

Peer Review File

Article information: <http://dx.doi.org/10.21037/atm-21-1318>

Reviewer A

Lee et al. reported the impact of Ligasure usage on the early postoperative outcome in liver transplantation (LT). They concluded that Ligasure was effective to prevent the bleeding and infectious complication after LT, so that it can contribute to the improvement of perioperative management of LT. The paper is generally well written and easy to read. My specific questions are as follows,

1. I guess also in Ligasure group, the authors used the monopolar cautery. If so, the groups should be defined as “monopolar only group” and “Monopolar with Ligasure group”. Please specify the groups more accurately with appropriate definition. If the authors use Ligasure with monopolar cautery, how do you use them properly during surgery?

Reply: Thanks for your kind comments. In the text, Ligasure was mainly used to separate and mobilize tissues adjacent to the liver during total hepatectomy. In hilar dissection, monopolar cautery was used in both groups, and among other procedures, Ligasure was used in Ligasure group as much as possible.

In our study, the case of using only monopolar and the case of using Ligasure was compared. In previous research about energy device in other surgery (ex. Gastric. Colon), it was not described as Ligasure with monopolar cautery even they use monopolar cautery in some procedure. Therefore we described it as Ligasure group vs monopolar cautery group.

2. What was the indication to use Ligasure in this study?

Reply: It was not used for any special indication. However, if there is a history of abdominal surgery in the past, it was considered to be used to perform adhesiolysis a little more easily. However, as shown in Table 1, the difference in the frequency of abdominal surgery between the two groups was not significant.

In addition, Ligasure device was not always available, and if the indication were used separately, it could have acted as a bias for the study. Since this study was conducted as a retrospective study, I think that the fact that the Ligasure use was decided according to the unexpected situation would have helped to reduce the bias of the study.

3. The sentence in Page 8, line 15 is incorrect. I guess “the right hepatic vein after clamping,,,” should be replaced by “the right hepatic vein was divided after clamping,,,”, for example.

Reply: Thanks for the kind comment. The pointed out has been modified as recommended.

(Page 8 line 23)

4. It should be better to compare the amount of ascites before and/or after surgery, because not only bleeding, but lymphatic vessels might be well controlled by Ligasure.

Reply: Thanks for the expert comment. I think it will be good to compare the points pointed out by the reviewers. However, since the amount of ascites will depend on the degree of portal hypertension rather than lymphatic vessel sealing. Therefore, the influence of GRWR, presence of collateral vessel (splenorenal shunt, gastric varix) was considered to be greater.

In addition, if the amount of ascites can be accurately measured before surgery, an accurate comparison will be possible through PSM, but this is expected to be very difficult methodologically. Thanks for the reviewer's good opinion.

Reviewer B

The authors aimed to compare the surgical outcomes of the 69 recipients who underwent recipient hepatectomy with LigaSure (LigaSure group) and 118 recipients who underwent with monopolar cautery using propensity score matching (PSM).

Major Comments:

1. Before PSM univariate and multivariate regression analyses is recommended to identify independent predictive factors of bleeding. If the type of energy device used is not identified as an independent risk factor for bleeding, in that case to perform a PSM has less added value.

Reply: Thanks for the advice. It is very important to match the various baseline characteristics in PSM. Total bilirubin, PT INR, and PIVKA were considered significant factors of bleeding in the analysis of 187 patients before PSM. Since the number of case is not large, even if it is not a significant factor in the multivariate regression analysis, It is better to match the potential risk factor of bleeding (ex, platelet count, GRWR, etc) and severity of HCC for reducing heterogeneity between

the two groups.

Since the statistical factors pointed out by the reviewers are already included in the PSM, it is acceptable to compare the results of the two groups. Thank you very much for the detailed advice.

2. Important methodological information is missing:

a) The caliper used for PSM in order to identify the best trade-off between homogeneity and the retained sample size. I strongly recommend the authors to review Rubin and Rosenbaum method for PSM (Rosenbaum PR, Rubin DB. Constructing a Control Group Using Multivariate Matched Sampling Methods That Incorporate the Propensity Score. *Am Stat*, 1985 Feb;39(1):33. Available from: <https://www.jstor.org/stable/2683903?origin=crossref>).

b) An interesting point in this study is if the device used was in function of the surgeon preference, in that case, the surgeon should be added as a confounding factor and it is important to consider it to perform the PSM method.

3. Before PSM patients' demographics the only difference was recipient age. It would be interesting to show postoperative results before and after PSM.

Reply: We used the nearest-neighbor method at a ratio of 1:1 based on 14 covariates. And this part is described in the method section. We are grateful for any advice on specific PSM methods.

In our center, several surgeons participate in surgery. It is divided into anastomosis of hepatic vein and portal vein, hepatic artery, and bile duct, but in this study, the part using Ligasure to be compared is part of mobilization and postoperative bleeding control, and was mainly performed by one surgeon. Because of this, I don't think that surgeon acted as a confounding factor.

I don't think it makes much sense to compare the two groups without PSM. In particular, age is considered to have the potential to affect complications after surgery, so I don't think it is of great significance to compare pre-PSM.

Thank you for the advice of our expert reviewers.

Reviewer C

The authors perform a comparison of N=69 liver transplant recipients who underwent recipient hepatectomy with LigaSure to N=118 recipients in which hepatectomy was performed with monopolar cautery.

-How was decision to utilize LigaSure or monopolar cautery made? Were all the LigaSure assisted hepatectomies performed by the same surgeon while a different surgeon performed all the monopolar hepatectomies? If so, this could lead to a large potential bias.

Reply: It was not used for any special indication. However, if there is a history of abdominal surgery in the past, it was considered to be used to perform adhesiolysis a little more easily. However, as shown in Table 1, the difference in the frequency of abdominal surgery between the two groups was not significant.

In addition, Ligasure device was not always available, and if the indication were used separately, it could have acted as a bias for the study. Since this study was conducted as a retrospective study, I think that the fact that the Ligasure use was decided according to the unexpected situation would have helped to reduce the bias of the study.

In our center, several surgeons participate in surgery. Whole procedures of LT are divided into Recipients hepatectomy (mobilization/Hilar dissection), hepatic vein and portal vein anastomosis, hepatic artery anastomosis, bile duct anastomosis and bleeding control with abdominal wound closure. In this study, the part where Ligasure is used is part of mobilization and postoperative bleeding control, and were mainly performed by one surgeon. Because of this, surgeon factor was not working as a confounding factor.

-Hepatectomy time and blood loss during hepatectomy are VERY surgeon dependent. There are many different techniques to minimize blood loss and increase speed when removing a liver. What were the typical cautery settings during the hepatectomy in the authors' center? Are staplers used for hepatectomy?

Reply: We have previously described high hilar dissection with hilar control first. This method reduces intraoperative bleeding and allows a hepatectomy to be performed very quickly. Ligasure was used for other parts except hilar dissection, mobilization was performed by one person as possible, and other methods were not used between the two groups. The only difference is the difference between using Ligasure or monopolar cautery when performing mobilization. The cautery setting is mainly 35~40watt, and when bleeding control, it can be raised to 70watt.

During hepatectomy, stapler is mainly used for division of the MHV+LHV common trunk, it is usually not used any other part of recipient hepatectomy.

-Please clarify if the liver transplants in this study were performed using the "piggyback" technique?

Reply: Our center usually uses the piggy back method in LDLT and DDLT. It seems that there was no mention of this in the text, so it was described additionally. Thanks for your comments

-The study demonstrated no difference in operative blood loss, blood transfusion, operative time or hepatectomy time between the 2 groups. The authors do find that in this study, patients in the LigaSure group had shorter hospital stay, lower rate of re-operation and lower rate of secondary complications. I find it a bit difficult to accept that using the LigaSure somehow decreases overall complications despite no difference in operative blood loss, OR time etc. There are many valid ways to perform a transplant hepatectomy, and certainly using a LigaSure is one of them. That being said, which technique is best largely depends on the operator. I think in the present study in the absence of randomization it is very difficult to demonstrate causation between LigaSure and postoperative complication rate. Clearly in the study sample there is an association between the two, but causation is another matter. The bias would be even more apparent if different surgeons were using the 2 techniques. The authors might be better to change the conclusion to demonstrate no-inferiority of LigaSure. This conclusion would be more acceptable given the data and study design in the present study.

Reply: Thank you very much for the meticulous and accurate comments from the reviewers.

This is a retrospective study, and since complex factors are involved in postoperative bleeding, it seems difficult to conclude that Ligasure is good with this study alone.

Therefore, a well-designed randomized control study is required, which is described in the discussion section. There is currently an ongoing study (SEALIVE), but the results have not yet been published, and no retrospective comparative studies have been reported before. Therefore, although there are limitations in retrospective studies, I think that this paper, which minimizes and compares the bias between the two groups through a technique PSM, is meaningful itself.

Although there is no difference in bleeding during surgery, frequent postoperative bleeding event, reoperation, and lengthening of hospital stay are possible. Ligasure has superior advantages in vessel sealing. Therefore, even if there is little bleeding during surgery, delay bleeding is promoted and easy because monopolar cautery is quicker to dissection and stop bleeding during surgery, especially in the case of Gerota's fascia or triangular ligaments, which occurs later when the patient's blood pressure rises. Therefore, the possibility of postoperative bleeding was higher than

that of intraoperative bleeding, resulting in higher reoperation, high hematoma infection, and longer hospital stay after reoperation.

However, according to the reviewer's opinion, the energy device alone is not explained, and because of the limitations of this study, it is assumed that the above results have occurred, but I cannot definitively say that. In this regard, I think that more large-scale studies and RCTs need to be supported in order to draw an accurate conclusion.

We changed our conclusion as reviewer's recommendation. Thank you for your kind comments. (Page 14 Line 24~)

-A previous small study looked at LigaSure for recipient hepatectomy (1). This should be included in the references.

1) Lamattina JC, Hosseini M, Fayek SA, Philosophe B, Barth RN. Efficiency of the LigaSure vessel sealing system for recipient hepatectomy in liver transplantation. *Transplant Proc.* 2013 Jun;45(5):1931-3.

Reply: We have added the thesis recommended as a reference. Thanks for your kind comments

Reviewer D

This manuscript presents a retrospective, single center cohort comparing the effectiveness of LigaSure and monopolar cautery study during recipient hepatectomy in terms of intra- and postoperative complications. The authors performed propensity score matched analysis in 138 recipients. They found higher rate of postoperative infections and bleeding complications in the monopolar cautery group, however there were no differences in intraoperative bleeding.

I read this manuscript with interest and I have several questions and comments to the authors:

1. Abstract section:

- Please put in the abstract how many patients were included in PPSM analysis
- In the conclusion you mentioned that secondary infection related to bleeding – how can you be sure that all secondary infection was related to bleeding?

Reply: Thanks for your comments. We added the above to the abstract according to the reviewer's opinion.

All nine patients with infection complications were those with bleeding, and hematoma infection and fluid collection after reoperation were the cause of the infection. I described it like that in the conclusion.

2. Introduction section

- please revise the 3rd and 4th sentence in the first paragraph as they are not clear to me (i.e complication is per se included in morbidity)

Reply: Thank you for your kind opinion. I corrected the awkward part of the context.

3. Results section

- How many patients were included in PSM analysis – please add this information to the text as it is visible only in the table

Reply: We specified that 187 patients (69 ligatures and 118 monopolars) were enrolled. It was described in the method session that the PSM was performed at 1:1, and therefore 69:69 subjects were compared.

- The definition of the bleeding control time should be given in the method sections

Reply: Thanks for the good comment. According to the reviewer's opinion, the definition of the bleeding control time was additionally described in the method session.

- Why do you include the bleeding control time in the analysis, as bleeding in part of operation may be also related to vascular anastomoses and not use of the device? It was also longer on the LigaSure group, so it is not clear to me why. Could you comment on this?

Reply: We usually control bleeding at the anastomosis site as soon as possible, especially before bile duct anastomosis, if major bleeding is determined to be stable after control, then conduct bile duct anastomosis. Therefore, bleeding control after completion of anastomosis mainly catches oozing bleeding from triangular ligament or Gerota's fascia. Monopolar cautery hemostasis in a short period of time, but Ligasure takes 2-3 seconds longer to operate, so the average time is longer, it is described in the discussion part.

- The mean blood loss is relatively high – ca. 5000 ml. Could you explain this?

Reply: This study included patients with DDLT as well as LDLT. In Korea, since the MELD allocation system was introduced in 2016, liver allocation can only be obtained with a MELD score of around 40 due to organ shortage. Because of this, the severity is high and there are many cases of bleeding.

- What do you mean by non-B non-C liver cirrhosis?

Reply: It is a Cryptogenic LC. Since Korea is an HBV epidemic area, and LC mainly due to HBV and HCV occupies a large number of cases, it is often classified and described as NBNC LC in cases other than these two cases.

- Could you explain that despite there was no differences in the intraoperative blood loss and amount of RBC transfusions between the groups you concluded that LigaSure group has lower infection rate due to less blood loss?

Reply: Although there was little bleeding during surgery, postoperative bleeding was low in ligasure group because of the high frequency of delay bleeding and subsequent reoperation in monopolar group.

- In table 2 I would only present the complications that might be influenced by blood loss

Reply: Thanks for your comments. Since postoperative bleeding as well as other complications are also related to bleeding, this should be described in order to be able to compare the exact outcomes between the two groups. Hypotension due to postoperative bleeding can cause cardiovascular complications, and postoperative blood transfusion is also associated with rejection.

4. Discussion section:

- The second paragraph is not relevant for the discussion – it can be omitted

Reply: In this section, it would be better to leave it as it is, since other reviewers asked for an explanation of the reason why several variables were added to the PSM. This is a paragraph with a specific explanation on how the variables used in PSM relate to surgery, so why not leave it as it is.

- What do you mean by: ...energy device was generally not used in anastomosis procedures?

Reply: This section describes the reason for comparing the time spent when using the energy device rather than comparing the total surgical time in the outcome item. The time taken for anastomosis is not an item to be compared in this study, and the anastomosis time is not included as a comparison item in a study comparing energy devices and monopolar because there are more factors that affect the donor mutation

and the patient's blood vessel status. I thought it would be better not.

- The second paragraph on page 13 is not clear – have you observed more infections in the patients who had re-laparotomies for bleeding? If so it should be clearly stated in the result section.

Reply: Thanks for your comments. All nine patients with infection complications were those with bleeding, and hematoma infection and fluid collection after reoperation were the cause of the infection. I described it like that in the conclusion.

- In the conclusions leave out two sentences about HCC, as they are not relevant to your study or transfer them to the discussion.

General comment: please check again the language clarity and accuracy

Reply: Thanks for your all kind comments. I agree with the reviewer's opinion. However, we are also paying attention to the relationship between the sealing effect of energy devices and cancer recurrence, and we are conducting research on this. When PSM was performed, PSM was performed in consideration of the severity of liver cancer, and there were aspects that expected positive results for this.

However, there is still no evidence that the sealing effect of energy devices is helpful in preventing cancer recurrence. However, in theory, since the no touch technique is attracting attention in oncologic surgery, a paragraph is included to suggest the related follow-up studies.

Since this study has not been able to reach a conclusion, it may not be appropriate to put it in the conclusion, but there are aspects that have been added to encourage further research and to encourage other researchers. I moved this paragraph to discussion as your recommendation. (Page 14 line 18)

Reviewer E

It was not clear to me until I read the data tables at the very end of the document why the frequencies for the monopolar cautery treatment were out of 69 and not 118. I now understand that was due to propensity score matching, but I had to intuit that. To avoid reader confusion in the final document I recommend being more specific about that in the abstract "Methods:" paragraph and the Methods section 2.1. Just a simple sentence (or extension to the final sentence) to make it clear that as a result of the propensity score match a comparable subset of 69 of the 118 monopolar cautery cases was compare to the 69 LigaSure cases (provided that understanding is correct).

Reply: Thanks for the good point. According to the reviewer's opinion, in order to

prevent confusion among readers, it was stated in section 2.1 that a comparison was performed between 69 patients in each of the two groups through PSM.