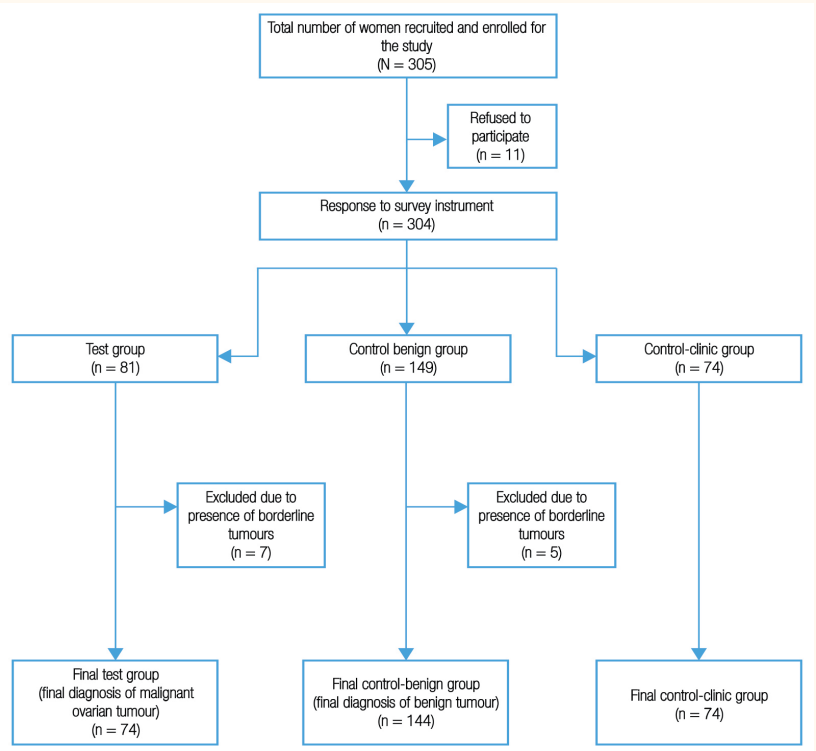

Figure 1: Figure 1: CONSORT (Consolidated Standards of Reporting Trials) flow chart detailing the population of the current hospital-based prospective case-control study.
**Diagnosis of malignant ovarian tumours were based on clinical features.*

Table 1: Demographic characteristics reported among test and control groups at an Indian university hospital (N = 292)

Characteristic		n (%)		
		Test group (n = 74)	Control group (n = 218)	
			Control-benign group (n = 144)	Control-clinic group (n = 74)
Median age in years (range)		47 (12–75)	34 (14–75)	48 (25–81)
Parity	Nulliparous	17 (23)	64 (44.4)	6 (8.1)
	Primiparous	11 (14.9)	29 (20.1)	6 (8.1)
	Multiparous	46 (62.2)	51 (35.4)	62 (83.8)
BMI in kg/m²	<18	4 (5.4)	3 (2)	0
	18–24.9	47 (63.5)	112 (84.7)	61 (82.4)
	25–29.9	21 (28.4)	27 (18.8)	12 (16.2)
	≥30	2 (2.7)	2 (1.4)	1 (1.4)
Menstrual status	Pre-menopausal	35 (47.3)	115 (79.9)	35 (47.3)
	Menopausal	39 (52.7)	29 (20.1)	39 (52.7)

BMI = body mass index.

Ethical approval for this study was granted by the Institutional Ethics Committee of Kasturba Hospital, Manipal, India (#IEC124/2010). Written informed consent was obtained from all participants before inclusion in the study.

Results

Of the 305 women enrolled in the study, 304 completed the survey (response rate: 99.7%). A total of 12 patients were excluded from the final analysis (seven from the test group and five from the control-benign group) as their final histopathology assessments revealed borderline ovarian tumours. Thus, the final cohort consisted of 292 women [Figure 1]. Of these, 74 made up the test group while 218 made up the control group. For the latter group, the women were subdivided into a control-benign subgroup (n = 144) and control-clinic subgroup (n = 74). The demographic characteristics of the cohort are presented in Table 1.

The symptom index was positive for ovarian cancer for 71.6% of women in the test group as opposed to only 11.5% of women in the control group. This difference was statistically significant (P <0.001). The majority of clustered symptoms were reported to occur more frequently among the test group in comparison to the control group, including abdomen/pelvic pain

Table 2: Positive modified Goff Symptom Index[10] for ovarian malignancy and distribution of symptom clusters reported among test and control groups at an Indian university hospital (N = 292)

Variable	n (%)		*P* value
	Test group (n = 74)	Control group (n = 218)	
Symptom cluster			
Abdominal pain/pelvic pain	33 (44.6)	17 (7.8)	<0.001
Increased abdominal size/bloating	41 (55.4)	13 (6.0)	<0.001
Difficulty in eating/ feeling full	34 (45.9)	7 (3.2)	<0.001
Increased urinary frequency/urgency	0 (0.0)	3 (1.4)	0.573
Positive* modified Goff Symptom Index[10]	53 (71.6)	25 (11.5)	<0.001

**The symptom index was considered to be positive for ovarian cancer if any symptoms were reported to have occurred >12 times a month and total duration since the onset of the symptom was <1 year.*

(44.6% versus 7.8%), increased abdominal size/bloating (55.4% versus 6.0%) and difficulty in eating/feeling full (45.9% versus 3.2%). These three symptom clusters were statistically significant predictors of ovarian cancer according to the histopathological findings [Table 2].

Urinary symptoms were not indicated among any women in the test group. In contrast, three women in the control group complained of urinary frequency/urgency. While one patient in the test group complained of increased urinary frequency, the total duration since the onset of the symptom was >1 year. As urinary symptoms were absent from the test group, this symptom cluster was excluded from the logistic regression analysis. All of the other symptom clusters were independent predictors of ovarian cancer according to the logistic regression analysis [Table 3].

In the test group, there were six patients with stage IV ovarian cancer, 43 with stage III, six with stage II and 17 with stage I. Two patients were not staged as one had a Krukenberg tumour and the other had synchronous endometrial cancer. A total of 60 patients had epithelial cancer, seven had germ cell cancer, six had sex cord-stromal tumours and one had a Krukenberg tumour.

The results of the symptom index were analysed according to cancer stage among individuals in the test group. The symptom index was found to be positive in 83.3% of stage IV patients and 76.7% of stage III patients. However, it was also positive in 64.7% and 50% of those with stage I and stage II cancer, respectively. On correlating the symptom index with histology findings, the symptom index was found to be positive among 78% of those with epithelial cancer, 71.5% of those with germ cell cancer and 16.6% of those with sex cord-stromal tumours.

Table 3: Independent logistic regression analysis of the Goff Symptom Index[9] for ovarian malignancy and symptom clusters reported among test and control groups at an Indian university hospital (N = 292)

Variable	OR	95% CI	*P* value
Symptom cluster			
Abdominal pain/pelvic pain	09.5	04.84–18.68	<0.001
Increased abdominal size/ bloating	19.6	09.49–40.41	<0.001
Difficulty in eating/feeling full	26.6	10.61–61.82	<0.001
Positive* Goff Symptom Index[9]	19.5	10.12–37.50	<0.001

OR = odds ratio; CI = confidence interval.

**The symptom index was considered to be positive for ovarian cancer if any symptoms were reported to have occurred >12 times a month and total duration since the onset of the symptom was <1 year.*

A total of 21 patients in the test group had negative symptom index results. Of these, seven experienced abdominal pain and one had bloating; however, these symptoms occurred <12 times a month. Four patients experienced a loss of appetite and weight, four presented with menstrual irregularities, two presented with postmenopausal bleeding, one reporting having backache and two developed features of hyperandrogenism. In terms of histology, a negative symptom index was reported by 16.3% of those with epithelial cancer, 28.6% of those with germ cell tumours, 83.3% of those with sex cord-stromal tumours and 100% of those with a Krukenberg tumour.

The clinical significance of each symptom cluster was calculated in terms of sensitivity, specificity and positive and negative predictive values. Increased abdominal size and bloating were the most sensitive symptoms (55.4%). Although the sensitivity of individual clusters was approximately 50%, adding them together resulted in the sensitivity of the index increasing to 71.6% [Table 4].

The new symptom cluster added to the MGSI (loss of appetite and weight) was one of the most common clusters reported among women with ovarian cancer. A total of 34 women (45.9%) in the test group reported having these symptoms. The addition of these two symptoms to the MGSI was therefore compared to the MGSI in terms of sensitivity and specificity [Table 5]. Adding this symptom cluster to the modified symptom index increased the sensitivity of the test from 71.6% to 77%, without compromising the specificity, which remained at 88.5%.

Table 4: Clinical efficacy of individual symptom clusters and the modified Goff Symptom Index[10] in predicting ovarian malignancy among test and control groups at an Indian university hospital (N = 292)

Variable	Percentage			
	Sensitivity	Specificity	PPV	NPV
Symptom cluster				
Abdominal pain/pelvic pain	44.6	92.2	66.6	83.0
Increased abdominal size/bloating	55.4	94.0	75.9	86.1
Difficulty in eating/ feeling full	45.9	96.8	82.9	84.0
Increased urinary frequency/ urgency	0.0	98.6	0.0	74.3
Positive* modified Goff Symptom Index[10]	71.6	88.5	67.9	90.1

PPV = positive predictive value; NPV = negative predictive value.

**The symptom index was considered to be positive for ovarian cancer if any symptoms were reported to have occurred >12 times a month and total duration since the onset of the symptom was <1 year.*

Discussion

Ovarian cancer cases have a high frequency of late diagnosis and associated mortality.[11] As a result, there is a dire need to focus research on effective methods of screening for and detecting ovarian cancer at an early stage. Unfortunately, no screening test or surveillance strategy to date has achieved this goal. Van Nagell *et al*. determined that neither sonography nor CA 125 testing were cost-effective or practical for ovarian cancer screening in the general population, revealing that 5,200 ultrasound scans were needed in order to detect one case of invasive cancer.[12] Furthermore, even when assessing cancer incidence among a high-risk cohort, Liede *et al*. reported that the combination of sonography and CA 125 testing did not prove efficacious in reducing mortality or morbidity.[13]

After exploring the symptomatology of ovarian cancer patients, Goff *et al*. noted that women with ovarian cancer frequently reported symptoms prior to diagnosis, although these symptoms were usually non-specific.[14,15] Based on the hypothesis that recognition of this symptom pattern would serve as a simple and cost-effective screening tool, Goff *et al*. proposed their original symptom index in 2007.[9] The original GSI included six symptoms clustered into three groups (pelvic/abdominal pain; increased abdominal size/bloating; and difficulty in eating/feeling full).[9] The GSI was considered positive for ovarian cancer if any of those six symptoms occurred >12 times per month and had been present for <1 year. In the confirmatory sample, the index had a sensitivity of 56.7% and 79.5% for early- and advanced-stage cases, respectively.[9] Specificity was 90% for women >50 years of age and 86.7% for women <50 years of age.[9] This original symptom index was found to be an effective triage tool for ovarian malignancies in the current studied cohort of Indian women. Patients with a positive symptom index should therefore be referred to an appropriate medical centre for an evaluation of potential ovarian cancer.

Table 5: Clinical efficacy of the modified Goff Symptom Index[10] for ovarian malignancy and the same index with two new additional symptoms (loss of appetite and weight) among test and control groups at an Indian university hospital (N = 292)

Symptom index	Percentage			
	Sensitivity	Specificity	PPV	NPV
MGSI[10]	71.6	88.5	67.9	90.1
Current index*	77.0	88.5	69.5	91.9

MGSI = modified Goff Symptom Index; PPV = positive predictive value; NPV = negative predictive value.

**Addition of two new symptoms (loss of appetite and loss of weight) to the MGSI proposed by Kim et al.[10]*

Kim *et al*. supported the efficacy and validity of the GSI in a Korean population, with sensitivity and specificity rates of 65.5% and 84.7%, respectively.[10] Two urinary symptoms (urgency/frequency) were added to the original GSI and found to be an independent predictor of ovarian cancer.[10] However, the two urinary symptoms added by Kim *et al*. in the MGSI were not an important predictor of ovarian malignancy in the current study. Urinary symptoms were not common among the studied Indian cohort, perhaps due to the younger median age of the test group and smaller tumour sizes. Urinary symptoms were also not included by Goff *et al*. in their index as addition of these symptoms did not result in improved sensitivity of the index.[9] Thus, further research is required to find the significance of this particular symptom cluster before including it among future ovarian cancer symptom indexes.

In the current study, the two new symptoms added—loss of appetite/weight—were found to be significantly present in the test group. Furthermore, when this symptom cluster was included, the sensitivity of the index increased by 5.4% without compromising the specificity of the test. These results suggest that this variable should be added to the original index proposed by Goff *et al*.[9] Although borderline ovarian tumours were excluded from the final analysis, a

subanalysis of this group showed the symptom index to be positive in 11 out of 12 cases (91.6%).

To the best of the authors' knowledge, this is the first study to correlate a symptom index with histological types of ovarian malignancies. The symptom index used in the current study was found to hold well for epithelial cancer and, to some extent, for germ cell tumours. However, the role of this symptom index in detecting sex cord-stromal and Krukenberg tumours was found to be limited. This may be because sex cord-stromal tumours present early due to bleeding and symptoms related to an altered hormonal *milieu*, unlike epithelial ovarian cancers.[16]

Hoskins *et al*. reported that only 15% of women in their study were familiar with the symptoms of ovarian cancer.[17] Creating awareness of these symptoms with an emphasis on the frequency and duration of individual symptoms could influence women to seek healthcare advice earlier, thus minimising diagnostic delays and reducing mortality related to late diagnoses. The early detection of ovarian cancer will be much less difficult when well-informed women work in tandem with clinicians.

The results of the current study should be interpreted in light of some limitations. The population was heterogeneous and included a small number of patients. Additionally, this was a hospital-based study and the results may therefore not be representative of the Indian population in general.

Conclusion

The original GSI was an effective triage tool in the studied cohort of Indian women and the results supported the value of an ovarian cancer symptom index which can be used among women with non-specific symptoms. Furthermore, the addition of two new symptoms (loss of appetite/weight) to the MGSI increased the sensitivity of the test, without diminishing specificity. However, the two urinary symptoms of the MGSI were not found to be an important predictor of ovarian malignancy. Further research is needed to assess the efficacy of including these symptoms in the GSI. Awareness of ovarian cancer symptoms should be promoted among health workers as well as the general population in order to minimise delays in diagnosis and treatment of ovarian cancer.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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