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Preoperative detection of serum phosphorylated neurofilament heavy chain subunit predicts postoperative delirium: a prospective observational study

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Background & Aims. Elderly surgical patients are susceptible to development of postoperative delirium. Interventions for postoperative delirium have little effect on its progression, indicating the importance of early detection and prevention. This study investigated preoperative biomarkers to predict postoperative delirium.

Methods. Delirium-related serum biomarkers were measured before the start of surgery in patients who underwent esophageal cancer surgery and were compared between patients who did and did not develop postoperative delirium.

Results. Fifteen of 96 patients (15.6%) developed postoperative delirium. Brain-derived phosphorylated neurofilament heavy subunit was preoperatively detected in 80% of patients with postoperative delirium. The preoperative interleukin-6 (IL-6) concentration was significantly higher whereas the concentrations of plasminogen activator inhibitor-1 (PAI-1) was significantly lower in patients with postoperative delirium. Detection of phosphorylated neurofilament heavy subunit was associated with postoperative delirium independent of age (adjusted odds ratio, 5.86; 95% confidence interval, 1.60-29.03; p = 0.0064). The sensitivity and specificity of postoperative delirium detection was increased when age was combined with detection of phosphorylated neurofilament heavy subunit.

Conclusions. Preoperative evaluation of phosphorylated neurofilament heavy subunit can predict postoperative delirium independent of age. Early detection of serum phosphorylated neurofilament heavy subunit before surgery may enable clinicians to identify patients at risk for postoperative delirium and start early intervention.

Key words: postoperative delirium, biomarkers, cancer surgery

List of abbreviations

PD: postoperative delirium
CAM-ICU: the Confusion Assessment Method for the Intensive Care Unit

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ICDSC: the Intensive Care Delirium Screening Checklist
ICU: intensive care unit
pNF-H: phosphorylated neurofilament heavy subunit
CNS: central nervous system
PECAM-1: platelet endothelial cell adhesion molecule-1
MMP-9: matrix metalloprotease-9
PAI-1: plasminogen activator inhibitor-1
IL-6: interleukin-6
BBB: blood brain barrier
CSF: cerebrospinal fluid
NRS: Numeric Rating Scale
NSE: Neuron-specific enolase
ApoE: apolipoprotein E

BACKGROUND & AIMS

Postoperative delirium (PD) is a complication that occurs in 30 to 50% of elderly patients and is associated with a significant increase in length of hospital stay, cost of care, and mortality [1,2]. Older age, male sex, dementia, mild cognitive impairment, laboratory abnormalities, drugs including opioids, surgery, anaesthesia, high pain levels, anaemia, infections, acute illness, and acute exacerbation of chronic illness are commonly identified as risk factors for the development of delirium [3].

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [4] and the Intensive Care Delirium Screening Checklist (ICDSC) [5] are commonly used to screen for delirium in critically ill patients in the intensive care unit (ICU). A meta-analysis of the diagnostic accuracy of these screening tools revealed that the ICDSC had a pooled sensitivity of 74% and a specificity of 82% whereas the CAM-ICU had a pooled sensitivity of 80% and a pooled specificity of 96% to detect delirium [6]. However, it can still be difficult to predict PD, and delayed diagnosis can lead to brain atrophy, even in patients who recover from PD [7].

On the basis of a previous report that linked the incidence of PD to brain atrophy [8], we measured the serum concentration of phosphorylated neurofilament heavy subunit (pNF-H), a major cytoskeletal protein of central nervous system (CNS) axons, in patients with PD. Although pNF-H is normally undetectable in blood samples of healthy patients, it was detected in 56.1 to 65.2% of patients who experienced PD [9,10], suggesting that neural damage is accompanied by PD development. In addition, we previously reported that elevation of the serum pNF-H levels was correlated with the progression of delirium-related CNS damage, which was associated with platelet endothelial cell adhesion molecule (PECAM)-1 [9]. Therefore, pNF-H may serve as a biomarker of neural tissue damage, which is exacerbated by the effects of perioperative mediators involved in inflammation-induced coagulation/fibrinolysis. The increase in matrix metalloprotease (MMP)-9 and plasminogen activator inhibitor (PAI)-1 disrupts the integrity of the blood brain barrier (BBB), resulting in neurodegenerative progression in the aged brain [11,12].

In addition, significant concentrations of pro- and anti-inflammatory markers are detectable in the serum and cerebrospinal fluid (CSF) after surgery in elderly adults [13,14], and different anaesthetic agents may modulate immune signaling pathways [15,16]. Zhang et al. [17] reported that dexmedetomidine suppresses postoperative elevation of pro-inflammatory cytokines such as interleukin (IL)-6 and reduces the incidence of PD in elderly patients over the first 3 days after hip fracture surgery.

These findings suggest that management of anaesthesia in surgery and sedation in the ICU can affect cognitive outcomes. Accordingly, perioperative intervention may be able to reduce the risk of PD in high-risk elderly patients. However, preoperative biomarkers that can be used for early prediction of PD have not yet been identified. In this study, we hypothesised that (1) chronic neurodegeneration is present in the elderly patients before surgery; (2) acute exacerbation of neural damage is triggered by surgical stress, resulting in PD development, and (3) patients with CNS markers that are detectable before surgery can be susceptible to PD. Therefore, this study aimed to investigate whether serum biomarkers, CNS-derived biomarkers, and pNF-H can predict PD in elderly patients to identify patients at risk and allow prevention. Additionally, the link between the pNF-H level and factors involved in inflammation and coagulation/fibrinolysis was explored.

PATIENTS AND METHODS

Ethics

The study was approved by the Ethical Committee of the University of Tokyo [Approval ID:10051] and conducted in hospitals of the University of Tokyo from October 2016 to June 2019. The local ethics committee of each institution approved the trial protocol and written informed consent was obtained from each patient. The study was registered in the University Medical Information Network (UMIN trial ID: UMIN000010329).

Study population

Patients scheduled to undergo oesophageal cancer surgery were eligible for inclusion. The surgical procedure consisted of open, robot-assisted, or mediastinoscope-assisted esophagectomy. All patients undergoing oesophageal cancer surgeries were admitted to the ICU. The exclusion criteria were as follows: (1)

patients with a score of 4 on the American Society of Anesthesiologists physical classification; (2) patients with a history of clinically relevant cognitive dysfunction or a neurological disorder diagnosed by a neurologist before surgery according to the patient's records, and (3) patients who were regularly prescribed tranquilizers that could influence PD [18].

Patient assessment

In the first 3 days after surgery, delirium-associated symptoms were screened by the attending nurses at least three times a day during regular ward rounds using the CAM-ICU. Patients with suspected PD underwent further assessment using the ICDSC to confirm the diagnosis. The postoperative pain intensity was evaluated using the Numeric Rating Scale (NRS), with 0 indicating no pain and 10 indicating the worst possible pain [19]. The total amount of fentanyl equivalents used during surgery was the exposure variable as previously described [20,21]. The fentanyl equivalent conversion factors for 1 μg of fentanyl were 1 μg of remifentanil and 100 μg of morphine.

Measurement of biomarkers

Blood samples were collected from an arterial blood pressure monitoring line immediately after induction of anaesthesia and before the start of surgery in the operating room and stored at -20°C. Neuron-specific enolase (NSE), platelet endothelial cell adhesion molecule-1 (PECAM-1), matrix metalloprotease-9 (MMP-9), PAI-1, and IL-6 were measured using a multiplex immunoassay (Luminex® Assay Human Premixed Multi-Analyte Kit; R&D, Rockville, MD, USA) according to the manufacturer's protocol. Measurement of pNF-H was performed using an enzyme-linked immunosorbent assay (Modrice, Czech Republic) according to the manufacturer's protocol; the threshold concentration for detection was 70.5 ng/mL. All samples were measured in duplicate.

Statistical analysis

Statistical analyses were performed using JMP Pro software version 16 (SAS Institute, Cary, NC, USA). Patient characteristics and log-transformed biomarker concentrations were compared using the Wilcoxon rank-sum test or Pearson's chi-square test. Logistic regression based on the log-transformed concentration of the potential candidate variables was performed to identify independent parameters and biomarkers for PD as previously reported [22]. $P < 0.05$ was considered significant.

RESULTS

A total of 120 patients who underwent elective oesophageal cancer surgery and provided written informed consent for participation were screened (Fig. 1). Two eligible patients were excluded based on the criteria. Blood samples were not collected from 20 patients who were reintubated in the ICU or operating room, or admitted to the ICU under intubation because of unstable haemodynamics. In addition, two patients who underwent other surgical procedures were excluded. Patients between 47 and 85 years old were enrolled in this study. PD occurred in 15 of 96 patients (15.6%) in the first 3 days after surgery. PD patients were significantly older than those who did not experience PD (Tab. I). Preoperative opioid use were significantly correlated with PD. Regarding intraoperative parameters, the surgical procedure, combination of epidural anaesthesia with general anaesthesia, and were also correlated with PD (Tab. II). Neither the total amount of opioids used during surgery nor the postoperative pain intensity designated by the NRS (Supplementary Table I) differed between the two groups. A significantly higher proportion of PD patients were positive for pNF-H before surgery (Tab. III). In addition, the preoperative IL-6 concentration was significantly higher in PD patients. However, multivariate logistic regression analysis showed that factors involved in inflammation and coagulation/fibrinolysis were not associated with the detection of pNF-H (Supplementary Table II). Preoperative detection of pNF-H (adjusted odds ratio, 5.86; 95% confidence interval, 1.60-29.03; p = 0.0064) and age (adjusted odds ratio, 1.12; 95% confidence interval,1.03-1.23; p = 0.0062) were independent factors associated with PD (Tab. IV), even in the analysis including preoperative

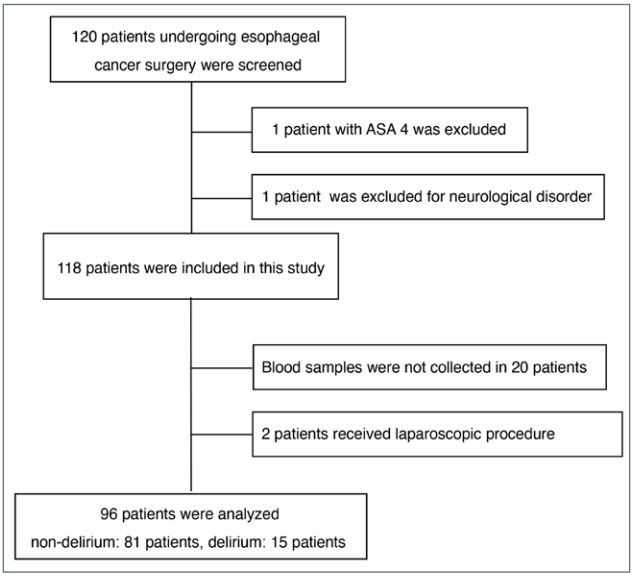

Figure 1. Flow-chart indicating the number of patients excluded and included in the data analysis.

Table I. Patient characteristics.

Variable	Non-PD	PD	*P*-value
	n = 81	n = 15	
Age (y)	67 ± 9	74 ± 7	0.0021
Gender (M/F)	69/12	13/2	0.8813
BMI	21.9 ± 3.0	21.4 ± 2.8	0.5624
ASA-PS 1/2/3 (n)	14/45/22	0/8/7	0.1226
Smoker never/past/current (n)	8/65/8	2/12/1	0.8675
Preoperative adjuvant chemotherapy	30/51	3/12	0.2019
Preoperative adjuvant radiation therapy	73/8	12/3	0.2582
Preoperative complication			
Ischemic heart disease	71/10	11/4	0.3507
Diabetes mellitus	68/13	10/5	0.1152
COPD	68/13	13/2	0.7901
Cerebrovascular disease	73/8	13/2	0.6873
History of cancer surgery	65/16	13/2	0.5585
Preoperative opioid use	80/1	12/3	0.0008

Abbreviations: PD: postoperative delirium; BMI: body mass index; ASA-PS: American Society of Anesthesiologists physical status; COPD: chronic obstructive pulmonary disease

Table II. Intraoperative data and postoperative analgesia.

Variable	Non-PD	PD	*P*-value
	n = 81	n = 15	
Surgical procedure	33/35/13	13/1/1	0.0044
1. open 2. robot-assisted 3. laparoscopy			
Type of anesthetics	9/30/42	1/5/9	0.8002
Propofol/desflurane/sevoflurane (n)			
Combination of epidural anesthesia (yes/no)	81/0	13/2	0.0009
Total use of fentanyl (i.v., mg/kg)	10.3 ± 4.4	12.6 ± 7.4	0.2496
Total use of remifentanil (i.v., mg/kg)	46.3 ± 31.8	46.0 ± 31.5	0.9724
The use of pethidine (i.v., n)	77/4	14/1	0.7820
Use of morphine (epi, n)	40/41	9/6	0.4499
Total amount of opioids; FE (mg/kg)	56.8 ± 32.2	58.8 ± 36.6	0.8491
Anesthesia time (min)	495 ± 95	466 ± 109	0.3409
Operation time (min)	426 ± 97	400 ± 88	0.3212
Bleeding volume (cc)	355 ± 283	488 ± 310	0.1389
Infusion volume (cc)	3865 ± 1035	3663 ± 1066	0.5076
Transfusion volume (cc)	387 ± 445	574 ± 367	0.0947

Abbreviations: PD: postoperative delirium; FE: fentanyl equivalent

Additional Table I. Postoperative type and onset of delirium, analgesic use, and pain intensity.

Variable	Non-PD	PD	*P*-value
	n = 82	n = 14	
Type of PD (hyperactive, hypoactive, mixed)	NA	9/3/3	NA
Onset of PD postoperative day 0/1/2/3	NA	7/2/3/3	NA
Total postoperative use of fentanyl (mg/kg) POD3	51.8 ± 25.7	75.8 ± 47.4	0.0749
NRS on postoperative day 1	2.0 ± 1.5	1.9 ± 1.5	0.8146
NRS on postoperative day 2	2.0 ± 1.4	1.8 ± 1.3	0.5074
NRS on postoperative day 3	1.7 ± 1.5	1.3 ± 1.1	0.1769

PD: postoperative delirium; NRS: numerical rating scale; POD: postoperative day

Additional Table II. Correlation of phosphorylated neurofilament heavy subunit positivity with other laboratory measurements.

Variable	Univariable OR	95% CI	P-value
WBC	1.00	1.00	0.0598
CRP	0.90	0.45-1.74	0.7633
Log ApoE	0.60	0.34-1.38	0.2289
Log P-selectin	1.12	0.56-2.23	0.7518
Log PECAM-1	0.91	0.48-1.74	0.7797
Log PAI-1	0.73	0.35-1.49	0.3902
Log IL-6	1.48	0.98-2.42	0.0637

OR: odds ratio; CI: confidential interval; WBC: white blood cell; CRP: C-reactive protein; ApoE: apolipoprotein E; PECAM-1: platelet endothelial cell adhesion molecule-1; PAI-1: plasminogen activator inhibitor-1; IL-6: interleukin-6

use of opioids as a covariate (Supplementary Table III). The specificity of PD diagnosis increased when age was combined with pNF-H detection. (Supplementary Table IV).

DISCUSSION

Preoperative detection of pNF-H was significantly associated with PD (Tab. III). Because pNF-H detection was associated with PD independent of age (Tab. IV), the specificity of age for indicating PD development improved when combined with preoperative pNF-H detection (Supplementary Table IV).

Postoperative pain, opioid analgesia, and systemic inflammation have been identified as delirium risk factors [23-25]. Recently, the use of combined epidural and general analgesia was suggested as a way to reduce PD risk. The incidence of postoperative delirium within 7 days was significantly lower in patients who received epidural–general anaesthesia (1.8%) than that in the general anaesthesia group (5.0%) [26]. However, a higher frequency of combined anesthesia in PD patients resulted in little difference in the NRS score and postoperative opioid use between PD and non-PD patients (Table II and Supplementary Table I) in our study. Consistent with previous studies [3], the surgical procedure was significantly associated with development of PD (Tab. II). These surgical stresses can cause increased production of the serum mediators involved in inflammation and coagulation/fibrinolysis, which are associated with PD development [8], although we did not evaluate serum mediators in the postoperative period. However, before surgery, the IL-6 concentration was higher in PD patients than that in patients who did not develop PD, suggesting that patients in a proinflammatory state before surgery may have a higher risk of PD regardless of postoperative conditions.

Blood brain barrier disruption induced by systemic inflammation can cause neuronal damage [25]. We previously reported that P-selectin was the only independent

Table III. Candidate plasma parameters to predict postoperative delirium.

Variable	Non-PD	PD	*P*-value
	n = 81	n = 15	
pNF-H positivity +/-	33/48	12/3	0.0051
WBC	11348 ± 4816	1500 ± 8084	0.1096
CRP	0.45 ± 0.60	0.71 ± 0.74	0.2295
Log NSE	9.61 ± 0.63	9.41 ± 0.67	0.2847
Log Apo E	10.16 ± 0.50	9.80 ± 0.20	< 0.0001
Log P selectin	10.85 ± 0.58	10.54 ± 0.58	0.0723
Log PECAM-1	9.42 ± 0.62	9.13 ± 0.63	0.1210
Log MMP-9	8.96 ± 0.93	9.09 ± 0.93	0.6147
Log PAI-1	10.92 ± 0.47	10.47 ± 0.88	0.0700
Log IL-6	0.06 ± 1.01	0.82 ± 1,.00	0.0141

Abbreviations: PD: postoperative delirium; pNF-H: phosphorylated neurofilament heavy subunit; WBC: white blood cell; CRP: C-reactive protein; NSE: neuron-specific enolase; ApoE: apolipoprotein E; PECAM-1: platelet endothelial cell adhesion molecule-1; MMP-9: matrix metalloproteinase-9; PAI-1: plasminogen activator inhibitor-1; IL-6: interleukin-6

Table IV. Logistic regression analysis for prediction of postoperative delirium.

Variable	Univariable OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
Age	1.11	1.03-1.21	0.0041	1.12	1.03-1.24	0.0062
pNF-H	5.82	1.69-27.00	0.0042	5.86	1.60-29.03	0.0064

Abbreviations: OR: odds ratio; CI: confidence interval; pNF-H: phosphorylated neurofilament heavy subunit

Additional Table III. Logistic regression analysis for prediction of postoperative delirium with preoperative use of opioids as a covariate.

Variable	Univariable OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
Age	1.11	1.03-1.21	0.004	1.09	1.00-1.19	0.032
Preoperative use of opioids	20.0	2.35-423.06	0.006	41.67	1.20-1441.16	0.018
pNF-H	5.82	1.69-27.00	0.004	7.42	1.49-37.02	0.005

Abbreviations: OR: odds ratio; CI: confidence interval; pNF-H: phosphorylated neurofilament heavy subunit

Additional Table IV. Sensitivity and specificity for postoperative delirium by age with and without phosphorylated neurofilament heavy subumit positivity.

With pNF-H positivity	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82
Sensitivity	0.8	0.8	0.60	0.47	0.47	0.47	0.47	0.40	0.40	0.33	0.33	0.33	0.27	0.20	0.20	0.20	0.20
Specificity	0.69	0.74	0.72	0.80	0.85	0.85	0.89	0.90	0.93	0.93	0.94	0.96	0.96	0.98	0.98	0.98	0.99
Without pNF-H positivity	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82
Sensitivity	1.00	0.93	0.73	0.60	0.60	0.60	0.60	0.53	0.53	0.47	0.47	0.40	0.33	0.27	0.27	0.27	0.27
Specificity	0.36	0.41	0.46	0.54	0.67	0.68	0.72	0.74	0.79	0.80	0.81	0.84	0.86	0.89	0.89	0.91	0.95

variable associated with pNF-H detection whereas PECAM-1 was associated with serum pNF-H levels in pNF-H-positive patients on the postoperative day 3 [9]. In our present study, the preoperative PECAM-1 value was not associated with preoperative pNF-H detection. According to our current and previous findings, these markers of endothelial damage, including PECAM-1 and MMP-9, could be induced after the induction of the systemic inflammatory condition, possibly exacerbating axonal damage after surgery. The time course of these marker levels in the perioperative periods should be further investigated.

The neuron-specific cytoskeletal protein pNF-H is responsible for protecting neurofilaments from degeneration [27]. Elevation of the serum pNF-H concentration has been reported in mild traumatic brain injury patients on days 1 and 3 after injury. Moreover, the pNF-H concentration has been correlated with brain injury severity. Similarly, NSE is a prognostic marker following traumatic and anoxic brain injury [28,29]. It has been previously reported that higher plasma NSE concentrations are associated with mortality and delirium in critically ill septic patients [30]. However, the concentration of NSE, which is enriched in neuronal cell bodies and a potential marker of neuronal damage in PD patients, was not different between groups in our study (Tab. III). Although the discrepancy in the correlation of delirium with pNF-H and that of NSE has not been demonstrated elsewhere, a correlation between pNF-H and apolipoprotein E (ApoE) under stressful conditions has been previously proposed [31]. In cultured neurons and the brains of Alzheimer's disease patients, p-NF-H interacts with ApoE to form neurofibrillary tangles. It is likely that pNF-H rather than NSE is genetically linked to PD because the ApoE epsilon 4 allele has been correlated with PD [32]. The link between pNF-H and ApoE should be further investigated further in PD patients.

Hyperphosphorylation of NF-H has been reported in the brains of elderly patients as well as patients with Alzheimer's disease [33]. In addition, the serum pNF-H concentration is elevated in the early pre-diagnostic stage of patients with amyotrophic lateral sclerosis [34]. Therefore, pNF-H, rather than NSE, may be detectable in the early stages of neurodegenerative progression in the elderly. Consistent with the common understanding that elderly individuals with mild cognitive impairment and dementia are susceptible to PD [3], the baseline pNF-H level was increased in PD patients before surgery (Tab. III). Future studies should examine the change in pNF-H concentration in PD patients throughout the entire perioperative period.

In contrast to IL-6 elevation, the preoperative PAI-1 value tends to be lower in non-PD patients than that in PD patients (Tab. III). Plasma concentrations of PAI-1 have been consistently associated with development of delirium in the ICU, with higher PAI-1 concentrations associated with fewer delirium/coma-free days in the full cohort and a longer duration of delirium among survivors [35]. However, Whether PAI-1 explains cognitive impairment in neurological disorders is still controversial [36]. Alternatively, tumor cells produce PAI-1 [37], and this might mask the serum level of non-tumor-derived PAI-1. To investigate the involvement of the fibrinolytic system in the

development of PD, changes in PAI-1 levels throughout the perioperative periods should be evaluated.

This study has several limitations. First, the presence of mild cognitive impairment is a known risk factor for PD [38]. However, the preoperative cognitive functional status was not screened. Similarly, development of delirium preoperatively after admission was not assessed either in this study. Second, a meta-analysis recently revealed that poor functional status preoperatively, including frailty, is associated with PD in elective surgery patients aged 65 years or older [39]. In addition, polypharmacy is an independent risk factor for PD in elderly patients [40]. These reports suggest that preoperative assessment for delirium risk is important, especially in elderly patients as previously suggested [41]. Although the association between preoperative status and PD was not be explored because of the small number of patients with PD in this study, the utility of CNS-derived markers such as pNF-H is useful in patients with frailty and cognitive decline should be investigated.

CONCLUSIONS

Detection of the presence of serum pNF-H before surgery is significantly associated with PD in ICU patients after esophageal cancer surgery. Early detection of serum pNF-H before surgery may enable clinicians to identify patients at risk for PD. Thus, the optimal modes of anaesthesia and sedation could be selected for patients with detectable pNF-H. Furthermore, early detection of high-risk patients would allow close patient monitoring and preventative interventions in the ICU.

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Conflict of interest statement

The department to which M. Hasegawa-Moriyama belongs is supported by Shionogi Co., Ltd. (Osaka, Japan), Nippon Zoki Pharmaceutical Co., Ltd. (Osaka, Japan), and Heartfelt Co., Ltd. (Kumamoto, Japan). Kanji Uchida has collaborative research agreement and accompanied from research funding with Nihon Kohden Corporation (Tokyo, Japan) and Nipro Corporation (Osaka, Japan) concerning topics unrelated to the present study. The funder had no role in the study design or collection, analysis, or interpretation of data.

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Author contributions

KM acquired patient data. MH-M performed the statistical analyses, interpreted the data, and wrote the initial draft of the manuscript. RI, KY, and NS assisted KM with data acquisition. MS, MK, YS and TO contributed to the study concept and design and manuscript editing. KU wrote and reviewed the final version of the manuscript. All contributors approved the final version.

Ethical consideration

The study was approved by the Ethical Committee of the University of Tokyo [1261-(4)]. The local ethics committee of each institution approved the trial protocol and written informed consent was obtained from each patient. The study was registered in the University Medical Information Network (UMIN trial ID: UMIN000037699). We confirmed that all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Data availability

Anonymised data from this study are available from the corresponding author for academic purposes upon reasonable request.

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