Original Article

# A worse ECOG-PS is associated with 30-day mortality among patients over 90 years old in non-cardiac surgeries: A single-center retrospective study

Running title: Pre-operative frailty is associated with surgical outcome.

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Abstract

Background: A growing number of older patients are undergoing surgeries. The reliable pre-operative predictive factors of surgical mortality among older patients remained unclear. This study compared the predictive factors for 30-day survival in patients over 90 years old after their non-cardiac surgery.

Methods: A retrospective study at Nippon Medical School hospital was performed for patients aged >90 years who underwent non-cardiac surgeries between 2010 and 2020. Measurements included age, gender, American Society of Anesthesiologists physical status (ASA-PS), pre-operative Charlson score, pre-operative fall risk assessment, Eastern Cooperative Oncology Group performance status (ECOG-PS), the modified 5-item frailty index (mFI-5), the presence of intra-operative transfusion, post-operative complications, and 30-day survival post-surgery.

Results: A total of 327 cases of elective surgery and 149 cases of emergency surgery were examined. The non-survival group (n=20, 4.2%) had significantly worse pre-operative ASA-PS in emergency cases (non-survival vs. survivor group, 2.8 [2-3] vs. 2.3 [1-4], p=0.045), ECOG-PS (3.0 [2-4] vs. 1.0 [0-4], p<0.001), and mFI-5 values (3.0 [1-4] vs. 1.0 [0-3], p<0.001), more emergency cases (75.0% vs. 36.2%, p=0.004), and a greater need for intra-operative transfusion (55.0% vs. 13.4%, p<0.001). Among the frailty assessment methods, ECOG-PS was the most efficient for 30-day mortality (area under curve, ECOG-PS: 0.98, p<0.001; mFI-5: 0.86, p<0.001; Charlson score: 0.53, p=0.71; fall risk assessment: 0.55, p=0.44). Kaplan-Maier curves and a multivariate logistic regression analysis demonstrated that ECOG-PS>3 was significantly associated with 30-day mortality (ECOG-PS: Kaplan-Maier curve, p<0.001, Log-rank test; odds ratio 1.71, 95%CI: 1.35-2.16, p<0.001).

Conclusions: After non-cardiac surgery in patients >90 years old, ECOG-PS>3 was significantly correlated with 30-day mortality.

Key words: older patient; frailty; peri-operative characteristic; post-operative complication; surgical outcome

## Introduction

In Japan, older patients often undergo surgical treatment, even those over the age of 90 years. In 2021, 2.0% of the population of Japan was >90 years old [1], and they are able to undergo minimally invasive surgeries due to advancements in medical technology. These surgeries are especially useful for patients with compromised health, such as older patients and high-risk patients. It is known that older patients undergoing standard surgeries are at higher risk compared to younger patients undergoing similar surgeries [2, 3]. Some perioperative management guidelines recommend using intensive patient monitoring and multimodal pain management for older patients [4, 5]. Several studies have analyzed the pre-operative risk factors for mortality among older patients, using assessment tools including American Society of Anesthesiologists physical status (ASA-PS), the rate of pre-operative complications, the Charlson score [6], the fall risk assessment [7], the modified 5-item frailty index (mFI-5) [8], and the Eastern Cooperative Oncology Group performance status (ECOG-PS) [9]. Frailty is a key factor in the peri-operative management of older patients, but when limited to patients aged >90, there has been no consensus regarding the optimal assessment methods or scales due to the absence of data. There are no previous reports from Japan, focusing on the predictive factors of surgical mortality among high-aged patients, which will be essential as the basis for the pre-operative evaluation and the informed consent. Therefore, the aim of the present study is to identify the reliable pre-operative predictive factors of non-cardiac surgical mortality in patients over the age of 90, by the analysis of the perioperative patient characteristics and mortality.

## Materials and Methods

In this retrospective study, we collected the data (from medical and anesthesia records) of adults aged >90 years who had received any type of anesthesia for non-cardiac surgery at Nippon Medical School Hospital between April 2010 and December 2020. This study was approved by the Ethics Committee of Nippon Medical School Hospital, Bunkyo, Tokyo, Japan on 18 December 2020 (no. B-2020-236). An opt-out recruitment of participants was available for patients aged >90 years and had received any type of anesthesia for non-cardiac surgery at Nippon Medical School Hospital between April 2010 and December 2020. Patients who underwent multiple surgeries during the same hospital stay were excluded from the study.

The following parameters were analyzed: age, gender, body mass index (BMI), ASA-PS, pre-operative Charlson score [6], the pre-operative fall risk assessment [7], mFI-5 [8], ECOG-PS [9], type of anesthesia, indication(s) for surgery, surgery site, duration of anesthesia, duration of surgery, volume of fluid administered during surgery, volume of blood loss, the presence of intra-operative transfusion (red cell concentrates [RCCs], fresh frozen plasma [FFP], platelets, and albumin), the use of an electroencephalogram (EEG) monitor, the duration of hospital stay, post-operative complications (hypoxia, delirium diagnosed by psychiatrists, and aspiration pneumonia), and 30-day survival after surgery. Hypoxia was defined as 'oxygen saturation (SpO2) under 95% with room air after surgery', and aspiration pneumonia defined as 'a newly diagnosed pneumonia after surgery with an episode of vomiting or aspiration'. The presence of post-operative delirium was determined based on the recorded symptoms and/or a diagnosis by psychiatrists. We divided the patients into groups based on the type of surgery outcome: the non-survival group and the survivor group. Subgroup analyses was performed between emergency and elective cases (see, result section).

## Statistical Analysis

All numerical data are expressed as the median (range). Difference between survival group and non-survival group, within the emergency and within elective were assessed by the Mann-Whitney test or Chi-square test using Prism ver. 5.0 software (GraphPad Software, La Jolla, CA) unless otherwise specified, and receiver operating characteristic (ROC) curves of the various pre-operative assessments' sensitivity for mortality were performed using the same software. The cut-off threshold for ROC curves were set to maximize their sensitivity and specificity (Youden's index). Multivariate logistic regression analysis, Wilcoxon analysis, and Kaplan-Maier curves were performed using JMP ver. 11.0 (SAS Institute, Tokyo). Multivariate logistic regression analysis was performed to investigate the pre-operative factors related to 30-day survival after emergency surgery. Two explanatory variables, one per 10 survival number, were applied to multivariate logistic regression analysis: abdominal surgery and ECOG-PS>3. ECOG-PS was selected from the pre-operative frailty assessments, and abdominal surgery was from other preoperative factors. Statistical significance was set at p-values <0.05.

## Results

The cohort of 476 patients aged >90 years comprised 0.6% of a total of 79,860 cases of surgeries in which anesthesia was administered at our hospital during the study period. Among these, 327 patients underwent elective surgeries, and 149 patients underwent emergency surgeries.

The comparison of perioperative conditions between the non-survival and the survivor groups

The patient characteristics are summarized in Table 1. Among 476 patients, 20 (4.20%) had not survived as of 30 days after their non-cardiac surgeries. Age, gender, and BMI showed the same tendency between the non-survival and the survivor groups. Compared to the survivor group, the non-survival group had significantly more emergency surgeries (36.2% vs. 75.0%, p=0.004) and more cases with pre-operative ventilation (2.4% vs. 20%, p=0.004).

The distribution of surgery sites was similar in the non-survival and the survivor groups, respectively: head/neck, 20.0% vs. 9.65%; abdomen, 65.0% vs. 42.5%; extremities, 15.0% vs. 33.9%; and superficial, 0.0% vs. 8.99%; p= 0.058, Chi-square test. General anesthesia (GA) was used for most patients in both the non-survival and the survivor groups (85.0% vs. 84.6%, p=1.00). The post-operative ventilation was more required in the non-survival group than in the survivor group (40.0% vs. 3.29%, p<0.001).

Post-operative complications were observed in 66 patients (13.9%): 5 patients in the non-survival group (25.0%) and 61 patients in the survivor group (13.9%) (p=0.17). There were no significant differences in the incidence of postoperative complications, except for hypoxia (non-survival, 40.0% vs. survivor, 2.41%, p<0.001). The hospital stays of the non-survival group were significantly shorter than those among the survivor group (length of hospital stay: 12.5 days vs. 21.0 days, p=0.047).

Risk factors of surgical mortality

Regarding the pre-operative assessment scales, the ASA-PS, ECOG-PS and mFI-5 showed significant differences between the non-survival and the survivor groups, but the Charlson score and fall risk assessment did not (ASA-PS: 2.8 [2-3] vs. 2.3 [1-4], p=0.11, ASA-PS E: 2.8 [2-3] vs. 2.3 [1-4], p=0.045, ECOG-PS: 3.0 [2-4] vs. 1.0 [0-4], p<0.001, mFI-5: 2.5 [1-4] vs. 1.0 [0-3], p<0.001, Charlson score: 2.4 [0-4] vs. 2.3 [0-8], p=0.93, fall risk assessment: 2.2 [1-3] vs. 2.0 [1-3], p=0.67, Mann-Whitney test). To determine the efficient pre-operative assessment method, we compared the ROC curves of each of the pre-operative assessments' sensitivity for 30-day mortality (Fig. 1).

[Figure 1 here]

The area under the curve (AUC), p-values, cut-off thresholds with sensitivity and specificity were summarized as Table 2.

Relationship between requirement of general anesthesia and mortality in emergency cases

To clarify the correlation between emergency surgery and ECOG-PS, the subgroup analysis was performed. The emergency group had worse ECOG-PS than the elective group significantly (the emergency group vs the elective group, p<0.001, Chi-square test), including severe multiple organ dysfunction (i.e., renal dysfunction requiring HD, catecholamine use, arrhythmia, and pre-operative ventilation). Thus, the further analysis was performed among the emergency group and the elective group, respectively. We analyzed the pre-operative factors that showed a significant different in the characteristic analysis (i.e., abdominal surgery and the ECOG-PS) by conducting a multivariate logistic regression analysis for 30-day survival after emergency surgery (Table 3). That analysis revealed, among the emergency cases, a significant association between 30-day mortality and the ECOG-PS>3 (odds ratio [OR] 1.71, 95% confidence interval [CI]: 1.35-2.16, p<0.001), and abdominal surgery (OR: 9.38, 95%CI: 1.01-86.73, p= 0.049). Also, the Kaplan-Maier curves revealed that a worse ECOG-PS both in the emergency and the elective cases was significantly associated with a worse 30-

day survival rate (Fig. 2, ECOG-PS, $p<0.001$, the emergency group, $p<0.001$, the elective group, $p<0.001$).

[Figure 2 here]

## Discussion

This retrospective study analyzed the risk factors of 30-day mortality after non-cardiac surgery among patients aged >90 years. The total cases of 476 patients were analyzed including 149 emergency surgery cases (31.3%), and the overall survival rate was 95.8%. The comparison of ROC curves demonstrated that the ECOG-PS was the most efficient pre-operative assessment method for predicting 30-day mortality. The results of the multivariate regression analysis also indicated that ECOG-PS>3 was an independent factor associated with 30-day mortality, especially in the emergency group.

It is also known that worse frailty as evaluated by the ECOG-PS and mFI-5 and other assessment tools is associated with the surgical outcome in adult patients [9-11]. Especially among older patients, pre- and/or post-operative frailty or comorbidity are well-recognized as predictive factors of mortality, in addition to the functional evaluation scales [12, 13]. The ASA-PS was reported as a predictive factor of surgical outcomes among all ages in 1996 [14]. The optimal methods for evaluations of frailty (especially in older patients) have been discussed for many years, and frailty evaluations have varied widely, including fall risk assessments [7], the ECOG-PS [9], and the mFI-5 [8]. ECOG-PS was originally generated for the evaluation of cancer patients, which simply consisted of bed-based time ratio in patient’s daily life, and independently associated with the postoperative 30-day mortality in a cohort of high-risk emergency surgery patients [9]. A large comparative study with all-age patients demonstrated that the mFI-5 and mFI-11 were both effective to predict surgical outcomes [15] and post-operative complications [16]. When the data have been limited to patients aged >90, there has been no consensus about the predictive factors for post-operative mortality. Our present investigation, limited to patients aged >90, is the first to compare frailty assessments' efficiency, and our findings indicate that the ECOG-PS is the most efficient tool for estimating 30-day mortality, especially in the emergency cases in this patient population. Our data indicated that, in more flail patients, symptoms in disease such as cholecystitis or colorectal emergency tend to be missed earlier because patients could not tell to care giver or family, possibly leading to the disease progression.

The 30-day mortality and post-operative complication rate in the present study were lesser values compared to previous reports, with no association between delirium and 30-day mortality. Several investigations have analyzed risk factors of post-operative mortality among older patients, but few concerned patients aged ≥90 years. Studies of patients aged ≥80 years reported 8%–10% mortality at 30 days after non-cardiac surgery [17, 18], a 50% rate of post-operative dysfunction, and a rate 20%–32% of post-operative complications [17, 19]. Some study with patients aged ≥75 showed that post-operative delirium, observed in 36% of the patients, was associated with increased mortality, institutionalization, and dependency, but not with an increased risk of re-admission on follow-up [20]. These differences could be due to adequate pre-operative evaluations, appropriate patient monitoring, and/or the advances in surgical treatments, anesthetics, and the early detection of post-operative complications.

This retrospective analyses of these 476 geriatric patients showed that a worse ECOG-PS was independently associated with 30-day mortality. However, our study has some limitations to address. It was a retrospective analysis at a single hospital with a single race background. There are no previous reports from Japan where with the large population of patients aged >90, focusing on the predictive factors of surgical mortality among high-aged patients. The surgical indications for high-aged patients especially in the emergency cases could be differ from the countries, the cultural backgrounds, and the medical resources. In addition, we evaluated only the patients' anesthesia and medical records, and thus other potential complications may have been missed. Dementia, delirium, and other post-operative complications may be included if other definitions of post-operative complications are applied. Our present findings are still meaningful due to the relatively large number of patients aged >90 years, which will be essential as the basis for the pre-operative evaluation and the informed consent. A prospective international multi-centered study with larger numbers of such patients is necessary for further investigations.

## Conclusion

The present study analyzed the predictive factors of 30-day mortality after non-cardiac surgery among 476 patients aged >90 years. Especially in emergency surgery, pre-operative ECOG score should be considered as predictive factors for mortality.

Conflict of Interest: The authors declare no conflict of interest.

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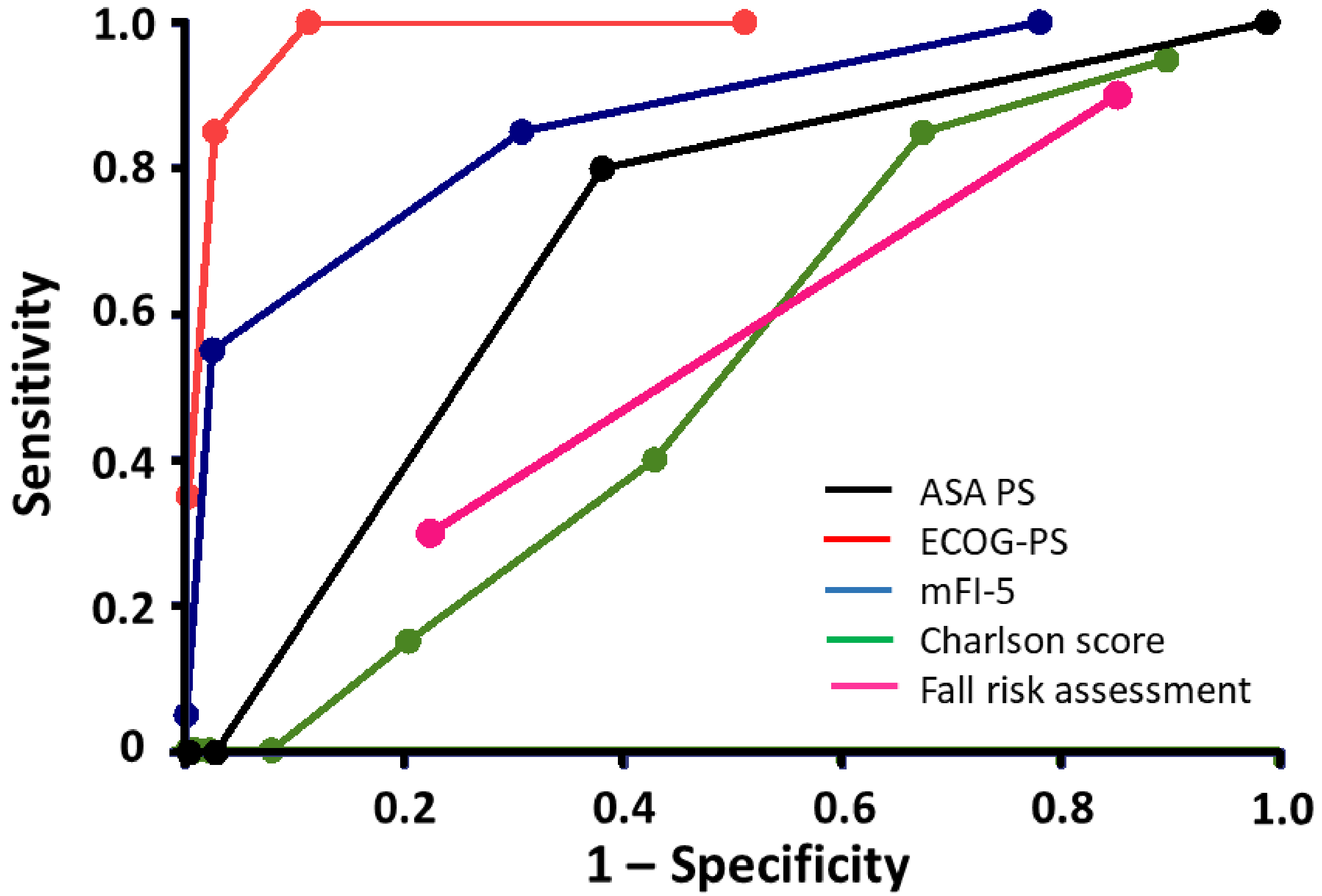
Figure legends

Figure 1. The comparison of ROC curves of pre-operative assessments for 30-day mortality. ASA PS: American Society of Anesthesiologists physical status; ECOG-PS: Eastern Cooperative Oncology Group performance status; mFI-5: the modified 5-item frailty index.

Figure 2. The Kaplan–Meier curves up to postoperative day 30. a: Kaplan–Meier curves for ECOG-PS up to 30 days after emergency surgery (n = 149, p<0.001, Log-rank test). b: Kaplan–Meier curves for ECOG-PS up to 30 days after elective surgery (n = 327, p<0.001, Log-rank test). ECOG-PS: Eastern Cooperative Oncology Group performance status.

Fig 1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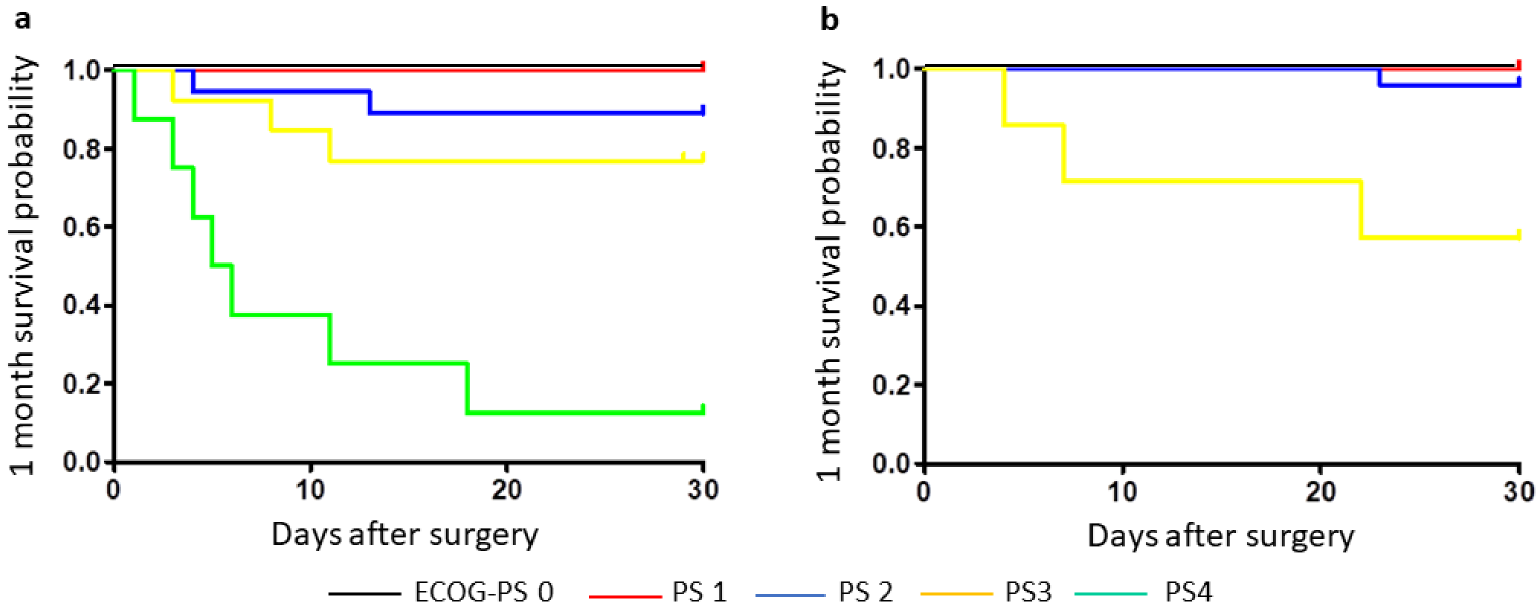
ECOG-PS
mFI-5
Charlson score
Fall risk assessment

Fig 2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PS 2
PS3
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Table 1. Preoperative and intraoperative patient characteristics

| | Non-survival | Survivor | p-value |
|---|---|---|---|
| **Patient characteristics** | | | |
| Patients, n (%) | 20 (4.20) | 456 (95.8) | – |
| Age, median, [IQR] | 92.3 [90–98] | 92.4 [90–102] | 0.83 |
| Female/male, n (%) | 12 (60.0) /8 | 293 (64.3%) /163 | 0.81 |
| BMI, median [IQR] | 20.5 [13.7–23.8] | 20.8 [12.3–32.5] | 0.73 |
| Emergency surgery, n (%) | 14 (70.0) | 135 (29.6) | 0.003 |
| ASA-PS, 1/2/3/4/5, n (%) | 0 / 1 (5.0) / 5 (25.0) / 0 / 0 | 5 (1.1) / 203 (44.5) / 112 (24.6) / 1 (0.2) / 0 | 0.11 |
| 1E/2E/3E/4E/5E, n (%) | 0 / 4 (20.0) / 11 (55.0) / 0 / 0 | 0 / 74 (16.2) / 49 (10.8) / 10 (2.2) / 2 (0.4) | 0.045 |
| Charlson score, median [IQR] | 2.4 [0–4] | 2.3 [0–7] | 0.93 |
| Fall risk assessment, I/II/III, n (%) | 2 (10.0) / 12 (60.0) / 6 (30.0) | 68 (15.0) /286 (62.7) / 102 (22.4) | 0.67 |
| ECOG-PS, 0/1/2/3/4, n (%) | 0 / 0 / 3(1.5) / 10(50.0) / 7(3.5) | 225(49.3) / 180(39.5) / 39(8.6) / 11(2.4) / 1(0.2) | < 0.001 |
| mFI-5, 0/1/2/3/4, n (%) | 0 / 3(15.0) / 4(20.0) / 11(55.0) / 1(5.0) | 103(22.6) / 214(46.9) / 128(28.1) / 10(2.2) / 1(0.2) | < 0.001 |
| Pre-operative ventilation, n (%) | 4 (20.0) | 13 (2.9) | 0.004 |
| **Intra-operative characteristics** | | | |
| Surgical site, n (%) | | | 0.058 |
| Head/neck | 4 (20.0) | 44 (9.7) | |
| Abdominal | 13 (65.0) | 194 (42.5) | |
| Extremity | 3 (15.0) | 155 (34.0) | |
| Superficial | 0 | 41 (9.0) | |
| Other | 0 | 22 (4.8) | |
| General anesthesia, n (%) | 17 (85.0) | 386 (84.7) | 1.000 |
| Anesthesia time, min, median [IQR] | 225 [92–375] | 186 [23–769] | 0.05 |

| | | | |
|---|---|---|---|
| Surgery time, min, median [IQR] | 159 [59–326] | 115 [6–635] | 0.01 |
| Fluid volume, mL, median [IQR] | 3215 [430–7760] | 1243 [100–5100] | < 0.001 |
| Volume of blood loss, mL, median [IQR] | 464.3 [0–3910] | 86.7 [0–1431] | < 0.001 |
| The presence of transfusion, n (%) | 11 (55.0) | 61 (13.4) | < 0.001 |
| Urine, mL, median [IQR] | 319.3 [5–1150] | 164.6 [0–1900] | 0.008 |
| EEG monitor, n (%) | 6 (30.0) | 124 (27.2) | 0.80 |
| Post-operative ventilation, n (%) | 8 (40.0) | 15 (3.3) | < 0.001 |
| Post-operative results | | | |
| Perioperative complications, n (%) | 5 (25.0) | 61 (13.4) | 0.18 |
| Delirium | 1 (5.0) | 39 (8.6) | 1.00 |
| Aspiration pneumonia | 0 | 4 (0.9) | 1.00 |
| Hypoxia | 8 (40.0) | 11 (2.4) | < 0.001 |
| Cerebral infarction | 0 | 4 (0.9) | 1.00 |
| Ventilation-associated pneumonia | 1 (5.0) | 0 | 1.00 |
| Shunt occlusion | 0 | 1 (0.2) | 1.00 |
| Congestive heart failure | 1 (5.0) | 0 | 1.00 |
| Infection | 0 | 1 (0.2) | 1.00 |
| The length of hospital stay, days, median [IQR] | 12.5 [0–30] | 21.0 [2–147] | 0.047 |

Data are shown as patient number (%) or median [range]. BMI: body mass index; ECOG-PS: Eastern Cooperative Oncology Group performance status; mFI-5: the Modified 5-item Frailty Index; ASA-PS: American Society of Anesthesiologists physical status; EEG: electroencephalogram.

*$p<0.05$

Table 2. The comparison of ROC curve results of pre-operative assessments.

| Assessment methods | AUC | Threshold | Sensitivity | Specificity | p-value |
|---|---|---|---|---|---|
| ASA-PS | 0.70 | 2.5 | 0.80 | 0.62 | 0.003 |
| ECOG-PS | 0.98 | 2.5 | 0.85 | 0.98 | <0.001 |
| mFI-5 | 0.86 | 1.5 | 0.85 | 0.69 | <0.001 |
| Charlson score | 0.53 | 1.5 | 0.85 | 0.33 | 0.77 |
| Fall risk assessment | 0.55 | 2.5 | 0.30 | 0.78 | 0.44 |

AUC: Area under the curve; ASA-PS: American Society of Anesthesiologists physical status; ECOG-PS: Eastern Cooperative Oncology Group performance status; mFI-5: the modified 5-item frailty index.

Table 3. Multivariate logistic regression analysis for 30-day mortality after emergency non-cardiac surgery among older patients.

| Variable | Odds ratio [95%CI] | p-value |
|---|---|---|
| Abdominal surgery | 9.38 [1.01-86.73] | 0.049 |
| Pre-operative ECOG-PS>3 | 1.71 [1.35-2.16] | p<0.001 |

ECOG-PS: Eastern Cooperative Oncology Group performance status.