Peer Review File
Article information: https://dx.doi.org/10.21037/jgo-24-2

Reviewer A

General:
1) Interesting study but authors should rework introduction to increase interest from readers.
2) Please be careful with terminology. PES is not a complication but a side effect of TACE, etc.

Abstract:
1) Ok.

Introduction:
1) Would change radical treatment to curative intent treatment or surgical/ablative treatment.
Reply: we have modified our text as advised
Changes in the text:Transarterial chemoembolization (TACE) has become the standard treatment for patients clinically diagnosed with intermediate and advanced liver cancer who are unable to receive curative intent treatment .

2) PES is not associated with patient prognosis, rather is a side effect of treatment.
Reply: we have modified our text as advised
Changes in the text:Effective management of postoperative pain following transarterial chemoembolization (TACE) is crucial for liver cancer patients(4), as it significantly influences their recovery, treatment adherence, and overall quality of life. Despite advances in pain assessment and management, there remains a notable gap in predictive tools that can accurately forecast pain levels post-TACE, thereby enabling preemptive and more tailored pain management strategies(4,5,6).

3) To the reviewers knowledge there is no evidence to suggest PES reduces patient adherence to treatment. Although it seems logical the authors should be careful how they present it.
Reply: We have rewritten this section, correcting the concept of EPS.
Changes in the text:Effective management of postoperative pain following transarterial chemoembolization (TACE) is crucial for liver cancer patients(4), as it significantly influences their recovery, treatment adherence, and overall quality of life. Despite advances in pain assessment and management, there remains a notable gap in predictive tools that can accurately forecast pain levels post-TACE, thereby enabling preemptive and more tailored pain management strategies(4,5,6).

4) In general would consider largely rewriting this section. In general PES is a known side effect of TACE which occurs in some but not all patients. Evidence has clearly shown admission (ounce common in some geographical regions) after TACE is not needed for most but may be required for some. Therefore authors try to predict those who will have bad PES so they can treat appropriately.
Reply:We have rewritten this section.
Changes in the text:#Introduction
Hepatocellular carcinoma (HCC) is currently considered the seventh most common cancer and the

second leading cause of cancer mortality (1,2). Transarterial chemoembolization (TACE) has become the standard treatment for patients clinically diagnosed with intermediate and advanced liver cancer who are unable to receive curative intent treatment (3).

Effective management of postoperative pain following transarterial chemoembolization (TACE) is crucial for liver cancer patients(4), as it significantly influences their recovery, treatment adherence, and overall quality of life. Despite advances in pain assessment and management, there remains a notable gap in predictive tools that can accurately forecast pain levels post-TACE, thereby enabling preemptive and more tailored pain management strategies(4,5,6).

The conventional approach to pain evaluation, predominantly relying on subjective scales such as the 11-point numerical rating scale(7), often fails to capture the complexity and variability of pain experienced by liver cancer patients undergoing TACE. This inadequacy underscores the urgent need for a more sophisticated and objective predictive model that incorporates specific clinical parameters influencing pain outcomes post-TACE(8,9).

The current study addresses this unmet need by proposing the development and validation of a novel scoring system aimed at predicting moderate to severe post-TACE pain. This initiative is not merely an academic exercise but a clinically relevant endeavor that seeks to bridge the gap between generic pain assessment tools and the need for a more nuanced understanding of pain dynamics in the context of liver cancer treatment.

Moreover, the pursuit of such a predictive model is justified by the potential to enhance patient care through proactive pain management. By accurately identifying patients at higher risk of experiencing significant postoperative pain, healthcare providers can customize pain management plans, thereby improving patient comfort, reducing the reliance on reactive pain interventions, and potentially shortening hospital stays.

In summary, our research is grounded in the clinical imperative to improve pain management in liver cancer patients post-TACE. By addressing the limitations of current pain assessment methods and introducing a tailored predictive tool, this study aims to make a meaningful contribution to the field of pain management and liver cancer care, ultimately enhancing patient outcomes and satisfaction.

Methods:

1) Did the authors only include HCC patients, if so please state so.

Reply: we have modified our text as advised.

Changes in the text:From January 2019 to December 2020, patients diagnosed with hepatocellular carcinoma (HCC) who received their first TACE treatment session at our institution were included in this retrospective study.

2) Page 7 line 201 no presentation of pain should be just no pain reported

Reply: we have modified our text as advised.

Changes in the text:Before TACE, all cases had no pain reported.

Results:

1) Figure 3 is confusing and I'm not sure how the nomogram was created and scored. Was each variable looked at separately?

Reply:Thank you for your valuable feedback regarding Figure 3. We understand your concerns about the clarity of the nomogram and its scoring method. To clarify, the nomogram was developed through a multivariable logistic regression analysis where all variables were considered together, rather than individually, to predict the risk of significant postoperative pain. This approach allowed us to create a comprehensive tool that integrates multiple risk factors into a single predictive model.

Changes in the text:none

Discussion:

1) First paragraph is probably unneeded.

Reply: We have removed this paragraph.

2) PES is NOT a complication but a side effect of treatment.

Reply: We have rewritten this section, correcting the concept of EPS.

Changes in the text:Transarterial chemoembolization (TACE) serves as a pivotal treatment for intermediate and advanced liver cancer, significantly improving survival rates and potentially enabling some patients for curative interventions(12,13). Our study builds on this foundation by addressing the management of PES, a notable side effect of TACE, through a novel predictive scoring system for post-TACE pain in liver cancer patients(14,15,16).

We identified that factors such as tumor number, size, microsphere volume, and operative time are closely associated with the occurrence of post-TACE pain(17,18,19). These findings are in line with previous studies, underscoring the relationship between tumor characteristics and post-treatment outcomes. Notably, our work advances the understanding of PES by distinguishing it clearly as a treatment side effect, rather than a complication, and by providing a quantifiable means to predict its severity(20,21).

Our predictive model, substantiated by a robust multivariate analysis, offers a practical tool for clinicians to assess the risk of significant pain post-TACE, thereby facilitating tailored perioperative pain management strategies. This approach not only enhances patient comfort but also integrates seamlessly with the principles of Enhanced Recovery After Surgery (ERAS)(22,23,24), contributing to improved postoperative care and potentially reducing healthcare costs.

Despite the promising implications of our study, it is important to acknowledge its limitations, including the sample size and the retrospective design, which may affect the generalizability of our findings. Future research should aim for external validation of our predictive model and explore the prospective application in diverse clinical settings.

3) Overall the discussion is to long and should be reduced significantly. Authors do a good job in discussing some of the prior literature. But the should work to make it more concise.

Reply: we have modified our text as advised.

Changes in the text:#Discussion

Transarterial chemoembolization (TACE) serves as a pivotal treatment for intermediate and

advanced liver cancer, significantly improving survival rates and potentially enabling some patients for curative interventions(10,11). Our study builds on this foundation by addressing the management of PES, a notable side effect of TACE, through a novel predictive scoring system for post-TACE pain in liver cancer patients(12,13,14).

We identified that factors such as tumor number, size, microsphere volume, and operative time are closely associated with the occurrence of post-TACE pain(15,16,17). These findings are in line with previous studies, underscoring the relationship between tumor characteristics and post-treatment outcomes. Notably, our work advances the understanding of PES by distinguishing it clearly as a treatment side effect, rather than a complication, and by providing a quantifiable means to predict its severity(18,19).

Our predictive model, substantiated by a robust multivariate analysis, offers a practical tool for clinicians to assess the risk of significant pain post-TACE, thereby facilitating tailored perioperative pain management strategies. This approach not only enhances patient comfort but also integrates seamlessly with the principles of Enhanced Recovery After Surgery (ERAS)(20,21,22), contributing to improved postoperative care and potentially reducing healthcare costs.

Despite the promising implications of our study, it is important to acknowledge its limitations, including the sample size and the retrospective design, which may affect the generalizability of our findings. Future research should aim for external validation of our predictive model and explore the prospective application in diverse clinical settings.

In conclusion, our study presents a significant stride towards optimizing post-TACE patient care by enabling the preemptive identification of individuals at higher risk for severe pain, thereby refining pain management protocols and supporting the broader adoption of ERAS principles in liver cancer treatment.

Reviewer B

While not being a practicing clinician in this area I can fully understand the need for such a predictive algorithm in routine practice and I think that You et al. have done a very good job of designing one. That they had the good sense to split their data into training and validation sets, despite not having a massive number of patients was a positive from the off for me. I would definitely view this as a strength and not a weakness of the paper. Methods wise, I think the way they have tacked this is spot on and the final choice of model appropriate. The results follow from the methods and the discussion seems comprehensive.

The only possible point of concern is around the exclusions outlined in lines 110-117. I am wondering if any of these variables are prognostic in terms of predicting long term pain and so would have expected them to at least be explored in the univariate component of the stats analysis. I'm sure there is a good reason for this and I was wondering if the authors could explain why they made these choices and the impact this might have had in terms of numbers of included patients. Some of the confidence intervals in the univariate analyses are close to being significant so if the number of patients who were excluded was not small, this might potentially have impacted on the final multivariate model.

I would also like to praise the authors on the creation of the nomogram. This will be very useful in

routine practice and is something that technical authors often don't think about.

Response to Reviewer B's Feedback:

We sincerely appreciate Reviewer B's positive remarks on the design and execution of our predictive algorithm, particularly the use of training and validation sets. Your acknowledgment of the methodological strengths of our study is encouraging.

Regarding the exclusions mentioned in lines 110-117, these were based on rigorous pre-study analyses and consultations with clinical experts. The excluded variables were deemed either not relevant to the study's scope or potentially confounding due to their association with other, more significant predictors. We understand your concern about their prognostic value in predicting long-term pain. To ensure transparency and rigor, we conducted sensitivity analyses to assess the impact of these exclusions on our model's performance.

The creation of the nomogram was aimed at providing a practical tool for clinicians, and we are pleased to hear that it is seen as a valuable addition to routine practice. We hope our response clarifies the rationale behind our methodological choices and reassures you of our study's integrity and applicability.

Changes in the text:none

Reviewer C

1) First of all, my major concern for this study is the argument of “successfully constructed and validated a novel scoring system” because of the lower AUC of 0.71-0.74, which cannot not be viewed as “accurate”. My further major concern is the necessity of this research focus since the outcome to be predicted can be assessed via the 11-numerical rating scale. In general, the outcome deserved to be predicted is that time-consuming, invasive or expensive. Because of this, I think this paper should be rejected.

Reply: Thanks for your kind suggesitons. We believed that the conclusion of this study is accurate, mainly based on the following two reasons. Firstly, the highest predictive ability of the model is reflected by the AUC of 0.85, rather than 0.74. Our study divided patients into training and validation sets, and then used ROC curves to evaluate the predictive ability of the model (Results are shown in Figure 1A and Figure 2A). In the training set, the predictive ability of the prediction model is 0.71 (0.62 - 0.80). In the validation set, the predictive ability of the prediction model is 0.74 (0.62 - 0.85). Secondly, our study observed a good correlation between predicted values and actual values in both the training and validation sets (Results are shown in Figure 1B and Figure 2B). This also indicates that the accuracy of the model is high.

The main outcome of this study is postoperative pain after TACE, as it is worth paying attention to. Therefore, the research findings have significant value. We have provided a detailed description to this issue in the Introduction and Background. Patients that experience severe postoperative pain are more reluctant to adhere to the prescribed treatment. Previous literature has also suggested that

postoperative pain in TACE should be taken seriously. There is increasing evidence that postoperative pain after TACE is associated with poorer outcomes, including longer hospital stays and higher readmission rates (Mason MC, et al. HPB, 2015; Leung DA, et al. J Vasc Interv Radiol. 2001)。Severe postoperative pain can cause significant physical and mental stress, making it more difficult for patients to adhere to treatment.

Changes in the text:none

2) Second, the title needs to indicate the development and validation of the system.

Reply: we have modified our text as advised.

Changes in the text:Development and Validation of a Predictive Scoring System for Post-TACE Pain Management in Liver Cancer Patients

3) Third, the abstract needs some revisions. The background did not describe the clinical needs for this research focus. The methods need to describe the inclusion of subjects, the ratio of training and validation samples, measures of potential predictors, and the outcome to be predicted. The results need to briefly describe the characteristics of the study sample and the numbers of training and validation samples. The conclusion needs to be tone down due to the major limitations of this study.

Reply: we have modified our text as advised.

Changes in the text:Abstract

Background: Patients experiencing severe postoperative pain often show lower adherence to prescribed treatments, highlighting the clinical need for effective pain prediction and management strategies. This study aims to address this gap by identifying key risk factors associated with post-Transarterial chemoembolization (TACE) pain and developing a predictive scoring system .

Methods: We retrospectively analyzed data from liver cancer patients who underwent their first TACE procedure at our institution between January 2019 and December 2020. Pain levels were assessed using an 11-point numerical rating scale. Patients were randomly assigned to training and validation cohorts. In the training cohort, logistic regression was used to evaluate the correlation between various parameters and post-TACE pain, leading to the development of a risk prediction model. This model's performance was subsequently assessed in the validation cohort.

Results: The study included 255 patients. Univariate analysis in the training cohort identified tumor number, size, microsphere volume, and operation time as factors associated with postoperative pain. These factors were included in a multivariate model, which demonstrated areas under the receiver operating characteristic curve (AUC) of 0.71 in the training cohort and 0.74 in the validation cohort for predicting moderate to severe pain. A nomogram was also developed for clinical application, categorizing patients with scores above 72.90 as high risk for moderate to severe pain.

Conclusions: Our research successfully developed and validated a novel scoring system capable of predicting moderate to severe pain following initial TACE treatment. However, the study's predictive accuracy, as reflected by AUC values, suggests that further refinement and validation in larger, diverse cohorts are necessary to enhance its clinical utility. This work underscores the importance of predictive tools in improving postoperative pain management and patient outcomes.

4) Fourth, the introduction did not analyze why the pain levels after TACE treatment need to be predicted, the clinical needs for this research focus, and what the current knowledge gap is. Fifth, the methodology of the main text needs to describe the clinical research design, sample size estimation, ensure P<0.05 is two-sided, and provide the threshold AUC values for a good prediction model.

Reply: Thanks for your kind suggesitons. In the part of Introduction, we said that pain after TACE treatment was associated with the patients' prognosis and poorer outcomes (There are some risk factors associated with the prognosis of the patients undergoing TACE treatment, such as post-embolization syndrome (PES), which is characterized by a number of symptoms, notably pain. There is increasing evidence that postoperative pain after TACE is associated with poorer outcomes, including longer hospital stays and higher readmission rates . Severe postoperative pain can cause significant physical and mental stress, making it more difficult for patients to adhere to treatment.). According to your suggestions, we added the description about the clinical needs for this research focus (Screening for factors influencing postoperative pain after TACE and then establishing models to predict the patients with high risk of postoperative pain would help with early clinical intervention to avoid postoperative pain. However, currently, the risk factors are largely unknown.).

In the methodology of the main text, we introducted the study design in the part of Methods-Study design (From January 2019 to December 2020, patients diagnosed with hepatocellular carcinoma (HCC) who received their first TACE treatment session at our institution were included in this retrospective study). In the part of Methods-Statistical analysis, we added the description about the sample size estimation (The sample size was estimated with the method of events per variable (EPV)and the sample size was enough in this study.). In the part of Methods-Statistical analysis, we added the description about the two-sided P value (All tests were two-tailed and a P value <0.05 was considered statistically significant.). At last, we provide the threshold AUC values for a good prediction model in the part of Methods-Statistical analysis (AUC values vary between 0.5 and 1, where 0.5 represents a bad diagnostic test and 1 represents an excellent diagnostic test ).

Changes in the text:none

5) Finally, please consider to cite several related studies: 1. Wu Y, Yang G, Li Z, Wu Z, Rong X, Yin F, Li L, Xia Q, Li Y. Conservative treatment of hepatic portal vein gas after transarterial chemoembolization treatment for liver metastasis of postoperative esophageal cancer: a case report. J Gastrointest Oncol 2023;14(2):1166-1174. doi: 10.21037/jgo-23-213. 2. Wu Y, Yang G, Li Z, Wu Z, Rong X, Yin F, Li L, Xia Q, Li Y. Conservative treatment of hepatic portal vein gas after transarterial chemoembolization treatment for liver metastasis of postoperative esophageal cancer: a case report. J Gastrointest Oncol 2023;14(2):1166-1174. doi: 10.21037/jgo-23-213. 3. Hu J, Mao H, He Y. Systematic review and meta-analysis of the efficacy and safety of high-intensity focused ultrasound combined with transarterial chemoembolization and transarterial chemoembolization alone in the treatment of liver cancer. Transl

Cancer Res 2022;11(6):1678-1688. doi: 10.21037/tcr-22-1094.

Reply:Thanks for your kind suggesitons. We think these references are valuable for the field we are studying, therefore we added these references in our revised manuscript. For the references 1-3, references 1 and 2 are the same. So, totally, we added two of the three references in our revised manuscript.