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OPEN PEER REVIEW

Alpha Human Papillomavirus Types and Genotype Distribution in Psoriasis Patients: A Cross-Sectional Regional Study in Turkey

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1 Original submission

1 comment · 16 Sep 2024

Referee 1 Reviewer

MINOR REVISION 16 Sep 2024

Dear editor
In this study, the authors have investigated the epidemiology of HPV group alpha viruses in the skin nodules of patients with psoriasis. The study is well-written and provides good information to the reader. Considering that there are no similar studies on the relationship between alpha-group HPV viruses and psoriasis, the study is sufficiently innovative for publication. In my view, this manuscript can be accepted for publication in the journal after the following corrections:
1- In the introduction section, probable high-risk virus types should also be mentioned. In some studies, some papillomaviruses have been classified in this way.
2- Considering that the relationship between beta papillomaviruses and psoriasis was mentioned in the discussion, it is better to mention the role of this group of viruses and their relationship with psoriasis in the introduction section.
3- Please refer to the sample inclusion criteria in the method section. By what criteria were these patients selected? And if there was an exclusion criterion, it should be mentioned. For example, how were other similar skin diseases differentiated?

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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.

Respond to Reviewers' Comments

Reviewer 1:

1. The issue that worries me about your manuscript is the limitations of your study, please address them in the discussion section
Limitations Not Explicitly Mentioned in the Text

Respond: The limitations of the study were mentioned in lines 221-229.

"Our study has several limitations. First, due to its cross-sectional design, we could not assess whether HPV persisted in the patients over the long term. As a result, we were unable to determine the relationship between the identified genotypes and the severity of the disease. Another limitation is that we focused on a limited number of HPV genotypes. While there are few references in the literature regarding the relationship between beta and gamma HPV types associated with cutaneous lesions and psoriasis, evidence concerning the association between alpha HPV and psoriasis is lacking. To address this gap, our study evaluated only the presence of alpha HPV, excluding beta and gamma HPV types."

2. Lack of Longitudinal Data:
The study did not follow up with patients over time to observe the persistence or clearance of HPV infections, nor the potential progression of HPV related cutaneous lesions in psoriasis patients. Longitudinal studies would provide more insight into the dynamics of HPV infection and its potential role in psoriasis development or exacerbation.

Respond: While longitudinal studies would offer deeper insights into the dynamics of HPV infection and its potential role in the development or worsening of psoriasis, these aspects were not examined in this study, as it was designed as a cross-sectional study.

3. Limited Genotype Focus:

The study primarily focused on alpha HPVs and did not extensively investigate other HPV types (such as beta or gamma HPVs), which are more commonly associated with skin conditions. This narrow focus may have led to an underestimation of the overall HPV prevalence in psoriasis patients, and it misses the opportunity to explore the broader spectrum of HPV's involvement in skin pathology.

Respond: Although the literature contains limited references regarding the relationship between beta and gamma HPV types associated with cutaneous lesions and psoriasis, there is a significant lack of evidence concerning the link between alpha HPV and psoriasis. To address this gap, our study specifically evaluated the presence of alpha HPV, excluding beta and gamma HPVs from consideration. In the discussion section of the study, we addressed the detection rates of beta HPVs in psoriasis patients and explored their genotypic distributions.

4. Selection Bias:

The psoriasis patients were selected from those presenting at a dermatology outpatient clinic, which could lead to a selection bias. These patients might have more severe or treatment resistant forms of psoriasis, which may not represent all individuals with the condition, particularly those who do not seek clinical care regularly.

Respond: "To form the patient group for the study, we randomly selected individuals with psoriasis lesions who had been diagnosed with psoriasis based on their medical records and were actively undergoing follow-up care. We contacted these patients by phone, informed them about the study, and invited them to visit the outpatient clinic to provide samples. Consequently, the patient group is free from bias, as it includes patients not limited to those experiencing psoriasis flare-ups or those who only visit the outpatient clinic for clinical care." (line 76-83)

5. Potential Confounding Factors:

The study does not account for potential confounding factors, such as patients' immune status, the presence of other infections, comorbidities, or previous HPV vaccinations, which could influence both HPV infection rates and psoriasis severity. Without controlling for these variables, the associations between HPV infection and psoriasis may be confounded.

Respond: The mentioned information was added to Table 1.

6. Methodological Limitations in HPV Detection and Genotyping:

The study relies on PCR and direct sequencing for HPV detection and genotyping, which may have certain technical limitations:
Lack of Quantitative Data: The study did not quantify the viral load, which could have provided additional insights into the severity or clinical relevance of the HPV infections detected.

Respond: In our review of the literature examining the relationship between HPV and psoriasis, we found that most studies focused on detecting and distributing viral genotypes rather than evaluating viral load. In our study, we conducted in-house PCR and sequence analysis using the resources available in our laboratory. Our goal was to raise awareness by identifying HPV genotypes and their distribution among psoriasis patients compared to control groups.

7. No Assessment of Psoriasis Severity:

The study does not correlate HPV presence or genotype with the severity or type of psoriasis, which would be critical for understanding whether specific HPV genotypes are more prevalent in certain psoriasis phenotypes or disease severities.

Respond: In this study, the patient group was formed by randomly selecting individuals diagnosed with psoriasis who presented with lesions. Since the patients were not specifically chosen from those experiencing a flare-up of the condition, the study did not aim to establish a relationship between disease severity and HPV genotype. However, future longitudinal studies may pursue this avenue. Consequently, the relationship between HPV genotypes and types of psoriasis could be examined, as well as whether different genotypes influence the severity of the disease.

8. Limited Assessment of Treatment Impact: The analysis of PUVA treatment impact on HPV prevalence is limited, with only a binary distinction (treated vs. untreated). It does not consider the duration, frequency, or cumulative dose of PUVA therapy, which could have a more nuanced effect on HPV infection risk. Additionally, it does not explore other treatments (e.g., biologics or systemic immunosuppressants) that could impact HPV prevalence.

Respond: The patients' clinical history and laboratory data were retrieved from hospital medical records [age, sex, comorbidity, treatments; PUVA (0,5-2 J/cm^2) and immunosuppressants (methotrexate, verxant, Enbrel etc.]. (line 70-72)

9. Lack of Functional or Mechanistic Studies:

The study does not explore the mechanisms by which HPV might contribute to psoriasis pathogenesis. While the study suggests that HPV may provide an environment for keratinocyte proliferation, it does not provide direct evidence or experimental data to support this hypothesis.

Respond: The study stated psoriasis is a chronic inflammatory disease with a complex pathogenesis. According to the literature, there is an increase in the release of certain cytokines due to infection with HPV, which is associated with increased keratinocyte proliferation. However, since our laboratory cannot conduct studies on the disease's pathogenesis and it is not included in our study's design, we did not perform such an investigation. Nevertheless, our findings highlight that mucosal types of HPVs can be found in the skin and raise awareness for future pathogenesis studies.

Reviewer 2:
Dear editor
In this study, the authors have investigated the epidemiology of HPV group alpha viruses in the skin nodules of patients with psoriasis. The study is well-written and provides good information to the reader. Considering that there are no similar studies on the relationship between alpha-group HPV viruses and psoriasis, the study has enough innovation for publication. In my view, this manuscript can be accepted for publication in the journal after the following corrections:

1- In the introduction section, Probable high-risk virus types should also be mentioned. In some studies, some papillomaviruses have been classified in this way.

Respond: It has been corrected as follows in line with the suggestions.

Line 33 “Probable high-risk HPV” genotypes added.

2-Considering that the relationship between beta papillomaviruses and psoriasis was mentioned in the discussion, it is better to mention the role of this group of viruses and their relationship with psoriasis in the introduction section.

Respond: A paragraph about beta papillomaviruses has been added (line 37-46)

"A paragraph about beta papillomaviruses has been added." Recent metagenomic analyses [4] have revealed that the highest prevalence of HPV is found in the skin (61%), followed by the vagina (41.5%), mouth (30%), and gut (17.3%). More than 95% of all viral sequences detected in skin samples belong predominantly to the beta and gamma HPV genera [5]. Beta HPV types, such as HPV-5, HPV-8, and HPV-9, are common viruses that can lead to widespread infections, although they are typically asymptomatic. Persistent infections with beta HPV in keratinocytes have been shown to increase the risk of actinic keratosis. Beta HPV is present in the skin of 40% of immunocompetent individuals with squamous cell carcinoma (SCC) and in 80% of organ transplant recipients with SCCs. Additionally, beta HPV types 17, 20, and 38 appear to be significantly associated with SCCs [6].”

Added references

[4]. Ma, Y., Madupu, R., Karaoz, U., Nossa, C. W., Yang, L., Yooseph, S., et al. (2014). Human papillomavirus community in healthy persons, defined by metagenomics analysis of human microbiome project shotgun sequencing data sets. Journal of virology, 88(9), 4786-4797. https://doi.org/10.1128/jvi.00093-14

[5]. Bzhalava, D., Mühr, L. S. A., Lagheden, C., Ekström, J., Forslund, O., Dillner, J., et al. (2014). Deep sequencing extends the diversity of human papillomaviruses in human skin. Scientific reports, 4(1), 1-7. https://doi.org/10.1038/srep05807

[6]. Brianti, P., De Flammineis, E., Mercuri, S. R. (2017). Review of HPV-related diseases and cancers. New Microbiol, 40(2), 80-85.

3- Please refer to the sample inclusion criteria in the method section. By what criteria were these patients selected? And if there was an exclusion criterion, it should be mentioned, for example, how were other similar skin diseases differentiated?

Respond: Participants' inclusion and exclusion criteria were added to the Study population and sample collection section. (line 76-83)

“Individuals aged 18 and older who had been diagnosed with psoriasis and did not have any other skin diseases were included in the study. This was conducted following standard guidelines, which involved reviewing patient history, performing clinical examinations, and conducting laboratory tests, with patients being randomly selected. The control group consisted of healthy individuals visiting the dermatology clinic. These participants had no history of psoriasis or skin cancer and displayed no clinical signs of viral warts. Additionally, it was confirmed that none of their first- or second-degree relatives had a history of psoriasis.”

Reviewer Assistant Comments:

These comments were generated by AI based on your manuscript. Please review them and consider incorporating the suggestions to enhance your article.

To comprehensively review the study "Alpha Human Papillomavirus Types and Genotype Distribution in Psoriasis Patients," I will use the STROBE checklist for cross-sectional studies, as the study design appears to be observational and cross-sectional. Below is a detailed review based on the STROBE checklist:

Title and Abstract
1. **Title (1a)**: The title should indicate the study’s design. The current title "Alpha Human Papillomavirus Types and Genotype Distribution in Psoriasis Patients" does not specify that it is a cross-sectional study.

Respond: The title of the article was edited to indicate the design of the study.
"Alpha Human Papillomavirus Types and Genotype Distribution in Psoriasis Patients: A Cross-Sectional Regional Study in Türkiye"

2. **Abstract (1b)**: The abstract should provide an informative and balanced summary of what was done and what was found. The provided abstract is clear and includes the background, objectives, methods, results, and conclusion.

Introduction
3. **Background/Rationale (2)**: The background explains the scientific context and rationale for the study, which is well addressed by stating the unclear role of HPVs in psoriasis.

4. **Objectives (3)**: The objectives are clearly stated: to investigate the presence of alpha human papillomavirus in skin scrapings of psoriasis patients and determine its genotype distributions.

Methods
5. **Study Design (4)**: The study design should be presented early in the paper. It is not explicitly stated that this is a cross-sectional study.

Respond: It has been corrected as follows in line with the suggestions.
Line 7 “Methods: The study, which has a cross-sectional design, included…”
Line 67 “The study used a cross-sectional design and included 53 psoriasis patients…”

6. **Setting (5)**: The setting, locations, and relevant dates should be described. The study mentions the inclusion of 53 psoriasis patients and 47 healthy individuals but does not specify the locations or dates of data collection.

Respond: It has been corrected as follows in line with the suggestions.
Line 68-72“..Dermatology Outpatient Clinic of Mersin University Hospital between December 2020 and May 2021 and 47 healthy individuals in Mersin province, Türkiye. The patients' clinical history and laboratory data were retrieved from hospital medical records [age, sex, comorbidity, treatments; PUVA (0,5-2 J/cm2) and immunosuppressants (methotrexate, verxant, Enbrel etc.]. Informed consent was obtained from all patients. “

7. **Eligibility Criteria (6a)**: The eligibility criteria for participants and the sources and methods of selection should be provided. The study mentions the inclusion of psoriasis patients and healthy individuals but lacks detailed eligibility criteria.

Respond: Eligibility criteria for participants were added to the Study population and sample collection section (lines 76-83).

“Individuals aged 18 and older who had been diagnosed with psoriasis and did not have any other skin diseases were included in the study. This was conducted following standard guidelines, which involved reviewing patient history, performing clinical examinations, and conducting laboratory tests, with patients being randomly selected. The control group consisted of healthy individuals visiting the dermatology clinic. These participants had no history of psoriasis or skin cancer and displayed no clinical signs of viral warts. Additionally, it was confirmed that none of their first- or second-degree relatives had a history of psoriasis.”

8. **Variables (7)**: All outcomes, exposures, predictors, potential confounders, and effect modifiers should be clearly defined. The study defines the detection of HPV DNA and its genotypes as the primary outcomes.

Respond: The study included 53 psoriasis patients who presented to the Dermatology Outpatient Clinic of Mersin University Hospital between December 2020 and May 2021 and 47 healthy individuals in Mersin province, Türkiye. Among the psoriasis patients, there were 27 males and 26 females, with mean ages of 50.9 ± 12.71 and 49.74 ± 12.46, respectively. Additionally, the control group included 47 healthy individuals, with 25 males and 22 females, and their mean ages were 36.37 ± 11.03 and 35.91 ± 10.94, respectively.

9. **Data Sources/Measurement (8)**: For each variable of interest, the sources of data and methods of assessment should be described. The study details the use of consensus primer sequences for PCR amplification and direct DNA sequence analysis for genotype determination.

10. **Bias (9)**: Efforts to address potential sources of bias should be described. The study does not mention any specific efforts to address bias.

Respond: The information is mentioned in lines 76 to 83.

“To form the patient group for the study, we randomly selected individuals with psoriasis lesions who had been diagnosed with psoriasis based on their medical records and were actively undergoing follow-up care. We contacted these patients by phone, informed them about the study, and invited them to visit the outpatient clinic to provide samples. Consequently, the patient group is free from bias, as it includes patients not limited to those experiencing psoriasis flare-ups or those who only visit the outpatient clinic for clinical care.”

11. **Study Size (10)**: The study size and how it was determined should be explained. The study includes 53 psoriasis patients and 47 healthy individuals but does not explain how these numbers were determined.

Respond: According to the literature, the HPV positivity rate among individuals diagnosed with psoriasis is 60%, while the positivity rate among healthy individuals without a history of psoriasis is 20% (Salem et al, 2010) ethical Source 1). Based on this information, a total of 54 patients with psoriasis and 47 healthy individuals were included in the study to ensure that the difference between the case and control groups would be statistically significant, with a 5% Type I error rate and at least 80% power. The minimum required sample size was calculated using G*Power 3.1.9.2.

Salem, S. A. M., Fakkar, N. M. Z., Fathi, G., El-Reheem, S. M. A., El-Tabakh, A. A. E. M., & Ragab, D. M. (2010). Comparative study of human papilloma virus in untreated and ultraviolet-treated psoriatic patients. Photodermatology, photoimmunology & photomedicine, 26(2), 78-82.

12. **Quantitative Variables (11)**: The handling of quantitative variables in the analyses should be explained. The study does not discuss this aspect.

Respond: In this study, no quantitative variable other than ‘Age’ was used. The descriptive statistics of the Age variable are summarized in Table 1.

13. **Statistical Methods (12a)**: All statistical methods used, including those to control for confounding, should be described. The study does not detail the statistical methods used for analysis.

Respond: The information is mentioned in lines 123-128.

14. **Statistical Methods (12b)**: Methods used to examine subgroups and interactions should be described. The study mentions comparisons between patients who received PUVA treatment and those who did not but does not detail the methods.

Respond: Patients who had received psoralen ultraviolet A (PUVA) or light therapy at any time in the past were compared with those who had never received PUVA therapy during their disease.

15. **Statistical Methods (12c)**: Explanation of how missing data were addressed should be provided. The study does not mention missing data.

Respond: There is no missing data in the study.

16. **Statistical Methods (12d)**: If applicable, analytical methods taking account of sampling strategy should be described. This is not applicable here.

17. **Statistical Methods (12e)**: Any sensitivity analyses conducted should be described. The study does not mention sensitivity analyses.

Respond: No sensitivity analysis was performed in the study.

Results
18. **Participants (13a)**: Numbers of individuals at each stage of the study should be reported. The study reports the total number of participants but does not provide a detailed flow of participants.

Respond: Figure added.

19. **Participants (13b)**: Reasons for non-participation at each stage should be given. This is not mentioned.

Respond: Line 144-145 “Psoriatic lesions had spread to the entire body in 14 patients, and therefore no lesion-free area samples could be collected from these patients.” The sentence was added to the results section.

20. **Participants (13c)**: Consider the use of a flow diagram. A flow diagram is not provided.

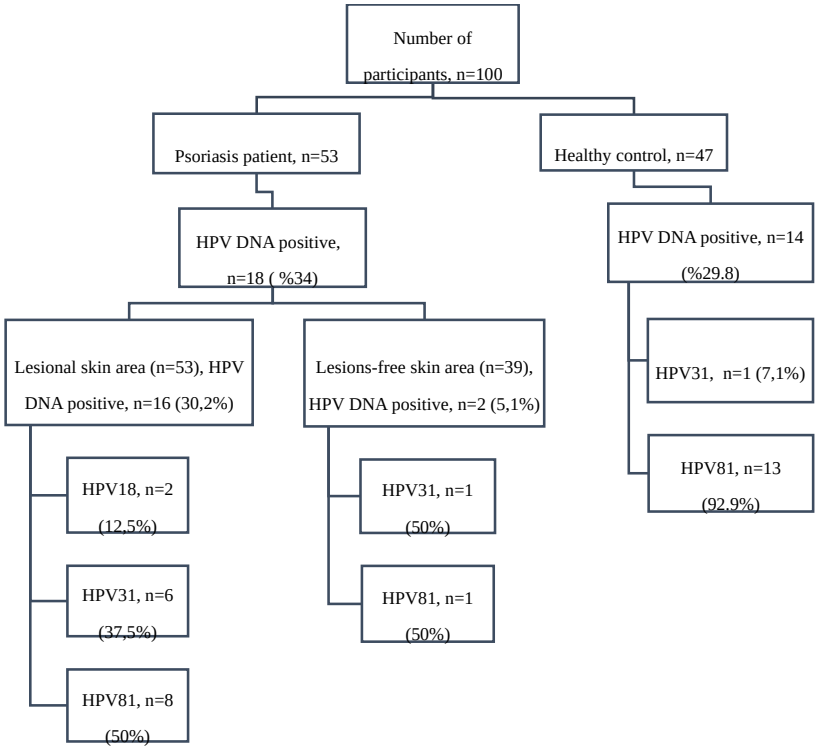


Figure 1. Rates of HPV DNA positivity and distributions of genotypes in the patient and control groups.

21. **Descriptive Data (14a)**: Characteristics of study participants should be given. The study does not provide detailed demographic or clinical characteristics of the participants.

Respond: Demographic and clinical characteristics of participants have been included in Table 1.

22. **Descriptive Data (14b)**: Indicate the number of participants with missing data for each variable of interest. This is not mentioned.

Respond: All participants provided complete data for every variable of interest, with no missing entries.

23. **Outcome Data (15)**: Report numbers of outcome events or summary measures. The study reports the detection rates of various HPV genotypes.

Discussion
24. **Key Results (18)**: Summarize key results with referning study objectives. The study summarizes the detection rates of HPV genotypes in psoriasis patients and healthy individuals.

Respond: Line 165-168 “Our cross-sectional study investigated the presence and genotypes of alpha HPVs in psoriasis patients and healthy individuals. As a result, the rates and genotypes of alpha HPV in psoriasis patients and healthy individuals, and the genotype distributions between the groups were summarized.”

25. **Limitations (19)**: Discuss the limitations of the study, taking into account sources of potential bias or imprecision. The study does not discuss its limitations.

Respond: The limitations of the study were mentioned in lines 221-229.

26. **Interpretation (20)**: Provide a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. The study provides an interpretation but does not discuss limitations or results from similar studies.

Respond: Limitations of the study and comments on the findings were added to the end of the discussion and in the results section.

27. **Generalisability (21)**: Discuss the generalisability of the study results. The study does not discuss the generalisability of its findings.

Respond: “We also believe that the genotypes identified in our study may lead to studies that will investigate the effects on keratinocyte differentiation.” sentence added to lines 237-239.

Other Information

28. **Funding (22)**: Give the source of funding and the role of the funders. The study does not mention funding sources.
Respond: Funding is mentioned in the study in lines 239-241.

Funding: “This study was supported by Mersin University Scientific Research Projects Unitas project with the number of “2021-1-TP2-4117”

Summary
The study provides valuable insights into the presence and genotype distribution of alpha human papillomavirus in psoriasis patients. However, it lacks several key elements required for a comprehensive cross-sectional study report, such as detailed eligibility criteria, statistical methods, participant characteristics, and discussion of limitations and generalisability. Addressing these gaps would strengthen the study's validity and reliability.

For further improvement, the authors should consider revising the manuscript to include these missing elements, ensuring adherence to the STROBE guidelines for cross-sectional studies .

2 Revision 1

0 comments

No public comments in this round.