Reply reviewer#1

This study included 48 patients with advanced gastric cancer. Mainly studies the correlation between liver metastasis and the effect of immunotherapy. The results of the study found that patients with liver metastases have poorer immunotherapy effects. This provides a reference for clinical treatment. It also provides directions for clinical research.

There are several comments:

1. The language needs polishing. For example: "Prediction of patient's outcome Based on the 2023 worldwide cancer epidemiology figures"

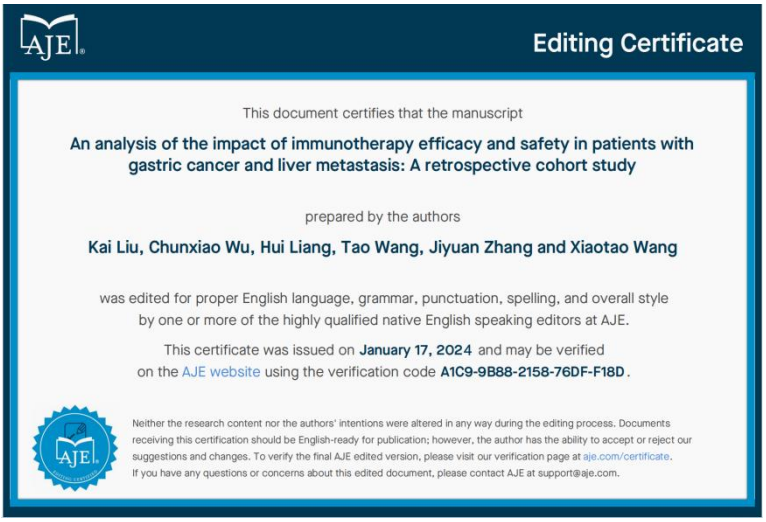
Reply 1: Thank you for your advice.

Your suggestions are of great significance to the improvement of our manuscript. We have proofread and revised the full English grammar of the manuscript according to your requirements, and the revision has been marked in yellow on the manuscript. In addition, please see the attachment for the relevant documents of English language polishing and modification of the manuscript.

Gastric cancer is the fifth most common type of cancer and has the fourth highest death rate among all cancers [1–3]. The combination of fluorouracil and platinum is the predominant first-line chemotherapy treatment for HER2-negative advanced gastric cancer that is unresectable [4]. Nevertheless, its efficacy is limited, and the overall survival (OS) rate is notably poor (median OS<1 year). Several phase III clinical trials [5–8] have demonstrated that the combination of chemotherapy and immunotherapy can enhance treatment efficacy and raise the overall survival rate in individuals diagnosed with advanced gastric cancer.

Despite this, the liver is an immune organ, and liver metastases not only stop the liver from responding to immunotherapy, but they also weaken the immune system as a whole, which means that systemic immunotherapy doesn't work very well [9]. Backward studies [10–13] have shown that having liver metastases in people with non-small cell lung cancer and melanoma can lower the response rate, progression-free survival (PFS), and overall survival (OS) rates of immunotherapy patients. This effect is observed regardless of other parameters, such as tumor mutation load and PD-L1 expression [14]. Nevertheless, there is a lack of studies examining the impact of liver metastases on the effectiveness of immunotherapy in individuals diagnosed with gastric cancer.

This study retrospectively examined patients with advanced gastric cancer who received immunotherapy in the undergraduate department. The objective was to determine the impact of liver metastases on the efficacy of immunotherapy in individuals diagnosed with gastric cancer.



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An analysis of the impact of immunotherapy efficacy and safety in patients with gastric cancer and liver metastasis: A retrospective cohort study

prepared by the authors

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2. What content is expressed in Table1 and Table2 respectively, please explain in detail in the manuscript.

Reply 2: Thank you for your advice.

In the paper, Table 1 and Table 2 present key data on the efficacy and safety of immunotherapy in patients with gastric cancer and liver metastases in this study, respectively. Table 1 covers basic patient characteristics, changes in tumor biological indicators before and after immunotherapy, and adverse events during treatment. Table 1 provides a comprehensive picture of the patient's starting status, biological changes during treatment, and the safety of immunotherapy.

Table 2 focuses on quantitative analysis of treatment effects, including key indicators such as overall survival and progression-free survival. Through Table 2, we can clearly understand the overall efficacy performance of immunotherapy in patients with gastric cancer and liver metastases, providing readers with intuitive and comprehensive data support.

Together, these two tables build the data supporting framework for the paper, providing readers with insight into the efficacy and safety of immunotherapy in this patient population. Through detailed data presentation, we aim to provide a practical reference for clinical practice while promoting in-depth thinking about the potential use of immunotherapy in the treatment of gastric cancer and liver metastases. I hope this explanation can meet the requirements of the reviewers. Thank you for your attention.

After modification and supplement in our manuscript:

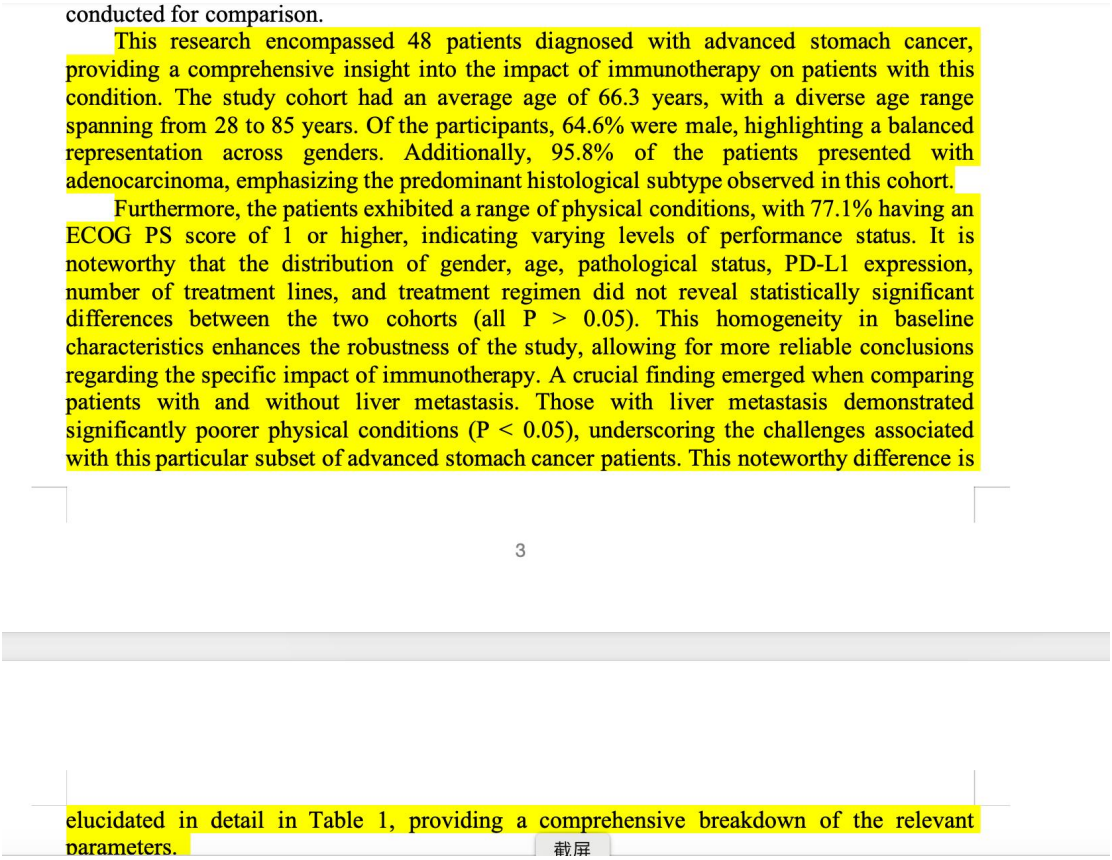
This research encompassed 48 patients diagnosed with advanced stomach cancer, providing a comprehensive insight into the impact of immunotherapy on patients with this condition. The study cohort had an average age of 66.3 years, with a diverse age range spanning from 28 to 85 years. Of the participants, 64.6% were male, highlighting a balanced representation across genders. Additionally, 95.8% of the patients presented with adenocarcinoma, emphasizing the predominant histological subtype observed in this cohort.

Furthermore, the patients exhibited a range of physical conditions, with 77.1% having an ECOG PS score of 1 or higher, indicating varying levels of performance status. It is noteworthy that the distribution of gender, age, pathological status, PD-L1 expression, number of treatment lines, and treatment regimen did not reveal statistically significant differences between the two cohorts (all $P > 0.05$). This homogeneity in baseline characteristics enhances the robustness of the study, allowing for more reliable conclusions regarding the specific impact of immunotherapy.

A crucial finding emerged when comparing patients with and without liver metastasis. Those with liver metastasis demonstrated significantly poorer physical conditions ($P < 0.05$), underscoring the challenges associated with this particular subset of advanced stomach cancer patients. This noteworthy difference is elucidated in detail in Table 1, providing a comprehensive breakdown of the relevant parameters.

Table 1 serves as a pivotal component of the study, elucidating patients' baseline

characteristics, including demographic details, pathological features, and key indicators of physical condition. The statistical comparability between cohorts ensures that observed outcomes can be attributed to the impact of immunotherapy rather than pre-existing differences. This meticulous examination of patient profiles enhances the generalizability of the study's findings and contributes valuable insights into tailoring immunotherapeutic approaches for patients with advanced stomach cancer.



conducted for comparison.

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Among the 48 patients diagnosed with gastric cancer, 15 with liver metastasis and 20 without liver metastases encountered adverse effects from immunotherapy. Notably, five patients with liver metastases and seven without experienced Grade 3 or higher treatment-related side events. Importantly, no treatment-related adverse events led to withdrawal or mortality in either group. The predominant adverse events encompassed vomiting, nausea, and exhaustion in both cohorts. These findings underscore the tolerability of immunotherapy in advanced gastric cancer, with a manageable incidence of adverse effects. The absence of treatment-related withdrawals or fatalities suggests a favorable safety profile, providing reassurance for the clinical application of immunotherapy in this patient population.

2.4 Comparative analysis of immunotherapy-induced adverse effects in gastric cancer patients with liver metastases and those without liver metastasis

Out of the 48 patients diagnosed with gastric cancer, 15 patients who had liver metastasis and 20 patients who did not have liver metastases experienced adverse effects due to immunotherapy. Five patients with liver metastases and seven patients without liver metastasis experienced Grade 3 or higher treatment-related side events. There were no instances of treatment-related adverse events leading to withdrawal or death in either group of patients.

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Table 2. Comparison of adverse reactions of immunotherapy in patients with advanced gastric cancer with liver metastasis and no liver metastasis grade 1~2 [n(%)]

Adverse reaction	Liver metastasis (n=20)	No liver metastasis grade 1~2 (n=28)	χ2	P
All events related to treatment	10（50.0）	13（46.4）	0.06	0.999
Nausea	7（35.0）	7（25.0）	0.565	0.528

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3. Specific treatment options for each patient should be presented.

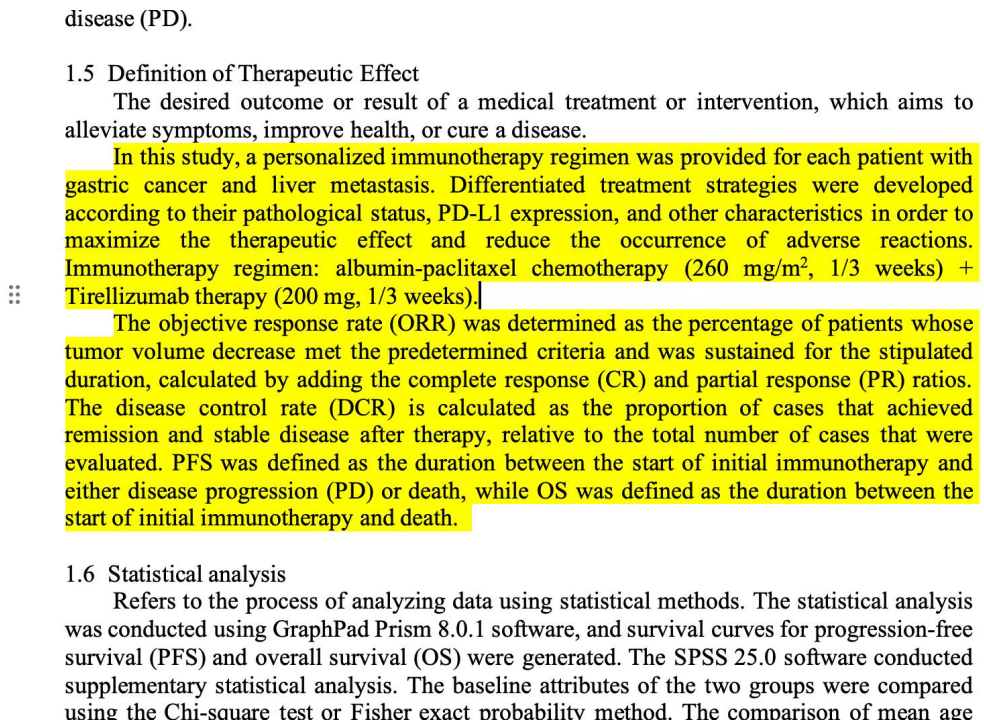
Reply 3: Thank you for your advice.

Thank the experts for their valuable advice. In our retrospective cohort study, the specific treatment that will be provided to each patient is a matter of deep concern to us. Through detailed analysis of patient baseline characteristics, tumor biological indicators, and changes before and after treatment, we will provide personalized treatment recommendations in the paper. This includes developing more precise immunotherapy strategies for patients based on the presence or absence of liver metastases, pathological status, and PD-L1 expression. We believe that this measure will further improve the efficacy and safety of immunotherapy in patients with gastric cancer and liver metastases, and provide more practical guidance for clinical practice. Thanks to the expert advice, we will do our utmost to ensure the depth and accuracy of the paper in the personalization of treatment protocols.

After revised content in section of methodology:

In this study, a personalized immunotherapy regimen was provided for each patient with gastric cancer and liver metastasis. Differentiated treatment strategies were developed according to their pathological status, PD-L1 expression, and other characteristics in order to maximize the therapeutic effect and reduce the occurrence of adverse reactions. The specific treatment regimen was: albumin-paclitaxel chemotherapy (260 mg/m2, 1/3 weeks) + tirellizumab therapy (200 mg, 1/3 weeks).

The objective response rate (ORR) was determined as the percentage of patients whose tumor volume decrease met the predetermined criteria and was sustained for the stipulated duration, calculated by adding the complete response (CR) and partial response (PR) ratios. The disease control rate (DCR) is calculated as the proportion of cases that achieved remission and stable disease after therapy, relative to the total number of cases that were evaluated. PFS was defined as the duration between the start of initial immunotherapy and either disease progression (PD) or death, while OS was defined as the duration between the start of initial immunotherapy and death.



disease (PD).

1.5 Definition of Therapeutic Effect

The desired outcome or result of a medical treatment or intervention, which aims to alleviate symptoms, improve health, or cure a disease.

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1.6 Statistical analysis

Refers to the process of analyzing data using statistical methods. The statistical analysis was conducted using GraphPad Prism 8.0.1 software, and survival curves for progression-free survival (PFS) and overall survival (OS) were generated. The SPSS 25.0 software conducted supplementary statistical analysis. The baseline attributes of the two groups were compared using the Chi-square test or Fisher exact probability method. The comparison of mean age

4. It is recommended to use low, medium and high to distinguish tissue differentiation types.

Reply 4: Thank you for your advice.

We have complied with your request to use low, medium and high to distinguish tissue differentiation types in Table 1. Thanks again for your advice.

Clinical features	Hepatic metastases (n=20)	No hepatic metastases (n=28)	$\chi 2$	*P*
Age/year				
<65	4 (20.0)	11 (39.3)	2.02	0.212
≥65	16 (80.0)	17 (60.7)		
Gender				
Male	13 (65.0)	18 (64.3)	0.003	0.999
Female	7 (35.0)	10 (35.7)		
ECOG score				
0	6 (30.0)	5 (17.8)	9.116	0.011
1	8 (40.0)	22 (78.6)		
2	6 (30.0)	1 (3.6)		
Histological type				
Low	19 (95.0)	27 (96.4)	2.117	0.347
Medium	0 (0.0)	1 (3.6)		
High	1 (5.0)	0 (0.0)		
PD-L1 expression				
≥1%	9 (45.0)	11 (39.3)	0.206	0.902
<1%	10 (50.0)	15 (53.6)		
Unknown	1 (5.0)	2 (7.1)		

5. Have these patients been tested for MSI/TMB?

Reply 5: Thank you for your advice.

In our study, MSI/TMB testing was not uniformly performed in all patients. This is due to a number of considerations, including the financial situation of patients and the failure to uniformly plan the use of the test. In actual clinical practice, MSI/TMB detection may be restricted by many factors such as patient resource limitations and medical system, resulting in the inability to perform this detection on all patients.

We understand the importance of MSI/TMB testing for individualized treatment decisions, but limitations in the study prevented us from covering all patients. Our study was designed to fully understand the impact of immunotherapy in a broad patient population, and non-uniform MSI/TMB testing does not affect our understanding of the overall efficacy and safety of immunotherapy in the treatment of gastric cancer and liver metastases. We will transparently present this limitation in the discussion section and encourage further exploration in this area of future research. Thanks to the expert's advice, we will pay more attention to data collection and reporting in related areas.