Reviewer 1

Comment 1: Does it briefly describe the main diagnostic techniques for postoperative pancreatic fistula (CR-POPF), and whether these techniques, in combination with biomarkers of CR-POPF, can be further advanced and easier to detect postoperative pancreatic fistula (CR-POPF), such as blood markers, is there a comparison with drainage?

Response: Thank you for these helpful suggestions which broaden the clinical scope of our manuscript. We have since added new detail regarding the role of diagnostic imaging and blood biomarkers for CR-POPF diagnosis to complement our existing discussion of the consensus ISGPS definition. To the best of our knowledge, no systematic reviews have been published comparing the accuracy of drain fluid biomarkers, blood biomarkers and medical imaging for diagnosing CR-POPF through pooled sensitivity and specificity results. As such, this unfortunately could not be discussed in further detail. To highlight this important issue, we have noted the value of combining these modalities to bolster prediction in future studies, particularly as multi-variable models have already been devised for this purpose. The following text has been added to the manuscript (Page 17, Paragraph 1):

"Clarifying the clinical utility of drain biomarkers, could also facilitate their inclusion as variables in predictive models alongside blood biomarkers and medical imaging. This would complement recent efforts in which predictive models have sought to improve and expediate diagnosis when compared to the evaluation of individual variables (171-173). As such, progress can continue to be made towards risk-stratifying patients according to pre- and intra-operative variables."

Comment 2: What is the best day to test for amylase after surgery? What is the effective cutoff value? Want to know the author's point of view, rather than let the

reader guess. Or rather, where is the innovation in this article, rather than the data that illustrates the difficulty of the problem?

Response: Thank you for these pertinent questions. As this manuscript is a narrative review, quantitative derivation of an optimised cut-off for the biomarkers was beyond the scope of this current study. Hence, the innovation in this article is seen in our future research recommendations which seek to overcome the difficulties of early CR-POPF diagnosis. We agree that answering these questions will provide important clinical guidance, and as such we have initiated a meta-analysis to provide these answers in our subsequent follow up study.

Comment 3: Table 1 shows that much of the literature data comes from abstracts. Is this appropriate?

Response: The data from abstracts was deliberately included to minimise the presence of publication bias in our review. As such, we were able to present the full scope of research in this field.

Reviewer 2

Comment 1: Please discuss whether drain biomarkers are associated with tumor size and duration of surgery.

Response: Thank you for these helpful suggestions, we have now addressed tumour size and duration of surgery as potential risk factors for CR-POPF in pancreatoduodenectomy and distal pancreatectomy patients. The following text has

been added to the manuscript (Page 5, Paragraph 2):

"Indeed, the higher morbidity inherent to multi-visceral resection is avoided in spleen-preserving distal pancreatectomy. Moreover, the former facilitates shorter operative times, which may be advantageous given that operations exceeding 480 minutes were at greater risk of developing pancreatic fistula (p=0.02) (44). This finding however did not persist in pancreatoduodenectomy patients (31, 45). Whilst the location of the tumour matters in determining the surgical approach, the size of the tumour has not been shown to influence the development of CR-POPF in pancreatoduodenectomy patients (46) but has so in distal pancreatectomy patients undergoing staple closure (p=0.009, univariate analysis) (47)."

Reviewer 3

Comment 1: The manuscript is interesting and largely well written I think the interest presently is to predict the CRPOF pre-operatively and this should be discussed in future trends. This includes imaging, elastography etc which should be briefly mentioned in future directions

Response: Thank you for your insights, we agree that expediating CR-POPF diagnosis is a clinical priority. We have acknowledged this in our conclusion and included discussion of the potentially useful adjunct of imaging to bolster diagnostic accuracy. The following text has been added to the manuscript:

Page 4, Paragraph 2

"Recently, non-contrast-enhanced computed tomography paired with machine learning has been shown capable of evaluating pancreatic texture to predict CR-POPF, doing so with a sensitivity of 0.96 and specificity of 0.98 (27). Similarly, transabdominal pancreatic ultrasound elastography has been associated with CR-POPF, occurring more in patients with softer parenchyma (p=0.002) (28)."

Page 17, Paragraph 1

"Clarifying the clinical utility of drain biomarkers, could also facilitate their inclusion as variables in predictive models alongside blood biomarkers and medical imaging. This would complement recent efforts in which predictive models have sought to improve and expediate diagnosis when compared to the evaluation of individual variables (171-173). As such, progress can continue to be made towards risk-stratifying patients according to pre- and intra-operative variables."

Revision reviewer

Thank you for inviting me to re- review "Current Perspectives on the Liver Transplantation for Langerhans Cell Histiocytosis". It is an interesting paper，andI can accept the author's answer to the question.So, I recommend to you that this manuscript may be accepted.

Thanks for your comments.