PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The prevalence of autoimmune thyroid disease in patients with psoriasis: a meta-analysis
AUTHORS	Zhang, Xiaochao; Zhang, Suhan; Wu, Ruifang; Li, Siying; Su, Yuwen; Zhang, Peng

VERSION 1 – REVIEW

REVIEWER	Fethney, Judith University of Sydney, School of Nursing
REVIEW RETURNED	19-Aug-2021

GENERAL COMMENTS	General Overall I found the article to be well written and the meta-analysis to have been rigorously done. There are only a few minor edits required. Abstract 'All studies included had moderate to high quality and representative, and published in recent years'. Can the authors please clarify what they mean by 'representative'. 'The heterogeneity in the pooled data cannot be ignored, and couldn't improve by subgroup analysis.' Change to 'The heterogeneity in the pooled data cannot be ignored, and was not improved by subgroup analysis'. Some grammatical errors, eg Data extraction: second sentence 'The following information in the included studies were extracted:…' should read 'The following information in the included studies was extracted:…' In Table 3 'Definition of psoriasis', not clear what criteria was used for Wang et al, as the authors say 'Ps was diagnosed by at least 2 outpatient visits or 1 hospital admission' but surely there must have been some clinical criteria? I don't know whether it is just a feature of the way the figures are presented to the reviewer, but not all figures have labels only Figure 5 is labelled as Fig 5. Discussion

	Second sentence: 'While the study by Khan SR et al. is the first meta-analysis of studies on the association between AITD and the risk of psoriasis incidence22'. Point 1. This is not a proper sentence, delete While and begin sentence with 'The study by Khan…' Point 2: '…association between AITD and the risk of psoriasis incidence' isn't an appropriate way to report this. Should be either a) '…association between AITD and the risk of psoriasis', or b) '…association between AITD and the incidence risk of psoriasis' Sixth sentence: Considering that psoriasis is a type of discosmetic dermatosis that is easy to be concerned about, patients with psoriasis are more likely to be active about seeing a doctor regarding their condition than patients with AITD. Change to As psoriasis is a type of discosmetic dermatosis and therefore likely to be of concern, patients with psoriasis are more likely to be active about seeing a doctor regarding their condition than patients with AITD. Limitations There appears to be a contradiction. In the section Main findings, the authors state 'We hypothesize that the inconsistency of the study designs was the major source of heterogeneity'. In the Limitations, they state '…different study designs were not the main source of heterogeneity'. Can this please be clarified.

REVIEWER	Lin, Lifeng Florida State University, Department of Statistics
REVIEW RETURNED	19-Aug-2021

GENERAL COMMENTS	This manuscript presents a systematic review and meta-analysis on autoimmune thyroid disease. This review is pre-registered at PROSPERO. Some terminologies were not used accurately. My specific comments are as follows. It seems that this study did not assess the risk of bias of individual studies. Although in the PRISMA checklists (item 11) the authors claimed that the assessment was on page 6, it seems that the authors confused the concept of risk of bias with publication bias. The former is a concept of bias within studies, which may be assessed using tools such as ROBINS for non-randomized studies (https://doi.org/10.1136/bmj.i4919), and the latter is a concept of bias between studies. The terminologies in the subsection of "Data synthesis and analysis" have many issues. For example, the first letter of "Odds" (line 35, page 6) does not need to be capitalized. Similarly, the first letters of "Confidence Intervals" (line 38, page 6) do not need to be capitalized. "The inconsistency index (I^2)" (line 43, page 6) may be changed to "The I^2 statistic", as inconsistency does not equate to heterogeneity. For the "Funnel chart" (line 53, page 6), "F" should not be capitalized; this is more commonly called "funnel plot". The "Analysis" in line 56 on page 6 does not need to be capitalized. In line 4 on page 7, "forest charts, funnel charts" can be changed to "forest plots, funnel plots".

	In line 56 on page 6, “Publication bias was considered when p < 0.05.” I think the authors meant “Publication bias was considered statistically significant when p < 0.05).” Usually, the statistical powers of many methods for detecting publication bias were low, so the significant level for publication bias is often set to 0.1, instead of 0.05. Page 6, lines 51-53, “A fixed effects model was applied if I^2 <= 50% and the random effects model was applied when I^2 > 50%.” This is not a good criterion for deciding the use of fixed-effects or random-effects model, as I^2 may be subject to large uncertainties. I would suggest the authors use the random-effects model throughout the analyses. It was unclear which statistical method was used to implement the meta-analysis model, but I guess that the authors used the popular DerSimonian-Laird method. This approach is generally inferior to several alternative meta-analysis methods, such as the restricted maximum-likelihood (REML) method, which is recommended. See, for example, Cornell et al. (https://doi.org/10.7326/M13-2886) and Langan et al. (https://doi.org/10.1002/jrsm.1316). In addition to presenting the confidence interval of the meta-analysis results, the authors may consider presenting the prediction interval, which has been advocated in the meta-analysis community and may better appraise the extent of heterogeneity. See, for example, Riley et al. (https://doi.org/10.1136/bmj.d549) and IntHout et al. (http://dx.doi.org/10.1136/bmjopen-2015-010247). Lines 22-25 on page 8, “The results of Egger’s test suggested no significant publication bias was evident (p = 0.066, figure 3C).” I think the result of publication bias was interpreted incorrectly. First, as I mentioned earlier, the significance level for publication bias is often set to 0.1, so the p-value of 0.066 is considered significant at this significance level. Second, in the funnel plot (figure 3B instead of 3C?), there is a clear pattern of asymmetry, where small studies with large standard errors tend to have large ORs, while small studies with OR=1 (or log OR = 0) seem to be missing. Therefore, I would say these results support the existence of publication bias.

REVIEWER	Mansour, Abbas University of Basrah College of Medicine
REVIEW RETURNED	16-Oct-2021

GENERAL COMMENTS	The prevalence of autoimmune thyroid disease in patients with psoriasis: a meta-analysis -Although the exact mechanism of association remains unknown, several studies have implicated the role of TH-1 cell-mediated inflammation in the immunopathogenesis of psoriasis and autoimmune thyroid disease. (1) -Control for beta-blocker use in thyroid disease not studied. Beta-blockers are among the drugs documented to be strongly linked to induction and exacerbation of psoriasis and may be a source of residual confounding. (2) -Psoriasis and thyroid dysfunction relied on self-reports, which are subject

	to recall bias. Some of the studied used in this metanalysis were self-reports. -Accordingly, we recommend that every dermatologist be conscious of this association and suggest those thyroid-related examinations, such as thyroid function test and analysis of thyroid antibodies, be included in the routine tests for patients with psoriasis. This recommendation is not based on evidence and not cost effective. 1-Ruffilli I, Ragusa F, Benvenga S, et al. Psoriasis, psoriatic arthritis, and thyroid autoimmunity. Front Endocrinol (Lausanne). 2017;8:139. 2-Balak, Deepak, and Enes Hajdarbegovic. "Drug-Induced Psoriasis: Clinical Perspectives." Psoriasis: Targets and Therapy Volume 7 (2017): 87-94.

REVIEWER	Zhang, Jin-an Jinshan Hospital of Fudan University
REVIEW RETURNED	20-Oct-2021

GENERAL COMMENTS	Major revision. This meta-analysis aimed to study the prevalence of autoimmune thyroid disease in patients with psoriasis. This study has certain research value and clinical significance. However, this article needs to be revised in many places. 1. Literature Searches are incomplete. The author is advised to search more databases to expand the number of studies. 2. The authors noted that the AHRQ Scale was used for cross-sectional studies, but it was not seen in Table 3 with only NOS scores. 3. Record screening and data extraction were performed by only two independent authors. How disagreements were solved among two independent reviewers during the systematic search, quality assessment and data extraction? 4. There is still a considerable heterogeneity as in your limitation. This is the most serious problem with this study. Meta-regression analysis is then strongly recommended. 5. There are some spelling and grammatical mistakes in the article. Maybe someone who is proficient in English is advised to polish the language.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Dr. Judith Fethney, University of Sydney
1.‘All studies included had moderate to high quality and representative, and published in recent years’. Can the authors please clarify what they mean by ‘representative’.
Response: Thank you for your question. “Representative” means that the included studies come from different countries, and the number of cases in each group is greater than 50, so as to minimize the sample deviation caused by geographical factors or small samples.

2.‘The heterogeneity in the pooled data cannot be ignored, and couldn’t improve by subgroup analysis.’
Change to
‘The heterogeneity in the pooled data cannot be ignored, and was not improved by subgroup analysis’.
Response: Thank you for your comments. I have revised the sentence.

3.Some grammatical errors, eg
Data extraction: second sentence ‘The following information in the included studies were extracted:…’ should read ‘The following information in the included studies was extracted:…’
Response: Thank you for your comments. I have revised the sentence.

4. In Table 3 ‘Definition of psoriasis’, not clear what criteria was used for Wang et al, as the authors say ‘Ps was diagnosed by at least 2 outpatient visits or 1 hospital admission’ but surely there must have been some clinical criteria?
Response: Thank you for your question. The clinical criteria is from The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We have added it to Table 3.

5. I don’t know whether it is just a feature of the way the figures are presented to the reviewer, but not all figures have labels only Figure 5 is labelled as Fig 5.
Response: Thank you for pointing out the problem. We were not intended to present like that. It was a mistake. We have corrected this mistake in the updated manuscript.

6. Second sentence: ‘While the study by Khan SR et al. is the first meta-analysis of studies on the association between AITD and the risk of psoriasis incidence22’.
Point 1. This is not a proper sentence, delete While and begin sentence with ‘The study by Khan…’
Point 2: ‘…association between AITD and the risk of psoriasis incidence’ isn’t an appropriate way to report this. Should be either
a) ‘…association between AITD and the risk of psoriasis’, or
b) ‘…association between AITD and the incidence risk of psoriasis’
Response: Thank you for your comments. We have modified the sentence in the revision file.

7.Sixth sentence: Considering that psoriasis is a type of discosmetic dermatosis that is easy to be concerned about, patients with psoriasis are more likely to be active about seeing a doctor regarding their condition than patients with AITD.
Change to
As psoriasis is a type of discosmetic dermatosis and therefore likely to be of concern, patients with psoriasis are more likely to be active about seeing a doctor regarding their condition than patients with AITD.
Response: Thank you for your comments. We have modified the sentence in the revision file.

8.Limitations
There appears to be a contradiction. In the section Main findings, the authors state ‘We hypothesize that the inconsistency of the study designs was the major source of heterogeneity’. In the Limitations, they state ‘…different study designs were not the main source of heterogeneity’. Can this please be clarified.
Response: Thank you for your question. In the beginning, we just assumed that research design might be the main contributing factor to high heterogeneity of the present meta-analysis. However, the assumption was undermined after subgroup analysis based on different study designs. The expression in the section Main findings may be ambiguous, so we have rephrased it. The corresponding revised contents are shown below:

“In order to determine whether or not the inconsistency of the study designs was the primary source of heterogeneity, the subgroup analysis based on different study designs was conducted. However, the heterogeneity was not limited by subgroup analysis; hence the heterogeneity in this meta-analysis was not caused by inconsistency of the study design.”

Reviewer: 2 Dr. Lifeng Lin, Florida State University
1.It seems that this study did not assess the risk of bias of individual studies. Although in the PRISMA checklists (item 11) the authors claimed that the assessment was on page 6, it seems that the authors confused the concept of risk of bias with publication bias. The former is a concept of bias within studies, which may be assessed using tools such as ROBINS for non-randomized studies (https://doi.org/10.1136/bmj.i4919), and the latter is a concept of bias between studies.
Response: Thank you for your valuable suggestions. I carefully learned how to use the ROBINS-I tool to assess the risk of bias in the present meta-analysis. Table 4 shows the results of assessment.

2.The terminologies in the subsection of “Data synthesis and analysis” have many issues. For example, the first letter of “Odds” (line 35, page 6) does not need to be capitalized. Similarly, the first letters of “Confidence Intervals” (line 38, page 6) do not need to be capitalized. “The inconsistency index (I^2)” (line 43, page 6) may be changed to “The I^2 statistic”, as inconsistency does not equate to heterogeneity. For the “Funnel chart” (line 53, page 6), “F” should not be capitalized; this is more commonly called “funnel plot”. The “Analysis” in line 56 on page 6 does not need to be capitalized. In line 4 on page 7, “forest charts, funnel charts” can be changed to “forest plots, funnel plots”.
Response: Thank you for your comments. We have modified these sentences in the revision file.

3.In line 56 on page 6, “Publication bias was considered when $p < 0.05$.” I think the authors meant “Publication bias was considered statistically significant when $p < 0.05$).” Usually, the statistical powers of many methods for detecting publication bias were low, so the significant level for publication bias is often set to 0.1, instead of 0.05.
Response: Thank you for your comments. According to your comments, we have revised the corresponding parts of the article and believe that there was publication bias. The corresponding revised contents are shown below:
“Publication bias was assessed by funnel plot and Egger’s test (Publication bias was considered when $p < 0.1$).” in the Methods section
“The funnel plot for the publication bias is shown in figure. 3B. The results of Egger’s test showed significant publication bias ($p = 0.036$, figure. 3C).” in the Results section

4.Page 6, lines 51-53, “A fixed effects model was applied if I^2 <= 50% and the random effects model was applied when I^2 > 50%.” This is not a good criterion for deciding the use of fixed-effects or random-effects model, as I^2 may be subject to large uncertainties. I would suggest the authors use the random-effects model throughout the analyses.
Response: Thank you for your comments. According to your comments, we have revised the corresponding parts of the article and used the random-effects model throughout the analysis.

5. It was unclear which statistical method was used to implement the meta-analysis model, but I guess that the authors used the popular DerSimonian-Laird method. This approach is generally inferior to several alternative meta-analysis methods, such as the restricted maximum-likelihood (REML) method, which is recommended. See, for example, Cornell et al. (https://doi.org/10.7326/M13-2886) and Langan et al. (https://doi.org/10.1002/jrsm.1316).
Response: Thank you for your suggestion. DerSimonian-Laird method is the most common statistical method used in many meta-analyses, so we also used it for our analysis. However, your professional suggestion made us realize that the restricted maximum-likelihood (REML) method is a better choice. Therefore, we have made a re-analysis using the REML method.

6. In addition to presenting the confidence interval of the meta-analysis results, the authors may consider presenting the prediction interval, which has been advocated in the meta-analysis community and may better appraise the extent of heterogeneity. See, for example, Riley et al. (https://doi.org/10.1136/bmj.d549) and IntHout et al. (http://dx.doi.org/10.1136/bmjopen-2015-010247).
Response: Thank you for your suggestion. According to your suggestion, we added data on prediction interval in the revised manuscript. The corresponding revised contents are shown below:
“The meta-analysis showed that patients with psoriasis had a higher prevalence of AITD than the controls (OR = 1.76, 95% CI: 1.35 - 2.28, Z = 4.25, p <0.01). The prediction interval ranged from 0.79 to 2.73, and the heterogeneity was severe (I^2 = 92.72%).”

7. Lines 22-25 on page 8, “The results of Egger’s test suggested no significant publication bias was evident (p = 0.066, figure 3C).” I think the result of publication bias was interpreted incorrectly. First, as I mentioned earlier, the significance level for publication bias is often set to 0.1, so the p-value of 0.066 is considered significant at this significance level. Second, in the funnel plot (figure 3B instead of 3C?), there is a clear pattern of asymmetry, where small studies with large standard errors tend to have large ORs, while small studies with OR=1 (or log OR = 0) seem to be missing. Therefore, I would say these results support the existence of publication bias.
Response: Thank you for your valuable suggestion. According to your suggestion, we have revised the corresponding parts and believe that there was publication bias.

Reviewer: 3 Dr. Abbas Mansour, University of Basrah College of Medicine
1.-Although the exact mechanism of association remains unknown, several studies have implicated the role of TH-1 cell-mediated inflammation in the immunopathogenesis of psoriasis and autoimmune thyroid disease. (1)
Response: Thank you for your suggestion. We made the discussion as you suggested and cited this reference.

2.-Control for beta-blocker use in thyroid disease not studied. Beta-blockers a.re among the drugs documented to be strongly linked to induction and exacerbation of psoriasis and may be a source of residual confounding. (2)
1-Ruffilli I, Ragusa F, Benvenga S, et al. Psoriasis, psoriatic
arthritis, and thyroid autoimmunity. Front Endocrinol
(Lausanne). 2017;8:139.
2-Balak, Deepak, and Enes Hajdarbegovic. "Drug-Induced Psoriasis: Clinical Perspectives."
Psoriasis: Targets and Therapy Volume 7 (2017): 87-94.
Response: Thank you very much for your valuable comments. According to your comments, we have made the supplement in the Discussion section and cited the researches you mentioned.

3.-Psoriasis and thyroid dysfunction relied on self-reports, which are subject to recall bias. Some of the studied used in this metanalysis were self-reports.
Response: Thank you for your comments. The data on psoriasis and thyroid dysfunction included in the article were derived from the medical record system/medical insurance database. At the same time, we evaluated the qualities of the articles to avoid recall bias.

4. -Accordingly, we recommend that every dermatologist be conscious of this association and suggest those thyroid-related examinations, such as thyroid function test and analysis of thyroid antibodies, be included in the routine tests for patients with psoriasis.
This recommendation is not based on evidence and not cost effective.
Response: Thank you for your suggestion. We have revised the advice as follows,

“Accordingly, we recommend that every dermatologist be conscious of this association and suggest necessary examinations and intervention be considered as soon as possible when patients with psoriasis have suspicious AITD-related symptoms.”

Reviewer: 4 Dr. Jin-an Zhang, Jinshan Hospital of Fudan University
1. Literature Searches are incomplete. The author is advised to search more databases to expand the number of studies.
Response: Thank you for your suggestion. We have added the Scopus database and updated the search time to November 1st, 2021, thus including more studies.

2. The authors noted that the AHRQ Scale was used for cross-sectional studies, but it was not seen in Table 3 with only NOS scores.
Response: Thank you for your question. The score “6” corresponding to the study of Kiguradze et al. in Table 3 was the AHRQ score. To avoid confusion, we placed an asterisk besides the score to make an explanation.

3. Record screening and data extraction were performed by only two independent authors. How disagreements were solved among two independent reviewers during the systematic search, quality assessment and data extraction?
Response: Thank you for your comments. When two independent reviewers had disagreements during the systematic search, quality assessment, and data extraction, the third author would join and then make a decision through discussion. The information was supplemented in Methods section of the revised manuscript. The corresponding revised contents are shown below:
“The assessments were carried by two authors (X Zhang and S Zhang), and checked by the third author(R Wu).”

4. There is still a considerable heterogeneity as in your limitation. This is the most serious problem with this study. Meta-regression analysis is then strongly recommended.
Response: Thank you for your suggestion. As you suggested, we conducted the meta-regression analysis, which helped us find the possible sources of high heterogeneity. We added the results to the updated manuscript. The corresponding revised contents are shown below:
“We further conducted a meta-regression analysis to explore the reason for between-study heterogeneity. Seven variables were included in the regression model, covering average age, sex ratio, nation (China or other counties), race (Caucasian or non-Caucasian), sample size, clinical types of psoriasis (psoriasis vulgaris or psoriatic arthritis), and scope of research on AITD (all studies were divided into two categories: the one focusing on the loss-of-function disorder of the thyroid gland alone; another one focusing on both the loss-of-function disorder and hyperfunction disorder of the thyroid gland). When the criterion was set as $p<0.1$, sample size ($\beta = -0.40$, S.E. = 0.20, $p = 0.07$) and scope of research on AITD ($\beta = 0.45$, S.E. = 0.15, $p = 0.02$) were the potential sources of high heterogeneity.”

5. There are some spelling and grammatical mistakes in the article. Maybe someone who is proficient in English is advised to polish the language.
Response: Thank you for pointing out the mistakes. We have double-checked the English language throughout the text for a better reading experience. Please see the updated manuscript.

VERSION 2 – REVIEW

REVIEWER	Fethney, Judith University of Sydney, School of Nursing
REVIEW RETURNED	03-Dec-2021

GENERAL COMMENTS	Psoriasis meta analysis – revised manuscript I have reviewed the revised manuscript and am satisfied my earlier comments were addressed. After addressing the comments of all reviewers, the paper is a much better read. However, I have noticed a few minor grammatical errors and errors of expression. Data extraction Current text: In case of dispute, the third author(R Wu) would reassess and reach an agreed decision after discussion Suggest re-wording this as 'When disagreements could not be resolved through consensus by the two authors, these were referred to the third author (R Wu) and resolved through discussion. Re-word as this paragraph as follows: The Newcastle-Ottawa Scale (NOS)18 was used to assess the quality of the included cohort and case-control studies. The quality of the study was scored on three dimensions: selection, comparability, and exposure/outcome. Studies that achieved 0-3, 4-6, 7-9 scores were considered of low, moderate and high quality respectively. Additionally, the tools recommended by the Agency for Healthcare Research and Quality (AHRQ)19 were used for the cross-sectional studies. Eleven items were included in AHRQ. The study was assigned one point if the answer "Yes", otherwise no points were assigned. Studies that achieved 0-3, 4-7,and 8-11 points were considered of low, moderate and high quality respectively. Moreover, the ROBINS-I was used to assess the risk of bias.20 The assessments were carried by two authors (X Zhang and S Zhang), and checked by the third author (R Wu). Current text: The meta-analysis was performed using the Stata 16.0 software. We used the odds ratio (OR) and 95% confidence intervals (CI) to describe the differences between groups. The statistical difference was considered significant when $p < 0.05$. Re-word as : The meta-analysis was performed using Stata 16.0 software. We used odds ratios (OR) and 95% confidence intervals (CI) to describe the differences between patients with and without psoriasis. Differences were considered statistically significant when $p < 0.05$. Patient and public involvement Re-word as 'No patients or members of the public were involved in this review'. Quality of studies The authors use the plural term 'qualities' when referring to the quality of studies. This should always be the singular term, 'quality' regardless of how many studies are included.

	Current text: The only cross-sectional study checked with AHRQ was a moderate quality study due to confounding controlling was not clear. Re-word as: The only cross-sectional study checked with AHRQ was a moderate quality study as the method for control of confounding was not clear. Heterogeneity analysis Current text: '…and scope of research on AITD (all studies were divided into two categories: the one focusing on the loss-of-function disorder of the thyroid gland alone; another one focusing on both the loss-of-function disorder and hyperfunction disorder of the thyroid gland). When the criterion was set as $p<0.1$, sample size ($\beta = -0.40$, S.E. = 0.20, $p = 0.07$) and scope of research on AITD ($\beta = 0.45$, S.E. = 0.15, $p = 0.02$) were the potential sources of high heterogeneity.' Re-word as 'and scope of research on AITD (all studies were divided into two categories: one focusing on the loss-of-function disorder of the thyroid gland alone and the other focusing on both the loss-of-function disorder and hyperfunction disorder of the thyroid gland). When statistical significance was set as $p<0.1$, sample size ($\beta = -0.40$, S.E. = 0.20, $p = 0.07$) and scope of research on AITD ($\beta = 0.45$, S.E. = 0.15, $p = 0.02$) were the potential sources of high heterogeneity. Paragraph beginning 'Besides, we removed three studies…'. Delete 'Besides'. Sentence beginning 'The results indicated that these three studies might also contribute to on severe heterogeneity of previous analysis. Re-word as 'The results indicated that these three studies may have contributed to severe heterogeneity in the previous analysis. Sensitivity analysis and publication bias Current text: Therefore, the results of the analysis were reliable and stable. Re-word as: Therefore, the results of the analysis were considered reliable and stable Common pathogenesis of psoriasis and AITD Abnormal does not capitals Implications for practice Current text: Owing to no access to the information on drug application not provided by original researches, drug exposure may be a source of residual confounding in the present study and a potential risk factor for concurrence of psoriasis and AITD, apart from the reasons mentioned above. Re-word as: As information relating to patient medications was not provided by in the original research, drug exposure may be a source of residual confounding in the present study and a potential risk factor for concurrence of psoriasis and AITD, apart from the reasons mentioned above

REVIEWER	Mansour, Abbas

	University of Basrah College of Medicine
REVIEW RETURNED	22-Dec-2021

GENERAL COMMENTS	All points done

REVIEWER	Zhang, Jin-an Jinshan Hospital of Fudan University
REVIEW RETURNED	17-Dec-2021

GENERAL COMMENTS	All my concerns were well addressed。

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1 Dr. Judith Fethney, University of Sydney

Comments to the Author: I have reviewed the revised manuscript and am satisfied my earlier comments were addressed. After addressing the comments of all reviewers, the paper is a much better read. However, I have noticed a few minor grammatical errors and errors of expression.

Response: Thank you for your valuable suggestions, and we have modified the grammatical errors and errors of expression in the revised manuscript.

Reviewer: 3 Dr. Abbas Mansour, University of Basrah College of Medicine

Comments to the Author: All points done

Response: Thank you for your valuable suggestions.

Reviewer: 4 Dr. Jin-an Zhang, Jinshan Hospital of Fudan University

Comments to the Author: All my concerns were well addressed

Response: Thank you for your valuable suggestions.