**Peer Review File**
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## Review comments:

## Comment 1:

Bile duct injury (BDI) is a rare complication in gallbladder surgery. In the worst case, all of these conditions may evolve into septic shock and patient death, especially if not identified in time. How to identify bile duct injury early?

## Reply 1:

There are several factors that lead to early recognition of iatrogenic injury, among which the most important is the surgeon awareness about the possibility of causing iatrogenic damage and therefore put into practice a series of measures otherwise unnecessary.

For example, the presence of bile in the operating field at the end of the cholecystectomy must undoubtedly suggest a biliary injury. Similarly, the presence of vascular-biliary structures in continuity of the gallbladder after the alleged section of the duct and cystic artery must make one suspect a technical error and recognition.

In addition, once the gallbladder is extracted, the surgeon must check that the clips, used in the laparoscopic procedure, are positioned correctly and that there is no damaged bilious duct.

If an injury is suspected, it will be necessary to carry out a cholangiography that allows to make a diagnosis of it. In fact, if there is an open lesion, spreading of the contrast medium is observed in the neighbouring areas, while if it is a closed injury, there is a stop in the progression of the contrast medium at the obstruction, which is mostly due to a unwell placed clip during the intervention.

Unfortunately, however, intra-operative recognition of BDI is not frequent (<25- 30%) and above all only few surgeons perform a cholangiography during the surgery to verify that the permeability of the ducts is maintained. Nowadays, it is recommended to use intra-operative cholangiography when:

- there are anatomical abnormalities of the biliary ducts or an injury is suspected during the intervention

- there is an acute gallbladder or a history of recurrent acute gallbladder.

If the surgeon has adequate imaging preparation, it is recommended the use of laparoscopic ultrasound that is less invasive and a valid alternative to intra-operative cholangiography.

## Comment 2:

The authors of this study should have a unified classification system for the optimal timing of prosthetic surgery to compare data from different databases and case series. Is there a unified classification system?

## Reply 2:

At the time of the study, there was no unified classification system in literature. Thus, we decided to apply a two weeks cut-off parameter, as it seemed to be the best choice to provide a significant analyses of the data.

## Comment 3:

The incidence of cholangitis after BD anastomosis ranged from 0.4% to 11%. The main reason was the increase of intrabiliary pressure caused by bile duct stricture. Is there any measure to prevent cholangitis after BD anastomosis before operation?

## Reply 3:

A proper monitoring of alkaline phosphate values (>410 IU/L) could prevent this complication as confirmed by literature and the data collected in this study.

Clinical stabilization of patients to prevent any further hospitalization in the intensive care unit is another relevant factor that reduces the risk of cholangitis after anastomosis.

A pre-surgery anatomic-clinical study is also relevant for the execution of a correct anastomosis that is an essential condition to reduce post-operative cholangitis risk.

The control of the inflammatory picture and intra-abdominal infection before surgery is a way to prevent the risk of cholangitis. Therefore, the placement of a percutaneous drainage, evacuating all collections of bile or biological material is recommended.

## Comment 4:

If the anastomosis is performed mainly by experienced surgeons, the incidence of complications, especially cholangitis, is much lower. In addition, this confirms the importance of immediate referral to a specialized hepatobiliary surgical center. What are the criteria for an experienced surgeon?

## Reply 4:

The key point is that surgeons must be trained to laparoscopy that projects on the screen a 2- dimensional picture of the abdominal anatomy. That could create a misinterpretation of the reality if the operator is not skilled.

Therefore, the safety rules to perform a good intervention are:

- the operator must have practical experience of diagnostic laparoscopy

- it must acquire the basic gestures to operate remotely with simulators

- it must carry out the intervention on animals where the gestures become more difficult due to the most frequent respiratory acts and bleeding

- it must observe or better help an already trained surgeon

The American College of Surgeons has established a well-structured training process and fixed the conditions to carry out laparoscopic interventions. Among the rules, the surgeon has to participate at about 80 cholecystectomies in an accredited centre before doing this type of intervention by itself. The capability of performing intra-operative cholangiography is also a mandatory requested skill.

## Comment 5:

Immediate drainage of the site and secondary referral to a tertiary professional hepatobiliary center seems to be the best way to ensure that iatrogenic lesions are resolved: "drain now, repair later.". For different cases, what is the best time to repair?

## Reply 5:

In cases, albeit few, of immediate recognition of the injury, positioning of a drainage and sending to a third level centre the best repair time in terms of success of the intervention and outcome of the patient is 3-4 days.

## Comment 6:

Interestingly, although there are some references in the literature, it is interesting to note that the selection of days for early or late intervention is mainly based on local practice, especially the time required to address complex acute competition rather than standardized parameters. Are there standardized steps to assess the best timing for intervention?

## Reply 6:

The clinical cases analysed did not allow to find standardized steps to assess the best time for intervention. Each case had a different clinical history therefore was not possible to find any statistical correlation among them.