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ORIGINAL ARTICLE

The relationship between perioperative central venous oxygen saturation and postoperative complications in highly invasive gastroenterological surgery

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Abstract

Purpose: Operations for malignant diseases of the bile duct, pancreas, and esophagus are the most invasive gastroenterological surgeries. The frequency of complications after these surgeries is high, which affects the postoperative course and mortality. In patients who undergo these types of surgeries, continuous monitoring of the perioperative central venous oxygen saturation ($ScvO_2$) is possible via a central venous catheter. We aimed to investigate the relationship between continuously monitored perioperative $ScvO_2$ values and postoperative complications.

Methods: The medical records of 115 patients who underwent highly invasive gastroenterological surgeries and $ScvO_2$ monitoring from April 2012 to March 2014 were analyzed. Sixty patients met the inclusion criteria, and their $ScvO_2$ levels were continuously monitored perioperatively. The relationship between $ScvO_2$ levels and major postoperative complications, defined as Clavien–Dindo grade ≥ III, was examined using uni- and multivariate analysis.

Results: Thirty patients developed major postoperative complications. The adequate cut-off value derived from receiver operating curves of the postoperative average $ScvO_2$ levels for predicting major complications was 75%. Multivariate analysis revealed that low average postoperative $ScvO_2$ levels ($p = 0.016$) and blood loss ≥ 1000 mL ($p = 0.039$) were significant predictors of major postoperative complications.

Conclusions: Low perioperative $ScvO_2$ values were associated with an increased risk of major postoperative complications. Continuous $ScvO_2$ monitoring will help prevent postoperative complications.

KEYWORDS
anastomotic failure, central venous oxygen saturation, gastroenterological surgery, postoperative complications, surgical site infection

1 | INTRODUCTION

Surgical procedures for malignant diseases of the bile duct, pancreas, and esophagus are lengthy and highly invasive, involving complicated procedures ranging from resection to reconstruction.[1–4] The frequency of postoperative complications in these invasive gastroenterological surgeries is high, which has a significant effect on morbidity and mortality.[2–4] Therefore, continuous monitoring of key risk indicators are necessary to predict complications and facilitate early therapeutic interventions.

Many postoperative complications in gastroenterological surgery, including anastomotic failure and surgical site infection, are reportedly caused by metabolic disturbances due to a decrease in tissue oxygenation.[5,6] Anastomotic failure is the most critical complication in gastroenterological surgery. Although indocyanine green fluorescence imaging and a Doppler blood flow meter are used to evaluate anastomotic blood flow, they are usually only used before performing anastomosis.[7,8] Moreover, these devices are not used after surgery to predict anastomotic failure. It has also been reported that surgical site infection,[6] liver dysfunction,[9] postoperative cognitive dysfunction, and delirium[10,11] are associated with reduced tissue oxygenation, which greatly affects the postoperative course.

The central venous oxygen saturation ($ScvO_2$) value is an index that reflects the balance between oxygen supply and consumption, which may be useful in predicting postoperative complications. The factors affecting $ScvO_2$ are cardiac output, hemoglobin concentration, inspired oxygen concentration, and tissue oxygen consumption.[12] When tissue oxygen consumption exceeds the oxygen supply, complications occur due to tissue hypoxia. $ScvO_2$ is used as an index of the supply–demand balance of oxygen in the tissues, which is similar to mixed venous oxygen saturation (SvO_2) used in highly invasive surgeries.[13] $ScvO_2$ can be monitored via a central venous catheter, unlike SvO_2 which requires the insertion of a catheter into the pulmonary artery; therefore, measurements of $ScvO_2$ are minimally invasive unlike SvO_2.[14]

There are only a few studies on whether $ScvO_2$ can be used to predict postoperative complications; one study has reported that postoperative complications can be reduced by monitoring intraoperative $ScvO_2$ and by performing therapeutic interventions in high-risk surgical patients.[15] Few previous reports exist on the continuous monitoring of $ScvO_2$ during lengthy and highly invasive operations for malignant diseases of the bile duct, pancreas, and esophagus.[9,16,17] Reports on the use of $ScvO_2$ as an index of perioperative management, apart from those for specific operations such as heart surgery[18] and liver transplant,[19] are scarce. No consensus has been reached for the target value of perioperative $ScvO_2$.

A randomized controlled trial of patients with sepsis revealed that targeting $ScvO_2 \geq 70\%$ during initial resuscitation from severe sepsis or septic shock could reduce in-hospital mortality[20]; this has been strongly recommended in the Surviving Sepsis Campaign Guidelines.[21] However, multicenter randomized controlled trial[22] did not confirm these findings, and the evaluation of $ScvO_2$ in patients with sepsis remains controversial.[23] The factors leading to low ScvO2 values in patients with postoperative complications remain unclear.

In this study, we aimed to investigate the relationship between continuously monitored $ScvO_2$ values in the intra-/postoperative periods and postoperative complications in patients undergoing major hepatobiliary, pancreatic, and esophageal surgeries and define the target $ScvO_2$ value.

2 | METHODS

2.1 | Patients

We retrospectively analyzed the electronic health records of 115 consecutive patients who underwent gastroenterological surgeries and $ScvO_2$ monitoring in the Department of Gastroenterological Surgery II, Hokkaido University Hospital from April 2012 to March 2014. Nine patients who underwent surgical procedures other than radical resection and 46 patients with incomplete $ScvO_2$ data, including improper pre-, intra-, or postoperative measurements or inaccurate values [signal quality index (SQI) = 4; Unacceptable] were excluded from the study. A total of 60 patients who underwent radical surgery for hepatobiliary, pancreatic, and esophageal diseases were included in the study and their medical records were analyzed to obtain information on background factors, surgical procedure performed, and postoperative complications. Postoperative complication was defined as any event affecting a patient that is undesirable, unintended, and a direct result of operative procedure. In this study, we evaluated the in-hospital postoperative complication as per the Clavien–Dindo classification, and defined Clavien–Dindo grades ≥ III as major complication. The patients were divided into two groups depending on whether the major complication has happened or not (Figure 1). The two groups were compared in terms of background factors, surgical outcomes, and $ScvO_2$ values.

This study was approved by the institutional review board (authorization number: 020–0272) and conformed to the provisions of the Declaration of Helsinki. The records of patients who refused access to their data were excluded from the analysis.

2.2 | Monitoring of $ScvO_2$

A PreSep oximetry catheter and Vigileo monitor (Edwards Lifescience Corporation, California, USA) were used to monitor the $ScvO_2$. Patients were placed under ultrasound and fluoroscopy to confirm that the target of the catheter tip was 2 cm distal to the tracheal bifurcation, as this position was considered to have the best SQI based on a pilot study in our department. The preoperative $ScvO_2$ was recorded and the Vigileo monitor was calibrated after the catheter placement. The intra- and postoperative $ScvO_2$ levels were monitored continuously using a Vigileo monitor for up to 12 h after surgery. The $ScvO_2$ values were recorded every 20 s. All recorded

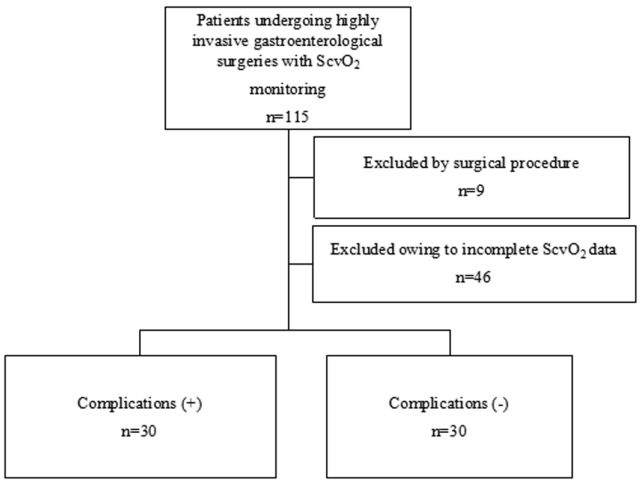

FIGURE 1 Flow diagram of this study. The intraoperative $ScvO_2$ of 115 patients was monitored. Nine patients were excluded due to the surgical procedure received and 46 patients were excluded because of incomplete $ScvO_2$ data. The remaining 60 cases were included. Major complications graded as Clavien–Dindo ≥ III were observed in 30 patients. $ScvO_2$, central venous oxygen saturation.

$ScvO_2$ values were summed up and divided by the total number of measurements to calculate the average $ScvO_2$.

2.3 | Statistical analyses

Continuous data were evaluated with the Mann–Whitney U test and nominal data with the chi-square test. The limit for inclusion of new terms was set at $p<0.05$, and a multiple logistic regression model was used to identify independent risk factors for major postoperative complications. Univariate analysis was used to compare the $ScvO_2$ values and background factors between patients with and without major postoperative complications. Receiver operating curves (ROC) were generated to identify the cut-off values of postoperative $ScvO_2$ for predicting major complications, and the area under the ROC curve was calculated. The analysis was performed using EZR (Ver. 1.42, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria),[24] and significance was set at $p<0.05$.

3 | RESULTS

The mean age of the patients in our cohort was 65 (range, 13–80) years. The surgical procedures performed included the following 17 liver lobectomies, 17 pancreaticoduodenectomies, three hepat opancreaticoduodenectomies, 11 esophagectomies, and 12 others (e.g. distal pancreatectomies, and partial hepatectomies). The mean duration of the surgical procedures was 629 (range, 311–994) min, and the mean blood loss was 1677 (range, 120–8510) mL. Major complications were observed in 30 patients (30/60, 50%). The most common complication was anastomotic failure seen in 17 patients (28%). Seven patients underwent a reoperation (12%), and postoperative mortality was 3% (2/60 patients) (Table 1). Univariate analysis of $ScvO_2$ values and major complications revealed that the intraoperative and postoperative average ($p=0.032/0.014$) and lowest ($p=0.047/0.040$) $ScvO_2$ values were associated with major postoperative complications (Table 2). Univariate analysis of the background factors showed that only factor associated with major postoperative complications was blood loss ($p=0.015$) (Table 3).

We selected postoperative average $ScvO_2$ for the multivariate analysis and ROC because intraoperative $ScvO_2$ fluctuated greatly due to the introduction of anesthesia and surgical intervention. Moreover, range of postoperative average $ScvO_2$ value is wider, which is advantageous as an indicator (Figure 2). The cut-off values of postoperative $ScvO_2$ derived from ROC curves was set to 75%

TABLE 1 Patient demographics and complications.

Background factors	Number of patients (%), $n=60$ or mean (range)
Age, years	65 (13–80)
Sex, male/female	39/21
BMI, kg/m^2	22.7 (16.8–31.6)
ASA status, 1/2/3	9/48/3
Surgical procedure	
Liver lobectomy	17 (28)
PD	17 (28)
HPD	3 (5)
Esophagectomy	11 (18)
Others (e.g., DP, partial hepatectomy.)	12 (20)
Length of operation, min	629 (311–994)
Blood loss, mL	1677 (120–8510)
Complication	
Anastomotic failure	17 (28)
Intra-abdominal/thoracic abscess	13 (22)
Sepsis	11 (18)
Bleeding	10 (17)
Organ dysfunction	6 (10)
Re-operation	7 (12)
CD grade	
IIIa	22 (37)
IIIb	2 (3)
IVa	2 (3)
IVb	2 (3)
V	2 (3)
Major complications	30 (50)

Note: The definition of a major complication of Clavien–Dindo grade III or higher.

Abbreviations: ASA, American Society of Anesthesiologists physical status; BMI, body mass index; CD, Clavien–Dindo; DP, distal pancreatectomy; HPD, hepatopancreaticoduodenectomy; min, minute; PD, pancreaticoduodenectomy.

TABLE 2 Univariate analysis of $ScvO_2$ value and major postoperative complications.

$ScvO_2$ value	Patients without major complications ($n=30$)	Patients with major complications ($n=30$)	p
Preoperative $scvo_2$, % (range)	67.9 (51.0–83.4)	65.6 (49.4–80.9)	0.23
Intraoperative $scvo_2$, average %	80.3 (61.9–91.7)	77.5 (68.2–86.1)	0.032*
Intraoperative $scvo_2$, lowest % (range)	67.4 (40–83)	61.3 (27–80)	0.047*
Postoperative $scvo_2$, average % (range)	81.0 (65.6–93.3)	75.3 (47.3–86.1)	0.014*
Postoperative $scvo_2$, lowest % (range)	61.2 (43–89)	48.6 (14–78)	0.040*

Note: The definition of a major complication is a complication graded Cravien-Dindo grade III or higher.
Abbreviation: $ScvO_2$ central venous oxygen saturation.
*Significant p value.

TABLE 3 Univariate analysis of background factors and major complications.

Background factor	Patients without major complications ($n=30$)	Patients with major complications ($n=30$)	p
Age, years	66 (13–78)	69 (45–80)	0.17
Sex, male/female	18/12	21/9	0.59
BMI, kg/m^2 (range)	23.4 (18.2–31.3)	22.0 (16.8–31.6)	0.060
ASA status, 1/2/3	4/25/1	5/23/2	0.16
Surgical procedures Liver lobectomy/ pancreatectomy/ esophagectomy	9/12/9	14/12/4	0.23
Length of operation, min (range)	594 (311–931)	622 (419–994)	0.21
Blood loss, mL (range)	887 (170–7680)	1715 (120–8510)	0.015*
Diabetes, +/−	5/25	6/24	1.0
Heart disease, +/−	5/25	2/28	0.24
Pulmonary dysfunction, +/−	6/24	7/23	0.76

Note: The definition of a major complication is a complication graded Clavien-Dindo grade III or higher.
Abbreviations: ASA, American Society of Anesthesiologists physical status; BMI, body mass index.
*Significant p value.

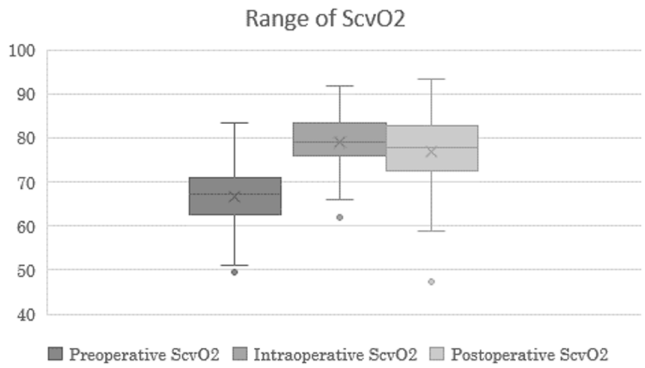

FIGURE 2 Range of perioperative $ScvO_2$. The postoperative $ScvO_2$ was monitored for up to 12 h. $ScvO_2$, central venous oxygen saturation.

(Figure 3). After multivariate analyses, postoperative $ScvO_2$ values ($p=0.016$) and blood loss ≥ 1000 mL ($p=0.039$) were found to be independently associated with major postoperative complications (Table 4).

Sub analysis was done by grouping patients into postoperative $ScvO_2 \leq 75\%$ group and $ScvO_2 > 75\%$ group. No significant differences were found between two groups in the comparison of perioperative factors. The incidence of any complication and perioperative factors were compared. Significant differences in major complications ($p=0.025$) and anastomotic failure ($p=0.035$) were identified between the two groups (Table 5).

4 | DISCUSSION

The main finding of this study was the association of low intra- and postoperative $ScvO_2$ values with an increased risk of major postoperative complications after highly invasive gastroenterological surgery. Supporting our results, the association of intraoperative $ScvO_2$ values with anastomotic failure in colectomy and postoperative organ dysfunction in surgical patients has been reported.[9,25]

Our results suggest that optimization of $ScvO_2$ may contribute to the prevention of major postoperative complications and

anastomotic failure. The supply of high concentration oxygen is known to be effective in preventing surgical site infection,[26] and $ScvO_2$ can be a useful index of tissue oxygenation. The average value of $ScvO_2$ in a healthy person is about above 70%.[13] In our study, we set the cut-off line for $ScvO_2$ at 75%, which is higher than the average of a healthy person. According to our result, the postoperative $ScvO_2$ should be maintained high, to prevent the postoperative complication. Low $ScvO_2$ can be caused by respiratory distress, anemia, etc. Oxygenation should be facilitated by proper management, including reintubation and blood transfusion in case of low $ScvO_2$.

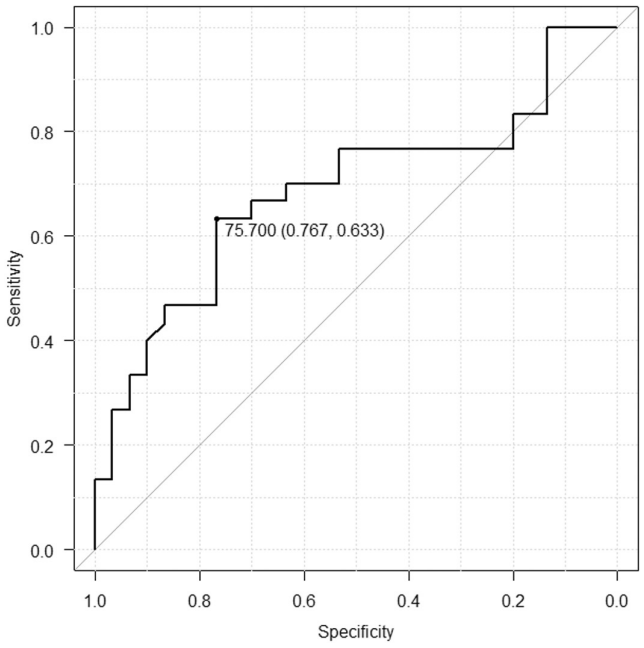

FIGURE 3 ROC curve of postoperative $ScvO_2$ (average) and major complications; 75% was the most suitable threshold. ROC, receiver operating characteristics; $ScvO_2$, central venous oxygen saturation.

Of 14 patients who had developed major complications with perioperative $ScvO_2 < 75\%$, half were observed anemia: one had intraoperative blood loss of more than 2000 mL, one had intraoperative Hb below 8.0 g/dL, and five cases had both. This indicates that intraoperative blood loss plays a significant role in the decline in $ScvO_2$ value. In contrast, two cases in low perioperative $ScvO_2$ group with blood loss less than 500 mL had also developed complications. Cardiotonic agents should be considered for decreased cardiac output, and treatment needs to be commenced if there are signs of sepsis. Reduction of $ScvO_2$ can be caused by multiple factors. Cause-specific approaches and target thresholds should be considered based on individual patient characteristics and clinical context.

Several procedures exist to monitor $ScvO_2$, including intermittent or continuous monitoring and choosing the lowest or the average values. $ScvO_2$ varies greatly depending on the status of the patient; therefore, we applied continuous $ScvO_2$ monitoring and analyzed the average values of $ScvO_2$ instead of considering the lowest values. Continuous $ScvO_2$ monitoring and evaluation of the average value makes it possible to eliminate bias caused by the intraoperative state of patients, and the risk of complications can be predicted more accurately. Sankar et al. reported that continuous monitoring of $ScvO_2$ and therapeutic intervention in patients with sepsis improved prognosis as compared to intermittent monitoring.[27]

Perioperative monitoring of $ScvO_2$ may be a more sensitive indicator of oxygen supply–demand balance than other types of

TABLE 4 Multivariable analyses of postoperative $ScvO_2$ values (average) and major complications.

	Univariate			Multivariate		
Factor	**OR**	**95% CI**	***p* Values**	**OR**	**95% CI**	***p* Values**
Age (≥70 years)	2.41	0.82–7.10	0.11			
Sex (Male)	1.56	0.53–4.53	0.42			
BMI (≥25 kg/m^2)	0.88	0.75–1.03	0.12			
ASA (1/2 or 3)	0.77	0.19–3.20	0.72			
Surgical procedure (liver lobectomy or pancreatectomy/ esophagectomy)	0.36	0.10–1.33	0.13			
Length of operation (≥600 min)	1.50	0.53–4.17	0.44			
Blood loss (≥1000 mL)	3.14	1.07–9.27	0.038*	3.39	1.06–10.8	0.039*
Diabetes (+/−)	1.25	0.34–4.64	0.74			
Heart disease (+/−)	0.36	0.06–2.01	0.24			
Pulmonary dysfunction (+/−)	1.22	0.36–4.17	0.75			
Postoperative $scvo_2$ (average, ≤75%)	4.37	1.32–14.5	0.016*	4.69	1.33–16.95	0.016*

Note: The definition of a major complication is a complication graded Clavien-Dindo grade III or higher.

Abbreviations: ASA, American Society of Anesthesiologists physical status; BMI, body mass index; CI, confidence interval; OR, odds ratio; $ScvO_2$, central venous oxygen saturation.

*Significant *p* value.

TABLE 5 Comparison of perioperative factors affect $ScvO_2$ and complications based on a 75% mean postoperative $ScvO_2$ cut-off value.

Factor	$ScvO_2 \leq 75\%$ ($n=19$)	$ScvO_2 > 75\%$ ($n=41$)	p
Respiratory dysfunction (+/−)	2/17	11/30	0.18
Preoperative $scvo_2$ values(range)	66.9(53.7–79.0)	66.7(49.4–83.4)	0.93
Perioperative lowest hemoglobin concentration(range)	8.5(6.3–11.5)	8.4(5.9–12.8)	0.83
Blood transfusion (+/−)	8/11	16/25	0.63
Average cardiac output(range)	4.6(3.4–6.6)	4.6(3.2–7.2)	0.85
Complication (+/−)			
Anastomotic failure	9/10	8/33	0.035*
Intra-abdominal/thoracic abscess	6/13	7/34	0.30
Sepsis	6/13	5/36	0.086
Bleeding	4/15	6/35	0.67
Organ dysfunction	1/18	5/36	0.65
Reoperation	4/15	3/38	0.19
Major complications	14/5	16/25	0.025*

Note: The definition of a major complication is a complication graded Clavien-Dindo grade III or higher.
Abbreviation: $ScvO_2$, central venous oxygen saturation.
*Significant p value.

monitoring. For example, perioperative peripheral capillary oxygen saturation (SpO_2) and central venous pressure (CVP) are monitored continuously to evaluate the tissue oxygenation status[28]; however, unlike $ScvO_2$, the SpO_2 and CVP values do not vary significantly (SpO_2 is often 95%–100% throughout surgery) and therefore are not sensitive indicators. In this study, $ScvO_2$ demonstrated a wide fluctuation range of approximately 40%–90% and was therefore considered a more sensitive indicator of oxygen supply–demand balance. Perioperative monitoring of serum lactate is another method used to evaluate the tissue oxygen supply–demand balance.[29] Study has shown that serum lactate values are useful in monitoring patients with septic shock.[30] However, serum lactate is typically measured withy blood gas analyses. Continuous serum lactate measurement will require specialized equipment, which is not clinically practical.

In contrast to the hyperdynamic state of sepsis, which $ScvO_2$ is commonly higher. In our study, high $ScvO_2$ values did not adversely affect postoperative outcomes. This difference may be due to differences in sepsis and perioperative pathology. Investigating the underlying pathophysiological mechanisms would require further research, including experimental and mechanistic studies.

Our study demonstrates that intra- and postoperative $ScvO_2$ were associated with major postoperative complications in highly invasive gastroenterological surgeries for hepatobiliary, pancreatic, and esophageal diseases.

This study has some limitations. First, 46 patients were excluded from the study due to incomplete $ScvO_2$ data. In our institution, fluoroscopy was used to confirm the position of the catheter tip at 2 cm distal to the tracheal bifurcation, as this position was considered to have the best SQI index based on a pilot study done by our department. Despite this, some patients presented poor SQI indices and were excluded from this study. The optimal position of the catheter tip for accurate $ScvO_2$ monitoring and the confirmation method used are subjects for future research. Second, this study was conducted as a single-center, retrospective study; for this reason, many factors regarding perioperative management were not assessed, which created bias in the data regarding postoperative complications. Third, the intra- and postoperative oxygen supply was determined by the anesthesiologist, which affected the $ScvO_2$ values. Although we estimated the cut-off value of postoperative $ScvO_2$ as 75%, further research is required to determine its validity and ability to facilitate the prevention of postoperative complications.

5 | CONCLUSIONS

In this study, we observed that low intra- and postoperative $ScvO_2$ were associated with an increased risk of major postoperative complications in highly invasive gastroenterological surgery. The adequate cut-off value of postoperative $ScvO_2$ for predicting major complications was estimated at 75%. Continuous intra- and postoperative $ScvO_2$ monitoring and therapeutic interventions may facilitate the prevention of postoperative complications. Further studies are required to reveal the underlying mechanisms of decreased $ScvO_2$ in patients with postoperative complications and to validate the potential benefits of $ScvO_2$ monitoring.

AUTHOR CONTRIBUTIONS

D.M. did the study design, analyzed the data, interpreted the results, and wrote the manuscript. T.S. is the corresponding author of the manuscript; contributed to conception and design, analyzed data, revised the article. Y.K. contributed to the conception and design, interpreted and offered analyses of the results. Y.W. verified the

study design and contributed to the process of the ethics review and statements. S.H. supervised the hole research and revised the article. All of the authors made substantial contributions to the study concept or the data analysis or interpretation, revised it critically for important intellectual content, approved the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work.

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FUNDING INFORMATION

We have no funding of interest to declare.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENTS

Approval of the research protocol: This study was approved by the institutional review board (authorization number: 020–0272) and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013), available at: https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/.
Informed consent: In accordance with the Japan Ethical Guidelines for Medical and Health Research Involving Human Subjects, informed consent was obtained from all participants on the Hokkaido University Hospital website (https://www.huhp.hokudai.ac.jp/wp-content/uploads/2021/03/020-0272.pdf).
Registry and the Registration No. of the study/Trial: N/A.
Animal Studies: N/A.

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