

Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: A systematic review and meta-analysis

SUPPLEMENTAL DIGITAL CONTENT FILE 2

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1. Detailed description of statistical methods

1.1 Meta-analysis:

For direct pair-wise comparisons we used a fixed-effect model with the Peto method to calculate the pooled odds ratios of binary outcomes. Therefore the command *metan* was used in STATA with the following options:

metan r1 f1 r2 f2, or peto

Studies without any events in both groups (VOL and TIVA) provide no information about the odds ratio and were excluded from the meta-analysis. Afterwards, the *metafunnel* command produced funnel plots.

1.2 Network meta-analysis:

1.2.1 Assumptions

Based on RCTs with pairwise as well as multi-arm comparisons, network meta-analysis allows comparing multiple treatments in one statistical model simultaneously and ranking the treatments. Direct and indirect comparisons are used and combined within network meta-analysis.

The idea of indirect comparison is to estimate the effect size of the comparison of e.g. isoflurane vs. sevoflurane via the effect estimates of the comparisons TIVA vs. isoflurane and TIVA vs. sevoflurane where TIVA is the common comparator.

Since indirect comparison breaks randomization, network meta-analysis requires transitivity and consistency in addition to the basic assumptions of ordinary meta-analysis to get valid results. The transitivity assumption ensures that the basis for valid indirect comparison is created conceptually. This implies that the common comparator treatment of indirect comparisons has to be similar and that the studies across the comparisons are similar with respect to effect modifiers. Consistency can be determined from the data by comparing direct and indirect effect estimates and checking if they are in agreement. We ensured the transitivity assumption to be met by carefully selecting our trials with respect to the predefined PICOS criteria¹.

1. Caldwell DM: An overview of conducting systematic reviews with network meta-analysis. Systematic Reviews 2014; 3: 109-12

1.2.2. Code

The network meta-analysis was done using multivariate meta-analysis for the four possible treatments of all studies. The treatment codes are 1=TIVA, 2=isoflurane, 3=sevoflurane and 4=desflurane.

First, the dataset needed to be prepared for the network meta-analysis. There should be one single row per study with the counts for events r_i and the counts for no events f_i (where $i=\text{treatment}=1, 2, 3, 4$). TIVA was defined as reference treatment. There has to be data for the reference treatment in every study. For studies without TIVA, we therefore included trivial data for TIVA ($r_1=0.0001$, $f_1+r_1=0.001$). In addition, we did a 0.5 zero-cell correction.

Since TIVA was defined as reference treatment, the comparisons 2vs1, 3vs1 and 4vs1 represent the basic parameters of our model. The comparisons without TIVA (2vs3, 2vs4 and 3vs4) are the functional parameters of our model. For the comparisons against TIVA we determined the effect estimates, in our case the log odds ratios

$$b_i = \log \text{OR}_{i\text{vs}1} = \log((r_i/f_i)/(r_1/f_1)) \quad \text{with } i=2,3,4$$

as well as the variance of the log odds ratios

$$V_{ii} = \text{variance}(\log \text{OR}_{i\text{vs}1}) = 1/r_i + 1/f_i + 1/r_1 + 1/f_1 \quad \text{with } i=2,3,4.$$

Finally, we calculated the covariance for each pair of comparisons against TIVA

$$V_{ij} = \text{cov}(\log \text{OR}_{i\text{vs}1}, \log \text{OR}_{j\text{vs}1}) = 1/r_1 + 1/f_1 \quad \text{with } i=2,3,4; j=2,3,4 \text{ and } i \neq j.$$

Stata provides the *mvmeta* command to perform multivariate meta-analysis. The complete command of our analysis reads as follows:

mvmeta b V, bscov(prob M) eform

where the variables b^* are our estimates of the log odds ratios and the variables V_{ii} and V_{ij} form the variance-covariance matrix. We assumed equal heterogeneities for all comparisons by using the *bscov(prob)* option with the matrix M (*mat M=I(3)+J(3,3,1)*). The *eform* option

tells STATA to calculate odds ratios. We produced the forest plots of our results with the *intervalplot* command.

Finally, we estimated the ranking probabilities. Adding the *longparm* and *pbest()* option to the *mvmeta* command leads to the calculation of the ranking probabilities:

```
mvmeta b V, bscov(prop M) longparm pbest(min, all zero gen(prob) reps(20000))
```

Predictive probabilities we derived from the following command:

```
mvmeta y S, bscov(prop P) longparm pbest(min, all zero gen(pred_prob) reps(20000)  
predict)
```

The *sucra* command produces plots of these ranking probabilities:

```
sucra prob*, mvmeta comp(pred_prob*)
```

Figure 1

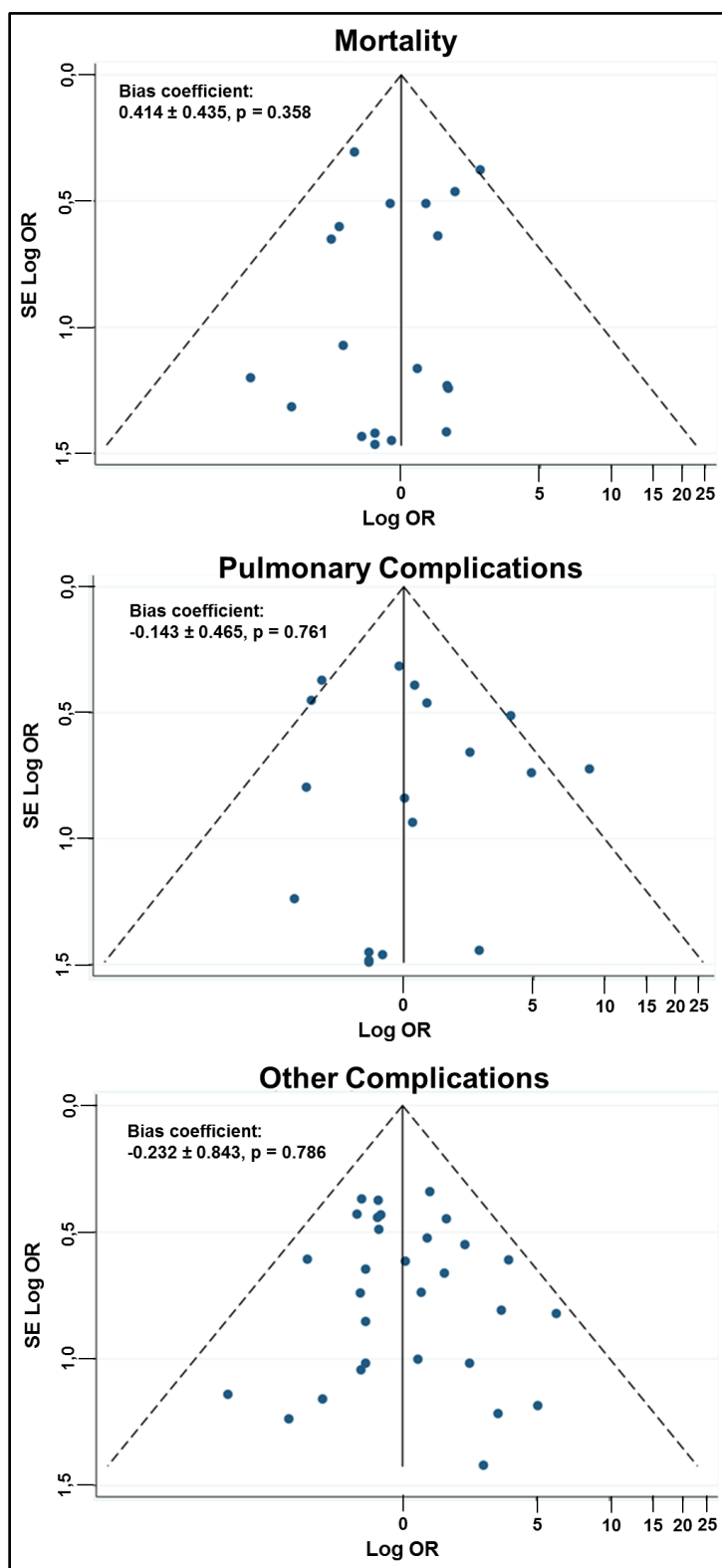


Figure 1 – Funnel plots. Funnel plots are shown with 95% pseudo-confidence intervals. Bias coefficient was calculated using Egger's regression. Statistical significance was accepted at $p < 0.05$. Log OR: logarithmic odds ratio, SE Log OR: standard error of the logarithmic odds ratio, Mortality: longest reported mortality, PPCs: postoperative pulmonary complications.

Figure 2

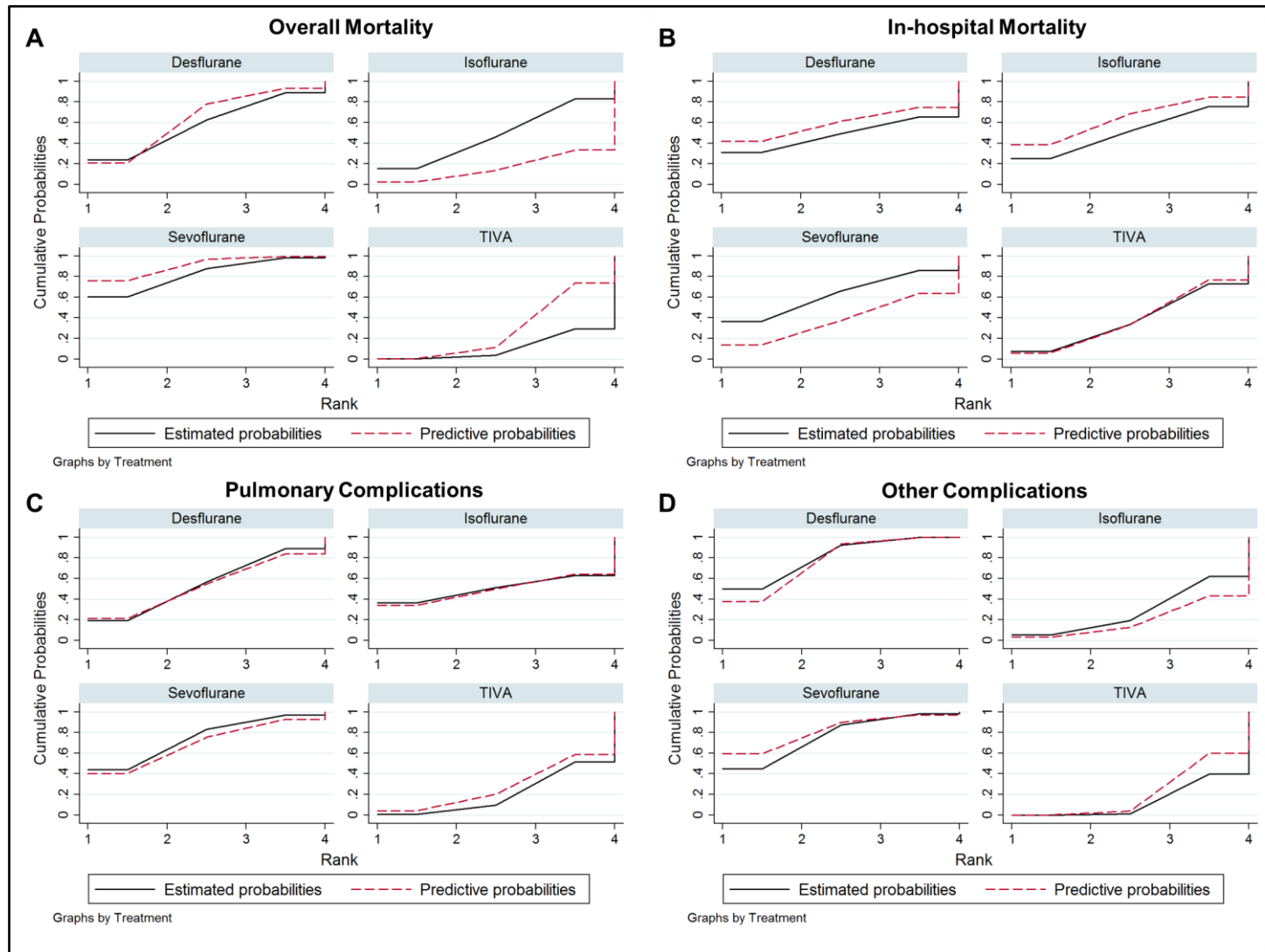


Figure 2: Plots of cumulative ranking probability of overall mortality (A), in-hospital mortality (B), postoperative pulmonary complications (C), and other postoperative complications (D) in patients who underwent cardiac surgery.

Figure 3

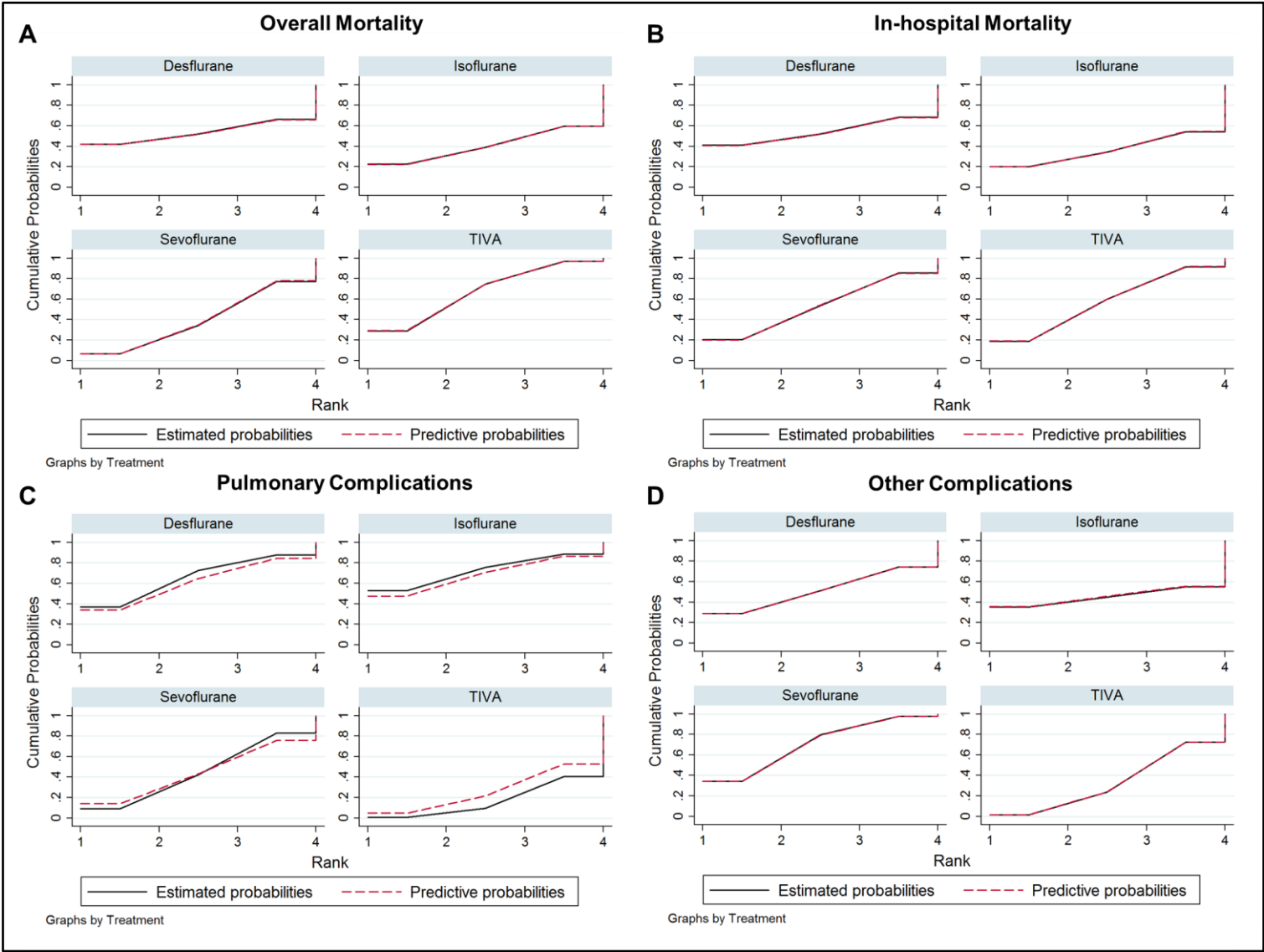


Figure 3: Plots of cumulative ranking probability of overall mortality (A), in-hospital mortality (B), postoperative pulmonary complications (C), and other postoperative complications (D) in patients who underwent non-cardiac surgery.

Figure 4: Intensive care unit (ICU) length of stay of cardiac surgery patients. Values are given as mean differences. SD = standard deviation, CI = confidence interval, IV: instrumental variable, df: degrees of freedom, I^2 : heterogeneity. References refer to Table 5 of the supplemental digital content file.



Figure 5

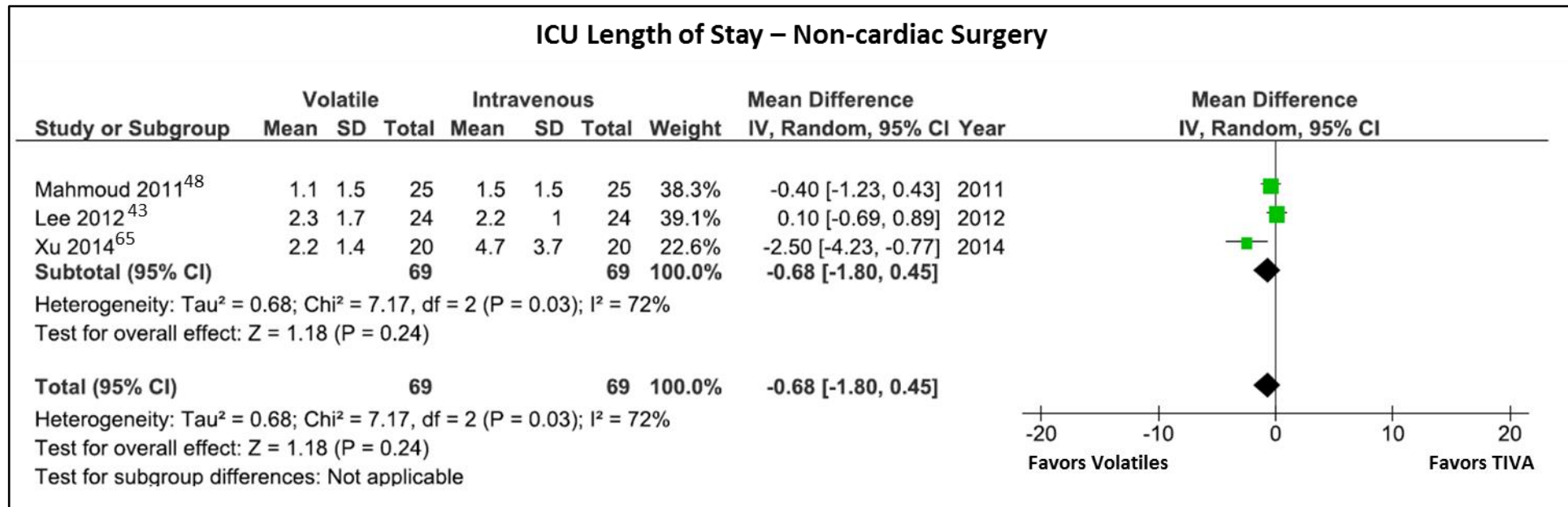


Figure 5: Intensive care unit (ICU) length of stay of non-cardiac surgery patients. Values are given as mean differences. SD = standard deviation, CI = confidence interval, IV: instrumental variable, df: degrees of freedom, I^2 : heterogeneity. References refer to Table 5 of the supplemental digital content file 1.

Figure 6

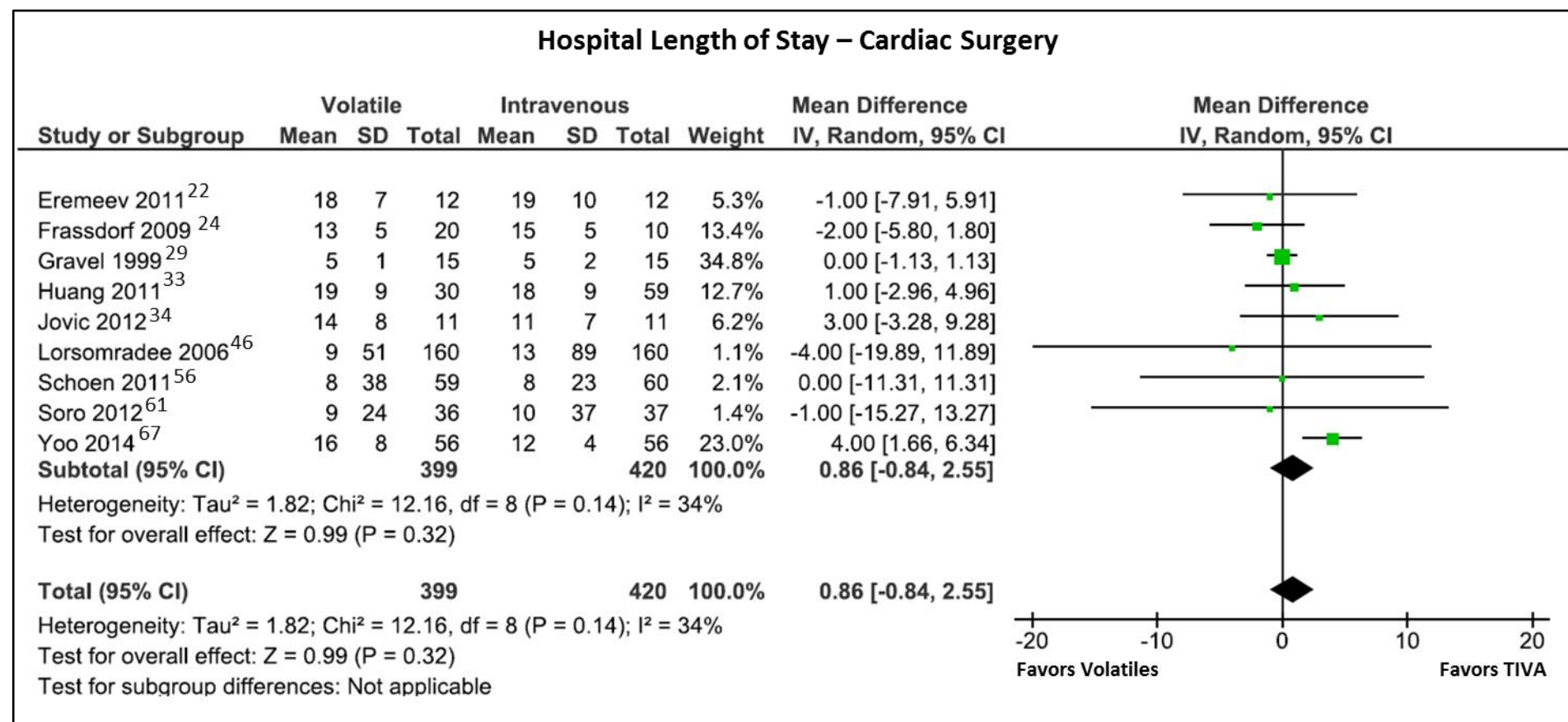


Figure 6: Hospital length of stay of cardiac surgery patients. Values are given as mean differences. SD = standard deviation, CI = confidence interval, IV: instrumental variable, df: degrees of freedom, I^2 : heterogeneity. References refer to Table 5 of the supplemental digital content file 1.

Figure 7

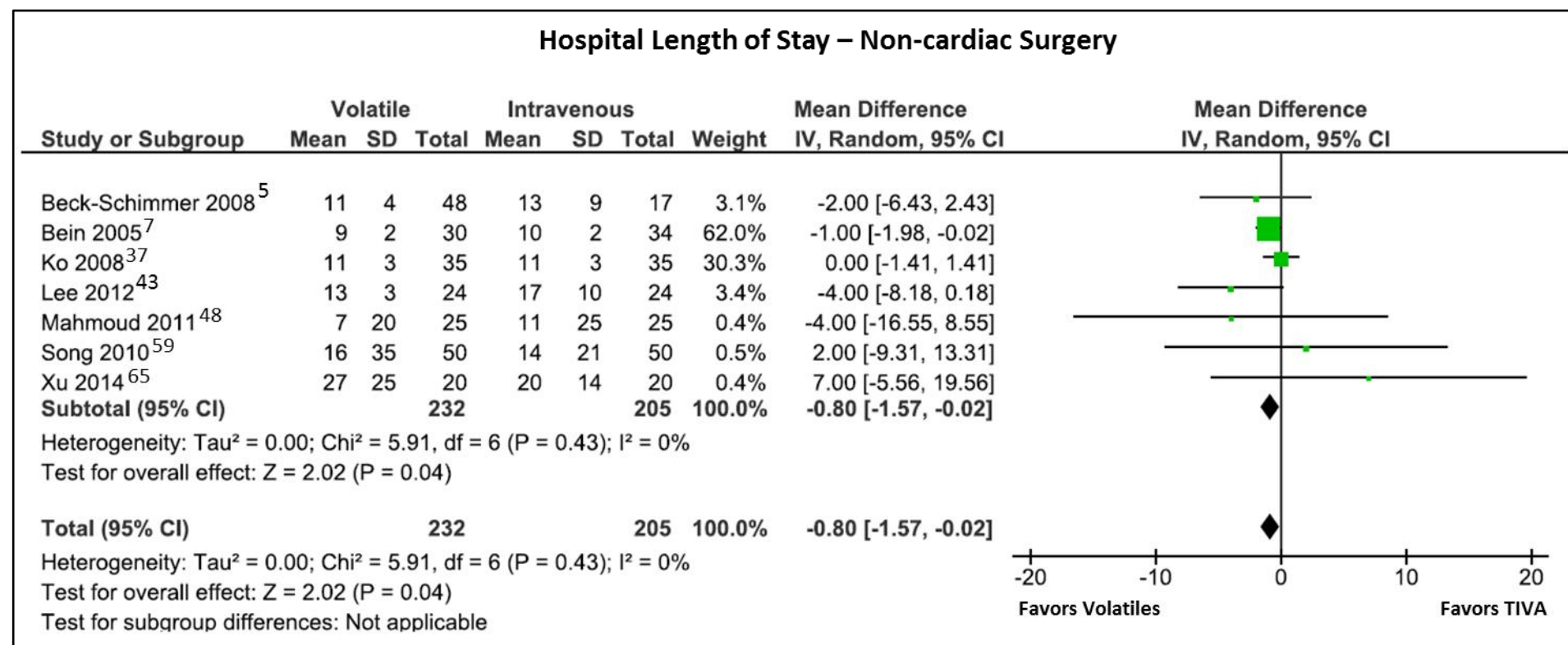


Figure 7: Hospital length of stay of non-cardiac surgery patients. Values are given as mean differences. SD = standard deviation, CI = confidence interval, IV: instrumental variable, df: degrees of freedom, I^2 : heterogeneity. References refer to Table 5 of the supplemental digital content file 1.