Peer Review File

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Reviewer A:

Authors reported data re the 'economic sustainability' of robotic major and poster-superior segments. This is a retrospective study from two Italian centres. 47 robotic, 101 LLS and 124 OLS were included. Authors concluded that RLS would seem to offer economic advantages compared to OLS, since higher intra-operative costs are counterbalanced by a more favourable peri-operative outcome. The cost evaluation is much needed and there is an important message. However, as authors outlined, this is a retrospective study from a relatively small cohort.

Few comments:

- **Comment 1:** Were all the consecutive patients from the study period included? If so, please mention this. If not, how are these patients selected to be included in the study?

Reply 1*: Thank you for your comment. We confirm that the patients considered in the analysis, who meet the specified inclusion criteria, were selected consecutively.*

Changes in the text: *We revised the manuscript accordingly. In the section "Study Design", we add the word "consecutive" to clarify (line 98 of the PDF document).*

- **Comment 2:** patients who underwent specific liver resections (major and right posterior) were included in the study. How were the patients selected for open, lap and robotic procedures? Please clarify

Reply 2: *Thank you for your comment. We revised the manuscript in order to be clearer to the readers respect to the selection criteria used for the surgical approach.*
All cases underwent thorough evaluation in weekly multidisciplinary meetings comprising the surgical team, pathologist, radiologist, oncologist, anesthetists, and navigator nurse. During these meetings, an overall operative plan was presented, taking into account the patient's characteristics, comorbidities, as well as the pathological, anatomical, and radiological features of the disease. This comprehensive discussion guided the selection of the surgical approach. To ensure consistency, recent exclusion criteria for minimally invasive liver surgery were strictly followed. These criteria included cases involving multiple, bilobar, and complex parenchymal sparing resections, lesions encasing the inferior vena cava/hepatic veins potentially requiring patching or prosthesis, suspected infiltration of the hepatic/portal vein, the need for portal vein thrombectomy and/or vascular reconstruction, advanced hilum infiltrating tumors, anesthesiological contraindications to pneumoperitoneum (e.g., severe cardio-pulmonary disease), and cases necessitating vascular resection and reconstruction.
Please let us know if the revised manuscript is clearer. Moreover, we would kindly underline that the exclusion criteria for the minimally invasive approach are stated in line 117-122 of the PDF document.

Changes in text: *"All cases underwent a comprehensive evaluation in formal weekly institutional multidisciplinary meetings, involving the surgical team, pathologist, radiologist, oncologist, anaesthetists, and navigator nurse. These meetings facilitated the development of an overall operative plan, considering patient characteristics, comorbidities, and the pathological, anatomical, and radiological features of the disease, guiding the selection of the surgical approach. Strict adherence to recent exclusion criteria for minimally-invasive liver surgery was maintained." (line 136-139 of the PDF document).*

- **Comment 3:** There are several definitions of economic sustainability and I have copy pasted one here: Economic sustainability is the approach whereby economic activities are conducted in such a way as to preserve and promote long-term economic well-being. Do authors believe this is about economic sustainability or is it a type of cost-analyses?

Reply 3: *Thank you very much for your comment. Based on your suggestion we modified the title of the manuscript. Our analysis is surely closer to a "cost-analysis" instead of facing the issue of the sustainability from the National Health Service (NHS) perspective.*

Changes in text: *The new title of the manuscript is: "*EVALUATION OF THE ECONOMIC IMPACT OF THE ROBOTIC APPROACH IN MAJOR AND POSTERO-SUPERIOR SEGMENT LIVER RESECTIONS: A MULTICENTER RETROSPECTIVE ANALYSIS*". We also replaced the word "sustainability" with the word "impact" in the background section of the abstract (line8 of the PDF document).*

- **Comment 4:** There are two aspects of the cost analysis reported here - intra-op and post-operative costs. For the intra-op costs the costs were extrapolated from literature and not real time costs. Though this was well explained in the limitations, such a cost-assessment weighs down the message in the manuscript. and, Is there a need to compare histopathology exam costs? how could it be different between the operative approaches? and also for the anaesthesia costs?

Reply 4**:** *Thank you for your comment. When calculating intraoperative costs, we employed both the TD-ABC method and the national tariffs for the majority of the parameters within this category. This includes factors such as the cost per minute for health professionals involved in the procedures and the blood transfusion requirements measured in milliliters. Disposable device costs were determined by extrapolating data from the adjudication prices in regional tenders, which aligns with the Italian context. For reusable devices and anesthetic medical agents, we had to rely on references from the existing literature, as specific data related to the procedures conducted in our facilities were not available. It is worth noting that costs associated with histopathology exams and anesthesia, as well as sterilization costs, remained consistent across the approaches we utilized. As you rightly pointed out, these costs do not significantly affect the differential analysis. Nonetheless, we included them to ensure precision in the overall cost assessment of the procedures. Regarding this last point, we revised the manuscript accordingly.*

Changes in text: *"In the context of intraoperative costs, it is important to note that histopathology*

exam, anaesthesia and sterilization costs remained consistent, regardless of the approach employed. The authors chose to include these costs in the analysis because they contribute to a more accurate estimate of the total procedure costs, even though they do not have any impact in terms of differential analysis" (we add this sentence in line 320 of the PDF document).

- **Comment 5**: the post-operative outcomes and the reduced post-operative costs are significant. Do authors believe that this needs better highlighted?

Reply 5: *Thank you for your suggestion. We added a sentence highlighting this result in the discussion section.*

Changes in text: *"Thus, it is crucial to emphasize that among the statistically significant findings of our analysis, we have observed notable post-operative outcomes and, correspondingly, a reduction in post-operative costs related to RLS group. This observation potentially reinforces the robustness of the conducted cost analysis" (line 456 of the PDF document).*

- Comment 6: why was there a significant difference in the ICU stay? Is this a subjective cautious management of initial cohort of RLS patients? Or is it because patients needed ICU? If there was a need for longer ICU stay because of the differences in the patient or tumor characteristics, please clarify? similarly, re antibiotic therapies - why should there be more usage in robotic group?

Reply 6: *Thank you for your feedback. We view the approach adopted for ICU stay as a precautionary measure. Regarding antibiotic therapy, it is noteworthy that in the robotic group, while there is no statistically significant difference, patients who underwent hilar lymphadenectomy are more prominently represented, and these cases more frequently necessitate post-operative antibiotic treatment.*

Changes in text: *"Moreover, regarding the ICU stay it is worth to mention that the results in terms of absorption of direct healthcare costs for the robotic approach could be overestimated since authors considering a cautious management of the initial cohort. On the other hand, in order to give an explanation on the higher usage and costs of antibiotic treatment in the RLS group, it is relevant to reference that in this group, patients who underwent hilar lymphadenectomy are more prominently represented, and these cases more frequently necessitate post-operative antibiotic treatment." (line 456 of the PDF document)*

- **Comment 7:** how do authors explain that the blood loss was higher in open surgery compared to the more novel robotic approach? more liberal vascular occlusion?

Reply 7: *Thank you for your comment. Consistent with the findings in the scientific literature, our results confirm that minimal invasive approaches are associated with lower blood loss compared to open approach. Moreover, regardless of the approach employed, it is important to note that primary extraparenchymal vascular control was always achieved before transection (Pringle maneuver) in all three comparative groups.*

Changes in text: *"Lastly, regardless of the approach employed, primary extraparenchymal vascular control was always achieved before transection (Pringle maneuver)" (line 163 of the PDF document).*

Reviewer B:

This is a two institutional study aiming to analysis the cost differences of challenging hepatectomy between Open, Lap and Rob.
The topic is very interesting as it is still representing an important issue for the healthcare.

Generally speaking, giving the heterogeneity and bias, it is hard to do cost analysis in surgery. But, this study can give some insight regarding the cost differences of these approaches.

In my opinion, the study can be improved with some suggestions and insight. In the discussion, I suggest the authors to include some previous cost analysis of rob vs open and lap, even regarding some other type of surgeries.

Reply: *Thank you for your suggestion. We revised the manuscript adding in the discussion section previous comparative cost analysis of the robotic approach in general surgery.*

Changes in text: *"Several studies have evaluated the cost effectiveness of robotic surgery in several fields [41-47]. In urological surgery, when radical prostatectomy is concerned, the robotic approach seems to have higher costs that are not compensated by the reduced hospital stay. On the contrary, other procedures, such as cystectomy and partial nephrectomy, seem to be more cost-effective [42]. In general surgery, some authors have been shown to lower overall cost by reducing complications, improving operative times, and cutting down on supplies [43-47]. In more complex cases, such as hepatectomies, the reduction of complications, hospital stay, and readmissions could translate into a real cost benefit, even if the initial acquisition and intraoperative costs are higher" (line 378 of the PDF document).*

References:

41. *Barbash GI, Glied SA. New technology and health care costs—The case of robot-assisted surgery. N Engl J Med 2010;363:701–704*
42. *Ahmed K, Ibrahim A, Wang TT, et al.. Assessing the cost effectiveness of robotics in urological surgery—A systematic review. BJU Int 2012;110:1544–1556*
43. *Byrn JC, Hrabe JE, Charlton ME. An initial experience with 85 consecutive robotic-assisted rectal dissections: Improved operating times and lower costs with experience. Surg Endosc 2014;28:3101–3107*
44. *Bedeir K, Mann A, Youssef Y. Robotic single-site versus laparoscopic cholecystectomy: Which is cheaper? A cost report and analysis. Surg Endosc 2016;30:267–272*
45. *Hagen ME, Pugin F, Chassot G, et al.. Reducing cost of surgery by avoiding complications: The model of robotic Roux-en-Y gastric bypass. Obes Surg 2012;22:52–61*

46. *Wright JD, Ananth CV, Tergas AI, et al.. An economic analysis of robotically assisted hysterectomy. Obstet Gynecol 2014;123:1038–1048*
47. *Anderson JE, Chang DC, Parsons JK, Talamini MA. The first national examination of outcomes and trends in robotic surgery in the United States. J Am Coll Surg 2012;215:107–114.*

These are my suggestions:

- **Comment 1:** Histopathological exam cost. Could you justify why this should be included? Cost can be very different if they are benign or malignant disease. Giving the differences among groups, maybe they should be removed.

Reply 1: *Thank you for your comment. It is worth noting that costs associated with histopathology exams, anesthesia and sterilization remained consistent across the approaches we utilized. As you rightly pointed out, these costs do not significantly affect the differential analysis. Nonetheless, we included them to ensure precision in the overall cost assessment of the procedures. Regarding this last point we revised the manuscript accordingly.*

Changes in text: *"In the context of intraoperative costs, it is important to note that histopathology exam, anaesthesia and sterilization costs remained consistent, regardless of the approach employed. The authors chose to include these costs in the analysis because they contribute to a more accurate estimate of the total procedure costs, even though they do not have any impact in terms of differential analysis" (we add this sentence in line 320 of the PDF document).*

- **Comment 2:** Definition of intensive care? it was a post operative care? All patients after surgery goes to normally to this care? This is an important issue as sometime Intensive care is confused with the normal post operative care unit, which is less expensive compared with the intensive care where usually patients go when they have an organ failure. Is it the same unit if they have some failure? And if they are not, cost are different?

Reply 2: *In our context, only specific selected patients pass through the intensive care setting. It is not expected a standard postoperative intensive care unit. The costs associated with the ICU have been calculated using the methodology described in the paper by Tan et al. (cost were inflated to 2022), where the author discusses the direct cost analysis of proper intensive care unit stays.*

Changes in text: "None"

- **Comment 3:** In a supplementary document you can share the cost of the robotic and laparoscopic disposable.

Reply 3: *Thank you for your suggestion. We can certainly provide these cost details in response to your inquiry. However, we recommend not including them in the supplementary material. This is because the acquisition prices were derived by extrapolating data that aligns with the Italian context,*

using an average of price adjudications in regional tenders from Lombardia and Lazio Regions. Consequently, the acquisition costs may not precisely represent the actual expenses associated with disposable devices but are intended for the scope of our analysis only. Please find enclosed the cost data utilized in our cost analysis.

Misonix	432,13 € *
Caiman	178,43 €
Maryland	574,51 €
Thunderbeat	585,00 €
Voyant	249,00 €

** Cost per usage*

Changes in text: *"None"*

- **Comment 4:** Please define the main reasons for conversion. Also, it might be interesting to make a sub analysis to see how much a conversion can cost additionally

Reply 4: *Thank you for your comment and for your suggestion. The reasons for conversion has been classified in: technical difficulties, oncological radicality, intraoperative hemorrhage, anesthesiologic issues, adhesions due to previous surgery and injury to adjacent organs. No patients have been converted for the latter classification. The main reason for conversion in both the minimally invasive groups has been "technical difficulties". More patient in the laparoscopic group have been converted due to oncological radicality, but there is not a statistically significant difference between the two minimally invasive groups. Likewise, overall, the conversion rate was reduced in RLS group even still not reaching statistical significance. In addition, we performed the sub analysis you kindly suggested but since there is no statistical significance, we chose to report only the differential results of this comparative costs sub-analysis. However, we integrated the manuscript in accordance to what you suggested.*

Changes in text: *"The reasons for conversion has been classified in: technical difficulties, oncological radicality, intraoperative hemorrhage, anesthesiologic issues, adhesions due to previous surgery and injury to adjacent organs" (line 130 of the PDF document).*

"Referring to the reason for conversion no patients have been converted for injury to adjacent organs. The main reason of conversion in both the minimally invasive groups has been "technical difficulties". More patient in the laparoscopic group have been converted due to oncological radicality, but there is not a statistically significant difference between the two groups." (line 306 of the PDF document)

"The cost of conversion for the two minimally invasive groups was express as an additional cost, calculated as a percentage. This was determined by taking the ratio between the mean cost of converted resections to the mean cost of completed resections" (line 240 of the PDF document).

"The additional cost of conversion was + 37.13% for the LLS group and + 28.52 % for the RLS group. However, this difference between the two minimally invasive groups did not reach statistical significance" (line 334 of the PDF document).

- **Comment 5:** Define why some cases have been done by open approach. it is important to see the selection criteria

Reply 5: *Thank you for your comment. We revised the manuscript in order to be clearer to the readers respect to the selection criteria used for the surgical approach.*
All cases underwent thorough evaluation in weekly multidisciplinary meetings comprising the surgical team, pathologist, radiologist, oncologist, anesthetists, and navigator nurse. During these meetings, an overall operative plan was presented, taking into account the patient's characteristics, comorbidities, as well as the pathological, anatomical, and radiological features of the disease. This comprehensive discussion guided the selection of the surgical approach. To ensure consistency, recent exclusion criteria for minimally invasive liver surgery were strictly followed. These criteria included cases involving multiple, bilobar, and complex parenchymal sparing resections, lesions encasing the inferior vena cava/hepatic veins potentially requiring patching or prosthesis, suspected infiltration of the hepatic/portal vein, the need for portal vein thrombectomy and/or vascular reconstruction, advanced hilum infiltrating tumors, anesthesiological contraindications to pneumoperitoneum (e.g., severe cardio-pulmonary disease), and cases necessitating vascular resection and reconstruction.
Please let us know if the revised manuscript is clearer. Moreover, we would kindly underline that the exclusion criteria for the minimally invasive approach are stated in line 117-122 of the PDF document.

Changes in text: *"All cases underwent a comprehensive evaluation in formal weekly institutional multidisciplinary meetings, involving the surgical team, pathologist, radiologist, oncologist, anaesthetists, and navigator nurse. These meetings facilitated the development of an overall operative plan, considering patient characteristics, comorbidities, and the pathological, anatomical, and radiological features of the disease, guiding the selection of the surgical approach. Strict adherence to recent exclusion criteria for minimally-invasive liver surgery was maintained." (line 136-139 of the PDF document).*

- **Comment 6:** Mortality, morbidity was calculated up to 90 days?

Reply 6: *Thank you for your comment. The primary objective of our study was to perform a comparative cost analysis for the three surgical approaches. Therefore, we focused on very short terms perioperative outcomes in order to accurately assess the economic resources required for the surgical procedures. Therefore, we considered in hospital mortality and morbidity rate to facilitate a better understanding of our economic analysis. By excluding longer-term confounding factors, not strictly related to the surgical procedures, our aim was to prevent potential impacts on the costs analysis.*

Changes in text: *"None"*

- **Comment 7:** Did you included the readmission in the overall hospitalization stay?

Reply 7: *Thank you for your comment. The readmission rate within 30 days of discharge was consistent across all three groups (approximately 10%). However, readmission was not taken into account as the comparative economic analysis specifically aimed to consider expenditure drivers closely linked to surgical procedures. It is the authors' opinion that the rate of re-hospitalization might introduce confounding factor into the analysis as it could arise from reasons unrelated to the type of operation performed or reasons not strictly connected with the surgical procedures.*

Changes in text: "None"

- **Comment 8:** In the Rob Lap technique, any CUSA or specific laparoscopic energy device used? It is important to know the percentage as we can get a better picture of pure Rob vs Rob Lap

Reply 8: *Thank you for your comment. Both the centers included in the study used the Misonix as ultrasonic device. Specifically, 55,3% of patients who underwent RLS are performed with Rob Lap approach.*

Changes in text*: "Specifically, 55,3% of patients who underwent RLS were performed with Robo-Lap approach. Both the referring centers object of the analysis used the Misonix® device." (line 149 of the PDF document)*

Reviewer C:

The manuscript is well-organized, offering a comprehensive analysis of robotic liver surgery (RLS) compared to open and laparoscopic approaches, focusing on feasibility, clinical outcomes, and economic factors.

The authors meticulously analyze data from two high-volume Italian centers, presenting real-world evidence regarding current practices and their economic implications for the healthcare system. However, it's important to acknowledge that the study's applicability might be confined to this specific patient population and healthcare setup. Notably, the innovative use of time-driven activity-based costing (TD-ABC) for the economic analysis merits appreciation.

The cost analysis section is thorough, providing valuable insights into the economic aspects of all three surgical approaches. The authors conclude their manuscript by emphasizing that robotic resection seems to offer economic advantages over open resections. Despite higher intraoperative costs, these are offset by more favorable perioperative outcomes. They suggest that as new robotic systems are introduced and the marketplace becomes more competitive, costs associated with RLS will likely decrease, promoting its broader adoption within minimally invasive techniques. Despite RLS being associated with higher costs than laparoscopic surgery (LLS), its role in enhancing

minimally invasive feasibility and reducing conversions may encourage the allocation of complex cases to the robotic approach.

As follows, some specific comments and suggestions for improvement:

- **Comment 1:** The introduction provides a clear overview of the context of the study. Still, it would be helpful to emphasize more clearly the research gap that this study aims to address. You mention the uncertain effect of robotic surgery on financial expenditure, but you could elaborate on why this is an important gap in the current literature.

Reply 1: *Thank you for your suggestion. In the introduction section, we enrich the affirmation "among factors limiting its spread, the most mentioned in literature is cost" with data extrapolated from the cited manuscript.*

Changes in text: *"In a recent survey conducted across 103 European liver centres to assess the adoption of the robotic approach, respondents identified uncertain effect on financial expenditure as the predominant obstacle, with 80% citing it as a significant disadvantage"(line 73 of the PDF document).*

- **Comment 2:** In the methods section the criteria for including or excluding patients in the study are complex. Consider breaking down these criteria into a bulleted or numbered list for easier comprehension.

Reply 2: *Thank you for your suggestion. We used numbered lists to present the exclusion criteria for the study population and the exclusion criteria for the minimally invasive approaches, aiming to facilitate the readers' comprehension.*

Changes in the text:
"Exclusion criteria were the following:

i. *age under 18;*
ii. *non elective admission;*
iii. *two stage hepatectomies, including Associating Liver Partitioning and Portal vein ligation for Staged hepatectomy (ALPPS);*
iv. *cyst unroofing and pericystectomies." (line 112-114 of the PDF document)*

"The following disease characteristics were considered as exclusion criteria for a minimally invasive (laparoscopic or robotic) approach over the entire period:

i. *lesions strictly adjacent or infiltrating the hepatocaval confluence or inferior vena cava;*
ii. *lesions with presumed infiltration of the hepatic vein of the future liver remnant;*
iii. *patients with portal vein thrombosis requiring portal vein thrombectomy;*
iv. *patients with more than 10 liver lesions and/or requiring more than 10 resection areas;*
v. *Anaesthesiologic contraindications to pneumoperitoneum (e.g., severe cardio-pulmonary disease)." (line 117-122 of the PDF document)*

- **Comment 3:** In the criteria and process for selecting patients for each surgical approach patients' treatment preferences has been influenced the final allocation?

Reply 3: *Thank you for your question. In recent year, has been an increasing interest in shared decision making in health care since it increase patients' satisfaction, compliance with treatments and better outcomes. However, despite the recognized benefits of patient-centered medicine, the selection criteria for the surgical approach must align with specific technical requirements, which should not be influenced by the preferences of patients.*

Changes in the text: *the criteria and process for selecting patients for each surgical approach were not affected by patients' treatment preferences (line 140 of the PDF document).*

Reference:

24. *Molinari M, El-Tawil K, Swaid F, Fiorentini G, Bou-Samra P, Sharma C, Liu H, Rahman SH, Hurton S, Tsung A. Patients' treatment preferences for potentially resectable tumors of the head of the pancreas. HPB (Oxford). 2020 Feb;22(2):265-274.*

- **Comment 4:** Explain the methodology of your cost analysis in more detail, particularly the TD-ABC approach. This might include a simplified description of how the methodology works. Discuss potential limitations or biases in the TD-ABC method, which should be acknowledged.

Reply 4: *Thank you for your comment. In response, we have included a more comprehensive description of the TD ABC method in the methods section, with the hope that it provides greater clarity for the readers.*

Changes in the text: *"This technique is based on the concept that the performance of a service consumes activities which then consume resources. TD-ABC attempts to assign costs to each of these activities and/or resources so that total costs can be better understood and managed. It differs from traditional accounting in that it is based on the activities that drive costs. This allows one to manage processes by having clearer understanding of what drives costs and how increases in efficiency affect costs. Many quality improvement techniques also break process into discreate units. This is done to standardize processes, improve then, and eliminate unnecessary variability [36]." (line 216 of the PDF document).*

Reference:

36. *Goldberg MJ, Kosinski L. Activity-based costing and management in a hospital-based GI unit. Clin Gastroenterol Hepatol. 2011 Nov;9(11):947-949.*

- **Comment 5:** In the result section, the presentation of patient characteristics is clear and helps readers understand the composition of the study cohorts. However, the relevance of some characteristics (e.g., rate of previous abdominal surgery) to the research question is not discussed.

Reply 5: *Thank you for your observation. In the discussion section, we provide to delve into the*

significance of this patient characteristic, its relevance and contribution to the overall interpretation of our results.

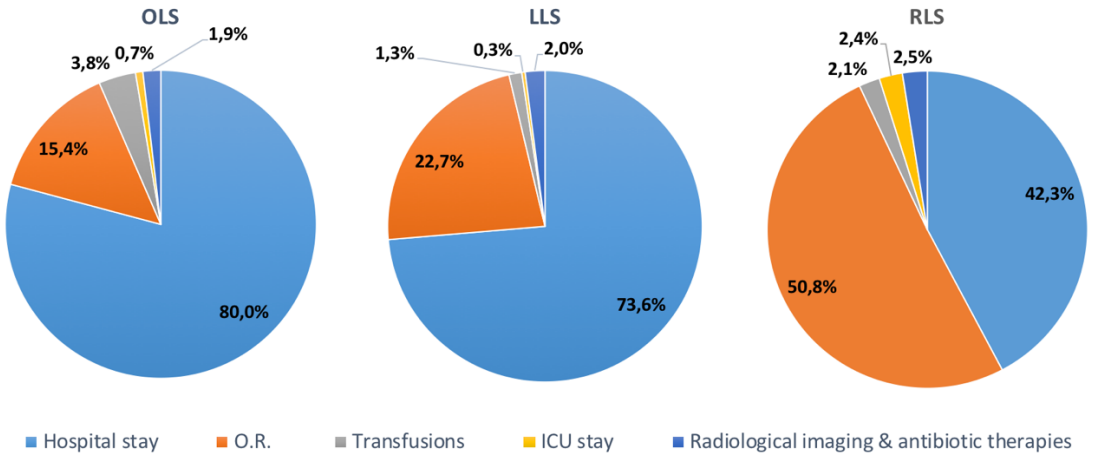
Changes in the text: *"Furthermore, it is important to highlight that in the robotic group, a significantly higher percentage of patients had a history of previous abdominal surgery (78.72% vs. 56.43% for LLS vs. 50% for OLS, p=0.003). Notably, this did not lead to an increased conversion rate due to adhesions. This outcome underscores the efficacy of robotic instruments, likely facilitating effective adhesiolysis even in the most challenging cases." (line 452 of the PDF document)*

- **Comment 6:** Consider including visual aids, such as charts or graphs, to illustrate the cost comparison between open, laparoscopic, and robotic approaches. Visuals can help readers quickly grasp the differences.

Reply 6: *Thank you for your suggestion: In response we have incorporated a visual analysis depicting the distribution of costs among the OLS, LLS and RLS groups to facilitate a comprehensive comparison of expenses.*

Changes in the text: *"The analysis of cost distribution (Figure 1) reveals that in the OLS and LLS groups, a substantial portion of resources is absorbed by postoperative hospitalization costs (80% of total costs for the OLS group and 73,6 % of total costs for the LLS group). In contrast, for the RLS group, the predominant resource absorption occurs during intraoperative costs (50,8% of total costs), although this is counterbalanced by a notable reduction in hospitalization-associated costs (42,3% of total costs)."(line 334 of the PDF document)*

"Figure 1. Costs distribution between OLS, LLS and RLS groups



Legend: O.R., Operative Room; ICU stay, Intensive Care Unit stay." (line 350)

- **Comment 7:** In the discussion context, I suggest to consider the following reference to enhance

the credibility of your claims when comparing the procedure of lymphadenectomy between the two minimally invasive techniques: "Fiorentini G. Challenges and Technical Innovations for an Effective Laparoscopic Lymphadenectomy in Liver Malignancies. J Laparoendosc Adv Surg Tech A. 2019 Jan;29(1):72-75. doi: 10.1089/lap.2018.0568."

***Reply** 7: Thank you for your comment. We have incorporated the suggested reference suggested to enhance the credibility of our assertions.*

***Changes in the text:** "such as performing an oncologically adequate lymph nodal dissection" (line 422 of the PDF document).*

Reference:

48. *Fiorentini G, Ratti F, Cipriani F, Catena M, Paganelli M, Aldrighetti L. Challenges and Technical Innovations for an Effective Laparoscopic Lymphadenectomy in Liver Malignancies. J Laparoendosc Adv Surg Tech A. 2019 Jan;29(1):72-75.*

- **Comment 8:** Suggest cost-saving strategies in robotic surgery. For example, how might the cost of RLS decrease over time due to improved surgeon proficiency and what measures can be taken to reduce the financial expenditure of the robotic platform?

***Reply 8:** Thank for your comment. We emphasized that a shorter learning curve in robotic surgery could provide an economic advantage, particularly in terms of cost-effectiveness analysis.*

***Changes in the text:** "Finally, there is a growing awareness of the fact, that the robotic learning curve in liver surgery is faster than the laparoscopic one. A steeper learning curve in comparison to laparoscopic liver surgery can be seen as a further advantage of the robotically assisted technique. Passing the learning curve helps to achieve a better cost-effectiveness, as operation time is decreasing and surgical outcomes are improving." (line 452 of the PDF document)*

Reference:

52. *Spiegelberg J, Iken T, Diener MK, Fichtner-Feigl S. Robotic-Assisted Surgery for Primary Hepatobiliary Tumors-Possibilities and Limitations. Cancers (Basel). 2022 Jan 6;14(2):265.*

- **Comment 9:** Consider providing specific recommendations for future research in the field. For instance, suggest areas where additional research is needed, such as assessing long-term patient outcomes, evaluating cost-saving measures, or exploring the impact of new robotic systems.

***Reply 9**: Thank for your comment. We have incorporated your suggestions to refine the future investigations recommended in this field.*

***Changes in the text:** "Future research endeavors should delve into assessing long-term patient outcomes, refining cost-saving measures, and exploring the implications of new robotic systems to enhance the overall effectiveness and applicability of robotic liver surgery in clinical practice." (line 501 of the PDF document).*

Incorporating these comments and suggestions, your manuscript can become more comprehensive, and insightful, which will enhance its contribution to the field of hepatobiliary surgery and economics.

Reviewer D:
The authors have carried out an economic analysis comparing costs between open, robotic and laparoscopic liver resections. Their main finding was that RLS/LLS was associated with reduced costs compared to OLS, primarily due to significantly longer LOS after open surgery.

Major comments

- **Comment 1:** Various data (eg R0 rate, and liver-specific complications) clearly indicate that the three groups are not well matched and indicates selection bias, such that (as one would expect) open procedures were more complex. The added complexity of the OLS cases (compared to RLS and LLS) is likely to explain the significantly longer LOS (12 days) in this group compared to 5-6 days in RLS/LLS groups, due to more complications. In other published series, including RCTs, the benefit of LLS/RLS over OLS in terms of hospital stay is in the region of 1-2 days difference. The difference of 6 days in this study is very high and likely due to more complications in OLS, which must be attributed to the higher complexity of the liver resection rather than due to the operative approach (ie open v lap v robot). It is the 6 day difference in LOS that is responsible for the higher postoperative costs of OLS and nullifies the excess intraoperative cost of RLS. What were the relative costs of OLS/RLS/LLS in patient who had no complications? What was the median LOS in uncomplicated cases?

Reply 1: *Thank you for your comment. An initial simple comparison was conducted without performing a propensity score analysis, which certainly represents a future perspective of development and methodological refinement. As discussed in the previous sections (lines 469-479 of the PDF document), there are substantial differences between patients undergoing minimally invasive surgery and those undergoing open surgery in terms of the severity of comorbidities, disease complexity, anatomical characteristics, and the need for extensive hepatic resections. These factors, which constitute the primary reason for patients undergoing open surgery to experience a higher rate of post-operative complications and, consequently, longer hospital stays, cannot be overcome, as they themselves serve as exclusion criteria for the minimally invasive approach. For this reason, in our effort to provide a realistic scenario, we believe that the selection biases you mentioned are, to some extent, inherent in clinical practice and challenging to overcome. We agree that the results in terms of length of hospital stay (LOS) observed in our study are more pronounced compared to the existing literature, as our study specifically focuses on the most complex cases among possible hepatic resections. However, we can present the results by considering the median LOS, as you suggested, as a limitation of the analysis. In fact, when considering uncomplicated cases, the results in terms of LOS are largely similar. As you rightfully pointed out, this does not offset the excess intraoperative cost of the robotic-assisted liver surgery (RLS).*

Changes in text:

Methods: "A comparative sub-analysis of intra- postoperative and total costs was performed for patients who had no postoperative complications" (line 240 of the PDF document)

Results (postoperative outcomes): "However, analysing the sub-population of patients with no postoperative complications, the median length of stay became similar among the three groups (4,5 days for the OLS group, 4 days for the two minimally invasive groups)."(line 314 of the PDF document)

Results (costs analysis): "In addition, a detailed sub-analysis was conducted to compare the intra-, postoperative and total costs among patients who experience no postoperative complications (Table 4). By narrowing our focus to this specific subgroup, the authors found that the total costs associated with robotic surgery were 82.16% higher than those in the OLS group and 67.58% higher than those in the LLS group. Interestingly, intraoperative costs remained consistent with the main comparative analysis. Notably, the primary factor affecting postoperative costs - specifically the cost of hospital stay - did not exhibit substantial differences among the three groups in this sub-analysis (€3.105 for the OLS group, €3.131 for the LLS group, and €3.068 for the RLS group). (line 334 of the PDF document)

Table 4 Comparison of intra-, postoperative, and total costs between not-complicated OLS, LLS and RLS groups within an intention-to-treat analysis.

	OLS €		LLS €		RLS €	Absolute difference	Absolute difference	Difference %		Difference %
	n = 16		n = 34		n = 33	RLS vs OLS	RLS vs LLS	RLS vs OLS		RLS vs LLS
	mean (€)	dev. std.	mean (€)	dev. std.	mean (€)	dev. std.				
Medical staff	759 €	241 €	1.020 €	322 €	1.099 €	391 €	340 €	79 €	44,75%	7,69%
Surgical devices	443 €	0 €	581 €	165 €	3.861 €	242 €	3.418 €	3.280 €	771,14%	564,38%
Intraoperative transfusions	- €	- €	11 €	66 €	31 €	99 €	31 €	20 €	NA	171,31%
Sterilization*	198 €	- €	198 €	- €	198 €	- €	- €	- €	0,00%	0,00%
Anaesthesia*	117 €	- €	117 €	- €	117 €	- €	- €	- €	0,00%	0,00%
Histopathological Exam*	75	- €	75	- €	75	- €	- €	- €	0,00%	0,00%
Total intraoperative costs	**1.592 €**	241 €	**2.003 €**	324 €	**5.381 €**	563 €	3.788 €	3.378 €	237,90%	168,64%
Hospital stays	3.105 €	1.293 €	3.131 €	1.199 €	3.068 €	1.160 €	-37 €	- 63 €	-1,19%	-2,01%
Intensive Care Unit stays	- €	- €	99 €	401 €	204 €	557 €	204 €	105 €	NA	106,06%
Antibiotic therapies	- €	- €	41 €	111 €	87 €	181 €	87 €	46 €	NA	112,05%
Postoperative transfusions	179 €	389 €	30 €	126 €	81 €	337 €	-98 €	51 €	-54,75%	171,60%
Imaging & procedures	16 €	52 €	14 €	49 €	91 €	238 €	75 €	77 €	479,72%	552,47%
Total postoperative costs	**3.300 €**	1.463 €	**3.315 €**	1.428 €	**3.531 €**	1.734 €	231 €	216 €	7,00%	6,52%
Total cost	**4.892 €**	1.647 €	**5.318 €**	1.436 €	**8.911 €**	1.848 €	4.019 €	3.594 €	82,16%	67,58%

** Costs were identified by an extensive reviewed of the scientific literature.*

*** Values are expressed as mean ± standard deviation (SD); Unit measure: Euro.*

Legend: NA, not applicable.

Discussion: In the economic sub-analysis of patients without postoperative complications, total costs for robotic surgery were notably higher than those for open and laparoscopic approaches.

This increase was primarily due to the variations in hospital stay expenses, which, in this case, were relatively similar among the three groups. This economic finding aligns with the clinical observation that the median LOS was 4.5 days for the OLS group, 4 days for the LLS group, and 4 days for the RLS group. Consequently, the initial hypothesis is further supported, indicating that the robotic approach is particularly advantageous for high-risk hepatectomies prone to postoperative complications, such as complex liver resections (line 457 of the PDF document).

- **Comment 2:** What were the costs of converted cases?

Reply 2: *Thank you for your question. We integrated the manuscript in accordance to what you suggested. However, since the costs of conversions did not reach a statistically significant difference between the two minimally invasive groups we chose to report only the differential results of this comparative costs sub-analysis. Given this methodology, our analysis revealed that, on average, a converted surgery from the LLS approach costs approximately 32.3% more than a non-converted surgery, and 28.7% more when analyzing the RLS group.*

Changes in text: *"The cost of conversion for the two minimally invasive groups was express as an additional cost, calculated as a percentage. This was determined by taking the ratio between the mean cost of converted resections to the mean cost of completed resections" (line 240 of the PDF document).*

"The additional cost of conversion was + 37,13% for the LLS group and + 28,52 % for the RLS group. However, this difference between the two minimally invasive groups did not reach statistical significance" (line 334 of the PDF document).

- **Comment 3:** It is not clear why the authors chose to restrict the analysis to only complex resections. It may be worthwhile to do an economic analysis of major hepatectomy only.

Reply 3: *Thank you for your comment. As mentioned in the introduction section, based on the most recent evidence in literature, our hypothesis is that robotics might confer the most relevant advantages in the context of complex liver resection, including both major hepatectomies and resections of the posterior-superior segments. In particular, in a prior investigation, Cipriani et al[*] conducted a comparative analysis of laparoscopic and robotic liver surgeries, stratifying the resections based on varying levels of difficulty. The findings support the theoretical advantages of robotics particularly in facilitating postero-superior and major liver resections. The result of this study prompted the authors of the current manuscript to specifically concentrate their analysis on patients undergoing this particular pool of liver resections.*
In accordance with your suggestion, we expanded upon this concept with the aim of enhancing reader comprehension.

[*] Cipriani F, Fiorentini G, Magistri P, Fontani A, Menonna F, Annecchiarico M, Lauterio A, De Carlis L, Coratti A, Boggi U, Ceccarelli G, Di Benedetto F, Aldrighetti L. Pure laparoscopic versus robotic liver resections: Multicentric propensity score-based analysis with stratification according to difficulty scores. J Hepatobiliary Pancreat Sci. 2022 Oct;29(10):1108-1123.

Changes in the text: *"In particular, in a prior investigation, Cipriani et al. conducted a comparative analysis of laparoscopic and robotic liver surgeries, stratifying the resections based on varying levels of difficulty. The findings support the theoretical advantages of robotics particularly in facilitating postero-superior and major liver resections. The result of this study prompted the authors to specifically concentrate the current analysis on this specific setting to address the issue of comparative costs of open vs laparoscopy vs robotic approach as a primary endpoint." (line 87 of the PDF document)*

- **Comment 4:** Higher grade 3+ complications in OLR / RLR = what were these complications?

Reply 4: *Thank you for your comment. According with the Clavien-Dindo classification, we reported the severe complications observed in the two groups in the following table, that we have included in the supplementary materials. A sub-analysis of patients who developed major complications was performed, breaking down severe complications into different grades. No statistically significant differences were observed between the OLS and RLS groups. However, we enrich the discussion session with an additional consideration, that according to the authors deserve mention.*

Changes in the text*:" Nevertheless, it is essential to highlight that in the robotic group, cardiovascular accidents constituted 33.3% of severe complications. While the limited sample size prevents definitive conclusions, this data could be interpreted as a potential consequence of extended operative times, exposing patients to prolonged pneumoperitoneum (Supplementary materials, Table 5)." (line 457 of the PDF document)*

"Supplementary materials. (line 459 of the PDF document

Table 5: Comparative sub-analysis of severe complications between the OLS and the RLS groups.

Severe complications (Clavien-Dindo 3-5)	OLS *(n=23)*	RLS *(n=9)*	p-value
3a:	11 (47.8)	6 (66.6)	0.337
Bile leak	5 (21.7)	1 (11.1)	
Ascites	1 (4.3)	0 (0.0)	
Collection	4 (17.4)	2 (22.2)	
Bowel obstruction	1 (4.3)	0 (0.0)	
Cardiovascular disease	0 (0.0)	3 (33.3)	
3b	8 (34.7)	3 (33.3)	0.938
Haemorrhage	2 (8.69)	1 (11.1)	
Bowel obstruction	2 (8.69)	2 (22.2)	
Pneumothorax	1 (4.3)	0 (0.0)	
Choleperitoneum	3 (13.0)	0 (0.0)	
4a	2 (8.69)	0 (0.0)	0.361
Liver failure	1 (4.3)	0 (0.0)	
Respiratory failure	1 (4.3)	0 (0.0)	
4b	1 (4.3)	0 (0.0)	0.525

Multiorgan failure	1 (4.3)	0 (0.0)	
5	1 (4.3)	0 (0.0)	0.525
Death	1 (4.3)	0 (0.0)	

** The distribution of dichotomous categorical variables is expressed by percentages (absolute frequency)."*

- **Comment 5:** Data and cost of hospital readmissions should be included in the analysis.

Reply 5: *Thank you for your comment. The readmission rate within 30 days of discharge was consistent across all three groups (approximately 10%). However, readmission was not taken into account as the comparative economic analysis specifically aimed to consider expenditure drivers closely linked to surgical procedures. It is the authors' opinion that the rate of re-hospitalization could be a confounding factor in the analysis as it could arise from factors unrelated to the type of operation performed or reasons not closely related with the surgical procedures.*

Changes in text: *"None"*

- **Comment 6:** Conclusions in the abstract and main manuscript are far too long.

Reply 6: *Thank you for your feedback. We appreciate your insights and have addressed the concerns raised regarding the length of the conclusions in both the Abstract and Main text. In response, we have meticulously rewritten both sections, placing a heightened emphasis on the significant results of our study.*

Changes in the Text:

Abstract: "RLS offers economic advantages over OLS, as initial higher costs are offset by better perioperative outcomes. The evolving robotic marketplace is expected to drive down RLS costs, promoting widespread adoption in minimally invasive procedures. Despite its higher costs than LLS, RLS's ability to enhance minimally invasive feasibility makes it a preferred choice for complex cases, reducing the need for conversions." (line 30 of the PDF document)

Conclusions: "The study emphasizes the potential advantages of RLS in complex resections and underscores the need for a thorough economic analysis for cost-effectiveness, providing real-world evidence and detailed economic insights using a TD-ABC model. Despite RLS incurring higher total intraoperative costs, including ICU stays and surgical devices, when compared to OLS and LLS groups, it demonstrated lower total postoperative costs, resulting in an overall cost of €10,637, compared to €13,961 for OLS. Anticipated reductions in acquisition costs with the introduction of new robotic systems and increased market competition make robotic surgery a favored minimally invasive technique. As adoption expands, proficiency among surgeons and healthcare providers is expected to lead to streamlined procedures, shorter operative times, and improved patient outcomes, contributing to lowered overall costs associated with RLS. Over time, standardization and proficiency in using robotic systems have the potential to optimize workflow, reduce complications, and yield cost savings. However, it is essential to consider factors such as maintenance, upgrades, and ongoing training when evaluating the overall cost-effectiveness of robotic technology. A

comprehensive long-term cost analysis should encompass these elements to grasp the economic implications of widespread adoption in minimally invasive techniques". (line 506 of the PDF document)

Minor comments

- **Comment 1:** I found the paper difficult to read with frequent grammatical errors. I would recommend getting the paper proofread. Examples below:

a. Line 9 atherogenicity
b. Line 28 – sentence does not read well and needs to be rewritten
c. Line 308 – "Despite the postoperative morbidity was similar" is grammatically incorrect.
d. Line 380 – "total costs resulted lower than the control group" is grammatically incorrect.
e. Line 443 – should be counterbalanced not counterbalance
f. Line 444 – should be advanced not advance

Response 1: *Thank you for your feedback. In response to your suggestion, the paper has been reviewed and edited by a native English speaker.*

Changes in the Text:
All the text have been revised. With reference to your suggestions:
a. Line 9 – heterogeneity
b. Line 28 - were slightly offset
c. Line 308 - Despite the postoperative morbidity being similar
d. d. Line 380 – total costs resulted lower than those of the control group
e. e. Line 443 – should be counterbalanced
f. f. Line 444 – should be advanced

Reviewer E:

The authors carried out an economic analysis comparing open, laparoscopic, and robotic liver resection using a time-driven activity-based costing (TD-ABC) model. Their study highlights the potential advantages of robotic approach in difficult liver resections.

Major concerns:

- **Comment 1:** Conclusions are too long in both Abstract and Main text. The most important results and their opinion in this study are indistinct.

Reply 1: *Thank you for your feedback. We appreciate your insights and have addressed the concerns raised regarding the length of the conclusions in both the Abstract and Main text. In response, we have meticulously rewritten both sections, placing a heightened emphasis on the significant results of our study.*

Changes in the Text:

Abstract: "RLS offers economic advantages over OLS, as initial higher costs are offset by better perioperative outcomes. The evolving robotic marketplace is expected to drive down RLS costs, promoting widespread adoption in minimally invasive procedures. Despite its higher costs than LLS, RLS's ability to enhance minimally invasive feasibility makes it a preferred choice for complex cases, reducing the need for conversions." (line 30 of the PDF document)

Conclusions: "This study emphasizes the potential advantages of RLS in complex resections and underscores the need for a thorough economic analysis for cost-effectiveness, providing real-world evidence and detailed economic insights using a TD-ABC model. Despite RLS incurring higher total intraoperative costs, including ICU stays and surgical devices, when compared to OLS and LLS groups, it demonstrated lower total postoperative costs, resulting in an overall cost of €10,637, compared to €13,961 for OLS. Anticipated reductions in acquisition costs with the introduction of new robotic systems and increased market competition make robotic surgery a favored minimally invasive technique. As adoption expands, proficiency among surgeons and healthcare providers is expected to lead to streamlined procedures, shorter operative times, and improved patient outcomes, contributing to lowered overall costs associated with RLS. Over time, standardization and proficiency in using robotic systems have the potential to optimize workflow, reduce complications, and yield cost savings. However, it is essential to consider factors such as maintenance, upgrades, and ongoing training when evaluating the overall cost-effectiveness of robotic technology. A comprehensive long-term cost analysis should encompass these elements to grasp the economic implications of widespread adoption in minimally invasive techniques". (line 506 of the PDF document)

- **Comment 2:** The short-term results in open liver resection seemed to be not necessary in this study. The comparison with open and minimally invasive liver resection is lack of novelty.

Reply 2: *Thank you for your valuable comments. We appreciate your feedback on the short-term results in open liver resection and the perceived lack of novelty in the comparison with open and minimally invasive liver resection. It's important to note that this study primarily focuses on the economic evaluation of robotic liver surgery versus laparoscopic and open approaches. While we acknowledge the apparent lack of novelty in the short-term comparison, we emphasize the importance of including these results for several reasons. Firstly, they provide a baseline understanding of the immediate outcomes associated with each surgical approach, which is crucial for contextualizing the subsequent economic analysis. Secondly, by presenting short-term results, even if not novel, we aim to offer a comprehensive view of the overall surgical landscape and highlight any potential variations or outliers among the groups. Moreover, these short-term outcomes serve as a critical input for the economic evaluation. In cases where short-term results demonstrate significant heterogeneity across groups, it could impact resource utilization, recovery trajectories, and overall healthcare costs. Including these results in our analysis ensures that the subsequent economic evaluation is conducted on a solid foundation, enhancing the reliability and applicability of the findings.*

Changes in the text: *"None".*

- **Comment 3:** Laparoscopic anatomical liver resections have been already standardized in the high-volume hepatobiliary centers over the world. The authors should specialize to compare the economic sustainability in laparoscopic and robotic liver resection.

Reply 3: *Thank you for your insightful comment. We acknowledge the established technical standardization in laparoscopic anatomical liver procedures. However, our study explicitly addresses the enduring challenge of significant variability in previous cost analyses of minimally-invasive procedures. This persistent variability, despite the standardization of laparoscopic approaches to anatomical liver resections, is rooted in diverse cost calculation techniques and choices of devices, potentially impacting outcomes. Notably, the conventional comparison of broad categories of liver resections often overlooks the considerable initial purchase costs of the robotic platform, influencing hospital resource utilization.*
Our study is designed to contribute valuable insights by conducting a meticulous economic analysis using a time-driven activity-based costing (TD-ABC) model. This approach allows for a detailed comparison of open, laparoscopic, and robotic approaches, leveraging real-world data from two high-volume Italian centers with well-established liver resection programs. Focusing specifically on procedures of high technical complexity, our study aims to provide a comprehensive understanding of the comparative costs within a clinically relevant context.

Changes in the text: *"None".*

Minor concerns:

- **Comment 1:** The authors did not describe in detail how they allocate the three groups. Was the approach selected depend on the surgeon's preference?

Reply 1: *Thank you for your comment. We revised the manuscript in order to be clearer to the readers respect to the selection criteria used for the surgical approach.*
All cases underwent thorough evaluation in weekly multidisciplinary meetings comprising the surgical team, pathologist, radiologist, oncologist, anesthetists, and navigator nurse. During these meetings, an overall operative plan was presented, taking into account the patient's characteristics, comorbidities, as well as the pathological, anatomical, and radiological features of the disease. This comprehensive discussion guided the selection of the surgical approach. To ensure consistency, recent exclusion criteria for minimally-invasive liver surgery were strictly followed. These criteria included cases involving multiple, bilobar, and complex parenchymal sparing resections, lesions encasing the inferior vena cava/hepatic veins potentially requiring patching or prosthesis, suspected infiltration of the hepatic/portal vein, the need for portal vein thrombectomy and/or vascular reconstruction, advanced hilum infiltrating tumors, anesthesiological contraindications to pneumoperitoneum (e.g., severe cardio-pulmonary disease), and cases necessitating vascular resection and reconstruction.
Please let us know if the revised manuscript is clearer. Moreover, we would kindly underline that

the exclusion criteria for the minimally invasive approach are stated in line 117-122 of the PDF document.

***Changes in the Text**: "All cases underwent a comprehensive evaluation in formal weekly institutional multidisciplinary meetings, involving the surgical team, pathologist, radiologist, oncologist, anaesthetists, and navigator nurse. These meetings facilitated the development of an overall operative plan, considering patient characteristics, comorbidities, and the pathological, anatomical, and radiological features of the disease, guiding the selection of the surgical approach. Strict adherence to recent exclusion criteria for minimally-invasive liver surgery was maintained." (line 136-139).*

- **Comment 2:** The authors should show the reason why the type of the hepatectomy is divided to Major hepatectomy and Postero-superior sectionectomy (Table 1). What is the meaning of division to two types?

***Reply 2:** Thank you for your clarification. The division of hepatectomy types into Major Hepatectomy and Postero-Superior Sectionectomy in Table 1 serves the purpose of enhancing clarity in our baseline characteristics presentation. Since our focus is on conducting an economic evaluation specifically for major and postero-superior liver resections within three surgical approaches (robotic, laparoscopic, and open) to liver resections, this subdivision can add valuable insight into the distribution among technically challenging resections.*
By explicitly reporting the rates of patients undergoing major or postero-superior resections in Table 1, we aim to offer a clear overview of the patient distribution among these specific categories. This detailed breakdown facilitates a better understanding of the distribution and ensures that our economic analysis is appropriately contextualized within the scope of major and postero-superior liver resections.

***Changes in the text:** "None".*

- **Comment 3:** Why was the R0 resection rate low in OLS (Table2)?

***Reply 3:** Thank you for your insightful comment. The lower R0 resection rate in OLS reported in Table 2 can be attributed, in part, to the inclusion of several cases of perihilar cholangiocarcinoma. This specific subset of cases, characterized by extensive tumor involvement and the need for potentially vascular resections, typically requires an open surgical approach and is characteristically burdened by low rates of R0 resections.*
Even when excluding cases of perihilar cholangiocarcinoma from the analysis, it is crucial to note that the OLS group managed a higher proportion of technically challenging cases. These cases, marked by major tumor burden and the potential infiltration of vascular structures, are often addressed using an open approach due to the complexity of the surgery. Consequently, the OLS group may exhibit higher probabilities of R1 resections when compared to the extremely low rates achieved with a minimally invasive approach.

***Changes in the text:** "Instead, the lower rate of R0 resections in the OLS group can be attributed*

to the fact that this group dealt with a higher proportion of technically challenging cases. These cases, characterized by a major tumor burden and the potential infiltration of vascular structures, are frequently addressed using an open approach due to the complexity of the surgery." (line 45 of the PDF document)