SYSTEMATIC REVIEW AND META-ANALYSIS

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

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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

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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.

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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 died 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.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description                 |
|--------------|-----------------------------|
| ICH          | intracranial hemorrhage     |
| IE           | infective endocarditis      |

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
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. For dichotomous outcomes, odds ratios (ORs) were calculated for every single study by means of 2×2 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. 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 \( \chi^2 \) 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,7 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 studies7,23–26,29–36 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 mortality,28 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 al7 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, 1.00–2.98) for random slope and intercept model and to an OR of 1.68 (95% CI, 0.95–2.98) for random intercept 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
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 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. 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). |
| 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). |
| 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 d (n=17)        | |
|                   |                                      | >21 d (n=24)         | |
| Raman (2016)²⁹     | 6                                    | ≤10 d                | No neurological deterioration regardless of the surgical timing. |
|                   |                                      | <7 d (n=5)           | |
| Yoshioka (2014)³⁴  | 30                                   | 8–14 d (n=8)         | 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)³⁷ | 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. |
|                   |                                      | 2–28 d (n=12)        | 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. |
|                   |                                      | >28 d (n=21)         | |

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

register “ICE-PLUS (International Collaboration on Endocarditis-PLUS),” 863 patients with IE had an indication for surgery.¹⁴ 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 IE¹¹,¹²: 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...
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 than in operated on patients.7

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.
Furthermore, the recommendations of the current guidelines\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. The European Society of Cardiology Task Force (2015) has decided to adapt the level of evidence to a class IIa recommendation for delayed surgery. 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 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 al 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, 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). 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 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). Okita et al and Diab et al 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. 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. 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
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.
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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., 204      | *****     | **            | ***     |
| 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 | Age (mean ± SD or median (IQR), years) | Preoperative features | EuroSCORE II (%); mean ± SD or median (IQR) | Indication for surgery |
|----------------------|---------------|------------------|--------------|----------------------------------|----------------------------------------|----------------------|-------------------------------------------|-----------------------|
| Diab et al., 2020    | single centre | 34               | 21           | ≤7 d                             | 8-14; 15-28, >28                       | m/f: 30/4             | 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           | >28 d                            | -                                      | -                     | -                                         | -                     | -         | -         | -         | -         | -         |
| Kume et al., 2018    | single centre | 25               | 17           | <14 d                            | > 14 d                                 | m/f: 20/5              | A-24%, M-76%, T-12%                      | -                     | -         | 11.8 ± 11.5 | 13 (31%) | -         | -         |
| Okita et al., 2016   | multicentre   | 54               | 13           | ≤7 d                             | 8-21; >21                             | m/f: 34/20             | A-37%, M-70%                             | 26 (48%)              | 38 (32%) | -         | 26 (22%) | 14 (12%) | 70 (59%) |
| Yoshioka et al., 2014| single centre | 30               | 5            | ≤7 d                             | 8-14; 15-28, >28                       | m/f: 17/13             | A-20%, M-66%, B-13%                      | 9 (30%)               | 14 (46%) | -         | -         | -         | -         |
| Yeates et al., 2010  | single centre | 3                | 1            | <14 d                            | > 14 d                                 | -                     | A-25%, B-75%                             | -                     | -         | -         | -         | -         | -         |
| Eishi et al., 1995   | multicentre   | 34               | 2            | not clear ( <1, <14, <28d )      | -                                      | -                     | -                                         | -                     | -         | -         | -         | -         | -         |
| Raman et al., 2016   | single centre | 6                | 5            | ≤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            | ≤14 d                            | 15-21; >21                            | -                     | -                                         | 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) / p-value | OR (95% CI) / p-value     |
| Early             |                     |                           |
| Late              | —                   | —                         |
| Early             | 1.68 (0.95 to 2.98) / 0.074 | 2.28 (1.18 to 4.39) / 0.014 |
| Time point:       |                     |                           |
| 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.
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).

| Study                      | Early Surgery | Late Surgery | Odds Ratio | OR  | 95%-CI    |
|----------------------------|---------------|--------------|------------|-----|-----------|
| time = 7 days              |               |              |            |     |           |
| Okita et al., 2016         | 2             | 13           | 1          | 41  | 7.27 [0.60; 87.85] |
| Yoshioka et al., 2014      | 1             | 5            | 5          | 25  | 1.83 [0.15; 22.37] |
| Yeates et al., 2010        | 0             | 1            | 1          | 2   | 0.33 [0.01; 16.80] |
| Eishi et al., 1995         | 1             | 2            | 2          | 5   | 5.40 [0.29; 101.28] |
| Raman et al., 2016         | 1             | 5            | 5          | 32  | 1.00 [0.02; 40.26] |
| Diab et al., 2020          | 6             | 21           | 2          | 11  | 1.80 [0.30; 10.90] |
| Random effects model       | 11            | 47           | 12         | 112 | 2.58 [0.84; 7.96]   |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.95$ |

| time = 14 days             |               |              |            |     |           |
| Yoshioka et al., 2014      | 1             | 11           | 3          | 19  | 0.53 [0.05; 5.86]   |
| Garcia-Cabrera et al., 2013| 3             | 4            | 4          | 8   | 3.00 [0.21; 42.62] |
| Yeates et al., 2010        | 0             | 1            | 1          | 2   | 0.33 [0.01; 16.80] |
| Eishi et al., 1995         | 1             | 2            | 2          | 5   | 5.40 [0.29; 101.28] |
| Diab et al., 2020          | 7             | 26           | 1          | 6   | 1.84 [0.18; 18.68] |
| Random effects model       | 12            | 44           | 14         | 67  | 1.44 [0.44; 4.69]   |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.80$ |

| time = 21 days             |               |              |            |     |           |
| Okita et al., 2016         | 3             | 30           | 0          | 24  | 6.24 [0.31; 126.87] |
| Yeates et al., 2010        | 0             | 1            | 1          | 2   | 0.33 [0.01; 16.80] |
| Garcia-Cabrera et al., 2013| 5             | 7            | 2          | 5   | 3.75 [0.33; 42.47] |
| Eishi et al., 1995         | 2             | 7            | 2          | 5   | 2.30 [0.33; 16.22] |
| Random effects model       | 10            | 45           | 7          | 58  | 3.04 [0.85; 10.93] |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.99$ |

| time = 28 days             |               |              |            |     |           |
| Yoshioka et al., 2014      | 2             | 20           | 2          | 10  | 0.44 [0.05; 3.74]   |
| Yeates et al., 2010        | 0             | 1            | 1          | 2   | 0.33 [0.01; 16.80] |
| Eishi et al., 1995         | 2             | 13           | 4          | 21  | 0.77 [0.12; 4.96] |
| Diab et al., 2020          | 8             | 29           | 0          | 3   | 2.77 [0.13; 59.48] |
| Random effects model       | 12            | 63           | 7          | 36  | 0.81 [0.24; 2.72]   |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.99$ |

Random effects model

Heterogeneity: $I^2 = 6\%$, $\tau^2 < 0.0001$, $p = 0.39$

Test for subgroup differences: $\chi^2 = 2.83$, df = 3 ($p = 0.42$)

Favors Early Surgery Favors Late Surgery

1 0.01 0.1 1 10 100
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).

| Study            | Early Surgery | Late Surgery | Odds Ratio | OR  | 95% CI |
|------------------|---------------|--------------|------------|-----|--------|
| time = 7 days    |               |              |            |     |        |
| Okita et al., 2016 | 3             | 13           | 2.16       | [0.44; 10.63] |
| Yoshoka et al., 2014 | 0             | 5            | [0.36; 135.52] |
| Yeates et al., 2010 | 0             | 1            | [0.24; 37.67] |
| Eishi et al., 1995 | 1             | 2            | 7.00       | [0.49; 189.11] |
| Raman et al., 2016 | 0             | 5            | 9.65       | [0.20; 83.52] |
| Diab et al. 2020 | 6             | 21           | 4.18       | [1.24; 14.05] |
| Random effects model | 10         | 47           | 4.18       | [1.24; 14.05] |
| Heterogeneity: I² = 0%, τ² = 0, p = 0.79 |

| time = 14 days   |               |              |            |     |        |
| Kume et al., 2018 | 0             | 17           | 0.14       | [0.01; 3.92] |
| Yoshoka et al., 2014 | 0             | 11           | 3.00       | [0.24; 37.67] |
| Garcia-Cabrera et al., 2013 | 2             | 4            | 7.00       | [0.36; 135.52] |
| Yeates et al., 2010 | 0             | 1            | 4.12       | [0.20; 83.52] |
| Eishi et al., 1995 | 1             | 2            | 4.12       | [0.20; 83.52] |
| Diab et al. 2020 | 6             | 26           | 2.98       | [0.61; 14.62] |
| Random effects model | 9             | 61           | 2.98       | [0.61; 14.62] |
| Heterogeneity: I² = 0%, τ² = 0, p = 0.98 |

| time = 21 days   |               |              |            |     |        |
| Okita et al., 2016 | 6             | 30           | 2.75       | [0.50; 15.08] |
| Yeates et al., 2010 | 0             | 1            | 3.00       | [0.21; 42.62] |
| Garcia-Cabrera et al., 2013 | 3             | 7            | 0.96       | [0.09; 10.23] |
| Eishi et al., 1995 | 1             | 7            | 2.07       | [0.66; 6.61] |
| Random effects model | 10          | 45           | 2.07       | [0.66; 6.61] |
| Heterogeneity: I² = 0%, τ² = 0, p = 0.75 |

| time = 28 days   |               |              |            |     |        |
| Salsun et al., 2018 | 0             | 17           | 0.35       | [0.04; 3.58] |
| Yoshoka et al., 2014 | 0             | 20           | 1.94       | [0.09; 42.48] |
| Yeates et al., 2010 | 0             | 1            | 0.78       | [0.15; 4.05] |
| Eishi et al., 1995 | 1             | 13           | 0.78       | [0.15; 4.05] |
| Diab et al. 2020 | 6             | 29           | 1.94       | [0.09; 42.48] |
| Random effects model | 7             | 80           | 1.94       | [0.09; 42.48] |
| Heterogeneity: I² = 0%, τ² = 0, p = 1.00 |

Random effects model | 36            | 233          | 1.89       | [1.09; 3.25] |

Test for subgroup differences: $\chi^2 = 2.72$, df = 3 ($p = 0.44$)