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Letter to the editor

Prognostic significance of Lymph Node Ratio (LNR): Clinical insights and strategies for routine clinical practice

To the Editor,

Huang and colleagues have provided some valuable insights into the utility of Lymph Node Ratio (LNR) as a prognostic variable in Oral Squamous Cell Carcinoma, via their systematic review and meta-analysis study, published in the Journal of Oral Oncology [1]. Using the results of the study, the authors draw upon the conclusion that LNR may be a viable independent biomarker in OSCC. Although these conclusions are valid in the context of a said singular study conducted by Huang et al., other studies have presented varying clinical results and findings. We believe that highlighting these studies should be able to provide a better perspective on the clinical considerations of Huang and colleagues' study.

Is LNR an independent or additional prognosticator?

In 2014, a study conducted by Künzel et al. validated the prognostic utility of LNR in oral cavity cancer. However, they did not present it as an independent prognostic marker, stating that it was an additional prognostic factor to be used alongside other established prognostic factor [2]. Similarly, another study by Roberts et al. in 2016, performed a comparative analysis of the prognostic utility of positive Lymph Node number (pN), LNR and American Joint Committee on Cancer (AJCC) N staging. The resulting data showed that LNR and AJCC trailed behind pN in prognostic efficacy, with pN providing the highest overall prognostic value [3]. However, a study by Ding and colleagues, published in 2018, conforms to Huang et al.'s study, suggesting that LNR was a robust prognostic factor in oral cavity cancer, with implications for risk stratifications [4]. Although it is well documented that LNR is a powerful prognostic tool in oral cancers, the debate as to whether it capable of being used as an independent prognostic marker, or must be integrated into a panel of similar prognostic markers, is still ongoing, and must be considered to give adequate perspective to the results of Huang et al.'s study.

Comprehensive publication bias of literature based meta-analysis

Additionally, we also recommend that the authors present their analysis of publication bias in the form of Funnel Plots in their study, or at least as supplementary data, as this would greatly benefit readers. Fig. 1 and Table 1 depicts the publication bias analysis performed in Huang et al.'s study, in the form of a Funnel Plot.

Study protocol registration

We would also recommend that future systematic reviews and meta-analysis protocols use the PROSPERO database to register their protocols, prior to conducting of the review, as it offers an additional level of dissemination to the study being performed [5].

Measurement of heterogeneity of the included studies

Furthermore, as the I^2 statistic has the potential for bias in the small meta-analysis, we suggest that the authors use the Cochran's Q and Tau^2 parameters for adding additional reliability to their measurement of heterogeneity [6–10].

We hope that the points presented are able to give context to Huang et al.' study with regards to the current sphere of research and future clinical utility, and will serve to benefit readers and future researchers.

Both Classic and the Orwin fail-safe N informs the likelihood that studies are absent from the meta-analysis and that these studies if included in the analysis, would shift the estimated effect size of HR of LNR prognostic value toward the null. Big studies tend to be included in the meta-analysis regardless of their prognostic effect. Given this circumstances, there will be an inverse correlation between study size and effect size. Begg and Mazumdar rank order correlation was computed (Kendall's tau b) between the intervention effect and the standard error (which is driven primarily by sample size). Duval and Tweedie's Trim and Fill test sanctions imputing the missing studies that are likely to fall, add them to the analysis, and then recompute the combined prognostic effects of LNR.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors confirmed that they have no competing interests.

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Authors' contributions

RJ is chiefly conceived of this critical idea and review and led the development of the letter to the editor. Both RJ and CK wrote the first

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Table 1
Table 4: Publication bias of the included studies of LNR prognosis.

Groups	Clinical outcomes	Classic fail-safe N		Orwin fail-safe N	Begg and Mazumdar			Duval and Tweedie – Q value
		Z value for observed studies	P value for observed studies	HR	Tau with continuity correction	Z value with continuity correction	P value − 2 tailed	
Group 1	pN+ Group A Overall Survival	6.829	0	1.931	0	0	1	18.034
Group2	pN+ Group A Disease-specific Survival	7.705	0	1.785	0	0	1	25.489
Group 3	pN+ Group A Disease free Survival	5.814	0	2.269	0	0	1	1.748
Group 4	pN- & pN+ Group B Overall survival	9.985	0	2.588	0.472	1.772	0.076	18.113
Group 5	pN- & pN+ Group B Disease-specific survival	7.271	2.733	2.733	0	0	1	10.143
Group 6	pN- & pN+ Group B Disease free survival	6.01361	0	1.881	0.6667	1.04447	0.29627	13.443
Group 7	pN- & pN+ Group B Locoregional Disease free survival	8.889	0	5.213	0.1666	0.339	0.734	2.216

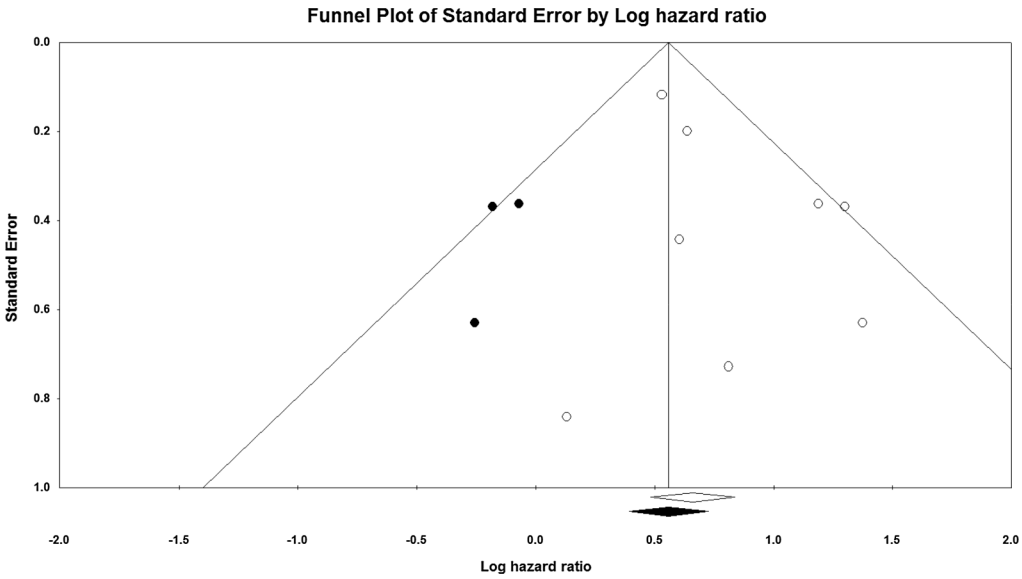

Fig. 1. Funnel plot of observed and imputed studies of pN+ Group a overall survival. This figure represents the possible bias between the included studies concerning pN+ Group A Overall Survival. Each point in the funnel plot represents an individual cohort or study and this plot has been constructed utilising CMA Software (Version 3.3.070, USA).

draft of the letter, and SS, KL and MRM critically revised and edited successive drafts of the manuscript. RJ, CK, SS, MRM, RN, GKM, and SS read and approved the final version of the manuscript.

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