Peer review

Lu, Kristie, and Ayman Reffai. 2025. "The Role of Epstein-Barr Virus in the Pathogenesis of NasoPharyngeal Carcinoma." *Journal of High School Science* 9 (1): 239–55.

This review presents content available in the public domain (however see below as it leaves much out). Therefore, it does not contribute significantly to the existing corpus of knowledge in the field. It does not satisfy the Journal's expectations of a review manuscript as seen here: https://jhss.scholasticahq.com/for-authors, for authors, types of manuscripts, review manuscripts. The manuscript can be rendered publishable if the author incorporates a 'perspectives' section and adequately addresses points 1 and 3. Please note that merely reproducing verbiage will not qualify, please offer quantifiable, workable proposal(s) that provide depth to the discussion of early detection, and which may not be available in the public domain.
In addition, please make sure that you have covered ALL content related to NPC. See point 6.

1.The problem with this disease is to be able to detect routinely and non-invasively; preferably as part of primary health care visits; i.e. Early detection. The early detection should be based on commonly occurring, easily diagnosible (without invasive prodeures or costly instrumentation) signs and symptoms at the primary physician level. In addition, the detection should be sensitive and specific. This condition hence lends itself to either a clinical symptom algorithm or a ML algorithm. The feature set could include (for example), headaches (location, frequency…), nasal congestion (frequency, responsiveness to medicine, becoming resistant to OTC medicines such as nasal decongestants etc…), nasal bleeding (frequency etc.), person origin from endemic geographical region of the globe (china, SE asia, N.Africa, Inuit populations), consumption of salted fish or salted preserved vegetables when young (https://doi.org/10.1093/jnci/82.4.291 ?, https://doi.org/10.1093/ajcn/nqab114, (preserved food consumption at younger ages), lump in neck, ear infections increased frequency, belonging to the male sex, hearing loss or tinnitus, occupational exposure to volatile chemicals,nitrosamines, fumes, smoke dust etc. Smoking and alcohol consumption and family history of NPC. Candidates at risk can then be suitably screened so that false positive results are brought to a minimum.

2.see https://doi.org/10.1002/cam4.7144, where the authors state "…..Accredited population-based screening tools in NPC-endemic regions remain lacking. 15 Given the close association between NPC and Epstein–Barr virus (EBV) infection, anti-EBV IgA serological tests, including VCA-IgA and EBNA1-IgA, have been recommended for NPC screening. 16 However, these tests have a positive predictive value (PPV) as low as approximately 4%, 16 , 17 causing >95% of the testing population to undergo unnecessary clinical examinations. Consequently, both compliance and screening efficiency for early diagnosis of NPC remain low. Measurement of circulating plasma cell-free EBV DNA levels was proposed as a potential screening tool, 1 but it was discovered to have low sensitivity in identifying patients with early-stage NPC. 18 In endemic areas, prevalent latent EBV infection in the general population also caused a high false-positive rate. 19 , 20 These drawbacks have limited the use of EBV DNA as a mass screening tool……", threfore, it is doubtful if EBV related serological or genetic testing is effective for early diagnosis of NPC.

3.Under a 'perspectives' section, you may want to propose the development of an ML model. The model would take populations with EB virus infections (latent or active) who present as NPC negative and attempt to distinguish those populations from EB virus infections who present as NPC positive. The information can be prospective or retrospective. Based on this data, the ML algorithm should be able to identify clinical parameters (blood tests, dental findings, symptoms etc., see point 1) that would accurately classify EB+NPC+ from EB+NPC-. Such an algorithm may expand the diagnosis to non-

endemic areas. This would mitigate the concern raised in point 1 where the false positive rate from testing EBV related serological or genetic data is too high. This may already have been researched; please perform a thorough search of the literature. In addition see point 1 where I have listed common fetures that could be used in a diagnostic or an ML algorithm.

4.see https://doi.org/10.1038/s41746-024-01403-2, a smartphone app that claims to detect NPC with high sensitivity and specificity. Please perform a thorough search of the literature and discuss in the manuscript.

5.Nomograms and diagnostic algorithms: https://doi.org/10.1200/jco.2010.33.7741, https://doi.org/10.1016/j.annonc.2020.12.007

6.Substantial content has been left out of this review. Rather than comment on speciics, I refer the author to https://doi.org/10.3389/fmicb.2023.1116143. Please make sure ALL the content presented in this reference is also presented and adequately described in your manuscript. Note that this will result in significant expansion of content in your manuscript and references may need to be renumbered as a consequence.

Dear Reviewer and Editor,

Thank you for your thorough review and for giving me the opportunity to improve my manuscript. I have carefully addressed all of your comments and revised the manuscript accordingly. Below is a summary of my revisions:

1. **Addressing Reviewer Points 1 and 3**
    - I have added a new “Perspectives” section proposing a novel machine learning (ML) model that integrates clinical, demographic, and serological data to distinguish EBV-positive individuals with NPC from those without the disease. This approach highlights the potential for early detection through routine, non-invasive screening.
2. **Addressing Reviewer Point 2**
    - In the “Diagnosis” section, I discussed the limitations of serological testing and EBV-based biomarkers for mass screening in the general population, emphasizing the low positive predictive value (PPV) and high false-positive rates. I have also included recent studies that explore risk assessment models and the use of ML and artificial intelligence (AI) to refine and improve early detection strategies.
3. **Addressing Reviewer Points 4 and 5**
    - In the “Diagnosis” section, I included a discussion of Yue et al.’s smartphone application, “Nose-Keeper,” along with other AI-powered imaging techniques, discussed in other relevant studies, employed in NPC screening and diagnosis. I also examined the limitations of the “Nose-Keeper” model. In addition, I discussed the integration of ML with nomograms as a promising tool for clinical decision-making.
4. **Addressing Reviewer Point 6**
    - We have incorporated all relevant content from the Su et al. reference. This information is integrated into the “Carcinogenesis,” “Diagnosis,” and “Treatment” sections. I have also revised the “Abstract,” “Introduction,” and “Conclusion” to reflect these updates and to ensure consistency throughout the manuscript.

5. **Reference Renumbering**
    - All references have been appropriately renumbered.
6. **Consistent Citation Style**
    - I have converted all references to the Vancouver style, ensuring uniformity across the manuscript.

      I appreciate your valuable feedback, which has helped me significantly enhance the clarity and comprehensiveness of my work. I look forward to your further comments or questions.

Thank you for addressing my comments. Before I recommend accept, please address the following formatting issues.

1.Make the reference parentheses (brackets) curved (), not []. Please make this change throughout the text.

2.Include an Abbreviations section. Include ALL abbreviations in the manuscript (even if they are full-formed'ed' in the text. Please make sure to include ALL abbreviations.

3.The references need to be properly formatted. If a reference has more than 6 authors, the first 6 authors must be listed then followed by an et al. The DOI links must be live. Not DOI:, rather; https://doi.org/XXXX. Please make sure the link redirects to the correct webpage. The references must be consistent in format. Please make sure to address this point thoroughly else it will delay the processing of your manuscript.

4.convert the 'key features of the proposed ML model" into a table

Please makes these changes to the attached manuscript only and resubmit when done.

Thank you for addressing my concerns. Accept