TRANSLATIONAL CANCER RESEARCH

Peer Review File

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Reviewer A

Major points

Comment 1: In the study, the definition of interstitial pneumonia (IP) is not clear. While the authors might use the word "IP" as the consequence of infection, respiratory physicians usually discriminate IP from infection. As the authors stated, the diagnoses of IP in this study were imperfect. I speculate that the patients with IP in this study contain 2 different types of patients. The first one is the patients with the respiratory infection after immunosuppression. Another one is the patients with drug-induced interstitial pneumonia caused by the activated hematologic cells such as lymphocytes. Laboratory findings including βD glucan, high-resolution computed tomography (HRCT) findings, and bronchoalveolar lavage (BAL) findings are useful to diagnose IP. Please analyze these data at the occurrence of IP.

Reply: Thank you for your pertinent comments. We value your suggestion very much. As we all known, IP is a heterogeneous group of disorders and the list of causes of IP is broad. In this study, patients with exposure history to occupational and environmental agents, especially to inorganic or organic dusts, and drug-induced pulmonary toxicity were excluded. And patients with rheumatic diseases and sarcoidosis were also excluded. Therefore, as the reviewer speculated, the most possible causes of IP in this study is occurrence of opportunistic infection and drug-induced interstitial pneumonia. In our study, all patients diagnosed with IP had typical imaging findings of chest CT, and other helpful auxiliary examinations included clinical evaluation, laboratory tests, pulmonary function tests, BAL and lung biopsy. It is a pity that most patients refused to receive invasive approaches such as BAL or lung biopsy, which is a limitation of the study.

Changes in the text: We have added inclusion and exclusion criteria in the text. We have also improved the results of these examination at the occurrence of IP. (see Page 5, Line 1-4)

Comment 2: The authors should review table 1. The ratio (%) in “All patients” column means the number of patients to the whole patients. Meanwhile, in “With IP” and “Without IP” column, the ratios were calculated to the number of all patients with each factor. I’m confused. I think that the ratio to the patients in each column should be shown here.

Reply: Thank you for your careful and candid comments. To make the table more accurate and rigorous, we revised the table 1 and updated new table.
Changes in the text: We have revised the table 1. (see table 1)

Comment 3: The authors stated low lymphocytes number is the risk of IP in this cohort. However, absolute lymphocyte number (ALN) in the majority of the patients with IP showed in Table 1 was over 1.0*10^9 cells/L. How many patients with IP showed the reduced ALN?

Reply: Thank you for your comment. To take the table more accurate to understand, we have modified our table 1.
Changes in the text: We have modified table 1 (see table 1).

Comment 4: The authors should note the state of approval of the ethics committee about this study.

Reply: Thank you for your suggestion. The study protocol was approved by the Ethic Committee of Zhejiang Cancer hospital, Hangzhou, China, and was performed in

accordance with ethical principles of the Helsinki Declaration. The number of ethical approval document is IRB-2020-19.

Changes in the text: The number of ethical approval document has been added in "Ethics statement" part and marked in red. (see Page 12, Line 2)

Minor points

Comment 1: In line 55-57, the authors stated the radiological findings of IP in previous studies. Although two radiologists were included in this study, the radiological findings in this cohort were not included in the manuscript. The authors should show the result of radiologic findings in this cohort.

Reply: Your suggestion is very important for our study. The typical imaging findings of IP on chest CT included diffuse or limited ground-glass opacities, irregular shadow of bronchovascular wall, linear shadow and lung field concentration. This is a comprehensive pulmonary imaging diagnosis, and it is difficult and unnecessary to make a statistic analysis of a specific radiologic finding.

Changes in the text: We have improved the typical imaging findings of IP on chest CT in manuscript, and we also added the results of radiological findings. (see Page 5, Line 19-22)

Comment 2: In line 68, the word "X2-test" should be converted to chi-square test or c (in symbol font)2 test.

Reply: We really appreciated your reminder. We have revised the statistic method description as the reviewer suggested.

Changes in the text: We have converted X2-test to chi-square test in method section. (see Page 6, Line 14)

Comment 3: In line 182-183, the authors speculated the smoking history and pulmonary disease could be a reason that male sex was the contributor of risk. To answer the question, they should have added positive smoking history and/or basic lung disease as a variable in multivariate analysis.

Reply: Thank you for your suggestion, which is very important for our manuscript. We have analyzed smoking history and basic pulmonary disease in univariate analyses, but both factors are not significantly related to IP, so we did not include them in multivariate analysis. But as the reviewer mentioned, the speculation "smoking history and pulmonary disease could be a reason that male sex was the contributor of risk" is not logical, so we have deleted this sentence.
Changes in the text: We have modified this sentence in manuscript. (see Page 10, Line 22)

Comment 4: In Table 1, CD3 and CD8 were expressed as mean (Q1-Q3). Why only CD4 was expressed as mean and SD?

Response: Thank you for your comment. CD3, CD4, CD8 are all continuous variables. Normal distribution test showed that CD4 is normally distributed, so we expressed it as mean and SD. But CD3 and CD8 are non-normal distribution, so we expressed it as mean (Q1-Q3).
Changes in the text: There is no change of this part.

Reviewer B

Comments 1: Line 27 on page 2. RCHOP is the front-line therapy for DLBCL but not for all types of B-cell NHL nowadays. R containing regimen may be better here.

Reply: Your suggestion is very important for our study. We have made relevant revision according to your comment.

Changes in the text: We have modified this sentence in the text. (see Page 4, Line 2-3)

Comment 2: Line 30 on page 2. Interstitial pneumonia (IP) includes pulmonary infections and non-infection pneumonia like drug-related IP.

Reply: You raised a very important question, which is very important to improve the quality of our manuscript. IP is a heterogeneous group of disorders that are classified together because of similar clinical, radiographic, physiologic, or pathologic manifestations. Many infectious or non-infectious factors can cause IP.

Changes in the text: To avoid ambiguity, we have revised this sentence. (see Page 4, Line 6-9)

Comment 3: Line 31-34 on page 2. “Data from …… RCHOP-like chemotherapy” What does it mean? Was TMP-SMX playing a key role on prophylaxis of IP? I cannot draw this conclusion from the paper. Why should we use SMZ for prophylaxis?

Reply: Thank you for your comments on this issue. This sentence explained the background of this study. We observed that many lymphoma patients develop IP during rituximab containing chemotherapy. We speculated opportunistic infection increased in immunocompromised hosts after immunochemotherapy. Among various pathogens, PCP infection is the most important and fatal. Previous studies have confirmed that TMP-SMX is a prophylactic drug that is specifically used for the prophylaxis and treatment of PCP infections. Therefore, patients with B-cell NHL received prophylactic treatment of TMP-SMX during chemotherapy in our institute since 2014.

Changes in the text: Considering these are not main content of this manuscript and effect understanding, we have revised this sentence. (see Page 4, Line 11-14)

Comment 4: Line 42-44 on page 2. Why did the authors choose the dose of TMP-SMX? 480mg qd? It is not the routine way clinically.

Reply: Thank you for your reminder. The optimal administration schedule for prophylactic TMP-SMX is not well defined. In previous studies, TMP-SMX is variously administered once daily, twice daily two times per week, two consecutive days per week, twice weekly, or three days per week. A meta-analysis has concluded that lower doses of TMP-SMX were an effective means of improving tolerance without compromising the prophylactic efficacy. In our hospital, prophylactic administration of TMP-SMX is once daily, and analysis showed this administration schedule is effective and low toxic.

Changes in the text: There is no change of this part.

Comment 5: Line 54-56 on page 3. Lymphoma infiltrating lung or radiation-induced pneumonia should be exclude from IP.

Reply: Thank you for your helpful suggestion. In our study, patients with radiation-induced pneumonia have been excluded. But imaging findings of lymphoma infiltrating lung is different from IP, so we did not exclude patients with lymphoma infiltrating lung. In addition, the table 1 showed that there was no statistical difference in the proportion of patients with lung lymphoma infiltration between the two groups with and without IP.

Changes in the text: We have modified the exclusion criteria in the text. (see Page 5, Line 1-4)

Comment 6: Line 60-65 on page 3. The laboratories tests in the present report were not enough to excluded infections. Molecular assays or serologic studies for tuberculosis, EBV, influenzas, fungal pathogens, Mycoplasma, Chlamydia, and so on were missing. NGS could also be considered for complicated cases. Only 2 of 24 patients with IP had confirmed pathogens, and BAL was performed in only 4 of them. Since no virus infection, fungal infection, or PCP was confirmed, the authors should explain the use of antifungal agents, Ganciclovir, and TMP-SMX.

Reply: Thank you for your comments. In fact, a variety of infectious processes can cause interstitial opacities on chest radiograph, and these infections often occur in immunocompromised hosts, such as patients receiving chemotherapy. To treat pulmonary infections in immunocompromised patients, empiric therapy should be started as soon as possible. Because multiple simultaneous processes are common in these patients, and the most common pathogens include bacteria, fungi and viruses. Therefore, we usually give patients antibacterial therapy combined with antifungal therapy. Because patients infected by virus or PCP usually have specific imaging findings, so when patients are suspicious of virus or PCP infection, antivirus or TMP-SMX of treating dose are chosen as other treatment at that time. Meanwhile, initial broad empiric regimens should be modified as new microbiologic data are obtained. Blood or body fluid analysis are routinely performed for pathogen identification. Other laboratory tests, pulmonary function testing, BAL and lung biopsy may help to narrow the differential diagnosis. NGS is a helpful method in some complicated cases. But most patients with IP responded well to treatment and the cost of NGS is high, so NGS is not performed in this study. A limitation of this retrospective study is that minority patients received BAL and no clear microbiologic diagnosis was obtained in all patients. But patients with IP recovered from IP after treatment. It indicated that our treatment strategies for IP is effective.

Changes in the text: We have improved and revised content of IP treatment section in the text. (see Page 7, Line 19-21)

Comment 7: Line 112 on page 5. "1x109/L" is wrong.

Reply: We are very sorry for our negligence of formatting errors.
Changes in the text: We have corrected this figure in new manuscript. (see Page 8, Line 18)

Comment 8: Line 159-160 on page 7. "Wang and colleagues …… IP negative patients." A reference is missing.

Reply: Thank you for your reminder.
Changes in the text: We have added the refence in new manuscript. (see Page 10, Line 2)

Comment 9: Line 182-183 on page 8. "We speculate ……" What does this mean? The speculation is farfetched in multivariate analysis (Table 2).

Reply: Your suggestion is very important for our study. As you analyzed, after reviewing the manuscript, we found that the speculation is not logical.
Changes in the text: We have deleted this sentence and revised this part in new manuscript. (see Page 10, Line 20-22)

Comment 10: Digital gibberish was found page 13. And "P value" is shown as "! value".

Reply: We are very sorry for our negligence of formatting errors.

Changes in the text: We have corrected the symbol in new manuscript. (see tables)

Comment 11: Some important factors were not included in the analysis (Table 2). It includes chemotherapy regimens, lymphoma types, stages, IPI, and cycles of chemotherapy. These factors may impact the incidence of IP.

Reply: You raise a very important question. When analyzing the possible risk factors of IP, these factors were all not related to IP occurrence. So we just showed the results of the most important factors we thought.

Changes in the text: There is no change of this part.

Comment 12: The manuscript needs help from native English speaker.

Reply: Thank you for your comments on this issue. To make the manuscript more fluent to understand, the overall writing of the manuscript has been reviewed and polished by professional editors.

Changes in the text: The whole manuscript has been polished by professional editors. (see words in red)