Low surgical Apgar score in older patients with gynecological cancer is a risk factor for postoperative complications and 1-year mortality: A multicenter retrospective cohort study

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Abstract. Little is known about preoperative and intraoperative risk factors for postoperative complications in older patients with gynecological cancer. The present retrospective multi-institutional study included 173 older patients with primary gynecological cancer between January 2015 and December 2015 at four institutions. The cancer stage, medical history, Charlson comorbidity score, body mass index (BMI), subjective global assessment, fall risk assessment, American Society of Anesthesiologists physical status classification, surgical Apgar score (SAS), type of surgery and 1-year postoperative mortality were investigated. Multivariate analysis revealed that BMI and mental illness were risk factors for postoperative complications, and low SAS increased the risk for both postoperative complications and mortality within 1 year. Receiver operating characteristic curve analysis of postoperative complications in terms of SAS revealed that low SAS predicted high risk with a sensitivity of 85.7% and a specificity of 46.5%, and high SAS predicted low risk with a sensitivity of 21.4% and a specificity of 95%. The present results suggest that SAS, which is an intraoperative assessment, may be useful for assessing the risks of postoperative complications and mortality within 1 year. It is important to develop a preoperative assessment tool that can predict a low SAS score and reflect the postoperative prognosis of older patients with gynecological cancer.

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Introduction

In Japan, the elderly comprised 27.7% of the total population in 2017, making it the world's most rapidly aging society. Moreover, 19.89 million women in Japan are aged 65 years or over and account for 30.6% of the female population. By 2040, the elderly populations of other Asian countries such as South Korea, Singapore, and Thailand are predicted to reach levels similar to the current level in Japan (1).

Given this background, gynecologists are expected to treat an increasing number of older patients in the future. Among the elderly, there is wide individual variation in health status, ranging from robust individuals to frail elderly with serious underlying conditions. Frail individuals who develop gynecological cancer are often treated surgically, but postoperative complications may arise and affect their activities of daily living. Greater efforts to reduce such complications are required on the part of gynecologists. However, sufficient evidence supporting the prediction of elderly gynecological patients who are more likely to develop postoperative complications has not yet been obtained.

During assessment of the indications for surgery, gynecologists often rely on ambiguous methodology, thereby risking under- or over-treatment. Preoperative frailty assessments have been useful for predicting postoperative complications, but these have been conducted in a variety of ways and no standard assessment has been established. This multicenter study was conducted to identify the preoperative and intraoperative risk factors for postoperative complications in older patients with gynecological cancer. In this study, we focused on postoperative complications and short-term prognosis.

Materials and methods

Patients. The study subjects included elderly patients aged ≥65 years who were diagnosed with primary gynecological cancer between January 2015 and December 2015 at four Japanese university hospitals located in major cities (Osaka

University Hospital and Yokohama City University Hospital) and in rural areas (Ryukyu University Hospital and Fukui University Hospital). Age, family composition, number of children, type of cancer, cancer stage, medical history, Charlson comorbidity score (CCS), body mass index (BMI), subjective global assessment (SGA), fall risk assessment, American Society of Anesthesiologists physical status classification, surgical Apgar score (SAS), type of surgery, and 1-year postoperative mortality were investigated retrospectively and compared between subjects who did and did not develop complications.

The SAS, which was developed by Gawande *et al* (2) for patients undergoing open colectomy, is an index for assessing a patient's general condition during surgery and has been shown to be useful for predicting complications after general and vascular surgery. Similar to the Apgar score used for neonatal evaluation at birth, the SAS is scored out of 10, with a higher score indicating a better condition. It is very simple to use, and evaluates patients on the basis of the three parameters of estimated blood loss, lowest mean blood pressure, and lowest heart rate. It can be calculated postoperatively from anesthesia records. One tool for assessing the probability of postoperative complications is the web-based National Surgical Quality Improvement Program Surgical Risk Calculator, which was developed by the American College of Surgeons (3) and can show the percentage probability of the occurrence of serious complications for each parameter. Although it has allowed patients to understand the assessment results more easily, it has been reported by some studies to not be particularly well suited to gynecological cancer surgery (4,5).

Family composition was classified as living with others, living alone, or other, such as institutional resident or unknown. The type of cancer was classified as cervical cancer, uterine cancer, uterine sarcoma, ovarian cancer, or vaginal/vulvar cancer. Staging was according to the International Federation of Gynecology and Obstetrics clinical staging system or the surgical staging system (6-8). In the medical history, hypertension was defined as a patient who had undergone medical treatment, excluding cases that were treated only with diet or exercise. Coronary artery disease was defined as a definitive diagnosis obtained by cardiac catheterization or other testing. Arrhythmia was defined as present only if the patient had undergone medical treatment. Heart dysfunction was defined as grade 2 or worse aortic valve insufficiency, aortic stenosis, mitral insufficiency, or tricuspid insufficiency, as confirmed by echocardiography, excluding grade 1 conditions that did not affect daily life. Cerebrovascular disorder was defined as noted in the medical records. Rheumatoid arthritis was defined as treatment with antirheumatic drugs. Mental illness was defined as schizophrenia, major depressive disorder, or a similar disorder that had been diagnosed and treated with oral psychotropic agents, excluding treatment only with sleep medications. Dementia was defined as noted in the patient's medical history, regardless of oral medication intake. Asthma and dyslipidemia were defined as noted in the patient's medical history. Diabetes mellitus was defined as treatment with oral medication or insulin, excluding treatment only with diet or exercise. Osteoporosis was defined as noted in the patient's medical history, based on treatment that had been provided,

or when strongly suspected due to femoral neck fracture or a similar event in the patient's clinical history.

The CCS was formulated as a preoperative comorbidity score in 1987 by Charlson *et al* (9). In the present study, the version revised by Quan *et al* (10) in 2011 was used. The CCS classifies patients according to the weight of 12 different medical conditions, with a higher score indicating more severe comorbidities. The BMI was classified as normal or obese, based on a cutoff value of 25 kg/m^2. Using the malnutrition risk score upon hospital admission, the SGA was scored on a 3-point scale as low (1), moderate (2), or high (3). The postoperative fall risk was assessed using somewhat different criteria among the different institutions, but an assessment that broadly conformed to the Fall Assessment Score Sheet, which was included in the Medical Safety Manual for Healthcare Professionals (11) published by the Japan Medical Association, was used.

As a measure of the patient's general condition during surgery, the SAS was calculated on the basis of estimated blood loss, lowest mean blood pressure, and lowest heart rate. Similar to the neonatal evaluation at birth, it was scored out of 10, with a higher score indicating a better condition (Table I). Receiver operator characteristic (ROC) curve analysis was performed to assess the ability of the SAS to predict postoperative complications in the elderly; the determined SAS cutoff values were used to divide the patients into 3 groups, including high risk (8-10), moderate risk (4-7), and low risk (0-3) for postoperative complications.

Postoperative complications were analyzed using the Clavien-Dindo classification, following the Japan Clinical Oncology Group criteria for postoperative complications (12). Complications were defined as Clavien-Dindo classification grade III or above and requirement for surgical, endoscopic, or interventional radiology treatment or intensive care. Cases that improved with medication alone were excluded.

Statistical analysis. Statistical analysis was performed using Fisher's exact test for comparisons between the 2 groups, and logistic regression analysis was performed for univariate and multivariate analysis. A P-value <0.05 was considered to indicate statistical significance. Sensitivity and specificity were evaluated using ROC curves. All data were analyzed using SPSS version 21 statistical software (IBM Inc., Armonk, NY, USA).

Results

Patients' characteristics. The patients' characteristics are shown in Table II. A total of 173 patients (mean age 72.54 years) were enrolled from the four institutions. Overall, 76.3% of the patients were living with their husband or other family members, and 87.3% had children.

The most common types of cancer were endometrial cancer (46.8%) and ovarian cancer (28.9%), both of which are increasing in Japan. In 62.4% of cases, the cancer was identified as stage I. The medical history of many patients included hypertension (46.2%), dyslipidemia (26.0%), and diabetes (14.5%), all of which are lifestyle diseases. The incidence of dementia was 1.2%, which was significantly lower than the estimated prevalence of 17.9% among Japanese

Table I. Surgical Apgar score.

Variable	Score				
	0	1	2	3	4
Intraoperative estimated amount of bleeding, ml	>1,000	601-1,000	101-600	≤100	
Minimal mean arterial blood pressure, mmHg	<40	40-54	55-69	≥70	
Minimum heart rate, beats/minutes	>85	76-85	66-75	56-65	≤55

Table II. Patient characteristics.

Characteristic	Value
Number	173
Age, years (mean ± SD)	72.54±6.289
Family composition, n (%)	
Living alone	41 (23.7)
Living with others	102 (59.0)
Other	30 (17.3)
Children, n (%)	
No	21 (12.1)
Yes	151 (87.3)
Unknown	1 (0.6)
Cervical cancer, n (%)	16 (9.2)
Endometrial cancer, n (%)	81 (46.8)
Uterine sarcoma, n (%)	12 (6.9)
Ovarian cancer, n (%)	50 (28.9)
Vaginal/vulvar cancer, n (%)	14 (8.1)
Stage, n (%)	
I	108 (62.4)
II	15 (8.7)
III	38 (22.0)
IV	11 (6.4)
Metastatic	1 (0.6)
Surgical procedure, n (%)	
No open surgery	11 (6.4)
Open surgery without retroperitoneal operations	80 (46.2)
Open surgery with retroperitoneal operations	82 (47.4)
G3 or worse complications, n (%)	
No	159 (91.9)
Yes	14 (8.1)
Death within 1 year postoperatively, n (%)	
No	148 (85.5)
Yes	10 (5.8)
Unknown	15 (8.7)

people aged ≥65 years in 2012. This was most likely because of the presence of undiagnosed cases or because surgery was not indicated for patients with dementia. Of those patients who underwent abdominal surgery, the number of cases who underwent retroperitoneal surgery was about the same as the number who did not (46.2 vs. 47.4%). Ten patients (5.8%) who underwent surgery died within 1 year postoperatively.

Postoperative prognosis. Grade 3 or worse postoperative complications occurred in 14 patients (8.1%). There was 1 case of grade 5 complication of postoperative death caused by sepsis. Postoperative death within 1 year was significantly more frequent in patients with postoperative complications than in those without postoperative complications (Table III). Univariate analysis was carried out to investigate the parameters associated with postoperative complications and death within 1 year postoperatively. On univariate analysis (Table IV), BMI, mental illness, and SAS were significantly associated with postoperative complications, whereas cancer stage, CSS, and SAS were significantly associated with death within 1 year postoperatively. Multivariate analysis by logistic regression (Table V) revealed that BMI and mental illness were risk factors for postoperative complications, whereas low SAS increased the risk for both postoperative complications and death within 1 year postoperatively.

Surgical apgar score. The number and percentage of patients in each SAS score are shown in Table VI. ROC analysis of the SAS for postoperative complications showed an area under the curve (AUC) of 0.649 (P=0.016). An SAS of ≤6 points predicted postoperative complications with a sensitivity of 64.3% and specificity of 64.2%. The SAS risk classification predicted high risk with sensitivity of 85.7% and specificity of 46.5% and low risk with sensitivity of 21.4% and specificity of 95% (Fig. 1).

Discussion

In the present study, older gynecological cancer patients with a preoperative history of mental illness, high CCS, obesity, or low intraoperative SAS were found to be more likely to develop postoperative complications, and patients with a low SAS and those who developed postoperative complications were more likely to die within 1 year postoperatively. In particular, low SAS was an independent risk factor not only for the development of postoperative complications, but also for death within 1 year postoperatively.

A previous study reported that the lower the SAS, the higher the probability of major complications or death (2). Subsequently, the SAS was used in a large-scale study (13) and for gynecological surgery (14,15). In a previous single-center study, we found that intraoperative SAS was useful for

Table III. Association between postoperative complications and death within 1 year postoperatively.

G3 or worse postoperative complications	Death within 1 year postoperatively		Total, n	P-value
	No, n	Yes, n		
No	139	7	146	0.030[a]
Yes	9	3	12	
Total	148	10	158	

[a]Fisher's exact test, G3 or worse postoperative complications vs. death within 1 year postoperatively.

Table IV. Univariate analysis.

Variable	Value	G3 or worse complications		Death within 1 year postoperatively	
		P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)
Patient characteristics					
Age, years (mean ± SD)	72.54±6.289	0.91	1.00 (0.91-1.09)	0.24	1.06 (0.96-1.17)
Children, n (%)	21 (12.1)	0.98	1.01 (0.23-15.19)	0.98	0.97 (0.11-8.26)
Obesity (BMI ≥25 kg/m^2)		0.03	3.54 (1.16-10.78)	0.29	0.32 (0.04-2.62)
Living with other family members		0.46	2.53 (0.22-29.29)	0.15	8.75 (0.45-168.60)
Medical history, prevalence (%)					
Hypertension	80 (46.2)	0.40	1.61 (0.54-4.86)	0.39	1.77 (0.478-6.51)
Coronary artery disease	11 (6.4)	>0.99	-	>0.99	-
Arrhythmia	11 (6.4)	>0.99	-	0.47	2.24 (0.248-20.22)
Cardiac dysfunction	12 (6.9)	0.98	1.04 (0.12-8.66)	0.47	2.24 (0.248-20.22)
Cerebrovascular impairment	15 (8.7)	>0.99	-	0.22	2.83 (0.54-14.87)
Rheumatoid arthritis	1 (0.6)	>0.99	-	>0.99	-
Mental illness	5 (2.9)	0.03	8.67 (1.32-56.97)	0.24	4.00 (0.40-39.60)
Dementia	2 (1.2)	>0.99	-	>0.99	-
Asthma	8 (4.6)	0.64	1.67 (0.19-14.64)	>0.99	-
Diabetes	25 (14.5)	0.99	0.99 (0.21-4.69)	0.71	0.67 (0.08-5.58)
Dyslipidemia	45 (26.0)	0.82	1.15 (0.34-3.87)	0.38	1.80 (0.48-6.71)
Osteoporosis	14 (8.1)	0.89	0.86 (0.11-7.14)	>0.99	-
Stage (1 or 2 vs. 3 or 4)		0.24	2.01 (0.69-6.12)	0.01	7.47 (1.83-30.42)
Surgical procedure (retroperitoneal operations)		0.73	0.86 (0.35-2.07)	0.12	0.70 (0.26-1.87)
Assessment score, mean ± SD					
CCS sore	2.54±1.45	0.40	1.14 (0.84-1.54)	0.01	1.43 (1.10-1.86)
SGA score	1.10±0.40	0.22	2.14 (0.63-7.25)	0.07	0.29 (0.93-12.53)
Fall risk assessment	1.61±0.56	0.08	0.37 (0.13-1.12)	0.06	0.27 (0.07-1.07)
ASA preoperative risk assessment	1.88±0.53	0.84	0.90 (0.32-2.54)	0.16	2.39 (0.71-8.07)
SAS score	6.83±1.96	0.02	0.72 (0.55-0.94)	0.01	0.64 (0.46-0.89)

BMI, body mass index; CSS, Charlson comorbidity score; SGA, Subjective Global Assessment; ASA, American Society of Anesthesiologists; SAS, surgical Apgar score; SD, standard deviation; CI, confidence interval.

predicting postoperative complications in gynecological patients, including those without cancer (16). Moreover, the World Health Organization recommended the use of the SAS for safe surgery guidelines in the World Alliance for Patient Safety documents (17). The SAS cannot be used to assess the capability of patients to withstand surgery, because it is based on intraoperative data; however, it may be helpful in determining the requirement for postoperative intensive care. Based on our ROC analysis, high-risk patients had a high probability of requiring treatment for postoperative complications,

Table V. Multivariate analysis using logistic regression analysis.

	G3 or worse complications		Death within 1 year postoperatively	
Variable	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)
SAS score	0.04	0.74 (0.55-0.99)	0.05	0.69 (0.47-0.99)
Obesity (BMI ≥25 kg/m^2)	0.02	4.35 (1.27-14.88)	0.56	0.52 (0.06-4.68)
CCS score	0.87	1.03 (0.72-1.48)	0.23	1.21 (0.89-1.66)
Mental illness	0.02	11.68 (1.43-95.48)	0.47	2.96 (0.16-55.88)
Stage 1 or 2 vs. 3 or 4	0.45	1.69 (0.43-6.64)	0.11	3.65 (0.75-17.76)

SAS, surgical Apgar score; BMI, body mass index; CSS, Charlson comorbidity score.

Table VI. Number and percentage of patients with each SAS.

SAS score	Number	Percentage
1	1	0.6
2	3	1.7
3	7	4.0
4	14	8.1
5	19	11.0
6	22	12.7
7	31	17.9
8	36	20.8
9	35	20.2
10	5	2.9

SAS, surgical Apgar score.

Figure 1. Receiver operating characteristic curve analysis of the surgical Apgar score for postoperative complications (area under the curve, 0.694; P=0.016). The cut-off points are shown for the high- and moderate-risk groups (arrowhead) and for the moderate- and low-risk groups (arrow).

whereas low-risk patients had >95% probability of not developing postoperative complications. Although the present study did not distinguish between open and laparoscopic surgery, it is important to note that SAS was originally developed for use in open surgery. Moreover, attempts have been made to determine the utility of the SAS for predicting perioperative complications during robotic-assisted radical hysterectomy, in which blood loss is low (18). Especially in endometrial cancer, the usefulness of minimally invasive surgery in the elderly has been reported (19,20), and it is necessary to examine the usefulness of SAS in minimally invasive surgery in the future.

In the present study, history of mental illness, obesity, and low SAS were all risk factors for developing postoperative complications. Even a serious mental illness may not always be detected on standard preoperative tests, such as blood tests, urinalysis, electrocardiography, and plain radiography. Therefore, clinicians are likely to be unaware that such patients are at high risk. However, patients with psychiatric disorders tend to complain less actively about their symptoms because of the nature of their illness. Furthermore, the analgesic and sedative effects of psychotropic medications may have led these patients to have higher pain thresholds and to be less aware of postoperative abnormalities. In fact, around half of patients who were less likely to seek medical attention were reported to have physical disorders, and many cases were not
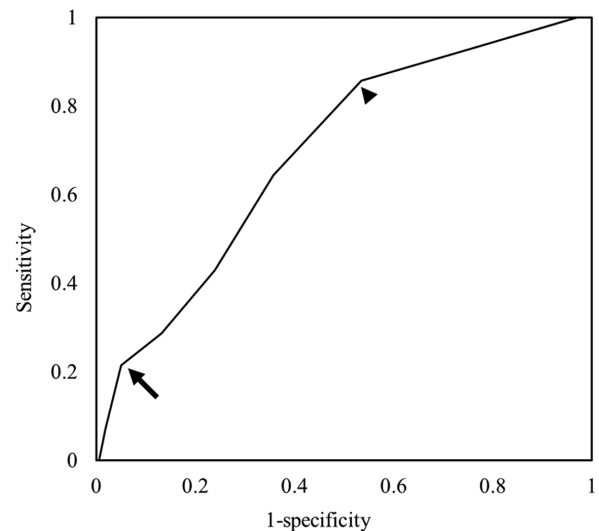
correctly diagnosed (21). Patients on psychotropic medications were reported to have a high risk for venous thromboembolism (VTE) (22,23), and those with schizophrenia were known to have an increased risk for not only VTE, but also respiratory failure (24). In a pooled analysis of 3 GINECO phase 2 trials by Tinquaut et al (25), depression and the Hospital Anxiety and Depression Scale score were associated with survival. In the present study, although mental illness was not found to have a direct association with death within 1 year postoperatively, it increased the risk for postoperative complications. These results suggest that the presence of mental illness in older patients with a gynecological malignancy may be associated with resistance to treatment. It is important to note that the present study defined postoperative complications as those with grade III or higher Clavien-Dindo classification, thereby excluding medically treated postoperative complications such as delirium. Therefore, the incidence of complications in patients with mental illness may have been underestimated. Clinicians should manage such patients with greater caution. To the best of our knowledge, no study has identified the association of postoperative complications with widely

used antidepressants, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or noradrenergic and specific serotonergic antidepressants. This is an important topic for future research.

As previously mentioned, the present study showed that patients with low SAS and those who developed postoperative complications were more likely to die within 1 year postoperatively. However, the direct causality between postoperative complications and increased risk for death, as well as the possible confounding effect of a poor general condition on death within 1 year as a result of postoperative complications, was unclear. Nevertheless, because our analysis showed that SAS was an independent risk factor for death within 1 year postoperatively, patients with low SAS scores may require careful postoperative follow-up. Of the 3 patients who developed postoperative complications and died within 1 year, 1 patient was classified as CCS 2, SAS 3, and did not have a mental illness; 1 patient was CCS 2, SAS 4, and did not have a mental illness; and 1 patient was CCS 9, SAS 5, and had a mental illness.

Based on our results, SAS may be useful for assessing the risks for postoperative complications and death within 1 year postoperatively. In the present study, the only predictor of death within 1 year postoperatively was the SAS score, which is an intraoperative assessment, and no preoperative predictive factor was identified. The Vulnerable Elders Survey-13 (VE-13) has been shown to be useful for pre-chemotherapy assessment (26), but other studies have found that the preoperative Comprehensive Geriatric Assessment and GA-GYN scores were not predictive of postoperative outcomes (27,28). Therefore, a preoperative risk assessment score for the treatment of older patients with gynecological cancer has yet to be established. New preoperative assessment tools that can anticipate low SAS scores and reflect the postoperative prognosis of older gynecologic patients must be addressed and developed.

This study had a number of limitations. First, this study did not collect data on postoperative treatment. However, this study analyzes the short-term prognosis of one year, and we believe that the impact of the choice of postoperative treatment on the prognosis is limited. Although this was a multicenter analysis, it included only 173 patients from four hospitals. More gynecological institutions in Japan need to take part in clinical studies. In addition, alternative questions were used in the survey about postoperative complications. Therefore, in the 14 patients who developed postoperative complications, the detailed breakdown of conditions, such as infection, ileus, and thrombosis, was unknown. With the expected rise in the number of older patients who require treatment for gynecological cancer, the effects of newer psychotropic medications and the increasing use of laparoscopic surgery necessitate further study.

In conclusion, the SAS may be useful for assessing the risks of postoperative complications and death within 1 year postoperatively. It is important to develop a preoperative assessment tool that can predict a low SAS score and reflect the postoperative prognosis of older gynecological cancer patients.

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Availability of data and materials

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

Authors' contributions

KK, MY, and YY wrote the manuscript. KK, MY, MAS, MS, YU, YA and YY collected and analyzed data, and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was reviewed and approved by the institutional review boards of University of Fukui, Yokohama City University Graduate School of Medicine, Osaka University Graduate School of Medicine and University of the Ryukyus before the start of the present study. Informed consent was obtained in the form of an opt-out option on the website.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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