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Letter to the editor

Diagnostic implications of miRNAs in Liquid Biopsy for Oral Squamous Cell Carcinoma (OSCC): Clinical validity and interpretation

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To the Editor,

Recently the focus on studies assessing the predictability of miRNAs as a prognostic/diagnostic biomarker in cancers has gained momentum. Though there are some studies on this line of interest, Rapado-Gonzalez *et al.*'s study adds to the existing pool of research by placing a particular focus on the diagnosis of Oral Squamous Cell Carcinoma using miRNAs biomarkers [1]. Rapado-Gonzalez and colleagues' study presents an exciting new approach to this field, via assessment of the sensitivity and specificity of the various miRNAs as a diagnostic marker. However, there are a few significant issues and improvements that are required to be highlighting to add context to the applicability of the study to clinical scenarios.

Is miRNA ubiquitous in their diagnostic effect on OSCC?

A primary issue observed is the combined analysis of all miRNA under a single banner. All miRNAs are not ubiquitous in their effect on cancer, with some having an oncogenic effect and others, tumour-suppression effects [2,3]. Although Rapado-Gonzalez *et al.* assessed the Odds Ratio (OR), sensitivity and specificity for single miRNA assays, combining assays of different miRNAs into a single banner, assuming equivalent impact of each on diagnosis is a notable major leap. In essence, although the presented study tells us that miRNAs as a whole may be an excellent diagnostic marker, it does not identify which specific miRNA are useful as diagnostic markers. This severely limits clinical applicability.

Diagnostic Odds Ratio (DOR) of positive likelihood Ratio (PLR)

Another point of consideration would be the Diagnostic Odds Ratio (DOR) of Positive Likelihood Ratio (PLR). At first glance, the pooled DOR of PLR for miRNAs in OSCC indicates strong diagnostic effects; however, further observations show that four studies were included to generate the final results [4]. A DOR of 4.31 (according to the authors results for PLR) means there is an approximately 260% increase in the odds of (the probability of having) OSCC, given a positive miRNA expression test result [5]. Additionally, when we consider that even better established clinical indicators such as perineural invasion and lymph node ratio are associated with ORs for the diagnostic impact of < 2.8, the conclusions reached by Rapado-Gonzalez *et al.*'s studies, seems imprecise and requires further clinical validation [6,7].

Threshold effect of diagnostic value of miRNAs and analysis of heterogeneity

A use of Cochran's Q test and Higgins I^2 statistic is not recommended in diagnostic test accuracy of miRNAs in Liquid Biopsy for Oral Squamous Cell Carcinoma to estimate an existence and degree of heterogeneity since they do not account for study variation due to threshold effect [8]. It is recommended to estimate the degree of closeness of 16 included studies results to SROC, as well as by evaluating how much more substantial 95% prediction regions are matched with 95% confidence regions [9–11].

We also recommend that the meta-analysis could be improved from the inclusion of the Tau square statistics. Though the Chi-square and I-square are informative, they may not be enough because they do not consider the threshold effects. Considering the between-study heterogeneity in diagnostic parameters and applications of a random-effects model for meta-analysis, Tau Square, as the parameter calculating heterogeneity between the diagnostic effects of miRNA test accuracy, could potentially improve the clarity of the results obtained from Rapado-Gonzalez et al. [12].

Effects of individual miRNAs

It is also observed that the subgroup analysis conducted in the current study is not stratified based on the type of miRNA. Therefore, as multiple different miRNAs are pooled together into a single analysis, the pathophysiological effects are assumed to be overlapping, when in actuality, the effects of individual miRNAs are distinct [13]. This is a major assumption that has not been addressed by the authors and serves to hinder the objective of the study.

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Different liquid biopsies having a comparable miRNA

Furthermore, the assumption of miRNA from different samples (such as saliva, blood, etc.) having a comparable miRNA is also proposed as questionable. Studies have shown that the frequency of miRNA signatures varies between different body sources, and comparing these can lead to misleading conclusions [14], a limitation that needs addressing.

Comparison with the previous meta-analysis

Finally, considering that other similar systematic-review and meta-analyses studies exist, focusing on closely associated/overlapping topics such as Head and Neck cancer (inclusive of OSCC) and prognosis/diagnosis, the purpose of this study needs to be clearly defined, particularly in-context to these other similar studies [3]. Especially considering that Rapado-Gonzalez *et al.*'s paper shares literature with these previous studies, while also drawing from a much smaller pool of research.

We feel that above points should be addressed. Given the current relevance of this field to clinical medicine/treatment, it is crucial that the research that fuels it is free of any possible reproach when under scientific scrutiny.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data and materials

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Authors' contributions

RJ predominantly conceived this review and led the development of the letter to the editor. Both RJ and CK wrote the first draft of the letter, and GR, RRM, SKG, HCC, and PS critically revised and edited successive drafts of the manuscript. RJ, CK, GR, RRM, SKG, HCC and PS read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Rama Jayaraj (PhD, MPH)[a,g,*], Chellan Kumaraswamy[b], Greg Raymond[c], M. Ravishankar Ram[d], Suresh Kumar Govind[e], Harish C. Chandramoorthy[f], Peter Shaw[a]

[a] *Department of Artificial Intelligence, Nanjing University of Information Science and Technology (NUIST), Jiangsu, China*

[b] *School of Public Health, The University of Adelaide, North Terrace Campus, Adelaide, SA 5005, Australia*

[c] *Flinders University Northern Territory Medical Program, CDU Campus, Ellengowan Drive, Darwin, Northern Territory 0909, Australia*

[d] *Department of Genetics and Molecular Biology, Institute of Biological Sciences, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia*

[e] *Department of Parasitology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia*

[f] *Department of Microbiology and Clinical Parasitology, College of Medicine, King Khalid University, PO. Box # 641, 61421 Abha, Saudi Arabia*

[g] *Theme Lead -Health Profession and Society – Advanced Studies, Northern Territory Medical Program (NTMP), College of Medicine and Public Health, Flinders University, CDU Campus, Ellengowan Drive, Darwin, Northern Territory 0909, Australia*

E-mail addresses: Rama.Jayaraj@flinders.edu.au (R. Jayaraj), greg.raymond@flinders.edu.au (G. Raymond), mravishankarram@um.edu.my (M. Ravishankar Ram), suresh@um.edu.my (S.K. Govind), hshkonda@kku.edu.sa (H.C. Chandramoorthy), 100001@nuist.edu.cn (P. Shaw).

[*] Corresponding author at: Department of Artificial Intelligence, Nanjing University of Information Science and Technology (NUIST), Jiangsu, China.