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# Utility of the surgical Apgar score for predicting the short- and long-term outcomes in non-small-cell lung cancer patients who undergo surgery

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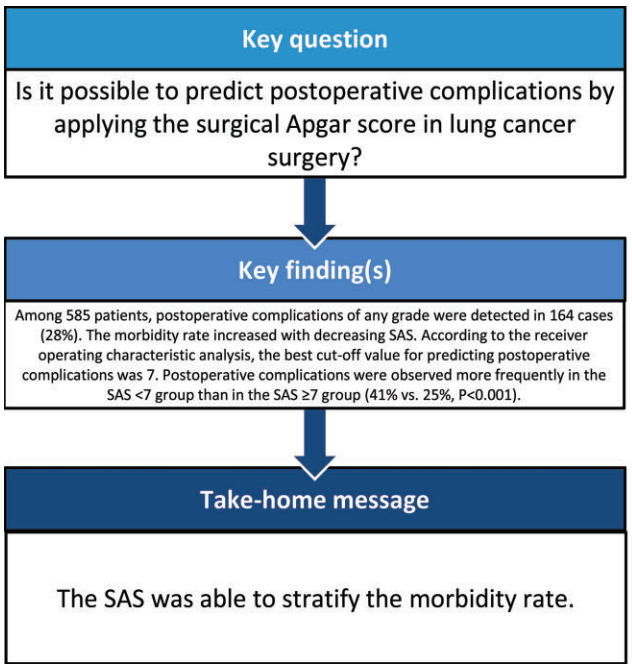


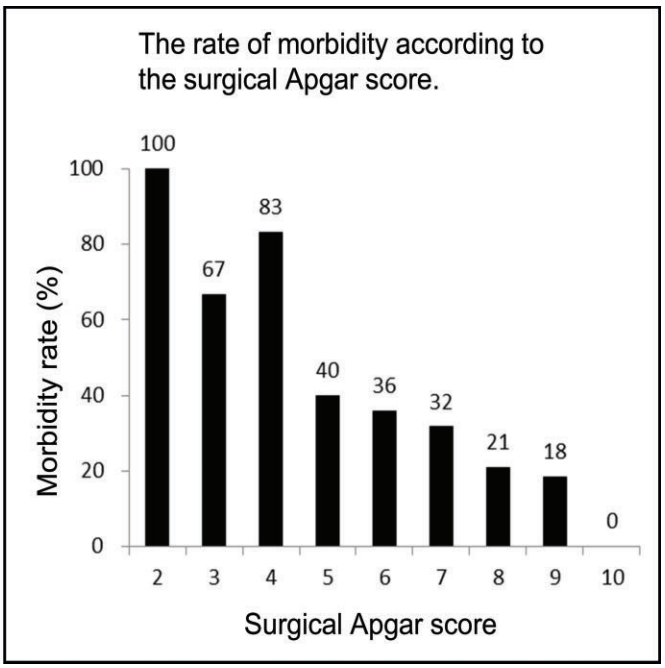


## Abstract

**OBJECTIVES:** The surgical Apgar score (SAS) is a simple score that predicts postoperative complications based on 3 intraoperative valuables. The present study evaluated the association between the SAS and postoperative outcomes in non-small-cell lung cancer patients who underwent surgery.

**METHODS:** A total of 585 patients who underwent lung resection were enrolled in the present study. We calculated the SAS of each patient and investigated its influence on the short- and long-term outcomes.

**RESULTS:** Postoperative complications of any grade were detected in 164 cases (28%). The morbidity rate increased with decreasing SAS. When all the patients were divided into 2 groups (SAS <7 vs ≥7), postoperative complications were observed more frequently in the SAS <7

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group than in the SAS ≥7 group (41% vs 25%, $P < 0.001$). In the multivariate analysis, the SAS was an independent risk factor for postoperative complications (odds ratio: 1.64 [1.03–2.61], $P = 0.036$). In terms of long-term outcomes, the 5-year disease-free survival (54.1% vs 73.2%, $P < 0.001$) and overall survival (73.8% vs 83.0%, $P = 0.031$) were significantly worse in the SAS <7 group than in the SAS ≥7 group. In a multivariate analysis, however, the SAS was not found to be an independent prognostic factor for either disease-free survival (hazard ratio: 1.39 [0.97–2.00], $P = 0.075$) or overall survival (hazard ratio: 0.90 [0.57–1.42], $P = 0.642$).

**CONCLUSIONS:** The SAS reflected preoperative and intraoperative characteristics and was able to stratify the morbidity rate, suggesting it to be a useful predictor of short-term outcomes in non-small-cell lung cancer patients who undergo surgery.

**Keywords:** Surgical Apgar score • Non-small-cell lung cancer • Postoperative complications

**ABBREVIATIONS**

| | |
|---|---|
| ACT | Adjuvant chemotherapy |
| ASA-PS | American Society of Anesthesiologists physical status |
| CEA | Carcinoembryonic antigen |
| DFS | Disease-free survival |
| EBL | Estimated blood loss |
| HR | Heart rate |
| MAP | Mean arterial blood pressure |
| NSCLC | Non-small-cell lung cancer |
| OS | Overall survival |
| RATS | Robot-assisted thoracic surgery |
| ROC | Receiver operating characteristic |
| SAS | Surgical Apgar score |
| VATS | Video-assisted thoracic surgery |

## INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide [1]. Although surgery has been the first-line treatment for patients with resectable non-small-cell lung cancer (NSCLC), some suffer from postoperative complications. Therefore, risk assessment tools are crucial for improving the postoperative management and outcomes.

Thus far, a number of risk prediction models have been developed [2, 3]. However, most of them evaluate outcomes based on only preoperative characteristics. Accordingly, these models do not account for the influence of intraoperative characteristics [4]. In this context, a risk assessment tool that accounts for intraoperative characteristics as well as preoperative characteristics of patients is needed.

The surgical Apgar score (SAS) is a simple score that was proposed in 2007 to predict postoperative complications or death [5]. Similar to the original Apgar score used in obstetrics, the SAS is a 10-point scoring system, with low scores associated with worse outcomes. The SAS was expected to be used immediately after surgery and calculated by the summation of 3 intraoperative valuables: lowest heart rate (HR), lowest mean arterial blood pressure (MAP) and estimated blood loss (EBL). Although some reports investigated the association between the SAS and postoperative outcomes in the field of thoracic surgery [6, 7], its significance in patients with resectable NSCLC is unknown.

In the present study, we retrospectively evaluated the relationship between the SAS and the short- and long-term outcomes in NSCLC patients who underwent surgery.

## METHODS

### Ethical statement

The study protocol was approved by the Ethics Review Board for Clinical Studies at Osaka University (control number 18237, 26 September 2018). Requirement for written informed consent was waived by the Ethics Review Board.

### Patients

Between 2010 and 2016, operations with curative intent were performed under general anaesthesia on 631 NSCLC patients in our institution. Patients with missing data ($n = 10$) were excluded from the analysis. To ensure the accuracy of intraoperative haemodynamics, those who were monitored for vital signs only with a sphygmomanometer ($n = 36$) were also excluded, leaving 585 patients in this study.

A review of anaesthesia records for each patient provided the vital signs measured every 20 s via an arterial line. The lowest MAP and lowest HR between skin incision and closure as well as EBL were extracted. The SAS was calculated by summing these 3 parameters according to Table 1 [5].

Medical records were inspected as well to evaluate patients' characteristics, including their medical history (pulmonary, cardiovascular and cerebrovascular diseases, metabolic diseases, kidney diseases) and laboratory data [haemoglobin, serum carcinoembryonic antigen (CEA)]. In the present study, 'atherosclerotic disease' is defined as aortic aneurysm, atherosclerosis obliterans and carotid artery stenosis. Missing CEA values ($n = 15$) were replaced by the median value (3 ng/ml) in the analyses. Pathological staging was determined based on the International Association of Study of Lung Cancer Staging Manual in Thoracic Oncology, 7th edition [8].

**Table 1:** Surgical Apgar score

| | 0 points | 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 (1/min) | >85 | 76–85 | 66–75 | 56–65 | ≤55 |

## Treatment strategy

The application and details of induction therapy were described previously [9]. The type of surgical procedure, approach and extent of lymph node dissection were decided depending on the patients' respiratory function, comorbidities and tumour characteristics. In brief, lobectomy and systemic lymph node dissection (ND2) were performed as a standard surgery. The indications for sublobar resection with curative intent were ground-glass nodule lesions or solid dominant lesions smaller than 1.5 cm in size in patients with a poor respiratory function or other co-morbidities. Generally, video-assisted thoracic surgery or robot-assisted thoracic surgery (RATS) was selected in patients with clinical stage I cancer [10]. Combined resection in the present study consisted of the following: chest wall association and resection of the superior vena cava, aorta, diaphragm, pericardium or phrenic nerve [11].

Systemic anaesthesia was maintained using inhalation agents or intravenous remifentanil and propofol continuous infusion. Patients who received both inhalation agents and remifentanil were assigned to the inhalation anaesthesia group [12]. Thoracic epidural anaesthesia was induced if there were no contraindications. EBL was calculated as follows:

(total fluid volume collected within the suction canister − irrigation) + (weight of the used − dry gauze).

During this study period, patients who had a tumour of >2 cm in maximum diameter or who had lymph node involvement were considered to be candidates for adjuvant chemotherapy (ACT). Basically, oral 5-fluorouracil-based chemotherapy was administered for 2 years, if the tumour was an adenocarcinoma of >2 cm without lymph node metastasis [13]. In the case of lymph node involvement, the patient received 4 cycles of an intravenous platinum-based regimen. The decision of whether to administer ACT was made by the cancer board in each case.

## The evaluation of surgical outcomes

Postoperative complications or perioperative death were defined as any complications or death within 30 days after the operation and those occurring at any time during the same hospital stay. Postoperative complications were assessed according to the Japan Clinical Oncology Group postoperative complications criteria (JCOG PC criteria) and stratified according to the Clavien–Dindo classification [14]. If more than 1 complication had occurred in a single patient, the most severe grade was documented. In the present study, the following postoperative complications were taken into consideration: cardiopulmonary [atrial arrhythmia, ventricular arrhythmia, myocardial infarction, prolonged air leak (lasting >7 days), pneumonia, airway stenosis, atelectasis, acute respiratory distress syndrome, bronchopleural fistula, pulmonary embolism, pulmonary oedema, pleural effusion, respiratory failure requiring home oxygen therapy or reintubation, empyema, chylothorax, nerve palsy (recurrent or phrenic nerve), postoperative bleeding, lung torsion], infection (surgical site infection, other infections), central nervous system (stroke, delirium), gastrointestinal (dysphagia, paralytic ileus, cholecystitis) and others (no adverse event terms).

Regular postoperative follow-up was performed for the surveillance of lung cancer recurrence, as described previously [9]. In the present study, the cause of the death was determined based on charts or certification of death, as described previously [15].

## Statistical analyses

All statistical analyses were conducted using the JMP Pro software program, ver. 16.0 (SAS Institute, Cary, NC, USA) and the SAS software program (ver. 9.4, SAS Institute). Clinical parameters were compared using Student's *t*-test and the chi-squared test. The receiver operating characteristic (ROC) analysis of the SAS was performed to determine an appropriate cut-off value to predict postoperative complications. A multiple linear regression analysis was performed to investigate the association between clinical factors and the SAS. The variance inflation factor values of all the variables were <5. The disease-free survival (DFS) and overall survival (OS) were evaluated with the Kaplan–Meier method, with the date of lung resection set as the starting point (follow-up range: 1–107 months, median: 49 months). Because lung cancer-specific and non-lung cancer-specific deaths were considered to be 2 competing outcomes, the cumulative incidence of death curves was compared using Gray's test. The logistic regression model and Cox-constant proportional hazards model were used to assess the effects of covariates on the postoperative complications, DFS and OS. The difference between groups was analysed, and a *P*-value of <0.05 was considered statistically significant. In the present study, there was no prespecified plan to adjust for multiple comparisons; therefore, the inferences drawn from them may not be reproducible.

# RESULTS

## Patient characteristics

The patient characteristics are summarized in Table 2. The mean age of all patients was 67.8 years old. There were 341 men (58%) and 244 women (42%) in this study. RATS procedures were performed in 2 patients. The numbers and proportions of patients with each SAS were as follows: 2 points, 1 (0%); 3 points, 4 (1%); 4 points, 5 (1%); 5 points, 21 (4%); 6 points, 81 (14%); 7 points, 209 (36%); 8 points, 222 (38%); 9 points, 39 (7%); 10 points, 3 (1%).

## Short-term outcomes and their association with the surgical Apgar score

Postoperative complications occurred in 164 patients (28%). The details of the postoperative complications are summarized in Table 3. Two patients (0.3%) died after surgery.

Figure 1A shows the relationship between the SAS and the rate of postoperative complications. The morbidity rate was stratified by the SAS. Figure 1B shows the ROC curve for predicting postoperative complications of all grades by the SAS. The area under the ROC curve was 0.61 (95% confidence interval, 0.56–0.66). According to the ROC analysis, the best cut-off value for predicting postoperative complications was 7.

## Patient characteristics according to the surgical Apgar score

Of 585 patients, 112 patients (19%) had an SAS of <7. The proportion of male patients was significantly higher in the SAS <7 group. The respiratory function, which included the percentage of the predicted forced expiratory volume in 1 s and the

**Table 2:** Patient characteristics

| Characteristics | All patients (*n* = 585) | SAS <7 (*n* = 112) | SAS ≥7 (*n* = 473) | *P*-Value |
|---|---|---|---|---|
| Age | 67.8 ± 10.1 | 68.8 ± 9.2 | 67.5 ± 10.3 | 0.253 |
| Sex | | | | |
| Men | 341 (58) | 76 (68) | 265 (56) | 0.022 |
| Women | 244 (42) | 36 (32) | 208 (44) | |
| Body mass index | 22.3 ± 3.0 | 22.1 ± 3.2 | 22.3 ± 2.9 | 0.573 |
| Preoperative respiratory function | | | | |
| %VC | 101.1 ± 14.4 | 100.0 ± 15.5 | 101.4 ± 14.1 | 0.365 |
| %FEV1.0 | 92.8 ± 18.0 | 88.8 ± 19.2 | 93.7 ± 17.6 | 0.009 |
| %DLco | 90.3 ± 22.2 | 84.7 ± 19.4 | 91.7 ± 22.6 | 0.003 |
| Medical history | | | | |
| Hypertension | 211 (36) | 35 (31) | 176 (37) | 0.238 |
| Diabetes mellitus | 85 (15) | 13 (12) | 72 (15) | 0.329 |
| Cerebrovascular disease | 41 (7) | 8 (7) | 33 (7) | 0.951 |
| Coronary artery disease | 43 (7) | 10 (9) | 33 (7) | 0.477 |
| Atherosclerotic disease | 50 (9) | 10 (9) | 40 (9) | 0.872 |
| Chronic kidney disease | 57 (10) | 9 (8) | 48 (10) | 0.498 |
| COPD | 158 (27) | 46 (41) | 112 (24) | <0.001 |
| ILD | 48 (8) | 13 (12) | 35 (7) | 0.145 |
| Induction therapy | 23 (4) | 14 (13) | 9 (2) | <0.001 |
| Preoperative haemoglobin (g/dl) | 13.3 ± 1.6 | 13.2 ± 1.7 | 13.3 ± 1.5 | 0.544 |
| Preoperative CEA (ng/ml) | 13.7 ± 196.5 | 53.1 ± 448.3 | 4.4 ± 7.4 | 0.018 |
| ≤5 | 401 (69) | 64 (57) | 337 (71) | 0.015 |
| >5 | 169 (29) | 44 (39) | 125 (26) | |
| Unknown | 15 (3) | 4 (4) | 11 (2) | |
| ASA-PS | | | | |
| 1 | 131 (22) | 17 (15) | 114 (24) | 0.117 |
| 2 | 406 (69) | 84 (75) | 322 (68) | |
| 3 | 48 (8) | 11 (10) | 37 (8) | |
| General anaesthesia | | | | |
| Total intravenous anaesthesia | 498 (85) | 95 (85) | 403 (85) | 0.919 |
| Inhalation anaesthesia | 87 (15) | 17 (15) | 70 (15) | |
| Locoregional anaesthesia | | | | |
| Thoracic epidural anaesthesia | 528 (90) | 96 (86) | 432 (91) | 0.189 |
| Thoracic paravertebral block | 27 (5) | 8 (7) | 19 (4) | |
| None | 30 (5) | 8 (7) | 22 (5) | |
| Surgical approach | | | | |
| Open thoracotomy | 215 (37) | 66 (59) | 149 (32) | <0.001 |
| VATS | 370 (63) | 46 (41) | 324 (69) | |
| Type of resection | | | | |
| Pneumomectomy | 5 (1) | 3 (3) | 2 (0) | 0.001 |
| Bilobectomy | 12 (2) | 4 (4) | 8 (2) | |
| Lobectomy | 421 (72) | 91 (81) | 330 (70) | |
| Segmentectomy | 93 (16) | 11 (10) | 82 (17) | |
| Wide wedge resection | 54 (9) | 3 (3) | 51 (11) | |
| Lymph node dissection | | | | |
| Hilar and mediastinal | 361 (62) | 86 (77) | 275 (58) | 0.001 |
| Hilar | 77 (13) | 12 (11) | 65 (14) | |
| None | 147 (25) | 14 (13) | 133 (28) | |
| Combined resection | 17 (3) | 10 (9) | 7 (2) | <0.001 |
| Operative time (min) | 221.4 ± 85.3 | 278.4 ± 117.3 | 207.9 ± 69.3 | <0.001 |
| Intraoperative lowest mean arterial pressure (mmHg) | 48.3 ± 8.2 | 42.7 ± 8.6 | 49.6 ± 7.5 | <0.001 |
| Intraoperative lowest heart rate (1/min) | 50.8 ± 8.5 | 56.4 ± 9.1 | 49.5 ± 7.8 | <0.001 |
| Intraoperative bleeding (ml) | 186.1 ± 512.9 | 563.1 ± 1075.1 | 96.9 ± 109.3 | <0.001 |
| Transfusion | 21 (4) | 19 (17) | 2 (0) | <0.001 |
| Postoperative complications | | | | |
| All grade | 164 (28) | 46 (41) | 118 (25) | 0.001 |
| Grade ≥3 | 54 (9) | 15 (13) | 39 (8) | 0.091 |
| Length of hospital stay (days) | 20.9 ± 15.8 | 27.8 ± 24.7 | 19.3 ± 12.3 | <0.001 |
| Size of tumour (mm) | 27.4 ± 16.5 | 33.4 ± 17.1 | 26.0 ± 16.0 | <0.001 |
| Pathological N stage | | | | |
| N0 | 522 (89) | 89 (79) | 433 (92) | <0.001 |
| N1 | 27 (5) | 8 (7) | 19 (4) | |
| N2 | 36 (6) | 15 (14) | 21 (4) | |
| Pathological stage (7th) | | | | |
| 0 (pCR) | 6 (1) | 4 (4) | 2 (0) | <0.001 |
| IA | 351 (60) | 42 (38) | 309 (65) | |
| IB | 105 (18) | 26 (23) | 79 (17) | |
| IIA | 46 (8) | 7 (6) | 39 (8) | |
| IIB | 26 (4) | 13 (12) | 13 (3) | |
| IIIA | 43 (7) | 18 (16) | 25 (5) | |
| IV | 8 (1) | 2 (2) | 6 (1) | |

*Continued*

**Table 2:** Continued

| Characteristics | All patients ($n = 585$) | SAS <7 ($n = 112$) | SAS ≥7 ($n = 473$) | *P*-Value |
|---|---|---|---|---|
| Histology | | | | |
| Adenocarcinoma | 455 (78) | 74 (66) | 381 (81) | <0.001 |
| Non-adenocarcinoma | 130 (22) | 38 (34) | 92 (19) | |
| SAS | | | | |
| 2 | 1 (0) | 1 (1) | | |
| 3 | 4 (1) | 4 (4) | | |
| 4 | 5 (1) | 5 (4) | | |
| 5 | 21 (4) | 21 (19) | | |
| 6 | 81 (14) | 81 (72) | | |
| 7 | 209 (36) | | 209 (44) | |
| 8 | 222 (38) | | 222 (46) | |
| 9 | 39 (7) | | 39 (8) | |
| 10 | 3 (1) | | 3 (1) | |

Continuous values are shown as the mean ± standard deviation, whereas categorical values are shown as the total number (proportion).

ASA-PS: American Society of Anesthesiologists physical status; atherosclerotic disease: including carotid artery stenosis, aortic aneurysm, atherosclerosis obliterans; CEA: carcinoembryonic antigen; COPD: chronic obstructive pulmonary disease; DLco: diffusing capacity for carbon monoxide; FEV: forced expiratory volume; ILD: interstitial lung disease (radiological findings); pCR: pathological complete response; SAS: surgical Apgar score; VATS: video-assisted thoracic surgery (including robot-assisted thoracic surgery); VC: vital capacity.

**Table 3:** Details of postoperative complications

| | SAS <7 ($n = 112$) | | | | | | SAS ≥7 ($n = 473$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clavien–Dindo grade | 1 | 2 | 3 | 4 | 5 | All grades | 1 | 2 | 3 | 4 | 5 | All grades |
| Cardiopulmonary | | | | | | | | | | | | |
| Atrial arrhythmia | 0 | 12 | 0 | 0 | 0 | 12 | 0 | 29 | 0 | 0 | 0 | 29 |
| Myocardial infarction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Prolonged air leak | 4 | 2 | 2 | 0 | 0 | 8 | 10 | 8 | 8 | 0 | 0 | 26 |
| Pneumonia | 0 | 4 | 0 | 0 | 0 | 4 | 0 | 5 | 1 | 1 | 0 | 7 |
| Nerve palsy | 3 | 0 | 0 | 0 | 0 | 3 | 4 | 2 | 1 | 0 | 0 | 7 |
| Postoperative bleeding | 0 | 2 | 1 | 0 | 0 | 3 | 0 | 0 | 4 | 0 | 0 | 4 |
| Empyema | 0 | 0 | 3 | 0 | 0 | 3 | 0 | 0 | 4 | 0 | 0 | 4 |
| Chylothorax | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 4 | 0 | 0 | 6 |
| Atelectasis | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 1 | 0 | 4 |
| Airway stenosis | 0 | 0 | 3 | 0 | 0 | 3 | 0 | 1 | 0 | 0 | 0 | 1 |
| Respiratory failure | 0 | 1 | 0 | 1 | 0 | 2 | 0 | 1 | 0 | 1 | 0 | 2 |
| ARDS | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 |
| Bronchial fistula | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 2 |
| Pulmonary oedema | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pleural effusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 2 |
| Infection | | | | | | | | | | | | |
| Surgical site infection | 0 | 1 | 1 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 1 |
| Other infections | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 6 | 0 | 0 | 0 | 7 |
| Central nervous system | | | | | | | | | | | | |
| Delirium | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 4 |
| Stroke | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 |
| Gastrointestinal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 3 |
| Others | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 5 |
| Total | 7 | 24 | 12 | 2 | 1 | 46 (41%) | 17 | 62 | 33 | 5 | 1 | 118 (25%) |

ARDS: acute respiratory distress syndrome; SAS: surgical Apgar score.

percentage of the predicted diffusing capacity for carbon monoxide, was poorer in the SAS <7 group. The SAS <7 group had a larger proportion of patients with COPD and who had received induction therapy.

With respect to operative factors, more patients underwent open thoracotomy (59% vs 32%, $P < 0.001$) and hilar and mediastinal lymph node dissection (77% vs 58%, $P < 0.001$) in the SAS <7 group. As anticipated, there were significant differences among the values of the SAS components between the 2 groups: the lowest MAP was lower (42.7 vs 49.6 mmHg, $P < 0.001$), the lowest HR was higher (56.4 vs 49.5/min, $P < 0.001$) and intraoperative bleeding was greater (563.1 vs 96.9 ml, $P < 0.001$) in the SAS <7 group. The SAS <7 group had a longer length of hospital stay (28 vs 19 days, $P < 0.001$).

In terms of pathological factors, the average tumour size (33.4 vs 26.0 mm, $P < 0.001$) and the proportion of pathological N2 (14% vs 4%, $P < 0.001$) and non-adenocarcinoma histology (34% vs 19%, $P < 0.001$) were larger in the SAS <7 group.

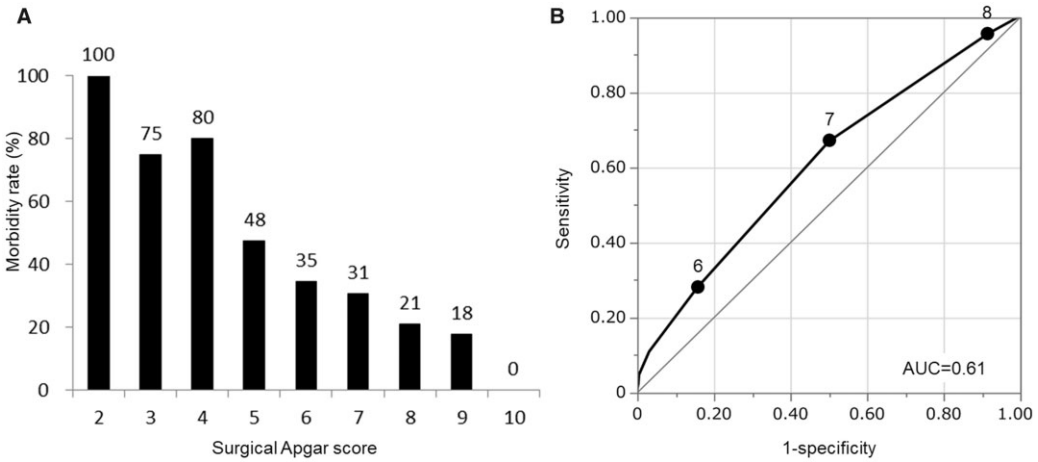


**Figure 1:** Association between the surgical Apgar score and postoperative complications. (**A**) The rate of morbidity according to the surgical Apgar score. (**B**) The receiver operating characteristic analysis of the surgical Apgar score. AUC: area under the curve.

## Association between the surgical Apgar score and short-term outcomes

On comparing the SAS <7 and ≥7 groups, postoperative complications of all grades occurred significantly more frequent in the SAS <7 group than in the SAS ≥7 group (41% vs 25%, $P < 0.001$). Grade ≥3 postoperative complications were observed more frequently in the SAS <7 group than in the SAS ≥7 group (13% vs 8%, $P = 0.091$); however, the difference was not statistically significant.

Table 4 shows the results of univariate and multivariable analyses of clinical factors associated with postoperative complications. As a result, the American Society of Anesthesiologists physical status (ASA-PS), histology and SAS (odds ratio: 1.64 [1.03–2.61], $P = 0.036$) were determined to be independent predictors of postoperative complications.

## Association between the surgical Apgar score and long-term outcomes

The relationship between the SAS and ACT is summarized in Supplementary Material, Table S1. The SAS <7 group had a larger proportion of candidates for ACT (68% vs 54%, $P = 0.007$). However, the rate of treatment initiation and treatment compliance and chemotherapy regimens of the candidates in the 2 groups did not differ to a statistically significant extent.

Figure 2 describes the DFS and OS according to the SAS. Both the DFS (54.1% vs 73.2%, $P < 0.001$) and OS (73.8% vs 83.0%, $P = 0.031$) were significantly worse in the SAS <7 group than in the SAS ≥7 group.

Table 5 shows the result of a multivariable analysis for the DFS. According to the results, the body mass index, preoperative CEA and pathological stage were independent prognostic factors. However, the SAS was not significantly associated with DFS (hazard ratio: 1.39 [0.97–2.00], $P = 0.075$). Regarding OS, the following variables were assigned due to the limited number of observed events: 'respiratory dysfunction' was defined as the percentage of predicted vital capacity <80%, the percentage of the predicted forced expiratory volume in 1 s <80% and the percentage of the predicted diffusing capacity for carbon monoxide <80%; 'vascular disease' was defined as cerebrovascular disease, coronary artery disease and atherosclerotic disease; and 'respiratory disease' was defined as chronic obstructive pulmonary disease and interstitial lung disease (radiological findings). A multivariable analysis was performed based on patient, operative and tumour factors that possibly affect OS (sex, history of respiratory dysfunction, vascular disease, respiratory disease, preoperative CEA, ASA-PS, surgical approach, pathological stage, histology and SAS). As shown in Supplementary Material, Table S2, the sex, vascular disease, ASA-PS and pathological stage were determined to be independent predictors of the OS. However, the SAS was not significantly associated with the OS (hazard ratio: 0.90 [0.57–1.42], $P = 0.642$).

## Cause of death analysis according to the surgical Apgar score

The causes of death are summarized in Supplementary Material, Table S3. Of the 106 patients who died at the time of writing this report, 67 patients (63%) died of lung cancer and 39 patients (37%) died of other diseases. Supplementary Material, Fig. S1 shows the lung cancer-specific and non-lung cancer-specific cumulative incidence of death curves according to the SAS. The SAS was not a significant risk factor for either lung cancer-specific death (hazard ratio: 1.59 [0.93–2.71], $P = 0.094$) or non-lung cancer-specific death (hazard ratio: 1.48 [0.72–3.04], $P = 0.286$).

## Factors influencing the surgical Apgar score

We performed a multiple regression analysis to determine the clinical factors influencing the SAS besides the intraoperative lowest HR, MAP and EBL (Table 6). As a result, 3 clinical factors (surgical approach, operation time and transfusion) were shown to be significantly associated with the SAS.

**Table 4:** Results of univariate and multivariable analyses of clinical factors, including the surgical Apgar score, influencing postoperative complications

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-Value | OR (95% CI) | *P*-Value |
| Age (≥75/<75 years old) | 1.24 (0.83–1.84) | 0.289 | | |
| Sex (men/women) | 1.81 (1.23–2.64) | 0.002 | 1.34 (0.87–2.07) | 0.185 |
| Body mass index (<25/≥25) | 1.48 (0.88–2.49) | 0.144 | | |
| %VC (<80/≥80) | 1.36 (0.68–2.73) | 0.382 | | |
| %FEV1.0 (<80/≥80) | 1.16 (0.76–1.77) | 0.491 | | |
| %DLco (<80/≥80) | 0.96 (0.65–1.41) | 0.821 | | |
| Hypertension (+/-) | 1.15 (0.98–1.67) | 0.461 | | |
| Diabetes mellitus (+/-) | 1.49 (0.92–2.42) | 0.109 | | |
| Cerebrovascular disease (+/-) | 0.82 (0.39–1.71) | 0.591 | | |
| Coronary artery disease (+/-) | 1.76 (0.93–3.33) | 0.084 | | |
| Atherosclerotic disease (+/-) | 1.81 (1.00–3.29) | 0.052 | | |
| Chronic kidney disease (+/-) | 1.21 (0.67–2.17) | 0.534 | | |
| COPD (+/-) | 1.50 (1.01–2.22) | 0.045 | 1.02 (0.65–1.60) | 0.934 |
| ILD (+/-) | 0.84 (0.43–1.67) | 0.626 | | |
| Induction therapy (+/-) | 2.04 (0.88–4.74) | 0.099 | | |
| Preoperative haemoglobin (<12/≥12) | 0.84 (0.52–1.34) | 0.465 | | |
| Preoperative CEA (>5/≤5) | 1.41 (0.93–2.14) | 0.104 | | |
| ASA-PS (3/1–2) | 2.14 (1.17–3.91) | 0.013 | 1.96 (1.02–3.76) | 0.043 |
| General anaesthesia (TIVA/inhalation) | 1.10 (0.66–1.84) | 0.719 | | |
| Locoregional anaesthesia (none or TPVB/TEA) | 1.10 (0.61–2.00) | 0.752 | | |
| Surgical approach (open thoracotomy/VATS) | 1.82 (1.26–2.62) | 0.002 | 1.17 (0.75–1.82) | 0.498 |
| Type of resection (lobectomy or more/segmentectomy or less) | 1.81 (1.15–2.85) | 0.010 | 1.46 (0.75–2.86) | 0.268 |
| Lymph node dissection (hilar and mediastinal/none or hilar) | 1.49 (1.02–2.18) | 0.042 | 1.15 (0.65–1.71) | 0.637 |
| Combined resection (+/-) | 2.35 (0.89–6.19) | 0.085 | | |
| Transfusion (+/-) | 1.98 (0.82–4.79) | 0.130 | | |
| Pathological stage (II–IV/I) | 1.66 (1.10–2.52) | 0.017 | 1.05 (0.65–1.71) | 0.838 |
| Histology (non-Ad/Ad) | 2.43 (1.62–3.66) | <0.001 | 1.77 (1.11–2.83) | 0.017 |
| Surgical Apgar score (<7/≥7) | 2.10 (1.36–3.22) | 0.001 | 1.64 (1.03–2.61) | 0.036 |

Ad: adenocarcinoma; ASA-PS: American Society of Anesthesiologists physical status; atherosclerotic disease: including carotid artery stenosis, aortic aneurysm, atherosclerosis obliterans; CEA: carcinoembryonic antigen; CI: confidence interval; COPD: chronic obstructive pulmonary disease; DLco: diffusing capacity for carbon monoxide; FEV: forced expiratory volume; ILD: interstitial lung disease (radiological findings); OR: odds ratio; TEA: thoracic epidural anaesthesia; TIVA: total intravenous anaesthesia; TPVB: thoracic paravertebral block; VATS: video-assisted thoracic surgery (including robot-assisted thoracic surgery); VC: vital capacity.

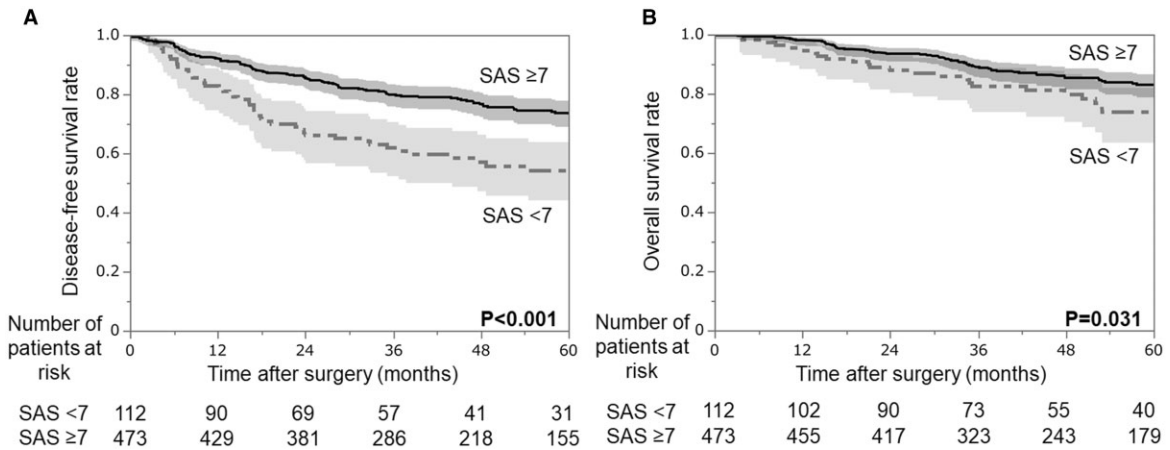


**Figure 2:** The disease-free and overall survival according to the surgical Apgar score. Kaplan–Meier curves showing the disease-free (**A**) and overall (**B**) survival with 95% confidence intervals. (**A**) The 5-year disease-free survival of the surgical Apgar score <7 patients was significantly worse than that of the surgical Apgar score ≥7 patients (54.1% vs 73.2%, $P < 0.001$). (**B**) The 5-year overall survival of the surgical Apgar score <7 patients was significantly worse than that of the surgical Apgar score ≥7 patients (73.2% vs 83.0%, $P = 0.031$). SAS: surgical Apgar score.

## DISCUSSION

In the present study, we revealed that the postoperative complication rate could be stratified by the SAS. Furthermore, the SAS was independently associated with postoperative complications.

The SAS is distinguished from other perioperative risk assessment tools by the fact that it takes intraoperative characteristics into account. The primary determinants of surgical outcomes are generally considered to be patient pathophysiological risk factors and the surgical quality [16]. Conventional risk models, such as

**Table 5:** Results of univariate and multivariable analyses of clinical factors, including the surgical Apgar score, influencing the disease-free survival

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Age (≥75/<75 years old) | 1.08 (0.77–1.51) | 0.659 | | |
| Sex (men/women) | 1.69 (1.22–2.34) | 0.002 | 1.22 (0.82–1.80) | 0.329 |
| Body mass index (<25/≥25) | 2.00 (1.19–3.34) | 0.009 | 2.03 (1.19–3.48) | 0.010 |
| %VC (<80/≥80) | 2.05 (1.25–3.34) | 0.004 | 1.53 (0.88–2.66) | 0.132 |
| %FEV1.0 (<80/≥80) | 1.57 (1.13–2.19) | 0.008 | 0.82 (0.54–1.25) | 0.358 |
| %DLco (<80/≥80) | 1.51 (1.10–2.06) | 0.010 | 1.11 (0.78–1.58) | 0.577 |
| Hypertension (+/-) | 1.18 (0.86–1.61) | 0.303 | | |
| Diabetes mellitus (+/-) | 1.29 (0.86–1.92) | 0.218 | | |
| Cerebrovascular disease (+/-) | 1.14 (0.65–2.01) | 0.644 | | |
| Coronary artery disease (+/-) | 1.45 (0.87–2.43) | 0.158 | | |
| Atherosclerotic disease (+/-) | 1.17 (0.71–1.94) | 0.531 | | |
| Chronic kidney disease (+/-) | 1.61 (1.02–2.55) | 0.041 | 1.43 (0.89–2.32) | 0.141 |
| COPD (+/-) | 1.43 (1.03–1.99) | 0.031 | 1.09 (0.72–1.66) | 0.670 |
| ILD (+/-) | 2.76 (1.82–4.17) | <0.001 | 1.29 (0.79–2.12) | 0.307 |
| Induction therapy (+/-) | 2.98 (1.69–5.25) | <0.001 | 1.05 (0.50–2.20) | 0.902 |
| Preoperative haemoglobin (<12/≥12) | 1.27 (0.88–1.84) | 0.196 | | |
| Preoperative CEA (>5/≤5) | 2.24 (1.62–3.08) | <0.001 | 1.41 (1.00–1.99) | 0.048 |
| ASA-PS (3/1–2) | 2.07 (1.32–3.24) | 0.002 | 1.31 (0.80–2.15) | 0.281 |
| General anaesthesia (TIVA/inhalation) | 1.09 (0.70–1.71) | 0.707 | | |
| Locoregional anaesthesia (none or TPVB/TEA) | 1.31 (0.82–2.09) | 0.263 | | |
| Surgical approach (open thoracotomy/VATS) | 2.82 (2.07–3.83) | <0.001 | 1.33 (0.91–1.95) | 0.140 |
| Type of resection (lobectomy or more/segmentectomy or less) | 1.40 (0.96–2.04) | 0.081 | | |
| Lymph node dissection (hilar and mediastinal/none or hilar) | 1.22 (0.89–1.68) | 0.216 | | |
| Combined resection (+/-) | 3.03 (1.55–5.94) | 0.001 | 1.03 (0.47–2.28) | 0.943 |
| Transfusion (+/-) | 1.52 (0.74–3.09) | 0.252 | | |
| Pathological stage (II–IV/I) | 4.43 (3.25–6.02) | <0.001 | 2.80 (1.91–4.11) | <0.001 |
| Histology (non-Ad/Ad) | 2.55 (1.86–3.50) | <0.001 | 1.32 (0.90–1.93) | 0.162 |
| Surgical Apgar score (<7/≥7) | 2.13 (1.53–2.97) | <0.001 | 1.39 (0.97–2.00) | 0.075 |

Ad: adenocarcinoma; ASA-PS: American Society of Anesthesiologists physical status; atherosclerotic disease: including carotid artery stenosis, aortic aneurysm, atherosclerosis obliterans; CEA: carcinoembryonic antigen; CI: confidence interval; COPD: chronic obstructive pulmonary disease; DLco: diffusing capacity for carbon monoxide; FEV: forced expiratory volume; HR: hazard ratio: ILD: interstitial lung disease (radiological findings); TEA: thoracic epidural anaesthesia; TIVA: total intravenous anaesthesia; TPVB: thoracic paravertebral block; VATS: video-assisted thoracic surgery (including robot-assisted thoracic surgery); VC: vital capacity.

the Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity [2] and the American College of Surgeons' National Surgical Quality Improvement Program [3], usually predict postoperative outcomes based on calculations of known preoperative risk factors. In contrast, the SAS is a simple score that reflects intraoperative characteristics in addition to clinical characteristics of patients. An increased blood loss causes intravascular volume depletion and leads to a lower blood pressure and a higher HR. Furthermore, the intraoperative MAP and HR are greatly affected by anaesthesia management, such as the anaesthetic depth, fluid volume control and use of vasoactive agents, as well as the patient's physical background [17]. Indeed, Regenbogen *et al.* [4] compared the prognostic value of SAS before and after adjusting for a detailed risk-prediction model and concluded that the SAS is a useful indicator of the surgical quality. These observations suggest that the SAS is a better tool for predicting the postoperative course of patients immediately after surgery than other risk prediction models.

Although calculated only based on intraoperative characteristics, the SAS reflected patient pathophysiological risk factors. The lower SAS group had poorer physical background factors, such as lower respiratory function values, and larger proportions of patients with COPD and previous induction therapy. An explanation of this result is that oxygen supply shortage due to impaired respiratory function induces an increased HR. Another explanation is that systemic inflammation accompanying COPD or induction therapy causes endothelial dysfunction [18], which results in intraoperative hypotension due to impaired vascular homeostasis [19]. Because of these reasons, patients with lower SAS values were vulnerable to surgical stress and may be predisposed to postoperative complications.

In terms of the short-term outcomes, the SAS cut-off value of 7 according to the result of ROC analysis drew a clear line between postoperative complication rates in this study. In the field of thoracic surgery, a review of 6 cohort studies revealed that an SAS cut-off value of ≤6 had discriminative power for patients at high morbidity risk who underwent oesophagectomy [20], which is consistent with our results. A hypothesized mechanism for the relationship between the SAS and postoperative complications is that organ hypoperfusion represented by the low SAS causes potential organ dysfunction [21]. Some reports support this hypothesis, suggesting that an unstable intraoperative haemodynamic is correlated with negative surgical outcomes [22]. In the present study, it was also shown that the SAS, together with the ASA-PS, was an independent predictor of postoperative complications. This result implies that intraoperative characteristics as shown by the SAS are no less important than patient's medical comorbidities presented by the ASA-PS. Accordingly, the SAS can anticipate postoperative complications after thoracic surgery. However, the area under the ROC curve was 0.61, which indicates moderate predicative ability. To overcome this limitation, it may be practical to utilize the SAS for assessing the necessity of

**Table 6:** Results of multiple linear regression analysis: association between clinical factors and the surgical Apgar score

| Variables | Partial regression coefficient | Standard regression coefficient (β) | *P*-Value |
|---|---|---|---|
| Age | -0.003 | -0.026 | 0.531 |
| Sex (men = 1/women = 0) | -0.059 | -0.054 | 0.268 |
| Body mass index | 0.026 | 0.073 | 0.064 |
| %VC | -0.000 | -0.000 | 0.999 |
| %FEV1.0 | 0.000 | 0.006 | 0.929 |
| %DLco | 0.003 | 0.061 | 0.156 |
| Hypertension (yes = 1/no = 0) | 0.054 | 0.048 | 0.214 |
| Diabetes mellitus (yes = 1/no = 0) | 0.036 | 0.024 | 0.524 |
| Cerebrovascular disease (yes = 1/no = 0) | -0.050 | -0.024 | 0.522 |
| Coronary artery disease (yes = 1/no = 0) | 0.131 | 0.064 | 0.116 |
| Atherosclerotic disease (yes = 1/no = 0) | 0.042 | 0.022 | 0.571 |
| Chronic kidney disease (yes = 1/no = 0) | 0.108 | 0.060 | 0.115 |
| COPD (yes = 1/no = 0) | -0.071 | -0.059 | 0.225 |
| ILD (yes = 1/no = 0) | -0.138 | -0.071 | 0.065 |
| Induction therapy (yes = 1/no = 0) | -0.079 | -0.029 | 0.495 |
| Preoperative haemoglobin (g/dl) | -0.006 | -0.009 | 0.840 |
| Preoperative CEA (ng/ml) | -0.000 | -0.025 | 0.498 |
| ASA-PS | -0.082 | -0.041 | 0.321 |
| General anaesthesia (TIVA = 1/inhalation = 0) | 0.017 | 0.011 | 0.757 |
| Locoregional anaesthesia (none or TPVB = 1/TEA = 0) | -0.041 | -0.023 | 0.559 |
| Surgical approach (open thoracotomy = 1/VATS = 0) | -0.093 | -0.084 | 0.033 |
| Type of resection (lobectomy or more = 1/segmentectomy or less = 0) | 0.001 | 0.001 | 0.988 |
| Lymph node dissection (hilar and mediastinal = 1/none or hilar = 0) | -0.049 | -0.045 | 0.412 |
| Combined resection (yes = 1/no = 0) | -0.194 | -0.061 | 0.149 |
| Operative time (min) | -0.003 | -0.271 | <0.001 |
| Transfusion (yes = 1/no = 0) | -0.609 | -0.213 | <0.001 |
| Intercept | 6.761 | | <0.001 |

ASA-PS: American Society of Anesthesiologists physical status; atherosclerotic disease: including carotid artery stenosis, aortic aneurysm, atherosclerosis obliterans; CEA: carcinoembryonic antigen; COPD: chronic obstructive pulmonary disease; DLco: diffusing capacity for carbon monoxide; FEV: forced expiratory volume; ILD: interstitial lung disease (radiological findings); TEA: thoracic epidural anaesthesia; TIVA: total intravenous anaesthesia; TPVB: thoracic paravertebral block; VATS: video-assisted thoracic surgery (including robot-assisted thoracic surgery); VC: vital capacity.

intensive care in the immediate postoperative period and to subsequently develop management plans that also consider other risk prediction models.

Interestingly enough, our analysis suggested the potential association between the SAS and long-term outcomes in NSCLC patients. A recent study that surveyed oesophageal cancer patients also concluded that the SAS was a long-term prognostic factor after oesophagectomy [7]. Possible interpretations of these observations are as follows: changes in the immune function, which is related to a low SAS, may promote the cancer cell survival. A lower MAP and higher HR are thought to reflect systemic inflammatory response syndrome during surgery, and such substantial surgical stress induces immunosuppression [23]. These reactions reduce patients' immunity against tumour cells and may support potential micrometastasis [7]. Indeed, anaesthetic management can reportedly alter immunosuppressive effects through the control of cytokine profiles, thereby affecting the long-term outcomes [24]. Although the SAS was not an independent prognostic factor, the above-mentioned evidence may support why improving the SAS can be associated with favourable long-term outcomes. The present study also showed that the lung cancer-specific and non-lung cancer-specific death rates, in addition to the ACT, did not differ to a statistically significant extent between the SAS <7 and SAS ≥7 groups. Further investigations are necessary to understand the relationship between the SAS and long-term outcomes.

To our knowledge, this is the first study to investigate the clinical factors affecting the SAS in NSCLC surgery. Given that the intraoperative characteristics can be influenced by the surgical quality as quantified by the SAS, it is intriguing to speculate which elements are most influential on the SAS. A multiple linear regression analysis demonstrated that the surgical approach (open thoracotomy), operation time and transfusion were significantly associated with a reduction in the SAS in the present study. Osarogiagbon and D'Amico [25] advocated lung cancer oncologic quality resection criteria as surgical quality measures: recommendations for the anatomic extent of resection, the completeness of resection and the lymphadenectomy procedure performed. Thoracic surgeons should thus choose the optimal surgical approach, reduce the operation time and make an effort to avoid transfusion while satisfying these criteria to achieve better surgical outcomes. The current major challenges in thoracic surgery, such as the development of a minimally invasive approach for early-stage cancer, represented by uniportal video-assisted thoracic surgery or RATS, and the application of less-invasive approaches for advanced cancer, will be effective in improving the surgical quality. It should also be noted that sometimes a minimally invasive approach and operation time are trade-off in relation to each other. Therefore, thoracic surgeons should consider the balance between the difficulty of the procedure and the operation time. As unplanned postoperative ICU admissions, which

are more likely to occur in thoracic surgery, are considered to be a risk factor for poor postoperative outcomes [26], a low SAS may be 1 reason to take ICU admission into account in high-risk patients. We believe that the SAS is a useful indicator for perioperative management.

### Limitations

Several limitations associated with the present study warrant mention. First, the surgical technique and anaesthesia management were not unified because of advances made during the long study period. Second, this was a retrospective single-center analysis and the number of patients was limited. A multicentre study with a larger study population would be desirable.

## CONCLUSION

The morbidity rate was stratified by the SAS and was significantly higher in the SAS <7 group than in the SAS ≥7 group. The SAS was found to be a useful predictor for short-term outcomes in NSCLC patients who underwent surgery.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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None.

**Conflict of interest:** none declared.

### Data availability

Data are available from the corresponding author with the permission of Osaka University Hospital. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Author contributions

**Akihiro Nagoya:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing—original draft. **Ryu Kanzaki:** Conceptualization; Supervision; Validation; Writing—review & editing. **Kenji Kimura:** Data curation. **Eriko Fukui:** Data curation. **Takashi Kanou:** Data curation. **Naoko Ose:** Data curation. **Soichiro Funaki:** Data curation. **Masato Minami:** Data curation. **Makoto Fujii:** Formal analysis. **Yasushi Shintani:** Supervision; Writing—review & editing.

### Reviewer information

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