Endobiliary ablation combined with immune nutrition improve the quality of life for patients with advanced malignant obstructive jaundice

General Recommendation: Good - publish after minor revision

Comments to Editor:
First of all, thank you for the invitation you sent to me regarding my participation as a reviewer in your journal. I am at your disposal for any further information and contact. Regarding the article I have reviewed It is an article with a small number of patients regarding a relatively uncommon group of diseases biliary tumors. I suggested revision with a few changes, because I think that some parts of the main manuscript are a little bit confusing. The authors followed some well known checklists which are very helpful to keep the right order in writing a manuscript to present their methods and results. I did not comment on language and grammatical errors, as you have asked me to do so. I hope that my comments will be helpful to the authors and I believe that after the changes I and rest reviewers have suggested, the manuscript will come up to your expectations and be published in your journal, as this article adds to the literature citing some previous relevant studies properly.

Comments to Author:
Congratulations to the authors for their work. In my opinion this randomized trial should be published, although the small number of patients included. However, I have some recommendations for improving your manuscript.

Title and abstract
The title reflects the main message of the study. Regarding the abstract I suggest you present the methods with more details as well as the results. I give an example of a rephrased abstract:
Background. In patients with advanced malignant obstructive jaundice (MOJ), it remains an intractable problem to maintain biliary patency, because repeated stent occlusion and poor immune condition may lead to serious infection. The aim of this study is to investigate the effect of endobiliary ablation combined with immuno-nutrition (IN) on advanced MOJ.

Methods. A prospective randomized pilot study of patients undergoing percutaneous transhepatic biliary drainage (PTBD) for advanced MOJ was conducted. From January 2018 to December 2020 patients fulfilling eligibility criteria were enrolled and randomized into two groups: patients received only PTBD and standard early enteral nutrition were defined as the control group and those who underwent additional endobiliary ablation and early IN on basis of the standard therapy were defined as the study group. Primary outcome was assessment of the quality of life based on time of resuming normal daily activities, duration of stent patency and the overall survival (OS). Secondary outcomes included time before relief of jaundice, duration of hospital stay, inflammatory responses and clinical complications.

Results. 59 patients were included: 28 in the control group and 31 in the study group. Baseline characteristics were well balanced between 2 groups. No statistically significant difference was found in time of resuming normal daily activities between the two groups. However, the study group presented statistically longer median duration of stent patency and survival time compared to the control group (stent patency 10.2 month vs. 6.8 months, survival 9.6 months vs. 7.1 months). The median time for relief of jaundice and the incidence of infection were similar between 2 groups, but values of inflammatory response markers 3 days after operation were significantly lower in the study group. No significant difference was found between 2 groups as for the overall incidence of complications.

Conclusion. Endobiliary ablation combined with post-operative IN therapy can significantly improve the quality of life for patients with advanced MOJ.

Key Words: Immuno-nutrient; Endobiliary ablation; Malignant obstructive jaundice; Quality of life; Infection.

Introduction
Some sentences are not so well comprehensible. I would rephrase to:
Malignant obstructive jaundice (MOJ) is usually secondary due to biliary stricture caused by malignancies originating from pancreatic head, Vater ampulla, gallbladder, bile duct or adjacent metastasis of lymph nodes. Because of the unresectability at the time of diagnosis and insensitivity to chemo-radiotherapy in most patients, MOJ usually predicts a poor prognosis[1]. If MOJ is not handled in time, it may lead to severe adverse events, resulting in life-threatening dysfunctions of multiple organs, delaying anti-tumor treatment and reducing the quality of life[2]. Although percutaneous transhepatic biliary drainage (PTBD) combined with stent implantation has become the first-choice of palliative care for unresectable MOJ, it remains an intractable problem to maintain biliary patency because of repeated stent occlusion related to tumor overgrowth, epithelial hyperplasia and biofilm deposition[3,4]. Furthermore, due to poor immune condition,
Material and Methods

I would avoid mentioning the number of patients enrolled in the methods part. Also, regarding the 3rd inclusion criterion, does it include patients with either serum bilirubin greater than 35 or cholangitis OR does it include patients with serum bilirubin greater than 35 with/or cholangitis? In the first case, please mention cholangitis as a separate criterion. Additionally, regarding the exclusion criteria, please mention coagulation disorders as a separate criterion, not together with ascites. I would rephrase the protocol design and eligibility criteria parts to:

Protocol Design
This pilot prospective randomized open label study was respectively approved by the ethical committee of Fu Xing hospital and Chinese PLA Air Force Medical Center. From January 2018 to December 2020, patients with advanced MOJ were randomized into the control group (patients received the standard therapy of biliary stent implantation through PTBD pathway) and the study group (patients received endobiliary ablation and early IN therapy on basis of the standard therapy). Patients were assessed for eligibility immediately after admitted into hospital and the simple randomization sequence was electronically generated for those eligible for this study. All enrolled patients were allocated using numbered opaque sealed envelopes and actual assignment was performed after opening the envelope. This study was conducted in accordance with the Declaration of Helsinki, with written informed consent obtained from all participants. The recruitment process is outlined in Figure 1.

Patient Eligibility
Patients were included into this study only if all listed criteria were met: a pathological confirmation of malignant biliary stricture by CT or MR; [...] The exclusion criteria were the following: a severe dysfunction of vital organs; a i surgical history of extrahepatic bile duct or duodenum; a refractory ascites; a LE severe coagulation disorder; a dysfunction of immune or blood system; or 6 condition of cachexia.

Statistical Analysis
Statistical analysis in the methods part is ok

Results
Please avoid mentioning the word "accident" for cardiovascular events. You can use the words event, complication etc. Small changes in some sentences are needed so that the manuscript could be more appropriate. Please rephrase to:

[......] Seven patients (22.6%) of the study group and 5 patients (17.9%) of the control group were still alive just at the time of data analysis. Median duration of stent patency of the study group was 10.2 month (range 4.6-16.7), 95% confidence interval (CI): 7.8-11.4), statistically longer than that of the control group (median of 6.8 months, range: 1.4-13.5, p<0.015). The median survival time, which was calculated from PTBD until death or last follow-up, was 9.6 months in the study group (range 2.4-17.1, 95% CI: 8.6-10.7), and 7.1 months in the control group (range 2.6-16.4, 95% CI: 6.2-8.5), presenting significant difference (p<0.017). [.....]

Secondary outcomes
Table 4 summarizes other clinical outcomes. In the study group, the mean baseline of total bilirubin was 204.8 (172±58.4) μmol/L with the direct bilirubin level of 164.7 (133±49.2) μmol/L, and the median time for relief of jaundice was 12.3 days. As a comparison, total bilirubin in the control group was 197.5 (164±53.9) μmol/L, with the direct bilirubin level of 153.2 (118±49.6) μmol/L, and the median time for relief of jaundice was 12.7 days. No significant difference was found between 2 groups (p>0.05). The median duration of hospital stay after PTBD was also similar (7.3 vs 7.1 days) between 2 groups. As for the inflammatory response, the incidence of infection (body temperature≥38.5℃, white blood cells and neutrophil percentage exceeding the normal levels) of the study group was 22.6% (7/31), similar to the 21.4% (6/28) of the control group. Values of C-reactive protein (CRP), IL-1, IL-6, and TNF-alpha, as inflammatory response markers 3 days after operation, were significantly lower in the study group (P<0.05). Other complications related to the interventional procedures happened in 13 patients of the study group and 9 patients of the control group, without severe complications demanding emergent intervention or surgery for both groups. No significant difference was found as for the overall incidence of various complications
Tables and Graphics

Conclusions are clear. Please mention the need for more randomized trials to reach more reliable conclusions systematically addressed in the near future [21].

Discussion

Please include at the end of Discussion part a paragraph mentioning the limitations of your study (small number of patients, etc.) as well as the knowledge that your study adds to the bibliography and other advantages (randomised trial, etc.). Please mention PGE3 with capital letters as you do with PGE2. Also, I am a little bit confused with the following sentences: "Because stents remained patent at the time of last follow-up or death, the median OS in the study group was even shorter than the duration of stent patency." I suppose you mean that as long as the stent patency is longer than the median survival time of the patients they do not experience complications and clinical symptoms. If I am wrong please rephrase this sentence, so that the readers could reach the conclusion easily. Moreover, I am not sure if all these biochemical procedures, you mention at the discussion part, are relevant to your manuscript. Please shorten these comments and make your point clearer in a shorter way. Some parts need rephrasing as the following:

Discussion

MOJ indicates an advanced stage of carcinomas and implantation of biliary stent has become a widely accepted palliative treatment for patients who radical resection could not be performed. Endobiliary ablation results in localized tumor necrosis by delivering high amount of thermal energy and can prevent stent occlusion in theory. In a systemic study containing 150 cases, we have reported the long-term outcome of endobiliary ablation of prolonging the duration of stent patency by destroying the malignant biliary stricture just inside the biliary tract and provided strong evidence of the efficacy of endobiliary ablation for unresectable MOJ [11]. However, an inevitable situation, that always accompanied the procedure, was the increased incidence of complications after ablation, especially the incidence of severe infections can reach as high as 30%-50%, leading to prolonged hospital stay and increased costs [12]. The low immunity, caused by MOJ, intestinal bacterial translocation due to the destruction of intestinal mucosal barrier and retrograde infection related to stent implantation ultimately, leads to enterogenous endotoxin into the blood, resulting in severe sepsis, multiple organ dysfunction syndrome (MODS), or even death [13]. From our experience, ablation could destroy the integrity of the mucosalayer and increase the risk of biliary infection. This study is the first randomized trial investigating the effects of early initiated immune-modulating nutritional support in MOJ patients after endobiliary ablation.

The safety of early EN in MOJ patients with unstable hemodynamics has been corroborated in many studies. The ESPEN guidelines have clarified that the amount and type of dietary fat significantly affects adipose tissue function and systemic metabolism, and plays an important impact on postoperative recovery [14]. Fatty acids (FA) are hydrocarbon chains with carboxyl group at one end and methyl group at the other one. In fact, excessive pro-inflammatory reaction after stent implantation or endobiliary ablation is an important cause of systemic inflammatory response syndrome, which can even lead to MODS. Studies have shown that ω-3 pufas have certain anti-tumor and anti-inflammatory effects, because they bind to the phospholipid layer of cell membrane and affect cell membrane structure and fluidity, inhibiting the expression of related signal pathways, and then inhibiting the over-expression of inflammatory cells. In addition, ω-3 pufas can affect the over-expression of Cox, induce the transformation of PGE2 into PGE3, and influence Hippo pathway, thus regulating the inflammatory responses [20]. Although endobiliary ablation was not planned for improving the short-term patency of the stent, because stent blockage rarely happened in 3-6 months and most patients with unresectable MOJ had died of tumor progression, the development of various subsequent therapy targeted on tumor has significantly improved the OS, making it very important to keep the stent patent for long time. As we found in our study, the percentage of patients who died of tumor progression rather than indirect complications was increased after endobiliary ablation. Combined endobiliary ablation and IN therapy improved the quality of life for patients with unresectable MOJ by alleviating clinical symptoms, providing opportunity for subsequent tumor-targeted therapy, without increasing additional complications and delaying recovery. This happened, because stents remained patent at the time of last follow-up or death, while the median OS even for the study group, who presented the longest OS between the two groups, was shorter than the duration of stent patency.

This pilot study supports the feasibility of early initiation and acceptable tolerance to IN among MOJ patients after endobiliary ablation and PTBD intervention. Its results may be used for planning future studies investigating different immune modulating effects of IN, as these topics are among the top nutritional questions that need to be systematically addressed in the near future [21].

Conclusions

Conclusions are clear. Please mention the need for more randomized trials to reach more reliable conclusions...
Please make corrections to table 3. Tumor-progression affects 21 out of the 28 patients of the control group meaning that the percentage is 75% not 32.7%. Also, regarding the lines with results of: Duration of stent patency, Death, Overall survival, I suppose that you have written the results of the control group in the study group's column and vice versa. Furthermore, the numbers are close to the results you mention in the manuscript, but not equal. For example, you mention in table 3 that the duration of stent patency is 10.6 for control group and 7.0 for study group, while in your manuscript you mention that the duration of stent patency is 6.8 for control group and 10.2 for study group. The same regards the section Postoperative stay in hospital in table 4. Also, there is an unnecessary parentheses sign at the number reflecting the result of CRP levels in control group in table 4.

References
References are ok. Check that they follow the publication guidelines of the journal.

General comments to the Authors
Congratulations to the authors for their work. In my opinion this randomized trial should be published, although the small number of patients included. However, I have some recommendations for improving your manuscript.