Response to reviewers' comments

Reviewer #1:

Structure and Organization The overall structure of the article is clear, but certain sections could benefit from further improvement in terms of organization and logical flow. For example: Section division: The parts on "Immunosuppressive Drugs" and "Immunomodulatory Treatments" could be divided into smaller subsections, specifically discussing the mechanisms of action, therapeutic effects, and potential side effects of each drug category.

Response: We have reorganized the manuscript as suggested for logical flow.

Conclusion: A brief summary could be added at the end to summarize the pros and cons of various drugs and offer suggestions for future research. Scientific Rigor Evidence Support: The references and data cited in the article are comprehensive, but at times the description of certain studies is too brief. It is recommended to provide more detail on the scale, methods, and limitations of some studies when mentioning their results. For example, regarding the "RECOVERY trial," it would be beneficial to further clarify key details such as participant characteristics, sample size, and other important information to better assess the generalizability and representativeness of the study.

Response: **We have improved the conclusion further as suggested to include the pros and cons of various drugs and offered suggestions for future research. Regarding the 'Recovery trial, mice were used for the study and not humans.**

Side Effects Discussion: When discussing drug side effects, a more detailed explanation of their mechanisms is needed, especially regarding drug interactions. For example, a deeper exploration of how the use of steroids and immunosuppressants can lead to issues such as "cytokine storms" and diabetes would be beneficial, including the physiological mechanisms involved.

Response: The mechanism of drug side effects and interaction have been added to the manuscript as suggested.

Language and Expression Grammar and Terminology: The language in the article is generally clear, but some sentences could be simplified to enhance readability. For example, "This inflammatory state also changes endothelial permeability, resulting in endothelial barrier dysfunction causing more pro-inflammatory cytokines to leak through and perpetuate the inflammatory response" can be rephrased as: "This inflammatory state changes endothelial permeability, leading to endothelial barrier dysfunction, which causes more pro-inflammatory cytokines to leak, further exacerbating the inflammatory response."

Response: We have simplified this statement to enhance readability as suggested.

Consistency of Terminology: The article covers multiple immunomodulators and their mechanisms, and it is recommended to ensure consistency in terminology to avoid using different terms for the same concept, especially when describing the same class of drugs.

Response: We have checked the manuscript and made corrections to ensure consistency in terminology, as suggested.

Additional Details Discussion of CRISPR/Cas13: The discussion on CRISPR/Cas13 is somewhat brief. It is suggested to expand this section by providing a more detailed explanation of the potential applications of CRISPR/Cas13 in SARS-CoV-2 infections, along with more experimental data supporting its effectiveness.

Response: We have expanded the discussion on CRISPR/Cas13 as suggested.

Role of Supplements: When discussing the role of supplements such as vitamin C and vitamin D, it would be helpful to provide more empirical research findings. For instance, regarding EGCG and green tea, it would strengthen the discussion to cite relevant clinical or experimental data.

Response: We have improved the discussions in these areas as suggested with available references

References and Data Updates Citations: The references cited in the article cover many important research findings, but some data may be outdated. It is recommended to check for more recent studies to ensure the references reflect the latest scientific advances. Data Support: When mentioning the effects of certain drugs, it would enhance the credibility of the article to provide specific clinical research data or trial results (e.g., effect size, degree of clinical improvement, etc.).

Response: We have checked and updated the references as well as their data and we discussed the results of the trials mentioned. The references can be utilized for further reading.

Role of Vitamin D in the Respiratory System Importance of Vitamin D: Vitamin D plays a key role in maintaining immune system health, particularly in the immune function of the respiratory system. Vitamin D deficiency is a common global health issue, especially during the COVID-19 pandemic, where patients with vitamin D deficiency are more susceptible to infection and severe COVID-19 outcomes. It is recommended to strengthen the discussion of the role of vitamin D in the respiratory system, especially in COVID-19 patients with vitamin D deficiency.

Response: We have strengthened the discussion on the role of Vitamin D in Covid-19 infection

Reviewer #2:

Dear author, I have read your manuscript titled "COVID-19 Management in Patients with Comorbid Conditions" with great interest. Overall, it is a comprehensive and informative paper that makes a valuable contribution to the field of COVID-19 research. However, there are several areas where improvements could be made to enhance the quality and impact of the manuscript.

Response: Thank you

Firstly, in the methodology section, it would be beneficial to provide more details about the search strategy used for the literature review. For example, you could mention the specific search terms used in each database and any limitations or filters applied. This would help readers to better understand the scope and comprehensiveness of the review. Additionally, it would be useful to state the criteria for including or excluding studies in more detail. This would enhance the transparency and reproducibility of the research.

Response: We have rewritten the methodology as stated.

Secondly, in the results section, while the data is presented clearly, it could be further enhanced by providing more in-depth analysis. For example, when discussing the factors associated with

hospitalization and duration, you could explore the potential mechanisms underlying these associations. This would add more depth and understanding to the findings. Also, when presenting the results of different treatment modalities, it would be helpful to compare and contrast their effectiveness and safety profiles in more detail. This would assist clinicians in making more informed decisions about treatment options.

Response: We have added the potential mechanisms underlying the associations, as mentioned. We also compared and contrasted the treatment modalities as suggested.

Thirdly, in the discussion section, it would be beneficial to expand on the limitations of the current research. For example, you could discuss the potential biases in the studies included in the review and how these may have influenced the results. Additionally, you could explore the implications of the findings for future research directions. This would help to guide further research in the field.

Response: We have added a paragraph on the limitations of the research.

Finally, in terms of the overall structure and organization of the manuscript, it could be improved by ensuring a more seamless flow between the different sections. For example, the transition from the introduction to the methodology and then to the results could be made smoother. This would enhance the readability and coherence of the paper.

Response: We have reorganized the manuscript to enhance the readability and coherence of the paper

In conclusion, your manuscript has significant potential, and with the suggested improvements, it could make an even more valuable contribution to the understanding and management of COVID-19 in patients with comorbid conditions. I look forward to seeing the revised version of the manuscript. Best regards,

Response: Thank you for the suggestions to improve the manuscript.

Reviewer #3:

In the abstract section, add findings of the study: The abstract serves as a summary of the entire study. To improve it, include key findings such as statistical results, patterns, or insights that were revealed during the study. Clearly highlight the primary outcome, significant data points, or any conclusions drawn, ensuring that they align with the research objectives. Add motivation to the introduction section: The motivation explains why the research was undertaken. It should include the real-world importance of the topic, existing gaps in the literature, or pressing challenges that the study addresses. Clearly outline how this research contributes to the field or solves a specific problem.

Response: The abstract has been expanded, and now it includes key findings such as results, primary outcome, and conclusions

Add an abbreviation section before the references: An abbreviation section lists and defines all abbreviations and acronyms used in the paper, ensuring clarity for readers. Place this section before the references, formatted alphabetically, for easy access and understanding.

Response: We have added an abbreviation section before the references, as suggested.

Statistical methodology is not clear; kindly revise the entire paragraph: The statistical methodology section must precisely describe the techniques used for data collection, analysis, and interpretation. Specify the statistical tests applied, software used, and why these methods were chosen. Include details about sample size, assumptions, and validation procedures for reproducibility.

Response: The study is a narrative review, so no statistical methods were used in the study. Tables and figures were prepared studies used in the review.

Criteria for including articles/authenticity of the articles included in the research is not clear: Specify the inclusion criteria, such as relevance to the research question, publication timeframe, or peer-reviewed status, ensuring transparency in article selection. Clearly state how the authenticity of articles (e.g., source credibility, journal impact) was assessed. Including and excluding criteria is not clear: Provide detailed inclusion and exclusion criteria for selecting data or articles, such as age group, disease status, study design, or geographic focus. Explain how irrelevant or low-quality data were excluded to ensure consistency and rigor.

Response: We have rewritten the methodology as stated.

Add some updated studies for the literature: a. Prevalence of COVID-19 among patients with chronic obstructive pulmonary disease and tuberculosis: Incorporate recent findings that explore how these comorbidities influence the prevalence or severity of COVID-19.

Response: The literature has been updated to include the suggestion.

b. Role of the immune system sounds good: Expand on the immune system's role, incorporating updated studies, mechanisms, and its connection to the research focus. Role of immune system sounds good: Further develop this section by detailing immune responses, pathways, or factors relevant to the study. Include updated and peer-reviewed evidence for a robust discussion.

Response: We have added more information to this section as suggested

The conclusion sounds good: Since the conclusion is already strong, ensure it succinctly summarizes the study's findings, implications, and potential future directions without adding new information.

Response: We have strengthened the conclusion further as suggested.

1) Science Editor:

1 Scientific quality: The authors submitted a minireview of COVID-19 management in patients with comorbid conditions. The topic is within the scope of the journal.

(1) Classification: Grade B, Grade C, and Grade C;

(2) Summary of the Peer-Review Report: Overall, it is a comprehensive and informative paper that makes a valuable contribution to the field of COVID-19 research. However, there are several areas where improvements could be made to enhance the quality and impact of the manuscript. In the methodology section, it would be beneficial to provide more details about the search strategy used for the literature review. Additionally, it would be useful to state the criteria for including or excluding studies in more detail. This would enhance the transparency and reproducibility of the research.

Response: Thanks. **We have rewritten the methodology as stated.**

(3) References recommendations: The reviewer didn't request the authors to cite improper references published by him/herself.

(4) Manuscript Type: After verification, the manuscript type is "Minireviews".

2 Specific comments

(1) Country/Territory of origin: United States.

(2) The language classification is Grade B, Grade B and Grade B.

(3) Manuscript Title:

Except for capitalization of the first word, all other words are represented in lowercase (excluding specific words such as Crohn's disease).

(4) Authors and institution(s): Author names should be written out first (as first name, middle name initial (with no period) and family (sur)name) and typed in bold, followed by a comma and the complete name of the affiliated institution, city, province/state, postcode and country typed in non-bold. Examples for authors name and institutions are:

Yi-Fan Chang, Tao Liu, Chong-Qing Wei, Wei-Long Chang, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

(5) Please add the "Author contributions": The 'Author contributions' passage describes the specific contribution(s) made by each author. The author's names will be listed in the following format: full family (sur)name, followed by abbreviated first and middle names. For example, Bryan L Copple should be revised as Copple BL.

(6) Audio Core Tip: In order to attract readers to read the full-text article, we request that the first author make an audio file describing the final core tip. This audio file will be published online, along with the article. The author can invite English language editing company to assist in resolving the language issues of Audio Core Tip.

7) Reference numbers in the main text.

The format of in-text citation of references should be [References Number]. Please add the "[ ]". Example: The pathophysiology is thought to be due to an increased arterial flow that leads to secondary hepatocellular hyperplasia[1,2].

(8) There are issues with the references:

Please provide the PMID numbers (https://pubmed.ncbi.nlm.nih.gov/) to the reference list and list all authors of the references.

To ensure the accuracy of the references, please use "Edit References by Auto-Analyser" (https://www.f6publishing.com/Forms/main/ArticleReferenceTool.aspx) to edit the references of the manuscript.

(9) Figures.

Original figure documents. In the meantime, authors should provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor, and upload it to the file destination of “Image File” in the F6Pubishing system.

(10) Tables.

Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

(11) Please verify if all pictures (s) are original? If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published, and correctly indicate the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

3 Recommendation: Conditional acceptance.

Language Quality: Grade B (Very good)

Scientific Quality: Grade C (Good)

Response: We have addressed all the Science Editor’s comments stated above.

RESPONSE TO REVIEWERS' COMMENTS

1a Article Structure Introduction and Background: The background section effectively introduces the global impact of SARS-CoV-2 and the urgency of the pandemic, highlighting the risks for vulnerable populations. **It could further strengthen the brief review of COVID-19 epidemiology, particularly regarding the impact of specific diseases (such as COPD, heart disease, diabetes, etc.), to provide more background support for the subsequent discussion.**

Response: We have discussed the impact of specific diseases with COVID-19 in the introduction and background.

1b Treatment Methods and Current Status: The treatment section clearly outlines various treatment options, particularly immunomodulatory and antiviral drugs. The summary of current treatment options and the corresponding challenges demonstrates the author's deep understanding of current medical practices.

Response: Thank You.

1c Future Research Directions: The article clearly presents future research directions, especially the optimization of treatments for vulnerable populations and the study of long-term vaccine effects. This provides actionable recommendations for related research.

Response: Thank You

2a. Content Accuracy Immunomodulatory and Antiviral Drugs: The selection of drugs (such as immunomodulatory and antiviral drugs) is valuable, but further data on the specific drug effects and mechanisms should be added. For example, the effects and side effects of corticosteroids (such as dexamethasone) could be more thoroughly explained, along with clinical evidence of their mechanisms and applicable populations.

RESPONSE: We have updated the manuscript with the information below:

Dexamethasone is a synthetic glucocorticoid with potent anti-inflammatory, antisecretory and immunosuppressive effects thus, a crucial therapeutic agent in the management of severe SARS CoV-2 infections (severe COVID-19) which is characterized by excessive inflammation and exaggerated immune response or "cytokine storm" (Mehta, J., Rolta, R., Mehta, B.B., Kaushik, N., Choi, E.H., Kaushik, N.K. Role of Dexamethasone and Methylprednisolone Corticosteroids in Coronavirus Disease 2019 Hospitalized Patients: A Review, Front. Microbiol. 15 (13) (2022 Feb), 813358, https://doi.org/10.3389/fmicb.2022.813358). Its mechanism of action involves binding to the glucocorticoid receptors followed by a cascade of anti-inflammatory and immunosuppressive responses. Thus, it reinforces the immune responses in COVID-19 by promoting the expression of anti-inflammatory cytokines (IL-4, IL-10 and helper T-and B-cells), and reducing inflammation by inhibiting inflammatory transcription factors (Chen, R., Sun, Y., Lv, J., Dou, X., Dai, M., Sun, S., Lin, Y. Effects of Dexmedetomidine on Immune Cells: A Narrative Review, Front. Pharmacol. 2 (13) (2022 May), 829951, https://doi.org/10.3389/fphar.2022.829951). Dexamethasone has also been reported to regulate the ion

channels by activating sodium ion absorption through the epithelial sodium channel (ENaC) Na^+ channels and inhibition of chloride ion secretion through the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channels to reduce the airway fluid secretion thus preventing pulmonary edema.

2b. Vaccine Efficacy: The discussion on vaccine efficacy mentions the challenges posed by new variants but lacks a comparative analysis of different types of vaccines. For example, a comparison of mRNA vaccines and viral vector vaccines, as well as vaccine adjustments for variants, would be worth adding. Virus Variants: The article mentions the challenges of viral mutations but does not delve into the impact of different variants (such as Delta and Omicron). Further research could explore the clinical manifestations and immune escape characteristics of these variants.

Response: We have added these parts to the manuscript.

3. Clarity of Expression Word Precision: Overall, the language is clear and concise, making it easy to understand. However, certain phrases could be further refined. For example, "severe side effects in certain populations" could be changed to "serious adverse effects in specific populations" to make it more academic. Paragraph Transitions: Some transitions between paragraphs could be slightly adjusted. For example, after discussing the role of vaccines, there could be a direct transition to the discussion of vulnerable populations and treatment optimization, enhancing logical coherence.

RESPONSE: We have provided more clarity as suggested and have adjusted the paragraph transition.

4a. Future Research Directions Treatment Protocol Optimization: The article already proposes optimizing treatment protocols for vulnerable populations, which is highly valuable. It could further suggest prospective studies on different drug combination therapies, especially for specific groups. For instance, the combined use of immunosuppressive treatments and antiviral therapies to enhance clinical outcomes could be explored.

RESPONSE: We have added the statements below to address your comments

Due to the high transmissibility of SARS-CoV-2, the propensity of developing resistance to antiviral agents is quite high thus, the elderly and patients with chronic comorbidity are at the greatest risk of severe cases of COVID-19. However, younger patients can also develop long-term complications. Although, Remdesivir has been authorized by the FDA for emergency use, its clinical effectiveness is uncertain and its side effects like liver toxicity and allergic reactions have limited its use (Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Nov 5;383(19):1813-1826. doi: 10.1056/NEJMoa2007764). On the other hand, literature is replete with robust data demonstrating the effectiveness of dexamethasone in reducing mortality in hospitalized patients with severe COVID-19. However, its immunosuppressive effects can cause serious side effects like osteoporosis, glaucoma, diabetes and secondary infections (Chen F, Hao L, Zhu S, Yang X, Shi W, Zheng K, Wang T, Chen H. Potential Adverse Effects of Dexamethasone Therapy on COVID-19 Patients: Review and Recommendations. Infect Dis Ther. 2021 Dec;10(4):1907-1931. doi: 10.1007/s40121-021-00500-z). Other

side effects include neuropsychiatric complications, cardiovascular events, lung infections, liver damage etc. (Meybodi SM, Rabori VS, Salkhorde D, Jafari N, Zeinaly M, Mojodi E, Kesharwani P, Saberiyan M, Sahebkar A. Dexamethasone in COVID-19 treatment: Analyzing monotherapy and combination therapy approaches. Cytokine. 2024; 184:156794 doi: 10.1016/j.cyto.2024.156794). Therefore, combinations of therapeutic agents that can balance antiviral efficacy and immune modulation with minimal side effects would be critical to successful treatment of severe COVID-19 cases in comorbid conditions.

For example, a combination of therapeutic agents that target different stages of viral replication like nirmatrelvir and ritonavir (PAXLOVID^{TM}). Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2. However, it inhibits the CYP3A-mediated metabolism of nirmatrelvir leading to increased plasma concentration of nirmatrelvir, which is the active peptidomimetic inhibitor of SAR-CoV-2 protease (Mpro) (Lemaitrea, F., Grégoirec, M., Monchaude, C., Bouchetg, S., Saint-Salvih, B., Polarda, E., *et al.* Management of drug-drug interactions with nirmatrelvir/ritonavir in patients treated for Covid-19: Guidelines from the French Society of Pharmacology and Therapeutics (SFPT). Therapie 77 (2022) 509—521 https://doi.org/10.1016/j.therap.2022.03.005. Accessed on 3/30/2025). Also, combining antiviral agents with monoclonal antibodies can lower the risk of COVID-19 pathogenesis in comorbid patients by providing passive immunity especially in comorbid patients with chronic (immunosuppressed) conditions and reducing the propensity for breakthrough infections. For example, Calderón-Parra *et al.* studied the clinical efficacy and safety of antiviral-monoclonal antibodies combinations in high-risk immunocompromised patients. They concluded that a combination of sotrovimab and an antiviral agent was associated with reduced risk of COVID-19 progression and decreased mortality rate compared with monotherapy particularly in patients with severe humoral immunosuppression. They also affirmed that the adverse effects of combination therapy were mild and comparable with monotherapy(Calderón-Parra, J., Gutiérrez-Villanueva, A., Ronda-Roca, G., Jimenez, M.L.M., de la Torre, H., Ródenas-Baquero, M. *et al.* Efficacy and safety of antiviral plus anti-spike monoclonal antibody combination therapy vs. monotherapy for high-risk immunocompromised patients with mild-to-moderate SARS-CoV2 infection during the Omicron era: A prospective cohort study. International Journal of Antimicrobial Agents 63 (2024) 107095 https://doi.org/10.1016/j.ijantimicag.2024.107095. Accessed on 3/30/2025).

The exaggerated and uncontrolled release of pro-inflammatory cytokines (cytokine storm) through the Janus kinase-signal transducer and activation of transcription (JAK/STAT) pathway in severe COVID-19 patients can exacerbate the disease progression. Therefore, blocking the JAK/STAT signaling can reduce the release of cytokines like IL-2, IL-6, and TNF-α and consequently reduce disease progression. JAK inhibitors (Baricitinib/Tofacitinib) have been reported to inhibit members of numb-associated kinase (NAK) family like AP2-associated kinase 1 (AAK1) and cyclin G-associated kinase (GAK) which regulate the angiotensin-converting enzyme 2 (ACE-2) transmembrane protein, the receptor to which SARS-CoV-2 binds to infect humans. Thus, JAK inhibitors can effectively control the cytokine storm. The clinical effectiveness of several JAK inhibitors has been studied including Baricitinib, Ruxolitinib and Tofacitinib. Although they all bind directly to active kinases, they have varying affinity and relatively short half-life of 12.5 h, 4 h and 3 h for Baricitinib, Ruxolitinib and Tofacitinib respectively. However, Baricitinib has been shown to strongly inhibit JAK1 and JAC2 enzymes with low IC_{50} of 4.0-5.9 nM and 6.6-8.8 nM respectively suppressing both innate and adaptive immunity. Thus, Baricitinib has been strongly recommended particularly in combination with corticosteroids, in patients with severe COVID-19 cases. Combinations of immunomodulators like JAK Inhibitors and corticosteroids (dexamethasone) have also been reported to control hyperinflammation and cytokine storm. Similarly, IL-6 Inhibitors like Infliximab/Adalimumab can be combined with Remdesivir to regulate inflammation while maintaining antiviral action. (Huang, J., Zhou, C., Deng, J., Zhou, J. JAK inhibition as a new treatment strategy for patients with COVID-19. Biochemical Pharmacology 202 (2022) 115162 https://doi.org/10.1016/j.bcp.2022.115162. Accessed on 3/30/2025).

Recently, Saranya et al. developed a systematic framework for predicting and validating drug combinations for COVID-19 comorbidities, specifically type 2 diabetes and hypertension. They concluded that drug repurposing is an effective alternative to modifying the treatment of COVID-19 and its comorbidities. For example, the authors prioritized tocilizumab and gliclazide as effective drug combinations for the treatment of COVID-19 in patients with type 2 diabetes comorbidity while a combination of tocilizumab and lidocaine (or bacitracin) are effective in COVID-19 patients with food-borne bacterial infection comorbidity (Saranya, S., Thamanna, L., Chellapandi, P. Systems medicine framework for repurposable drug combinations for COVID-19 comorbidities. *Medicine in Omics* 2024; 11(August): 100038 https://doi.org/10.1016/j.meomic.2024.100038. Accessed on 3/30/2025).

4b Long-Term Vaccine Effects: Exploring the long-term effects of vaccines is an important research direction. It would be beneficial to suggest more cohort studies focusing on the long-term impact of vaccines on the immune system, particularly in populations with pre-existing immune impairments (such as patients undergoing cancer treatment or elderly populations).

Response: We have updated this comment under the Vaccine subheading. See below:

COVID-19 vaccines have a positive long-term impact on the immune system, even in populations with pre-existing immune impairments. Vaccination helps reduce the severity of illness and provides a critical layer of protection, especially for vulnerable groups like cancer patients and the elderly. COVID-19 vaccines are generally safe and effective for cancer patients, reducing the risk of severe illness, hospitalization, and death……...

4c Social Distancing and Non-Pharmaceutical Interventions: Regarding non-pharmaceutical interventions such as social distancing, future research should consider evaluating the long-term socio-economic impacts of these measures and explore how they can be efficiently implemented during future pandemics.

Response: We have rewritten this part to address your comments. See below:

Social distancing and other non-pharmaceutical interventions (NPIs) have been essential in controlling the spread of COVID-19, but their long-term socio-economic impacts warrant further investigation. Regarding the economic impact, social distancing measures can lead to significant job losses…….

5a. Specific Suggestions for Improvement Include More Clinical Data in the Treatment Section: It would be useful to provide more clinical data comparisons of different treatment methods, especially in the areas of immunomodulatory drugs and antiviral therapies, to help readers understand the practical effects of these treatments.

RESPONSE: Please refer to comment #4a.

5b Deepen the Discussion on Vaccine Research: For different types of vaccines and their effects, it is recommended to include more recent clinical trial data, especially regarding vaccine efficacy against variants.

Response: We have added this to the manuscript. See below:

CDC data for 2023-2024 reported that the updated COVID-19 vaccines were 54% effective in preventing COVID-19 from mid-September 2023 to January 2024 and provided significant protection against the XBB lineage and the JN.1 variant, which became dominant recently, 89. Also, a Systematic Review and Meta-Analysis by Zeng et al. 2022 reported the vaccine efficacy against the following variants……

5c Detailed Explanation of Side Effects: When discussing drug side effects, particularly for immunosuppressive and antiviral drugs, a more detailed explanation is needed regarding which specific populations may be at higher risk, providing clinicians with clear guidance.

RESPONSE: Please refer to comment #4a