







SYSTEMATIC REVIEW AND META-ANALYSIS

Surgical Timing in Patients With Infective Endocarditis and With Intracranial Hemorrhage: A Systematic Review and Meta-Analysis

Rita Musleh , MD; Peter Schlattmann , MD, MSc; Túlio Caldonazo, MD; Hristo Kirov, MD; Otto W. Witte , MD; Torsten Doenst , MD; Albrecht Günther , MD*; Mahmoud Diab , MD*

BACKGROUND: Intracranial hemorrhage (ICH) is one of the main causes for lack of surgery in patients with infective endocarditis (IE), despite the presence of surgical indications. We aimed to evaluate the impact of early surgery in patients with IE and with ICH on postoperative neurological deterioration and all-cause mortality and to elucidate the risk of 30-day mortality in patients who were denied surgery.

METHODS AND RESULTS: Three libraries (MEDLINE, EMBASE, and Cochrane Library) were assessed. The primary outcome was all-cause mortality, and the secondary outcome was neurological deterioration. Inverse variance method and random model were performed. We identified 16 studies including 355 patients. Nine studies examined the impact of surgical timing (early versus late) and were included in the meta-analysis. Only one study examined the fate of patients with IE and with ICH who were treated conservatively despite having an indication for cardiac surgery, showing higher mortality rates than those who underwent surgery (11.8% versus 2.5%). We found no significant association between early surgery, regardless of its definition, and a higher mortality (odds ratio [OR], 1.69; 95% CI, 0.95–3.02). Early surgery was associated with higher risk for neurological deterioration (OR, 2.00; 95% CI, 1.10–3.65).

CONCLUSIONS: Cardiac surgery for IE within 30 days of ICH was not associated with higher mortality, but with an increased rate of neurological deterioration. The 30-day mortality in patients with IE and with ICH who were denied surgery has not yet been sufficiently investigated. This patient group should be analyzed in future studies in more detail.

Key Words: infective endocarditis ■ intracranial hemorrhage ■ neurological deterioration ■ surgical timing

Infective endocarditis (IE) is a life-threatening disease that is associated with high morbidity and mortality.^{1,2} Cardiac surgery is indicated in >50% of cases.³ However, surgery is not performed in a significant number of patients, ranging from 26% to 40% of patients with IE, despite evident surgical indication.^{4,5} The 30-day mortality among those patients who were denied surgical treatment is as high as 63%.^{3,4,6,7} Intracranial hemorrhage (ICH) represents the reason for denial of

surgery in 15% of patients with IE.⁸ Although cardiac surgery can be life saving in IE, it also carries significant risks in the presence of ICH, which is mainly related to inevitable use of high-dose systemic anticoagulation during cardiopulmonary bypass, bearing the risks of further bleeding and neurologic deterioration. On the other hand, early surgery has been shown to prevent recurrent embolic events and decrease mortality in patients with IE.⁵

Correspondence to: Mahmoud Diab, MD, Department of Cardiothoracic Surgery, Friedrich-Schiller-University of Jena, Am Klinikum 1, 07747 Jena, Germany. Email: Mahmoud.diab@med.uni-jena.de

* A. Günther and M. Diab contributed equally.

Supplemental Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024401>

For Sources of Funding and Disclosures, see page 10.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](#) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Cardiac surgery within 30 days in infective endocarditis with intracranial hemorrhage was not associated with higher mortality, but with an increased rate of neurological deterioration.
- Patients with infective endocarditis who were treated conservatively, despite having an indication for cardiac surgery, showed a higher 30-day mortality than those who underwent surgery.

What Are the Clinical Implications?

- Future studies investigating the risk of cardiac surgery in infective endocarditis in the presence of intracranial hemorrhage should, to avoid any immortal-time bias, include patients who were denied surgery.

Nonstandard Abbreviations and Acronyms

ICH	intracranial hemorrhage
IE	infective endocarditis

To date, there are no randomized controlled trials to guide the management of patients with IE complicated with ICH. The current guidelines from the American Heart Association/American College of Cardiology and the European Society of Cardiology recommend delaying the cardiac surgery for at least 30 days in the presence of ICH in patients with IE to avoid neurological deterioration.^{1,2} However, these recommendations are based on observational studies with limited numbers of patients.⁹ In addition, the results of the studies comparing early versus late surgery in patients with IE and with ICH are exposed to immortal-time bias.¹⁰ Only patients surviving the 30-day interval after ICH onset were included in the group of late surgery. As mentioned above, around 63% of patients with IE with surgical indications die if surgery is not performed within 30 days. We herein aim to evaluate the impact of surgery within 30 days of ICH in patients with IE, bearing in mind the high mortality risk while waiting for the surgery.

METHODS

This analysis was prospectively registered on the International Prospective Register of Systematic Reviews in Health and Social Care (identification number CRD42021238479). Institutional review board approval was not required for this analysis as no human or animal subjects were involved.

The authors declare that all supporting data, including online supplementary files, are available within the article.

Search Strategy

A comprehensive literature search was performed to identify contemporary studies evaluating the association of surgical timing and postoperative outcome in patients with IE and with preoperative ICH. Searches included all studies between January 1995 and March 2021 in the following 3 databases: Ovid MEDLINE, Ovid EMBASE, and The Cochrane Library (Wiley). The computerized search included varying “AND” and “OR” combinations of the following keywords: infective endocarditis, intracranial hemorrhage, hemorrhagic infarction, stroke, subarachnoid hemorrhage, surgical timing, early surgery, cerebrovascular events, neurological deterioration, mycotic aneurysm, and hemorrhagic conversion.

Study Selection and Eligibility Criteria

The study selection was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis strategy.¹¹ After deduplication, records were screened by 2 independent reviewers (R.M. and A.G.). Any discrepancies and disagreements were resolved by a third author (M.D.). [Figure 1](#) shows the flowchart adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis group statement.¹¹

Data Abstraction and Quality Assessment

The data extraction and the quality assessment were performed independently by 2 different investigators (R.M. and A.G.) and verified by a third investigator (M.D.) for accuracy. The following variables were extracted: age, sex, valve involvement, vegetation size, EuroScore II, and surgery indication. All possible time cutoffs for the definitions of early surgery, within 7, 14, 21, and 28 days, were included. Risk of bias was assessed based on Newcastle-Ottawa assessment scale¹² (Table S1). Publication bias was assessed for the outcome of early surgery (Figure S1).

Outcomes and Effect Summary

The primary outcome was defined as all-cause mortality within 30 days of surgery. The secondary outcome was defined as postoperative neurological deterioration (worsened or new clinical neurological deficit or death attributable to a neurological event). Patients with a worsening of their imaging findings but without new clinical symptoms were not considered as having neurological deterioration. Specific subgroup analyses were performed with studies pooled

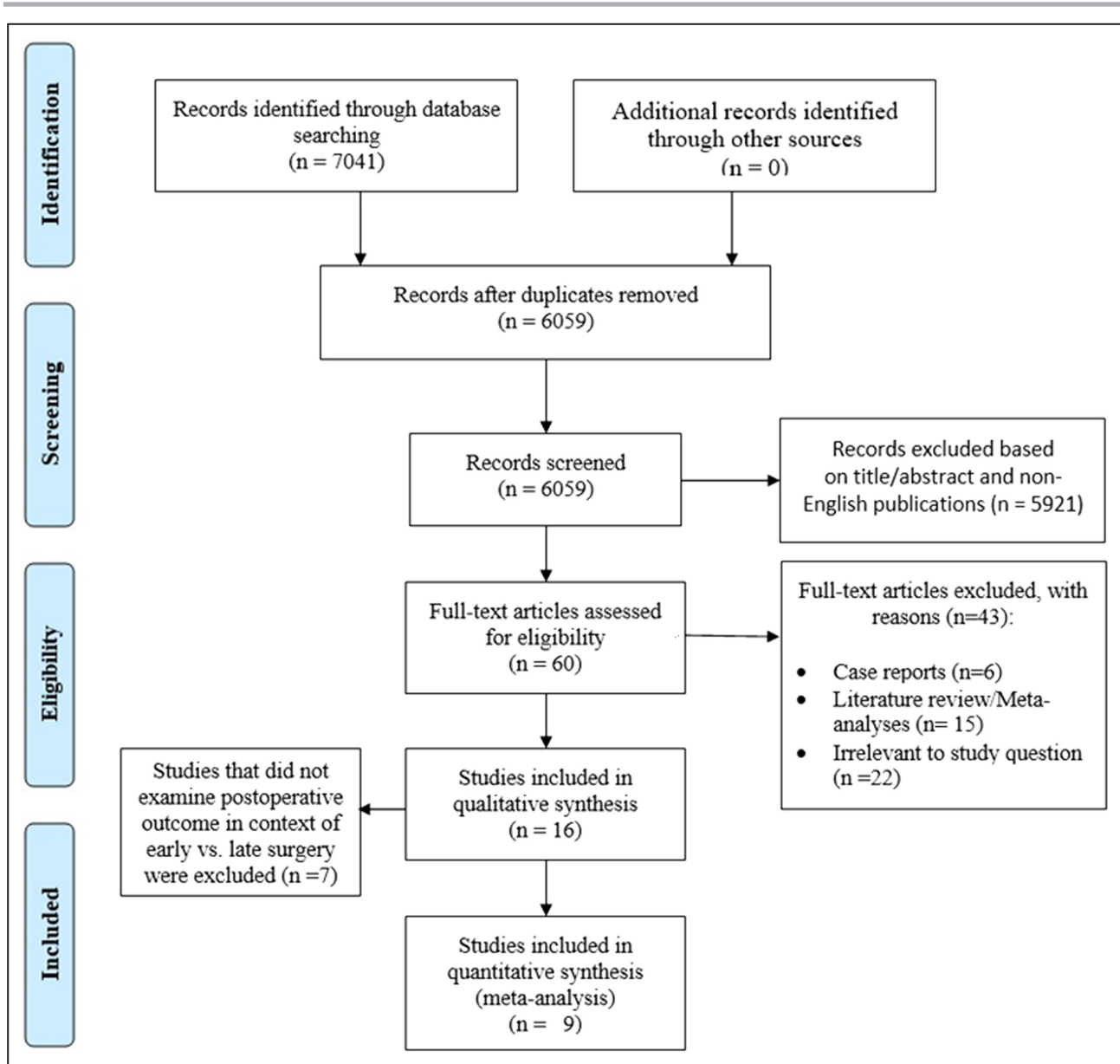


Figure 1. Study selection diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis group statement.¹¹

according to the definition of early surgery (<7, 14, 21, or 28 days of the ICH).

Statistical Analysis

Results were presented graphically using forest plots. Our statistical analysis covered the investigation of bias and heterogeneity in the meta-analysis. The Egger regression test was used to detect publication bias using the results for early surgery.¹³ For dichotomous outcomes, odds ratios (ORs) were calculated for every single study by means of 2x2 contingency tables. The average of the ORs summarizing cumulative effects at different time points was presented. Because

of correlated data, a generalized linear mixed model was used. First, we used the “hypergeometric-normal model” for the meta-analysis of ORs, which showed favorable results in simulation studies.^{14,15} This is essentially a mixed-effects conditional logistic model (based on the noncentral hypergeometric distribution) with the covariate early versus late surgery, where the random study-specific effects follow a normal distribution. This model, which takes the correlated data structure into account by conditioning on the study events, was applied to the all-cause mortality data. Because of numerical difficulties, we applied an approximate binomial model (ie, intercept-only logistic mixed-effects

regression model), where the noncentral hypergeometric distribution is approximated by a binomial distribution. Because there is no single best model available, we performed sensitivity analyses. For one, we applied a mixed-effects logistic regression model with bivariate normally distributed random intercept and random treatment effect (random slope and intercept model) with the covariate early versus late surgery. All these models were stratified by time point. Furthermore, we used a generalized linear mixed model with fixed effects for early versus late surgery and time point as categorical covariates together with a random intercept for each study (random intercept model).¹⁶

Heterogeneity was assessed using a likelihood ratio test comparing the respective models, the heterogeneity variance tau², and the I² measure.¹⁷ To deal with zero counts in individual studies displayed in the forest plots, 0.5 was added to all cell frequencies. No continuity correction was performed in the respective generalized linear mixed models because we are dealing with exact within-study likelihoods. Differences between subgroups were evaluated using a corresponding likelihood ratio or χ^2 test.¹⁸ The freely available statistical software environment R was used to perform the statistical calculations using the packages “meta,”¹⁹ “metafor” (hypergeometric-normal model, approximate binomial model, and random slope and intercept model),²⁰ and lme4 (random intercept model).²¹

RESULTS

Study Selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram outlining the study selection process is available in [Figure 1](#). A total of 7041 records were identified through database searching. After duplicate records were removed, a total of 6059 citations were retrieved and their titles and abstracts were screened. A total of 16 studies,^{7,8,22–35} with a total of 355 cases, met the eligibility criteria and were included in the qualitative synthesis. Among them, 7 studies did not give a clear definition of early surgery.^{24,26,30–33,35} Therefore, the remaining 9 studies,[†] with a total of 236 patients, were further included in the quantitative synthesis (meta-analysis). [Tables 1](#) and [2](#) demonstrate postoperative outcomes in all the studies included in the qualitative analysis only (n=7) and in the quantitative analysis (n=9), respectively.

Qualitative Assessment and Study Characteristics

Of the 16 studies included in the qualitative analysis, 13 studies^{7,23–26,29–36} found no association between neurological deterioration and early surgery, regardless

of its definition (<7, 14, 21, or 28 days). One study reported a higher mortality and neurological deterioration in patients who were operated on within 2 weeks (n=4).⁸ Two studies found a higher risk of postoperative neurological exacerbation²² or mortality²⁸ when patients were operated on before 7 days; however, the differences were not statistically significant.

The 9 studies included in the meta-analysis were all observational and retrospective. Three of them were multicentric. Four studies were conducted in Japan,^{23,25,28,34} and one each in Germany,²² France,⁷ Australia,²⁹ Spain,⁸ and the United States.³¹ [Table S2](#) demonstrates demographic characteristics of patients included in these studies. The mean age of patients ranged between 37 and 71 years, 57% to 88% were men, and 30% to 83% had large vegetations. Indication of surgery was reported only in a few studies: heart failure (22%–56%), uncontrolled infection (12%–21%), or high embolic risk (24%–59%).

Mortality Among Patients Who Were Denied Surgery Because of ICH

Among the 9 studies included in the meta-analysis, only 1 study reported mortality in patients with IE and with ICH who were treated conservatively, despite having a surgical indication. [Salaun et al](#)⁷ reported that among the 60 patients with IE and with an ICH who had an indication for surgery, 22 (37%) did not receive the surgery. In patients with ICH who had a surgical indication, 1-month mortality rate was higher in non-operated on compared with operated on patients (11.8% versus 2.5%, respectively). None of the operated on patients experienced a neurological deterioration, especially the 17 patients who were operated on within the first month after the ICH onset.

[Figure S2](#) illustrates a Kaplan-Meier curve extracted from available studies in literature to compare the cumulative survival of patients with IE with an indication of surgery who were treated surgically versus conservatively.

Quantitative Assessment (Meta-Analysis) Primary Outcome

[Figure 2](#) shows that early surgery, regardless of its definition, was not significantly associated with higher all-cause 30-day mortality (OR, 1.69; 95% CI, 0.95–3.02). Our sensitivity analysis led to an OR of 1.70 (95% CI, 1.00–2.90) for random slope and intercept model and to an OR of 1.68 (95% CI, 0.95–2.98) for random intercept model model ([Figure S3](#)).

Secondary Outcome

[Figure 3](#) shows that early surgery was associated with higher incidence of neurological deterioration (OR, 2.00; 95% CI, 1.10–3.65), which was most evident

[†]References 7,8,22,23,25,28,29,34,36.

Table 1. Literature Review Presenting the Postoperative Outcomes in the 7 Studies Included in the Qualitative Analysis Only

Literature (y)	Patients with IE and with Pre-ICH, n	Interval ICH-surgery	Outcomes/conclusions
Zhang (2020) ³⁵	35	<14 d (n=10) >14 d (n=25)	Rates of neurological complications were similar for early and late surgery groups (10.9% vs 11%). Early valve surgery for patients with IE complicated by stroke was not associated with perioperative neurological complications.
Lee (2018) ²⁶	9	≥4 wk, except in case of a causative mycotic aneurysm (urgent/emergent surgery might be performed after neurosurgery)	All patients had no postoperative strokes and survived to discharge. The only significant prognostic predictor was postoperative ICH ($P=0.04$) and not Pre-ICH ($P=0.78$). Surgical timing was not related to postoperative outcomes. Routine preoperative brain imaging to detect silent ICH or mycotic aneurysm is recommended.
Wan (2014) ³²	10	Median of 10±10.1 d	Early surgery was not associated with postoperative neurological complications. Nine patients showed no postoperative neurological complications. Only 1 patient presented postoperative SAH expansion, which resorbed spontaneously later.
Wilbring (2014) ³³	6	Median of 17±24 d	The outcomes were not related to the surgical timing.
			Two patients improved, 2 patients remained stable, and 2 patients had postoperative neurological deterioration, without leading to death.
Shang (2009) ³¹	16	Median of 12 d	Early surgery was associated with low rates of mortality. No postoperative neurological deterioration or hemorrhage expansion.
Ruttmann (2006) ³⁰	6	Median of 4 d	Neurological deterioration is not related to the surgical timing (<4 or >4 d).
			A total of 4 of 6 patients died. Causes of death: cardiac (n=1), septic shock (n=2), and neurological (n=1).
Gillinov (1996) ²⁴	7	Median of 22±2.8 d	Six patients showed no deterioration or even improvement of the postoperative neurological state. Only 1 patient with a ruptured mycotic aneurysm underwent clipping and died.

ICH indicates intracranial hemorrhage; IE, infectious endocarditis; Pre-ICH, preoperative ICH; and SAH, subarachnoid hemorrhage.

when surgery was performed within 7 days of the onset of ICH (OR, 4.18; 95% CI, 1.24–14.05). However, there was no statistical significance between subgroups ($\chi^2=2.72$; $df=3$; $P=0.44$). Our sensitivity analysis led to an OR of 1.89 (95% CI, 1.09–3.25) with random slope and intercept model and to an OR of 2.28 (95% CI, 1.17–4.39) with random intercept model (Figure S4).

Publication Bias

A funnel plot was created to assess possible publication biases (Figure S1A). The Egger linear regression test was then used to assess the symmetry of the plot (Figure S1B). The data suggested that the funnel plot was symmetrical (bias=0.56; $P=0.94$).

Results of generalized linear mixed model with covariates early versus late surgery and time point were demonstrated in Table S3.

DISCUSSION

In our study, we found in patients with IE with concomitant ICH no statistically significant association between

early surgery (within 30 days) and a higher mortality. However, early surgery was associated with increased risk of neurological deterioration. This was particularly evident when surgery was performed within 7 days after the onset of ICH. The results of the primary and secondary outcomes were consistent regardless of the statistical model chosen. Available data on patients with IE with a surgical indication, who were treated conservatively because of the presence of ICH, are scarce but show a higher mortality rate compared with those who were operated on. Our analysis highlights the importance of future clinical studies in this specific patient population to provide better guidance about the surgical decision and timing in patients with IE and with ICH.

Cardiac surgery represents the only treatment option in a significant proportion of patients with IE. Figure S2 summarizes available studies in literature comparing the cumulative survival of patients with IE with an indication of surgery who were treated surgically versus conservatively.^{3,4,6,7} It highlights the high mortality, especially within 30 days, among patients with surgical indications who are denied surgery for different reasons, including preoperative ICH. In the largest prospective multicenter

Table 2. Literature Review Presenting the Postoperative Outcomes in the Context of the Surgical Timing in the 9 Studies Included in the Final Quantitative Analysis

Literature (year)	Patients with IE and with Pre-ICH, n	Interval ICH-surgery	Outcomes/conclusions
Diab (2020) ²²	34	<7 d (n=21)	Risk of postoperative neurological exacerbation in patients with IE and with ICH might be overestimated. Postoperative neurological deterioration was higher in patients with IE and with Pre-ICH operated on within 7 d; however, the difference was not significant ($P=0.24$). Pre-ICH was not an independent predictor for postoperative neurological deterioration or hospital mortality in patients with IE ($P=0.84$).
		8–14 d (n=5)	
		15–28 d (n=3)	
		>28 d (n=2)	
		Unknown (n=2)	
Salaun (2018) ⁷	38	<28 d (n=17)	No neurological deterioration regardless of the surgical timing.
		Overall median of 34 d (n=38)	Higher mortality in conservatively treated patients with Pre-ICH ($P=0.005$).
Kume (2018) ²⁵	25	<14 d (n=17)	There was no difference in the postoperative bleeding rate and mortality between patients who had surgery within or after 14 d from the onset of ICH (log-rank $P=0.904$). Intracranial mycotic aneurysm is associated with ICH after valve surgery ($P=0.002$).
		>14 d (n=8)	
Okita (2016) ²⁸	54	<7 d (n=13)	Although statistically insignificant, early surgery (within 7 d) had higher incidence of hospital deaths in patients with ICH ($P=0.22$).
		8–21 (n=17)	
		>21 d (n=24)	
Raman (2016) ²⁹	6	≤10 d <7 d (n=5)	No neurological deterioration regardless of the surgical timing.
Yoshioka (2014) ³⁴	30	8–14 d (n=6)	No neurological deterioration or hemorrhage expansion, regardless of surgery timing (even when operated on within 2 wk). Only 2 patients with new postoperative ectopic asymptomatic hemorrhage. Four patients died because of organ and heart failure.
		15–28 d (n=9)	
		>28 d (n=10)	
Garcia-Cabrera (2013) ⁸	12	<14 d (n=4)	Higher mortality and neurological deterioration associated with early surgery within 2 wk. Outcome according to surgical timing: 4 patients within the first 2 wk (75% mortality, 50% new ICH), 3 patients operated on within the third week (66% mortality, 33% new ICH), and 5 cases operated on after 3 wk (40% mortality, 20% new ICH).
		14–21 d (n=3)	
		21 d (n=5)	
Yeates (2010) ³⁶	3	Median of 5.8 wk (3–60 d) with 1 of 3 patients operated <1 wk	No neurological deterioration regardless of the surgical timing.
Eishi (1995) ²³	34	<1 d (n=1)	Neurological deterioration is not clearly related to the surgical timing. No neurological deterioration in patients operated on 2–28 d after ICH, but 19% exacerbation in patients operated on >4 wk. Six patients died, with 1 neurological death in the 1 patient operated on within 24 h.
		2–28 d (n=12)	
		>28 d (n=21)	

ICH indicates intracranial hemorrhage; IE, infectious endocarditis; and Pre-ICH, preoperative ICH.

register “ICE-PLUS (International Collaboration on Endocarditis-PLUS),” 863 patients with IE had an indication for surgery.⁴ One quarter of these patients with surgical indication were treated medically only. The 30-day mortality in these patients ranged from 18% in low-risk patients to 59% in high-risk patients. Similar results were obtained from a French epidemiological study on patients with IE.⁶ The authors reported a 30-day mortality of 58% in patients with surgical indications who did not receive surgical treatment. Furthermore, a recent study from Spanish Collaboration on Endocarditis examined the effect of surgical indication on 30-day mortality in patients who were rejected for surgical treatment (n=538/1650). They reported 30-day mortality of

≈54% in patients with surgical indication attributable to heart failure and of ≈42% in those with surgical indication attributable to uncontrolled infection or embolic risk.³ The high rate of mortality in patients with surgical indications who did not receive surgical treatment within 30 days can be justified in the light of the current guideline recommendations for surgical timing in patients with IE^{1,2}: emergency surgery (within 24 hours) in the presence of heart failure or urgent surgery (<7 days) in cases with uncontrolled infection or increased risk of embolization. However, the same guidelines recommend delaying surgery for at least 30 days in IE complicated with ICH. This delay, based on the previously mentioned studies,^{3,4,6} may expose patients

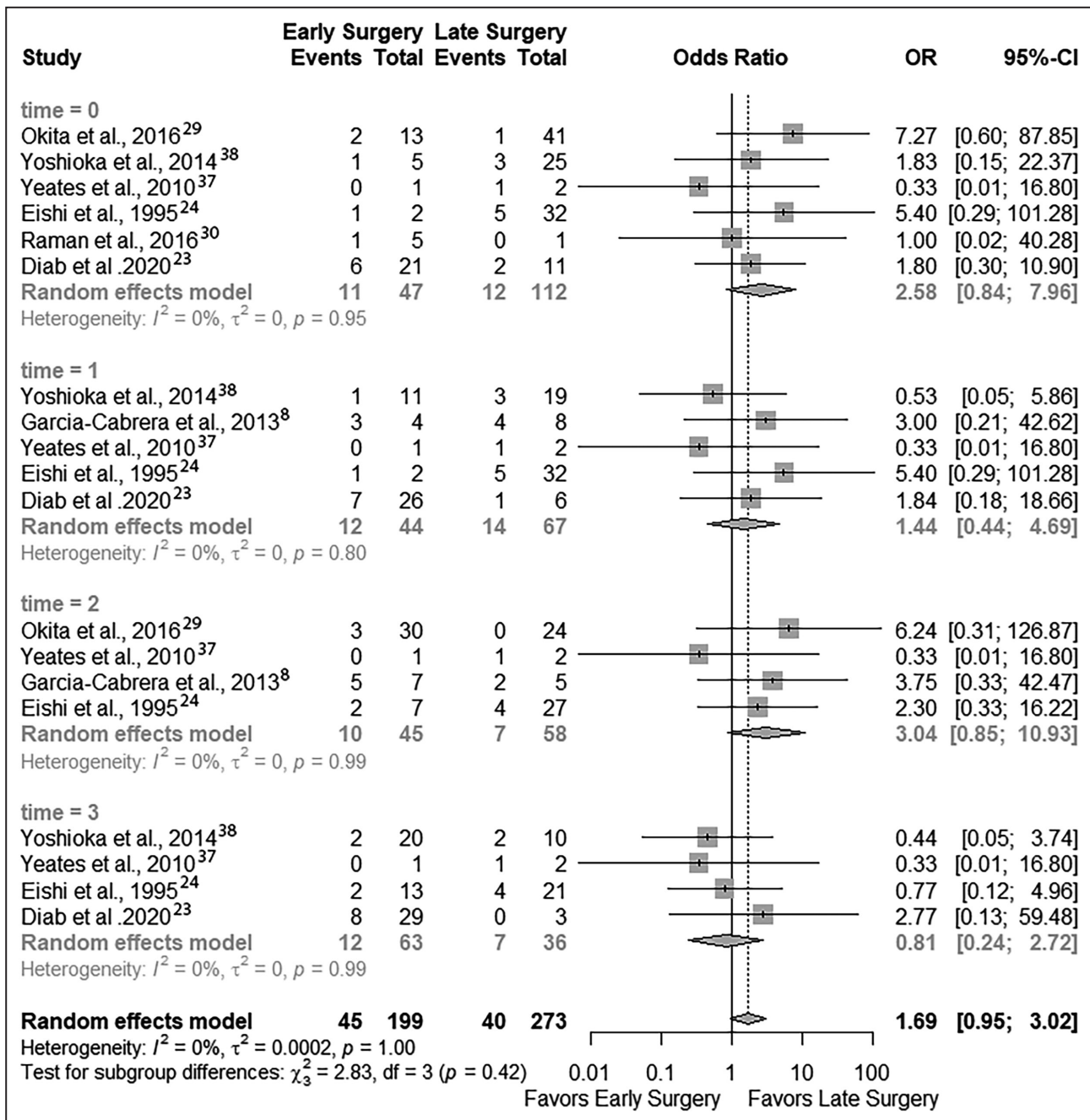


Figure 2. Forest plot of postoperative end point 1 (all-cause mortality within 30 days) in patients with infective endocarditis and with preoperative intracranial hemorrhage (ICH) who underwent early vs late valve surgery.

Studies were pooled into subgroups based on their definition of early and late surgery (<7 vs >7 days of ICH onset; <14 vs >14 days of ICH onset; <21 vs >21 days of ICH onset; <28 vs >28 days of ICH onset). Odds ratios (ORs) summarizing cumulative effects for all different time points were presented.

with surgical indications to at least 40% risk of 30-day mortality. Although these studies did not focus on ICH particularly, Chu et al reported that among patients who were denied surgery with available reasons, 13.2% were not operated on because of the presence of ICH.⁴ In fact, the presence of ICH in patients with IE reflects the disease severity,³⁷ emphasizing potential benefits of

early surgical treatment. Focusing on patients with IE with ICH, we found only one study comparing the fate of patients who were denied surgical treatment with those who were operated on. In this cohort study of 38 patients with IE with ICH and surgical indications, 30-day mortality was 4-fold higher in non-operated on than in operated on patients.⁷

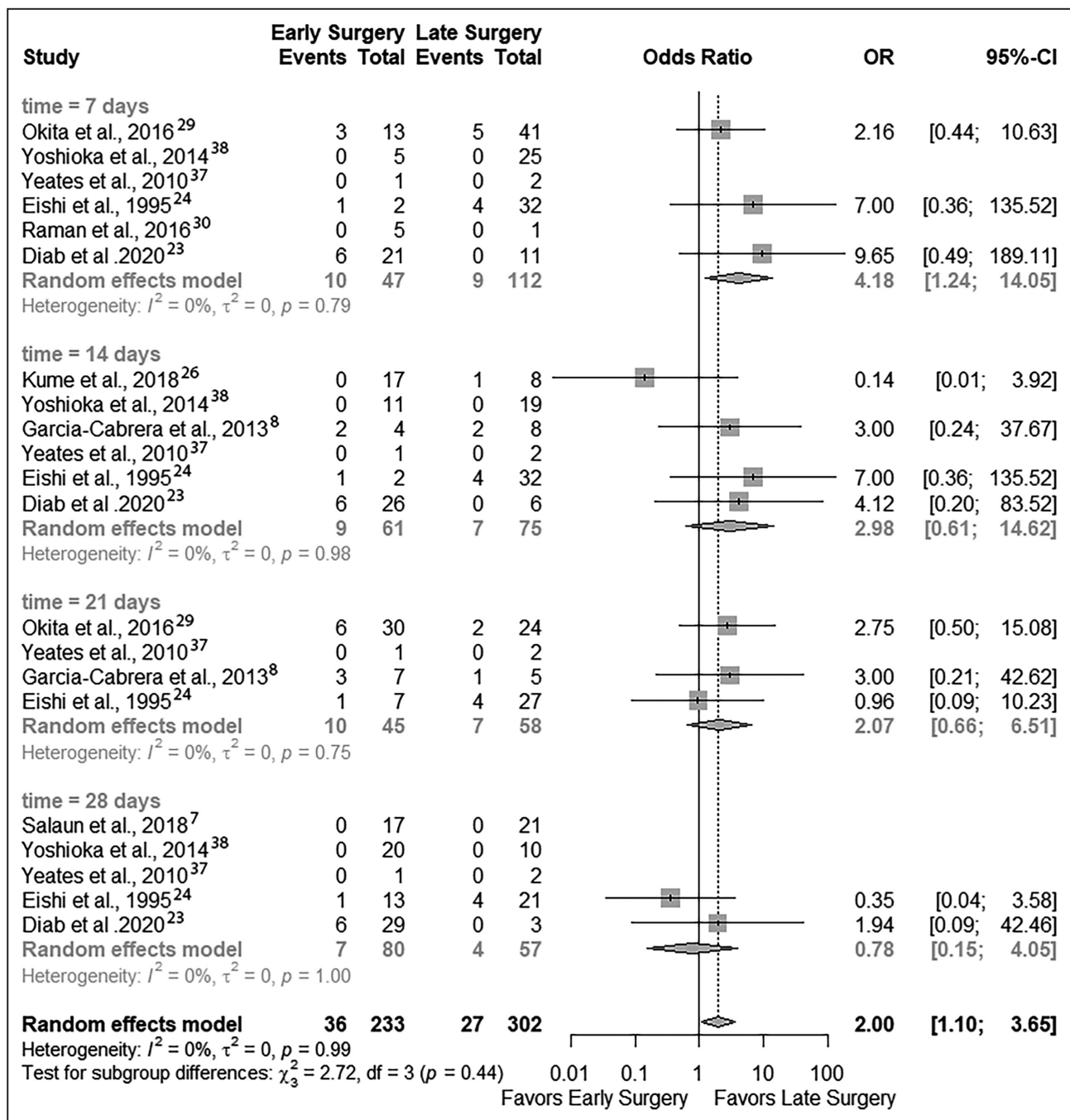


Figure 3. Forest plot of combined postoperative end point 2 (neurological deterioration) in patients with infective endocarditis and with preoperative intracranial hemorrhage (ICH) who underwent early vs late valve surgery.

Studies were pooled into subgroups based on their definition of early and late surgery (<7 vs >7 days of ICH onset; <14 vs >14 days of ICH onset; <21 vs >21 days of ICH onset; <28 vs >28 days of ICH onset). Odds ratios (ORs) summarizing cumulative effects for all different time points were presented.

Furthermore, the recommendations of the current guidelines^{1,2} to delay surgery for at least 30 days in IE complicated with ICH are based on retrospective studies, including limited numbers of patients.^{23,33,34} The largest of these studies is a multicenter study investigating the impact of neurological complications on outcome in 1345 patients with IE.⁸ However, in this

study, only 60 patients had a preoperative ICH and only 12 of them underwent surgery. Early mortality was reported in 3 of 4 patients, 2 of 3 patients, and 2 of 5 patients when surgery was performed within the first 2 weeks, in the third week, or after 3 weeks, respectively. Because of the limited evidence from this study and 2 new studies reporting a relatively low risk of

neurological deterioration in patients with IE undergoing surgery within 2 weeks after ICH,^{31,33} the European Society of Cardiology Task Force (2015) has decided to adapt the level of evidence to a class IIa recommendation for delayed surgery.² They further recommended, in case of urgent surgical indication, the mandatory implementation of a multidisciplinary approach within the endocarditis team. This recommendation is considered of high importance as the presence of ICH in IE reflects the disease severity,³⁷ and therefore necessitates a multidisciplinary approach.

It is worth noting that the term “intracranial hemorrhage” includes a wide spectrum of disease, ranging from asymptomatic microbleeds, hemorrhagic transformation of ischemic infarcts, subarachnoid hemorrhage (mostly attributable to mycotic aneurysm), and subdural hemorrhage. Notably, Salaun et al⁷ demonstrated a relation between prognosis and mechanism of hemorrhage with ICH (mycotic aneurysm, hemorrhagic transformation, or undetermined cause). They found that patients with ICH of undetermined cause had significantly higher postoperative mortality rates overall. However, most existing studies do not offer a clear definition of the characterization or intensity of the included ICH. This heterogeneity in presentation carries the risk of selection bias as well. Therefore, decisions on surgical timing in this group of patients are based on observational data, which are influenced by differences in presentation. This potentially confounds associations between surgical timing and clinical outcomes. In addition, another common limitation in most observational studies comparing early versus late surgery is the immortal-time bias,¹⁰ as previously mentioned. This leads to a speculative interpretation of a causal relationship between surgical timing and clinical outcomes.

The only available meta-analysis comparing the impact of surgical timing in IE complicated by neurological events, including ICH, was published by Tam et al (2018).³⁸ The study found no overall difference in postoperative neurologic deterioration or perioperative mortality when early surgery, regardless of its definition, was performed ($P=0.27$ and $P=0.47$, respectively). However, when they compared the subgroups of <28 and <21 days, they found a trend favoring delaying surgery up until 21 days, but not 28 days, based on small number of studies. Therefore, the authors recommended delaying the surgery for 21 days, if the clinical status allows. However, the authors of this meta-analysis also reported that early surgery was performed for clinical deterioration, which may have caused a selection bias and negatively influenced the outcomes in favor of late surgery.

In our systematic review, we demonstrated a growing body of literature challenging the current paradigm that surgery within 30 days of the onset of ICH

is associated with high mortality rates and neurologic exacerbation. Of the 16 studies included in the qualitative analysis, 13 studies^{7,23–26,29–36} found no association between neurological deterioration and early surgery, regardless of its definition (<7, 14, 21, or 28 days). Shang et al found even that early and aggressive surgery was associated with low rates of mortality. This study reported that unless the patient was comatose, the operation was not delayed because of neurologic symptoms or abnormalities on brain imaging, like cerebral infarction or subarachnoid blood, with the exception of larger hematomas (>2 cm).³¹ Okita et al²⁸ and Diab et al²² reported that only early surgery (within 7 days) might be associated with an increased rate of mortality and postoperative neurological deterioration; however, the difference was not statistically significant ($P=0.1$ and $P=0.24$, respectively). Involvement of interdisciplinary endocarditis team, including neurologists, neurosurgeons, and neuroradiologists, in IE cases with ICH should be encouraged to reduce “single specialist” bias.

Overall, the current guidelines are based on few numbers of observational studies, which are mostly subjected to selection and immortal-time bias. Moreover, most studies neither include a clear characterization of the hemorrhagic lesions nor the surgical indication of the patients operated on early. This often leads to a treatment selection bias in which more severely affected patients, who are more likely to have poorer outcomes, are operated on earlier. This negatively biases the outcome against performing early surgery. Moreover, the presence of frailty syndrome, defined as age-associated decline in physiological reserve and function of many organs, is an additional risk factor for suboptimal outcomes in patients undergoing cardiac surgery.^{39,40} Identifying patients with frailty before cardiac surgery may be relevant in decision making in patients undergoing surgery for IE. In a recent study, the 5-item FRAIL scale (fatigue, resistance, ambulation, illness, and loss of weight) was shown to be an independent predictor of 30-day mortality in patients undergoing heart valve surgery.^{41,42} None of the included studies in the meta-analyses assessed frailty syndrome.

Limitations

This work has the intrinsic limitations of trial-level meta-analysis of observational series, including the risk of methodological heterogeneity of the included studies and residual confounding. In addition, a treatment allocation bias/selection bias is likely present in all observational series comparing patients with different operative risk (patients who were operated on early often had urgent/emergent surgical indications and represent a higher-risk population). There was also a

concern of survivor bias in the late surgery cohort, and we do not know how many patients died while awaiting candidacy for surgery. Similarly, most studies did not report mortality among the patients who were treated conservatively without surgery. Another limitation was the lack of assessment of frailty syndrome in the included studies. This could have led to a better interpretation of our results.

CONCLUSIONS

Cardiac surgery for IE within 30 days of ICH was not significantly associated with higher mortality, but with an increased rate of neurological deterioration. The 30-day mortality in patients with IE with ICH who were denied surgery has not yet been sufficiently investigated. This patient population should be analyzed in more detail in future studies to provide better guidance about the surgical timing in patients with IE and with ICH.

ARTICLE INFORMATION

Received December 16, 2021; accepted March 9, 2022.

Affiliations

Department of Neurology (R.M., O.W.W., A.G.), Department of Medical Statistics, Computer Science and Data Science (P.S.), and Department of Cardiothoracic Surgery (T.C., H.K., T.D., M.D.), Jena University Hospital, Friedrich-Schiller-University Jena, Jena, Germany.

Sources of Funding

None.

Disclosures

Dr Günther received speaker's honoraria from Boehringer Ingelheim, Daichii Sankyo, Pfizer, and Ipsen. Dr Caldonazo is supported by the clinical scientist program (University Hospital of Jena). The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S3
Figures S1–S4

REFERENCES

- Baddour LM, Wilson WR, Bayer AS, Fowler VG, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486. doi: [10.1161/CIR.0000000000000296](https://doi.org/10.1161/CIR.0000000000000296)
- Habib G, Lancellotti P, Antunes MJ, Bongioni MG, Casalta J-P, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, lung B, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075–3128. doi: [10.1093/eurh/arty/ehv319](https://doi.org/10.1093/eurh/arty/ehv319)
- Ramos-Martínez A, Calderón-Parra J, Miró JM, Muñoz P, Rodríguez-Abella H, Valerio M, de Alarcón A, Luque R, Ambrosioni J, Fariñas MC, et al. Effect of the type of surgical indication on mortality in patients with infective endocarditis who are rejected for surgical intervention. *Int J Cardiol*. 2019;282:24–30. doi: [10.1016/j.ijcard.2019.01.014](https://doi.org/10.1016/j.ijcard.2019.01.014)
- Chu VH, Park LP, Athan E, Delahaye F, Freiburger T, Lamas C, Miro JM, Mudrick DW, Strahilevitz J, Tribouillet C, et al. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the international collaboration on endocarditis. *Circulation*. 2015;131:131–140. doi: [10.1161/CIRCULATIONAHA.114.012461](https://doi.org/10.1161/CIRCULATIONAHA.114.012461)
- Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, Song JM, Choo SJ, Chung CH, Song JK, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366:2466–2473. doi: [10.1056/NEJMoa1112843](https://doi.org/10.1056/NEJMoa1112843)
- Blanchard V, Pagis B, Richaud R, Moronval F, Lutinier R, Gallais K, Le Goanvic C, Fontan A, Girardot S, Ah-Kang F, et al. Infective endocarditis in French Polynesia: epidemiology, treatments and outcomes. *Arch Cardiovasc Dis*. 2020;113:252–262. doi: [10.1016/j.acvd.2019.12.007](https://doi.org/10.1016/j.acvd.2019.12.007)
- Salaun E, Touil A, Hubert S, Casalta J-P, Gouriet F, Robinet-Borgomano E, Doche E, Laksiri N, Rey C, Lavoute C, et al. Intracranial haemorrhage in infective endocarditis. *Arch Cardiovasc Dis*. 2018;111:712–721. doi: [10.1016/j.acvd.2018.03.009](https://doi.org/10.1016/j.acvd.2018.03.009)
- García-Cabrera E, Fernández-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, Lomas JM, Gálvez-Acebal J, Hidalgo-Tenorio C, Ruiz-Morales J, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation*. 2013;127:2272–2284. doi: [10.1161/CIRCULATIONAHA.112.000813](https://doi.org/10.1161/CIRCULATIONAHA.112.000813)
- Venn RA, Ning M, Vlahakes GJ, Wasfy JH. Surgical timing in infective endocarditis complicated by intracranial hemorrhage. *Am Heart J*. 2019;216:102–112. doi: [10.1016/j.ahj.2019.07.011](https://doi.org/10.1016/j.ahj.2019.07.011)
- Yadav K, Lewis RJ. Immortal time bias in observational studies. *JAMA*. 2021;325:686–687. doi: [10.1001/jama.2020.9151](https://doi.org/10.1001/jama.2020.9151)
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*. 2009;6:e1000097. doi: [10.1371/journal.pmed.1000097](https://doi.org/10.1371/journal.pmed.1000097)
- Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The newcastle-ottawa scale (nos) for assessing the quality of non-randomized studies in meta-analysis. 2000.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634. doi: [10.1136/bmj.315.7109.629](https://doi.org/10.1136/bmj.315.7109.629)
- Jackson D, Law M, Stijnen T, Viechtbauer W, White IR. A comparison of seven random-effects models for meta-analyses that estimate the summary odds ratio. *Stat Med*. 2018;37:1059–1085. doi: [10.1002/sim.7588](https://doi.org/10.1002/sim.7588)
- Stijnen T, Hamza TH, Özdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med*. 2010;29:3046–3067. doi: [10.1002/sim.4040](https://doi.org/10.1002/sim.4040)
- Platt RW, Leroux BG, Breslow N. Generalized linear mixed models for meta-analysis. *Stat Med*. 1999;18:643–654. doi: [10.1002/\(SICI\)1097-0258\(19990330\)18:6<643:AID-SIM76>3.0.CO;2-M](https://doi.org/10.1002/(SICI)1097-0258(19990330)18:6<643:AID-SIM76>3.0.CO;2-M)
- Ioannidis J. Interpretation of tests of heterogeneity and bias in meta-analysis. *J Eval Clin Pract*. 2008;14:951–957. doi: [10.1111/j.1365-2753.2008.00986.x](https://doi.org/10.1111/j.1365-2753.2008.00986.x)
- Pandis N. The chi-square test. *Am J Orthod Dentofacial Orthop*. 2016;150:898–899. doi: [10.1016/j.ajodo.2016.08.009](https://doi.org/10.1016/j.ajodo.2016.08.009)
- Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22:153. doi: [10.1136/ebmental-2019-300117](https://doi.org/10.1136/ebmental-2019-300117)
- Viechtbauer W. Conducting meta-analyses in R with the Metafor package. *J Stat Softw*. 2010;36:1–48.
- Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67:1–48.
- Diab M, Musleh R, Lehmann T, Sponholz C, Pletz MW, Franz M, Schulze PC, Witte OW, Kirchhof K, Doenst T, et al. Risk of postoperative neurological exacerbation in patients with infective endocarditis and intracranial haemorrhage. *Eur J Cardiothorac Surg*. 2020. doi: [10.1093/ejcts/ezaa347](https://doi.org/10.1093/ejcts/ezaa347)
- Eishi K, Kawazoe K, Kuriyama Y, Kitoh Y, Kawashima Y, Omae T. Surgical management of infective endocarditis associated with cerebral complications. Multi-center retrospective study in Japan. *J Thorac Cardiovasc Surg*. 1995;110:1745–1755. doi: [10.1016/S0022-5223\(95\)70038-2](https://doi.org/10.1016/S0022-5223(95)70038-2)
- Gillinov AM, Shah RV, Curtis WE, Stuart RC, Cameron DE, Baumgartner WA, Greene PS. Valve replacement in patients with endocarditis and acute neurologic deficit. *Ann Thorac Surg*. 1996;61:1125–1129. discussion 1130. doi: [10.1016/0003-4975\(96\)00014-8](https://doi.org/10.1016/0003-4975(96)00014-8)
- Kume Y, Fujita T, Fukushima S, Shimahara Y, Matsumoto Y, Yamashita K, Kawamoto N, Kobayashi J. Intracranial mycotic aneurysm is associated

- with cerebral bleeding post-valve surgery for infective endocarditis. *Interact Cardiovasc Thorac Surg*. 2018;27:635–641. doi: [10.1093/icvts/ivy126](https://doi.org/10.1093/icvts/ivy126)
26. Lee HA, Lin CY, Chen YC, Chen SW, Nan YY, Liu KS, Wu MY, Chang YS, Chu JJ, Lin PJ, et al. Surgical interventions of isolated active mitral valve endocarditis: predisposing factors and impact of neurological insults on final outcome. *Medicine (Baltimore)*. 2018;97:e0054. doi: [10.1097/MD.00000000000010054](https://doi.org/10.1097/MD.00000000000010054)
 27. Oh TH, Wang TK, Pemberton JA, Raudkivi PJ. Early or late surgery for endocarditis with neurological complications. *Asian Cardiovasc Thorac Ann*. 2016;24:435–440. doi: [10.1177/0218492316646903](https://doi.org/10.1177/0218492316646903)
 28. Okita Y, Minakata K, Yasuno S, Uozumi R, Sato T, Ueshima K, Konishi H, Morita N, Harada M, Kobayashi J, et al. Optimal timing of surgery for active infective endocarditis with cerebral complications: a Japanese Multicentre Study. *Eur J Cardiothorac Surg*. 2016;50:374–382. doi: [10.1093/ejcts/ezw035](https://doi.org/10.1093/ejcts/ezw035)
 29. Raman J, Ballal A, Hota B, Mirza S, Lai D, Bleck T, Lateef O. Reconstructive valve surgery within 10 days of stroke in endocarditis. *Asian Cardiovasc Thorac Ann*. 2016;24:523–529. doi: [10.1177/0218492316652746](https://doi.org/10.1177/0218492316652746)
 30. Ruttman E, Willeit J, Ulmer H, Chevchik O, Höfer D, Poewe W, Laufer G, Müller LC. Neurological outcome of septic cardioembolic stroke after infective endocarditis. *Stroke*. 2006;37:2094–2099. doi: [10.1161/01.STR.0000229894.28591.3f](https://doi.org/10.1161/01.STR.0000229894.28591.3f)
 31. Shang E, Forrest GN, Chizmar T, Chim J, Brown JM, Zhan M, Zoarski GH, Griffith BP, Gammie JS. Mitral valve infective endocarditis: benefit of early operation and aggressive use of repair. *Ann Thorac Surg*. 2009;87:1728–1734. doi: [10.1016/j.athoracsur.2009.02.098](https://doi.org/10.1016/j.athoracsur.2009.02.098)
 32. Wan S, Sung K, Park PW, Kim WS, Lee YT, Jun TG, Yang JH, Jeong DS, Cho YH. Stroke is not a treatment dilemma for early valve surgery in active infective endocarditis. *J Heart Valve Dis*. 2014;23:609–616.
 33. Wilbring M, Alexiou K, Tuan Nguyen M, Kappert U, Matschke K, Malte TS. Clinical course after surgical treatment of active isolated native mitral valve endocarditis. *J Cardiovasc Surg (Torino)*. 2014;55:279–286.
 34. Yoshioka D, Toda K, Sakaguchi T, Okazaki S, Yamauchi T, Miyagawa S, Nishi H, Yoshikawa Y, Fukushima S, Saito T, et al. Valve surgery in active endocarditis patients complicated by intracranial haemorrhage: the influence of the timing of surgery on neurological outcomes. *Eur J Cardiothorac Surg*. 2014;45:1082–1088. doi: [10.1093/ejcts/ezt547](https://doi.org/10.1093/ejcts/ezt547)
 35. Zhang LQ, Cho SM, Rice CJ, Khoury J, Marquardt RJ, Buletko AB, Hardman J, Wisco D, Uchino K. Valve surgery for infective endocarditis complicated by stroke: surgical timing and perioperative neurological complications. *Eur J Neurol*. 2020;27:2430–2438. doi: [10.1111/ene.14438](https://doi.org/10.1111/ene.14438)
 36. Yeates A, Mundy J, Griffin R, Marshall L, Wood A, Peters P, Shah P. Early and mid-term outcomes following surgical management of infective endocarditis with associated cerebral complications: a single centre experience. *Heart Lung Circ*. 2010;19:523–527. doi: [10.1016/j.hlc.2010.03.004](https://doi.org/10.1016/j.hlc.2010.03.004)
 37. Sonneviller R, Mourvillier B, Bouadma L, Wolff M. Management of neurological complications of infective endocarditis in ICU patients. *Ann Intensive Care*. 2011;1:10. doi: [10.1186/2110-5820-1-10](https://doi.org/10.1186/2110-5820-1-10)
 38. Tam DY, Yanagawa B, Verma S, Ruel M, Fremes SE, Mazine A, Adams S, Friedrich JO. Early vs late surgery for patients with endocarditis and neurological injury: a systematic review and meta-analysis. *Can J Cardiol*. 2018;34:1185–1199. doi: [10.1016/j.cjca.2018.05.010](https://doi.org/10.1016/j.cjca.2018.05.010)
 39. Afilalo J, Eisenberg MJ, Morin J-F, Bergman H, Monette J, Noiseux N, Perrault LP, Alexander KP, Langlois Y, Dendukuri N, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol*. 2010;56:1668–1676. doi: [10.1016/j.jacc.2010.06.039](https://doi.org/10.1016/j.jacc.2010.06.039)
 40. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation*. 2010;121:973–978. doi: [10.1161/CIRCULATIONAHA.108.841437](https://doi.org/10.1161/CIRCULATIONAHA.108.841437)
 41. World Health O. Who clinical consortium on healthy ageing: Topic focus: Frailty and intrinsic capacity: Report of consortium meeting, 1–2 December 2016 in Geneva, Switzerland. 2017.
 42. Duchnowski P, Szymański P, Kuśmierczyk M, Hryniewiecki T. Usefulness of frail scale in heart valve diseases. *Clin Interv Aging*. 2020;15:1071–1075. doi: [10.2147/CIA.S239054](https://doi.org/10.2147/CIA.S239054)

SUPPLEMENTAL MATERIAL

Table S1. Risk of bias assessed based on Newcastle-Ottawa assessment scale (NOS).

Observational study	Selection	Comparability	Outcome
Diab et al., 2020	****	**	**
Saluan et al., 2018	**	*	***
Kume et al., 2018	***	**	***
Okita et al., 2016	****	**	***
Yoshioka et al., 2014	****	**	***
Yeates et al., 2010	**	*	**
Eishi et al., 1995	***	*	**
Raman et al., 2016	**	*	**
Garcia-Cabrera et al., 2013	**	*	**

A study can be awarded a maximum of one star for each numbered item within the Selection (max 4*) and Outcome (max 3*) categories. A maximum of two stars can be given for Comparability.

Table S2. Demographic patient's characteristics of the nine observational studies included in the final analyses.

Observational study	Type of study	ICH patients (n)	Patients (n)		Definition of early/late surgery		Sex; n (m/f)	Age (mean \pm SD) or median (IQR), years	Preoperative features			Indication for surgery			
			Early	Late	Early	Late			Valve involvement (%)	Large vegetation (> 10-15mm) in n (%)	Staphylococci-n (%)	EuroSCORE II (%); mean \pm SD or median (IQR)	Heart Failure (NYHA class 3-4)	Uncontrolled infection	high embolic risk
Diab et al., 2020	single centre	34	21	11	≤ 7 d	8-14; 15-28, >28	m/f: 30/4	61 (47–71)	M-24%, A-35%, B-41%	21 (66 %)	15 (44 %)	25 (9–42)	19 (56 %)	7 (21%)	8 (24%)
Saluan et al., 2018	single centre	38	17	21	≤ 28 d	>28 d	-	-	-	-	-	-	-	-	-
Kume et al., 2018	single centre	25	17	8	<14 d	> 14 d	m/f: 20/5	56.8 \pm 20.1	A-24%, M-76%, T-12%	-	-	11.8 \pm 11.5	13 (31%)	-	-
Okita et al., 2016	multicentre	54	13	41	≤ 7 d	8-21; >21	m/f: 34/20	54.5 \pm 17.4	A-37%, M-70%	26 (48%)	38 (32%)	-	26 (22%)	14 (12%)	70 (59%)
Yoshioka et al., 2014	single centre	30	5	25	≤ 7 d	8-14; 15-28, >28	m/f: 17/13	62 (51–63)	A-20%, M-66%, B-13%	9 (30%)	14 (46%)	-	-	-	-
Yeates et al., 2010	single centre	3	1	2	<14 d	> 14 d	-	-	A.25%, B-75%	-	-	-	-	-	-
Eishi et al., 1995	multicentre	34	2	32	not clear (<1, <14, <28d)		-	-	-	-	-	-	-	-	-
Raman et al., 2016	single centre	6	5	1	≤ 7 d	8-10 d	m/f: 5/1	-	M-66.7%, B-33.3%	5 (83%)	-	-	-	-	-
Garcia-Cabrera et al., 2013	multicentre	12	4	8	≤ 14 d	15-21; >21 d	-	-	-	19 (4%)	-	-	-	-	-

IQR: interquartile range; SD: standard deviation; m: male; f: female; A: aortic; M: mitral; T, tricuspid; B: both/multiple; NYHA: New York Heart Association.

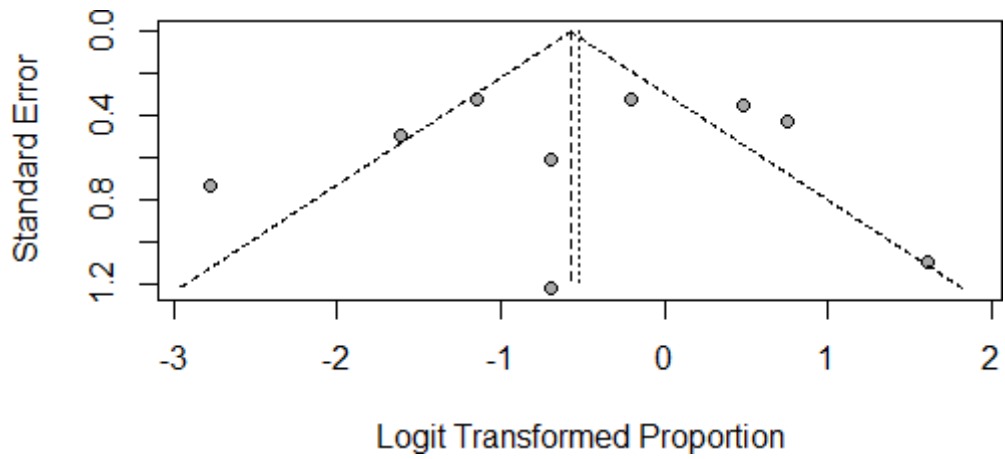
Table S3. Results of generalized linear mixed model with covariates early vs. late surgery and time point.

Characteristic	All-cause mortality		Neurological deterioration	
	OR (95% CI) ¹	p-value	OR (95% CI) ¹	p-value
Early				
Late	—		—	
Early	1.68 (0.95 to 2.98)	0.074	2.28 (1.18 to 4.39)	0.014
<i>Time point:</i>				
7 days	—		—	
14 days	1.08 (0.54 to 2.13)	0.83	0.94 (0.41 to 2.14)	0.89
21 days	0.97 (0.44 to 2.14)	0.93	0.86 (0.39 to 1.92)	0.72
28 days	0.90 (0.44 to 1.85)	0.77	0.72 (0.29 to 1.77)	0.47
Heterogeneity	Tau2= 0.69		Tau2= 2.97	
LRS early vs. late	0.26, df= 3, p = 0.96		0.61, df =3, p = 0.89	

OR = Odds Ratio; CI = Confidence Interval; Tau2: Heterogeneity variance; LRS = Likelihood Ratio Test

Figure S1. Publication bias tests: (A) Funnel plot; (B) Egger's linear regression test.

A



B

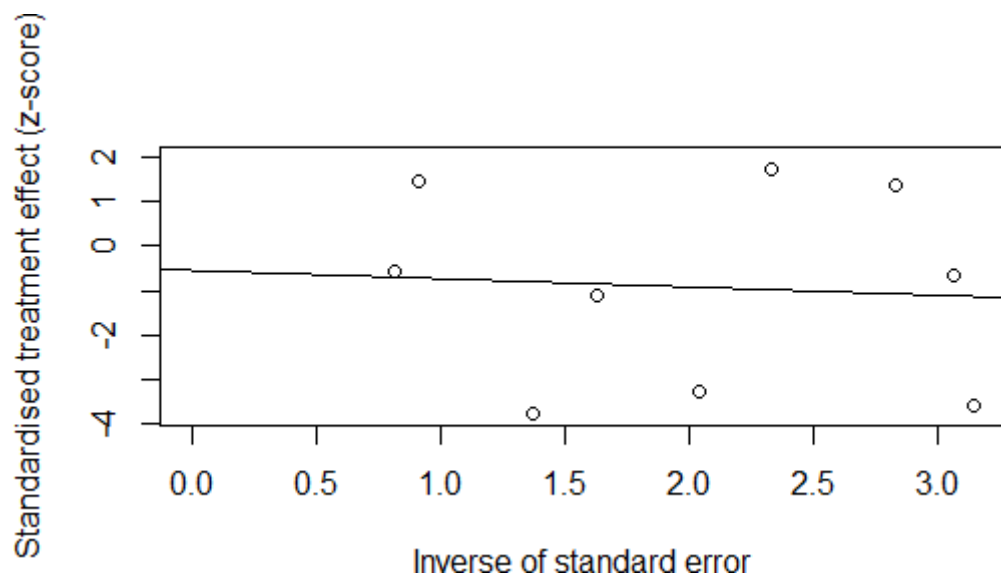


Figure S2. Kaplan-Meier Curve extracted from available studies in literature comparing the cumulative survival of IE-patients with an indication of surgery who were treated surgically vs. conservatively.

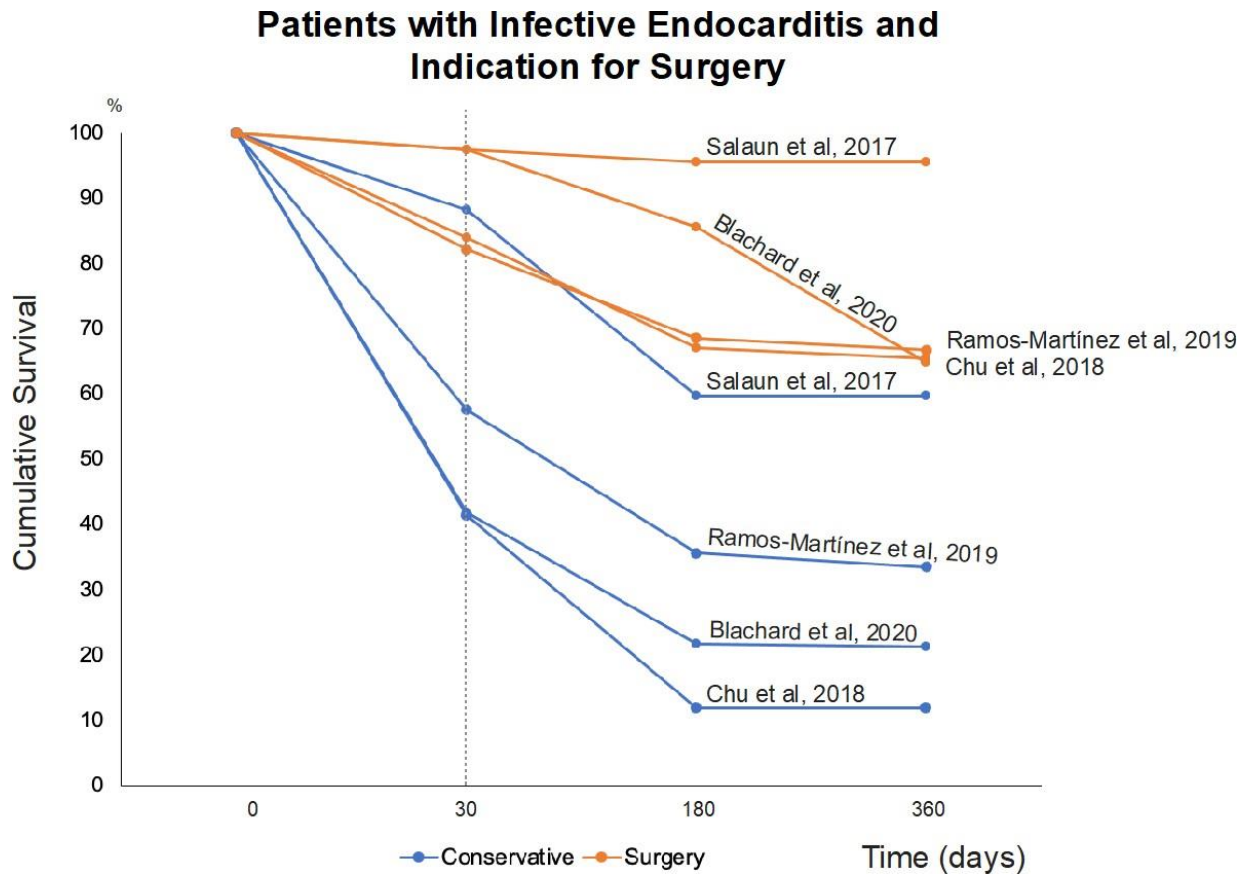


Figure S3. Forest plot of postoperative endpoint 1 (all-cause mortality within 30 days) in IE-patients with preoperative ICH who underwent early vs. late valve surgery with random slope and intercept model (RSM).

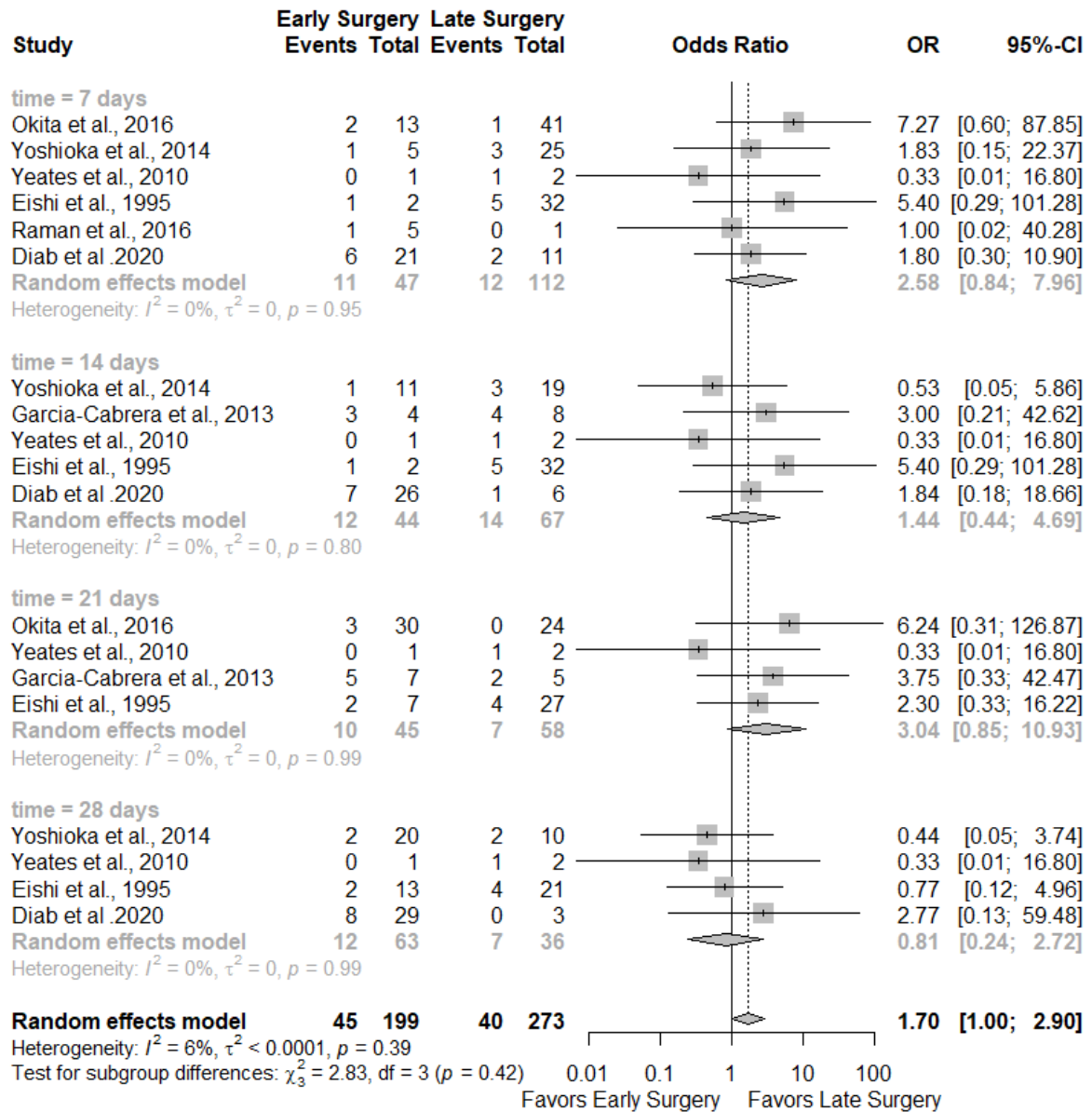


Figure S4. Forest plot of combined postoperative endpoint 2 (neurological deterioration) in IE-patients with preoperative ICH who underwent early vs. late valve surgery with random slope and intercept model (RSM).

