# Distant Survival for Patients Undergoing Surgery Using Volatile versus IV Anesthesia for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: A Retrospective study

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# Abstract

Background Hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT) have lower postoperative survival rate, and anesthesia type may have an effect on tumor recurrence and metastasis.Methods A retrospective study was conducted in Eastern Hepatobiliary Surgery Hospital, Shanghai, China, from January 1, 2008 to December 24, 2012. A total of 1513 HCC patients with PVTT were delivered in the study period. Patients receiving the volatile inhalational anesthesia (INHA) and total IV (TIVA) anesthesia were screen out for comparison. The primary outcome was 5-year overall survival (OS), and secondary outcomes included recurrence-free survival (RFS), postoperative adverse events and liver function. Cox regression analysis was applied to balance confounding variables and estimate risk factors for mortality. Then subgroup analysis of anesthesia type on potential risk factors which were acquired in the final multivariable model were performed.Results After exclusions are applied, 263 patients remain in the INHA group and 208 in the TIVA group. Patients receiving INHA anesthesia have a lower 5-year survival rate than that of patients receiving TIVA anesthesia [12.6% (95% CI, 9.0 to 17.3) vs. 17.7% (95% CI, 11.3 to 20.8), P=0.024]. Results from multivariable regression analysis also identify that INHA anesthesia is significantly associated with the OS ang RFS compared with TIVA anesthesia, with HR (95%CI) of 1.303 (1.065, 1.595) and 1.265 (1.040, 1.539), respectively. Subgroup analysis suggested that in more severe cancer patients, the worse outcome related to INHA might be more significant.Conclusion This retrospective analysis identifies that patients receiving TIVA have better survival rate compare to receiving INHA in HCC patients with PVTT. Future prospective researches are urgent to verify this difference and figure out underlying causes of it.


# Background

Volatile inhalational (INHA) and IV anesthesia (TIVA) are two methods commonly used to maintain general anesthesia, as both of them are safe and easy to control. However, some recent researches reported that INHA could cause worse postoperative outcomes compared to INHA in certain types of cancer patients. Dr. Wigmore et al.[1] did a retrospective analysis which firstly compared long-term survival in more than 7,000 patients undergoing cancer surgery, and reported that mortality of patients accepted INHA is approximately 50% greater than those accepted TIVA. Then several more studies and a meta-analysis reported similar results in different kinds of cancers[2]. Besides from these clinical evidences, animal researches also reported that administration of volatile inhalational agents is associated with up-regulation of tumorigenic growth factors including hypoxia-inducible factors (HIFs) and insulin-like growth factor (IGF)[3, 4], which are both reported to be associated with progression angiogenesis and cell proliferation in tumor.

Although the underlying mechanism remains undiscovered, these results have drawn due attention that anesthesia technique might be an independent risk factor for postoperative outcomes of cancer patients, including liver cancer. In fact, previous studies already reported that the MAC of sevoflurane is lower in patients with end-stage liver disease[5].

Thus, we hypothesize that administration of INHA might be associated with lower 5-year overall survival (OS) compared with TIVA in Hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT), an end-stage liver cancer with a high recurrence rate and reduced median survival time (MST) [7-10], as its generally accepted that in this kind of end stage cancer patients, even subtle differences in medication might lead to more significant effects on long-term outcome.

# Methods

### Study design

We retrospectively identified all patients who underwent aggressive surgical liver resection for selected HCC patients with PVTT at Eastern Hepatobiliary Surgery Hospital from January 1, 2008 to December 24, 2012. Exclusion criteria including: (1) no surgical treatment performed; (2) received mixed inhalational and intravenous anesthesia; (3) received additional procedures with different anesthesia or for other diseases afterwards; (4) less than 18 years old; (5) had an urgent or emergence surgery and (6) incomplete follow-up data. The research was approved by the Ethics Committee of the Eastern Hepatobiliary Surgical Hospital of China. Written informed consent was obtained from participants or their surrogates during hospitalization.

Baseline data retrospectively extracted including anesthetic technique, age at the time of surgery, sex, American Society of anesthesiologists' (ASA) physical status classification, preexisting diagnosis of diabetes or hypertension. Data related to patients' preoperative liver function and cancer statue are also documented including Child-Pugh score, alpha-fetoprotein (AFP), type of PVTT, tumor diameter as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

### Outcomes

The primary outcome was 5-year OS. Secondary outcomes were (1) recurrence-free survival; (2) 30-day mortality; (3) a set of major adverse cardiac events (MACE) that included myocardial infarction (MI), cardiac arrest, or newly diagnosed malignant arrhythmia; (4) multiple organ dysfunction (MOD) primarily induced of acute hepatic failure postoperatively; (5) blood loss and blood transfusion; (6) hospital length of stay.

### Anesthesia techniques

Patients were divided into two groups, based on INHA or TIVA they received for maintenance of anesthesia. Patients in the TIVA group received continuous infusions of propofol, and those in the INHA group received sevoflurane. Supplementary opioid for maintaining were used at the discretion of the anesthetist in all patients, mainly sufentanil and remifentanil, with the highest dose no more than 50 mg and 2 mg. No other sedative-hypnotic drugs were used.

Type of anesthesia was according to the anesthetist decision, mainly depending on the preference and proficiency of the anesthesiologist. Details of the surgical process as previously described[6].

### Statistical Analyses

The Kaplan–Meier method is used to calculate the overall survival and recurrence-free survival of patients from the date of surgery to the date of events. A univariable Cox regression analysis was applied and for variables with P less than 0.1 were then included into the multivariable model to identify risk factors.

Secondary outcomes are compared using chi-square or Mann-Whitney-Wilcoxon tests as appropriate. Missing values (all less than 5%) are filled by the average value of the variable. Significant difference defined as $P<0.05$ in a two-sided 5% α level. (SPSS version 22.0; IBM Inc., USA).

# Results

### Baseline characters and survival for all patients

A total of 1523 patients diagnosed of HCC with PVTT are delivered in the study period. After exclusions applied, 263 patients remained in the INHA group and 208 in the TIVA group (**Figure 1**). The mean age is 48.0 and 49.0 years old in TIVA and INHA groups. Patients are more likely to be male, have an ASA score of II, have a Child-Pugh grade of A or B, and more likely to have large hepatocellular carcinoma (>10cm). Five-year survival for all patients is 14.8% (95% CI, 11.3 to 17.6), and median survival for all patients is 9.0 month (95% CI, 7.9 to 10.0; T**able 1**).

### Primary outcome

Results of Kaplan–Meier survival analysis suggest that the 5-year OS of TIVA is better than INHA [12.6% (95% CI, 9.0 to 17.3) VS. 17.7% (95% CI, 11.3 to 20.8); P=0.024, **Figure 2**]. In multivariable analysis, we identify that INHA has a HR (95%CI) of 1.303 (1.065, 1.595) compare with TIVA in 5-year OS (**Table 2**).

### Secondary outcomes

Kaplan–Meier survival curves for RFS are also displayed in **Figure 2**. TIVA seems to be better than INHA (P=0.032). In multivariable Cox regression model, a worse outcome of INHA compared with TIVA also existed [HR (95% CI) of 1.265 (1.040, 1.539); **Table** 2**]**.

Other outcomes including 30-day mortality rate I, postoperative MACE and MOF rate, as well as blood loss, blood transfusion and length of stay in hospital are similar in both groups (**Table 3**).

### Subgroup analysis

In multivariable model, four more variables are associated with significant increase in the hazard of 5-year OS and RFS after multivariable analysis, they are Child-Pugh, AFP, diameter of hepatocellular carcinoma and PVTT type. We then did a subgroup Kaplan–Meier survival analysis to estimate the association of anesthesia type on postoperative OS and RFS in different sub-variable groups, there were Child-Pugh A; Child-Pugh B&C; tumor diameter<10cm; tumor diameter≥10cm; AFP<400ug/L;

AFP≥400ug/L; PVTT type□; PVTT type□; PVTT type□. The results suggested that INHA was associated with significant lower OS and RFS rate compared with TIVA in several sub-variable groups indicating more severe liver cancer statues, including tumor diameter≥10cm (**Figure 4B, 4D**); AFP≥400ug/L (**Figure 5B, 5D**); PVTT type□and PVTT type□(**Figure 6C, 6E, 6F**).

# Discussion

This retrospective analysis of 1513 HCC patients with PVTT evaluates long-term OS, RFS and several short term postoperative adverse events in patients receiving INHA using sevoflurane and TIVA using propofol. We identify that patients receiving INHA anesthesia had a lower 5-year OS and shorter median survival time than that of patients receiving TIVA anesthesia. Results from multivariable Cox regression analysis also show that INHA is a risk factor for survival. In subgroup analysis, significant worse outcomes were found in INHA in patients with more severe cancer diseases. No significant difference in postoperative adverse events, 30-day mortality and liver function are discovered between the two groups in this study.

### Clinical Evidence of anesthesia type on surgical outcomes

In recent years, the study of anesthesia type for postoperative outcomes have attracted due attention. Several retrospective clinical studies with large sample sizes are published according to our search. Enlund et al.[7] firstly did a retrospective analysis of 2,838 patients with breast, rectal, and colon cancer from a Swedish database. According to their results, overall survival for patients receiving propofol anesthesia is 4.7% higher at 1-yr and 5.6% at 5-yr, but after balance for confounders, the differences are not significant. Wigmore et al.[1] analyzed 7,030 patients who had elective cancer surgery over a 3-yr period. They suggested that patients had a worse outcome if they received volatile anesthesia, with an HR of 1.46 (95% CI, 1.29 to 1.66) for death compared with TIVA. In addition, Yan et al[8]. did a randomized controlled trail in 80 breast cancer patients and reported that total intravenous anesthesia can inhibit the release of VEGF-C induced by breast surgery, but didn't seem to be beneficial in the short-term recurrence rate of breast cancer. Yap et al[2]. further performed a meta-analysis with 9 retrospective studies and 1 RCT, they concluded that the use of TIVA was associated with improved RFS in all cancer types and improved OS in several certain types of cancer. Although these studies have achieved consistent results that TIVA anesthesia has a better long-term prognosis for patients undergoing tumor resection compared with INHA, the population enrolled in these studies variates a lot, and it is not yet possible to conclude that whether TIVA anesthesia is more beneficial for all cancer patients or for certain types of cancer. Our study achieves a result consistent with the previous studies that TIVA is superior to INHA in the long-term survival of HCC patients with PVTT. Notably, the cause or the molecular mechanisms to the different outcomes of these two anesthetic methods remains unexplored now.

## Laboratory evidence of anesthetics on tumors metastasis and recurrence

There have been a number of animal and laboratory studies investigated the mechanism of anesthetic agents on primary tumors metastasis and recurrence. Several proliferation-associated factors and cellular immune response have been repeatedly mentioned, for instance, T lymphocytes and NK cells are two major cytotoxic effector cells that participate in cell-mediated immune responses. Propofol has been demonstrated to have preservation effective on T lymphocyte activity and Th1 cytokine secretion, or even inhibits tumor growth in animal model[9-11]. Researchers also prove that sevoflurane could inhibit primary leukocyte integrin lymphocyte function and induced lymphocyte apoptosis through downregulation of LFA-1, thus promoting tumor recurrence and metastasis[12]. Moreover, Studies both in vivo[13] and in patients undergoing breast cancer surgery[14] have reported an inhibitory effect of sevoflurane anesthesia and propofol on natural killer cell function. According to their description, this effect is probably related to the dysfunction in CD16 cell and CD107α NK receptor after exposure to sevoflurane[15]. More recently, Bellanti et al.[16] demonstrated that propofol, not sevoflurane, prevents mitochondrial dysfunction and oxidative stress by limiting hypoxia-inducible factor 1 alpha (HIF-1α) activation in hepatic ischemia/reperfusion injury, thus protects liver function. HIF-1 governs the transcription of genes controlling proliferation and metastasis of tumor cells[17, 18], with previous researches already demonstrate that isoflurane administration could result in an up-regulation of HIF-1α in tumor[19]. However, currently there have no solid evidence to prove those theory in human body.

## HCC with PVTT

Hepatocellular carcinoma (HCC) ranges as the fifth most common malignancy tumor [20]. Indeed, even worse prognosis is reported in HCC patients with portal vein tumor thrombus (PVTT), with a reported rate of 20% and a reduced median survival time (MST) of around 2-4 months compared to patients without PVTT[21-24]. According to the Asia-Pacific guideline and some more recent researches, surgery is recommended as one of the beneficial multidisciplinary treatments for PVTT, as aggressive surgical resection is associated with a longer survival outcome, and even provide chances for complete cure with type I and II PVTT[25, 26]. Recent studies reported that under advanced perioperative management and skilled surgical operation, the in-hospital mortality of HCC patients with PVTT arrives an acceptable rate ranging from 3.7% to 10%[27, 28]. However, the knowledge about risk factors of postoperative mortality, cancer recurrence and other side events for HCC patients with PVTT still remains insufficient. Our result provides with extra evidence that for these patients, the application of TIVA, rather than INHA for anesthesia maintenance, might be a better choice, especially in patients with severe cancer statues.

## Limitations

Several methodological discrepancies and limitations of this study should be discussed. First, in our study cohort, there have more patients who are male, with an AS score of II, Child-Pugh score of A, and a large tumor size over 10cm. what's more, certain clinical data of treatment are not collected, including perioperative chemoradiotherapy, detailed surgical techniques, and usage of opioids during surgery. Opioids have been reported to have an effect on tumor cell proliferation and angiogenesis, as well as on tumor recurrence and metastasis. However, it's hard to accurately record and compare total amounts of opioid used in both groups during surgery as they are administered both continuously or in intermittent. In this study all patients accepted at least one of remifentanil or sufentanil treatment in standard dose.

In conclusion, this retrospective analysis of long-term overall survival demonstrates an HR (95%CI) of 1.303 (1.065, 1.595) in HCC patients with PVTT receiving INHA compared with TIVA in multivariable analysis. Future prospective researches are urgent to verify this difference and figure out underlying causes of it.

# List Of Abbreviations

HCC: Hepatocellular carcinoma; PVTT: portal vein tumor thrombus; INHA: volatile inhalational anesthesia; TIVA: total IV anesthesia; OS: overall survival; MST: median survival time; HIFs: hypoxia-inducible factors; IGF: and insulin-like growth factor; MACE: major adverse cardiac events; MOD: multiple organ dysfunction; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NLR: neutrophil-lymphocyte ratio; ASA: American Society of anesthesiologists' Assessment; AFP: alpha-fetoprotein.

# Declarations

### Ethics approval and consent to participate.

This trial had approval from the ethics committee of Eastern Hepatobiliary Surgical Hospital (EHBHHKY2012-02-028). All subjects participating in the current trial provided signed informed consent.

### Consent for publication.

Not applicable.

### Availability of data and materials.

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

### Competing interests.

The authors declare that they have no competing interests.

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**Authors' contributions**

XY Meng helped conduct the study, analyze the data, and write the manuscript; XP Zhang and HQ Wang conducted the study and analyze the data; conducted the study and analyzed the data; WF Yu helped design the study and revise the manuscript.

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# Tables

Table 1. Patient Baseline Characters.

| Variables | TIVA (N=208) | INHA (N=263) | P value |
|---|---|---|---|
| | N (%) | N (%) | |
| Sex (male) | 188 (90.4) | 239 (90.9) | 0.856 |
| ASA | | | |
| II | 186 (89.4) | 229 (87.1) | 0.191 |
| III | 22 (10.6) | 30 (11.4) | |
| IV | 0 (0) | 4 (1.5) | |
| Child-Pugh | | | |
| A | 184 (88.5) | 233 (88.6) | 0.662 |
| B | 22 (10.6) | 25 (9.5) | |
| C | 2 (0.4) | 5 (1.1) | |
| AFP (ug/L) | | | |
| <25 | 30 (14.4) | 54 (20.5) | 0.109 |
| 25-399 | 39 (18.8) | 45 (17.1) | |
| 400-999 | 12 (5.8) | 25 (9.5) | |
| ≥ 1000 | 127 (61.1) | 139 (52.9) | |
| Tumor Diameter (cm) | | | |
| <5 | 1 (0.4) | 2 (0.8) | 0.546 |
| 5-9.9 | 22 (10.6) | 36 (13.7) | |
| ≥10 | 185 (88.9) | 225 (85.6) | |
| PVTT | | | |
| 1 | 30 (14.4) | 40 (15.3) | 0.716 |
| 2 | 131 (63.0) | 163 (62.0) | |
| 3 | 47 (22.1) | 60 (22.8) | |
| | Mean (SD) | Mean (SD) | |
| Age (yr) | 48.0 (10.94) | 49.0 (9.73) | 0.078 |
| | Median (IQR) | Median (IQR) | |
| WBC ($10^9$/L) | 5.5 (4.2, 7.3) | 5.4 (4.3, 7.1) | 0.06 |
| ALT (U/L) | 47.8 (31.0, 66.0) | 45.0 (29.1, 67.3) | 0.903 |
| AST (U/L) | 49.0 (37.0, 69.0) | 52.0 (35.0, 71.0) | 0.820 |

ASA = American Society of Anesthesiologists; PVTT=Portal vein tumor thrombus; INHA=Volatile inhalational anesthesia; TIVA=Total IV anesthesia; WBC=White blood cells; NLR=Neutrophil–lymphocytes ratio.

Table 2. Cox Proportional Hazard Regression Analyses: Multivariable Model for Overall Survival and Recurrence-Free Survival.

| | Overall Survival | | | Recurrence-Free Survival | | |
|---|---|---|---|---|---|---|
| Variables | HR (95% CI) | | *P* Value | HR (95% CI) | | *P* Value |
| Anesthesia type (INHA/TIVA) | 1.303 | (1.065, 1.595) | 0.010 | 1.265 | (1.040, 1.539) | 0.019 |
| Child-Pugh | 1.897 | (1.491, 2.414) | 0.000 | 1.653 | (1.297, 2.105) | 0.000 |
| AFP (ug/L) | 1.099 | (1.010, 1.194) | 0.027 | 1.071 | (0.989, 1.160) | 0.093 |
| Tumor Diameter (cm) | 1.606 | (1.183, 2.181) | 0.002 | 1.492 | (1.123, 1.983) | 0.006 |
| PVTT | 1.160 | (0.989, 1.360) | 0.068 | | - | - |

* Overall categories comparison.

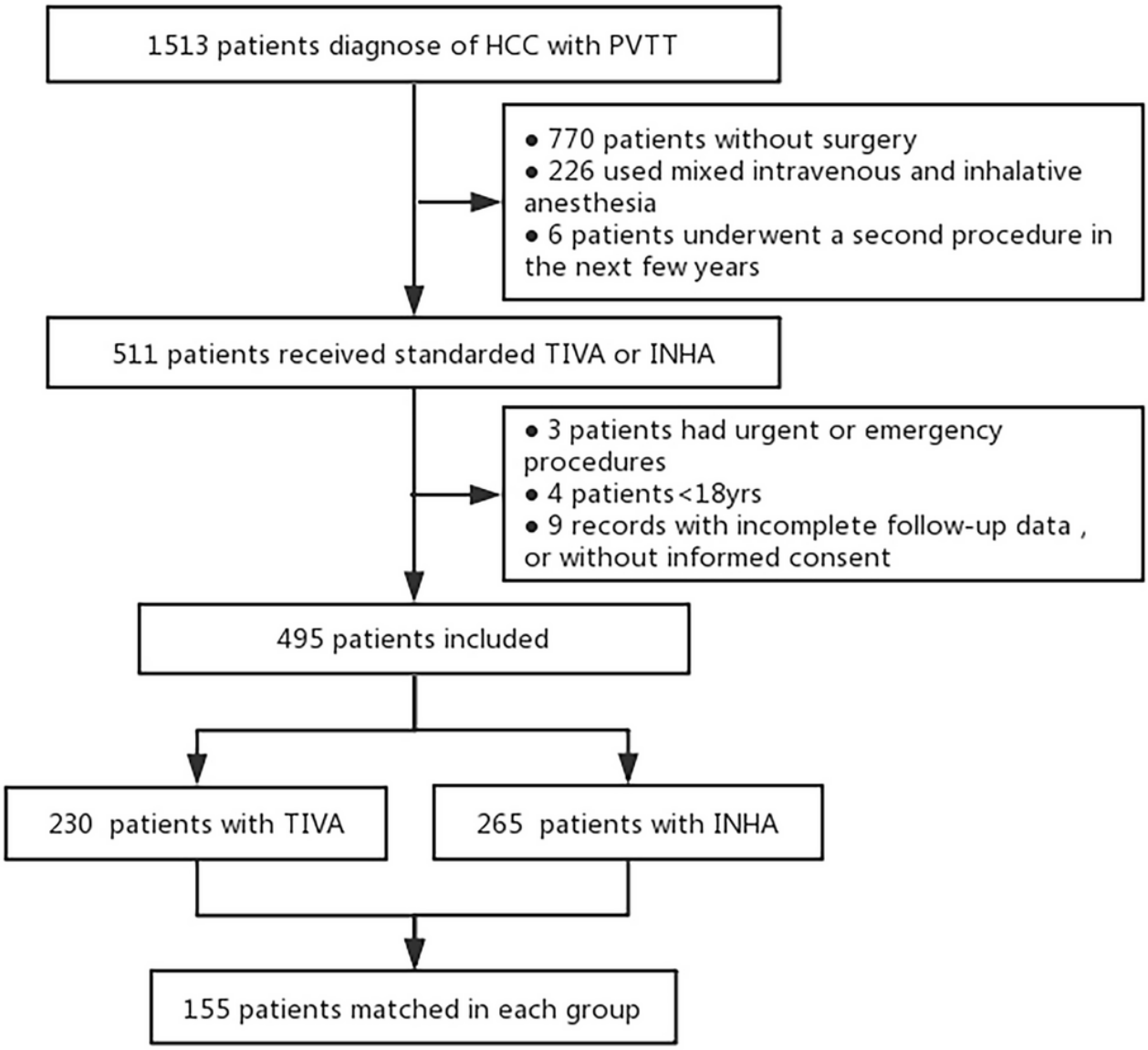
ASA = American Society of Anesthesiologists; PVTT=Portal vein tumor thrombus; INHA=Volatile inhalational; TIVA=Total IV anesthesia, NLR=Neutrophil–lymphocytes ratio.

Table 3. Adverse Outcomes

| | TIVA N (%) | INHA N (%) | *P* Value |
|---|---|---|---|
| Dichotomous Outcomes | | | |
| 30-day Mortality | 4 (2.1) | 11 (4.7) | 0.106 |
| MACE | 4 (2.1) | 11 (4.7) | 0.106 |
| MOD | 6 (3.3) | 9 (3.9) | 0.797 |
| Blood Transfusion | 80 (43.5) | 78 (33.5) | 0.189 |
| | Median (IQR) | Median (IQR) | |
| Continuous Outcomes | | | |
| Blood Loss | 400 (245,800) | 400 (300,800) | 0.301 |
| Length of Stay (days) | 15 (13,20) | 16 (13,20) | 0.920 |

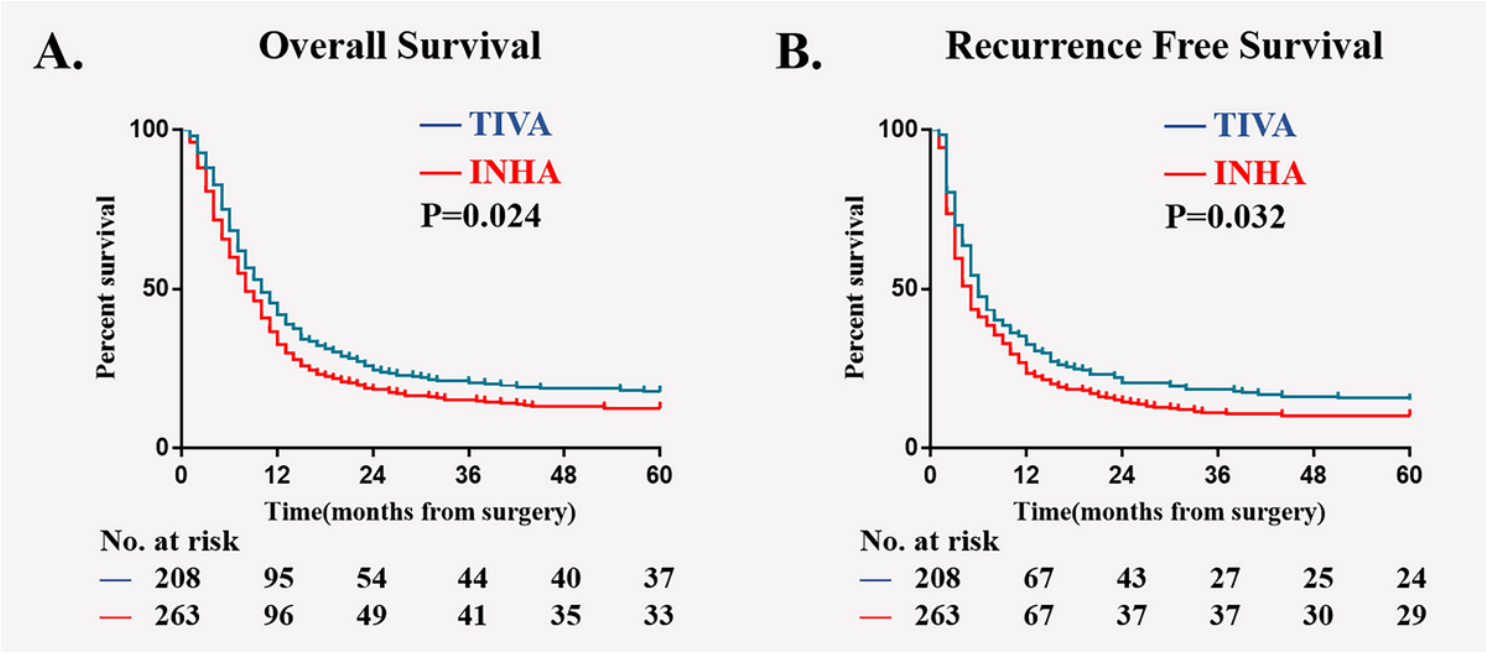
IQR = interquartile range; MACE = major adverse cardiac events; MOF = multiple organ failure; RR = risk ratio.

# Figures



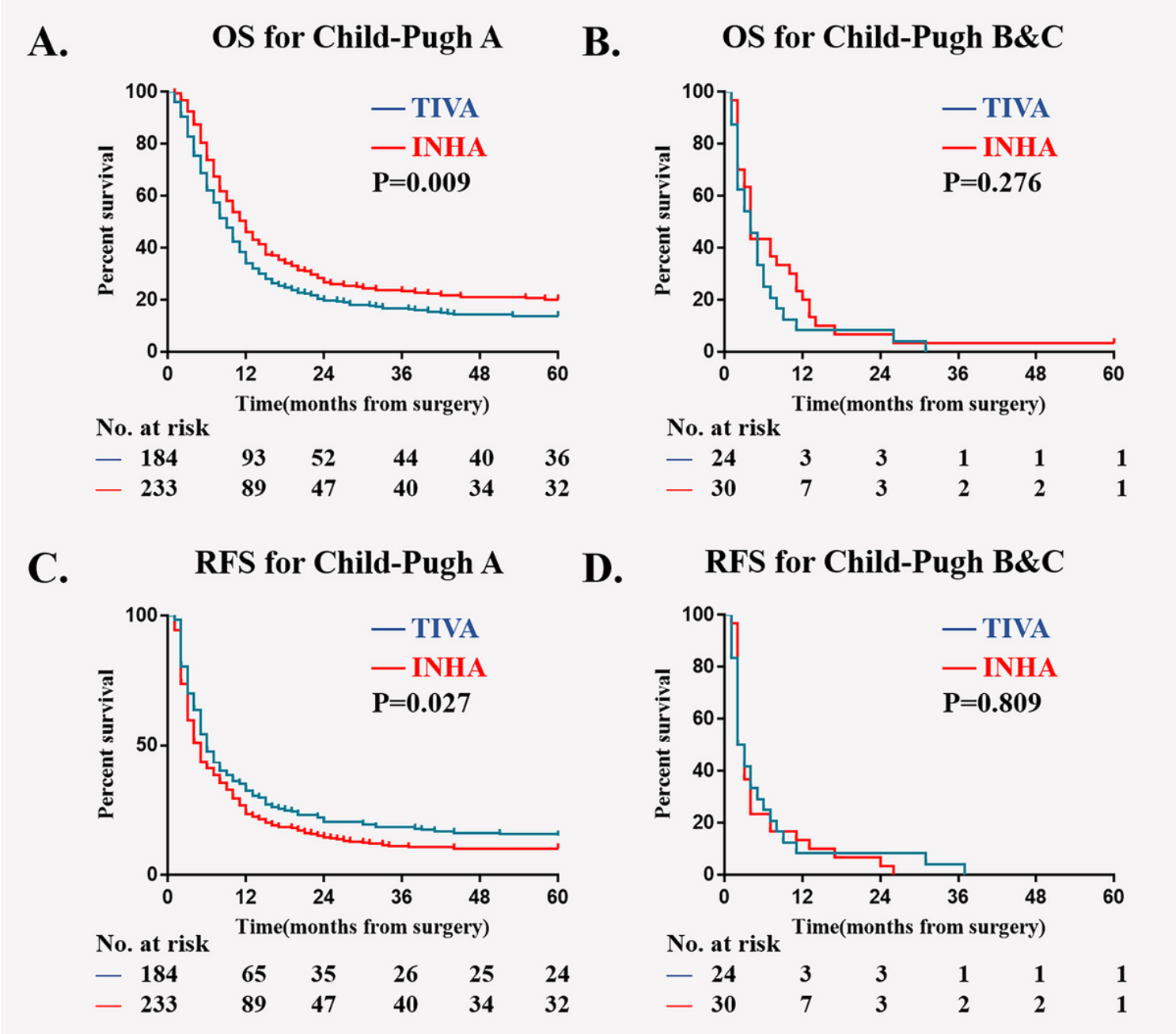

## Figure 1

Flow diagram detailing the selection of patients included in the retrospective analysis. INHA = volatile inhalational; TIVA = total IV anesthesia.



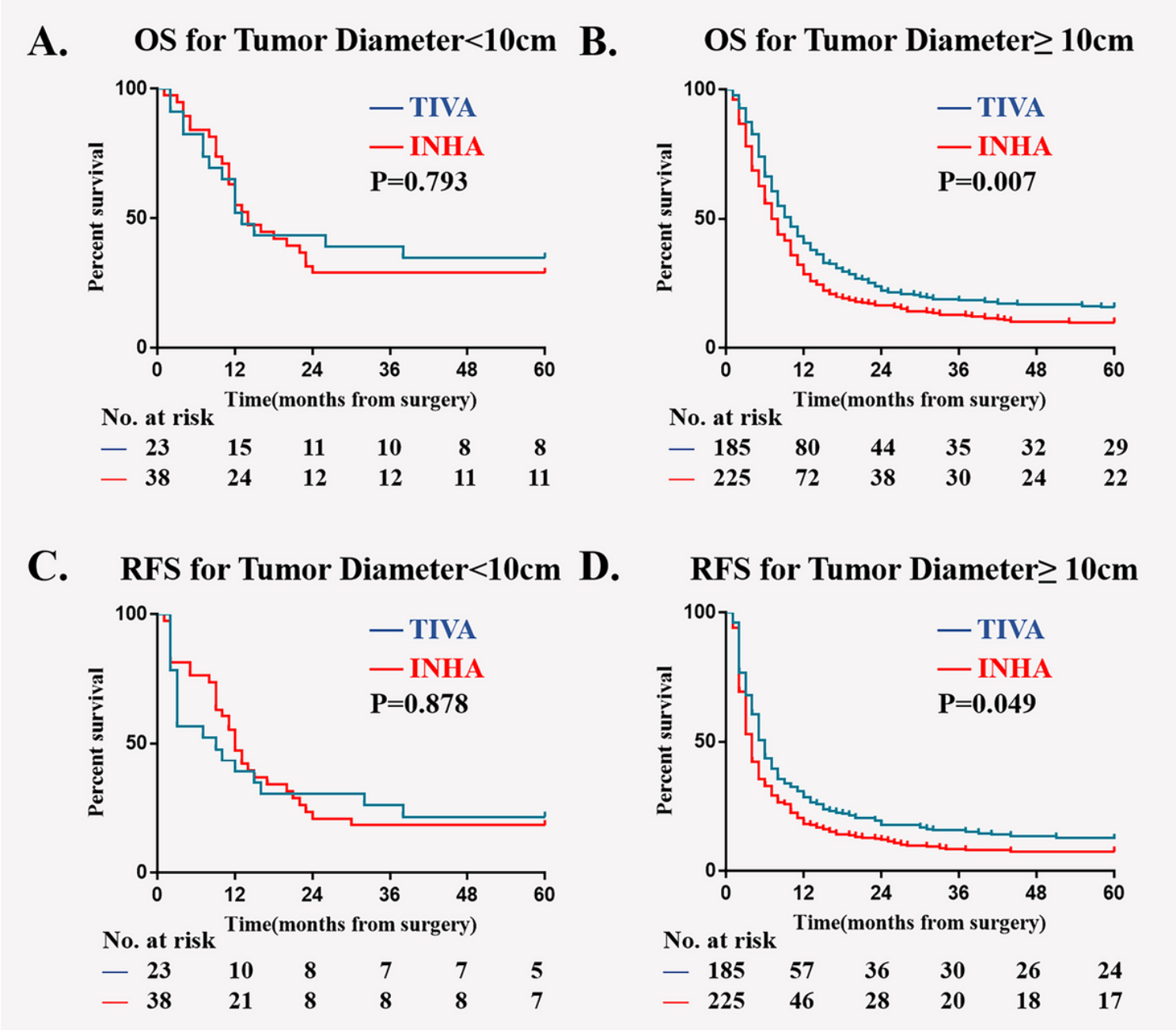

## Figure 2

Kaplan–Meier survival curves from the date of surgery by anesthesia type for (A) overall survival in patients before matching (P=0.007), (B) overall survival in patients after matching (P=0.044), (C) recurrence-free survival in patients before matching (P=0.020), (D) recurrence-free survival in patients after matching (P=0.081). INHA = volatile inhalational; TIVA = total IV anesthesia.



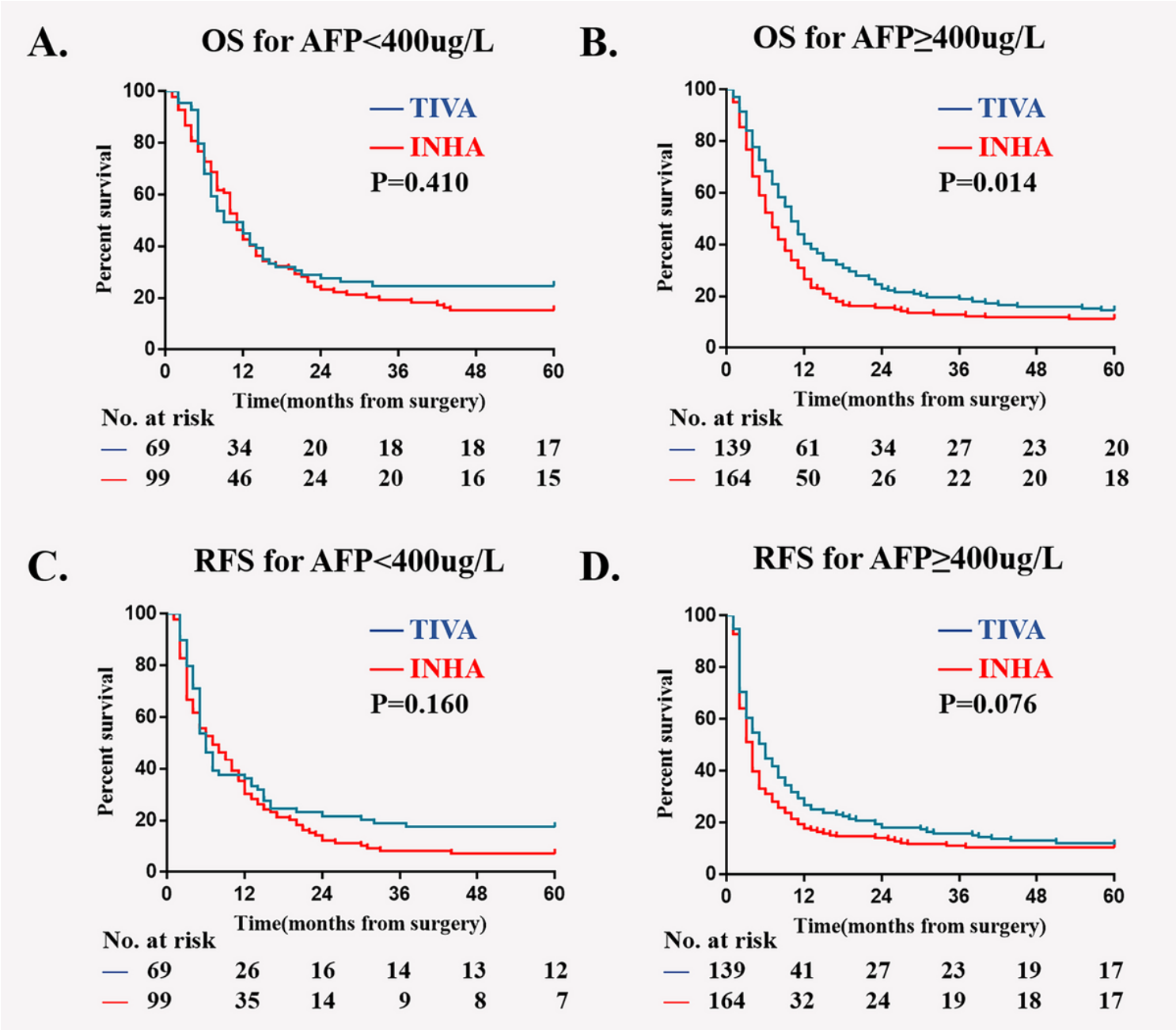

## Figure 3

Subgroup Kaplan–Meier survival analysis for anesthesia type on (A) OS in Child-Pugh A; (B) OS in Child-Pugh B&C; (C) RFS in Child-Pugh A; (D) RFS in Child-Pugh B&C.




## Figure 4

Subgroup Kaplan–Meier survival analysis for anesthesia type on (A) OS in tumor diameter<10cm; (B) OS in tumor diameter≥10cm; (C) RFS in tumor diameter<10cm; (D) RFS in tumor diameter≥10cm.




## Figure 5

Subgroup Kaplan–Meier survival analysis for anesthesia type on (A) OS in AFP<400ug/L; (B) OS in AFP≥400ug/L; (C) RFS in AFP<400ug/L; (D) RFS in AFP≥400ug/L.

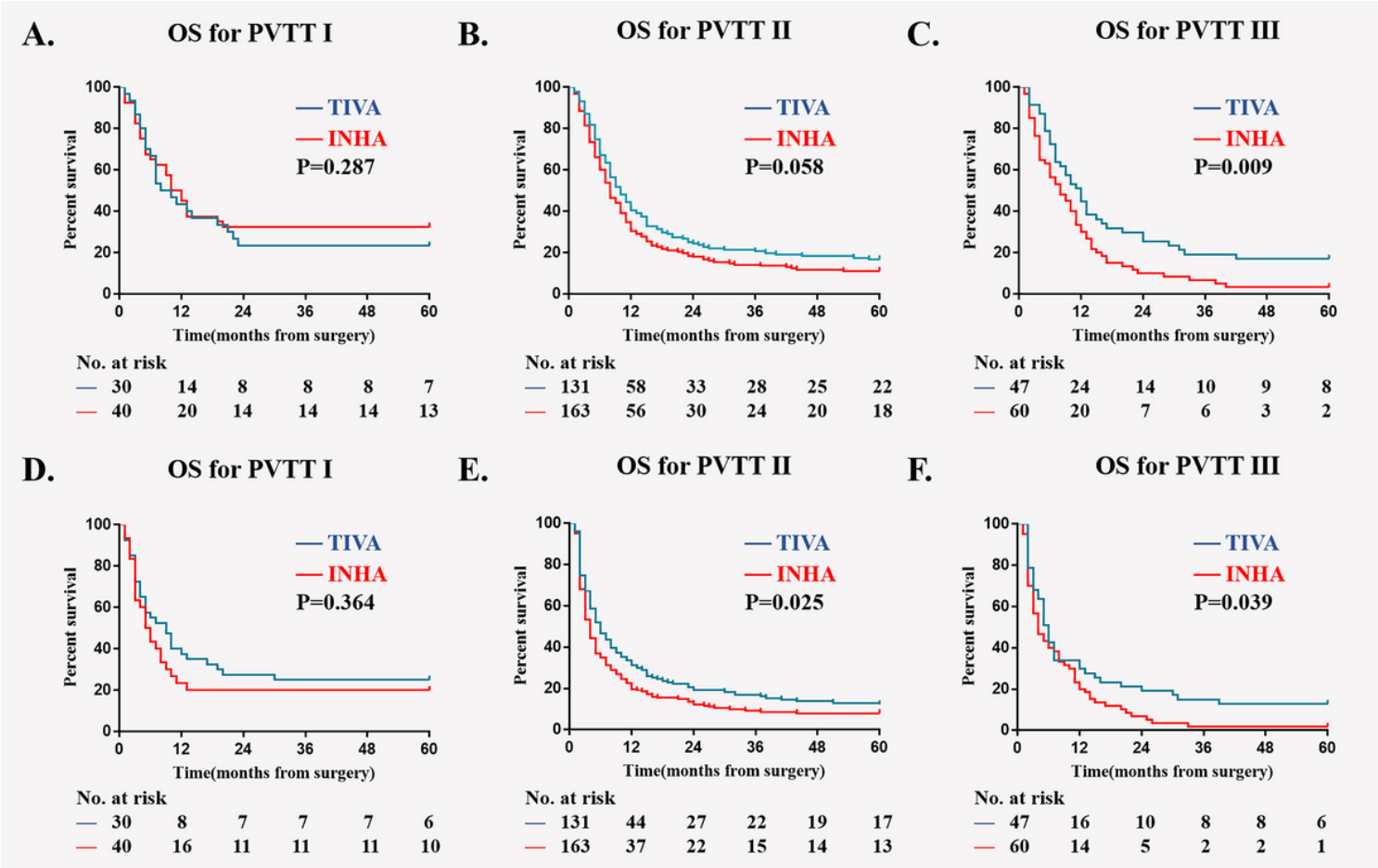



**Figure 6**

Subgroup Kaplan–Meier survival analysis for anesthesia type on (A) OS in PVTT type□; (B) OS in PVTT type□; (C) OS in PVTT type□; (D) RFS in PVTT type□; (E) RFS in PVTT type□; (F) RFS in PVTT type□.

# Supplementary Files

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

- supplementaltable1.pdf