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Meta-Analysis

Associations Between Clinicopathological Factors and Insulin-Like Growth Factor II mRNA-Binding Protein 3 Expression in Oral Squamous Cell Carcinoma: A Meta-Analysis

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Abstract

Objective: Insulin-like growth factor II mRNA-binding protein 3 (IMP3) is reportedly overexpressed in multiple cancer types, but its significance remains unknown. The aim of this meta-analysis was to clarify the relationships between IMP3 expression and clinicopathological factors in oral squamous cell carcinoma (OSCC). **Methods:** PubMed and Web of Science were searched for published studies that evaluated the relationships between IMP3 expression and clinicopathological factors until August 8, 2023. **Results:** Three studies comprising 383 patients were included in the analysis. No correlations between IMP3 expression in OSCC and TNM stage (odds ratio [OR]=2.03; 95% confidence interval [CI], 0.99-4.17; I^2=49%; p=0.05) and gender (OR=0.64; 95% CI, 0.34-1.20; I^2=29%; p=0.17) were detected in the meta-analysis. However, the heterogeneity was moderate, and the influence of publication bias was considered in this analysis. **Conclusion:** IMP3 expression was not related to the TNM stage or gender. However, additional studies and further clarifications of the functions of IMP3 are required to elucidate the relationship between IMP3 expression and the clinicopathological findings of OSCC in the future.

Keywords: *oral squamous cell carcinoma; IMP3; clinicopathological parameters; meta-analysis*

Background

Oral cancer accounts for almost 2% of all cancers [1] and the age-adjusted mortality rates caused by this malignancy have shown an increasing trend over the last decade [2]. Oral squamous cell carcinoma (OSCC) is the most common histological type of oral cancer, and surgical resection is the standard treatment for this disease. Patients with advanced cancer have a significantly worse quality of life than those with early cancer [3]. The identification of immune-positive markers associated with the clinicopathological factors in oral cancer is important because preoperative searches can be conducted to guide the treatment strategies.

Insulin-like growth factor II mRNA-binding protein 3 (IMP3) is a common biomarker for various cancers, including pancreatic cancer [4], lung cancer [5], renal cell carcinoma [6,7], and hepatocellular carcinoma [8]. It is associated with tumor cell proliferation [5,9], invasion [10], and metastasis [6-10]. Although there are several reports on the expression of this protein in OSCC [11-13], its significance remains unclear. The aim of this meta-analysis was to evaluate the associations between IMP3 expression and the clinicopathological factors in OSCC.

Methods

Search strategy

The meta-analysis was performed in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement [14]. The PubMed and Web of Science databases were evaluated for articles that evaluated

the relationships between IMP3 expression and the clinicopathological factors in OSCC until August 8, 2023. Additionally, the reference lists of the included papers were searched. The following search keywords were used: "oral squamous cell carcinoma," "IMP3," "Insulin-like growth factor II mRNA-binding protein 3," and "clinicopathological".

Eligibility criteria

Studies that examined the relationship between the clinicopathological factors and IMP3 expression via immunostaining in surgical OSCC specimens were selected. Studies published in languages other than Japanese or English, those that used cultured cells or animal experiments, case reports, and articles lacking data on the relationships between the clinicopathological factors and IMP3 expression were excluded from this meta-analysis.

Statistical analysis

The statistical analysis was performed using Review Manager 5.4 (Cochrane Collaboration, Oxford, UK). A random effects model was used due to the presumed population differences among the included studies; the effect estimates are presented with the 95% confidence interval (CI) values. The intervention effects were measured using odds ratios, and the heterogeneity among studies was calculated using the I^2 values. Publication bias was assessed using funnel plots for the primary endpoint.

Results

Study selection

Four studies were identified from the PubMed database, and one was identified from the Web of Science database (Figure 1). The full texts of a total of five articles were reviewed, out of which two did not examine the relationship between the clinicopathological factors and IMP3 in OSCC. Finally, three articles comprising a total of 383 patients were included in the analysis (Table 1).

Table 1. Characteristics of the studies included in this meta-analysis

S. No	First author	Population	Hospital facility	Period	No. of cases	IMP3 cut-off	Reference
1	Li S	South Korea	Severance hospital of south Korea	Jan 1994 - Dec 2002	96	30%	[11]
2	Clauditz TS	Germany	University medical Center Hamburg-Eppendorf	NA	222	> 0%	[12]
3	Li HG	China	Sun Yat-sen Memorial Hospital	1999 - 2006	65	> 0%	[13]

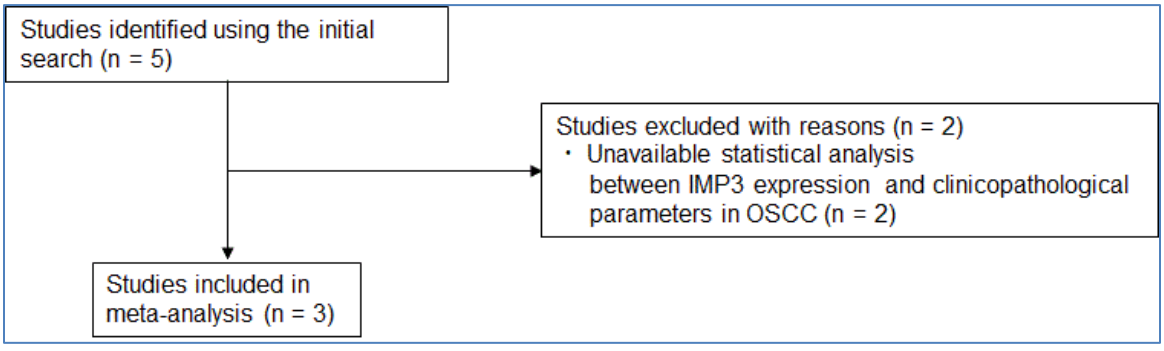

Figure 1. Flow chart showing the selection of studies for inclusion in this meta-analysis

Relationships between the clinicopathological factors and IMP3 expression

IMP3 expression in OSCC was not significantly affected by the TNM stage (OR=2.03; 95% CI, 0.99-4.17; I^2=49%; *p*=0.05; Figure 2A, Table 2) and gender (OR=0.64; 95% CI, 0.34-1.20; I^2=29%; p=0.17; Figure 2B, Table 2). Meta-analyses for other pathological factors, such as age, tumor differentiation, lymph node metastasis, and distant metastasis, were not performed due to data limitations. The funnel plot showed asymmetry, especially for the TNM stage, suggesting the possibility of publication bias (Figure 3).

Table 2. Meta-analysis results of enrolled IMP3 studies

Clinical parameters	Number of studies (number of patients)	OR (95%CI)	*p*-value
T stage (T1/2 *vs.* T3/4)	3 (301)	2.03(0.99-4.17)	0.05
Gender (male *vs.* female)	3 (306)	0.64(0.34-1.20)	0.17

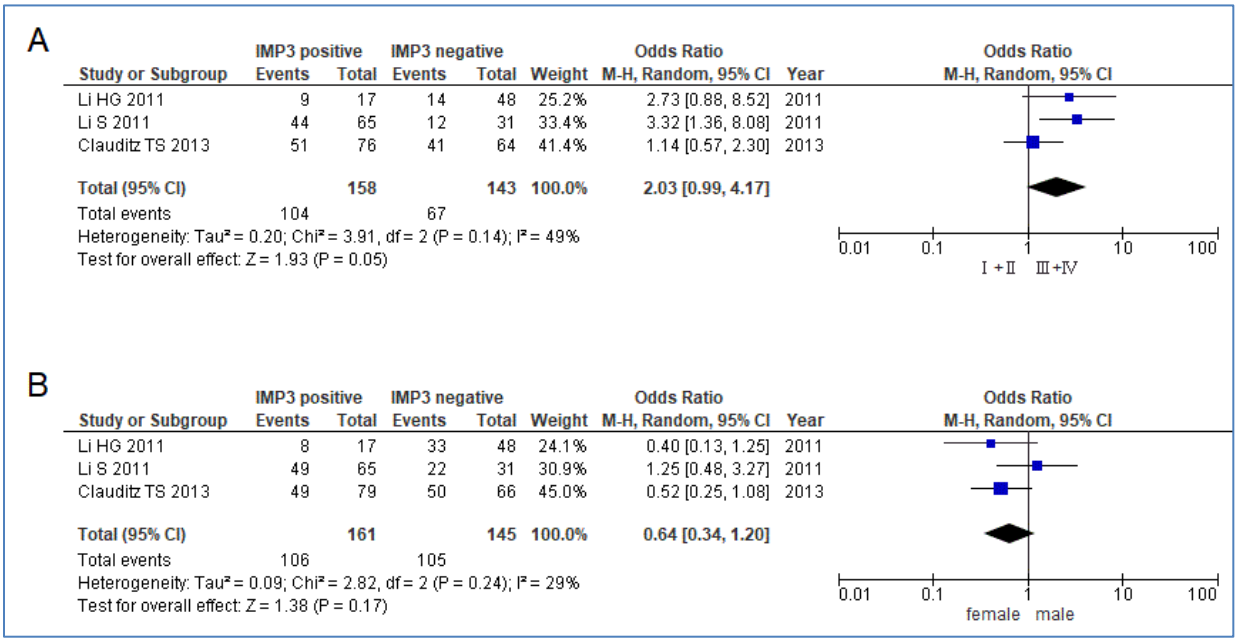

Figure 2. The meta-analysis for IMP3 expression and the clinicopathological parameters in OSCC. Forrest plots showing the correlations between IMP3 expression and TNM stage **(A)** and sex **(B)** in OSCC

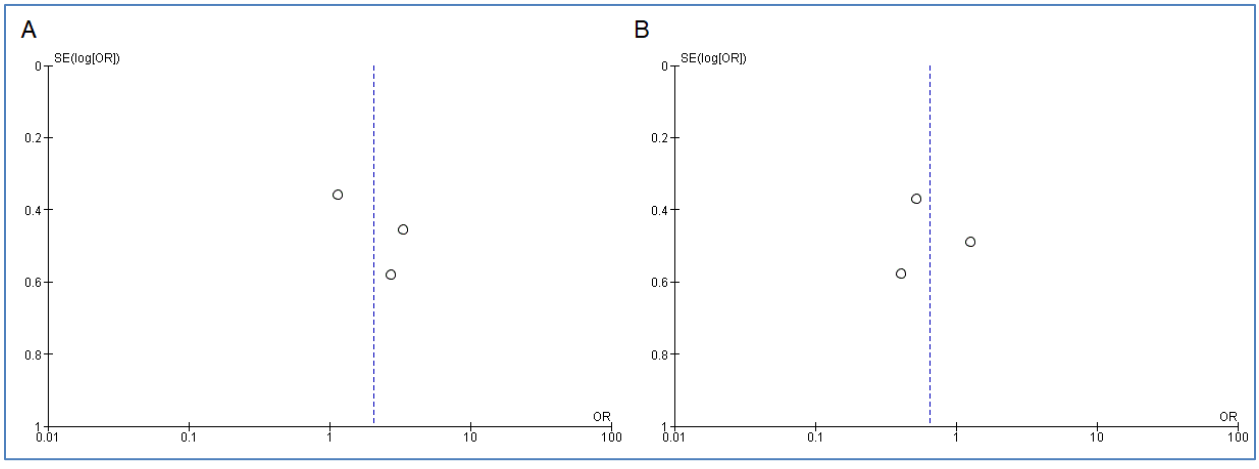

Figure 3. The funnel plot for CRP. (A) TNM stage and (B) sex

Discussion

IMP3 is an RNA-binding protein that binds to the mRNA as an insulin-like growth factor II (IGF-II) transcription factor [5,15]. The human IMP3 gene, located on chromosome 7p11.2 [16], is a member of the IMP family, which includes the IMP1, IMP2, and IMP3 genes [6]. This family of proteins plays a vital role in binding, transporting, and stabilizing the fetal subtypes of IGF-II mRNA during embryogenesis [17,18]. The IMP3 protein is widely expressed in human fetal tissues but is undetectable in normal adult tissues [4,17,19]. Furthermore, IMP3 is overexpressed in many cancers, including pancreatic cancer [15], renal cell carcinoma [6,7], endocervical carcinoma [20], endometrial carcinoma [21], ovarian cancer [22,23], and testicular cancer [24]. Although IMP3 overexpression is known to be associated with poor prognosis in ovarian carcinoma of clear cell subtype [22] and bile duct carcinoma [25], it is reported to be associated with improved prognosis in ovarian cancer [23]; however, the exact role of IMP3 in cancer remains unclear.

Li *et al.* reported that IMP3 overexpression is associated with tumor invasion and metastasis and is a poor prognostic factor in OSCC [11]. Another study demonstrated its association with carcinogenesis and cancer progression [9,26,27], particularly lymph node metastasis [13]. Furthermore, Clauditz *et al.* reported that IMP3 overexpression was associated with lymph node metastasis [12]. However, no association between IMP3 overexpression and TNM stage was observed in the present meta-analysis.

Notably, the number of articles evaluated in this meta-analysis was small, the heterogeneity was high, and the effect of publication bias cannot be denied in the funnel plot. The differences in race and the IMP3 immunostaining-positive cut-off may have influenced the heterogeneity in this study (Table 1).

Conclusions

Despite the limitations, this meta-analysis showed no associations between IMP3 expression and TNM stage or gender. Nonetheless, further studies elucidating the functions of IMP3 in OSCC are required to clarify the relationship between IMP3 expression and oral cancer.

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Conflicts of interest

The authors declare no conflict of interest.

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