Meta-analysis of the effect of the pringle maneuver on long-term oncological outcomes following liver resection

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Hepatic pedicle clamping reduces intraoperative blood loss and the need for transfusion, but its long-term effect on survival and recurrence remains controversial. The aim of this meta-analysis was to evaluate the effect of the Pringle maneuver (PM) on long-term oncological outcomes in patients with primary or metastatic liver malignancies who underwent liver resection. Literature was searched in the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (via PubMed), and Web of Science databases. Survival was measured as the survival rate or as a continuous endpoint. Pooled estimates were represented as odds ratios (ORs) using the Mantel–Haenszel test with a random-effects model. The literature search retrieved 435 studies. One RCT and 18 NRS, including 7480 patients who underwent liver resection with the PM (4309 cases) or without the PM (3171 cases) were included. The PM did not decrease the 1-year overall survival rate (OR 0.86; 95% CI 0.67–1.09; P = 0.22) or the 3- and 5-year overall survival rates. The PM did not decrease the 1-year recurrence-free survival rate (OR 1.06; 95% CI 0.75–1.50; P = 0.75) or the 3- and 5-year recurrence-free survival rates. There is no evidence that the Pringle maneuver has a negative effect on recurrence-free or overall survival rates.

Liver resection remains the only curative treatment for hepatic malignancies, and can improve long-term survival1. Improvements in surgical techniques, better selection of patients, and improved perioperative care have increased the number of hepatectomies performed worldwide each year1,2. There is growing evidence that excessive blood loss during hepatectomy and the subsequent need for blood transfusions may contribute to a poor outcome for non-cirrhotic and cirrhotic liver resections1,2. Perioperative blood transfusion has been associated with recurrence and poorer long-term survival due to an immune response dysfunction3.

Vascular occlusion techniques have been used by some surgeons during hepatic resection to minimize intraoperative blood loss, especially in large tumors or tumors that are adjacent to major vessels4,5. Pringle described a technique whereby transient hepatic inflow was occluded by clamping the portal triad. Portal clamping in the Pringle maneuver (PM) has been modified several times in form of intermittent portal clamping6,7 and selective portal clamping8. These modifications can control intraoperative blood loss and decrease the need for transfusion. Some surgeons believe that this reduction in the rate of blood transfusions can improve long-term oncological outcomes. On the other hand, some argue that the PM may increase the risk of ischemia–reperfusion injury to the liver, which may impair hepatocyte function4,6,7.

The present systematic review and meta-analysis aimed to evaluate the effect of the PM on long-term oncological outcomes in patients with primary or metastatic liver malignancies who underwent liver resection.

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**Results**

**Literature search strategy and included studies.** The literature search retrieved 435 studies excluding duplicates. Of these, 416 papers were excluded for various reasons, including redundant information and insufficient data on survival. In the end, 19 articles were included in the current meta-analysis (Fig. 1). During the primary evaluation, included articles were subdivided into three groups regarding their suggestions and conclusion on the effect of PM on oncological outcomes of the patients: in favor of the PM, neutral, and not in favor of the PM (Fig. 2).

**Risk of bias assessment for included studies.** Of the 19 articles included in this meta-analysis, only one was an RCT. This study included 80 patients (39 cases with PM and 41 cases without PM). The other 18 NRS included 7400 patients (4270 cases with PM and 3130 cases without PM). All studies were published between 2002 and 2020 (Table 1). As shown in Table 2, most studies had moderate bias.

**Recurrence-free survival rate.** *One-year recurrence-free survival rate.* One-year RFS rates were reported for 6758 patients from 17 studies (4223 patients were in the PM group and 2744 patients in the non-PM group). The recurrence of malignant hepatic lesions was reported in 1023 cases (24.2%) in the PM group and in 742 cases (27%) in the non-PM group. Meta-analysis indicated that the PM did not decrease 1-year RFS rate (OR 1.06; 95% CI 0.75–1.50; P = 0.75; Fig. 3A) using a random-effects model. There was considerable heterogeneity among the studies ($I^2 = 84%$; $P < 0.00001$).

*Three-year recurrence-free survival rate.* Recurrence of malignant lesions during the first 3 years after hepatectomy was reported in 6138 cases from 15 studies. Of these, recurrence was reported in 2037 patients (54.6%) in the PM group and in 1233 patients (51.1%) in the non-PM group. Meta-analysis revealed no significant dif-

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Figure 1. PRISMA flow chart of study selection.
ference in 3-year RFS rate between the groups (OR 0.99; 95% CI 0.74–1.34; P = 0.97) using the random-effects model (Fig. 3B). The studies that reported 3-year RFS rates were not homogeneous (I² = 81%; P < 0.00001).

Five-year recurrence-free survival rate. A total of 14 studies with 3781 patients in the PM group and 2591 patients in the non-PM group reported 5-year recurrence. As is seen in Fig. 3C, recurrence was reported in 2521 patients (66.67%) in the PM group and in 1862 patients (71.86%) in the non-PM group. The meta-analysis showed that 5-year RFS rate is not significantly different between the two groups (OR 0.82; 95% CI 0.65–1.04; P = 0.1) using the random-effects model (Fig. 3C). The studies that reported 5-year RFS rates were not homogeneous (I² = 67%; P = 0.0002).

Overall survival rates. One-year overall survival rate. Fifteen studies including 5569 patients reported the 1-year OS rate. Of these, 2776 patients (87.15%) were in the PM group and 2092 patients (87.7%) were in the non-PM group. According to our analysis using the random-effects model, the 1-year OS rate was not significantly different between the PM and non-PM group (OR 0.86; 95% CI 0.67–1.09; P = 0.22) (Fig. 4A). The I² was 31% with a P value of 0.12.

Three- and five-year overall survival rates. The 3-year OS rate was 64% in the PM group and 63.6% in the non-PM group. The 5-year OS rate was 46.11% in the PM group and 42.9% in the non-PM group (Fig. 4B,C). Meta-analysis indicated that the 3- and 5-year OS rates were not significantly different between the PM and non-PM groups.

Subgroup analysis. The type of malignant tumor (i.e., primary or metastatic) had no significant effect on the 1-year RFS rate in the PM and non-PM groups (primary tumors: OR 1.16; 95% CI 0.86–1.56; P = 0.34; metastatic tumors: OR 0.82; 95% CI 0.43–1.56; P = 0.56), nor did it have an effect on the 3-year RFS rate (primary tumors: OR 0.96; 95% CI 0.68–1.37; P = 0.84; metastatic tumors: OR 1.10; 95% CI 0.60–2.02; P = 0.77) or the 5-year RFS rate (primary tumors: OR 0.84; 95% CI 0.63–1.12; P = 0.24; metastatic tumors: OR 0.77; 95% CI 0.47–1.24; P = 0.28).

The type of malignant tumor had no significant effect on the 1-year OS rate in the PM and non-PM groups (primary tumors: OR 0.87; 95% CI 0.67–1.14; P = 0.31; metastatic tumors: OR 0.74; 95% CI 0.49–1.12; P = 0.15), nor did it have an effect on the 3-year OS rate (primary tumors: OR 1.04; 95% CI 0.85–1.29; P = 0.69; metastatic
tumors: OR 1.12; 95% CI 0.72–1.76; P = 0.61) or 5-year OS rate (primary tumors: OR 1.10; 95% CI 0.88–1.38; P = 0.39; metastatic tumors: OR 0.89; 95% CI 0.62–1.28; P = 0.53) (Supplemental Figs. 1 and 2).

Table 1. Characteristics of included studies.

| Author (year) | Country | Study type | Age Sample size | Type of hepatectomy | Duration of Pringle (min) | Type of Pringle | Diagnosis |
|---------------|---------|------------|----------------|---------------------|--------------------------|----------------|-----------|
| Al-Saeedi (2020) | Germany | Retrospective cohort | 58.4 60.5 50 159 | All patients underwent extended hepatectomy | 19 | Intermittent | HCC and CRLM |
| Lee (2019) | China | Retrospective cohort | 58 60.5 88 88 | Minor: 51 (58.0%) Major: 37 (42.0%) | Mean (range) 45 (15–87) | Intermittent | HCC |
| Famularo (2018) | Italy | Retrospective cohort | 65.1 67.6 176 265 | Minor: 153 (87.4%) Major: 22 (12.6%) | Mean (range) 23 (14–30) | Intermittent | HCC |
| Jiang (2017) | China | Retrospective cohort | NA NA 132 112 | | | Intermittent | HCC |
| Xu (2019) | China | Retrospective cohort | 58 60.5 88 88 | Minor: 51 (58.0%) Major: 37 (42.0%) | | | Continuous HCC |
| Hao (2017) | China | Retrospective cohort | 52.65 55 303 52 | Minor: 122 (40%) Major: 181 (60%) | | | Intermittent HCC |
| Hao (2016) | China | Retrospective cohort | 52.65 55 206 60 | Minor: 79 (38.3%) Major: 127 (61.6%) | 29.6 | Intermittent | HCC |
| Tsang (2015) | Canada | Retrospective cohort | 63.0 63.0 110 110 | Minor: 41 (37.2%) Major: 69 (63.3%) | Mean (range) 20 (15–30) | Intermittent | CRLM |
| Huang (2014) | China | Retrospective cohort | 56.65 54.2 931 618 | Minor: 592 (63.4%) Major: 416 (44.6%) | Mean (range) 47.4 (3–208) | Intermittent | HCC |
| Weiss (2013) | USA | Retrospective cohort | 62.7 64.3 874 54 | Minor: 286 (32.7%) Major: 548 (66.8%) | Mean (range) 35 (1–181) | Prolonged, short CRLM |
| Xia (2013) | China | Prospective cohort | 48 57 224 162 | Minor: 131 (58.4%) Major: 93 (41.5%) | Mean (range) 50 (30–98) | Intermittent | HCC |
| De Carlis (2013) | Italy | Case-matched | 61 61 60 60 | Minor: 36 (60%) Major: 24 (40%) | | | CRLM |
| Ferrero (2010) | Italy | Randomized-controlled | 61.3 64.8 39 41 | Minor: 19 (48.7%) Major: 20 (51.2%) | Mean (SD) 47.8 (17.2) | Intermittent | CRLM |
| Nijkamp (2010) | Netherlands | Retrospective cohort | NA NA 50 72 | All patients underwent partial hepatectomy | 21 (2–69) and 40 (20–90) | | Intermittent, continuous CRLM |
| Giulante (2010) | Italy | Retrospective cohort | 62 ± 10 188 355 | 228 cases (42%) underwent major hepatectomy 315 cases (58%) underwent minor hepatectomy | | | CRLM |
| Wang (2009) | Taiwan | Retrospective cohort | NA NA 114 359 | | | Intermittent | HCC |
| Wong (2008) | UK | Retrospective cohort | NA NA 289 274 | Minor: 19 (48.7%) Major: 150 (51.9%) | Mean (range) 22 (2–104) | Intermittent | CRLM |
| Tanaka (2008) | Japan | Retrospective cohort | NA NA 100 19 | | | Intermittent | HCC |
| Buell (2002) | USA | Retrospective cohort | 58 62.3 85 15 | | | Intermittent | CRLM |
Discussion

Intraoperative bleeding is one of the most common and life-threatening complications during liver surgery, and has been associated with increased long-term morbidity and mortality. In addition, intraoperative hemorrhage increases the rate of blood transfusions, which have a negative impact on long-term postoperative outcomes by reducing the patient's immune defense. Excessive bleeding and blood transfusion also reduce patient survival. Excessive intraoperative bleeding and vascular occlusion are both associated with an increased risk of postoperative surgical complications and unfavorable clinical outcomes. Therefore, the optimal approach to liver resection is to perform surgery without hepatic vascular occlusion while minimizing blood loss and the need for blood transfusion.

Despite several strategies to reduce intraoperative bleeding, the PM remains the most commonly used technique because it was shown to reduce blood loss with high efficacy in initial randomized trials. However, some studies have not confirmed these initial findings and have even suggested a higher risk of ischemia–reperfusion injury for healthy liver tissue. Furthermore, an increased rate of postoperative complications has been shown in patients who undergo PM during hepatectomies in some studies. To prevent liver injuries, portal pedicle clamping was modified in the PM to an intermittent approach. Despite this modification, the overall efficacy of

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Table 2. Assessment of study quality.

| Author (year) | Confounding | Participant selection | Classification of intervention | Deviation from intended intervention | Missing data | Outcome measurement | Selection of reported results | Overall bias |
|---------------|-------------|-----------------------|---------------------------------|-------------------------------------|-------------|---------------------|-------------------------------|-------------|
| Al-Saeedi (2020) | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Lee (2019)    | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Low         |
| Famularo (2018) | Low         | No information        | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Jiang (2017)  | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Xu (2017)     | Low         | No information        | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Hao (2017)    | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Hao (2016)    | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Tsang (2015)  | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Low         |
| Huang (2014)  | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Weiss (2013)  | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Xie (2013)    | Low         | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| De Carlis (2013) | Low       | Low                   | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Nijkamp (2010) | No information | Low                   | No information | Moderate | Low                 | Moderate                        | Moderate    |
| Giulianete (2010) | Low       | Low                   | Low                             | No information                      | Low         | Low                 | Moderate                        | Moderate    |
| Wang (2009)   | Low         | No information        | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Weng (2008)   | Low         | No information        | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Tanaka (2008) | Low         | No information        | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |
| Buell (2002)  | Moderate     | No information        | Low                             | No information                      | Low         | Low                 | No information                | Moderate    |

Cochrane risk of bias tool for randomized controlled trials

| First author | Ferrero (2010) | Bias arising from the randomization process | Some concerns |
|--------------|---------------|---------------------------------------------|---------------|
| Bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomization | Some concerns |
| Bias due to deviations from intended interventions | Some concerns |
| Bias due to missing outcome data | Low risk |
| Bias in measurement of the outcome | Some concerns |
| Bias in selection of the reported result | Some concerns |
| Overall bias | Some concerns |
the PM remains controversial. Whether the PM promotes liver injury remains a topic of debate. Furthermore, how the PM affects recurrence and survival in patients with malignant lesions who underwent hepatectomy is not well understood. Although some studies have suggested that prolonged PM increases recurrence, others have demonstrated no effect. For instance, Al-Saeedi et al. revealed that a PM of less than 20 min did not increase the recurrence rate after 3 years. Recent studies showed that the PM has no significant positive impacts on clinical outcomes after minor liver surgeries. However, major liver resections, which have more intraoperative

Figure 3. (A) Forest plot showing 1-year recurrence of hepatic malignant lesions. (B) Forest plot showing 3-year recurrence of hepatic malignant lesions after hepatectomy. (C) Forest plot showing 5-year recurrence of hepatic malignant lesions after hepatectomy.
blood loss, probably benefit more from the PM. To address this controversy, we performed a meta-analysis to compare the long-term oncological outcomes of hepatectomy with and without a PM. The PM, regardless of whether it is complete or intermittent, was shown to be an independent risk factor for cancer recurrence in one study. However, other studies have reported no negative impact of the PM on patient survival and disease recurrence. In a recent randomized-controlled trial, the intermittent PM did not affect disease-free survival after hepatectomy, but did improve the OS rate. The positive effect of the intermittent PM was particularly promising in patients with hepatic disorders such as cirrhosis. In the present analysis, we observed no significant differences in 1-, 3-, and 5-year survival between the PM and non-PM groups. Furthermore, subgroup analysis revealed no significant effects of tumor type (i.e., primary or metastatic) on 1-, 3-, and 5-year survival between the PM and non-PM groups. This is in accordance with previous findings from large patient cohorts and clinical trials.

Figure 4. (A) Forest plot showing 1-year survival of patients with hepatic malignant lesions. (B) Forest plot showing 3-year survival of patients with hepatic malignant lesions. (C) Forest plot showing 5-year survival of patients with hepatic malignant lesions.
The PM was shown to be a risk factor for disease recurrence in several studies. It has been hypothesized that ischemia during portal pedicle clamping causes microvascular damage by breaking adhesions between tumor cells and endothelial cells. The hepatic ischemia-perfusion cycle might increase the expression of E-selectin, which plays a crucial role in cancer cell metastasis. However, we found no significant increase in disease recurrence following hepatectomy with the PM, indicating that the PM is not associated with disease recurrence after hepatectomy.

During reperfusion, liver parenchymal cells are thought to be injured by cytokines and radical oxygen species, which are produced by active Kupffer cells. However, a meta-analysis reported no significant patient benefits of hemihepatic vascular occlusion over complete hepatic vascular occlusion, despite a lower rate of liver injury. This suggests that significant hepatic injury is not caused by the PM, and that the potential benefits outweigh the potential disadvantages. In addition, of enrolled studies in this meta-analysis, four studies (2335 cases) reported the number of patients with steatosis, and no significant difference was observed in means of fatty liver distribution among patients with and without PM. However, included studies failed to provide more detailed data on clinical or oncological impacts of liver texture characteristics (e.g. macrovesicular or microvesicular liver steatosis, or liver fibrosis) on outcomes of the pringle maneuver, which prohibited us from carrying out subgroup analyses.

A study by Fagenson et al. reported that patients undergoing minor liver resection and cases with metastatic disease had a worse outcome when PM was performed. This finding is in similar line with our previously published report. Our results showed that PM is useful in patients who underwent extended liver resection, but this surgical maneuver may not be beneficial in minor hepatectomies. It can be derived that PM is associated with encouraging early perioperative outcomes without worsening the long-term survival among well-selected patients. On this basis, it cannot be denied that the selection of patients undergoing PM plays a principal role in increasing of safety and efficacy of PM.

There are some limitations to the present study. The main weakness is the variability in PM techniques, underlying liver disease, tumor stage status, and preoperative liver function between the included studies. Due to lack of subgroup results regarding the underlying liver disease, especially liver cirrhosis, it was not possible to assess the impact of PM in cirrhotic patients. In addition, although several studies have compared the PM with non-PM techniques, the number of RCTs is low, and most studies have a retrospective design, which can have potential disadvantages. In addition, of enrolled studies in this meta-analysis, four studies (2335 cases) reported the number of patients with steatosis, and no significant difference was observed in means of fatty liver distribution among patients with and without PM. However, included studies failed to provide more detailed data on clinical or oncological impacts of liver texture characteristics (e.g. macrovesicular or microvesicular liver steatosis, or liver fibrosis) on outcomes of the pringle maneuver, which prohibited us from carrying out subgroup analyses.

In conclusion, the present study shows that the PM is a suitable surgical technique for managing intraoperative bleeding during liver resection, and does not increase tumor recurrence and long-term mortality. We believe that the PM is a useful and acceptable approach to major or extended liver resection. However, further studies in large patient cohorts and randomized trials are needed to comprehensively evaluate the advantages and disadvantages of this procedure.

Methods
This systematic review and meta-analysis was reported according the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.

Eligibility criteria. The research question was formulated according to the PICOS strategy.

- Population: all adult patients who underwent liver resection
- Intervention: PM during liver resection
- Comparators: no PM
- Outcome: overall or recurrence-free survival rates
- Study design: all study types methodological designs, including human subjects, except case series with less than ten patients, narrative or systematic reviews, letters, conference abstracts, and study protocols.

Duplicate publications or overlapping cohorts were excluded.

Search strategy. According to Goossen et al., the following databases were searched.

1.  Cochrane Central Register of Controlled Trials (CENTRAL)
2.  Medline (via PubMed)
3.  Web of Science

Databases were last searched for relevant publications in May 2020. The references of each included study were also searched for additional relevant articles. The combination of search terms is presented in Supplemental Text 1.

Study selection. Two investigators (SS and AH) independently screened all papers identified by the search strategy and selected eligible studies based on the PICOS criteria. Two authors (SAHS and AR) then reviewed and evaluated the full-text of eligible articles and extracted the data. Discrepancies were settled by a discussion with a third author (EK).
Outcomes and data items. Recurrence-free survival rate. The recurrence-free survival (RFS) rate was defined as the number of the patients who survived without signs of recurrence after primary liver resection. We measured the RFS after 1, 3, and 5 years.

Overall survival rate. The overall survival (OS) rate was defined as the number of patients who survived after liver resection, regardless of disease recurrence. We measured the OS at 1, 3, and 5 years.

Quality assessment. The Cochrane risk-of-bias tool was used to assess the quality of randomized-controlled trials (RCT) and the ROBINS-I tool was used to assess the quality of non-randomized studies (NRS). The Cochrane risk-of-bias tool evaluated several items, including bias arising from the randomization process, bias arising from the timing of identification and recruitment of individual participants in relation to the timing of randomization, bias due to deviations from intended interventions, bias due to missing outcome data, and bias in the selection of the reported result. The overall risk of bias was low if the study was judged to be at low risk of bias for all domains. There were some concerns of bias if some concern of bias was detected in at least one domain. The risk of bias was high if the study was judged to be at high risk of bias in at least one domain or if some concerns of bias were detected in multiple domains.

Statistical analysis. Statistical analyses were performed by RevMan version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Pooled results were analyzed using the Mantel–Haenszel method. Results were presented as odds ratios (OR) or as survival rates with 95% confidence intervals (CI).

Received: 9 October 2020; Accepted: 12 January 2021
Published online: 08 February 2021

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E.K., S.S., S.A.H.A.S., A.R., O.G. designed the study, collected and analyzed data, and wrote the manuscript. M.A., N.R., and C.R. contributed knowledge and revised the manuscript. H.O., P.P. and A.M. co-designed the study and revised the manuscript. All authors read and approved the final version of the manuscript.

Funding
Open Access funding enabled and organized by Projekt DEAL.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-021-82291-4.

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