

## ANESTHESIOLOGY

# Volatile *versus* Total Intravenous Anesthesia for Cancer Prognosis in Patients Having Digestive Cancer Surgery

## A Nationwide Retrospective Cohort Study

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### EDITOR'S PERSPECTIVE

#### What We Already Know about This Topic

- Experimental and clinical studies suggest that intravenous anesthesia may reduce cancer recurrence after potentially curative surgery

#### What This Article Tells Us That Is New

- Among more than 190,000 patients who had cancer surgery, overall and recurrence-free survival were comparable in patients who had propofol-based total intravenous and volatile anesthesia
- Selection of anesthetic approach should be based on factors other than putative effects on cancer recurrence

Volatile and intravenous anesthetic agents are commonly used for maintenance of anesthesia. Laboratory and animal studies have suggested that volatile anesthetic drugs are more likely to enhance the activity of cancer cells through suppression of immune cell function, modulation of the neuroendocrine stress response to surgery, and cancer cell signaling.<sup>1–3</sup> In contrast, intravenous anesthetic agents (e.g., propofol) have antiinflammatory and antioxidative effects that may protect against perioperative immune suppression. Previous experimental studies have demonstrated antitumor effects by direct regulation of key ribonucleic

### ABSTRACT

**Background:** Previous experimental and clinical studies have shown that anesthetic agents have varying effects on cancer prognosis; however, the results were inconsistent among these studies. The authors compared overall and recurrence-free survival in patients given volatile or intravenous anesthesia for digestive tract cancer surgery.

**Methods:** The authors selected patients who had elective esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, and rectal cancer surgery from July 2010 to March 2018 using the Japanese Diagnosis Procedure Combination database. Patients were divided into a volatile anesthesia group (desflurane, sevoflurane, or isoflurane with/without nitrous oxide) and a propofol-based total intravenous anesthesia group. The authors hypothesized that total intravenous anesthesia is associated with greater overall and recurrence-free survival than volatile anesthesia. Subgroup analyses were performed for each type of surgery.

**Results:** The authors identified 196,303 eligible patients (166,966 patients in the volatile anesthesia group and 29,337 patients in the propofol-based total intravenous anesthesia group). The numbers (proportions) of death in the volatile anesthesia and total intravenous anesthesia groups were 17,319 (10.4%) and 3,339 (11.4%), respectively. There were no significant differences between the two groups in overall survival (hazard ratio, 1.02; 95% CI, 0.98 to 1.07;  $P = 0.28$ ) or recurrence-free survival (hazard ratio, 0.99; 95% CI, 0.96 to 1.03;  $P = 0.59$ ), whereas instrumental variable analyses showed a slight difference in recurrence-free survival (hazard ratio, 0.92; 95% CI, 0.87 to 0.98;  $P = 0.01$ ). Subgroup analyses showed no significant difference in overall or recurrence-free survival between the groups in any type of surgery.

**Conclusions:** Overall and recurrence-free survival were similar between volatile and intravenous anesthesia in patients having digestive tract surgery. Selection of the anesthetic approach for these patients should be based on other factors.

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acid pathways and signaling in cancer cells in patients with gastric cancer, non–small cell lung cancer, breast cancer, and endometrial and esophageal squamous cell carcinoma.<sup>4–9</sup>

Several studies have compared overall survival or recurrence-free survival of patients with cancer who had volatile anesthesia *versus* total intravenous anesthesia. A meta-analysis of 10 studies (nine retrospective studies and one small randomized controlled trial) involving patients having breast, esophageal, gastric, colon, rectal, or non–small cell lung cancer surgery showed that total intravenous anesthesia was not associated with improved recurrence-free survival, but was associated with improved overall survival, compared to volatile anesthesia.<sup>10</sup> However, all studies in

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the meta-analysis were limited because of their small sample sizes and possibility of residual confounders.

We therefore conducted a large-scale study to compare overall survival and recurrence-free survival between volatile anesthesia and total intravenous anesthesia using a national inpatient database in Japan. The objective of the study was to evaluate the association of volatile anesthesia *versus* total intravenous anesthesia with cancer prognosis among patients having digestive cancer surgery. We hypothesized that total intravenous anesthesia is associated with a greater overall survival and recurrence-free survival than is volatile anesthesia.

## Materials and Methods

### Data Source

Patient data were extracted from the Japanese Diagnosis Procedure Combination database, the details of which have been previously described.<sup>11</sup> Briefly, the database includes administrative claims data and the following detailed patient data: age; sex; body mass index (BMI); diagnoses and comorbidities at admission; complications after admission recorded with text data in the Japanese language and encoded by *International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* codes; medical procedures encoded by Japanese original codes; tumor node metastasis classification of malignant tumors and cancer stage; medications; activities of daily living at admission (converted to Barthel Index); and discharge status. According to a previous validation study of the database, the recorded diagnoses of several common diseases (including malignant tumors, cardiac diseases, stroke, and renal diseases) have moderate sensitivity and high specificity, whereas the recorded procedures and drugs have high sensitivity and specificity.<sup>11</sup> The database includes administrative data on 7 million inpatients per year, accounting for approximately 50% of all acute care inpatients in Japan. More than 1,000 hospitals participate in the database voluntarily, and approximately 300 hospitals also provide outpatient data.

The requirement for informed consent was waived because the study was based on a secondary analysis of anonymous administrative data. This study was approved by the Institutional Review Board at The University of Tokyo (Institutional Review Board number 3501).

### Patient Selection

From the database, we obtained the records of patients who had elective esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, or rectal cancer surgery from July 1, 2010 to March 31, 2018 at 218 hospitals that provided outpatient data. The inclusion criteria were an age of greater than or equal to 18 yr at the time of the first surgery with volatile anesthesia or total intravenous anesthesia. We excluded patients who had anesthesia multiple times during the study period, those who were diagnosed

with a benign tumor or a malignant potential tumor, those who had spinal anesthesia, and those in whom nitrous oxide was used without volatile anesthesia. A malignant potential tumor is a tumor that is reported to be associated with a risk of malignancy, including intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, and Crohn's disease.

### Exposure

The exposure variable was having volatile anesthesia or total intravenous anesthesia. The patients were divided into two groups: (1) those who had volatile anesthesia using desflurane, sevoflurane, or isoflurane with/without nitrous oxide and (2) those who had propofol-based total intravenous anesthesia.

### Confounding Variables and Outcomes

We extracted information on baseline characteristics including age at the time of the first elective surgery, sex, BMI, length of stay, smoking status (current/past smoker or non-smoker), admission date of cancer recurrence, date of death, comorbidities at admission, complications after admission, type of surgery (esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, or rectal cancer surgery), year of surgery, cancer stage, use of epidural anesthesia, use of morphine, use of oxycodone, preoperative chemotherapy, preoperative radiotherapy, postoperative renal replacement therapy, intraoperative blood transfusion, type of hospital (academic or nonacademic), Barthel Index at admission, and hospital volume. The patients were categorized into four age groups (younger than 59, 60 to 69, 70 to 79, and 80 yr or older) because more than 65% of the patients were aged 60 to 79 yr. The BMI was divided into five categories based on the World Health Organization classifications of underweight (less than 18.5 kg/m<sup>2</sup>), normal weight (18.5 to 24.9 kg/m<sup>2</sup>), overweight (25.0 to 29.9 kg/m<sup>2</sup>), and obese (30.0 kg/m<sup>2</sup> or more). The tumor, node, metastasis cancer stages were determined by postoperative pathology and divided into 0 or I, II, III, and IV.

The Barthel Index is frequently used to measure performance in activities of daily living, with scores ranging from 0 to 100 points (higher scores indicate less disability). This index includes 10 items of mobility and self-care functions. We divided the Barthel Index into two groups (0 to 95 and 100) because more than 90% of the patients had a Barthel Index of 100.

For comorbidities at admission, each ICD-10 code for a comorbidity was converted into a Charlson Comorbidity Index score, which is widely used as a validated measure to predict in-hospital morbidity and mortality for each patient.<sup>12</sup> All patients were diagnosed with cancer; therefore, the lowest Charlson Comorbidity Index score was 2.

Hospital volume was defined as the average number of surgeries performed at each hospital annually and was

divided into three groups containing almost equal numbers of patients.

Perioperative complications were defined as the occurrence of the following diseases during the first perioperative period: cerebral infarction or hemorrhage (ICD-10 codes I60 to I64), acute coronary events (I21, I22, and I252), heart failure (I50), pulmonary embolism (I26), acute and subacute hepatic failure (K720), acute renal failure (N17), sepsis (A40 and A41), wound infection (T793 and T814), pneumonia (J12 to J18 and J69), and urinary tract infection (N390, T835, and N30). We also searched for anastomotic leakage using Japanese text.

The primary outcomes were recurrence-free survival and overall survival.

### Statistical Analysis

No statistical power calculation was conducted before the study because the sample size in our study was based on secondary use of administrative claims data and a fixed available sample.

The patient characteristics and type of surgery in each group are described using number and proportion for categorical variables and mean with SD for continuous variables. Standardized differences were used to compare the distribution of baseline covariates between treatment groups in observational studies. Small differences in the absolute standardized differences (less than 0.10) suggest balanced baseline characteristics between patients in the volatile anesthesia and total intravenous anesthesia groups.<sup>13</sup>

Kaplan–Meier survival analysis was used to compare overall survival and recurrence-free survival between the two groups. Cox proportional hazard regression models were used to compare the relationship between total intravenous anesthesia and overall survival or recurrence-free survival with adjustment for the following baseline variables: age, sex, BMI, smoking status, Charlson Comorbidity Index score, cancer stage, preoperative adjuvant therapy, postoperative adjuvant therapy, preoperative renal replacement therapy, preoperative or intraoperative blood transfusion, preoperative use of morphine or oxycodone, type of hospital (academic or nonacademic), hospital volume, Barthel Index at admission, and at least one postoperative complication. We used the Schoenfeld residuals test and complementary log plots to assess the proportional hazards assumption. The proportional hazards assumption was not violated in any of our analyses. Some data regarding the BMI, cancer stage, and Barthel Index at admission were missing. We used a complete case analysis for these missing values. Follow-up was censored on March 31, 2018 or the last outpatient record.

Observational studies have the potential for residual confounders due to measured and unmeasured baseline characteristics, which can lead to incorrect associations between the type of anesthesia and outcomes. One strategy to address this limitation is the use of an instrumental variable analysis designed to adjust for unmeasured confounding between

two groups, allowing the achievement of a pseudo-randomized controlled trial.<sup>14</sup> An instrumental variable analysis requires the following assumptions: (1) the instrumental variable is independent of the unmeasured confounding; (2) the instrumental variable is strongly associated with the treatment; and (3) the instrumental variable is associated with the outcome only indirectly through its effect on the treatment. The type of anesthesia performed mainly depends on the physician's preference; therefore, we used the proportion of total intravenous anesthesia use at each hospital as an instrumental variable. The proportion of total intravenous anesthesia use was defined as the number of patients who had total intravenous anesthesia divided by the number of all patients in each hospital. We conducted two-stage residual inclusions for the instrumental variable analyses to compare recurrence-free survival or overall survival between the volatile anesthesia and total intravenous anesthesia groups. We fit a first stage logistic model that predicts treatment assignment (volatile anesthesia and total intravenous anesthesia) with the instrumental variable and the aforementioned variables to estimate the probability of having total intravenous anesthesia. Next, the second stage model was fitted by regressing these outcomes on the performance of total intravenous anesthesia in a Cox regression model, along with the residuals from the first-stage model and the other variables.

We confirmed that the proportion of total intravenous anesthesia use at each hospital was not a weak instrument using a partial F test, with an F statistic of more than 10.<sup>15</sup>

Two additional approaches were performed as sensitivity analyses. First, we used Cox regression analyses after propensity score matching. We estimated the propensity score using a logistic regression model for the receipt of total intravenous anesthesia, incorporating the baseline characteristics of the aforementioned variables without postoperative adjuvant therapy and at least one postoperative complication. We set a caliper at 0.2 SD of the estimated logit of the propensity score and performed one-to-one propensity score matching of patients between the types of anesthesia using the nearest neighbor method without replacement. We estimated the balance in the propensity score-matched cohort using standardized differences. Second, we performed an instrumental variable analysis using the proportion of total intravenous anesthesia at each of 47 prefectures as another instrumental variable.

Subgroup analyses were performed for the type of cancer surgery. We evaluated the association between total intravenous anesthesia and the primary outcomes using Cox regression analyses. A two-tailed *P* value of less than 0.05 was considered statistically significant. All analyses were performed using Stata/MP 16.0 (StataCorp, USA).

### *A Priori versus Post Hoc Analyses*

As *a priori* analyses, we planned to perform Cox regression analyses and instrumental variable analyses using the

proportion of total intravenous anesthesia use at each hospital as an instrumental variable in all patients to evaluate the association between the type of anesthesia and outcomes. As a *post hoc* sensitivity analysis, we performed Cox regression analyses in propensity score–matched patients and instrumental variable analyses using the proportion of total intravenous anesthesia in each of 47 prefectures as another instrumental variable.

## Results

We selected 255,330 patients who had cancer surgery during the study period. We then excluded 52,209 patients who had anesthesia multiple times during the study period, 5,905 patients diagnosed with a benign tumor or a malignant potential tumor, 227 patients who had spinal anesthesia, and 686 patients who received nitrous oxide without volatile anesthesia. In total, 196,303 patients who met the inclusion criteria were divided into those who had volatile anesthesia using desflurane, sevoflurane, or isoflurane with/without nitrous oxide (volatile anesthesia group,  $n = 166,966$ ) and those who had propofol-based total intravenous anesthesia (total intravenous anesthesia group,  $n = 29,337$ ; fig. 1).

Table 1 shows the baseline characteristics of the patients, hospitals, and procedures for the overall study cohort and each of the two groups. Overall, 63,678 (32.4%) patients had colectomy and 61,056 (31.1%) had gastrectomy. The standardized differences for all variables suggested no differences between the volatile anesthesia and total intravenous anesthesia groups with the exception of male sex, academic hospital, year of surgery, and high hospital volume. The BMI data were missing for 1,856 (0.9%) patients, the cancer stage was missing for 39,342 (20.0%) patients, and the Barthel Index at admission was missing for 5,795 (3.0%) patients.

The median postoperative follow-up period was 639 days (interquartile range, 234 to 1,301 days) in the volatile anesthesia group and 768 days (interquartile range, 286 to 1,525 days) in the total intravenous anesthesia group.

The overall mortality rates in the volatile anesthesia and total intravenous anesthesia groups were 10.4% and 11.4%, respectively. The proportions of recurrence or death in the volatile anesthesia and total intravenous anesthesia groups were 18.3% and 18.8%, respectively.

The results of the Kaplan–Meier analysis are shown in figure 2 (overall survival) and figure 3 (recurrence-free survival). The 1-yr overall survival was 89.8% in the volatile anesthesia group and 90.0% in the total intravenous anesthesia group. The 1-yr recurrence-free survival was 80.8% in the volatile anesthesia group and 81.9% in the total intravenous anesthesia group.

Figure 4 shows the association between total intravenous anesthesia and overall survival or recurrence-free survival by Cox regression analyses. We found no significant difference in overall survival (hazard ratio, 1.02; 95% CI, 0.98 to 1.07;  $P = 0.28$ ) or recurrence-free survival (hazard ratio, 0.99; 95% CI, 0.96 to 1.03;  $P = 0.59$ ) between the volatile anesthesia and total intravenous anesthesia groups. Variables that were significantly associated with worse overall survival and recurrence-free survival were an age of older than 60 yr, male sex, underweight (BMI of less than 18.5 kg/m<sup>2</sup>), Charlson Comorbidity Index score of 3 or 4, cancer stage, preoperative adjuvant therapy, postoperative adjuvant therapy, preoperative renal replacement therapy, smoking, preoperative or intraoperative blood transfusion, preoperative use of morphine or oxycodone, academic hospital, Barthel Index, and at least one postoperative complication.

Figure 5 shows the association between total intravenous anesthesia and overall survival or recurrence-free survival by instrumental variable analyses. The F statistic was 27,416 ( $P < 0.001$ ), suggesting that the instrumental variable was strongly associated with the treatment assignment (volatile anesthesia or total intravenous anesthesia). Compared with volatile anesthesia, total intravenous anesthesia was not significantly associated with better overall survival (hazard ratio, 1.02; 95% CI, 0.95 to 1.09;  $P = 0.65$ ), but was significantly associated with better

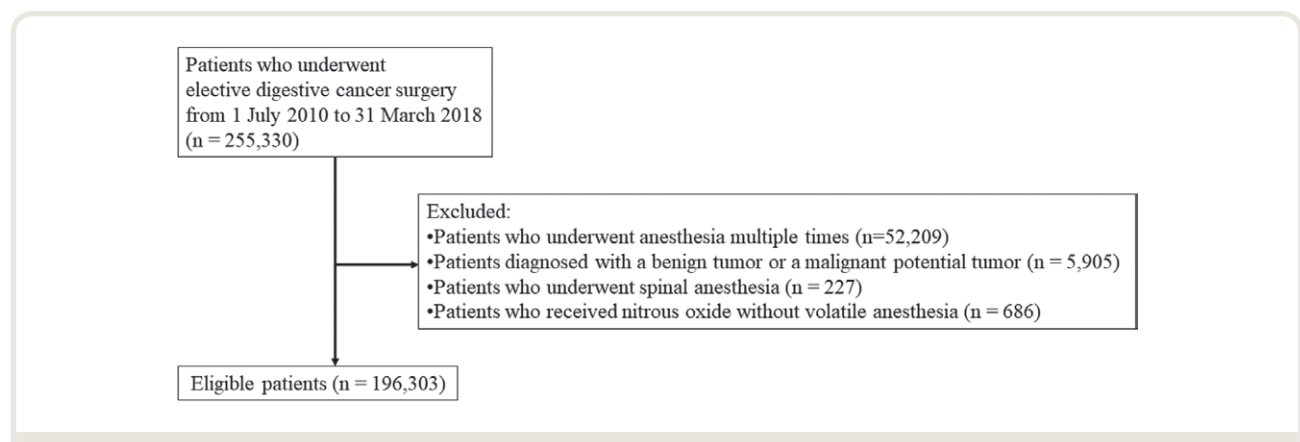


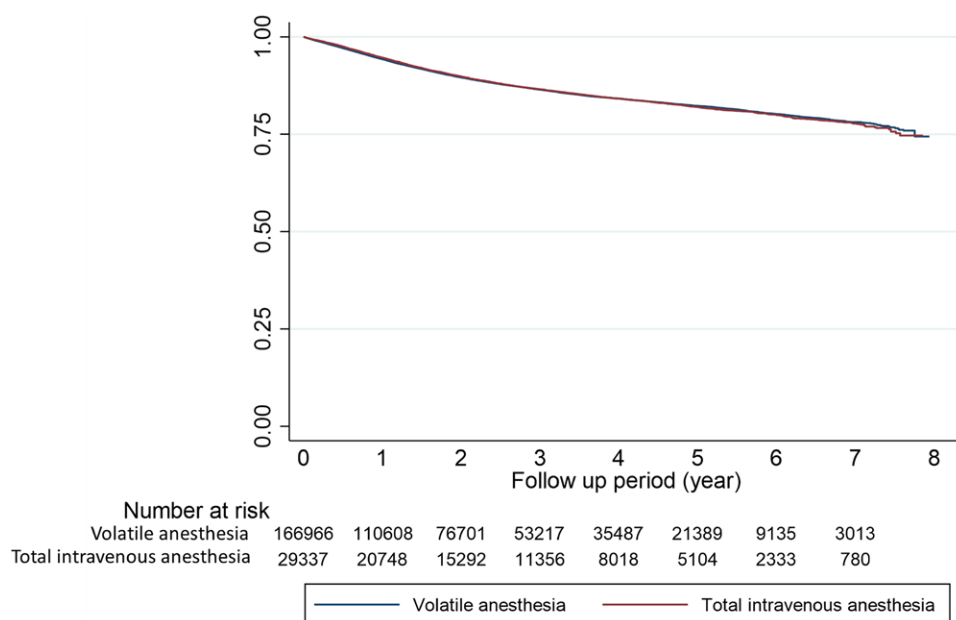
Fig. 1. Flow chart of patient selection.

**Table 1.** Baseline Characteristics of Patients, Hospitals, and Procedures

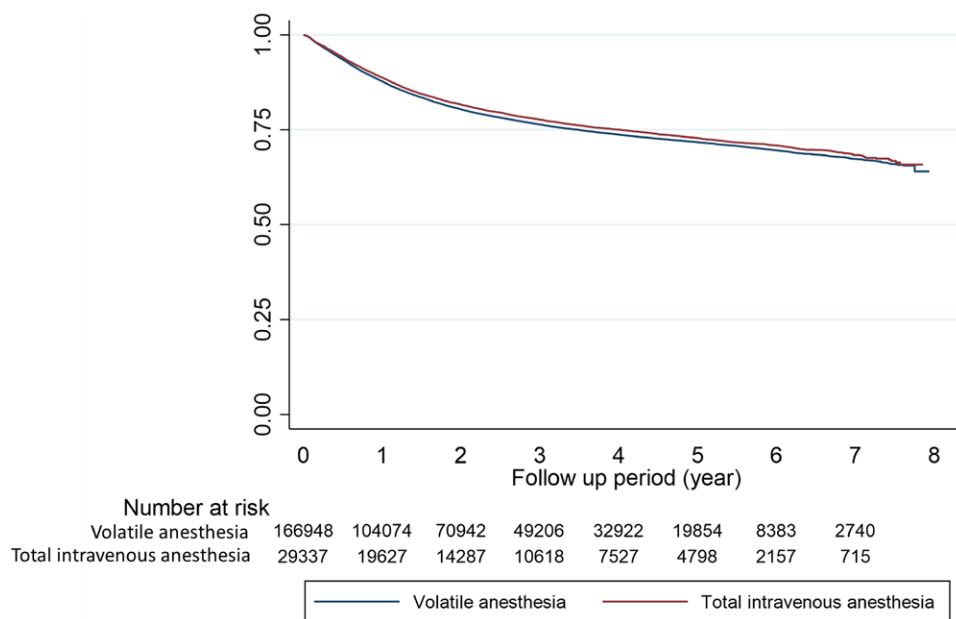
|   | Total<br>(n = 196,303) |        | Volatile<br>Anesthesia<br>(n = 166,966) |        | Total Intravenous<br>Anesthesia<br>(n = 29,337) |        | Absolute<br>Standardized<br>Difference |
|---|------------------------|--------|---|--------|---|--------|--|
| Age, yr                                 |                        |        |   |        |   |        |  |
| ≤ 59                                    | 32,806                 | (16.7) | 27,256                                  | (16.3) | 5,550   | (18.9) | 0.067                                  |
| 60–69                                   | 59,502                 | (30.3) | 50,477                                  | (30.2) | 9,025   | (30.8) | 0.013                                  |
| 70–79                                   | 70,514                 | (35.9) | 60,546                                  | (36.3) | 9,968   | (34.0) | 0.045                                  |
| ≥ 80                                    | 33,481                 | (17.1) | 28,687                                  | (17.2) | 4,794   | (16.3) | 0.028                                  |
| Sex, male                               | 122,254                | (62.3) | 105,345                                 | (63.1) | 16,909  | (57.6) | 0.114                                  |
| Body mass index, kg/m <sup>2</sup>      |                        |        |   |        |   |        |  |
| < 18.5                                  | 22,503                 | (11.5) | 19,014                                  | (11.4) | 3,489   | (11.9) | 0.015                                  |
| 18.5–24.9                               | 130,076                | (66.3) | 110,510                                 | (66.2) | 19,566  | (66.7) | 0.008                                  |
| 25.0–29.9                               | 36,545                 | (18.6) | 31,145                                  | (18.7) | 5,400   | (18.4) | 0.008                                  |
| 30.0–34.9                               | 4,585                  | (2.3)  | 3,982                                   | (2.4)  | 603   | (2.1)  | 0.029                                  |
| ≥ 35.0                                  | 738                    | (0.4)  | 652                                     | (0.4)  | 86  | (0.3)  | 0.021                                  |
| Missing                                 | 1,856                  | (0.9)  | 1,663                                   | (1.0)  | 193   | (0.7)  |  |
| Charlson comorbidity index              |                        |        |   |        |   |        |  |
| 2                                       | 143,545                | (73.1) | 121,402                                 | (72.7) | 22,143  | (75.5) | 0.066                                  |
| 3                                       | 12,664                 | (6.5)  | 10,884                                  | (6.5)  | 1,780   | (6.1)  | 0.022                                  |
| ≥ 4                                     | 40,094                 | (20.4) | 34,680                                  | (20.8) | 5,414   | (18.5) | 0.059                                  |
| Cancer stage                            |                        |        |   |        |   |        |  |
| 0 or I                                  | 55,440                 | (28.2) | 47,089                                  | (28.2) | 8,351   | (28.5) | 0.015                                  |
| II                                      | 42,002                 | (21.4) | 35,973                                  | (21.5) | 6,029   | (20.6) | 0.027                                  |
| III                                     | 42,195                 | (21.5) | 35,770                                  | (21.4) | 6,425   | (21.9) | 0.016                                  |
| IV                                      | 17,324                 | (8.8)  | 14,814                                  | (8.9)  | 2,510   | (8.6)  | 0.009                                  |
| Missing                                 | 39,342                 | (20.0) | 33,320                                  | (20.0) | 6,022   | (20.5) |  |
| Preoperative adjuvant therapy           | 10,528                 | (5.4)  | 9,205                                   | (5.5)  | 1,323   | (4.5)  | 0.051                                  |
| Postoperative adjuvant therapy          | 67,508                 | (34.4) | 57,000                                  | (34.1) | 10,508  | (35.8) | 0.037                                  |
| Preoperative renal replacement therapy  | 1,627                  | (0.8)  | 1,473                                   | (0.9)  | 154   | (0.5)  | 0.039                                  |
| Type of surgery                         |                        |        |   |        |   |        |  |
| Esophagectomy                           | 8,859                  | (4.5)  | 7,212                                   | (4.3)  | 1,647   | (5.6)  | 0.072                                  |
| Gastrectomy                             | 61,056                 | (31.1) | 51,701                                  | (31.0) | 9,355   | (31.9) | 0.010                                  |
| Hepatectomy                             | 18,095                 | (9.2)  | 15,976                                  | (9.6)  | 2,119   | (7.2)  | 0.086                                  |
| Cholecystectomy                         | 4,064                  | (2.1)  | 3,534                                   | (2.1)  | 530   | (1.8)  | 0.017                                  |
| Pancreatectomy                          | 16,045                 | (8.2)  | 13,972                                  | (8.4)  | 2,073   | (7.1)  | 0.043                                  |
| Colectomy                               | 63,678                 | (32.4) | 53,886                                  | (32.3) | 9,792   | (33.4) | 0.028                                  |
| Rectal cancer surgery                   | 24,506                 | (12.5) | 20,685                                  | (12.4) | 3,821   | (13.0) | 0.026                                  |
| Year of surgery                         |                        |        |   |        |   |        |  |
| 2010 (July–December)                    | 14,378                 | (7.3)  | 11,549                                  | (6.9)  | 2,829   | (9.6)  | 0.104                                  |
| 2011 (January–December)                 | 25,039                 | (12.8) | 20,330                                  | (12.2) | 4,709   | (16.1) | 0.114                                  |
| 2012 (January–December)                 | 24,109                 | (12.3) | 19,943                                  | (11.9) | 4,166   | (14.2) | 0.048                                  |
| 2013 (January–December)                 | 23,678                 | (12.1) | 19,811                                  | (11.9) | 3,867   | (13.2) | 0.013                                  |
| 2014 (January–December)                 | 24,194                 | (12.3) | 20,697                                  | (12.4) | 3,497   | (11.9) | 0.010                                  |
| 2015 (January–December)                 | 25,395                 | (12.9) | 22,020                                  | (13.2) | 3,375   | (11.5) | 0.045                                  |
| 2016 (January–December)                 | 26,172                 | (13.3) | 23,057                                  | (13.8) | 3,115   | (10.6) | 0.087                                  |
| 2017 (January–December)                 | 27,355                 | (13.9) | 24,166                                  | (14.5) | 3,189   | (10.9) | 0.100                                  |
| 2018 (January–March)                    | 5,983                  | (3.0)  | 5,393                                   | (3.2)  | 590   | (2.0)  | 0.069                                  |
| Epidural anesthesia                     | 141,896                | (72.3) | 120,751                                 | (72.3) | 21,145  | (72.1) | 0.042                                  |
| Smoking                                 | 92,023                 | (46.9) | 79,191                                  | (47.4) | 12,832  | (43.7) | 0.073                                  |
| Pre- or postoperative blood transfusion | 31,669                 | (16.1) | 27,520                                  | (16.5) | 4,149   | (14.1) | 0.058                                  |
| Preoperative morphine or oxycodone      | 961                    | (0.5)  | 816                                     | (0.5)  | 145   | (0.5)  | 0.002                                  |
| Academic hospital                       | 55,462                 | (28.3) | 49,968                                  | (29.9) | 5,494   | (18.7) | 0.209                                  |
| Hospital volume                         |                        |        |   |        |   |        |  |
| Low (< 125)                             | 64,711                 | (33.0) | 54,665                                  | (32.7) | 10,046  | (34.2) | 0.020                                  |
| Medium (125–245)                        | 65,509                 | (33.4) | 54,414                                  | (32.6) | 11,095  | (37.8) | 0.092                                  |
| High (> 245)                            | 66,083                 | (33.7) | 57,887                                  | (34.7) | 8,196   | (27.9) | 0.115                                  |
| Barthel Index                           |                        |        |   |        |   |        |  |
| 100                                     | 177,094                | (90.2) | 150,849                                 | (90.3) | 26,245  | (89.5) | 0.021                                  |
| 0–95                                    | 13,414                 | (6.8)  | 11,578                                  | (6.9)  | 1,836   | (6.3)  | 0.021                                  |
| Missing                                 | 5,795                  | (3.0)  | 4,539                                   | (2.7)  | 1,256   | (4.3)  |  |
| Complication after operation            |                        |        |   |        |   |        |  |
| At least one complication               | 15,280                 | (7.8)  | 15,280                                  | (9.2)  | 677   | (2.3)  | 0.025                                  |
| Cerebral infarction or hemorrhage       | 582                    | (0.3)  | 504                                     | (0.3)  | 78  | (0.3)  | 0.005                                  |
| Acute coronary events                   | 196                    | (0.1)  | 172                                     | (0.1)  | 24  | (0.1)  | 0.008                                  |
| Heart failure                           | 2,593                  | (1.3)  | 2,321                                   | (1.4)  | 272   | (0.9)  | 0.034                                  |
| Pulmonary embolism                      | 372                    | (0.2)  | 337                                     | (0.2)  | 35  | (0.1)  | 0.019                                  |
| Acute hepatic failure                   | 157                    | (0.1)  | 140                                     | (0.1)  | 17  | (0.1)  | 0.005                                  |
| Acute renal disease                     | 466                    | (0.2)  | 403                                     | (0.2)  | 63  | (0.2)  | 0.007                                  |
| Sepsis                                  | 1,780                  | (0.9)  | 1,559                                   | (0.9)  | 221   | (0.8)  | 0.019                                  |
| Wound infection                         | 5,320                  | (2.7)  | 4,503                                   | (2.7)  | 817   | (2.8)  | 0.008                                  |
| Pneumonia                               | 3,790                  | (1.9)  | 3,288                                   | (2.0)  | 502   | (1.7)  | 0.018                                  |
| Urinary tract infection                 | 1,165                  | (0.6)  | 970                                     | (0.6)  | 195   | (0.7)  | 0.012                                  |
| Anastomotic leakage                     | 96                     | (0.0)  | 81                                      | (0.0)  | 15  | (0.1)  | 0.002                                  |

Data are presented as n (%).

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**Fig. 2.** Kaplan–Meier analysis of overall survival.



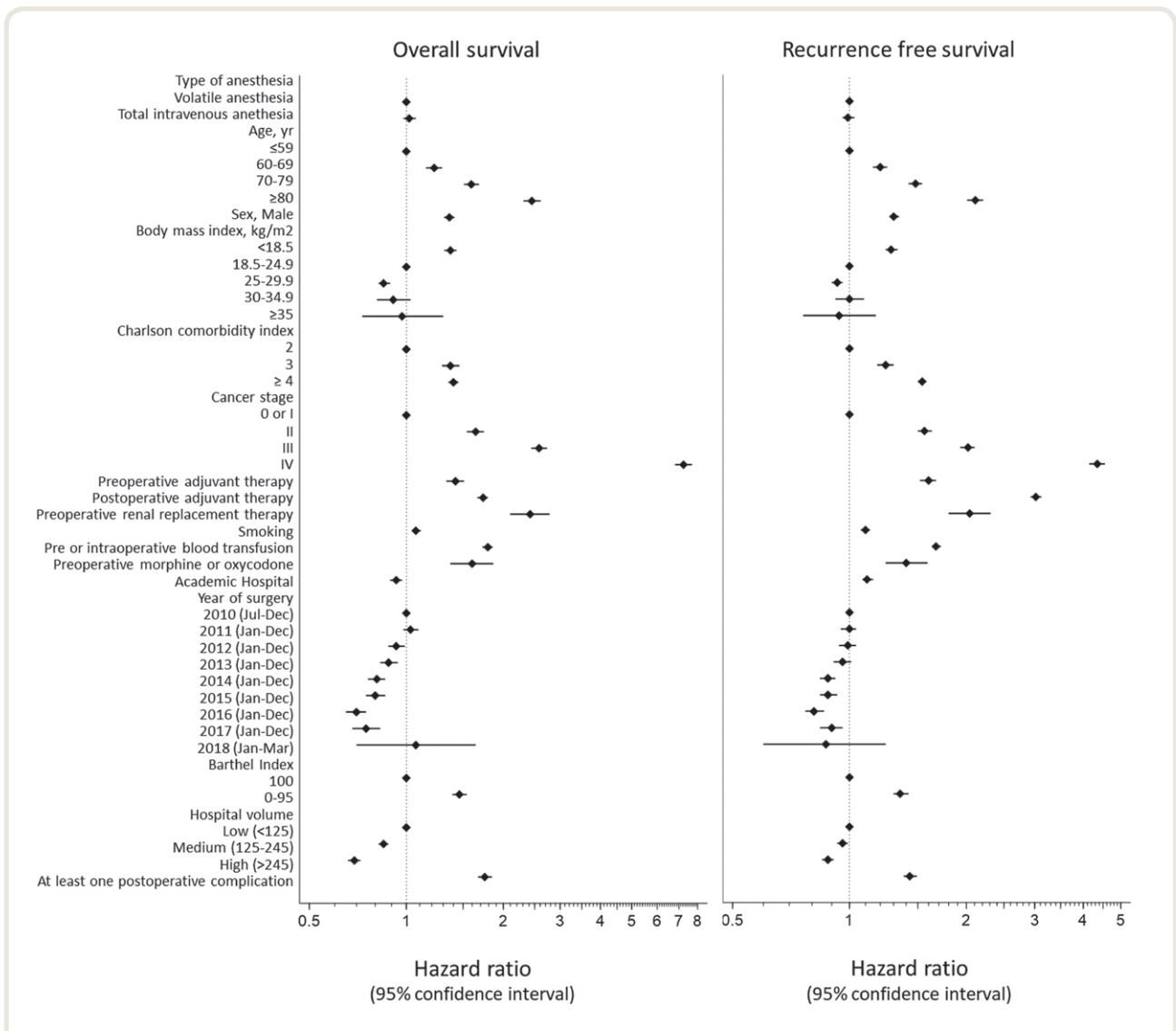
**Fig. 3.** Kaplan–Meier analysis of recurrence-free survival.

recurrence-free survival (hazard ratio, 0.92; 95% CI, 0.87 to 0.98;  $P = 0.01$ ).

Table 2 shows the results of the subgroup analyses for each type of cancer surgery. There was no significant difference in overall survival or recurrence-free survival between

the volatile anesthesia and total intravenous anesthesia groups in any type of surgery.

Supplemental Digital Content, table 1 (<http://links.lww.com/ALN/C420>) shows the patients' characteristics after propensity score matching. The distribution was well-balanced



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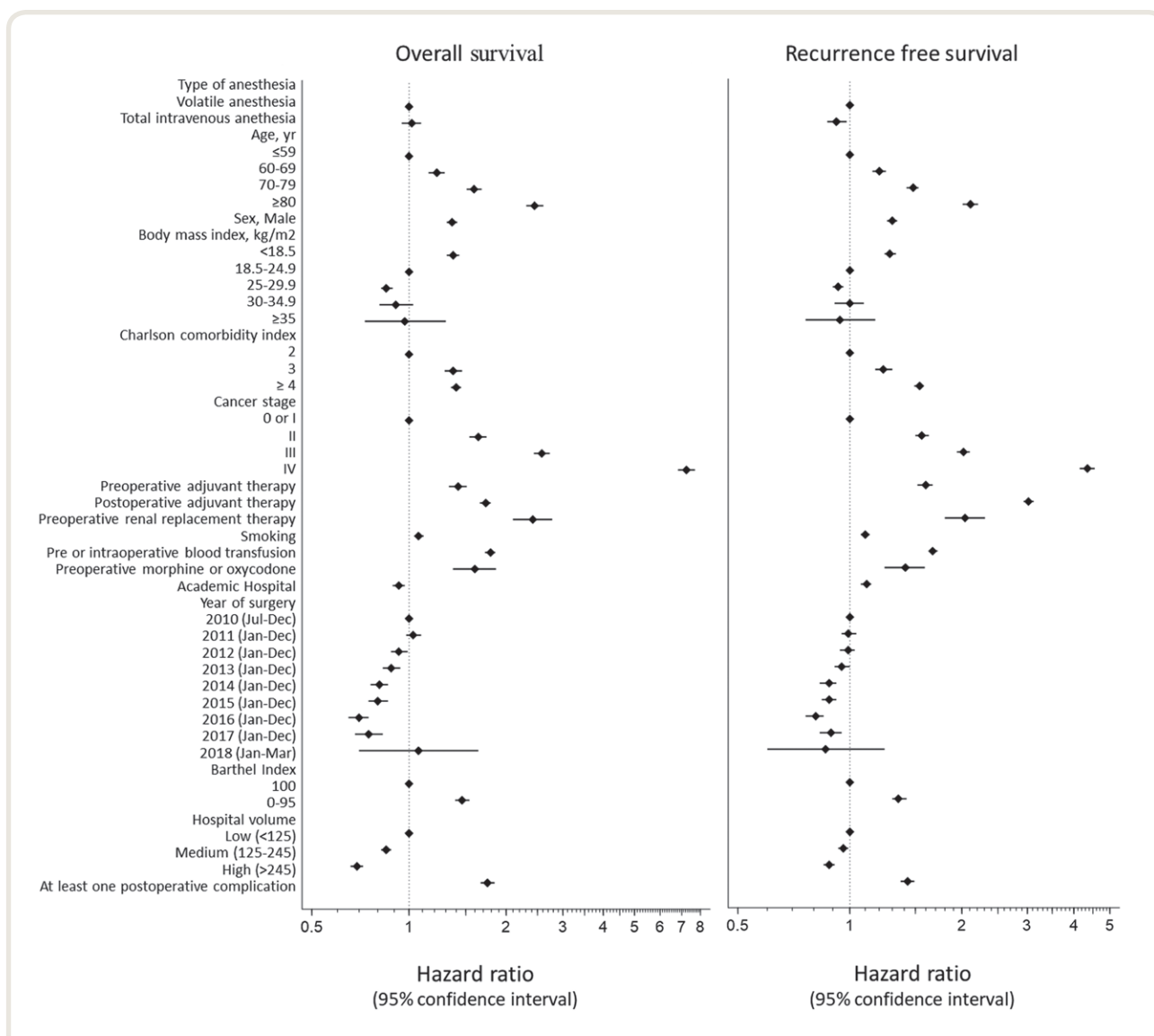
**Fig. 4.** Results of Cox regression analyses for recurrence-free survival and overall survival.

between the volatile anesthesia and total intravenous anesthesia groups. Supplemental Digital Content, table 2 (<http://links.lww.com/ALN/C421>) shows that total intravenous anesthesia was not significantly associated with improved overall survival (hazard ratio, 1.01; 95% CI, 0.79 to 1.21;  $P = 0.77$ ) or recurrence-free survival (hazard ratio, 1.00; 95% CI, 0.96 to 1.05;  $P = 0.94$ ) in the propensity score-matched cohort.

The results of the instrumental variable analyses using the proportion of total intravenous anesthesia in each of 47 prefectures as another instrumental variable were similar to those in the main analyses; total intravenous anesthesia was significantly associated with improved recurrence-free survival, but not significantly associated with improved overall survival, compared with volatile anesthesia (Supplemental Digital Content, table 3, <http://links.lww.com/ALN/C422>).

### Discussion

This study showed no significant association between total intravenous anesthesia and better overall survival in patients who had elective cancer surgery including esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, and rectal cancer surgery. We also found that total intravenous anesthesia was not significantly associated with better recurrence-free survival by the Cox regression analysis, but that it was significantly associated with better recurrence-free survival by the instrumental variable analysis. This difference in these results may reflect the control for unmeasured confounders by the instrumental variable analysis. However, the adjusted hazard ratio (95% CI) of total intravenous anesthesia for recurrence-free survival was 0.92 (0.87 to 0.98); therefore, the influence of total intravenous anesthesia on reducing cancer recurrence was small, if any.



**Fig. 5.** Results of instrumental variable analyses for recurrence-free survival and overall survival, in which the instrumental variable was defined as the proportion of total intravenous anesthesia at each hospital.

**Table 2.** Subgroup Analyses for Each Type of Surgery: Association of Volatile Anesthesia with Recurrence-free Survival and Overall Survival by Cox Regression

|                       | Recurrence-free Survival |           |         | Overall Survival |           |         |
|-----------------------|--------------------------|-----------|---------|------------------|-----------|---------|
|                       | Hazard Ratio             | 95% CI    | P Value | Hazard Ratio     | 95% CI    | P Value |
| Esophagectomy         | 1.02                     | 0.92–1.13 | 0.699   | 1.11             | 0.97–1.27 | 0.133   |
| Gastrectomy           | 0.96                     | 0.89–1.03 | 0.240   | 0.97             | 0.89–1.06 | 0.553   |
| Hepatectomy           | 1.07                     | 0.96–1.18 | 0.210   | 1.00             | 0.86–1.17 | 0.977   |
| Cholecystectomy       | 0.85                     | 0.70–1.04 | 0.110   | 0.83             | 0.65–1.05 | 0.120   |
| Pancreatectomy        | 0.96                     | 0.88–1.05 | 0.350   | 0.99             | 0.89–1.11 | 0.910   |
| Colectomy             | 0.99                     | 0.93–1.06 | 0.810   | 1.02             | 0.93–1.11 | 0.680   |
| Rectal cancer surgery | 0.92                     | 0.83–1.02 | 0.110   | 1.04             | 0.91–1.19 | 0.580   |



Many previous experimental studies have revealed a premetastatic effect of volatile anesthesia and a beneficial effect of propofol for various cancer cells. Laboratory studies of prostate or renal cancer cells have shown that isoflurane induces modulation of hypoxia-inducible factor 1- $\alpha$  (HIF-1 $\alpha$ ) or vascular endothelial growth factor, which may affect cancer recurrence after surgery.<sup>1,16</sup> One study of ovarian cancer cells demonstrated increased expression of genes related to metastasis after exposure to sevoflurane, desflurane, and isoflurane, while another study suggested that sevoflurane promoted metastatic potential and chemoresistance in renal carcinoma but not in non-small cell lung cancer.<sup>17,18</sup> In contrast, laboratory studies of propofol have shown antitumor effects in various cancers. A previous study of gastric cancer cells showed that propofol inhibited cell proliferation, invasion, and migration and promoted apoptosis.<sup>19</sup> Another study of non-small cell lung cancer showed that propofol disrupted upregulation of HIF-1 $\alpha$  in a dose-dependent manner and therefore reduced the migration and invasion of cancer cells.<sup>20</sup>

Clinical studies have shown conflicting results regarding whether total intravenous anesthesia may have a beneficial effect on cancer prognosis compared with volatile anesthesia. A previous meta-analysis of overall mortality (including three randomized clinical trials and five observational studies) suggested that total intravenous anesthesia might lead to decreased mortality compared with volatile anesthesia.<sup>21</sup> This result may be attributable to one large study that showed higher overall mortality in the volatile anesthesia group than total intravenous anesthesia group. However, this study did not adjust for potential confounders including the cancer stage and preoperative comorbidities.<sup>22</sup> Observational studies have shown inconsistent results. Total intravenous anesthesia was not associated with overall survival or recurrence-free survival in patients having breast cancer surgery.<sup>23</sup> Two other studies showed inconsistent results in terms of overall survival between propofol and sevoflurane in patients having gastric or rectal cancer surgery.<sup>24,25</sup>

Our findings showed little association between the type of anesthesia and cancer prognosis. The advantage of our study is the larger sample size than those in previous studies and the use of instrumental variable analyses to control for unmeasured confounders. Another advantage of the present study was the inclusion of various types of cancer in digestive organs.

In instrumental variable analyses, all individuals in the study population are assumed to be compliers. This is called the “monotonicity assumption.”<sup>26,27</sup> In the present study, compliers were those who were likely to receive total intravenous anesthesia in hospitals with a high preference for total intravenous anesthesia, whereas they were unlikely to receive total intravenous anesthesia in hospitals with a low preference for total intravenous anesthesia. Complex decision processes with multiple factors may violate the monotonicity assumption when using the physician’s preference as an instrument.<sup>26,27</sup> However, in the present study, the proportion of total intravenous anesthesia use at each hospital

as an instrumental variable may not violate the monotonicity assumption because the decision regarding the use of total intravenous anesthesia must be based only on anesthesiologists’ preferences, not on patients’ willingness; that is, most patients are considered to be compliers.

The current study had several limitations. First, retrospective observational studies are associated with the potential for residual confounding. We therefore performed propensity score-matched analyses, which were designed to balance variables between the two groups and thus reduce the potential measured confounding effect of each variable. In addition, instrumental variable analyses may help to account for unmeasured confounders such as laboratory data and surgical invasiveness. Second, we could identify only patients who died in a hospital in which the patients had cancer surgery; patients who died at home or in another institution could not be followed. Finally, the postoperative follow-up period was short (median of just over 2 yr); a study with a longer follow-up period of more than 5 yr is warranted.

In conclusion, the present study showed no significant difference in overall survival and little difference, if any, in recurrence-free survival between total intravenous anesthesia and volatile anesthesia.

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### Competing Interests

The authors declare no competing interests.

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