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OPEN PEER REVIEW

Investigating of Mood and Sleep Disorders in Patients with Restless Legs Syndrome: A Cross-Sectional Study

Lahya Afshari Saleh, Hadi Asadpour, Mahnaz Amini, Seyed Kaveh Hojjat, Ali Talaei, Hanieh Raji

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

4 comments · 30 Dec 2024 – 23 Jan 2025

Referee 1 Reviewer

MAJOR REVISION 30 Dec 2024

Dear Editor,

Thank you for sending me this manuscript. Some comments are provided to improve the manuscript titled "Investigating of mood and sleep disorders in patients with restless legs syndrome: A cross-sectional study":

1. In the objective of the abstract, the main purpose is to investigate mood and sleep disorders in patients with restless legs syndrome.

2. In the method section of the abstract, given that the study is cross-sectional, the time and place of the study must be written.

3. In the results section of the abstract, a significance level should be added at the end of each sentence.

4. In the conclusion section of the abstract, the results have been rewritten. It is better to summarize and add suggestions for future studies.

5. Please check the keywords against MeSH.

6. In the introduction:
- A reference is used in lines 100 to 104; it is not necessary to reference it twice.
- At the end of the introduction section, authors are expected to state the innovation of their study.
- What advantage do the findings of this study have over previous studies conducted in Iran?
- Has such research been conducted before?
- These are the questions that authors should answer in the introduction section.

7. In the Method:
- All scales and questionnaires should be fully introduced: background, number of questions, validity and reliability, evaluation method, measurement method, and in which studies they have been used.
- After introducing the instruments, the authors need to explain how the data were collected from the participants. Where, when, and how were the data collected? Did the participants record all the information themselves, or were your data collected from patient records? What other challenges did you face during data collection?
- Add study inclusion and exclusion criteria.

8. In the results:
- It is suggested that the tables be summarized.

9. In the discussion:
- In line 126, the reference should be corrected to 26.
- Separate the conclusion from the discussion.
- Study limitations should be added.

10. All references need to be edited based on the Vancouver style.

Referee 2 Reviewer

MAJOR REVISION 22 Jan 2025

Dear Author,
Thank you for submitting your manuscript to JJCDC. These are my comments that may help you improve your paper. Please see the journal's guidelines and revise your manuscript accordingly. You can use related published articles in your revision:

1. Abstract
-The abstract lacks specific numerical results (e.g., effect sizes, p-values) to support the claims.
-The conclusion is somewhat repetitive and could be more impactful by emphasizing the clinical implications of the findings.
-Rewrite the conclusion to emphasize the clinical significance of the findings and their potential impact on RLS management.

2. Introduction
-The literature review could be more focused on recent studies, particularly those from similar geographic or cultural contexts.
-The hypothesis or research objectives are not explicitly stated, which could confuse readers about the study's primary focus.
-Narrow the literature review to recent studies (e.g., within the last 5 years) that are directly relevant to the research question.
-Clearly state the research objectives or hypotheses at the end of the introduction.

3. Methodology
-The description of statistical methods is minimal, and there is no mention of controlling for potential confounders (e.g., comorbidities, medication use).
-Explain the sampling method and matching program. How did you match the two groups?
-Provide a rationale for the sample size and include power calculations to demonstrate the study's ability to detect significant effects.
-Expand the statistical analysis section to include details on how potential confounders were addressed (e.g., multivariate regression).

4. Results
-Some results are overinterpreted without sufficient statistical support (e.g., the inverse correlation between RLS score and hours slept is mentioned but not fully explored).
-The presentation of rare RLS variants is interesting but lacks depth in analysis or discussion.
-Include more detailed statistical results (e.g., confidence intervals, effect sizes) to support the claims.
-Provide a deeper analysis of rare RLS variants, including potential clinical implications.

5. Discussion
-The discussion could better integrate the findings on rare RLS variants, which are mentioned but not fully explored.
-The clinical implications of the findings are underemphasized, particularly regarding treatment strategies for RLS patients with comorbid mood disorders.
-Expand the discussion of rare RLS variants, including potential mechanisms and clinical significance.
-Highlight the clinical implications of the findings, such as the need for integrated treatment approaches for RLS and mood disorders.

6. Conclusion
-The conclusion is somewhat repetitive and could be more concise.
-It lacks a clear call to action or specific recommendations for future research.

-Rewrite the conclusion to be more concise and impactful, focusing on the study's key contributions.
-Include specific recommendations for future research, such as longitudinal studies to explore causal relationships.
Thank you very much indeed.

Associate Editor

MAJOR REVISION 23 Jan 2025

Dear Author,
Please revise your manuscript based on our reviewers' comments.
Thank you.

Editor-in-Chief

MAJOR REVISION 23 Jan 2025

Dear Author,
Thank you for submitting your manuscript to JJCDC. Based on our reviewers' comments, your manuscript needs some revision in all sections. Please revise and resubmit.
Thank you.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to reviewers for the article entitled: " *Investigating of mood and sleep disorders in patients with restless legs syndrome: A cross-sectional study":*

Dear Editor,

We are very thankful for reviewing our article. In this letter, responses to reviewer's comments are provided. The reviewer's comments are shown in bold, the response to the comments are underlined.

All of the corrections and changes in the manuscript are highlighted in yellow.

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1. In the objective of the abstract, the main purpose of which is to Investigating of mood and sleep disorders in patients with restless legs syndrome.

2. In the method section of the abstract, given that the study is cross-sectional, the time and place of the study must be written.

Author response: Thank you for your comment. The time and place was written

This cross-sectional study was conducted on patients with RLS registered in the sleep clinic at Mashhad University of Medical Sciences from 2019 to 2024.

3. In the results section of the abstract, a significance level should be added at the end of each sentence.

Author response: Thank you for your important commen.t It was added.

4. In the conclusion section of the abstract, the results have been rewritten. It is better to summarize and add suggestions for future studies.

Conclusion was corrected.

Enhancing awareness of RLS and its comorbidities is crucial for the accurate diagnosis and management of patients, which can subsequently improve sleep quality and alleviate mood disorders.

5. Please check keywords with Mesh.

Keywords was rechecked with Mesh and corrected.
excessive somnolence

6. In the introduction:
- A reference is used in lines 100 to 104, it is not necessary to reference it twice.

It was corrected.

- At the end of the introduction section, authors are expected to state the innovation of their study.
- What advantage do the findings of this study have over previous studies conducted in Iran?
- Has such research been conducted before?
- These are the questions that authors should answer in the introduction section.

Thank you for your valuable comment,The last paragraph of introduction was corrected and we try to answer these questions.

Epidemiological studies indicate variations in the prevalence of Restless Legs Syndrome (RLS), including differences in comorbidity profiles among various ethnic groups and geographic populations. In Iran, studies have reported differing prevalence rates of RLS in both the general population and individuals with various underlying health conditions.(4, 16, 17). While RLS can significantly affect sleep quality and contribute to anxiety and stress, the relationship between RLS and depression remains unclear (17). Given the inconsistent findings regarding the connection between RLS, sleep disorders, and depression, as well as the limited data available on the Iranian population, further research in this area appears to be essential. To our knowledge, this study is the first to investigate the prevalence of RLS among individuals who consulted a sleep clinic for the evaluation of sleep disorders.

7. In the Method:
- All scales and questionnaires should be fully introduced: background, number of questions, validity and reliability, evaluation method, measurement method, and in which studies they have been used.

We explained about questionnaires in the method. The explanations were highlighted with yellow color.

- **After introducing the instruments, the authors need to explain how the data was collected from the participants. Where, when, and how was the data collected? Did the participants record all the information themselves or was your data collected from patient records? What other challenges did you face during data collection?**

In the beginning of method, we explain about data collection:

This cross-sectional study was conducted on 399 patients clinically diagnosed with RLS who were referred to the sleep clinic registry of Mashhad University of Medical Sciences from 2019-2024. For all patients who refer to the sleep clinic, the necessary questionnaires were filled out by a trained technician and reviewed by sleep fellowship at the first visit.

- Add study inclusion and exclusion criteria.

Inclusion criteria was added. Each patient with four criteria include to our study.

Individuals who met all four criteria were considered RLS positive and included to our study, an urge to move limbs due to uncomfortable leg sensations, the constant need to move legs to relieve uncomfortable sensations, Symptoms worsen at night or during rest periods—improving the urge to move by getting up or moving. Patients with incomplete data were excluded.

8. In the results:
- It is suggested that the tables be summarized.

It was summarized, but after univariate and multivariate reanalyze the table 5 was added

9. In the discussion:
- In line 126, the correct reference is 26 and should be corrected.
- Separate the conclusion from the discussion.
- Study limitations should be added.

Thank you for your valuable comments, references were rechecked and conclusion was separated from discussion. Study limitation and future recommendation were added in the last of discussion.

The current study had some limitations. First, the study's cross-sectional nature limits its ability to establish causality between RLS and mood or sleep disorders. The second limitation is the study is limited to a single sleep clinic registry in Iran, which may limit the generalizability of the findings to broader populations. The last one is lack of objective Measures which may introduce reporting bias. Incorporating objective measures like actigraphy could enhance diagnostic accuracy. We recommend for future research, conduction of longitudinal studies to better establish causality between Restless Legs Syndrome (RLS) and associated mood or sleep disorders. Expand research to include multiple sleep clinics across different regions or countries to improve the generalizability of the findings. Utilize objective measures such as actigraphy, polysomnography, or neurophysiological assessments in future studies.

Conclusion

Restless Legs Syndrome (RLS) has significant effects on individual's mental health factors, such as their sleep quality and insomnia score, depression, anxiety, and stress. Understanding how various classes of antidepressant drugs interact with RLS is vital for optimizing treatment strategies for patients experiencing both mood disorders and sleep disturbances associated with RLS. It is essential to note that restlessness resembling RLS can manifest in various parts of the body.

10. All references need to be edited based on the Vancouver style.

References is based on the Vancouver style by endnote.

Reviewer 2:
1. Abstract
-The abstract lacks specific numerical results (e.g., effect sizes, p-values) to support the claims.

Thank you for your comment, It was corrected.

-The conclusion is somewhat repetitive and could be more impactful by emphasizing the clinical implications of the findings.

The conclusion was changed.
-Rewrite the conclusion to emphasize the clinical significance of the findings and their potential impact on RLS management.

Conclusion: Enhancing awareness of RLS and its comorbidities is crucial for the accurate diagnosis and management of patients, which can subsequently improve sleep quality and alleviate mood disorders. It is important to recognize that restlessness mimicking RLS can manifest in different areas of the body.

2. Introduction
-The literature review could be more focused on recent studies, particularly those from similar geographic or cultural contexts.
-The hypothesis or research objectives are not explicitly stated, which could confuse readers about the study's primary focus.
-Narrow the literature review to recent studies (e.g., within the last 5 years) that are directly relevant to the research question.-Clearly state the research objectives or hypotheses end of introduction.

Thank you for valuable commemts. Introduction was corrected.

Epidemiological studies indicate variations in the prevalence of Restless Legs Syndrome (RLS), including differences in comorbidity profiles among various ethnic groups and geographic populations. In Iran, studies have reported differing prevalence rates of RLS in both the general population and individuals with various underlying health conditions.(4, 16, 17). While RLS can significantly affect sleep quality and contribute to anxiety and stress, the relationship between RLS and depression remains unclear (17). Given the inconsistent findings regarding the connection between RLS, sleep disorders, and depression, as well as the limited data available on the Iranian

population, further research in this area appears to be essential. To our knowledge, this study is the first to investigate the prevalence of RLS among individuals who consulted a sleep clinic for the evaluation of sleep disorders.

Objective: This study aimed to assess the prevalence of RLS and identify comorbidities associated with the disorder.

3. Methodology
-The description of statistical methods is minimal, and there is no mention of controlling for potential confounders (e.g., comorbidities, medication use).- Explain about sampling method and matching program. How did you match two groups?

Thank you so much for valuable comment, but we had not two groups, we evaluated all of RLS Patients that were referred to sleep clinics.

-Provide a rationale for the sample size and include power calculations to demonstrate the study's ability to detect significant effects.

We evaluated all of available patients with RLS diagnosis.

-Expand the statistical analysis section to include details on how potential confounders were addressed (e.g., multivariate regression).

Thank you so much for valuable comment. univariate and multivariate regression was added and the results were written in table 5 and in the last part of results.

Univariate logistic regression was used to identify the influencing factors in increasing the risk of developing severe RLS. The Multivariate regression by the method of forward LR was performed.

4. Results
-Some results are overinterpreted without sufficient statistical support (e.g., the inverse correlation between RLS score and hours slept is mentioned but not fully explored).
-The presentation of rare RLS variants is interesting but lacks depth in analysis or discussion.

Rare variants of RLS identified in this registry included restless head, back, abdomen, bladder, and perineum syndrome, accounting for 11 cases (3.6%) among our patients. The mean age in this group was 44.26± 5.6 years and 7 patients were female.

-Include more detailed statistical results (e.g., confidence intervals, effect sizes) to support the claims.

Thank you for your valuable comment. Confidence interval was added to our results.

In table 1,3,5 confidence interval was added with green color.

-Provide a deeper analysis of rare RLS variants, including potential clinical implications.

The number of rare variants of RLS is limited (11) and there were related to different part of body, so it was not possible to analyze it separately.

5. Discussion
-The discussion could better integrate the findings on rare RLS variants, which are mentioned but not fully explored.

Thanks for good comment,

Understanding rare variants of RLS is crucial for accurately diagnosing diseases. The literature contains numerous case reports about these variants (31), highlighting the importance of recognizing that this condition is not limited to leg symptoms. In our sleep clinic 11 patients were diagnosed with restless in another organ that majority of these patients were female. These variants can be challenging to diagnose due to their atypical presentations. A thorough clinical history and symptom assessment are crucial.

-The clinical implications of the findings are underemphasized, particularly regarding treatment strategies for RLS patients with comorbid mood disorders.

Thank you so much for good comment, a paragraph was added about it.

Mood disorders treatment in RLS patients is challenging. Selective serotonin reuptake inhibitors (SSRIs) can exacerbate RLS symptoms due to their effects on serotonin levels in the brain, which can influence motor activity. Antidepressants with dopaminergic effects might provide relief RLS symptoms.(16) Patients are also experiencing depression or anxiety disorders alongside RLS, healthcare providers may consider a careful combination approach that includes both antidepressants and dopamine agonists.

-Expand the discussion of rare RLS variants, including potential mechanisms and clinical significance.

-Highlight the clinical implications of the findings, such as the need for integrated treatment approaches for RLS and mood disorders.

It was corrected .

In our sleep clinic 11 patients were diagnosed with restless in another organ that majority of these patients were female. Understanding rare variants of RLS is crucial for accurately diagnosing

diseases. The literature contains numerous case reports about these variants (31), highlighting the importance of recognizing that this condition is not limited to leg symptoms. . These variants can be challenging to diagnose due to their atypical presentations. A thorough clinical history and symptom assessment are crucial.

6. Conclusion
-The conclusion is somewhat repetitive and could be more concise.

Conclusion was corrected.

Conclusion

Restless Legs Syndrome (RLS) has significant effects on individual's mental health factors, such as their sleep quality and insomnia score, depression, anxiety, and stress. Understanding how various classes of antidepressant drugs interact with RLS is vital for optimizing treatment strategies for patients experiencing both mood disorders and sleep disturbances associated with RLS. It is essential to note that restlessness resembling RLS can manifest in various parts of the body.

-It lacks a clear call to action or specific recommendations for future research.

It was corrected.

-Rewrite the conclusion to be more concise and impactful, focusing on the study's key contributions.
-Include specific recommendations for future research, such as longitudinal studies to explore causal relationships.

The current study had some limitations. First, the study's cross-sectional nature limits its ability to establish causality between RLS and mood or sleep disorders. The second limitation is the study is limited to a single sleep clinic registry in Iran, which may limit the generalizability of the findings to broader populations. The last one is lack of objective Measures which may introduce reporting bias. Incorporating objective measures like actigraphy could enhance diagnostic accuracy. We recommend for future research, conduction of longitudinal studies to better establish causality between Restless Legs Syndrome (RLS) and associated mood or sleep disorders. Expand research to include multiple sleep clinics across different regions or countries to improve the generalizability of the findings. Utilize objective measures such as actigraphy, polysomnography, or neurophysiological assessments in future studies.

Thank you very much indeed.

2 Revision 1

2 comments · 16 Feb 2025 – 16 Feb 2025

Associate Editor

ACCEPT 16 Feb 2025

dear Author,
All comments have been revised, and this manuscript in its current version is acceptable. But there is a minor comment regarding the tables: you should combine the columns for the mean and standard deviation as M±SD. Please see our published articles.
Thank you

Editor-in-Chief

ACCEPT 16 Feb 2025

Dear Author,
This manuscript is acceptable. You should correct your table in the proof version based on our reviewers' comments. Combine M±SD in the tables.
Thank you