Effect of diabetes on patient-reported outcome measures at one year after laminoplasty for cervical spondylotic myelopathy

Kosei Nagata1,2, Junya Miyahara1,2, Hideki Nakamoto1,2, Naohiro Kawamura2,3, Yujiro Takeshita2,4, Akiro Higashikawa2,5, Takashi Ono2,6, Masayoshi Fukushima2,7, Rentaro Okazaki2,8, Nobuhiro Hara2,9, So Kato1,2, Toru Doi1,2, Yuki Taniguchi1,2, Yoshitaka Matsubayashi1,2, Sakae Tanaka1,2 & Yasushi Oshima1,2*

Although patients with diabetes reportedly have more peripheral neuropathy, the impacts of diabetes on postoperative recovery in pain and patient-reported outcome measures (PROMs) after laminoplasty for cervical spondylotic myelopathy (CSM) is not well characterized. The authors aimed to elucidate the effects of diabetes on neck/arm/hand/leg/foot pain and PROMs after laminoplasty CSM. The authors retrospectively reviewed 339 patients (82 with diabetes and 257 without) who underwent laminoplasty between C3 and C7 in 11 hospitals during April 2017–October 2019. Preoperative Numerical Rating Scale (NRS) scores in all five areas, the Short Form-12 Mental Component Summary, Euro quality of life 5-dimension, Neck Disability Index, and the Core Outcome Measures Index-Neck) were comparable between the groups. The between-group differences were also not significant in NRS scores and PROMs one year after surgery. The change score of NRS hand pain was larger in the diabetic group than the nondiabetic group. The diabetic group showed worse preoperative score but greater improvement in the Short Form-12 Physical Component Summary than the nondiabetic group, following comparable score one year after surgery. These data indicated that the preoperative presence of diabetes, at least, did not adversely affect pain or PROMs one year after laminoplasty for CSM.

Cervical spondylotic myelopathy (CSM) is a common and increasingly observed degenerative disorder causing spinal cord compression and neurological deterioration1. Surgical decompression via laminoplasty is the standard treatment for CSM and can prevent the progression of neurological deficits as well as improve neurological function and quality of life2. Surgical outcomes should be evaluated using patient-reported outcome measures (PROMs).

Diabetic neuropathy following diabetes mellitus can profoundly impair the quality of life. Diabetes mellitus is a chronic systemic disease characterized by multiple neurologic sequelae mainly associated with diabetic neuropathy, chronic peripheral pain due to microvascular changes, and irreversible nerve damage3–5. The reported prevalence of painful diabetic peripheral neuropathy shows wide variability (range, 3–65%) owing to differences in sampling methods and diagnostic criteria3–9. It is a well-known fact that patients with diabetic neuropathy have sensory disturbances in the extremities and typically show stocking-and-glove patterns of sensory deficit3,10.

1Department of Orthopaedic Surgery and Spinal Surgery, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. 2The University of Tokyo Spine Group (UTSG), Tokyo, Japan. 3Department of Spine and Orthopedic Surgery, Japanese Red Cross Medical Center, Tokyo, Japan. 4Department of Orthopedic Surgery, Yokohama Rosai Hospital, Kanagawa, Japan. 5Department of Orthopedic Surgery, Kanto Rosai Hospital, Kanagawa, Japan. 6Department of Spinal Surgery, Japan Community Health-Care Organization Tokyo Shinjuku Medical Center, Tokyo, Japan. 7Spine Center, Toranomon Hospital, Tokyo, Japan. 8Department of Orthopedic Surgery, Japanese Red Cross Saitama Hospital, Saitama, Japan. 9Department of Orthopedic Surgery, Japanese Red Cross Musashino Hospital, Tokyo, Japan. *email: yoo-tky@umin.ac.jp
Compromised vascularity and secondary peripheral neuropathy may affect the recovery of nerve roots even after surgical decompression.

Several reports showed diabetic effects on surgical outcomes after surgery for CSM, and their results were controversial[12,21–23]. These studies showed that diabetes had equivalent effects[21,24] or negative effects on gait, sensory, and bladder function[21].

Previous studies used JOA score, which was evaluated by doctors[21,24]. The other study was heterogeneous; including patients undergoing anterior cervical spine surgery or lumbar spine surgery[22]. Therefore, the diabetic effects on PROMs and pain after cervical laminoplasty surgery have not been well characterized in patients with CSM. In the present multicenter study investigating the surgical outcomes of laminoplasty for CSM, the authors aimed to investigate the impact of diabetes on pain as well as PROMs after laminoplasty for CSM with an adequately large sample size.

Materials and methods

Ethics. A prospective spine surgery registry was started at eight institutions in the greater Tokyo metropolitan area, after obtaining approval from the Clinical Research Support Center of the University of Tokyo Hospital (10,335-(3)) and the institutional review boards of all participating hospitals i.e., The University of Tokyo Hospital, Japanese Red Cross Medical Center, Yokohama Rosai Hospital, Kanto Rosai Hospital, Japan Community Health-social Organization Tokyo Shinjuku Medical Center, Toranomon Hospital, Japanese Red Cross Saitama Hospital, and Japanese Red Cross Musashino Hospital. The present study was carried out in accordance with the relevant guidelines and regulations/ethical principles of the Declaration of Helsinki. The authors have obtained informed consent form with opt-out method from patients.

Patients. The authors evaluated a consecutive cohort of patients who were diagnosed with CSM and underwent posterior cervical decompression at 11 different institutions between April 2017 and October 2019. Diagnosis was made by board-certified spine surgeons based on neurological examinations as well as MRI or myelography evaluations (existence of the effacement of subarachnoid space with spinal cord compression). The study's inclusion criteria were as follows: symptomatic CSM (at least one clinical sign of myelopathy), surgical level between C3 and C7, evidence of cervical spinal cord compression on magnetic resonance imaging or cervical myelogram-computed tomography, and no previous cervical spine surgery. The study's exclusion criteria were as follows: diagnosis of posterior longitudinal ligament ossification, spinal tumors, trauma, or infectious diseases; aged younger than 18 years; emergency surgery; surgery involving the thoracic spine; and fixation surgery.

Patient data collection. Data on the clinical characteristics of the patients, including age, sex, body mass index, current smoking history, American Society of Anesthesiologists (ASA) classification, and medical history, were retrospectively collected. Preoperative laboratory data were assessed. Patients with a fasting blood glucose level of 126 mg/dL and glycated hemoglobin (HbA1c) levels of 6.5% or those previously diagnosed with diabetes by a diabetes specialist were considered to have diabetes. Diabetes specialists at each hospital were able to sufficiently control the blood sugar levels of patients diagnosed with diabetes throughout the immediate perioperative period. Blood glucose levels were checked four times a day, and a sliding scale insulin coverage was adopted to avoid perioperative hyperglycemia until the patient's food intake stabilized. Surgical factors, including operative time and estimated blood loss, were registered. Surgeons in charge were asked to report all intraoperative complications, including nerve root damage and dural tear, and postoperative complications within 30 days after surgery.

Patient-reported outcome measures. At baseline and one year after surgery, all patients were asked to answer a booklet of questionnaires, including the Japanese version of the (1) Numerical Rating Scale (NRS), (2) the Short Form-12 Physical Component Summary (PCS), (3) Mental Component Summary (MCS), (4) Euro quality of life 5-dimension (EQ-5D)-3L to assess health-related quality of life[16], (5) Neck Disability Index (NDI) to assess pain-associated disability, and (6) Core Outcome Measures Index (COMI)-Neck[17]. The NRS measures the intensity of pain over the preceding 4 weeks; the scores range from 0 (no pain at all) to 10 (worst pain imaginable). To evaluate the diabetic effect on axial pain and residual radiculopathy, the authors analyzed the following five NRS domains; neck, arm, hand, leg, and foot pain. Each corresponding body part had been discussed in previous reports[15]. To determine treatment satisfaction, a 7-point Likert scale was used, wherein, the patients were asked to answer whether they were satisfied with the treatment, with possible answers of “very satisfied,” “satisfied,” “somewhat satisfied,” “neither,” “dissatisfied,” “somewhat dissatisfied,” and “very dissatisfied.”[17]

Statistical analysis. Baseline demographic and clinical characteristics in the diabetic and nondiabetic groups were compared using the Chi-square test for categorical variables and Student’s t-test for continuous variables. The Student’s t-test was used to examine intergroup differences with respect to pre- and postoperative NRS, PCS, MCS, EQ-5D, NDI, and COMI-Neck scores. For further evaluation of the difference in each outcome score, the authors calculated the adjusted p values by inverse probability weighting method after calculating propensity scores based on at least seven variables (age, sex, BMI, smoking status, ASA class, operative time, and estimated blood loss) as per a previous report[15,19]. The correlations between diabetes-related factors (preoperative HbA1c level and fasting blood sugar) and postoperative outcomes was measured using Spearman’s rank correlation coefficients. We defined the correlation as the value of ρ > 0.40 with p value < 0.05. All data analyses were performed using SPSS version 21.0 statistical software (SPSS, Inc., Chicago, IL, USA).
The sample size for this study was calculated using G*Power version 3.1. With an approximately 20–25% prevalence of diabetes as reported in a previous prospectively collected database10,13,20, a total sample size of at least 200 patients was required with a power of > 0.8, significance level of $P < 0.05$, and effect size of < 0.2.

**Results**

Among the 339 patients who satisfied the inclusion and exclusion criteria, 82 (24.2%) and 257 (75.8%) were grouped into the diabetic and nondiabetic groups, respectively (Fig. 1). No significant intergroup differences were observed with respect to age (mean 70.1 vs. 71.0 years, $P = 0.575$), male/female ratio (58 men:24 women vs. 175 men:82 women, $P = 0.653$), and current smoking status (12.2% smokers vs. 11.1% nonsmokers, $P = 0.454$) (Table 1). The diabetic group had a higher BMI (25.2 vs. 23.7 kg/m², $P = 0.012$) and included a higher percentage of patients with an ASA classification of ≥ 3 (19.5% vs. 8.0%, $P < 0.001$), hypertension (58.6% vs. 41.1%, $P = 0.022$), and hyperlipidemia (26.4% vs. 11.1%, $P = 0.006$) than the nondiabetic group. No significant intergroup differences were observed with respect to hemodialysis, rheumatoid arthritis, and past history of stroke. The diabetic group

![Figure 1. Flowchart of the study population.](image-url)

**Table 1.** Demographic and patient characteristics. *BMI* body mass index, *ASA* American Society of Anesthesiologists. $^a$The values are given as the mean and the standard deviation. $^b$The values are given as the percentage in each group.
had a significantly higher mean HbA1c level (7.0% vs. 5.8%, \(P < 0.001\)), fasting blood sugar (161.3 vs. 112.2 mg/dL, \(P < 0.001\)), and creatinine (1.4 vs. 1.0 mg/dL, \(P = 0.009\)) than the nondiabetic group. The diabetic group had a lower mean value of total cholesterol than the nondiabetic group (183.1 vs. 200.9 mg/dL, \(P = 0.001\)). Although the diabetic group had a lower value of mean low density lipoprotein cholesterol than the nondiabetic group, the difference was not statistically significant (97.4 vs. 110.4 mg/dL, \(P = 0.059\)).

No significant intergroup differences were observed with respect to operative time (139.7 vs. 136.2 min, \(P = 0.590\)) and estimated blood loss (102.0 vs. 98.4 mL, \(P = 0.855\)) (Table 2). No significant intergroup differences were observed in complications during surgery and within 30 days after surgery.

The absolute changes in NRS scores are shown in Table 3. Pre- and postoperative NRS scores in neck/arm/leg/foot were comparable between the two groups (\(P > 0.05\)). There were no significant differences in the change NRS scores in neck/arm/leg/foot with or without adjustment by propensity score. Although pre- and postoperative NRS hand pain scores showed no significant difference between the two groups, the change score of NRS hand pain was larger in the diabetic group than the nondiabetic group (1.2 vs. 0.3, \(P = 0.034\), Adjusted \(P = 0.017\)).

The trends in PROMs are shown in Table 4. The diabetic group had a lower preoperative PCS score than the nondiabetic group with or without adjustment (22.0 vs. 28.9, \(P = 0.001\), Adjusted \(P = 0.028\)), and no significant intergroup differences were observed in postoperative PCS scores (30.4 vs. 32.7, \(P = 0.324\)). Hence, the change score in PCS was larger in the diabetic group than the nondiabetic group, but the difference was not significant after the adjustment by the propensity score (8.4 vs. 3.7, \(P = 0.039\), Adjusted \(P = 0.151\)). No significant intergroup differences were observed in pre- and postoperative MCS, EQ-SD, NDI, and COMI-Neck scores. There is no at least moderate correlation between diabetes-related factors (preoperative HbA1c level and fasting blood sugar) and pain/PROMs (Sup Table 1).

Table 5 summarizes the answers to questions on satisfaction. The diabetic group tended to have a higher proportion of patients answering “very satisfied” or “satisfied” than the nondiabetic group, although the difference was not significant (58.5% vs. 47.5%, \(P = 0.081\)). The diabetic group had a higher total percentage of patients who answered “very satisfied,” “satisfied,” or “somewhat satisfied” than the nondiabetic group (74.4% vs. 64.6%, \(P = 0.001\)).

### Table 2. Comparison of surgical factors for patients with diabetes and those without diabetes. Other values are given as the percentage in each group. The values are given as the mean and the standard deviation.

| Outcome                        | Diabetic group (N = 82) | Nondiabetic group (N = 257) | \(P\) value |
|-------------------------------|------------------------|----------------------------|-------------|
| Operation time\(^a\) (min)    | 139.7 ± 45.9           | 136.2 ± 51.5               | 0.590       |
| Estimated blood loss\(^a\) (ml)| 102.0 ± 162.5          | 98.4 ± 153.7               | 0.855       |
| Nerve root damage (%)         | 0                      | 0                          | NA          |
| Dural tear (%)                | 1.2                    | 2.3                        | 0.863       |
| Surgical site infection (%)   | 3.7                    | 2.7                        | 0.952       |
| Urinary tract infection (%)   | 2.4                    | 0.8                        | 0.532       |
| Respiratory tract infection (%)| 2.4                    | 0.4                        | 0.294       |

### Table 3. Comparison of preoperative and postoperative numeric rating scales for patients with diabetes and those without diabetes. NRS numeric rating scale.

| NRSs                  | Outcome          | Diabetic Group | Nondiabetic Group | \(P\) value | Adjusted \(P\) value |
|-----------------------|------------------|----------------|-------------------|-------------|---------------------|
| NRS neck pain         | Preoperative     | 2.4 ± 2.9      | 2.8 ± 2.8         | 0.290       | 0.439               |
|                       | Postoperative    | 2.1 ± 2.3      | 2.0 ± 2.3         | 0.909       | 0.986               |
|                       | Change           | 0.3 ± 3.2      | 0.8 ± 2.9         | 0.169       | 0.334               |
| NRS arm pain          | Preoperative     | 3.1 ± 3.3      | 3.0 ± 3.0         | 0.797       | 0.649               |
|                       | Postoperative    | 1.9 ± 2.6      | 2.3 ± 2.8         | 0.253       | 0.208               |
|                       | Change           | 1.3 ± 3.6      | 0.6 ± 3.2         | 0.166       | 0.146               |
| NRS hand pain         | Preoperative     | 3.3 ± 3.3      | 3.0 ± 3.1         | 0.478       | 0.296               |
|                       | Postoperative    | 2.0 ± 2.7      | 2.6 ± 2.9         | 0.113       | 0.141               |
|                       | Change           | 1.2 ± 3.2      | 0.3 ± 3.3         | 0.034       | 0.017               |
| NRS leg pain          | Preoperative     | 2.6 ± 3.1      | 2.9 ± 3.0         | 0.505       | 0.565               |
|                       | Postoperative    | 2.5 ± 2.8      | 2.5 ± 2.9         | 0.968       | 0.738               |
|                       | Change           | 0.1 ± 3.3      | 0.3 ± 3.4         | 0.918       | 0.932               |
| NRS foot pain         | Preoperative     | 1.8 ± 2.9      | 1.9 ± 2.7         | 0.701       | 0.635               |
|                       | Postoperative    | 1.8 ± 2.5      | 1.7 ± 2.7         | 0.809       | 0.587               |
|                       | Change           | 0.0 ± 2.9      | 0.1 ± 2.7         | 0.189       | 0.628               |
Discussion

To the best of our knowledge, this has been the largest study that investigated the effects of diabetes on multiple NRS scores with PROMs following elective laminoplasty for CSM. In the present study, pre- and postoperative NRS scores for neck/arm/hand/leg/foot pain were comparable between the two groups. The diabetic group showed greater improvement in NRS hand scores than the nondiabetic group. No significant intergroup differences in pre- and postoperative MCS, EQ-5D, NDI, and COMI-Neck scores were noted. Although the diabetic group had lower preoperative PCS scores than the nondiabetic group, the postoperative PCS scores of the two groups were comparable. Moreover, patients in the diabetic group tended to be satisfied with the surgical results. Collectively, these data indicated that the presence of diabetes did not, at least, adversely affect surgical outcomes of laminoplasty for CSM.

The present study showed that the diabetic group had higher prevalence rates of ASA classification ≥ 3, consistent with the findings of a previous study. Although the diabetic group tended to have more risk factors, the current study revealed no intergroup differences with respect to perioperative complications. Strict glycemic control may play an important role. The mean and maximum HbA1c level was 7.0% and 8.9%, respectively, even in the diabetic group. This relatively strict glycemic control enforced by diabetes specialists before and after laminoplasty surgery may have contributed to the lack of intergroup differences not only in complications but also in the non-inferiority in pain control. Appropriate perioperative blood glucose control is associated with a reasonable recovery after cervical decompression or belief in self-efficacy and active behavior. Several trials have shown significant improvements in peripheral nerve function with intensive glucose control.

Only a few large-scale reports have investigated the effects of diabetes on laminoplasty using PROMs. In the present study, the diabetic and nondiabetic groups showed similar pre- and postoperative MCS/EQ-5D/NDI/COMI-Neck scores, except for PCS. Diabetes has been reported as a risk factor for neck and back pain. Armaaghan et al. argued that patients with diabetes showed minor improvements in the NDI or Oswestry Disability Index and EQ-5D scores compared with patients without diabetes. They analyzed patients undergoing back surgery and those undergoing neck surgery together and thereby making interpretation difficult. Alternatively,
Arnold et al. found that patients with diabetes did not differ from those without diabetes in terms of pre- and postoperative NDI\(^{14}\) and Nori et al. argued that diabetes did not negatively affect neck pain after posterior cervical decompression\(^{15}\). The present study was consistent with these reports\(^{14,14}\) in that diabetic patients had comparable postoperative outcomes and we showed this point by pain-assess PROMs. The effects of diabetes may differ between patient with back and neck pain. Given that diabetes impairs bone fusion, the effects of diabetes can be greater following posterior lumbar interbody fusion surgeries\(^{22}\), which contributes to mechanical instability and the occurrence of back pain\(^{31}\). In contrast, considering that cervical laminoplasty is not performed for the purpose of bone fusion, the effects of diabetes can be minor. These mechanisms can explain why no significant differences were observed for neck pain-associated outcome measures, including NRS neck pain, EQ-5D, NDI, and multidimensional COMI-Neck, in the current study.

In the present study, the diabetic group showed lower preoperative PCS scores than the nondiabetic group; however, the two groups had comparable postoperative PCS scores. This finding differed from that reported by Arnold et al.\(^{14}\); they reported no significant intergroup differences in preoperative PCS, but patients with diabetes experienced significantly lesser improvement than those without diabetes\(^{14}\). Our cohort had an average age of 70.8 years, while Arnold’s cohort had an average age of 56.4 years\(^{14}\). The relatively older our cohort with low preoperative PCS scores may have affected the difference. Because of the relatively low reliability of PCS for evaluation of health transition among patients aged 75 or over\(^{30}\), multiple PROMs should be used when the average age of the cohort is high. Low preoperative PCS scores can be associated with lower leg strength and proprioception\(^{14}\), which is greater risk of preoperative slower walking speed, especially in the elderly\(^{27,28}\). The slower walking speed due to diabetic neuropathy could mimic walking impairment due to CSM, resulting in early surgical intervention in the diabetic group. Early surgical intervention is an important factor for good clinical outcomes\(^{14}\) and can explain why the diabetic group in the present study had comparable postoperative PCS scores, despite having lower preoperative PCS scores. To prove this hypothesis, further large size studies linking duration of CSM symptoms and multiple PROMs are warranted.

The authors believe that this study adds to the contemporary knowledge related to the effect of diabetes on patients undergoing cervical posterior decompression surgery. However, some limitations of our study should be considered when interpreting our results. First, the current study did not analyze detailed information for diabetes except for preoperative HbA1c level. We were unable to collect detailed information on diabetes, including duration, medication history, or trend of HbA1c. Second, the follow-up duration was one year, not two years after surgery, although PROMs assessed at one year adequately predict long-term (24-month) outcomes\(^{30}\). Third, double door or open door laminoplasty was determined by the surgeon in charge at each participating hospital due to the multicenter study design. In addition, relatively elder cohorts may undergo laminoplasty for the purpose myelopathy rather than pain caused by radiculopathy and the effect of laminoplasty on peripheral may be limited.

Conclusions

The results of the present multicenter cohort study showed that diabetes did not adversely affect improvement in pain and PROMs one year after laminoplasty for CSM, although the diabetic group had lower preoperative PCS scores than the nondiabetic group. Under the strict glycemic control before and after surgery, surgeons can use this information when counseling patients who have CSM with diabetes about the expected outcomes of laminoplasty.

Received: 28 October 2021; Accepted: 30 May 2022
Published online: 11 June 2022

References

1. Fehlings, M. G., Tetzlaff, L. A., Wilson, J. R. & Skelly, A. C. Cervical spondylotic myelopathy: Current state of the art and future directions. Spine (Phila Pa 1976) 38, S1–8. https://doi.org/10.1097/BRS.0b013e3182a7e9d8 (2013).
2. Fehlings, M. G. et al. Efficacy and safety of surgical decompression in patients with cervical spondylotic myelopathy: Results of the AOspine North America prospective multi-center study. J. Bone Joint Surg. Am. 95, 1651–1658. https://doi.org/10.2106/JBJS.L.00589 (2013).
3. Vinik, A. I. Clinical practice. Diabetic sensory and motor neuropathy. N. Engl. J. Med. 374, 1455–1464. https://doi.org/10.1056/NEJMc1503948 (2016).
4. Ziegler, D. R. W. & Meisinger, C. Prevalence and risk factors of neuropathic pain in survivors of myocardial infarction with pre-existing diabetes. The KORA myocardial infarction registry. Eur. J. Pain 13, 582–587 (2009).
5. Erbas, T. E. M. & Yucel, A. Prevalence of peripheral neuropathy and painful peripheral neuropathy in Turkish diabetic patients. J. Clin. Neuropsychol 28, 51–55 (2011).
6. Abbott, C. A. M. R. & van Ross, E. R. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 34, 2220–2224 (2011).
7. Kim, S. S. W. J. & Kwon, H. S. Prevalence and clinical implications of painful diabetic peripheral neuropathy in type 2 diabetes: Results from a nationwide hospital-based study of diabetic neuropathy in Korea. Diabetes Res. Clin. Pract. 103, 522–529 (2014).
8. Alleman, C. J. W. K. & Hensen, M. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: a review of the literature. Diabetes Res. Clin. Pract. 109, 215–225 (2015).
9. Bouhassira, D. L. M. & Hartemann, A. Chronic pain with neuropathic characteristics in diabetic patients: A French crosssectional study. PLoS One 8, e74195 (2013).
10. Machino, M. et al. Characteristics of residual symptoms after laminoplasty in diabetic patients with cervical spondylotic myelopathy: A prospective cohort study. Spine (Phila Pa 1976) 42, E708–E715. https://doi.org/10.1097/BRS.0000000000001947 (2017).
11. Freedman, M. K. et al. The impact of diabetes on the outcomes of surgical and nonsurgical treatment of patients in the spine patient outcomes research trial. Spine (Phila Pa 1976) 36, 290–307. https://doi.org/10.1097/BRS.0b013e3181e9d8c (2011).
12. Armaghani, S. J., Archer, K. R., Rolfe, R., Demaio, D. N. & Devin, C. J. Diabetes is related to worse patient-reported outcomes at two years following spine surgery. J. Bone Joint Surg. Am. 98, 15–22. https://doi.org/10.2106/JBJS.O.00297 (2016).
Author contributions
K.N. and Y.O. conceived the study. J.M., H.N. and S.K. analyzed the data. T.D., Y.T., and Y.M. discussed the results. N.K., Y.T., A.H., T.O., M.F., R.O., and N.H. contributed data collection and result interpretation. K.N. wrote the initial draft. Y.O. and S.T. revised the manuscript. All authors reviewed the manuscript.

Funding
The manuscript submitted does not contain information about medical device(s)/drug(s). No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript. The study approval was given by the institutional review board of the Clinical Research Support Center of the University of Tokyo Hospital.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-13838-2.

Correspondence and requests for materials should be addressed to Y.O.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022