

Review

Associations between preoperative fibrinogen levels and clinicopathological factors in oral squamous cell carcinoma: A meta-analysis

Akemi Inoue*, Toshihide Matsumoto*, Yuka Ito*,
Zehao Jiang*, †Hiroyuki Takahashi*

†Correspondence: Kitasato University School of Allied Health Sciences, 1-15-1 Kitazato Minimi-ku, Sagami-hara, Kanagawa 252-0373, Japan

E-mail: hitakaha@med.kitasato-u.ac.jp

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* Kitasato University, School of Allied Health Sciences

ABSTRACT

Objectives: There is a lack of consensus among researchers regarding the relationship between preoperative fibrinogen levels and clinicopathological factors in oral squamous cell carcinoma (OSCC). The aim of this meta-analysis was to evaluate and clarify these associations in OSCC.

Methods: The PubMed, Web of Science, and Embase databases were examined for studies that evaluated the relationships between preoperative fibrinogen level and clinicopathological factors until October 12, 2023.

Results: Three studies comprising a total of 509 patients were included in the analysis. No correlations between preoperative fibrinogen levels and gender (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.34–2.55; $I^2=78\%$; $p=0.89$), the pT category (OR, 2.52; 95% CI, 0.75–8.46; $I^2=81\%$; $p=0.13$), lymph node metastasis (OR, 0.75; 95% CI, 0.37–1.51; $I^2=52\%$; $p=0.41$), and TNM stage (OR, 1.59; 95% CI, 0.64–3.93; $I^2=73\%$; $p=0.32$) were observed in the meta-analysis. However, the heterogeneity was found to be high or very high. The influence of publication bias was considered in this analysis.

Conclusion: Preoperative fibrinogen levels were not related to gender, the pT category, lymph node metastasis, or TNM stage in OSCC. The lack of sufficient data may render the data integration unreliable. Therefore, additional studies with larger sample sizes and similar cut-off values are required to validate the findings of this study.

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Key Words

Oral squamous cell carcinoma, fibrinogen, clinicopathological parameters, meta-analysis

I. Introduction.....

In Japan, oral cancer accounts for almost 1% of all cancers¹⁾ and an increasing number of cancer-related deaths²⁾. Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer, and surgical resection is the most common treatment for this disease. Patients with advanced cancer have a significantly worse quality of life than those with early cancer³⁾.

Several methods, including assessments of the preoperative fibrinogen level, have been tested for the early

detection and prognostic prediction of oral cancer^{4)–6)}. There is a lack of consensus among studies on the relationship between preoperative fibrinogen levels and clinicopathological factors in OSCC. Therefore, this study meta-analysis was conducted to evaluate and clarify the aforementioned associations in OSCC.

II. Materials and methods.....

Search strategy

This meta-analysis was performed in accordance with the 2020 Preferred Reporting Items for Systematic Re-

views and Meta-analyses Statement⁷⁾. The PubMed, Web of Science, and Embase databases were searched to identify articles on the relationship between preoperative fibrinogen levels and clinicopathological factors in OSCC, published until August 3, 2023. The following search keywords were used: “oral squamous cell carcinoma” [AND] “fibrinogen.” We searched all fields in the literature. Additionally, the reference lists of the included papers were examined. 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 clinicopathological factors and preoperative fibrinogen level were excluded from this study.

Statistical analysis

Statistical analysis was performed using Review Manag-

er 5.4 (Cochrane Collaboration, Oxford, UK) to combine the data and the effect estimate. A random effects model was used due to the presumed population differences among the included studies. The effect estimates are presented with their 95% confidence intervals (CIs). The intervention effects were measured using odds ratios (ORs), and the heterogeneity among studies was calculated using the I^2 values. Publication bias was assessed using funnel plots for the primary endpoint.

III. Results.....

Study selection

A total of 50, 24, and 69 studies were identified from the PubMed, Web of Science, and Embase databases (**Figure 1**). In the primary screening, the titles and abstracts were examined to exclude review articles, studies with

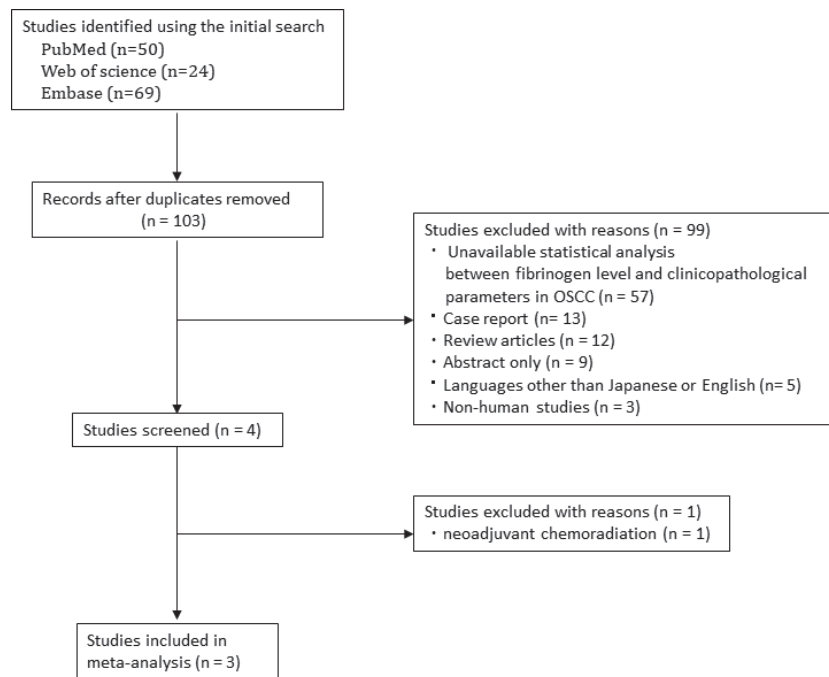


Figure 1 Flow chart for the selection of studies in this meta-analysis. OSCC, oral squamous cell carcinoma.

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

No.	First author	Journal (year)	Population	Hospital facility	Period	No. of cases.	FIB cut-off
1	Liang YJ	BMC Cancer. (2021)	China	Guanghua Hospital of Stomatology	January 2015 - December 2018	202	3.33 (g/L)
2	Caruntu A	Cancers (Basel). (2021)	Romania	Carol Davila Central Military Emergency Hospital	2016 - 2019	223	525 (mg/dL)
3	Inoue A	Hum Pathol. (2022)	Japan	Kitasato University Hospital	2014 - 2016	84	342 (mg/dL)

no., number; FIB, fibrinogen.

inappropriate research designs, non-human studies, and those published in languages other than Japanese and English. Of the five studies remaining after primary screening, two were excluded due to cases of advanced cancer or treatment by neoadjuvant chemoradiation. Finally, three articles with a total of 509 patients were included in the analysis (Table 1). Relationships between clinicopathological factors and preoperative fibrinogen levels.

The preoperative fibrinogen levels were not associated with gender (OR, 0.93; 95% CI, 0.34–2.55; $I^2=78\%$; $p=0.89$; Figure 2A), the pT category (OR, 2.52; 95% CI, 0.75–8.46; $I^2=81\%$; $p=0.13$; Figure 2B), which indicates the size or local extent of the primary tumor, lymph node metastasis (OR, 0.75; 95% CI, 0.37–1.51; $I^2=52\%$; $p=0.41$; Figure 2C), and TNM stage (OR, 1.59; 95% CI, 0.64–3.93; $I^2=73\%$; $p=0.32$; Figure 2D). Associations between fibrinogen levels and other clinicopathological factors, such as age and tumor differentiation, could not

be analyzed due to a lack of data. The heterogeneity, demonstrated by the I^2 values, was high or very high. The funnel plots for gender, the pT category, lymph node metastasis, and TMN stage demonstrated asymmetry, suggesting the possibility of publication bias (Figure 3).

IV. Discussion.....

Fibrinogen is a blood coagulation factor produced in the liver; it is converted into fibrin by thrombin to form fibers and strong fibrin clots⁸⁾⁹⁾. The expression of this classic acute phase reactant is considerably increased in the liver and blood during inflammatory conditions¹⁰⁾. In addition, hyperfibrinogenemia and a cancer-associated systemic inflammatory response are strongly associated with cancer progression and prognosis¹¹⁾. A meta-analysis of 17 studies revealed that higher pretreatment plasma fibrinogen levels predicted poor overall survival (OS) and disease- or progression-free survival in patients with

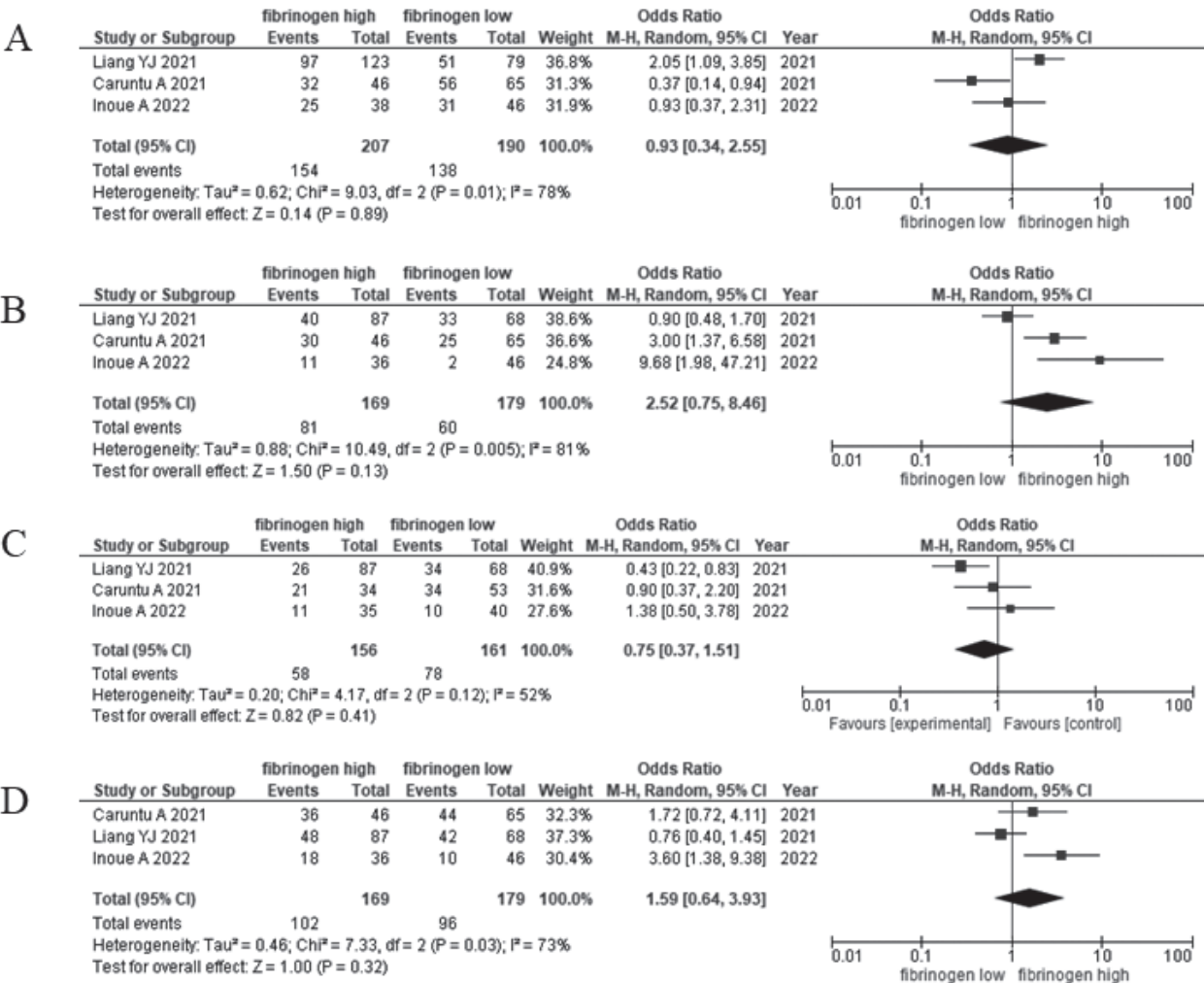


Figure 2 Meta-analysis for the fibrinogen level and clinicopathological parameters in OSCC. Forest plots showing the correlations between fibrinogen levels and gender (A), the pT category (B), lymph node metastasis (C), and TNM stage (D) in OSCC.

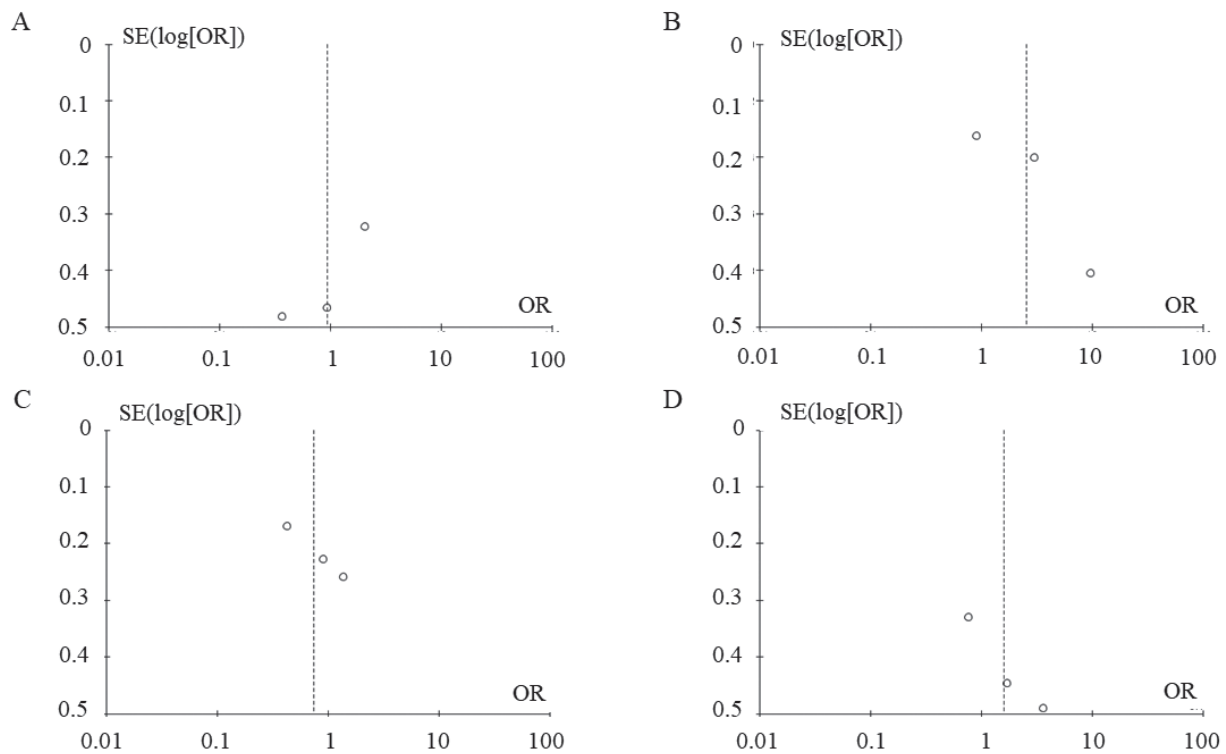


Figure 3 Funnel plots for the fibrinogen levels. (A) gender, (B) pathological pT category, (C) lymph node metastasis, and (D) TNM stage.

lung cancer¹²⁾. In a recent study, preoperative fibrinogen levels in colorectal cancer were correlated with several clinicopathological factors, including age, tumor differentiation status, tumor location, pT category, and TNM stage; moreover, an elevated fibrinogen level was independently correlated with poor OS and cancer-specific survival¹³⁾. However, no clear conclusions regarding the relationship between preoperative fibrinogen values and clinicopathological factors in OSCC have been reached.

In the current study, the preoperative fibrinogen levels were not associated with the clinicopathological features of OSCC. Inoue et al. and Caruntu et al. reported high preoperative fibrinogen levels and the pT category in OSCC^{5) 6)}. High preoperative fibrinogen levels were detected in many patients with advanced TNM stages in the studies by Liang et al.; additionally, several cases of lymph node metastasis due to the high preoperative fibrinogen levels were reported⁴⁾. Furthermore, according to Liang et al.⁴⁾, high levels of preoperative fibrinogen were more common in men, but no significant difference based on sex was observed in the studies by Inoue et al. and Caruntu et al.^{5) 6)}. Despite the concordant and inconsistent reports on the relationship between preoperative fibrinogen levels and clinicopathological factors, the I^2 statistics in all studies showed high or very high hetero-

geneity in OSCC.

One of the limitations of the current meta-analysis was the difference in the cut-off values that separated the high and low fibrinogen values in each study. Moreover, the number of articles included in this meta-analysis was low, resulting in high heterogeneity and publication bias. Nevertheless, our results indicate that preoperative fibrinogen measurement may not be useful in determining the treatment strategy. Additional studies using similar cut-off values and larger sample sizes are necessary to validate the findings of this study.

Abnormalities in the blood coagulation and fibrinolysis system are frequently observed in patients with malignant tumors, and these abnormalities are linked to the progression of DIC and thrombosis¹⁴⁾. In addition, the fibrinolysis system affects the growth and metastasis of malignant tumors¹⁵⁾. Several thrombin-related factors, such as plasminogen activator inhibitor-1 polymorphism¹⁶⁾, the low-production allele of the VEGF +936C/T polymorphism¹⁷⁾, coagulation factor XIII¹⁸⁾, and the 1040C/T polymorphism influencing thermal stability and activity of thrombin activatable fibrinolysis inhibitor¹⁹⁾, have been linked to oral carcinogenesis. As previously described, there are few reports on the relationships of the blood coagulation and fibrinolysis system with ma-

lignancy, including studies on fibrinogen in malignant tumors of the oral region.

V. Conclusions.....

Despite the limitations of this study, no associations of fibrinogen levels with gender, the pT category, lymph node metastasis, or TNM stage were observed. Nonetheless, further studies on the blood coagulation and fibrinolysis system, including fibrinogen, are required to confirm these findings in OSCC.

Conflicts of interest: none.

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