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| Question 1 | |
| **Should (PICO 1) CVS vs. other techniques be used for limiting the risk or severity of bile duct injury in patients undergoing laparoscopic cholecystectomy?** | |
| **Population:** | patients undergoing laparoscopic cholecystectomy |
| **Intervention:** | (PICO 1) CVS |
| **Comparison:** | other techniques |
| **Main outcomes:** | BDI |

# Assessment

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| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know | No direct comparative evidence was identified. The evidence for IOC vs. no IOC is addressed under guideline question number 4. One study that reviewed 65 videos of laparoscopic cholecystectomy with complications found that all videos with major BDIs (n=6) had not achieved an appropriate CVS while in a control group without complications after LC 72% had achieved the CVS. This comparison was considered flawed, however, due to the study not aiming to investigate the effectiveness of CVS and due to substantial amount of missing data, high risk of selection bias, confounding by surgeon skill or training, potential anatomical differences between groups, and by lack of standardization of severity of inflammation. Restricting the meta-analysis to single arm cohort studies of sample size >= 400 cases, the pooled incidence of BDI was 2 in a million cases when CVS was used (n= 4 studies with n= 5446 cases) versus pooled BDI incidence of 1.5 in 1000 cases when the infundibular technique was used (n=3 studies with 10,060 cases). This comparison, however, was deemed questionable by the GDG because of concerns regarding exchangeability of populations between the two intervention groups | The GDG considered based on their experience that although studies were not well designed to evaluate the effectiveness of CVS, the anticipated effect would have been large. Additionally, the existing evidence, although of questionable validity, was consistent with experience of the GDG in cases of BDI. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know | No comparative evidence was identified. The evidence for IOC vs. no IOC is addressed under guideline question number 4. One study that reviewed 65 videos of laparoscopic cholecystectomy with complications found that all videos with major BDIs (n=6) had not achieved an appropriate CVS while in a control group without complications after LC 72% had achieved the CVS. This comparison was considered too flawed, however, due to the study not aiming to investigate the effectiveness of CVS and due to substantial amount of missing data, high risk of selection bias, confounding by surgeon skill or training, potential anatomical differences between groups, and by lack of standardization of severity of inflammation. Restricting the meta-analysis to single arm cohort studies of sample size >= 400 cases, the pooled incidence of BDI was 2 in a million cases when CVS was used (n= 4 studies with n= 5446 cases) versus pooled BDI incidence of 1.5 in 1000 cases when the infundibular technique was used (n=3 studies with 10,060 cases). This comparison, however, was deemed questionable by the GDG because of concerns regarding exchangeability of populations between the two intervention groups | Obtaining the CVS may add time burden to laparoscopic cholecystectomy but any potential delay would be offset by the potential advantage to limit BDI |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Very low ○ Low ○ Moderate ○ High ○ No included studies |  |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Not applicable because BDI is the only decision-making outcome. |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |

# Conclusions

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| Recommendation |
| In patients undergoing laparoscopic cholecystectomy, we suggest that surgeons use the critical view of safety for anatomic identification of the cystic duct and artery (expert opinion).  ADDITIONAL CONSIDERATIONS: When the CVS cannot be achieved safely (e.g. due to pathologic alterations of, or native variations in biliary anatomy), it is suggested that surgeons consider intraoperative imaging by cholangiography (or laparoscopic ultrasonography) for anatomic identification (see guideline question #4) |
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| Justification |
| In the absence of reliable evidence, the GDG decided to rely on expert opinion to make this recommendation.  The rate of BDI remains unacceptably high. The morbidity of BDI is substantial (medical, economic, medico-legal) and the mortality of BDI is important. Event analysis of BDIs implicate methods of anatomic identification other than the CVS as potential causes of injury in essentially all cases evaluated. CVS is attainable in a majority (85-95%) of cases when attempted routinely. The safe extent of dissection in any case must always be tempered by surgical judgement, but there is no evidence that reasonable efforts to achieve the CVS have been harmful, and, therefore, use of CVS is logical. When operative conditions are difficult and the CVS cannot be reasonably achieved, alternative methods for either anatomic definition or conclusion of the operation are critical to prevention of BDI or other injury. |

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| Subgroup considerations |
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| Implementation considerations |
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| Monitoring and evaluation |
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| |  | | --- | | Research priorities | | There is a dearth of direct comparative evidence on the topic.  Future studies should compare planned CVS, infundibular technique, top-down technique, and IOC with each other in large registries specific to BDI’s that control for important confounders such as presence and severity of cholecystitis, surgeon experience and skill, and the cholecystectomy technique (ie laparoscopic, single incision, robotic, etc). Further, the fidelity of intervention (ie. appropriateness of the CVS) should be externally adjudicated by a video recording of the procedure.  A national database that tracks BDI, potential confounders and fidelity of intervention would help achieve this objective as randomized controlled trials are unlikely to be successful given the low incidence of BDI. | |

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| |  |  | | --- | --- | | Question 2 | | | **Should (PICO 2) subtotal cholecystectomy vs. top-down total cholecystectomy be used for limiting the risk or severity of BDI when the CVS cannot be achieved during lap chole?** | | | **Population:** | Patients undergoing lap chole where the critical view of safety cannot be achieved | | **Intervention:** | (PICO 2) subtotal cholecystectomy | | **Comparison:** | top-down technique | | **Main outcomes:** | BDI injury ; severity of BDI injury; Vascular injury ; 30 day mortality; Readmission |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know | No comparative evidence was identified addressing this key question. While a number of non-comparative case series report low BDI risk with the application of both these techniques, an indirect comparison of this evidence was not considered appropriate by the GDG because the majority of non-comparative studies were underpowered and the comparison was too flawed due to confounding by surgical expertise, patient population selection, and subjectivity in the judgment of severity of inflammation. | The GDG argued that in cases of severe inflammation where dissection of the ductal structures is deemed difficult by the surgeon, the best approach to limit BDI risk is to avoid dissection of the ductal structures with an anticipated large effect in reducing BDI. A subtotal cholecystectomy approach meets those criteria and was considered, therefore, preferable, while a total cholecystectomy technique by fundus first (top down) approach may be risky. The GDG opined that if the top down approach also avoids dissection of ductal structures, it may be equally as safe as subtotal cholecystectomy. | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know | No comparative evidence was identified addressing this key question. While a number of non-comparative case series report low BDI risk with the application of both these techniques, an indirect comparison of this evidence was not considered appropriate by the GDG because the majority of non-comparative studies were underpowered and the comparison was too flawed due to confounding by surgical expertise, patient population selection, and subjectivity in the judgment of severity of inflammation. | A systematic review of subtotal cholecystectomy case series identified a higher risk of bile leak in patients after subtotal cholecystectomy compared with reported rates of total cholecystectomy, especially if the fenestrating type is used ( van Dijk AH et al. J Am Coll Surg 2017;225:371 – 379). Other important complications are not likely to differ significantly between the two approaches. | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ● Very low ○ Low ○ Moderate ○ High ○ No included studies |  |  | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | No important uncertainty about the value patients place on BDI avoidance |  | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  | Expert opinion favors the intervention (80% agreement) (mention vote count here) | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | The GDG felt that both interventions would be acceptable by all involved stakeholders if proven effective | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | The GDG did not perceive any feasibility concerns |  Conclusions  |  | | --- | | Recommendation | | When the critical view of safety cannot be achieved and the biliary anatomy cannot be clearly defined by other methods (e.g. imaging) during laparoscopic cholecystectomy, we suggest that surgeons consider subtotal cholecystectomy over total cholecystectomy by the top down approach. (expert opinion) | |  |  |  | | --- | | Justification | | It is well accepted by surgeons that in select cases of laparoscopic cholecystectomy where the severity of the local inflammation prevents safe identification of biliary anatomy and acquisition of the critical view of safety, an alternative approach should be used that minimizes the risk of BDI. Both subtotal and top down cholecystectomy approaches have been reported in the literature to be useful under such difficult conditions. However, one study has implicated the top down approach under challenging operative conditions with contracted GB and chronic inflammation as a risk factor for BDI and combined vascular-biliary injury. The provided expert recommendation was influenced by this finding. It should be also noted that the GDG unanimously agreed that under challenging conditions BDI risk can be minimized both via subtotal or top down cholecystectomy as long as ductal dissection in the hepatocystic triangle is avoided (ie as long as surgeons avoid pursuing a total cholecystectomy under these challenging conditions) |  |  | | --- | | Subgroup considerations | |  |  |  | | --- | | Implementation considerations | |  |  |  | | --- | | Monitoring and evaluation | |  |  |  |  |  |  | | --- | --- | --- | --- | | |  | | --- | | **Research priorities** | | * Prospective studies that compare top-down vs subtotal cholecystectomy in the same patient population and under similar intraoperative conditions * Prospective studies that compare total vs subtotal cholecystectomy in the same patient population and under similar intraoperative conditions * Comparative studies between subtotal fenestrating vs reconstituting cholecystectomy |   **Question 3** | | | **Should video documentation of CVS (alone or in addition to written notes ) vs. photo documentation (alone or in addition to written notes) be used for limiting the risk or severity of BDI during lap chole?** | | | **Population:** | Patients undergoing laparoscopic cholecystectomy | | **Intervention:** | (PICO 3) requirements for one type of documentation of CVS | | **Comparison:** | another type of documentation or no doc | | **Main outcomes:** | Bile Duct Injury as approximated from the quality of CVS documentation |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ○ Small ● Moderate ○ Large ○  Varies ○ Don't know | No evidence was found that directly compared the impact of the alternative CVS documentation requirements on outcomes of bile duct injury and other complications of surgery. Indirect evidence on the proxy outcome of the quality of CVS is summarized below.   | Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Photographic documentation of CVS** | **Video documentation of CVS** | | Adjudicated good CVS documentation (as proxy for BDI risk) | 239 documentations from 152 patients (2 observational studies) | ⨁◯◯◯ VERY LOWa,b,c | **OR 1.35** (0.80 to 2.28) | Cannot be estimated as the numerical relationship the quality of documentation and BDI is not known. | |  1. Very serious indirectness due to surrogate outcome and associated uncertainty for predicting bile duct injury 2. Very serious imprecision due to wide confidence interval and small sample size 3. There is high ROB due to substantial missing data, non-blinded CVS quality assessments, and (in Plaisir 2001) unclear inter and/or intra-rater reliability of CVS quality assessors. | The GDG felt the use of notes as a benchmark for attainment of CVS was not reasonable given that notes are not externally adjudicatable and have been shown to not correlate well with photographic or video documentation. Hence, this guideline question inquired about the comparative benefits and harms of video versus photo documentation specifically.  Because direct evidence was not found of the comparison of interest, the GDG considered indirect linked evidence with the following rationale:  External independent assessment/audit of the documentation of CVS could inform assessors of the quality of CVS achieved by the primary surgeon(s). The better the documentation, the more accurate would be the independent assessment of the adequacy of CVS actually achieved intraoperatively. When included in program quality improvement initiatives, and provided as performance feedback to the primary surgeon(s), the GDG anticipated improvement in the risk of BDI as audit and feedback have previously shown to improve the quality of healthcare delivered [Ivers 2014]  The GDG, however, acknowledged that some of the links in the indirect evidence are currently missing (e.g. the link that improvement in the quality of healthcare delivered translates into improved patient outcomes). Nonetheless, employing a precautionary approach to enhance patient safety, the GDG agreed that the quality of CVS documentation, as judged by external independent assessors, is a relevant (albeit uncertain) proxy for BDI risk. | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know |  | Any time delays due to technical difficulties with added visual documentation could prolong patient exposure to anesthesia. | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ● Very low ○ Low ○ Moderate ○ High ○ No included studies | Indirect evidence was limited by study design, large missing data, non-blinded CVS quality assessment, and unclear inter or intra-rater reliability of CVD quality assessors in one study. |  | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  |  | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  |  | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know |  | There are potential concerns that video or even photo documentation could be used against surgeons from a medical-legal standpoint. | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | Video recording or image capture capability may not be feasible in all ORs due to variations in imaging systems and storage limitations. |   **Conclusions**   |  | | --- | | **Recommendation** | | Due to medico-legal concerns, feasibility, and acceptability there was a lack of agreement in the panel, and a recommendation could not be provided. | |  |  |  | | --- | | **Justification** | | The GDG opined that surgeons should strive to obtain the CVS during lap chole to minimize BDI risk (see recommendation to key question 1). The GDG felt that surgeon adoption of a documentation method for the CVS may promote its wider use and implementation and indirectly help reduce BDI risk. Further, existing evidence suggests that documentation of CVS in the operative record is often inadequate and inaccurate. The GDG proposed that CVS documentation should go beyond the operative report and include visual documentation (such as video) in addition to surgical notes. There was no consensus on this recommendation by attendees of the consensus conference, however. There was considerable discussion about medico-legal implications and push back from surgeons. Alternate wording that was considered included surgeons "be encouraged to document CVS by doublet photography or video". Another suggestion was that surgeons document in written reports how the anatomy was identified (since this is often omitted or unclear). The concept would not be to establish a mandate, but rather to increase over time use of doublet photography (or video documentation) in surgical practice. There were also concerns that malpractice defense attorneys may not be in favor of this. On the other hand, the value of documentation as a teaching or quality assurance tool is evident and has previously been shown to improve the quality of healthcare delivered. Ultimately, due to the above stakeholder input/concerns regarding acceptability, a recommendation was not made. |  |  | | --- | | **Subgroup considerations** | |  |  |  | | --- | | **Implementation considerations** | |  |  |  | | --- | | **Monitoring and evaluation** | |  |  |  | | --- | | **Research priorities** | | * Studies that assess whether documentation of CVS vs no documentation decreases risk and/or severity of BDI. * Studies that assess whether a requirement for documentation promotes a better dissection by surgeons. * Studies that assess whether one type of anatomic documentation, whether photos, videos, or IOC, however obtained, are superior in reducing the risk or severity of BDI.   Studies that use video, photo, and notes during laparoscopic cholecystectomy that are assessed by blinded third parties to assess for CVS quality to judge the diagnostic sensitivity/specificity for CVS. |  |  |  | | --- | --- | | Question 4 | | | **Should [PICO 4] intraoperative biliary imaging (e.g. intraoperative cholangiography, ultrasound, infrared fluorescent cholangiography) vs. no intraoperative biliary imaging be used for limiting the risk or severity of bile duct injury in patients undergoing laparoscopic cholecystectomy?** | | | **Population:** | patients undergoing laparoscopic cholecystectomy | | **Intervention:** | [PICO 4] intraoperative biliary imaging (e.g. intraoperative cholangiography, ultrasound, infrared fluorescent cholangiography) | | **Comparison:** | no intraoperative biliary imaging | | **Main outcomes:** | Bile duct injury during acute laparoscopic cholecystectomy; Recognition of bile duct in injury (BDI) in laparoscopic cholecystectomy patients with suspicion of BDI or unclear anatomy; |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | Evidence comparing intraoperative cholangiography (IOC) versus no intraoperative biliary imaging was considered in panel deliberations. No conclusive evidence was found for other types of biliary imaging. RCT evidence (n=9) for IOC was too underpowered for meaningful synthesis.  Pooled evidence from 14 studies that included 2.5 million patients demonstrated findings favoring IOC over no IOC in most of the studies providing adjusted estimates of effect but the benefit was greatest in the subgroup analysis for patients with acute cholecystitis in one study including 51,404 patients (Tornqvist et al., 2015). This study also provided a subgroup analysis in patients without acute cholecystitis showing no significant difference in the BDI risk with confidence intervals compatible both with important benefits and harms [OR= 0.97 (95% CI 0.74, 1.25)]. The overall meta-analytic estimate of effect was judged for certainty as summarized below.  For the subgroup of patients with intraoperatively suspected BDI, the use of IOC led to almost 3 fold increase in the odds of recognition of BDI compared with non-use of IOC.   | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with no intraoperative biliary imaging** | **Risk difference with [PICO 4] intraoperative biliary imaging (e.g. intraoperative cholangiography, ultrasound, infrared fluorescent cholangiography)** | | Bile duct injury during acute laparoscopic cholecystectomy follow up: range 1 months to 36 months | 2,540,704 (14 observational studies) | ⨁◯◯◯ VERY LOWa,b,c | **OR 0.81** (0.62 to 1.07) | Moderate | | | 320 per 100,000 | **61 fewer per 100,000** (121 fewer to 22 more) | | High | | | 2,000 per 100,000 | **374 fewer per 100,000** (751 fewer to 137 more) | | Recognition of bile duct in injury (BDI) in laparoscopic cholecystectomy patients with suspicion of BDI or unclear anatomy | 1256 (8 observational studies) | ⨁◯◯◯ VERY LOWa,d | **OR 2.97** (1.55 to 5.68) | Study population | | | 332 per 1,000 | **264 more per 1,000** (103 more to 406 more) |  1. Confounding by diagnostic indication is a serious concern because the reason for the intraoperative cholangiography (IOC) was often not reported. IOC could have been done to confirm an injury and thus bias the results against biliary imaging. Also, the majority of studies used administrative data coding with concerns about non-differential classifications bias. Further, studies did not account for surgeon factors (e.g. experience) which may be associated both with IOC use and BDI injury. 2. Most of the data contributing studies showed substantial overlap of 95% confidence intervals, however one large study including 472,367 patients (Lilley et al, 2017) demonstrated higher risk of BDI associated with the use of IOC. This was judged to be reflective of the use of IOC as a confirmatory test for BDI and as such at the risk of confounding by diagnostic indication. I-squared 87.2; p<0.0001 3. Confidence interval crosses the null which is compatible with a possibility of substantial risk reduction to no difference or even potential harms. 4. The relevant data originates in 1256 bile duct injuries in total, which was deemed sub-optimal information size. Four of 8 of the studies computed wide CI approaching or crossing the Null. Fragility index was zero. | The GDG provided a range for the baseline risk of BDI (i.e. risk without biliary imaging). Both estimates of absolute risk difference were judged moderate.  The GDG further concluded that the subgroup of patients with strong intraoperative suspicion of BDI will have a significantly higher baseline risk for BDI as well as at a higher risk for life threatening complications of undetected/unrepaired BDI. For this subgroup of patients, the GDG invoked one the five paradigmatic GRADE scenarios "*Life-threatening Situation*" for strong recommendations based on "low or very low certainty evidence".  The GDG also deliberated on the alternative approach of using laparoscopic ultrasound imaging. No evidence was found to support or refute its use. In trained hands, ultrasound may be an appropriate alternative to IOC. | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | Evidence comparing intraoperative cholangiography (IOC) versus no intraoperative biliary imaging was considered in panel deliberations. No conclusive evidence was found for other types of biliary imaging. RCT evidence (n=9) for IOC was too underpowered for meaningful synthesis.  Pooled evidence from 14 studies that included 2.5 million patients demonstrated findings favoring IOC over no IOC in most of the studies providing adjusted estimates of effect but the benefit was greatest in the subgroup analysis for patients with acute cholecystitis in one study including 51,404 patients (Tornqvist et al., 2015). This study also provided a subgroup analysis in patients without acute cholecystitis showing no significant difference in the BDI risk with confidence intervals compatible both with important benefits and harms [OR= 0.97 (95% CI 0.74, 1.25)]. The overall meta-analytic estimate of effect was judged for certainty as summarized below.  For the subgroup of patients with intraoperatively suspected BDI, the use of IOC led to almost 3 fold increase in the odds of recognition of BDI compared with non-use of IOC.   | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with no intraoperative biliary imaging** | **Risk difference with [PICO 4] intraoperative biliary imaging (e.g. intraoperative cholangiography, ultrasound, infrared fluorescent cholangiography)** | | Bile duct injury during acute laparoscopic cholecystectomy follow up: range 1 months to 36 months | 2,540,704 (14 observational studies) | ⨁◯◯◯ VERY LOWa,b,c | **OR 0.81** (0.62 to 1.07) | Moderate | | | 320 per 100,000 | **61 fewer per 100,000** (121 fewer to 22 more) | | High | | | 2,000 per 100,000 | **374 fewer per 100,000** (751 fewer to 137 more) | | Recognition of bile duct in injury (BDI) in laparoscopic cholecystectomy patients with suspicion of BDI or unclear anatomy | 1256 (8 observational studies) | ⨁◯◯◯ VERY LOWa,d | **OR 2.97** (1.55 to 5.68) | Study population | | | 332 per 1,000 | **264 more per 1,000** (103 more to 406 more) |  1. Confounding by diagnostic indication is a serious concern because the reason for the intraoperative cholangiography (IOC) was often not reported. IOC could have been done to confirm an injury and thus bias the results against biliary imaging. Also, the majority of studies used administrative data coding with concerns about non-differential classifications bias. Further, studies did not account for surgeon factors (e.g. experience) which may be associated both with IOC use and BDI injury. 2. Most of the data contributing studies showed substantial overlap of 95% confidence intervals, however one large study including 472,367 patients (Lilley et al., 2017) demonstrated higher risk of BDI associated with the use of IOC. This was judged to be reflective of the use of IOC as a confirmatory test for BDI and as such at the risk of confounding by diagnostic indication. I-squared 87.2; p<0.0001 3. Confidence interval crosses the null which is compatible with a possibility of substantial risk reduction to no difference or even potential harms. 4. The relevant data originates in 1256 bile duct injuries in total, which was deemed sub-optimal information size. Four of 8 of the studies computed wide CI approaching or crossing the Null. Fragility index was zero. | Potential undesirable effects such as radiation exposure, increased OR time (typically <15 mins) and cost were considered to be trivial to small by the panel with high certainty. As such, these outcomes were not deemed relevant to decision-making associated with this guideline question.  (Several studies have shown that the use of IOC adds approximately 10-16 minutes to operative time. One larger comparative study found a higher CBD stone detection rate (4.8 vs 1.0%) and intraoperative treatment rate for CBD stones (2.8 vs 0.7%) in patients who had IOC routinely. Buddingh KT et al JACS 2011; 213: 267-274) There was no difference in the utilization rates of either preop or postop ERCP. However, there was a trend toward fewer total interventions for CBD stones in the patients who underwent routine IOC (19.1% vs 24.2%, p= 0.067) ) | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ● Very low ○ Low ○ Moderate ○ High ○ No included studies | Evidence originated in observational studies of limited validity for causal inference. |  | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Not applicable as BDI is the sole decision-making outcome |  | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know |  | Although the evidence is of very low certainty, it favors intraoperative cholangiography with no important trade-offs with respect to undesirable effects as they were *a priori* judged to be trivial to small. | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | No research evidence addressing this criterion was identified. However, the panel’s opinion was that if BDI would be decreased by using IOC, performing IOC would be acceptable to all stakeholders. | Potential stakeholders include patients, hospitals, surgeons, and insurance providers. Acceptability of the intervention maybe different for different stakeholders. The main stakeholder for these recommendations is the Surgeon and the recommendation (for use of intervention in appropriate situations) would likely be acceptable to most surgeons. However, few surgeons who use IOC infrequently may be reluctant to utilize it. | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Research evidence addressing this criterion was not searched and reviewed, as it was not anticipated to exist by the experts on the panel. | Surgeons are expected to have the relevant skill set as part of their training and most also have adequate practice experience. Most hospitals and outpatient centers also have the required logistics and capacity to offer the intervention. |  Type of recommendation  |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention | | ○ | ○ | ○ | **●** | ○ |  Conclusions  |  | | --- | | Recommendation | | In patients with acute cholecystitis or history of acute cholecystitis, we suggest the liberal use of intraoperative cholangiography during laparoscopic cholecystectomy to mitigate the risk of bile duct injury (conditional recommendation, very low certainty of evidence).  In patients with uncertainty of biliary anatomy or suspicion of bile duct injury during laparoscopic cholecystectomy, we recommend that surgeons use intraoperative biliary imaging (in particular intraoperative cholangiography) to mitigate the risk of bile duct injury (strong recommendation, very low certainty of evidence).  Given that the evidence for the benefit of IOC in elective non-acute cholecystectomy is inconclusive, no recommendation addressing this scenario could be made.  Surgeons with appropriate experience and training may use laparoscopic ultrasound imaging as an alternative to IOC during laparoscopic cholecystectomy (expert opinion) | |  |  |  | | --- | | Justification | | Pooled evidence from 14 studies including greater than 2.5 million patients demonstrated findings favoring IOC over no IOC in most studies reporting adjusted risk estimates, but the benefit was greatest in patients with acute cholecystitis. Multiple studies have shown that IOC is associated with a higher rate of intraoperative recognition of BDI. Although the certainty of evidence is very low, this is a consistent finding across multiple studies. The potential benefit of IOC is early recognition and avoidance of potentially increasing the severity of BDI. This includes avoidance of excision of a portion of the bile duct and a higher level of injury which is often more difficult to repair and reconstruct. Because the certainty of the evidence favoring IOC is very low and some concerns remain, the panel decided to make a conditional recommendation favoring IOC. However, for patients with strong intraoperative suspicion of BDI, the baseline risk for BDI would be higher yielding greater absolute benefits as well as they would be at a higher risk for life threatening complications of undetected/unrepaired BDI. Further, evidence of very low certainty indicates an almost 3-fold increase in the odds of the recognition of BDI with IOC use. |  |  | | --- | | Subgroup considerations | |  |  |  | | --- | | Implementation considerations | |  |  |  | | --- | | Monitoring and evaluation | |  |  |  | | --- | | Research priorities | | The GDG proposed the following research priorities:  \*Evidence comparing the routine use of various imaging options versus their discretionary use by the surgeon ( IOC, US)  \*Head to head comparisons of various intraoperative biliary imaging modalities  \*Studies that compare intraoperative imaging to no imaging should document whether imaging was used pre-emptively or after an injury was suspected  \*Assessment of the role of near infrared cholangiography in delineation of biliary anatomy and avoidance of BDI, this maybe especially important in condition of cholecystitis.  \*To assess compliance with these guidelines, we will compare the utilization of IOC during acute cholecystitis 2 and 5 years after publication of these guidelines compared with current baseline.  To this end, the GDG also agreed that a national registry for all BDIs would be highly desirable. |  |  |  | | --- | --- | | Question 5A | | | **Should [PICO 5A] Near-infrared (NIR) intraoperative biliary imaging vs. IOC biliary imaging be used for limiting the risk or severity of BDI during laparoscopic cholecystectomy?** | | | **Population:** | limiting the risk or severity of BDI during laparoscopic cholecystectomy | | **Intervention:** | [PICO 5A] Near infrared intraoperative biliary imaging | | **Comparison:** | IOC biliary imaging | | **Main outcomes:** | BDI incidence and Severity ( as judged from visualization of CD, CBD, and Common hepatic duct) ; |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | There was no direct evidence available for BDI or other outcomes. The outcomes for ductal visualization, however were considered indirect evidence for BDI.   | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Impact** | | --- | --- | --- | --- | | BDI incidence and severity ( as judged from visualization of CD, CBD, and common hepatic duct) | 0 (4 observational studies) | ⨁◯◯◯ VERY LOWa,b,c,d,e | 4 observational studies provided data for the surrogate outcomes of visualization of cystic duct, common bile duct, and hepatic duct. Pooling of the data for visualization of each structure yielded inconsistent findings. RR for CD duct visualization was 1.1 (95% CI, 1.00-1.35; 43studies; total patients = 430). RR for CBD was 1.0 (95% CI, 0.97-1.03; 4 studies; total patients = 430). RR for common hepatic duct was 0.76 (95% CI, 0.58 -1.01; 4 studies; total patients = 300). |  1. Studies reported un-adjusted outcomes. 2. The systematic review Vlek et al had R-AMSTAR of 29 and most of the studies were highly subject to bias (moderate to severe) 3. Findings across the various ductal structures were inconsistent. 4. There are concerns about generalizability of the findings to general surgical practice as well as concerns about the surrogacy of ductal visualization for BDI. 5. There are wide confidence intervals, and n<500 patients across all 4 studies. |  | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | There was no direct evidence available for BDI or other outcomes. The outcomes for ductal visualization, however were considered indirect evidence for BDI.   | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Impact** | | --- | --- | --- | --- | | BDI incidence and severity (as judged from visualization of CD, CBD, and common hepatic duct) | 0 (4 observational studies) | ⨁◯◯◯ VERY LOWa,b,c,d,e | 4 observational studies provided data for the surrogate outcomes of visualization of cystic duct, common bile duct, and hepatic duct. Pooling of the data for visualization of each structure yielded inconsistent findings. RR for CD duct visualization was 1.1 (95% CI, 1.00-1.35; 3 studies; total patients = 430). RR for CBD was 1.0 (95% CI, 0.97-1.03; 4 studies; total patients = 430). RR for common hepatic duct was 0.76 (95% CI, 0.58 -1.01; 4 studies; total patients = 300). |  1. Studies reported un-adjusted outcomes. 2. The systematic review Vlek et al had R-AMSTAR of 29 and most of the studies were highly subject to bias (moderate to severe) 3. Findings across the various ductal structures were inconsistent. 4. There are concerns about generalizability of the findings to general surgical practice as well as concerns about the surrogacy of ductal visualization for BDI. 5. There are wide confidence intervals, and n<500 patients across all 4 studies. | The GDG noted that relying on near- infrared imaging must not be a substitute for good dissection and identification technique. | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ● Very low ○ Low ○ Moderate ○ High ○ No included studies |  |  | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  | This criterion is not applicable because BDI was the only decision-making outcome considered by the GDG. | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know | There is variability in the desirable and undesirable effects depending on the biliary structure being imaged. |  | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | If proven effective, NIR would probably be acceptable to surgeons. The learning curve may be deterrents to NIR use for some surgeons. However, support for NIR are ease of use, ability to map the anatomy repeatedly, use in flow with the operation, and it is less invasive and less technically demanding than IOC. | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | The GDG felt that the use of NIR would be technically feasible for most surgeons. However, many ORs may not have the imaging system required for near- infrared technology available, or readily available, and may encounter issues with practical feasibility. |  Conclusions  |  | | --- | | Recommendation | | Current evidence is insufficient to make a recommendation regarding use of near infrared cholangiography for identification of biliary anatomy during cholecystectomy compared to intraoperative cholangiography. | |  |  |  | | --- | | Justification | | Current evidence is insufficient to guide a recommendation. |  |  | | --- | | Subgroup considerations | |  |  |  | | --- | | Implementation considerations | |  |  |  | | --- | | Monitoring and evaluation | |  |  |  |  |  |  | | --- | --- | --- | --- | | |  | | --- | | Research priorities | | Near-infrared cholangiography should be assessed in large trials compared to intraoperative cholangiography with risk stratification and risk adjustment. Because BDI is unlikely to be captured in such trials, we additionally suggest these trials focus on proxy outcomes such as visualization of ductal structures, ability to obtain the critical view of safety, and complications including conversion to open cholecystectomy. In particular, this technology should be studied in difficult cholecystectomy patient populations that includes those with acute cholecystitis or history of acute cholecystitis, severe chronic cholecystitis, and obese patients. |  Question 5B | | | **Should near-infrared (NIR) intraoperative biliary imaging with White Light vs. White Light biliary imaging alone be used for limiting the risk or severity of BDI during laparoscopic cholecystectomy?** | | | **Population:** | limiting the risk or severity of BDI during laparoscopic cholecystectomy | | **Intervention:** | [PICO 5B Infrared intraoperative biliary imaging with White Light | | **Comparison:** | White Light biliary imaging alone | | **Main outcomes:** | BDI (as approximated from cystic duct, common hepatic duct, and CBD pre- and post-dissection visualization); |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | There was no direct evidence for BDI or other decision-making outcomes. One RCT (n of total patients = 640) demonstrated findings favoring near infrared for the visualization of various ductal structures (cystic duct, common hepatic duct and the CBD) pre and post-dissection. These were considered proxy evidence for BDI.    With IR compared to WL, for Pre-dissection there were:  - 288 per 1,000 more CBD visualized (95% CI, 202 more to 375 more)  - 308 per 1,000 more CD visualized (95% CI, 232 more to 377 more)  - 180 per 1,000 more CHD visualized (95% CI, 100 more to 275 more)    With IR compared to WL, for Post-dissection there were:  - 257 per 1,000 more CBD visualized (95% CI, 189 more to 313 more)  - 3 per 1,000 fewer CD visualized (95% CI, 47 fewer to 16 more)  - 218 per 1,000 more CHD visualized (95% CI, 138 more to 298 more)  Certainty for the aforementioned findings was judged Very Low for the following considerations:   * Risk of Bias = “serious” due to outcome ascertainment bias with non-blinded surgeons * Indirectness = “very serious” because of concerns about generalizability of the findings to general surgical practice as well as concerns about the surrogacy of ductal visualization for BDI. | A 2nd randomized trial that is comparing NIR to white light is currently underway (FALCON trial, NCT 02558556).    Although visualization of ductal structures is indirect evidence for BDI, the estimates of effect are not considered numerically proportional to the outcome of BDI. | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know |  | The GDG noted that relying on infrared imaging must not be a substitute for good dissection and identification technique. | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ● Very low ○ Low ○ Moderate ○ High ○ No included studies |  |  | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  | This criterion is not applicable because BDI was the only decision-making outcome considered by the GDG. | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know | The indirect evidence available favors NIR. |  | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know | No data to make a Judgment on this issue. |  | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | The ease of use and the broad integration of Infrared technology in different surgical fields would argue to the probably feasible nature of this intervention. |  |  Type of recommendation  |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | **●** | ○ | ○ |  Conclusions  |  | | --- | | Recommendation | | We suggest that the use of near infrared imaging may be considered as an adjunct to white light alone for identification of biliary anatomy during cholecystectomy {conditional recommendation, very low certainty of evidence}.  The GDG noted that relying on infrared imaging must not be a substitute for good dissection and identification technique {expert opinion}. | |  |  |  | | --- | | Justification | | Evidence from a single RCT suggests small benefit of near infrared cholangiography in addition to conventional white light compared to white light alone. This evidence was indirect with limitations as noted above.  The evidence should be further assessed once results of an additional randomized trial are available (FALCON trial: NCT02558556) |  |  | | --- | | Subgroup considerations | |  |  |  | | --- | | Implementation considerations | |  |  |  | | --- | | Monitoring and evaluation | |  |  |  | | --- | | Research priorities | | Near infrared cholangiography should be assessed in additional large trials compared to white light alone with risk stratification and risk adjustment. Because BDI is unlikely to be captured in such trials, we additionally suggest these trials focus on proxy outcomes such as visualization of ductal structures, ability to obtain the critical view of safety, and complications including conversion to open cholecystectomy. In particular, this technology should be studied in difficult cholecystectomy patient populations that includes those with acute cholecystitis or history of acute cholecystitis, severe chronic cholecystitis, and obese patients. |  |  |  | | --- | --- | | Question 6 | | | **Should surgical (complexity) risk [PICO6] stratification (risk factors or risk prediction models) guided surgery vs. alternative risk stratification or no risk stratification guided surgery be used for limiting the risk or severity of bile duct injury in candidates for laparoscopic cholecystectomy?** | | | **Population:** | Patients scheduled to undergo laparoscopic cholecystectomy | | **Intervention:** | Surgical (complexity) risk [PICO6] stratification (risk factors or risk prediction models) guided surgery | | **Comparison:** | Alternative risk stratification or no risk stratification guided surgery | | **Main outcomes:** | Bile duct injury (BDI) (quality of CVS as a proxy for BDI); conversion; complications; mortality |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | No evidence was found that directly addressed this question (either between risk stratification systems or between risk stratification and no stratification). | Existing evidence consists of prognostic risk association studies. There are no studies evaluating the effectiveness of using this prognostic information in the management of patients undergoing lap chole.  In a previous study that applied the 2013 Tokyo Guideline (TG13) risk stratification model retrospectively to patients with acute cholecystitis, BDI was found to be higher in patients with TG13 grades II and III acute cholecystitis (Tornqvist et al. World J Surg. 2016;40:1060–1067).  Another study compared the AAST vs. TG13 severity grading systems for predicting postoperative outcomes in patients with acute cholecystitis (Okamoto et al. J Hepatobiliary Pancreat Sci. 2018;25:55–72). This study showed that the AAST criteria had better AUC for predicting mortality (AUC 0.86 vs. 0.73), complications (AUC 0.76 vs. 0.63), and need for cholecystectomy tubes (AUC 0.80 vs. 0.68), all p<0.05. However, the incidence of bile duct injuries was too low to evaluate.  The literature also suggests, that factors that potentially increase the difficulty of laparoscopic cholecystectomy (such as male gender, increased age, chronic cholecystitis, obesity, liver cirrhosis, adhesions from previous abdominal surgery, emergency cholecystectomy, cystic duct stones, enlarged liver, cancer of gallbladder and/or biliary tract, anatomic variation, biliodigestive fistula, and limited surgical experience) could affect the BDI risk. | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | No evidence was found that directly addressed this question (either between risk stratification systems or between risk stratification and no stratification). |  | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Very low ○ Low ○ Moderate ○ High ● No included studies | No evidence was found that directly addressed this question (either between risk stratification systems or between risk stratification and no stratification). |  | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Since BDI is the main outcome for decision making, the GDG panel did not expect any patient uncertainty or variability. |  | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know | No evidence was found. |  | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | No evidence was found | Current risk stratification for the severity of acute cholecystitis exists; the GDG panel did not feel that there was harm in using such models and thought it would be acceptable to key stakeholders. | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | No evidence was found | The GDG panel did not perceive any feasibility issues with implementation of risk stratification systems. |  Conclusions  |  | | --- | | Recommendation | | No evidence-based recommendation can be made to answer this question. The following recommendations are based on expert opinion:  During operative planning of laparoscopic cholecystectomy and intraoperative decision-making, we suggest that surgeons consider factors that potentially increase the difficulty of laparoscopic cholecystectomy (such as male gender, increased age, chronic cholecystitis, obesity, liver cirrhosis, adhesions from previous abdominal surgery, emergency cholecystectomy, cystic duct stones, enlarged liver, cancer of gallbladder and/or biliary tract, anatomic variation, bilio-digestive fistula, and limited surgical experience).  For patients with acute cholecystitis, we suggest that surgeons may use the Tokyo Guidelines 18 (TG18), AAST classification, or another effective risk stratification model for grading for severity of cholecystitis and for patient management. | |  |  |  | | --- | | Justification | | No evidence was found to support evidence-based recommendations. GDG suggestions were based on existing evidence of association. Given that risk stratification models demonstrate that more severe cholecystitis is associated with higher BDI rates and complications, the GDG panel felt that assessing this risk and guiding surgical intervention based on risk would potentially limit risk and severity of bile duct injury. |  |  | | --- | | Subgroup considerations | |  |  |  | | --- | | Implementation considerations | |  |  |  | | --- | | Monitoring and evaluation | |  |  |  | | --- | | Research priorities | | Development of robust BDI risk prediction models is needed.  Large multi-institutional studies using clinical data are needed to demonstrate the effectiveness of risk stratification models for bile duct injury.  National clinical registry/database of BDI and LC is necessary to have the power to evaluate the effect of risk stratification on BDI rates. |  |  |  | | --- | --- | | Question 7 | | | **Should [PICO7] surgery guided by prior risk stratification that accounts for cholecystolithiasis vs. no risk stratification or alternative risk stratification be used for limiting the risk or severity of bile duct injury in candidates for laparoscopic cholecystectomy?** | | | **Population:** | Patients scheduled to undergo laparoscopic cholecystectomy | | **Intervention:** | [PICO7] surgery guided by prior risk stratification that accounts for cholecystolithiasis | | **Comparison:** | no risk stratification or alternative risk stratification | | **Main outcomes:** | Bile duct injury (BDI) (quality of CVS as proxy for BDI), Conversion; complications; mortality |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | **No evidence was found that directly addressed this question (either between risk stratification systems or between risk stratification and no stratification) and there are no risk stratification models that stratify patients on the presence or absence of gallstones.** | Current models that risk stratify patients and guide management, which include TG18, only apply to patients with calculous acute cholecystitis. Existing evidence on risk stratification models is also limited to prognostic risk association studies as opposed to studies evaluating the effectiveness of using the prognostic information in the management of patients undergoing lap chole. | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ○ Moderate ○ Small ○  Trivial ○ Varies ●Don't know | **No evidence was found that directly addressed this question (either between risk stratification systems or between risk stratification and no stratification) and there are no risk stratification models that stratify patients on the presence or absence of gallstones.** |  | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Very low ○ Low ○ Moderate ○ High ● No included studies | **No evidence was found that directly addressed this question (either between risk stratification systems or between risk stratification and no stratification) and there are no risk stratification models that stratify patients on the presence or absence of gallstones.** |  | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Since BDI is the main outcome for decision making, the GDG panel did not expect any patient uncertainty or variability |  | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know | No evidence was found | There are no existing models that risk stratify based on the presence of gallstones. | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ●  Probably yes ○ Yes ○ Varies ○  Don't know | No evidence was found | Current risk stratification for the severity of acute cholecystitis exist; the GDG panel did not feel that there was harm in using such models and thought it would be acceptable to key stakeholders. | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | No evidence was found | The GDG panel did not perceive any feasibility issues with implementation of risk stratification systems. |  Conclusions  |  | | --- | | Recommendation | | No evidence based recommendation can be made to answer this question.  No risk prediction models exist that incorporate the presence or absence of gallstones as a factor that increases bile duct injury or difficulty of laparoscopic cholecystectomy | |  |  |  | | --- | | Justification | | No risk stratification models exist for calculous vs. non-calculous disease. While acute cholecystitis has been associated with increased risk of BDI in many studies, BDI can happen in the setting of aberrant anatomy and often represents a mis-identification problem. |  |  | | --- | | Subgroup considerations | |  |  |  | | --- | | Implementation considerations | |  |  |  | | --- | | Monitoring and evaluation | |  |  |  |  | | --- | --- | | Research priorities | | | Development of risk stratification models that take into consideration the presence or absence of gallstones.  Studies that compare BDI risk in patients with and without gallstones (including calculous vs acalculous cholecystitis).  Large multi-institutional studies using clinical data are needed to demonstrate the effectiveness of risk stratification models incorporating gallstones for bile duct injury. | | | **Question 8** | | | **Should [PICO8] Immediate Cholecystectomy vs. Delayed Cholecystectomy be used for acute cholecystitis?** | | | **Population:** | acute cholecystitis | | **Intervention:** | [PICO8] Immediate Cholecystectomy | | **Comparison:** | Delayed Cholecystectomy | | **Main outcomes:** | Bile duct injury; Mortality; Conversion; Patients with complications; Duration of surgery; Length of total hospitalization; Wound infection; |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with Delayed Cholecystectomy** | **Risk difference with [PICO8] Immediate Cholecystectomy** | | Bile duct injury | 14220 (1 observational study) | ⨁◯◯◯ VERY LOWa,b,c | **RR 0.53** (0.31 to 0.90) | Study population | | | 5 per 1,000 | **3 fewer per 1,000** (4 fewer to 1 fewer) | | Mortality | 1293 (8 RCTs) | ⨁◯◯◯ VERY LOWb,d,e | **RR 1.03** (0.05 to 20.50) | Study population | | | 153 per 100,000 | **5 more per 100,000** (145 fewer to 2,982 more) | | Conversion | 1452 (12 RCTs) | ⨁◯◯◯ VERY LOWb,d,f | **RR 0.86** (0.65 to 1.13) | Study population | | | 154 per 1,000 | **22 fewer per 1,000** (54 fewer to 20 more) | | Patients with complications | 1268 (9 RCTs) | ⨁◯◯◯ VERY LOWb,d,f,g | **RR 0.66** (0.42 to 1.03) | Study population | | | 299 per 1,000 | **102 fewer per 1,000** (173 fewer to 9 more) | | Duration of surgery | 1276 (10 RCTs) | ⨁◯◯◯ VERY LOWb,d,f | - | The mean duration of surgery was **86** min | MD **13 min more** (8.13 fewer to 34.12 more) | | Length of total hospitalization | 1383 (11 RCTs) | ⨁⨁◯◯ LOWb,d | - | The mean length of total hospitalization was **7.3** days | MD **3.2 days fewer** (5.1 fewer to 1.3 fewer) | | Wound infection | 1145 (8 RCTs) | ⨁◯◯◯ VERY LOWb,d,h | **RR 0.57** (0.35 to 0.93) | Study population | | | 62 per 1,000 | **27 fewer per 1,000** (41 fewer to 4 fewer) |  1. Diagnosis of acute cholecystitis made by ICD code and not by TG guideline or histologic study. Confounding by severity grade of acute cholecystitis is a major concern. 2. Severity was not graded increasing the risk that higher severity patients were excluded from the study. 3. Data are fragile with a fragility index of 2. 4. Moderate risk of bias across the body of evidence because most of the larger studies included in the meta-analysis of Cao et al 2015 were given a score of 3 out 5 on the Jadad scale. 5. Low number of total events and wide confidence interval compatible with both substantial benefit and harm. 6. Wide confidence interval compatible with both important benefit, lack of benefit, or even important harm; additionally suboptimal information size. 7. Inconsistent results across trials included in meta-analysis [I-squared = 50.82, p=0.04]. 8. Fragility index is zero. Also imprecise confidence interval compatible with both meaningful benefit as well as lack of it. | The included randomized studies did not include acute cholecystitis severity grading raising the possibility that the subgroup of patients with moderate and severe cholecystitis were underrepresented. One large population study showed that grading of severity was critically important in evaluating the rate of bile duct injury in cholecystectomy for acute cholecystitis. In that study, patients with acute cholecystitis had a significantly higher bile duct injury rate than patients without acute cholecystitis primarily due to a higher BDI risk in patients with moderate cholecystitis (Tokyo Guidelines Grade 2). Patients with mild acute cholecystitis (Tokyo Guidelines Grade 1) did not have a higher incidence of bile duct injury. In severe acute cholecystitis (Tokyo Guideline Grade 3) there was a non-significant trend towards an increased rate of injury. In patients who had 1 or more prior attacks there was a significantly higher incidence of bile duct injury.  There is also concern that the existing evidence may be limited in its generalizability by the fact that there is variability in how the diagnosis of acute cholecystitis was made and there is reason to be concerned that the administrative diagnostic codes may have included patients with acute biliary pain but no acute inflammation. | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with Delayed Cholecystectomy** | **Risk difference with [PICO8] Immediate Cholecystectomy** | | Bile duct injury | 14220 (1 observational study) | ⨁◯◯◯ VERY LOWa,b,c | **RR 0.53** (0.31 to 0.90) | Study population | | | 5 per 1,000 | **3 fewer per 1,000** (4 fewer to 1 fewer) | | Mortality | 1293 (8 RCTs) | ⨁◯◯◯ VERY LOWb,d,e | **RR 1.03** (0.05 to 20.50) | Study population | | | 153 per 100,000 | **5 more per 100,000** (145 fewer to 2,982 more) | | Conversion | 1452 (12 RCTs) | ⨁◯◯◯ VERY LOWb,d,f | **RR 0.86** (0.65 to 1.13) | Study population | | | 154 per 1,000 | **22 fewer per 1,000** (54 fewer to 20 more) | | Patients with complications | 1268 (9 RCTs) | ⨁◯◯◯ VERY LOWb,d,f,g | **RR 0.66** (0.42 to 1.03) | Study population | | | 299 per 1,000 | **102 fewer per 1,000** (173 fewer to 9 more) | | Duration of surgery | 1276 (10 RCTs) | ⨁◯◯◯ VERY LOWb,d,f | - | The mean duration of surgery was **86** min | MD **13 min more** (8.13 fewer to 34.12 more) | | Length of total hospitalization | 1383 (11 RCTs) | ⨁⨁◯◯ LOWb,d | - | The mean length of total hospitalization was **7.3** days | MD **3.2 days fewer** (5.1 fewer to 1.3 fewer) | | Wound infection | 1145 (8 RCTs) | ⨁◯◯◯ VERY LOWb,d,h | **RR 0.57** (0.35 to 0.93) | Study population | | | 62 per 1,000 | **27 fewer per 1,000** (41 fewer to 4 fewer) |  1. Diagnosis of acute cholecystitis made by ICD code and not by TG guideline or histologic study. Confounding by severity grade of acute cholecystitis is a major concern. 2. Severity was not graded increasing the risk that higher severity patients were excluded from the study. 3. Data are fragile with a fragility index of 2. 4. Moderate risk of bias across the body of evidence because most of the larger studies included in the meta-analysis of Cao et al 2015 were given a score of 3 out 5 on the Jadad scale. 5. Low number of total events and wide confidence interval compatible with both substantial benefit and harm. 6. Wide confidence interval compatible with both important benefit, lack of benefit, or even important harm; additionally suboptimal information size. 7. Inconsistent results across trials included in meta-analysis [I-squared = 50.82, p=0.04]. 8. Fragility index is zero. Also imprecise confidence interval compatible with both meaningful benefit as well as lack of it. | The included randomized studies did not include acute cholecystitis severity grading raising the possibility that the subgroup of patients with moderate and severe cholecystitis were underrepresented. One large population study showed that grading of severity was critically important in evaluating the rate of bile duct injury in cholecystectomy for acute cholecystitis. In that study, patients with acute cholecystitis had a significantly higher bile duct injury rate than patients without acute cholecystitis primarily due to a higher BDI risk in patients with moderate cholecystitis (Tokyo Guidelines Grade 2). Patients with mild acute cholecystitis (Tokyo Guidelines Grade 1) did not have a higher incidence of bile duct injury. In severe acute cholecystitis (Tokyo Guideline Grade 3) there was a non-significant trend towards an increased rate of injury. In patients who had 1 or more prior attacks there was a significantly higher incidence of bile duct injury.  There is concern that the existing evidence may be limited in its generalizability by the fact that there is variability in how the diagnosis of acute cholecystitis was made and there is reason to be concerned that the administrative diagnostic codes may have included patients with acute biliary pain but no acute inflammation. | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ● Very low ○ Low ○ Moderate ○ High ○ No included studies | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with Delayed Cholecystectomy** | **Risk difference with [PICO8] Immediate Cholecystectomy** | | Bile duct injury | 14220 (1 observational study) | ⨁◯◯◯ VERY LOWa,b,c | **RR 0.53** (0.31 to 0.90) | Study population | | | 5 per 1,000 | **3 fewer per 1,000** (4 fewer to 1 fewer) | | Mortality | 1293 (8 RCTs) | ⨁◯◯◯ VERY LOWb,d,e | **RR 1.03** (0.05 to 20.50) | Study population | | | 153 per 100,000 | **5 more per 100,000** (145 fewer to 2,982 more) | | Conversion | 1452 (12 RCTs) | ⨁◯◯◯ VERY LOWb,d,f | **RR 0.86** (0.65 to 1.13) | Study population | | | 154 per 1,000 | **22 fewer per 1,000** (54 fewer to 20 more) | | Patients with complications | 1268 (9 RCTs) | ⨁◯◯◯ VERY LOWb,d,f,g | **RR 0.66** (0.42 to 1.03) | Study population | | | 299 per 1,000 | **102 fewer per 1,000** (173 fewer to 9 more) | | Duration of surgery | 1276 (10 RCTs) | ⨁◯◯◯ VERY LOWb,d,f | - | The mean duration of surgery was **86** min | MD **13 min more** (8.13 fewer to 34.12 more) | | Length of total hospitalization | 1383 (11 RCTs) | ⨁⨁◯◯ LOWb,d | - | The mean length of total hospitalization was **7.3** days | MD **3.2 days fewer** (5.1 fewer to 1.3 fewer) | | Wound infection | 1145 (8 RCTs) | ⨁◯◯◯ VERY LOWb,d,h | **RR 0.57** (0.35 to 0.93) | Study population | | | 62 per 1,000 | **27 fewer per 1,000** (41 fewer to 4 fewer) |  1. Diagnosis of acute cholecystitis made by ICD code and not by TG guideline or histologic study. Confounding by severity grade of acute cholecystitis is a major concern. 2. Severity was not graded increasing the risk that higher severity patients were excluded from the study. 3. Data are fragile with a fragility index of 2. 4. Moderate risk of bias across the body of evidence because most of the larger studies included in the meta-analysis of Cao et al 2015 were given a score of 3 out 5 on the Jadad scale. 5. Low number of total events and wide confidence interval compatible with both substantial benefit and harm. 6. Wide confidence interval compatible with both important benefit, lack of benefit, or even important harm; additionally suboptimal information size. 7. Inconsistent results across trials included in meta-analysis [I-squared = 50.82, p=0.04]. 8. Fragility index is zero. Also imprecise confidence interval compatible with both meaningful benefit as well as lack of it. |  | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability | Research evidence addressing this criterion was not search and reviewed as it was not anticipated to exist by the experts on the panel. | The guideline panel opined that there is no important uncertainty or variability in how much people value the outcomes of bile duct injury, mortality, complications, or wound infection. There is probably no important uncertainty or variability in how much people value the outcomes of conversion, duration of surgery, or length of total hospitalization. | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  |  | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Research evidence addressing this criterion was not searched and reviewed as it was not anticipated to exist by the experts on the panel. | Potential stakeholders include patients, hospitals, surgeons, and insurance providers. Acceptability of the intervention may be different for different stakeholders. Immediate cholecystectomy is likely acceptable to patients and insurance providers. It does place time and resource burdens on the surgeons and the hospitals initially but this is likely offset by the potential downstream benefits. | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Research evidence addressing this criterion was not searched and reviewed as it was not anticipated to exist by the experts on the panel. | The majority of hospitals have the required logistics and capacity to offer immediate cholecystectomy. |   **Type of recommendation**   |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention | | ○ | ○ | ○ | **●** | ○ |   **Conclusions**   |  | | --- | | **Recommendation** | | In patients presenting with mild acute cholecystitis (according to TG) we suggest cholecystectomy within 72 hours of symptom onset (conditional recommendation, very low certainty of evidence).  For patients with moderate and severe cholecystitis there is insufficient evidence to make a recommendation, particularly as it relates to the outcome of bile duct injury. | |  |  |  | | --- | | **Justification** | | The guideline panel examined the pooled effect estimates corresponding to the pre-specified outcomes. Given the very small magnitude of effect (i.e. the point estimate) suggesting clinical equivalence of the two management options with respect to these outcome, mortality, and duration of surgery were considered no more relevant for decision-making.  Although, certainty of evidence was judged very low given the imprecision in effect estimates and study limitations, the magnitude of benefits with respect to the outcomes of bile duct injury, wound infection, length of hospitalization, risk of conversion, and surgical complications consistently favored immediate cholecystectomy, judged overall as moderate. No recommendation is made for patients presenting with moderate and severe cholecystitis because the randomized studies did not include severity grading raising the possibility that these subgroups were underrepresented. One large population study showed that grading of severity was critically important in evaluating the rate of bile duct injury in cholecystectomy for acute cholecystitis. Patients with acute cholecystitis had a significantly higher bile duct injury rate than patients without acute cholecystitis and that was due to a higher rate in patients with moderate cholecystitis (Tokyo Guidelines Grade 2). Patients with mild acute cholecystitis (Tokyo Guidelines Grade 1) did not have a higher incidence of bile duct injury. In severe acute cholecystitis (Tokyo Guideline Grade 3) there was a non-significant trend towards an increased rate of injury. In patients who had prior attacks over more than 5 years there was a significantly higher incidence of bile duct injury. This conforms to results of multiple studies that show prior attacks of acute cholecystitis increase operative difficulty as evidenced by increases rates of conversion to open surgery. The present analysis is also limited by the fact that there is variability in how the diagnosis of acute cholecystitis is made and there is reason to be concerned that the administrative diagnostic codes may include patients with acute biliary pain but no acute inflammation. Due to these limitations the certainty of outcome for all of the outcomes studied was very low making this a conditional recommendation. |  |  | | --- | | **Subgroup considerations** | | As outlined in the recommendation and justification the subgroups of mild, moderate, and severe acute cholecystitis as defined by the Tokyo Guidelines need to be considered separately. |  |  | | --- | | **Implementation considerations** | |  |  |  | | --- | | **Monitoring and evaluation** | |  |  |  | | --- | | **Research priorities** | | There is a need for large population studies to determine the role of timing of cholecystectomy on bile duct injury. Because of the low incidence of major bile duct injury randomized trials cannot practically answer this question. These studies should use rigorous means of diagnosis and severity grading of acute cholecystitis in order to determine the contribution of early versus late cholecystectomy in bile duct injury. In addition, clear definitions of early and late cholecystectomy preferably defined from the time of onset of symptoms need to be developed according to inflammatory phase (see Table of suggested phases). The main reason that randomized studies are unlikely to answer the questions regarding bile duct injury is because the low incidence of bile duct injury would require approximately 4,000 patients per study arm.  Although not mentioned above, a serious limitation of all studies in this area is the failure to use a standard definition of “early” and “late” cholecystectomy. In randomized trials that are available there is large variability in the actual timing of early vs late cholecystectomy in relation to the onset of acute cholecystitis and the times do not necessarily relate to the evolution of inflammation. The importance of the timing of cholecystectomy relates to the degree of inflammation once acute cholecystitis sets in with the procedure becoming more technically challenging and thus potentially more dangerous when inflammation is intense. Therefore, the rationale for operating early is to operate before inflammation is too intense; alternatively, delaying operating until the inflammation has had a chance to become less intense (ie. after 6 weeks) and avoiding the intermediate period when it is most intense, may minimize inflammation related operative complications. The period of most intense inflammation would be expected to be between 10 days and 6 weeks. A further distinction can be made between 0 and 72 hours and between 72 hours and 10 days, as inflammatory changes increase in the second time window. As a result further studies should consider comparisons among the following phases of inflammation which correspond to the expected ease or difficulty of cholecystectomy related to the evolution of inflammation.  Phase 1. Onset of symptoms to 72 hours. Inflammation expected to be favorable for cholecystectomy. Tissue swelling due to edema.  Phase 2. 72 hours to 10 days. Inflammation expected to be less favorable for cholecystectomy. Tissue swelling and increased vascularity.  Phase 3. 10 days to 6 weeks. Inflammation expected to be much less favorable for cholecystectomy. Acute and chronic inflammation.  Phase 4. 6 weeks or later. Inflammation expected to be more favorable again for cholecystectomy. Predominately chronic inflammation.  There is also some justification for a period greater than 12 weeks but there is very little information in the literature that this time period had been the subject of study.  There are few high quality studies that have compared phase 2 (72 hours to 10 days) to phase 4 (greater than 6 weeks). The one study that did this found an advantage to operating in phase 2 versus phase 4 in terms of total adverse events (Roulin).  Studies considering the groups of patients that are not candidates for early cholecystectomy need to be performed. One study in patients with severe acute cholecystitis (Tokyo Guideline Grade 3) examined the safety of cholecystectomy in patients with different types of organ failure and found that early operation in patients presenting with renal or cardiac acute organ failure did well after early cholecystectomy. Patients with other reasons for organ failure had increased rate of post-operative complications.    In summary, studies reporting outcomes of patients with acute cholecystitis should include the timing of operative intervention (phases 1-4) since symptom onset and the severity of the disease according to the Tokyo guidelines. Based on the above rationale the guidelines development group provides the following specific recommendations for future studies:  1) Studies that examine the relationship between bile duct injury and acute cholecystitis should match patients at baseline both for severity grade of acute cholecystitis and history of prior attacks of acute cholecystitis. This recommendation is based on the finding that the incidence of major bile duct injury is significantly higher in moderate grade acute cholecystitis than in mild grade acute cholecystitis and the finding that the incidence of bile duct injury is higher in patients who have had prior attacks of acute cholecystitis than those who have not.  2) The diagnosis of acute cholecystitis should be documented in future studies following well accepted clinical criteria such as TG18 diagnostic criteria or histologic findings of acute inflammation or both. If documentation of acute cholecystitis is based on diagnostic codes, investigators should ensure that the diagnostic codes were based on the preceding criteria.  3) In acute cholecystitis for the purposes of reporting standardization and ability to compare results among studies, we suggest that the interval between onset of symptoms and time of operation should be defined in 4 phases (P1-4): P1: Symptom onset to 72 hours; P2: 72 hours to 10 days; P3: 10 days to 6 weeks; P4: > 6 weeks. We also recommend that studies define the onset of acute cholecystitis from the onset of patient symptoms rather than from the arrival of the patient to the hospital. |  |  |  | | --- | --- | | **Question 9** | | | **Should [PICO 9] subtotal cholecystectomy vs. total laparoscopic or open cholecystectomy be used for limiting the risk or severity of bile duct injury in patients who at the time of their operation have MARKED acute LOCAL INFLAMMATION or CHRONIC cholecystitis with biliary inflammatory fusion (BIF) of tissues and tissue contraction? ?** | | | **Population:** | Patients who at the time of their laparoscopic cholecystectomy are found to have marked inflammation (acute or chronic) | | **Intervention:** | [PICO 9] subtotal cholecystectomy | | **Comparison:** | total laparoscopic or open cholecystectomy | | **Main outcomes:** | Bile duct injury; |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | No direct head-to-head comparative evidence was found addressing this question. Making indirect qualitative comparisons from case series of subtotal cholecystectomy versus total cholecystectomy was considered critically flawed because of non-exchangeability of surgical populations due to confounding by indication for subtotal versus total cholecystectomy. |  | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | No direct head-to-head comparative evidence was found addressing this question. Making indirect qualitative comparisons from case series of subtotal cholecystectomy versus total cholecystectomy was considered critically flawed because of non-exchangeability of surgical populations due to confounding by indication for subtotal versus total cholecystectomy. |  | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Bile duct injury is the only decision-making outcome for this question. |  | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know |  |  | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know |  | As per patient factors and surgeon's skillset. | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | It is probably feasible to teach and practice this skill. Also, it is feasible to study this in the future. |   **Conclusions**   |  | | --- | | **Recommendation** | | No evidence-based recommendation can be made at this time. However, the GDG suggests that when marked acute local inflammation or chronic cholecystitis with biliary inflammatory fusion (BIF) of tissues/tissue contraction is encountered during laparoscopic cholecystectomy that prevent the safe identification of the cystic duct and artery, surgeons consider subtotal cholecystectomy either laparoscopically or open depending on their skill set and comfort with the procedure (expert opinion). | |  |  |  | | --- | | **Justification** | | Because no admissible direct or indirect evidence addressed this guideline question, the panel deemed that a subtotal cholecystectomy is likely to limit the risk for BDI by avoiding dissection in the hepatocystic triangle. Both open and laparoscopic surgical approaches were considered relevant based on patient and surgeon factors. |  |  | | --- | | **Subgroup considerations** | |  |  |  | | --- | | **Implementation considerations** | | - |  |  | | --- | | **Monitoring and evaluation** | | - |  |  | | --- | | **Research priorities** | | There is dearth of comparative evidence addressing this question. Both experimental and observational comparative studies are warranted that define the patient population based on intraoperative findings of severity of acute/ chronic inflammation.   |  |  | | --- | --- | | Question 10 | | | **Should [PICO 10] reduced port lap chole vs. standard port lap chole be used for limiting risk or severity of bile duct injury?** | | | **Population:** | Patients undergoing cholecystectomy | | **Intervention:** | [PICO 10] reduced port lap chole | | **Comparison:** | standard port lap chole | | **Main outcomes:** | Bile Duct Injury; Total severe grade III or more Clavien-Dindo complications; Port site hernia; Total postoperative analgesic use; Operative Time; Conversion to open; Cosmesis (patient self-reported outcome); QOL. |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **Anticipated absolute effects\* (95% CI)** | | **Relative effect (95% CI)** | **№ of participants (studies)** | **Certainty of the evidence (GRADE)** | **Comments** | | --- | --- | --- | --- | --- | --- | --- | | **Risk with standard port lap whole** | **Risk with [PICO 10] reduced port lap chole** | | Bile Duct Injury | No direct comparative evidence addressed this outcome. Indirect comparison was made from evidence from two systematic reviews (including total >507,918 patients) of single arm cohort studies of single port versus standard port approach. The pooled effect estimate for BDI was 0.72% (simple average of the data across studies) vs. 0.32 to 0.52% (pooled range) {Joseph et al., 2012 and Pucher et al. 2018) | | - | 2626 (45 observational studies) | ⨁◯◯◯ VERY LOWa,b |  | | Total severe grade III or more Dindo-Clavien complications | Study population | | **RR 2.02** (1.29 to 3.15) | 4518 (24 RCTs) | ⨁⨁⨁◯ MODERATEc |  | | 11 per 1,000 | **22 per 1,000** (14 to 34) | | Port site hernia | Study population | | **RR 2.69** (1.24 to 5.86) | 4222 (10 RCTs) | ⨁⨁◯◯ LOWc |  | | 3 per 1,000 | **7 per 1,000** (3 to 16) | | Total postoperative analgesic use | The mean total postoperative analgesic use was **0** mg | MD **3.78 mg lower** (13.78 lower to 6.22 higher) | - | 361 (3 observational studies) | ⨁◯◯◯ VERY LOWd,e,f |  | | Operative Time | The mean operative Time was **0** min | MD **9.6 min higher** (2.4 higher to 16.8 higher) | - | 2250 (11 RCTs) | ⨁⨁⨁◯ MODERATEg,h |  | | Conversion to open | Study population | | not estimable | 2049 (27 RCTs) | ⨁⨁◯◯ LOWg,i |  | | 2 per 1,000 | **0 per 1,000** (0 to 0) | | Cosmesis | The mean cosmesis was **0** SD | SMD **1.37 SD higher** (0.86 higher to 1.89 higher) | - | 2211 (18 RCTs) | ⨁⨁◯◯ LOWc,j,k |  | | QOL | The mean QOL was **0** SD | SMD **0.05 SD higher** (0.03 lower to 0.13 higher) | - | 2211 (18 RCTs) | ⨁⨁◯◯ LOWc,f,j |  |  1. Single arm cohort studies from separate systematic reviews of each intervention type compared indirectly with important limitations owing to study design and indirect comparison. There is also higher likelihood that the single port approach would have included more elective cases with concerns of confounding by indication. 2. Unclear as corresponding forest plots were not provided. However, substantial between study heterogeneity was noted in both systematic reviews. 3. (Arezzo 2018): majority of trials had high risk of bias due to concerns such as soundness of randomization and its concealment, or blinding of outcome assessors. However, authors report subgroup analyses of lower risk of bias studies showed consistent results. 4. (Qiu 2013): 2 non-randomized cohort studies and one RCT were included. The non-randomized studies received quality ratings of 6 and 8 (max 9 by modified Newcastle Ottawa scale), but the RCT was as possible high risk for sequence generation, concealment, incomplete outcome and selective reporting. 5. I-squared was 66%, however a forest plot of the studies was not provided by authors. 6. Imprecise due to confidence interval being compatible with both the potential for undesirable effect as well as desirable effect. 7. (From Milas2014):Single incision vs standard multiport laparoscopic cholecystectomy: updated systematic review and meta-analysis of RCTs) most studies were low to moderate quality, only 2 fulfilled all criteria of ROB Cochrane collaboration tool 8. Subgroup analysis stratifying based on risk of differential expertise bias, those 11 studies with low risk of differential expertise bias are reported. 9. Estimate not possible based on events reported. 10. Subgroup analysis is reported here for only those studies that declared "blinding of participants and personnel." 11. Despite subgroup analysis for studies reporting blinding of participants and personnel and stratifying cosmesis scores by postoperative period, heterogeneity as reflected in I2 value remained high. Additionally, results between different systematic reviews reflected great variation. | The outcomes on which results favored single port laparoscopic cholecystectomy were analgesic use, cosmesis and quality of life. The magnitude of these effects were imprecise as well as clinically small to trivial. | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know | | **Outcomes** | **Anticipated absolute effects\* (95% CI)** | | **Relative effect (95% CI)** | **№ of participants (studies)** | **Certainty of the evidence (GRADE)** | **Comments** | | --- | --- | --- | --- | --- | --- | --- | | **Risk with standard port lap whole** | **Risk with [PICO 10] reduced port lap chole** | | Bile Duct Injury | No direct comparative evidence addressed this outcome. Indirect comparison was made from evidence from two systematic reviews (including total >507,918 patients) of single arm cohort studies of single port versus standard port approach. The pooled effect estimate for BDI was 0.72% (simple average of the data across studies) vs. 0.32 to 0.52% (pooled range) {Joseph et al., 2012 and Pucher et al. 2018) | | - | 2626 (45 observational studies) | ⨁◯◯◯ VERY LOWa,b |  | | Total severe grade III or more Dindo-Clavien complications | Study population | | **RR 2.02** (1.29 to 3.15) | 4518 (24 RCTs) | ⨁⨁⨁◯ MODERATEc |  | | 11 per 1,000 | **22 per 1,000** (14 to 34) | | Port site hernia | Study population | | **RR 2.69** (1.24 to 5.86) | 4222 (10 RCTs) | ⨁⨁◯◯ LOWc |  | | 3 per 1,000 | **7 per 1,000** (3 to 16) | | Total postoperative analgesic use | The mean total postoperative analgesic use was **0** mg | MD **3.78 mg lower** (13.78 lower to 6.22 higher) | - | 361 (3 observational studies) | ⨁◯◯◯ VERY LOWd,e,f |  | | Operative Time | The mean operative Time was **0** min | MD **9.6 min higher** (2.4 higher to 16.8 higher) | - | 2250 (11 RCTs) | ⨁⨁⨁◯ MODERATEg,h |  | | Conversion to open | Study population | | not estimable | 2049 (27 RCTs) | ⨁⨁◯◯ LOWg,i |  | | 2 per 1,000 | **0 per 1,000** (0 to 0) | | Cosmesis | The mean cosmesis was **0** SD | SMD **1.37 SD higher** (0.86 higher to 1.89 higher) | - | 2211 (18 RCTs) | ⨁⨁◯◯ LOWc,j,k |  | | QOL | The mean QOL was **0** SD | SMD **0.05 SD higher** (0.03 lower to 0.13 higher) | - | 2211 (18 RCTs) | ⨁⨁◯◯ LOWc,f,j |  |  1. Single arm cohort studies from separate systematic reviews of each intervention type compared indirectly with important limitations owing to study design and indirect comparison. There is also higher likelihood that the single port approach would have included more elective cases with concerns of confounding by indication. 2. Unclear as corresponding forest plots were not provided. However, substantial between study heterogeneity was noted in both systematic reviews. 3. (Arezzo 2018): majority of trials had high risk of bias due to concerns such as soundness of randomization and its concealment, or blinding of outcome assessors. However, authors report subgroup analyses of lower risk of bias studies showed consistent results. 4. (Qiu 2013): 2 non-randomized cohort studies and one RCT were included. The non-randomized studies were received quality ratings of 6 and 8 (max 9 by modified Newcastle Ottawa scale), but the RCT was as possible high risk for sequence generation, concealment, incomplete outcome and selective reporting. 5. I-squared was 66%, however a forest plot of the studies was not provided by authors. 6. Imprecise due to confidence interval being compatible with both the potential for undesirable effect as well as desirable effect. 7. (From Milas2014): Single incision vs standard multiport laparoscopic cholecystectomy: updated systematic review and meta-analysis of RCTs) most studies were low to moderate quality, only 2 fulfilled all criteria of ROB Cochrane collaboration tool 8. Subgroup analysis stratifying based on risk of differential expertise bias, those 11 studies with low risk of differential expertise bias are reported. 9. Estimate not possible based on events reported. 10. Subgroup analysis is reported here for only those studies that declared "blinding of participants and personnel". 11. Despite subgroup analysis for studies reporting blinding of participants and personnel and stratifying cosmesis scores by postoperative period., heterogeneity as reflected in I2 value remained high. Additionally, results between different systematic reviews reflected great variation. | The undesirable effects for single port laparoscopic cholecystectomy include BDI, total severe complication, operative time, port site hernia and conversion to open procedure. The magnitude of these effects was conservatively judged moderate by the panel. | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Very low ○ Low ● Moderate ○ High ○ No included studies |  | The certainty of evidence was judged to be moderate. Although for individual outcomes the certainty ratings ranged from very low to moderate, the evidence on critical outcomes (BDI, severe complication) consistently favored standard port laparoscopic cholecystectomy with certainty rating for severe complications judged to be moderate. As such, the highest certainty evidence informed overall certainty. | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability | No direct evidence ranking patient value for the considered outcomes was available. | Although there may be variability in how much patients value cosmesis, the panel believes that almost all patients will value the remainder of outcomes greater than cosmesis alone. | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  | Although evidence favors standard port,  the panel acknowledged that in highly experienced hands, single port may yield similar outcomes as standard port. | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | Both procedures are already done in practice.  Highly experienced surgeons may still prefer opting for single port laparoscopic cholecystectomy, given concerns of generalizability of the evidence to their expertise. | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | Both procedures are already done in practice. |  Type of recommendation  |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | **●** | ○ | ○ | ○ |  Conclusions  |  | | --- | | Recommendation | | For patients requiring cholecystectomy, we suggest using a multi-port laparoscopic technique instead of single port/single incision technique (conditional recommendation, moderate certainty of evidence). | |  |  |  | | --- | | Justification | | Evidence of moderate certainty suggests outcomes are superior for standard port over reduced-port cholecystectomy/SILS, however, concerns were noted regarding the generalizability to, and acceptability by, surgeons highly experienced in single port laparoscopy. This recommendation pertains specifically to the comparison of single port laparoscopic cholecystectomy versus standard port laparoscopic cholecystectomy. |  |  | | --- | | Subgroup considerations | |  |  |  | | --- | | Implementation considerations | |  |  |  | | --- | | Monitoring and evaluation | |  |  |  | | --- | | Research priorities | | Large scale randomized trials powered to adequately detect biliary injury are desirable, but their feasibility is questionable in view of the large patient numbers required. The establishment of a prospectively maintained national and/or statewide database, including outcomes and complications, should be sought as it may be more likely to identify differences.  Study of comparative outcomes between these two techniques when surgeons are highly experienced might also shed light into the generalizability of the recommendations to highly experienced surgeons.  Patient surveys that rank |  |  |  | | --- | --- | | Question 11 | | | **Should [PICO 11] interval/delayed laparoscopic cholecystectomy vs. no additional treatment be used for patients previously treated by cholecystostomy?** | | | **Population:** | patients previously treated by cholecystostomy | | **Intervention:** | [PICO 11] interval/delayed laparoscopic cholecystectomy | | **Comparison:** | no additional treatment | | **Main outcomes:** | bile duct injury, 30-day mortality, duration of surgery, readmissions, complications of surgery, and conversion |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | No direct comparative evidence was found addressing this question. Making indirect comparisons from non-comparative cohort studies of patients treated by cholecystostomy who had no additional treatment versus studies of patients who had interval cholecystectomy was considered flawed because of non-exchangeability of the populations due to confounding in the predicted operative risks of the patients. Cohorts that did not undergo interval cholecystectomy were preferentially overrepresented by patients unfit for surgery. | The primary desirable anticipated effect of interval cholecystectomy, compared to not having the procedure, described in the reviewed cohort studies is avoidance of recurrent gallbladder-related symptoms which occurred in 20-50% of patients who did not undergo interval cholecystectomy. There is also some evidence that in this group recurrent symptoms were associated with urgent cholecystectomy, which has a higher rate of open cholecystectomy and post-operative complications. Based on expert opinion, the anticipated desirable effects were determined to be moderately substantial. | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | No direct comparative evidence was found addressing this question. Making indirect comparisons from non-comparative cohort studies of patients treated by cholecystostomy who had no additional treatment versus studies of patients who had interval cholecystectomy was considered flawed because of non-exchangeability of the populations due to confounding in the predicted operative risks of the patients. Cohorts that did not undergo interval cholecystectomy were preferentially overrepresented by patients unfit for surgery. | The primary undesirable anticipated effect of interval cholecystectomy, compared to not have the procedure, described in the reviewed cohort studies is increased cholecystectomy-related complications including mortality. In the largest cohort study, the 30-day mortality after interval cholecystectomy was 2%, however, this will vary significantly in patients determined to be fit for surgery and those determined to be unfit for surgery. There is no consideration in the available data of criteria stipulating who is not fit for surgery, so the proportion of the two groups cannot be determined. For this guideline recommendations the panel decided to distinguish two subgroups of patients guided by their fitness for surgery. Based on expert opinion, the risk of undesirable effects was small in the subgroup of patients that were determined to be fit for surgery. | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Very low ○ Low ○ Moderate ○ High ● No included studies | Existing empiric evidence was judged too flawed to inform the guideline recommendations. |  | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability | Research evidence addressing this criterion was not searched and reviewed as it was not anticipated to exist by the experts on the panel. | The guideline panel judged that there was no important uncertainty or variability in how much people value the outcomes of bile duct injury or cholecystectomy related complications. There is probably no important uncertainty or variability in how much people the outcome of recurrent gallbladder-related symptoms is valued. | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  | The guideline panel judged that in the subgroup of patients determined to be fit for surgery the balance of effects favors the intervention. In the subgroup of patients determined to be unfit for surgery, the balance of effects probably favors the alternative management option. | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know | Research evidence addressing this criterion was not searched and reviewed as it was not anticipated to exist by the experts on the panel. | Potential stakeholders include patients, hospitals, surgeons, and insurance providers. Acceptability of the intervention may be different for different stakeholders. The main stakeholder for these recommendations is the patient and the acceptability will vary based on the patient's surgical risks and risk-tolerance. | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Research evidence addressing this criterion was not searched and reviewed as it was not anticipated to exist by the experts on the panel. | Surgeons are expected to have the relevant skillset as part of their training and most also have adequate practice experience. Most hospitals and outpatient centers also have the required logistics and capacity to offer interval cholecystectomy. |  Conclusions  |  | | --- | | Recommendation | | In patients with acute calculous cholecystitis previously treated by percutaneous cholecystostomy who are good surgical candidates, we suggest that interval cholecystectomy is preferred after the inflammation has subsided. For poor operative candidates, we suggest a non-surgical approach that may include percutaneous stone clearance through the tube tract or tube removal and observation if the cystic duct is patent (expert recommendation in the absence of empiric evidence). | |  |  |  | | --- | | Justification | | Existing evidence was judged too flawed to inform this recommendation. The guideline panel, however, deliberated the following rationale to inform their expert opinions: Roughly 50 to 80% of patients who do not undergo interval (planned elective) cholecystectomy have no further problems after removal of the cholecystostomy tube, but the remainder will develop recurrent gallbladder-related symptoms and may require urgent cholecystectomy or repeat cholecystostomy tube placement. On the other hand, patients who undergo elective interval cholecystectomy are less likely to require urgent cholecystectomy and are more likely to have cholecystectomy completed laparoscopically with its associated benefits over open cholecystectomy. The available data is retrospective and it is likely that the patients selected for elective interval cholecystectomy were chosen for their perceived ability to tolerate surgery. If elective interval cholecystectomy is expanded to the group selected for observation, who as a group are less fit for surgery, there is the potential for worse outcomes. |  |  | | --- | | Subgroup considerations | | As outlined in the recommendation and justification, the subgroups of low-risk and high-risk surgical patients need to be considered separately. In addition there is evidence that the subgroups of patients with acalculous cholecystitis have different outcomes from the patients with calculous cholecystitis when no interval cholecystectomy is performed. [Noh, Chung, Kirkegard, Ozyer] |  |  | | --- | | Implementation considerations | |  |  |  | | --- | | Monitoring and evaluation | |  |  |  |  |  |  | | --- | --- | --- | --- | | |  | | --- | | Research priorities | | Studies are needed to characterize subgroups of patients both who are and who are not more likely to develop recurrent gallbladder symptoms after removal of the cholecystostomy tube in order to allow better selection of patients who should or should not have elective cholecystectomy. These studies should then inform subsequent studies investigating the effectiveness of interval cholecystectomy in surgically fit patients at high risk of recurrent biliary symptoms. |   **Question 12** | | | **Should [PICO 12] conversion of laparoscopic cholecystectomy to open cholecystectomy vs. no conversion be used for limiting the risk or severity of bile duct injury during difficult laparoscopic cholecystectomy?** | | | **Population:** | patients undergoing laparoscopic cholecystectomy that at the time of the procedure is judged to be difficult | | **Intervention:** | [PICO 12] conversion to open cholecystectomy | | **Comparison:** | no conversion | | **Main outcomes:** | bile duct injury |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | No evidence was found for the outcome bile duct injury or any of its proxy outcomes | No studies stratified patients based on intraoperative findings of difficult cholecystectomy to compare conversion versus no conversion outcomes | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | No evidence was found for the outcome bile duct injury or any of its proxy outcomes |  | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Not applicable as the panel considered bile duct injury as the only relevant decision-making outcome |  | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know |  |  | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know |  |  | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know |  |  |   **Conclusions**   |  | | --- | | **Recommendation** | | Current evidence is insufficient to make a recommendation in the difficult laparoscopic cholecystectomy regarding conversion vs no conversion to open cholecystectomy to limit/avoid bile duct injury. | |  |  |  | | --- | | **Justification** | | While numerous studies report risk factors and reasons for conversion of lap chole to open there are no available studies that compared BDI outcomes based on decision to convert versus not convert when the surgeon is faced with a difficult cholecystectomy. |  |  | | --- | | **Subgroup considerations** | | n/a |  |  | | --- | | **Implementation considerations** | | n/a |  |  | | --- | | **Monitoring and evaluation** | | n/a |  |  | | --- | | **Research priorities** | | We suggest the conduct of prospective and retrospective comparisons of clinical outcomes of various ‘bail-out’ options for the difficult cholecystectomy as assessed intraoperatively that include conversion to open, subtotal cholecystectomy, and procedure abandonment.  We suggest the development and of a ‘procedure difficulty score’ for laparoscopic cholecystectomy and study of its effectiveness in limiting BDI risk. |  |  |  | | --- | --- | | **Question 13** | | | **Should [PICO 13] surgeons taking a time out to verify the critical view of safety vs. no time out be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy?** | | | **Population:** | patients undergoing laparoscopic cholecystectomy | | **Intervention:** | [PICO 13] surgeons taking a time out to verify the critical view of safety | | **Comparison:** | no time out | | **Main outcomes:** | BDI |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ●Small ○ Moderate ○ Large ○ Varies ○ Don't know | No evidence was found for the outcome bile duct injury or any of its proxy outcomes | While no evidence exists to answer this question, the GDG panel felt based on experience that the incorporation of a momentary pause to verify the appropriateness of the CVS before any structures has the potential to decrease the risk of BDI. As the most common cause of BDI is a misperception of anatomy, the momentary pause is an opportunity to verify that what one is seeing is likely the correct anatomy. | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○  Don't know | No evidence was found for the outcome bile duct injury or any of its proxy outcomes |  | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Not applicable as the panel considered bile duct injury as the only relevant decision-making outcome |  | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know |  | This is based on expert opinion and surgical common knowledge. | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○  Don't know |  |  | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |   **Conclusions**   |  | | --- | | **Recommendation** | | Current evidence is insufficient to make an evidence-based recommendation. However, as best practice, we suggest that during laparoscopic cholecystectomy, surgeons conduct a momentary pause for the surgeon to confirm in his/her own mind that the critical view of safety has been attained before clipping or transecting ductal or arterial structures. (expert opinion) | |  |  |  | | --- | | **Justification** | | While no evidence exists to answer this question, the GDG panel felt that the incorporation of a momentary pause to verify the appropriateness of the CVS before any structures are divided should be considered by surgeons as it has the potential to decrease the risk and is easily implementable without significant effort or delay required. |  |  | | --- | | **Subgroup considerations** | | n/a |  |  | | --- | | **Implementation considerations** | | n/a |  |  | | --- | | **Monitoring and evaluation** | | n/a |  |  | | --- | | **Research priorities** | | We suggest incorporation of a “critical view momentary pause” in all prospective studies of laparoscopic cholecystectomy. |  |  |  | | --- | --- | | **Question 14** | | | **Should [PICO 14] two surgeons vs. one surgeon be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy?** | | | **Population:** | patients undergoing laparoscopic cholecystectomy | | **Intervention:** | [PICO 14] two surgeons | | **Comparison:** | one surgeon | | **Main outcomes:** | Bile duct injury (proxy outcomes: quality of the critical view of safety, 30-day mortality, conversion, complications of surgery) |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | No evidence was found for the outcome bile duct injury or any of its proxy outcomes |  | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | No evidence was found for the outcome bile duct injury or any of its proxy outcomes |  | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Not applicable as the panel considered bile duct injury as the only relevant decision-making outcome |  | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know |  |  | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know |  |  | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know |  |  |   **Conclusions**   |  | | --- | | **Recommendation** | | Current evidence is insufficient to make a recommendation regarding two vs one surgeons for limiting/avoiding bile duct injury in cholecystectomy. | |  |  |  | | --- | | **Justification** | |  |  |  | | --- | | **Subgroup considerations** | | n/a |  |  | | --- | | **Implemenstation Considerations** | | n/a |  |  | | --- | | **Monitoring and evaluation** | | n/a |  |  | | --- | | **Research priorities** | | Retrospective assessment of case notes where the involvement of multiple surgeons was recorded should be possible from billing, electronic records, or national databases that record this information, and linkage of these cases to outcomes could provide insight into the usefulness of two-surgeon cholecystectomy. The effect of access to and/or involvement of subspecialist hepatobiliary surgeons and impact on outcomes should also be assessed.  Prospectively, multi-center cohort studies are desirable to capture the effect of multiple surgeon involvement in clinical outcomes. |  |  |  | | --- | --- | | **Question 15** | | | **Should [PICO 15] critical view of safety coaching of surgeon vs. no specific critical view of safety coaching be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy?** | | | **Population:** | Surgeons performing laparoscopic cholecystectomy | | **Intervention:** | [PICO 15] critical view of safety coaching of surgeon | | **Comparison:** | no specific critical view of safety coaching | | **Main outcomes:** | BDI; (proxy: quality of CVS, Complications (minor/ major)) |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ○ Small ●Moderate ○ Large ○ Varies ○ Don't know | Two studies addressed this question but one was not considered appropriate for inclusion due to numerous flaws including being underpowered to detect BDIs, inclusion of bile leaks as BDIs, and confounding by surgeon skill (Nijssen et al 2016). In a group of five practicing surgeons who received CVS coaching, their scores on the Strasberg scale improved significantly from 1.75 at baseline to 3.75 after training (very low certainty evidence because of study design and fragility of effect) (Stefanidis et al 2017). | The GDG agreed that there was evidence from other surgical domains in support of this judgement. For example, the systematic reviews on coaching to enhance surgeons' operative performance: Min H, Morales DR, Orgill D, Smink DS, Yule S. Surgery. 2015 Nov;158(5):1168-91. | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know |  | No undesirable effects were perceived by the GDG | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ● Very low ○  Low ○ Moderate ○ High ○No included studies |  |  | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  |  | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ●  Favors the intervention ○ Varies ○ Don't know |  |  | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ● Probably yes ○  Yes ○ Varies ○ Don't know |  | The GDG felt that coaching interventions would be acceptable by most surgeons if proved effective. It is possible that some surgeons may object to coaching due to the time commitment | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | Subject to coach and other resource availability. |  Type of recommendation  |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention | | ○ | ○ | ○ | **●** | ○ |   **Conclusions**   |  | | --- | | **Recommendation** | | We suggest as best practice continued education of surgeons regarding the critical view of safety during laparoscopic cholecystectomy that may include coaching (conditional recommendation, very low certainty of evidence). | |  |  |  | | --- | | **Justification** | | Obtaining a high-quality “critical view” was considered paramount by the GDG to avoid biliary injury during laparoscopic cholecystectomy. Given that current evidence suggests that ~80% surgeons do not routinely obtain the CVS, and the benefits of education and coaching in improving performance and changing behavior demonstrated in several fields including surgery, the GDG felt that coaching should be employed to improve the quality of dissection and of the CVS and may lead to decreased risk of BDI. |  |  | | --- | | **Subgroup considerations** | | n/a |  |  | | --- | | **Implementation considerations** | | n/a |  |  | | --- | | **Monitoring and evaluation** | | n/a |  |  | | --- | | **Research priorities** | | Larger studies of critical view of safety coaching interventions are needed that demonstrate the effectiveness of coaching in changing surgeon behavior and reducing BDI. Optimal methods of training delivery (i.e. online, in-person didactic, OR-based proctorship) need to be determined. |  |  |  | | --- | --- | | **Question 16** | | | **Should [PICO 16] training of surgeons by simulation method or video-based education vs. alternative surgeon training be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy?** | | | **Population:** | patients undergoing laparoscopic cholecystectomy | | **Intervention:** | [PICO 16] training of surgeons by simulation method or video-based education | | **Comparison:** | alternative surgeon training | | **Main outcomes:** | Bile duct injury |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know | No empiric evidence was found for the outcome of bile duct injury or any of its proxy outcomes |  | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | No empiric evidence was found for the outcome of bile duct injury or any of its proxy outcomes |  | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Not applicable as the panel considered bile duct injury as the only relevant decision-making outcome |  | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know |  |  | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know |  |  | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know |  |  |   **Conclusions**   |  | | --- | | **Recommendation** | | Current evidence is insufficient to determine the benefit of simulation vs video-based vs alternative surgeon training modalities on limiting/avoiding bile duct injury. | |  |  |  | | --- | | **Justification** | | n/a |  |  | | --- | | **Subgroup considerations** | | n/a |  |  | | --- | | **Implementation considerations** | | n/a |  |  | | --- | | **Monitoring and evaluation** | | n/a |  |  | | --- | | **Research priorities** | | We suggest the conduct of prospective large-scale multi-center studies to determine the role of simulation vs video-based vs alternative surgeon training modalities on limiting/avoiding bile duct injury.  More realistic simulators incorporating immersive virtual technology and advanced haptics that enable training with aberrant biliary anatomy and difficult cholecystectomy procedures should be considered for development and their effectiveness studied. |  |  |  | | --- | --- | | **Question 17** | | | **Should [PICO 17] more vs. less surgeon experience be used for mitigating the risk of BDI associated with laparoscopic cholecystectomy?** | | | **Population:** | Patients undergoing laparoscopic cholecystectomy | | **Intervention:** | [PICO 17] more surgeon experience | | **Comparison:** | less surgeon experience | | **Main outcomes:** | BDI |   **Assessment**   |  |  |  | | --- | --- | --- | | **Desirable Effects**  How substantial are the desirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with less surgeon experience** | **Risk difference with [PICO 17] more** | | BDI | 60,618 (1 observational study) | ⨁◯◯◯ VERY LOWa | **RR 0.27** (0.13 to 0.57) | Study population | | | 458 per 100,000 | **334 fewer per 100,000** (398 fewer to 197 fewer) |  1. Study is based on administrative data which could bias the results towards the null. |  | | **Undesirable Effects**  How substantial are the undesirable anticipated effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with less surgeon experience** | **Risk difference with [PICO 17] more** | | BDI | 60,618 (1 observational study) | ⨁◯◯◯ VERY LOWa | **RR 0.27** (0.13 to 0.57) | Study population | | | 458 per 100,000 | **334 fewer per 100,000** (398 fewer to 197 fewer) |  1. Study is based on administrative data which could bias the results towards the null. | The GDG did not foresee any undesirable effects associated with more experienced surgeons performing the procedures as compared to less experienced | | **Certainty of evidence**  What is the overall certainty of the evidence of effects? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ● Very low ○ Low ○ Moderate ○ High ○ No included studies |  | Only one observational study based on administrative data | | **Values**  Is there important uncertainty about or variability in how much people value the main outcomes? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability | Not applicable as BDI is the only decision-making outcome |  | | **Balance of effects**  Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know |  |  | | **Acceptability**  Is the intervention acceptable to key stakeholders? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | This recommendation could limit professional skill development of younger surgeons | | **Feasibility**  Is the intervention feasible to implement? | | | | **Judgement** | **Research evidence** | **Additional considerations** | | ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know |  | It would be costly and disruptive in MAny community hospitals or rural areas (where only one surgeon may be available) or impossible to always have an experienced surgeon available for the implementation of this recommendation |   **Type of recommendation**   |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention | | ○ | ○ | ○ | **●** | ○ |   **Conclusions**   |  | | --- | | **Recommendation** | | We suggest that surgeons have a low threshold for calling for help from another surgeon when practical in difficult cases or when there is uncertainty of anatomy (conditional recommendation, very low certainty of evidence). | |  |  |  | | --- | | **Justification** | | Although the evidence is of very low certainty, a strong recommendation could be provided since the observed effect is very large and undesirable effects are almost nonexistent. Nevertheless, a strong recommendation was not provided by the GDG because of acceptability and feasibility considerations.  The GDG felt that senior support should be sought for difficult cases identified pre- or intra-operatively, or that referral to more experienced centers should be considered where such support is not available. |  |  | | --- | | **Subgroup considerations** | | n/a |  |  | | --- | | **Implementation considerations** | | n/a |  |  | | --- | | **Monitoring and evaluation** | | n/a |  |  | | --- | | **Research priorities** | | More good quality studies are needed that support or refute the findings of the one observational study included in this review  Development of effective BDI mitigating surgical training programs such as the SAGES safe chole initiative should be encouraged  Prospective comparisons of the effectiveness of the various BDI mitigating training methods on the laparoscopic cholecystectomy outcomes of early career surgeons should be considered.   |  |  | | --- | --- | | Question 18 | | | **Should [PICO 18] referral to a specialist with experience in biliary reconstruction vs. immediate (in the OR or early postoperative period) reconstruction by the operating surgeon be used for patients with bile duct injury during laparoscopic cholecystectomy ?** | | | **Population:** | patients with bile duct injury during laparoscopic cholecystectomy | | **Intervention:** | [PICO 18] referral to a specialist with experience in biliary reconstruction | | **Comparison:** | immediate (in the OR or early postoperative period) reconstruction by the operating surgeon | | **Main outcomes:** | Total serious or major adverse events ; 30 day mortality |  Assessment  |  |  |  | | --- | --- | --- | | Desirable Effects How substantial are the desirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | Direct evidence:  7 observational studies including a total of 1392 patients with BDI addressed this question and showed a large consistent effect across a number of outcomes [rates of cholangitis, bile leak, stricture, reoperation, other intervention, and death] favoring specialist surgeons over primary surgeons. The studies were judged to be at high risk of bias, however, due to unclear comparability and an unknown degree of missing data.  Given the high risk of bias in direct evidence, indirect evidence was additionally considered:  Abundant indirect evidence from other surgical domains has previously established a positive relationship between surgeon volume and surgical outcomes. An umbrella systematic review of 32 systematic reviews covering 15 surgical procedures found most reviews favored higher surgeon experience or volume (Morche J Systematic Rev 2016; 5:204). All quantitative, pooled data from this review are presented below; the non-pooled results from individual studies on the Norwood procedure, Trauma, Bariatric Surgery, Radical Prostatectomy, Total knee arthroplasty, and Coronary Artery bypass also supported the same relationship between improved outcomes and surgeon volume.    Footnote: Mortality and other surgical complications (lower OR) as well as patient survival (higher OR) when relevant all favored higher volume surgeons  The umbrella review was judged to be of good quality; it included systematic reviews ranging in quality from moderate to high. The studies summarized in the systematic reviews were observational. The little heterogeneity observed in the presented pooled effect estimates was not explained by the quality of individual systematic reviews. No important concerns were noted regarding inconsistency. In regards to indirectness, the GDG felt these findings were directly applicable to the repair of BDI and no concerns were noted. As such, the overall certainty of the evidence as per the GRADE approach was judged to be “low” given evidence from observational studies. | The GDG noted that the complexity and the type of surgery entailed in the repair of a major bile duct injury is significantly different than routine laparoscopic cholecystectomy procedures. Experience for laparoscopic cholecystectomy cannot be generalized to repairs of bile duct injuries. Existing direct and indirect evidence is consistent. | | Undesirable Effects How substantial are the undesirable anticipated effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know | as above | The GDG did not perceive there were significant undesirable effects associated with the repair of BDI in a specialized center Including patient transfer or any associated delay in treatment | | Certainty of evidence What is the overall certainty of the evidence of effects? | | | | Judgement | Research evidence | Additional considerations | | ○ Very low ● Low ○ Moderate ○ High ○ No included studies |  | The evidence provided was not downgraded for indirectness given no concerns were noted by the panel regarding the generalizability of the systematic review evidence. While the direct evidence was high risk of bias, the umbrella systematic review demonstrated a consistent association, often statistically significant, between surgeon volume and positive outcomes across many surgical specialties. | | Values Is there important uncertainty about or variability in how much people value the main outcomes? | | | | Judgement | Research evidence | Additional considerations | | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability |  | Evidence was not systematically searched for values and preferences as it was judged that there was no important variability in patient values for these life threatening complication | | Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | | | Judgement | Research evidence | Additional considerations | | ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  | The GDG deliberated as follows:  The complexity and the type of surgery entailed in the repair of a major bile duct injury is significantly different than routine laparoscopic cholecystectomy procedures. As such, experience for laparoscopic cholecystectomy cannot be generalized to repairs of bile duct injuries. The indirect evidence strongly supports the notion that bile duct repairs are more likely to be successful when undertaken by surgeons experienced in such procedures. No concerns were noted by the panel regarding the generalizability of the systematic review evidence. Further, the undesirable effects secondary to a potential delay related to a specialist referral were considered small or trivial, contingent to preparing the patient well for such a referral/transfer i.e. placement of drains by primary surgeon. As such, the balance of benefit and harms were judged to strongly favor the intervention. | | Acceptability Is the intervention acceptable to key stakeholders? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | While some surgeons with limited experience might prefer to repair BDI themselves, the GDG felt that it is important that surgeons and other stakeholders recognize that referring the patient with a BDI to an expert is a sign of good practice rather than a sign of failure. This policy should be encouraged rather than deterred. The surgeon who is performing gallbladder surgery should set up connections with HPB experts for consultation and referral. | | Feasibility Is the intervention feasible to implement? | | | | Judgement | Research evidence | Additional considerations | | ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | Areas with limited resources and availability of expertise may encounter feasibility issues in implementing this recommendation. |  Type of recommendation  |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** | | ○ | ○ | ○ | ○ | **●** |  Conclusions  |  | | --- | | Recommendation | | When a bile duct injury (BDI) has occurred or is highly suspected at the time of cholecystectomy or in the post-operative period, we recommend that the patient be promptly referred to a surgeon with experience in the management of BDI in an institution with a hepato-biliary disease multispecialty team.  When not feasible to do so in a timely manner, prompt consultation with a surgeon experienced in the management of BDI should be considered. (strong recommendation, low certainty of evidence) | |  |  |  | | --- | | Justification | | Overall low certainty evidence addressed this question favoring specialty referral for reconstruction of BDI. To justify the strong recommendation, the GDG invoked one of the 5 paradigmatic situations for strong recommendation originating in low or very low certainty of evidence (potential for catastrophic harm).  The complexity and the type of surgery entailed in the repair of a major bile duct injury is significantly different than routine laparoscopic cholecystectomy procedures. As such, experience for laparoscopic cholecystectomy cannot be generalized to repairs of bile duct injuries. The direct and indirect evidence supports the notion that bile duct repairs are much more likely to be successful when undertaken by surgeons experienced in such procedures. No concerns were noted by the panel regarding the generalizability of the systematic review evidence. Further, the undesirable effects secondary to a potential delay related to a specialist referral were considered small or trivial, contingent to preparing the patient well for such a referral/transfer, i.e. placement of drains by primary surgeon. As such, the balance of benefit and harms were judged to strongly favor the intervention. Consequences of a poorly repaired or failed repair of BDI include catastrophic harms such as cholangitis, bile leak, biliary stricture, sepsis, need for reoperation or other interventions, and liver failure all of which may potentially lead to death. |  |  | | --- | | Subgroup considerations | | None |  |  | | --- | | Implementation considerations | | Actions proposed should be geared to pre-empt any stakeholder objections.  Develop regional fast tract BDI referral pathways to offer advice and contribute to immediate treatment strategies. This should include referral of the patient and/or traveling of the specialist surgeon to the referral institution.  Share recommendation through society guidelines, oral presentations at meetings, scientific manuscripts and incorporation of the concept in surgical education. |  |  | | --- | | Monitoring and evaluation | | National registry of outcomes of gallbladder surgery that monitors management of BDI and its outcomes |  |  | | --- | | Research priorities | | Studies that compare patient outcomes after BDI repair when referred to a specialist versus repair by the primary surgeon should be undertaken.  The GP recommended interrupted time series or regression discontinuity analyses when surgical programs of healthcare systems officially adopt this policy. Ideally, programs should introduce this policy formally ensuring strict adherence, controlling for any time-varying effects and changes in patient population characteristics. | | | |