

Predictive Value of the Surgical Apgar Score on Postoperative Complications in Advanced Gastric Cancer Patients Treated with Neoadjuvant Chemotherapy Followed by Radical Gastrectomy: A Single Center Retrospective Study

Masato Hayashi

National Cancer Center Hospital <https://orcid.org/0000-0003-2437-056X>

Takaki Yoshikawa (✉ tayoshik@ncc.go.jp)

Masahiro Yura

National Cancer Center Hospital

Sho Otsuki

National Cancer Center Hospital

Yukinori Yamagata

National Cancer Center Hospital

Shinji Morita

National Cancer Center Hospital

Hitoshi Katai

National Cancer Center Hospital

Toshirou Nishida

National Cancer Center Hospital

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Abstract

Background: The surgical Apgar score (SAS) or modified SAS (mSAS) has been reported as a simple and easy risk assessment system to predict postoperative complications (PCs) in primary surgery for gastric cancer (GC). However, there are still few studies which revealed the SAS's utility in gastric surgery after neoadjuvant chemotherapy (NAC).

Methods: One hundred and fifteen patients who received NAC and R0 gastrectomy from 2008 and 2015 were included in this study. The SAS was determined by estimated blood loss (EBL), lowest intraoperative mean arterial pressure (LMAP), and lowest heart rate (LHR). The mSAS was determined by the EBL reassessed using the interquartile values. The predictive values of the SAS/mSAS for PCs were assessed with uni and multivariate analyses.

Results: Among 115 patients, 41 (35.7%) developed PCs. According to analyses with receiver operating characteristic (ROC) curve of the SAS and mSAS for predicting PCs, the cutoff value of the mSAS was set at 8. The rates of anastomotic leakage, pancreatic fistula, and arrhythmia in patients with high mSAS (>8) values were higher, compared to those with low (0-3) and moderate (4-7) mSAS values. A multiple logistic regression analysis detected operation time, Body Mass Index (BMI), and Diabetes Mellitus (DM) were independent risk factors for PCs. The mSAS was not a significant predictor.

Conclusions: Neither the SAS nor mSAS was a useful predictor of PCs in patients treated with NAC followed by radical gastrectomy. The predictive value of SAS/mSAS is limited in patients undergoing surgery after NAC.

Introduction

Gastrectomy with lymphadenectomy is a core treatment strategy to cure gastric cancer (GC) (1). Although several chemotherapy regimens, such as adjuvant chemotherapy or palliative chemotherapy, have been shown to be effective (2, 3), the prognosis of advanced GC is still unsatisfactory (4). In such situation, neoadjuvant chemotherapy (NAC) may be another attractive treatment to improve the patient's prognosis with advanced disease (5–7); however, surgery after NAC is associated with technical difficulties due to fibrosis induced by chemotherapy, which may cause morbidity. Because surgical complications can not only induce mortality but also decrease a patient's quality of life, the prediction of morbidity is quite important.

Previously, the surgical Apgar score (SAS) was reported as an easy and simple predictor of PCs in various operations, including gastrectomy (8–11). SAS is determined by the following intraoperative factors: estimated blood loss (EBL), lowest intraoperative mean arterial pressure (LMAP), and lowest heart rate (LHR). Moreover, the modified SAS (mSAS) using a cut off value of EBL has previously been proposed in assessing the PC risk in several types of surgery as well (12–15). However, previous studies investigating the SAS or mSAS only examined GC patients received primary surgery with or without adjuvant

chemotherapy. It still remains unclear whether the SAS or mSAS could be a sensitive predictor for GC patients undergoing surgery after NAC.

The aim of this present study was to investigate the utility of the SAS and mSAS in predicting morbidity of advanced GC patients treated with NAC and gastrectomy.

Methods

Participants

The medical records of patients at National Cancer Center Hospital, Tokyo, Japan, were retrospectively reviewed to select advanced GC patients who were treated with NAC and radical gastrectomy from January 2008 to December 2015. The inclusion criteria were (1) gastric adenocarcinoma without previous treatment, (2) the adenocarcinoma was histologically proved, (3) the patients received NAC and radical as a treatment. R1 or R2 resection cases were excluded from this study. R1 / R2 were defined as microscopic / macroscopic residual tumor (positive resection margin or CY1) following the Japanese Gastric Cancer Association Classification, respectively. (16).

Although NAC has not been a standard treatment strategy yet in Japan, the regimens of NAC were basically determined from the following clinical trials; (1) large type 3 or type 4 GC was treated according to the protocol of JCOG0501; (2) cT3/cT4 with any N, the protocol of the in-house study of S-1 and Oxaliplatin; and (3) para-aortic lymph node swelling or extensive nodal swelling along the major branched arteries (bulky-N), the protocol of JCOG0405 or JCOG1002.

Following the protocol of JCOG 0405 and JCOG1002, gastrectomy with D2 plus para-aortic nodal dissection was performed. And other trials needed D2 lymphadenectomy. The histological tumor regression of primary tumor was evaluated with the Japanese Classification of Gastric Carcinoma (JCGC) (17).

The definitions of SAS and mSAS

The SAS was calculated by the following three intraoperative factors: EBL, LMAP, and LHR (Table 1A) (8). The score is calculated from the total points of each category. We also calculated the mSAS in accordance with the method of Miki et al. (12). In the mSAS, the EBL cutoff value was determined based on its quartile values of the included patients. The median EBL was 519 ml, the 25th percentile was 305 ml, and the 75th percentile was 960 ml (Table 1B).

The Evaluation of Complication Severity

PC was defined as any morbidity occurring within 30 days after surgery. The severity was graded by using the Clavien-Dindo Classification (18, 19). In this study, only grade \geq IIIa complications were defined as PC.

Statistical Analyses

The SPSS software (IBM, Armonk, NY, USA, 25.0 version) was used in all analyses of this study. A nonparametric test (Mann-Whitney U test) was performed for continuous values, whilst, Pearson's chi-squared test or Fisher's exact test were for categorical values. A multiple logistic regression analysis with binary logistic regression was performed to determine the correlation between PCs and selected perioperative factors in patients who were treated with NAC and radical gastrectomy. Analyses with receiver operating characteristic (ROC) were performed to evaluate the utility of the SAS and mSAS in predicting PCs and to determine the optimum cutoff values of the scores. P values of < 0.05 were recognized statistically significant in 2 tailed statistical test.

Results

Postoperative Complications

One hundred twenty patients were treated with NAC follow by radical gastrectomy. Four patients were excluded due to R1 resection and 1 patient was excluded due to adenosquamous carcinoma. This study included 115 patients. Among them, 41 patients (35.7%) developed surgical morbidity and 74 (64.3%) did not. As for the incidence of PCs, it was 47 (40.9%). The most frequent morbidity was pancreatic fistula ($n = 21, 18.3\%$) followed by anastomotic leakage and bleeding ($n = 4, 3.5\%$ for each). The detail is shown in Table 2.

Determination of cutoff values for predicting postoperative complication using receiver operating characteristic curves

Figure 1 shows the ROC curves of the SAS and mSAS for predicting postoperative complications. Because the AUC of the mSAS was higher than that of the SAS, a further prediction analysis was done using the mSAS. And mSAS of 8 was set at the cutoff for high risk based on the curve for predicting complications in this population (Sensitivity: 0.85, 1-Specificity: 0.65).

Clinicopathological features of this population

Table 3 shows the clinicopathological features of this population between low mSAS (< 8) and high mSAS (≥ 8). It showed that low mSAS group included greater proportions of patients with PCs, male patients, smokers, high body mass index (BMI), total gastrectomy, and D3 lymphadenectomy. Furthermore, the body mass index (BMI), operation time, and EBL in the low mSAS group were significantly greater than those in high mSAS group. There were no significant differences in any other factors.

Table 1A
Surgical Apgar Score (SAS)

	0 point	1 point	2 points	3 points	4 points
Estimated blood loss (mL)	> 1000	601-1000	101-600	≤ 100	-
Lowest mean arterial pressure (mmHg)	< 40	40-54	55-69	≥ 70	-
Lowest heart rate (beats/min)	> 85	76-85	66-75	56-65	≤ 55

Surgical Apgar score was calculated with sum of the points for each category in the course of the procedure

Table 1B
modified Surgical Apgar Score (mSAS)

	0 point	1 point	2 points	3 points	4 points
Estimated blood loss (mL)	> 960	519-960	305-518	≤ 304	-
Lowest mean arterial pressure (mmHg)	< 40	40-54	55-69	≥ 70	-
Lowest heart rate (beats/min)	> 85	76-85	66-75	56-65	≤ 55

modified Surgical Apgar Score was calculated with sum of the points as well

Table 2
Details of Postoperative Complications

Complications	Grade according to Clavien Dindo Classification					Total (%)
	IIIa	IIIb	IVa	IVb	V	
Pancreatic fistula	21	0	0	0	0	21 (18.3%)
Anastomitic leakage	2	2	0	0	0	4 (3.5%)
Abdominal abscess	3	0	0	0	0	3 (2.6%)
Duodenal stump fistula	1	1	0	0	1	3 (2.6%)
Pneumonia	1	0	0	0	0	1 (0.9%)
Bleeding	3	1	0	0	0	4 (3.5%)
Lymph fistula	1	0	0	0	0	1 (0.9%)
Acute kidney failure	0	0	1	0	0	1 (0.9%)
Arrhythmia	0	0	1	0	0	1 (0.9%)
Others	7	1	0	0	0	8 (7.0%)
Total	39	5	2	0	1	47 (40.9%)

Table 3
Patients and clinicopathological features between low and high mSAS

Variables	All patients N=115	low mSAS < 8 83 (72.2%)	high mSAS ≥ 8 32 (27.8%)	p value
Age (yr)	63.3 (±10.8)	63.2 (±10.8)	63.8 (±10.9)	0.736
Gender				0.044
Male	81 (70.4%)	63 (75.9%)	18 (56.3%)	
Female	34 (29.6%)	20 (24.1%)	14 (43.8%)	
Body Mass Index (BMI)	22.3 (±3.3)	22.7 (±3.6)	21.1 (±2.8)	0.027
BMI ≥ 22	60 (52.2%)	46 (55.4%)	14 (43.8%)	0.001
Diabetes Mellitus	9 (7.8%)	7 (8.4%)	2 (6.3%)	1
Smoking history	73 (63.5%)	58 (69.9%)	15 (46.9%)	0.030
ASA-PS				0.703
1	11 (9.6%)	7 (8.4%)	4 (12.5%)	
2	94 (81.7%)	68 (81.9%)	26 (81.3%)	
3	10 (8.7%)	8 (9.6)	2 (6.3%)	
Tumor location ^a				0.097
Upper	46 (40%)	38 (45.8%)	8 (25.0%)	
Middle	39 (33.9%)	26 (31.3%)	13 (40.6%)	
Lower	20 (17.4%)	11 (13.3%)	9 (28.1%)	
Whole	10 (8.7%)	8 (9.6%)	2 (6.3%)	
ycStage				0.302
I	3 (2.6%)	3 (3.6%)	0	
II	47 (40.9%)	31 (37.3%)	16 (50.0%)	
III	65 (56.5%)	49 (59.0%)	16 (50.0%)	
NAC regimen				0.057
S-1 and cisplatin	74 (64.3%)	51 (61.4%)	23 (71.9%)	
S-1 and oxaliplatin	14 (12.2%)	8 (9.6%)	6 (18.8%)	
S-1, docetaxel and cisplatin	13 (11.3%)	10 (12.0%)	3 (9.4%)	
Others	14 (12.2%)	14 (16.9%)	0	
Surgical Procedure				0.001
Distal gastrectomy	29 (25.2%)	13 (15.7%)	16 (50.0%)	
Total gastrectomy	83 (72.3%)	68 (81.9%)	15 (46.9%)	

Other	3 (2.6%)	2 (2.4%)	1 (3.1%)	
Operation time (min)	337.1 (±111.1)	365.6 (±113.5)	263.4 (±59.8)	0.001
Surgical Apgar score	6.25 (±1.1)	5.77 (±1.2)	7.50 (±0.67)	0.001
modified Surgical Apgar Score	6.34 (±1.5)	5.65 (±1.2)	8.16 (±0.46)	0.001
Estimated blood loss (ml)	711.5 (±627.0)	898.1 (±644.3)	227.6 (±112.9)	0.001
Lowest mean arterial pressure	55.6 (±6.6)	54.8 (±6.5)	57.6 (±6.4)	0.034
Lowest heart rate	58.7 (±8.4)	59.8 (±8.8)	56.0 (±6.7)	0.034
Extent of lymphadenectomy				0.023
D2	48 (41.7%)	31 (37.3%)	17 (53.1%)	
D2+	40 (34.8%)	27 (32.5%)	13 (40.6%)	
D3	27 (23.5%)	25 (30.1%)	2 (6.3%)	
ypT ^a factor				0.346
0	4 (3.5%)	3 (3.6%)	1 (3.1%)	
T1a	1 (0.9%)	1 (1.2%)	0	
T1b	13 (11.3%)	10 (12.0%)	3 (9.4%)	
T2	17 (14.8%)	15 (18.1%)	10 (31.3%)	
T3	51 (44.3%)	36 (43.4%)	15 (46.9%)	
T4a	25 (21.7%)	15 (18.1%)	10 (31.3%)	
T4b	4 (3.5%)	3 (3.6%)	1 (3.1%)	
ypN ^a factor				0.781
0	39 (33.9%)	30 (36.1%)	9 (28.1%)	
1	24 (20.9%)	18 (21.7%)	6 (18.8%)	
2	26 (22.6%)	19 (22.9%)	7 (21.9%)	
3	26 (22.6%)	16 (19.3%)	10 (31.3%)	
M factor				0.725
0	104 (90.4%)	74 (89.2%)	30 (93.8%)	
1	11 (9.6%)	9 (10.8%)	2 (6.3%)	
ypStage ^a				0.392
0	3 (2.6%)	3 (3.6%)	0	
I	19 (16.5%)	16 (19.3%)	3 (9.4%)	

II	37 (32.3%)	25 (30.1%)	12 (37.5%)	
III	45 (39.1%)	30 (36.1%)	15 (46.9%)	
IV	11 (9.6%)	9 (10.8%)	2 (6.3%)	
PC ≥ IIIa	41 (35.7%)	35 (42.2%)	6 (18.8%)	0.029
Histological response of primary lesion				0.673
0	2 (1.7%)	2 (2.4%)	0	
1a	33 (28.7%)	24 (28.9%)	9 (28.1%)	
1b	30 (26.1%)	22 (26.5%)	8 (25.0%)	
2	47 (40.9%)	32 (38.6%)	15 (46.9%)	
3	3 (2.6%)	3 (3.6%)	0	

^aAccording to the seventh edition of the International Union Against Cancer tumor, node, metastasis (TNM) classification system

Table 4 shows the risk stratification of complications according to the mSAS, which was divided into 3 categories: low mSAS, 0–3; moderate mSAS, 4–7; high mSAS, 8–10. The risk of complication in the high mSAS group was significantly lower than that in the low mSAS group. The rates of pancreatic fistula, anastomotic leakage, and arrhythmia in the low mSAS group were significantly higher than those in the moderate and high mSAS groups (Pancreatic fistula in the low/moderate/high mSAS: 2 (50%)/17 (21.5%)/2 (6.3%), $p = 0.042$; anastomotic leakage: 1 (25%)/3 (3.8%)/0 (0%), $p = 0.035$; arrhythmia: 1 (25%)/0 (0%)/0 (0%), $p < 0.001$).

The logistic regression analysis of factors associated with postoperative complications

Table 5 shows univariate analysis and multiple logistic regression analysis for PCs. The univariate analysis revealed significant differences in gender, BMI, DM, smoking history, ycStage, operation time, EBL and mSAS. Except for EBL, these factors were included as covariates in a multiple logistic regression analysis of factors predicting complications. EBL was excluded from this analysis because it was an apparent confounding factor for the mSAS. In the multiple logistic regression analysis, BMI, DM and operation time were detected as independent risk factors for PCs. The mSAS was not identified as an independent predictor for PCs.

Table 4
Risk stratification of complication according to mSAS

	with complications N= 41 (35.7%)	without complications N= 74 (64.3%)	OR (95% CI)	p value
mSAS 0-3	3 (7.3%)	1 (1.4%)	1	
mSAS 4-7	32 (78.0%)	47 (63.5%)	0.23 (0.023-2.280)	0.208
mSAS 8-10	6 (14.6%)	26 (35.1%)	0.08 (0.007-0.875)	0.039

Table 5
univariate analysis and multiple logistic regression analysis for postoperative complications

Variables	univariate analysis			multiple logistic regression analysis		
	with complications N= 41 (35.7%)	without complications N= 74 (64.3%)	p value	OR	95% CI	p value
Gender			0.034			
Male	34 (82.9%)	47 (63.5%)		0.85	0.24-3.02	0.82
Female	7 (17.1%)	27 (36.5%)				
Body Mass Index (BMI)	24.4 (±3.2)	21.1 (±2.7)	< 0.001	3.74	1.33-10.51	0.012
Diabetes Mellitus	7 (17.1%)	2 (2.7%)	0.010	13.5	2.00-91.0	0.008
Smoking history	32 (78.0%)	41 (55.4%)	0.017	2.39	0.74-7.70	0.145
ycStage			0.020			
I	0 (0%)	3 (4.1%)		1.69	0.62-4.57	0.303
II	11 (26.8%)	36 (48.6%)				
III	30 (73.2%)	35 (47.3%)				
Operation time (min)	395.7 (±138.3)	304.7 (±76.2)	< 0.001	4.07	1.36-12.12	0.012
modified Surgical Apgar Score	5.88 (±1.6)	6.61 (±1.4)	0.018	0.9	0.63-1.27	0.54
Estimated blood loss (ml)	899.7 (±788.1)	607.2 (±492.7)	0.011	-	-	-
Lowest mean arterial pressure	56.2 (±6.4)	55.3 (±6.7)	0.057	-	-	-
Lowest heart rate	60.7 (±8.2)	57.6 (±8.4)	0.492	-	-	-

^aAccording to the seventh edition of the International Union Against Cancer tumor, node, metastasis (TNM) classification system

The analysis of confounding factors for the mSAS

Factors that were thought to affect the surgical outcome and mSAS, namely confounding factors for the mSAS, were focused on. The low mSAS group included significantly greater proportions of patients with high BMI and longer operation time than the high mSAS group. The proportion of patients with DM did not show the difference. (Table 3)

Discussion

The present study examined the predictive value of the SAS and mSAS for surgical complications in patients treated with NAC followed by radical gastrectomy. In the univariate analysis, no significant difference was observed in the SAS, but the mSAS, between patients with and without complications. The risk of complications was increased as the mSAS decreased. However, the mSAS was not an independent predictor of morbidity. As long as we know, this present study is the first report to evaluate the correlation between the SAS and complications in patients treated with NAC followed by radical gastrectomy.

Thus far, some previous studies have demonstrated the SAS's utility in predicting complications (9, 10, 20), other studies reported the usefulness of the mSAS but not the SAS (12, 14, 15). The utility of the SAS seems to depend on the type of surgery or the characteristics of the cohort. We considered the reasons why the SAS and mSAS were not risk factors for complications in the present study. In this study, high BMI, DM, and long operation time were identified as independent risk factors for PCs. In the low mSAS group, the proportions of patients with high BMI and a long operation time were higher in comparison to the high mSAS group, suggesting that these factors were confounders of the mSAS. These results suggested that patients with a high BMI or longer operation time easily develop surgical morbidities and that the predictive value of the mSAS was inferior to high BMI or a long operation time.

Anesthesia may have also influenced the results. LHR and LMAP, which are included in the SAS and mSAS, can easily be affected by anesthesia. Deep anesthesia can reduce arterial pressure without any bleeding. The use of high doses of opioids could prevent an increase in the heart rate caused by bleeding or dehydration. Theoretically, the mSAS should be evaluated with the same conditions of anesthesia. Unfortunately, anesthesia in our institution was managed by several doctors with different policies during the study period. The lack of statistical significance of the SAS and mSAS in predicting complications might have been influenced by these different managements.

This present study and the previous study by Miki et al. (12), reported that the mSAS significant predicted morbidity in patients undergoing primary surgery have some differences. First, the EBL of our population was much higher than that of their population. This could be explained by surgical difficulties, such as fibrosis induced by NAC or extensive lymphadenectomy, which was selected in more than half of the present cohort. These differences of the study population might lead to different result from the previous study. Second, our cutoff value of mSAS was much higher than the previous report, even though our EBL was higher. This might have been due to the very high incidence of complications in the present population. This point might be another reason to make discrepancy between our study and the previous one as well.

In this study, high BMI, DM, and long operation time were detected as risk predictor for PCs in patients treated with NAC. These factors are well known predictors of complications in primary surgery (21–24). High BMI is closely related to excessive visceral fat which may cause extend the operation time and impair lymph node dissection (25, 26), increasing the difficulty of the whole operation. Excessive visceral fat easily induces metabolic syndrome, including DM, which makes patients more susceptible to infection

and which can inhibit wound healing. And long operation time has been reportedly to be a risk factor of PCs, accelerating the speed of body metabolism and increasing the consumption of nutrition(24). These factors would not be changed after NAC.

This study included some limitations to be noted. First, this present study was a retrospective, single-center study. Although this study population was mostly limited to patients in prospective clinical trials, the possibility of several biases was not completely excluded. A prospective study with a large sample size is needed to confirm our results. Second, the sample size was small, therefore the predictive value of the mSAS might have been underestimated in this study.

In conclusion, this study could not show the utility of the SAS or the mSAS in predicting postoperative complications in patients who were treated with NAC followed by radical gastrectomy. The predictive value of SAS or mSAS for morbidity is limited in patients who undergo gastric cancer surgery after NAC.

Abbreviations

SAS:Surgical Apgar Score; mSAS:modified SAS; NAC:neoadjuvant chemotherapy; GC:Gastric Cancer; PC:Postoperative Complication; EBL:Estimated Blood Loss; LMAP:Lowest Mean Arterial Pressure; LHR; Lowest Heart Rate; ROC:Receiver Operating Curve; JCGC:Japanese Classification of Gastric Carcinoma; DM; Diabetes Mellitus; BMI:Body Mass Index.

Declarations

Availability of data and materials

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

Ethics Approval And Consent To Participate

This present study conforms to the Declaration of Helsinki. And it was approved by the Institutional Review Board (IRB) of the National Cancer Center Hospital (No: 2017-077).

Competing Interests

There is no competing interest.

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Authors' contributions

Masato Hayashi and Takaki Yoshikawa designed the study. And Masato Hayashi is a first author of this manuscript. Takaki Yoshikawa also checked the manuscript and advised the first author in the preparation of the manuscript. All other authors contributed to collection of data. Authors give approval of the version to be submitted and any revised version.

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Figures

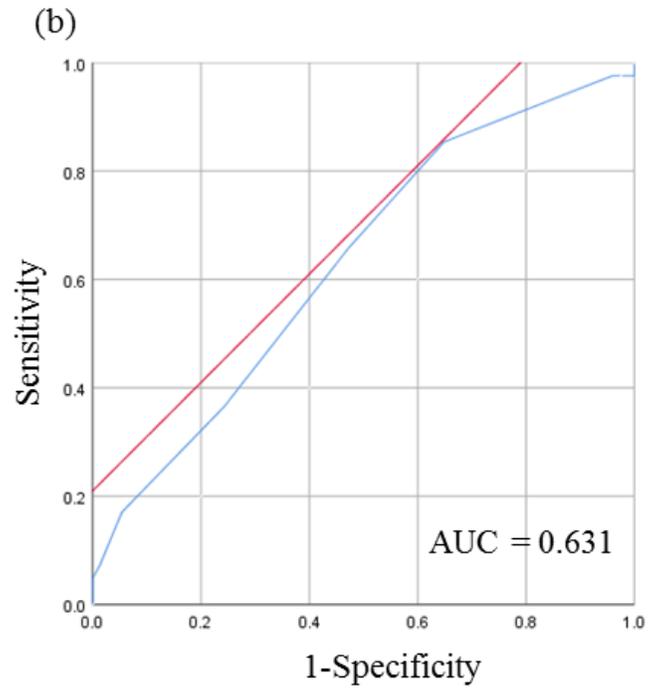
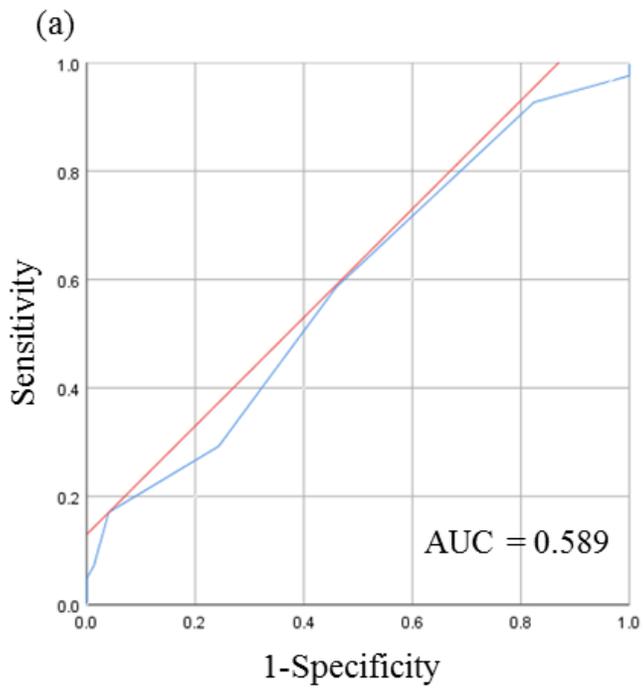


Figure 1

Receiver operating characteristic curves for the prediction of postoperative complications by (a) the SAS and (b) the mSAS. SAS, Surgical Apgar Score; AUC, Area Under the Curve.