Peer Review File

Article information: https://dx.doi.org/10.21037/jgo-23-75

Reviewer A

Comment 1:First, the title needs to indicate the clinical research design of this study, i.e., a retrospective cohort study.
Reply 1:Thank you very much for the suggestion.We have modified the title according to your suggestion.
Changes in the text: See Page 1,line 3-4.

Comment 2:Second, the abstract needs some revisions. The background did not explain why irAE can be a potential prognostic factor, what the potential clinical contribution of this analysis is, and what the knowledge gap is on the prognostic role of irAE. The methods cannot be all statistical methods, which need to describe the inclusion of subjects, the assessment of baseline clinical factors, follow up, and outcome measurements of efficacy and irAE. The results need to first briefly summarize the clinical characteristics of the study sample. The conclusion needs more detailed comments for the clinical implications of the findings.
Reply 2:Thank you for your valuable feedback on our abstract. We have carefully considered your comments and made the following revisions:
Background: We have revised the background section to provide a clearer explanation of why irAEs may be a potential prognostic factor, the clinical contribution of this analysis, and the knowledge gap regarding the prognostic role of irAEs.
Methods: We have added more information on the inclusion of subjects, the assessment of baseline clinical factors, follow up, and outcome measurements of efficacy and irAEs to provide a more detailed description of our methods.
Results: We have revised the results section to include a brief summary of the clinical characteristics of our study sample.
Conclusion: We have provided more detailed comments on the clinical implications of our findings in the conclusion section.
Changes in the text: See Page 1-3,line 29-72.

Comment 3: Third, the introduction of the main text needs a detailed review on known prognostic biomarkers for ESCC, have comments on the limitations of prior studies and the prognostic roles of these known biomarkers, and clearly explain why these known biomarkers are not optimal and why new biomarkers are needed. The potential clinical contribution of this research focus needs to be further clarified.
Reply 3:Thank you for your valuable feedback on our introduction. We have carefully considered your comments and made the following revisions:

In the revised introduction, we have provided a detailed review of known prognostic biomarkers for ESCC and commented on the limitations of these known biomarkers. We have also clearly explained why these known biomarkers are not optimal and why new markers are needed to improve prognostic accuracy in ESCC. Additionally, we have further clarified the potential clinical contribution of this research focus.
Changes in the text: See Page 4,line 106-118, 130-131.

Comment 4:Fourth, the methodology of the main text needs to describe the sample size estimation and details of the follow up. In statistics, please describe the details of adjusting for sex and age in the multiple Cox regression and how the prognostic factors were selected from the multiple Cox regression model.
Reply 4:Thank you for your valuable feedback on our methodology. We have carefully considered your comments and made the following revisions:
In the revised methodology section, we have added information on sample size estimation and details of the follow-up to provide a more thorough description of our study design. We added how prognostic factors were selected from the multiple Cox regression model.When conducting the Cox regression analysis, we adjusted for age and sex as these two factors may impact a patient's treatment efficacy, and adjusting for these variables was done to eliminate potential bias.
Changes in the text: See Page 5,line 142-148, Page 6,line 174-180, Page 6,line 189-196.

Comment 5:Finally, please consider to cite the below paper: Chen KB, Wu ZW, Huang Y, Kang MX, Lin LL, Jiang SS, Zhang H, Huang YJ, Chen L. Successful outcome of neoadjuvant PD-1 blockade, VEGFR-2 inhibitor plus chemotherapy for potentially unresectable esophagogastric junctional squamous cell carcinoma: a case report. Transl Cancer Res 2022;11(9):3329-3336. doi: 10.21037/tcr-22-789.
Reply 5:Thank you very much for the suggestion.We have followed your suggestion and cited this reference in our manuscript. Please refer to reference #19 for details.
Changes in the text: See Page 8,line 263.

Reviewer B

The paper titled “Immune-related adverse events as independent prognostic factors for camrelizumab in patients with esophageal squamous cell carcinoma: a retrospective cohort study” is interesting. The presence of irAEs in ESCC patients treated with anti-PD-1 therapy (camrelizumab) may serve as a clinical prognostic factor, indicating improved therapeutic effectiveness. These findings suggest that irAEs could be used as a potential marker to predict outcomes in this patient population. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) In the introduction of the manuscript, it is necessary to clearly indicate the current treatment strategy for ESCC patients and the factors that affect the prognosis and recurrence.

Reply 1:Thank you for your helpful comments.We appreciate your suggestion to clarify the current treatment strategy for ESCC patients and the factors that affect the prognosis and recurrence in the introduction of the manuscript. We revised the introduction accordingly to provide a more comprehensive overview of the current state of ESCC treatment.Regarding prognostic factors, we have reviewed relevant literature and found that the prognostic factors are not consistent in studies with different treatment regimens. Moreover, there is no consensus on whether there are specific prognostic factors for esophageal cancer. Therefore, this has not been reflected in the current manuscript.
Changes in the text: Page 3, line 95-96.

2) What is the tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors? It is recommended to add relevant content.
Reply 2:Thank you for your valuable insight. According to your review comments, we have conducted a multiple-factor logistic regression to examine whether there are differences in age, ECOG, smoking status, and other indicators between patients who experienced AE and those who did not (Please refer to the figure below.). The results showed that there were no significant differences between the two groups in all baseline indicators. This is consistent with our clinical practice, as effective predictive indicators for irAE have not been identified yet. Therefore, it is crucial to provide adequate patient management and follow-up to detect and manage irAEs as early as possible.

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Call:  glm(formula = group ~ sex + xiaoyu65sui + shoushu + fangliao +
    bolei + liver + lung + bone + lymph + other + ECOG + smoking,
    data = df)

Coefficients:
(Intercept)      sexMale  xiaoyu65sui      shoushu     fangliao
  1.000e+00    1.024e-15   -3.332e-16    3.400e-16   -2.178e-16
      bolei        liver         lung         bone        lymph
  6.554e-17   -2.510e-18   -4.603e-16    3.539e-16    9.774e-16
      other         ECOG      smoking
  2.124e-16    9.783e-17    5.990e-16

Degrees of Freedom: 80 Total (i.e. Null);  68 Residual
Null Deviance:      0
Residual Deviance: 3.88e-28     AIC: -5211
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Deviance Residuals:
      Min         1Q     Median         3Q        Max
7.772e-16  1.443e-15  1.887e-15  2.664e-15  4.774e-15

Coefficients:
              Estimate Std. Error    t value Pr(>|t|)
(Intercept)  1.000e+00  1.414e-15  7.071e+14   <2e-16 ***
sexMale      1.024e-15  6.397e-16  1.601e+00    0.114
xiaoyu65sui -3.332e-16  5.605e-16 -5.940e-01    0.554
shoushu      3.400e-16  5.643e-16  6.020e-01    0.549
fangliao    -2.178e-16  5.839e-16 -3.730e-01    0.710
bolei        6.554e-17  7.716e-16  8.500e-02    0.933
liver       -2.510e-18  7.281e-16 -3.000e-03    0.997
lung        -4.603e-16  5.715e-16 -8.050e-01    0.423
bone         3.539e-16  7.523e-16  4.700e-01    0.640
lymph        9.774e-16  6.866e-16  1.424e+00    0.159
other        2.124e-16  6.694e-16  3.170e-01    0.752
ECOG         9.783e-17  5.683e-16  1.720e-01    0.864
smoking      5.990e-16  4.309e-16  1.390e+00    0.169
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Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for gaussian family taken to be 5.706191e-30)

    Null deviance: 0.0000e+00  on 80  degrees of freedom
Residual deviance: 3.8802e-28  on 68  degrees of freedom
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3) What guidance can this research provide for the early identification and management of irAEs? How to provide treatment options for patients with advanced ESCC? It is recommended to add relevant content.

Reply 3: Thank you for your insightful question. Our research on the correlation between irAEs and treatment efficacy in cancer patients can provide valuable insights and guidance for the early identification and management of irAEs. By understanding the relationship between irAEs and treatment response, healthcare providers can monitor patients more closely and detect irAEs early, before they become severe or life-threatening. This can lead to earlier intervention and better management of irAEs, which can improve patients' quality of life and treatment outcomes. Additionally, our study provides insight into on the nuanced but significant role that irAEs play in the utilization of anti-PD-1 therapy in patients with ESCC, which may help to modernize ESCC treatment. As we mentioned, with appropriate monitoring and the application of standardized treatment to recognize and address toxic effects, ICI rechallenge would be safe . A rechallenge of ICI therapy may be an option for those patients with ESCC who experience ≥ grade 2 irAEs.Overall, our research has important implications for the management of irAEs in cancer patients and can contribute to the development of more effective and personalized cancer treatments.

4) What are the predictors of efficacy of immunotherapy? What is the application value of PD-1 inhibitors in neoadjuvant treatment of lung cancer? It is recommended that relevant information be added to the discussion.

Reply 4:Thank you for your review. The predictors of efficacy of immunotherapy include PD-L1, TMB and MSI-H. Anti-PD-1 therapies may be beneficial for patients with positive PD-L1 expression, high tumor mutation burden (TMB), and high microsatellite instability

(MSI-H), but the optimum prognostic biomarkers for ESCC are lacking. PD-L1 expression is influenced by multiple factors, such as detection methods, tissue source, sampling time and method, and the determination of PD-L1 expression threshold is controversial. In addition, some PD-L1-negative patients may also benefit from immunotherapy, so PD-L1 cannot be used as a single predictive indicator. Tumors with high TMB usually have more neoantigens, which can induce stronger immune responses. However, TMB detection methods vary and different methods may yield different results. The assessment of TMB is expensive and time-consuming, making it difficult to meet clinical needs. MSI-H is rare in patients with esophageal squamous cell carcinoma, so routine testing for MSI alone is not realistic, despite the potential value to those rare patients. Establishing easily accessible, cost-effective predictive factors to recognize patients with ESCC who might benefit from PD-1 inhibition is therefore urgently needed. That is why we have decided to choose an easily observable and cost-effective indicator for predicting the efficacy of immunotherapy.
Meanwhile, our manuscript focuses on the treatment of advanced esophageal cancer rather than lung cancer. We appreciate your interest in our research and would like to clarify that our study did not investigate the application value of PD-1 inhibitors in neoadjuvant treatment of lung cancer. Please let us know if there are any other questions or concerns.

5) What are the safety, activity and immune relevance of anti-PD-1 antibodies in cancer? It is recommended to add relevant content.
Reply 5: Thank you for your review and feedback. Anti-PD-1 antibodies are a type of immunotherapy that has shown promise in the treatment of various types of cancer. The safety, activity, and immune relevance of anti-PD-1 antibodies in cancer can be summarized as follows:
Safety: Anti-PD-1 antibodies are generally well-tolerated, but they can cause immune-related adverse events (irAEs) such as skin rash, diarrhea, and thyroid dysfunction.The occurrence of irAEs is not correlated with patients' baseline characteristics, cancer type, or physical condition, making it difficult to predict. Therefore, it is important to provide regular follow-up and monitoring to prevent adverse reactions from worsening.
Activity: Anti-PD-1 antibodies have shown activity in a variety of cancers, including melanoma, non-small cell lung cancer, and renal cell carcinoma. They work by blocking the PD-1 receptor on T cells, which can prevent cancer cells from evading the immune system.
Immune relevance: Anti-PD-1 antibodies are important for immune regulation and play a key role in the control of cancer cells. They act by inhibiting the PD-1 pathway, which is involved in immune suppression and tolerance. This leads to increased activation and proliferation of tumor-specific T cells, resulting in the destruction of cancer cells.Overall, anti-PD-1 antibodies represent an important and promising approach to cancer treatment. However, careful monitoring of patients is necessary to manage potential side effects and to optimize treatment outcomes. While we appreciate your interest in our research, we have decided to focus on the specific topic of our study and its relevance to the field of oncology.

6) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Immune-related adverse events and prognosis in patients with upper gastrointestinal cancer treated with nivolumab, PMID: 36636073”. It is recommended to quote the article.
Reply 6:Thank you for your valuable feedback. We appreciate your suggestion to include more comprehensive information in the introduction section of our manuscript and to cite

relevant literature as you commended. We revised the introduction accordingly. Thank you for recommending the literature, which has enabled us to improve the introduction section of our manuscript. With the help of this reference, we were able to provide a better overview of the topic in our manuscript.
Changes in the text: Page 4, ling 144-145.

7) What are the characteristics and evaluation criteria of immunotherapy? What are the effects of immunotherapy on tumor micrometastasis? It is recommended to add relevant content.
Reply 7: Immunotherapy is a type of cancer treatment that uses the body's own immune system to fight cancer cells. It has several key characteristics, including:
A.Targeted approach: Unlike traditional cancer treatments such as chemotherapy and radiation therapy, which can damage healthy cells along with cancer cells, immunotherapy specifically targets cancer cells.
B.Long-lasting effects: Immunotherapy can create a lasting immune response that continues to fight cancer cells even after treatment has ended.
C.Diverse mechanisms of action: Immunotherapy can work in different ways, such as boosting the immune system's ability to recognize and attack cancer cells, or blocking signals that cancer cells use to evade the immune system.
D.Potential for combination with other therapies: Immunotherapy can be combined with other cancer treatments, such as chemotherapy or targeted therapy, to enhance their effectiveness.
E.Potential for treating a variety of cancers: Immunotherapy has shown promising results in treating various types of cancer, including melanoma, lung cancer, and bladder cancer.
Overall, immunotherapy represents a promising approach to cancer treatment that offers unique advantages over traditional therapies.
When it comes to the evaluation criteria of immunotherapy, RECIST 1.1, iRECIST, and irRECIST are three commonly used criteria for evaluating tumor response in cancer patients undergoing treatment.
RECIST 1.1 is a widely used standard for assessing tumor response to treatment based on changes in tumor size. It measures the longest diameter of the tumor and classifies the response as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).
iRECIST is a modified version of RECIST that incorporates immune-related response criteria into the assessment of tumor response. iRECIST takes into account the unique features of immunotherapy, such as the potential for pseudoprogression (initial tumor growth before subsequent regression) and the delayed response to treatment, by including additional response categories such as immune-related CR (iCR) and immune-related progressive disease (iPD).
irRECIST is a further modification of iRECIST that includes the use of imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) to evaluate changes in tumor size and density. irRECIST takes into account the potential for changes in tumor density, which may indicate an immune response to treatment, as well as changes in tumor size.
In summary, iRECIST and irRECIST are modifications of RECIST 1.1 that incorporate immune-related criteria and imaging techniques to better evaluate tumor response in patients undergoing immunotherapy. While there are similarities between these criteria, they also have important differences that reflect the unique features of immunotherapy and the complexities of tumor response assessment in this setting.

Although iRECIST and irRECIST have been proposed as modifications of RECIST 1.1 to better evaluate tumor response in patients undergoing immunotherapy, RECIST 1.1 remains the most widely used and guideline-approved standard in clinical practice. Almost all large randomized controlled trials have used RECIST 1.1 to evaluate tumor response, and therefore, our study also adopted this standard. Despite the limitations of RECIST 1.1 in assessing tumor response to immunotherapy, it remains a valuable tool for evaluating tumor response in many clinical settings.