# Anesthetics and long-term survival after cancer surgery—total intravenous versus volatile anesthesia: a retrospective study

**Boohwi Hong**
Chungnam National University School of Medicine
**Sunyeul Lee**
Chungnam National University School of Medicine
**Yeojung Kim**
Chungnam National University Hospital
**Minhee Lee**
MediRedox
**Ann Misun Youn**
Chungnam National University Hospital
**Hyun Rhim**
Chungnam National University Hospital
**Seok-Hwan Hong**
Chungnam National University Hospital
**Yoon-Hee Kim**
Chungnam National University School of Medicine
**Seok-Hwa Yoon**
Chungnam National University School of Medicine
**Chaeseong Lim** ( limtwo2@gmail.com )
Chungnam National University College of Medicine https://orcid.org/0000-0002-2356-8999

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# Abstract

Background Intravenous anesthesia has been reported to have a favorable effect on the prognosis of cancer patients. This study was performed to analyze data regarding the relation between anesthetics and the prognosis of cancer patients in our hospital.

Methods The medical records of patients who underwent surgical resection for gastric, lung, liver, colon, and breast cancer between January 2006 and December 2009 were reviewed. Depending on the type of anesthetic, it was divided into total intravenous anesthesia (TIVA) or volatile inhaled anesthesia (VIA) group. The 5-year overall survival outcomes were analyzed by log-rank test. Cox proportional hazards modeling was used for sensitivity.

Results The number of patients finally included in the comparison after propensity matching came to 729 in each group. The number of surviving patients at 5 years came to 660 (90.5%) in the TIVA and 673 (92.3%) in the VIA. The type of anesthetic did not affect the 5-year survival rate according to the log-rank test ( P = 0.21). Variables associated with a significant increase in the hazard of death after multivariable analysis were male sex and metastasis at surgery.

Conclusion There were no differences in 5-year overall survival between two groups in the cancer surgery.


# Background

Over 200,000 new cancer patients are diagnosed in Korea each year and one in four deaths in this country is due to cancer[1]. Although much progress has been made in chemotherapy and radiation therapy, excision of cancer mass is still a good treatment option for solid tumor[2]. However, there is a possibility that cancer may metastasize or proliferate during surgery[3]. Surgery can spread cancer cells throughout the body[4], so both doctors and patients are sensitive to the prognosis after surgery. Cancer recurrence and metastasis will be determined by cancer propagation, patient immunity, and the like[5].

Methods of general anesthesia for tumor resection of malignant tumors include the use of volatile anesthetics and the use of intravenous anesthetics. There have been a number of studies regarding the possibility of using volatile inhaled anesthetics (VIA) to increase the incidence of hypoxia-inducible factors (HIF) and insulin-like growth factor, which are factors involved in tumor growth. There is a possibility of adverse effects on the prognosis of surgical patients. On the other hand, the intravenous anesthetic, propofol, has been reported to reduce the expression of HIF–1α and inhibit tumor growth[6].

In other hospital data, total intravenous anesthesia (TIVA) has been reported to have a favorable effect on the prognosis of cancer patients[7].The purpose of this study was to investigate whether there is a difference in the 5-year overall mortality between propofol-based TIVA and VIA in patients who underwent 5 major cancers surgery through the data from our hospital. Our hypothesis was that TIVA would show a high five-year survival rate after cancer surgery compared to VIA in our hospital.

## Methods

# Setting

The study was approved by the institutional review board of Chungnam National University Hospital (approval number CNUH 2017–08–018). The requirement for informed consent was waived in view of the retrospective nature of the study. This clinical trial has been registered at Clinical Research Information Service (registration number KCT0004101).

# Participants

We reviewed the medical records of patients who underwent surgical resection for gastric, lung, liver, colon, and breast cancer from January 2006 to December 2009. Patients who had undergone emergency surgery, with no follow-up after surgery, patients whose medical records could not be confirmed, patients whose anesthesia was changed during surgery, and patients who died during or immediately after surgery were excluded from the study. Patients who did not fulfill any of the variables examined in the medical record were excluded.

# Variables

Patient factors were age at the time of surgery, sex, body mass index (BMI), and American Society of Anesthesiologists (ASA) class. Surgical and anesthetic factors were the presence of hypertension and diabetes mellitus (DM), total anesthesia time, operation time, type of anesthesia (volatile inhalational anesthesia vs. total intravenous anesthesia), use of nitrous oxide, application of remifentanil infusion, and presence of metastasis at the time of surgery. We also investigated the patient's total length of hospital stay. We investigated the correlations between each of the factors and 5-year survival. Patients were followed-up only with regard to the primary outcome, i.e., overall survival.

# Data sources

All data related to the surgery were obtained from the hospital statistical records. Data related to anesthesia, metastasis, and deaths were obtained from the hospital electronic medical records. If we could not find an electronic medical record of the patient's survival at 5 years after surgery, the patient or caregiver was contacted.

# Statistics

The sample consisted of all subjects during the study period. All available patients were considered, and no *a priori* power analysis was conducted. To account for possible selection bias and confounding

factors[8], 1:1 ratio propensity score matching (PSM) was performed using the MatchIt package in R[9]. The dependent variable was set as a binary response of 0 or 1, and logistic regression analysis was performed by designating the covariate (age, sex, height, weight, BMI, ASA class, hypertension, DM, anesthesia time, operation time, metastasis, transfusion) to be corrected as an independent variable. The survival rate was different for each cancer, and the numbers of anesthetic methods used were different for each cancer. Therefore, we matched for each type of cancer.

Nearest neighbor matching was performed, which matches the absolute differences of the estimated propensity scores of all subjects in both groups from the smallest to the largest difference. Absolute standardized difference (ASD) was calculated to validate the suitability of PSM balance diagnostics between the two groups, with ASD < 0.1 for the covariate indicating that the two groups were sufficiently balanced.

After validating the balance of the matched data, the normality of continuous data was assessed using the Shapiro–Wilk test. If normality was satisfied, comparisons between groups were performed by independent *t* tests, with the results expressed as the mean ± standard deviation. If normality was not satisfied, groups were compared using the Mann–Whitney U test, with the results expressed as the median ([interquartile range]). Categorical data were compared using the chi-squared test or Fisher's exact test, as appropriate, with the results expressed as number (%).

Survival outcomes were analyzed by the log-rank test and expressed by the Kaplan–Meier plot. Cox proportional hazards modeling was used for univariate and multivariable analysis of demographic and clinical variables influencing the survival outcomes. The cut points of the continuous variables were obtained using the maxstst package, and the survival analysis was performed by dividing into two categories based on the cut points. The criteria divided into two categories are as follows. The age was 65 years old, height 165cm, weight 57kg, BMI 19.7, and anesthesia time was 210 minutes. Only the meaningful variables ($P < 0.2$) from univariate analysis were included in multivariable analysis. Akaike's Information Criterion was considered for final model selection by backward elimination. Associations with $P < 0.05$ were considered statistically significant. All Data were analyzed using R software version 3.5.2 (R Project for Statistical Computing, Vienna, Austria).

# Results

We reviewed the following items in the anesthesia and operation records of patients who underwent surgery. From January 2006 to December 2009, 2496 patients underwent resection of five major malignant tumors. After exclusion of 289 patients according to the exclusion criteria, the analysis were performed in a total of 2207 patients (Fig. 1). All patient information is shown in Table 1. Anesthesia was maintained by inhalation anesthesia in 1304 patients and TIVA in 903 patients undergoing surgery. The numbers of patients finally included in the comparison after propensity matching were 729 in each group.

# Anesthesia

In the TIVA group, all patients used propofol, and all patients were treated with remifentanil, except one patient treated with alfentanil. One patient in the TIVA group was treated with nitrous oxide, which was administered within 5 minutes after induction of anesthesia because the anesthesia machine was set up to automatically administer nitrous oxide when the fraction of inspired oxygen was reduced. There were no patients with epidural pain control or regional block.

# Five year survival: TIVA vs VIA

The numbers of surviving patients at 5 years were 829/903 (91.8%) in the TIVA group and 1214/1304 (93.1%) in the VIA group. After propensity matching, these numbers changed to 660/729 (90.5%) and 673/729 (92.3%) in each group. The type of anesthetic did not affect the 5-year survival rate according to the log-rank test and as expressed by the Kaplan–Meier plot in Fig. 2 ($P = 0.21$). Type of anesthesia showed no correlation with survival even in univariate analysis (HR = 1.26, CI = 0.88 to 1.79, $P = 0.21$).

# Sensitivity analysis: multivariable Cox regression analysis

The hazard ratios of the groups in the univariate model for the propensity matched groups are shown in Table 2. Male sex, high BMI, long anesthesia time, and metastasis affected risk of death in the univariate model. The hazard ratios of the groups in the multivariable model for the propensity matched groups are shown in Table 3. Variables associated with significant increases in the risk of death after multivariable analysis were male sex and the presence of metastasis at surgery. Only five variables were subject to multivariable analysis because the meaningful variables (P <0.2) from univariate analysis were included in multivariable model.

# Survival rate of each cancer

Survival was the highest in breast cancer, followed by colon and stomach cancer, and similar mortality in lung and liver cancer (Fig. 3). We divided the types of cancer and analyzed whether the factors influenced differently. The results of the analysis by type were similar to those of all cancers except for one. Statistical analysis performed for each type of cancer showed that stomach cancer patients without hypertension had a low survival rate according to the log-rank test and as expressed by the Kaplan–Meier plot in Fig. 4 ($P = 0.01$).

## Discussion

In this study, there was no effect of TIVA or VIA on the survival rate of the whole population of patients undergoing surgery for five major types of cancer. There was no significant association between the type of anesthetic used and prognosis following cancer surgery.

Each anesthetic has a different effect on immune regulation and cancer growth factor production[10–13]. There have been reports that propofol has better immunomodulatory properties than inhaled anesthetics[14–16]. Some studies have shown that survival rates after cancer surgery are better for patients receiving TIVA than in those receiving VIA[7, 17–19]. In a meta-analysis involving 21,000 patients, both recurrence-free survival and overall survival rates were higher in the TIVA group than in the volatile anesthesia group[20]. In one survey, most anesthesiologists preferred inhalation anesthesia[21]. However, as many as 43% of respondents feel that TIVA can reduce cancer recurrence, only 29% of anesthesiologists actually use TIVA for cancer surgery. Confusingly, there have been reports that neither TIVA nor volatile anesthesia affected the prognosis of cancer patients[22, 23], and the present study was consistent with these results.

In this study, hypertension was shown to be associated with 5-year survival only in gastric cancer patients on univariate analysis. As the effect of medication taken daily by hypertensive patients has not been investigated, it will be difficult to estimate accurately the mechanism underlying this observation. Hypertension may come with an advantage, at least for a subset of women with ovarian cancer[24]. New research from epidemiologists at Roswell Park Cancer Institute provided evidence that hypertension and diabetes as well as the use of medications to treat these common conditions may influence the survival of ovarian cancer patients. Hypertension was reported to be associated with lower risk of disease progression among patients with endometrioid tumors ($n$ = 339, HR = 0.54; 95% CI = 0.35 to 0.84). In Korea, hypertension is treated indiscriminately by combination therapy with aspirin or statins, which may be another explanation for these observations. Aspirin use may have only a small effect on gastric carcinoma[25]. One meta-analysis[26] showed that statins were inversely related to the risk of gastric cancer (RR = 0.56; 95% CI = 0.35 to 0.90). There is no way to know why patients who take medications for hypertension control, especially in stomach cancer, have a good prognosis in this study. To explain this observation, further studies are required to determine which medications were taken daily by patients with hypertension who underwent surgery for stomach cancer.

This study had some limitations, including its retrospective nature. Second, the size of the study population was small. This seems to have been solved to some extent by propensity matching. The third limitation is the use of overall survival as the primary outcome. There was no discrimination between deaths from cancer recurrences, deaths from other diseases, or sudden accidents. However, considering the very long average life span of Koreans[27], this is unlikely to be a problem. This may be why multivariable Cox regression analysis showed that age was not significant covariate.

# Conclusion

In conclusion, there were no differences in 5-year overall survival between the TIVA and VIA groups in the five major types of cancer surgery. Based on this result, it may not be concluded that propofol based TIVA is more suitable for cancer surgery than VIA. Unexpectedly, patients with hypertension showed better survival than patients without hypertension in the stomach cancer group. In order to increase the objectivity of these results, further studies with a larger number of patients are needed.

# List Of Abbreviations

ASA: American Society of Anesthesiologists

ASD: Absolute standardized difference

BMI: body mass index

CRIS: clinical research information service

DM: diabetes mellitus

HIF: hypoxia-inducible factors

PSM: propensity score matching

TIVA: total intravenous anesthesia

VIA: volatile inhaled anesthesia

# Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Chungnam National University Hospital (approval number CNUH 2017–08–018) and consent was waived.

Availability of data and materials

The raw data of the current study are available from the corresponding author on request.

Competing interests

The authors declare no conflict of interest.

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Authors’ contributions

Conceptualization, S. L., C. L., Y. K.; methodology, B. H. and S.-H. Y.; software, B. H.; validation, A.M. Y.,H. R.; formal analysis, B. H.; investigation, Y.-H. K.; resources, M. L.; data curation, H. R., Y. K.; writing-original draft preparation, B. H.; writing-review and editing, C. L., S. L., S.-H. H.; visualization, B. H.; supervision, C. L.; project administration, S.-H. H.; funding acquisition, C. L.

All authors have read and approved the manuscript.

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# Tables

Table 1. Data for Patients Overall and Matched Patients after Propensity Scoring

| | Overall Patients | | | | Matched Patients | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | TIVA (n=903) | VIA (n=1304) | ASD | *P* | TIVA (n=729) | VIA (n=729) | ASD | *P* |
| Age, yr | 58.0 [49.0;67.0] | 57.0 [48.0;67.0] | 0.098 | 0.018 | 58.0 [49.0;67.0] | 57.0 [48.0;67.0] | 0.003 | 0.861 |
| Sex | | | 0.233 | < 0.001 | | | 0.019 | 0.753 |
| Female | 404 (44.7%) | 734 (56.3%) | | | 337 (46.2%) | 344 (47.2%) | | |
| Male | 499 (55.3%) | 570 (43.7%) | | | 392 (53.8%) | 385 (52.8%) | | |
| Height, cm | 161.0 [154.0;166.0] | 159.0 [154.0;165.0] | 0.118 | 0.007 | 161.0 [154.0;166.0] | 161.0 [155.0;166.0] | 0.015 | 0.610 |
| Weight, kg | 60.0 [54.0;67.0] | 60.0 [54.0;67.0] | 0.002 | 0.368 | 60.0 [54.0;67.0] | 60.0 [53.0;67.0] | 0.023 | 0.527 |
| BMI, kg $m^{-2}$ | 23.6 [21.8;25.8] | 23.8 [21.8;26.1] | 0.062 | 0.210 | 23.6 [21.7;25.8] | 23.5 [21.5;25.8] | 0.039 | 0.577 |
| ASA class | | | 0.098 | 0.067 | | | 0.053 | 0.605 |
| I | 399 (44.2%) | 633 (48.5%) | | | 311 (42.7%) | 310 (42.5%) | | |
| II | 503 (55.7%) | 671 (51.5%) | | | 417 (57.2%) | 419 (57.5%) | | |
| III | 1 (0.1%) | 0 (0.0%) | | | 1 (0.1%) | 0 (0.0%) | | |
| Hypertension | | | 0.008 | 0.894 | | | < 0.001 | 1.000 |
| Yes | 233 (25.8%) | 341 (26.2%) | | | 188 (25.8%) | 188 (25.8%) | | |
| No | 670 (74.2%) | 963 (73.8%) | | | 541 (74.2%) | 541 (74.2%) | | |
| DM | | | 0.057 | 0.204 | | | 0.032 | 0.593 |
| Yes | 121 (13.4%) | 150 (11.5%) | | | 95 (13.0%) | 103 (14.1%) | | |
| No | 782 (86.6%) | 1154 (88.5%) | | | 634 (87.0%) | 626 (85.9%) | | |
| Anesthesia time, min | 230.0 [185.0;285.0] | 210.0 [170.0;260.0] | 0.166 | < 0.001 | 215.0 [180.0;260.0] | 220.0 [180.0;265.0] | 0.017 | 0.696 |
| Operation time, min | 190.0 [150.0;240.0] | 175.0 [135.0;220.0] | 0.146 | < 0.001 | 180.0 [149.0;220.0] | 180.0 [149.0;225.0] | 0.012 | 0.787 |
| Remifentanil infusion | | | | < 0.001 | | | | < 0.001 |
| Yes | 902 (99.9%) | 701 (53.8%) | | | 728 (99.9%) | 395 (54.2%) | | |
| No | 1 (0.1%) | 603 (46.2%) | | | 1 (0.1%) | 334 (45.8%) | | |
| Gas type | | | | < 0.001 | | | | < 0.001 |
| Des | 0 (0.0%) | 345 (26.5%) | | | 0 (0.0%) | 193 (26.5%) | | |
| Iso | 0 (0.0%) | 31 (2.4%) | | | 0 (0.0%) | 25 (3.5%) | | |
| Sevo | 0 (0.0%) | 927 (71.1%) | | | 0 (0.0%) | 511 (70%) | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Nitrous oxide | | | | < | | | | < |
| | | | | 0.001 | | | | 0.001 |
| Yes | 1 (0.1%) | 550 (42.2%) | | | 1 (0.1%) | 302 (41.4%) | | |
| No | 902 (99.9%) | 754 (57.8%) | | | 728 (99.9%) | 427 (58.6%) | | |
| Metastasis at surgery | | | 0.006 | 0.947 | | | 0.014 | 0.855 |
| Yes | 68 (7.5%) | 96 (7.4%) | | | 64 (8.8%) | 67 (9.2%) | | |
| No | 835 (92.5%) | 1208 (92.6%) | | | 665 (91.2%) | 662 (90.8%) | | |
| Transfusion | | | 0.056 | 0.252 | | | 0.038 | 0.626 |
| Yes | 19 (2.1%) | 39 (3.0%) | | | 10 (1.4%) | 7 (1.0%) | | |
| No | 884 (97.9%) | 1265 (97.0%) | | | 719 (98.6%) | 722 (99.0%) | | |
| Hospital stay, day | 13.0 [11.0;18.0] | 13.0 [10.0;18.0] | 0.014 | 0.238 | 13.0 [11.0;18.0] | 13.0 [10.0;18.0] | 0.023 | 0.355 |
| Survival, month | 60.0 [44.0;60.0] | 60.0 [45.0;60.0] | | 0.945 | 60.0 [40.0;60.0] | 60.0 [47.0;60.0] | | 0.523 |
| 5 years survival | | | | 0.291 | | | | 0.262 |
| Yes | 829 (91.8%) | 1214 (93.1%) | | | 660 (90.5%) | 673 (92.3%) | | |
| No | 74 (8.2%) | 90 (6.9%) | | | 69 (9.5%) | 56 (7.7%) | | |
| Cancer type | | | | < | | | | 1.000 |
| | | | | 0.001 | | | | |
| Breast | 154 (17.1%) | 475 (36.4%) | | | 154 (21.1%) | 154 (21.1%) | | |
| Colon | 362 (40.1%) | 188 (14.4%) | | | 188 (25.8%) | 188 (25.8%) | | |
| Liver | 37 (4.1%) | 90 (6.9%) | | | 37 (5.1%) | 37 (5.1%) | | |
| Lung | 44 (4.9%) | 103 (7.9%) | | | 44 (6.0%) | 44 (6.0%) | | |
| Stomach | 306 (33.9%) | 448 (34.4%) | | | 306 (42.0%) | 306 (42.0%) | | |

Number (%): chi-square test, median [interquartile range]: Mann–Whitney U test.

ASD = absolute standardized mean difference; BMI = body mass index; ASA = American Society of Anesthesiologists; TIVA = total intravenous anesthesia; VIA = volatile inhaled anesthesia; DM = diabetes mellitus; Des = desflurane; Iso = isoflurane; Sevo = sevoflurane.

Table 2. Hazard Ratios by Univariate Model

| | HR | 95% CI | *P*-value |
|---|---|---|---|
| Anesthesia type: TIVA vs VIA | 1.255 | 0.882 to 1.785 | 0.206 |
| Age, yr: > 65 vs ≤ 65 | 1.000 | 0.988 to 1.019 | 0.616 |
| Sex: male vs female | 1.602 | 0.990 to 1.034 | 0.011* |
| Height, cm: > 166 vs ≤ 166 | 1.012 | 0.990 to 1.004 | 0.283 |
| Weight, kg: > 57 vs ≤ 57 | 0.932 | 0.883 to 0.983 | 0.117 |
| BMI, kg $m^{-2}$: > 19.7 vs ≤ 19.7 | 0.932 | 0.883 to 0.983 | 0.010* |
| ASA class: II vs I | 1.248 | 0.870 to 1.790 | 0.228 |
| Hypertension: no vs yes | 1.200 | 0.788 to 1.828 | 0.394 |
| DM: no vs yes | 0.903 | 0.548 to 1.489 | 0.690 |
| Anesthesia time, min: > 210 vs ≤ 210 | 1.003 | 1.001 to 1.005 | 0.002** |
| Metastasis: no vs yes | 0.123 | 0.085 to 0.179 | < 0.001** |
| Transfusion: no vs yes | 0.684 | 0.169 to 2.769 | 0.595 |

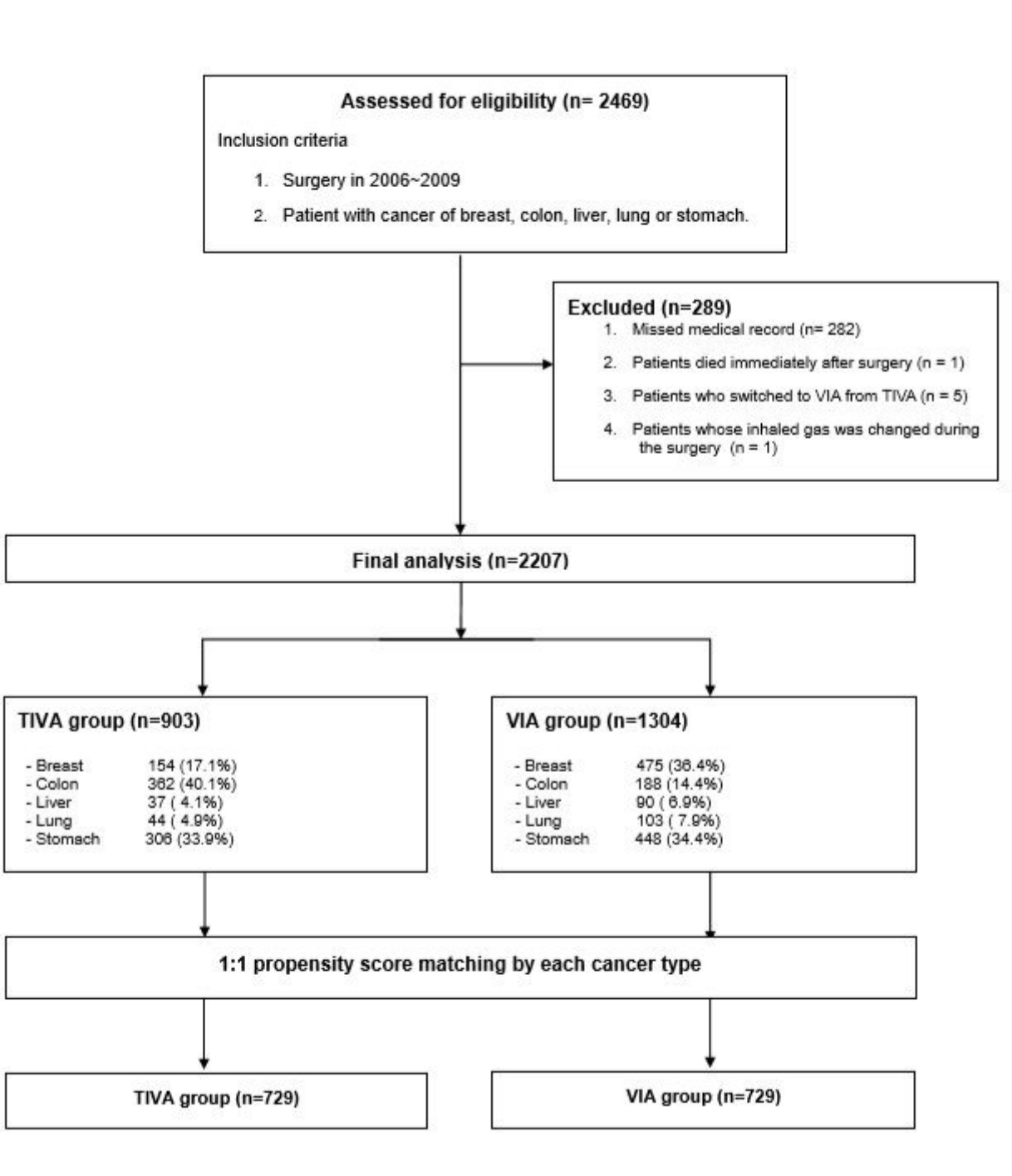
BMI = body mass index; ASA = American Society of Anesthesiologists; HR = hazard ratio; TIVA = total intr avenous anesthesia; VIA = volatile inhaled anesthesia; DM = diabetes mellitus; *$P$ < 0.05; **$P$ < 0.01.

Table 3. Hazard Ratios by Multivariable Analysis

| | Cancer type included | | | Cancer type excluded | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Sex: male vs female | 1.031 | 0.625 to 1.700 | 0.905 | 1.731 | 1.078 to 2.781 | 0.023* |
| Weight, kg: > 57 vs ≤ 57 | 0.990 | 0.956 to 1.026 | 0.591 | 0.980 | 0.946 to 1.016 | 0.275 |
| BMI, kg $m^{-2}$: > 19.7 vs ≤ 19.7 | 0.983 | 0.889 to 1.087 | 0.743 | 1.015 | 0.917 to 1.122 | 0.777 |
| Anesthesia time, min: > 210 vs ≤ 210 | 1.001 | 0.998 to 1.003 | 0.573 | 1.000 | 0.998 to 1.002 | 0.911 |
| Metastasis: no vs yes | 0.119 | 0.078 to 0.180 | < 0.001** | 0.132 | 0.088 to 0.199 | < 0.001** |
| Cancer type | | | | | | |
| Breast (reference) | | | | | | |
| Colon | 2.594 | 0.917 to 7.341 | 0.072 | | | |
| Liver | 8.168 | 2.556 to 26.104 | < 0.001** | - | - | - |
| Lung | 7.235 | 2.295 to 22.810 | < 0.001** | - | - | - |
| Stomach | 6.576 | 2.533 to 17.069 | < 0.001** | - | - | - |

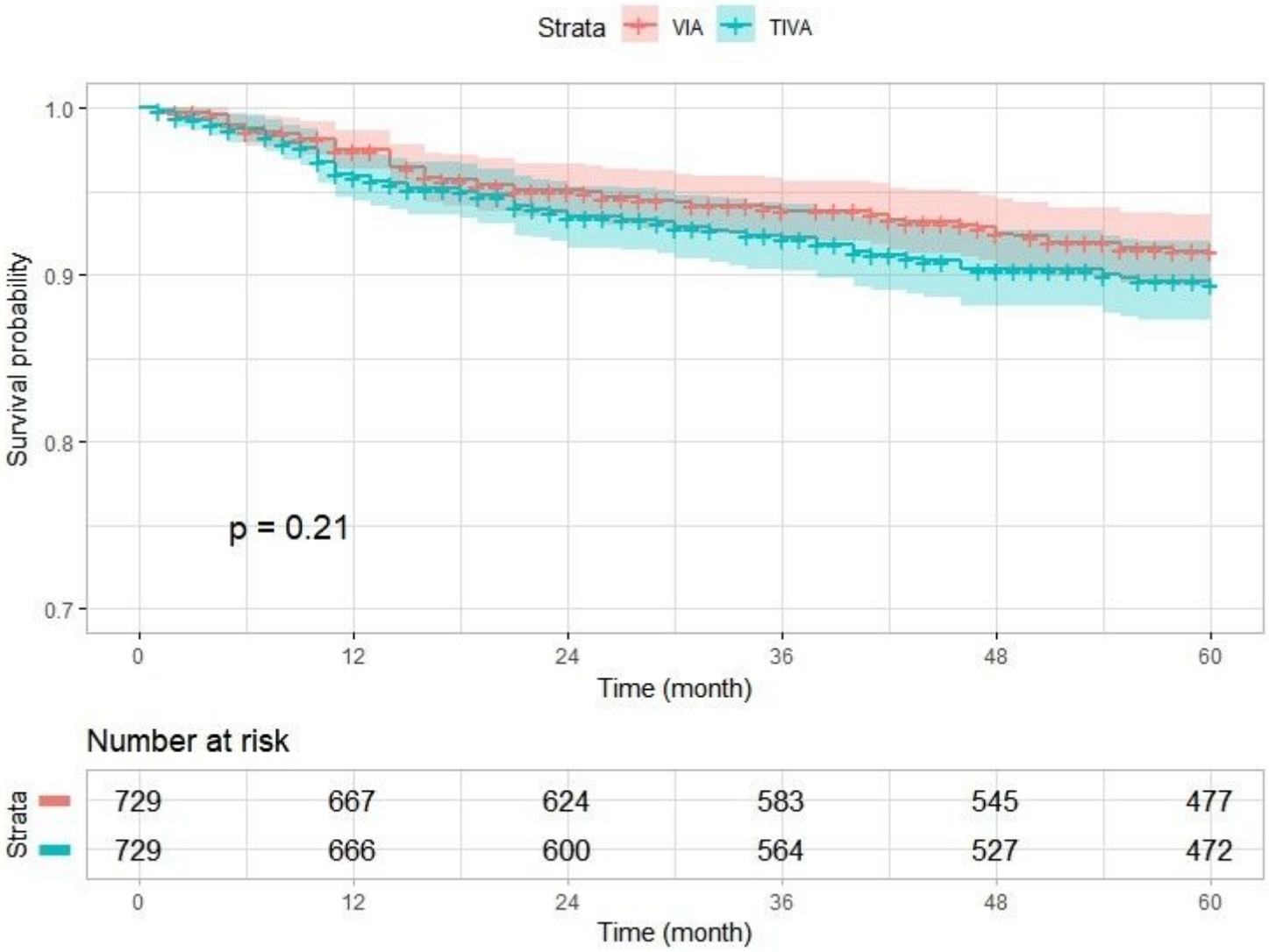
Only variables with a significance level of $P$ < 0.2 in univariable analysis were included in the multivariable model. BMI = body mass index; ASA = American Society of Anesthesiologists; HR = hazard ratio; TIVA = total intravenous anesthesia; DM = diabetes mellitus; *$P$ < 0.05; **$P$ < 0.01.

# Figures



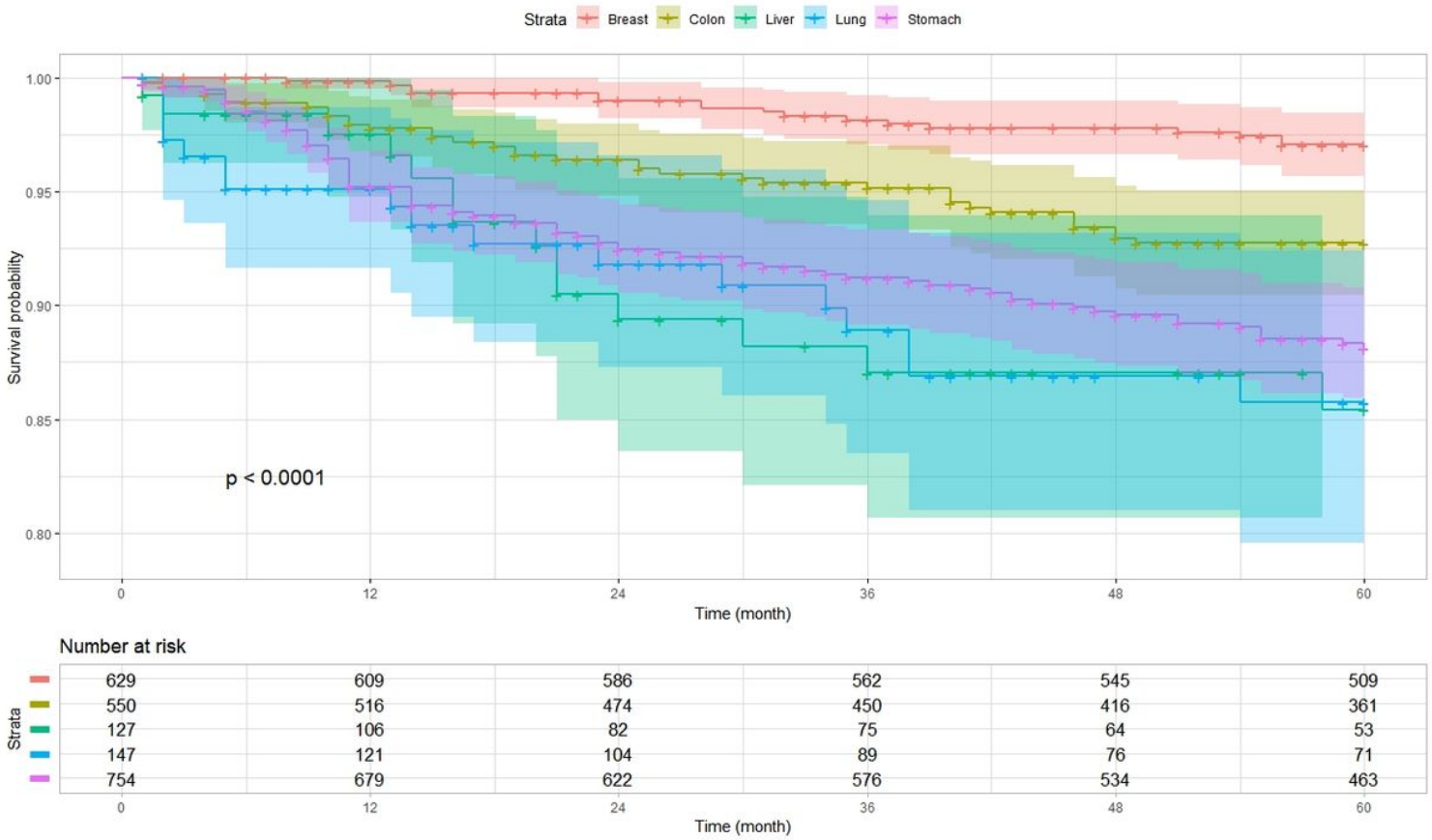

## Figure 1

Flow diagram. TIVA = total intravenous anesthesia; VIA = volatile inhaled anesthesia.




## Figure 2

Comparison of survival rate by Kaplan–Meier survival curves after propensity matching. VIA = volatile inhaled anesthesia group; TIVA = total intravenous anesthesia group.




## Figure 3

Kaplan–Meier survival curves grouped by cancer type.

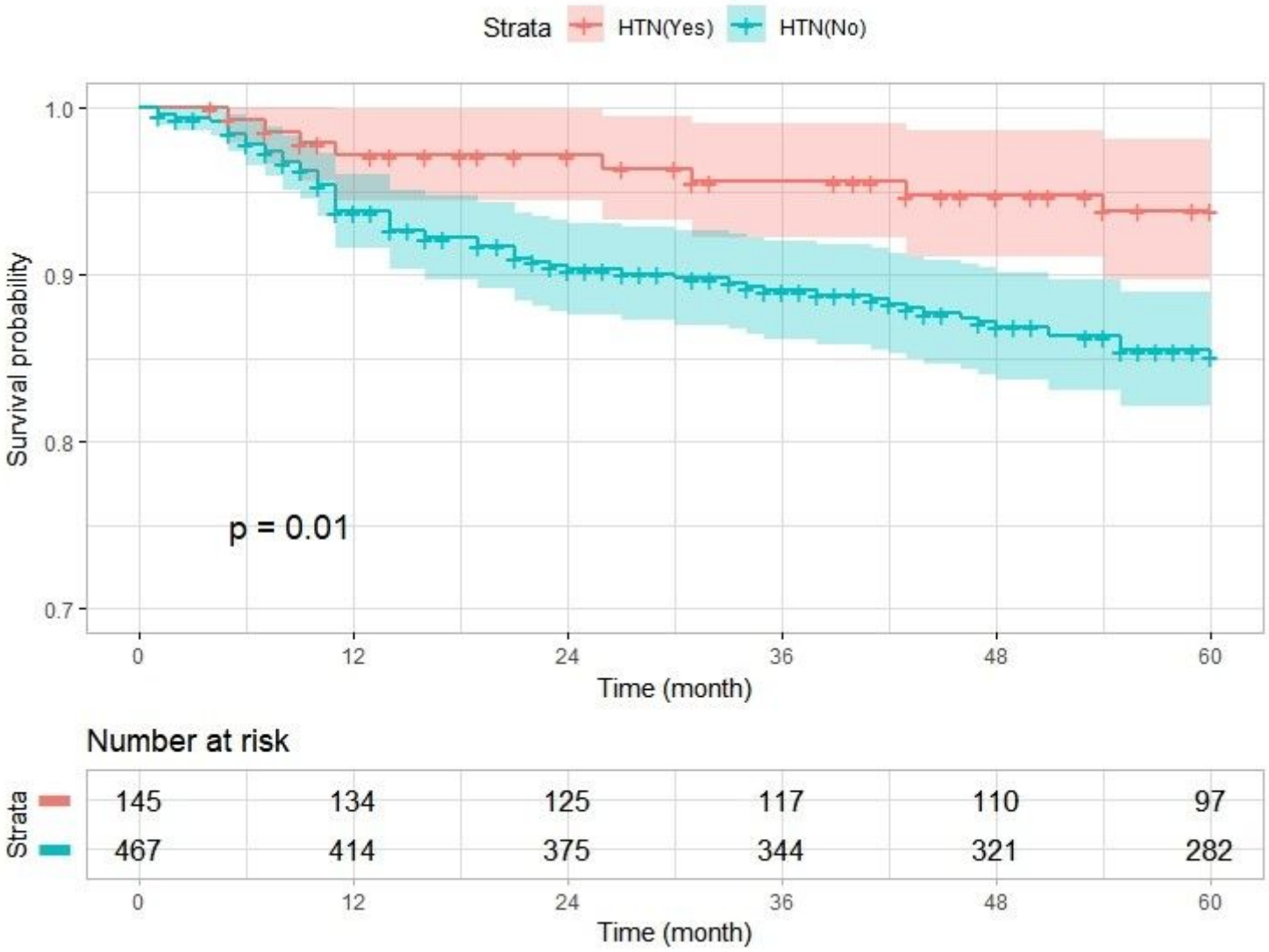



**Figure 4**

Kaplan–Meier survival curves according to hypertension after propensity matching in stomach cancer patients. HTN = hypertension history.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklist.doc