

Supplementary information to the manuscript

Prognostic and Clinicopathological Significance of Epidermal Growth Factor Receptor (EGFR) Expression in Oral Squamous Cell Carcinoma: Systematic Review and Meta-Analysis

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1. Search strategy

Table S1. Search strategy for each database, number of results, and execution date.

Database	Query/Search Strategy	Results/ Items found	Search time limits
PubMed	("Genes, erbB-1"[Mesh] OR "epidermal growth factor receptor"[all fields] OR "EGFR"[all fields] OR "erbb1"[all fields] OR "cerbb1"[all fields] OR "her1"[all fields] OR "pEGFR"[all fields] OR "phospho-EGFR"[all fields]) AND ("mouth"[MeSH] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("carcinoma, squamous cell"[MeSH] OR ("carcinoma"[All Fields] AND "squamous"[All Fields] AND "cell"[All Fields]) OR "squamous cell carcinoma"[All Fields] OR "Neoplasms"[Mesh] OR neopla*[All Fields] OR "cancer"[All Fields])	3192	November, 2022
Embase	('epidermal growth factor receptor'/exp OR 'epidermal growth factor receptor' OR 'EGFR' OR 'erbb1' OR 'cerbb1' OR 'her1' OR 'pEGFR' OR 'phospho-EGFR') AND ('mouth'/exp OR 'mouth') AND ('squamous cell carcinoma'/exp OR 'carcinoma' OR 'malignant neoplasm'/exp OR 'neoplas*' OR 'cancer')	2415	November, 2022
Web of Science	TS=("epidermal growth factor receptor" OR "EGFR" OR "erbb1" OR "cerbb1" OR "her1" OR "pEGFR" OR "phopho-EGFR") AND TS=("mouth") AND TS=("squamous cell carcinoma" OR neoplas* or "cancer")	5576	November, 2022
Scopus	TITLE-ABS-KEY("epidermal growth factor receptor" OR "EGFR" OR "erbb1" OR "cerbb1" OR "her1" OR "pEGFR" OR "phopho-EGFR") AND ("mouth" OR "oral") AND ("squamous cell carcinoma" OR neoplas* or "cancer")	1618	November, 2022
Total	12801		

2. Table S2. Characteristics of analyzed studies (n = 50).

Study	Year	Country	Publ. language	Study design	Recruitment period	Follow up m, mean±SD (range)	Sample Size, n	Sex M, n (%) F, n (%)	Age, mean±SD (range)	Tumour subsites	Tobacco, n (%)	Alcohol, n (%)	Areca, n (%)	Methods	Anti-EGFR antibody (clonality)	Dilution, incubation time, temperature, antigen retrieval	IHQ pattern	IHQ cutoff point (%)	EGFR + (%)
Mohanapure et al.	2022	India	English	Retrospective	2015-2019	NR	70	M: 47 (67.14) F: 23 (32.86)	52.86 (35-75)	Buccal mucosa Gingiva Hard palate Lip Retromolar trigone Tongue	41 (58.57)	21 (30)	7 (10)	IHQ	Clone EP-22 (monoclonal)	NR	Membrane	10	65 (92.86)
Wongpattaraworakul et al.	2022	United States	English	Retrospective	2005-2014	107 ± 37	143 Missing=3	M: 85 (58.22) F: 61 (41.78)	NR	Floor of mouth Gingiva Tongue Other	64 (44.14)	NR	NR	IHQ	Clone H11 (monoclonal)	1:200 NR NR	NR	10	59 (41.26)
Moratin et al.	2021	Germany	English	Retrospective	2010-2016	NR	222	M: 137 (61.7) F: 85 (38.3)	64.3 ± 11.1 (27-88)	Buccal mucosa Floor of mouth Lip Mandible Maxilla Oropharynx Tongue	NR	NR	NR	IHQ	D38B1 (monoclonal)	NR	Cytoplasm	33	NR
Pansini et al.	2021	Brazil	English	Retrospective	2010-2017	NR	97	M: 85 (72.0) F: 24 (20.3)	60	Buccal mucosa Floor of mouth Gingiva Hard palate Retromolar trigone Tongue Vestibule of mouth	51 (43.2)	52 (44.1)	NR	IHQ	D38B1 (monoclonal)	1:100 2-5 min Room temperature	Membrane Cytoplasm	Labelling index (intensity x cell count)	50 (51.55)
Tseng et al.	2021	Taiwan	English	Retrospective	1993-2006	60	429	NR	NR	NR	NR	NR	NR	IHQ	NR	1:50 Overnight 4°C	Membrane	NR	105 (24.48)
Sajjanar et al.	2020	India	English	Retrospective	NR	NR	34	M: 23 (67.65) F: 11 (32.35)	46.8 (23-65)	Buccal mucosa Gingiva Tongue Other	NR	NR	NR	IHQ	HPA018530 (polyclonal)	1:100 60 min NR	Membrane	Labelling index (intensity x cell count)	21 (61.76)
Shahsavari et al.	2020	Iran	English	Retrospective	NR	NR	46	M:25 (54.3) F:21 (45.7)	58.63±10.65	NR	NR	NR	NR	IHQ	NR	1:10 60 min NR	Membrane	10	17 (73.91)
Kappler et al.	2020	Germany	English	Retrospective	1998-2002	NR	45	M:31 (68.89) F:14 (31.11)	57	NR	NR	NR	NR	IHQ	D38B1 (monoclonal)	1:50 NR NR	Membrane	10	9 (20)
Yokokawa et al.	2020	Japan	English	Retrospective	NR	60	208	M:129 (62) F:79 (38)	59.1	Buccal mucosa Floor of mouth Gingiva	110 (52.9) Missing=10	141 (67.8) Missing=11	NR	IHQ	D38B1 (monoclonal)	NR 60 min Room temperature	Membrane	Labelling index (Intensity)	60 (28.85)
Etemad-Moghadam and Alaeddini	2019	Iran	English	Retrospective	NR	NR	50	M:28 (58.33) F:20 (41.67) Missing=2	63.3	NR	NR	NR	NR	IHQ	Clone H11 (monoclonal)	1:50 60 min NR	Membrane	Labelling index (intensity-cell count)	28 (56)

Rajan et al.	2019	United States	English	Retrospective	2005-2014	NR (NR- 157)	141	M: 82 (58.16) F: 59 (41.84)	62 (19-81)	Floor of mouth Gingiva Tongue Other	92	NR	NR	IHQ	Clone H11 (monoclonal)	1:200 30 min Room temperature	Membrane	10	71 (50.35)
Gurin et al.	2018	Czech Republic	English	Retrospective	2007-2012	62.7 (54.9-69.9)	77	M: 65 (84.4) F: 12 (15.6)	58.3 (39.6-72.3)	Oropharynx Tongue Other	NR	NR	NR	IHQ	Clone 5B7 (monoclonal)	NR	Membrane	10	37 (48.05)
Owusu-Afriyie et al.	2018	Ghan	English	Retrospective	2006-2014	NR	28	M:19 (67.86) F: 9 (32.14)	55.07 ± 17.33	NR	NR	NR	NR	IHQ	NR	NR	NR	Labelling index (intensity-cell count)	17 (60.71)
Singla et al.	2018	India	English	Retrospective	NR	NR	40	NR	NR	NR	NR	NR	NR	NR	NR	NR	Membrane	10	39 (97.5)
Christensen et al.	2017	Denmark	English	Retrospective	2000-2012	61.2 (1.2-190.8)	191	M: 126 (66) F: 65 (34)	Median 59 (23-89)	Floor of mouth Tongue	159 (83)	NR	NR	IHQ	NR	NR 32 min NR	NR	Labelling index (intensity-cell count)	77 (40.31)
Huang et al.	2017	Taiwan	English	Retrospective	1997 - 2004	96	135 Missing= 59	M:194 (100) F: 0 (0)	49.28 ± 11.34	NR	175 (90.2)	132	175	IHQ	Clone 25 (monoclonal)	1:100 NR NR	Membrane Cytoplasm Nuclear	Labelling index	48 (35.56)
Kimura et al.	2016	Japan	English	Retrospective	1998-2008	NR	24	NR	64.4 ± 11.2 (43-89)	NR	NR	NR	NR	IHQ	Clone 2-18C9 (monoclonal)	NR	Membrane Cytoplasm	10	14 (58.33)
Solomon et al.	2016	India	English	Retrospective	2008-2013	(18-60)	178	M:141 (79.21) F: 37 (20.79)	54.51 ± 13.43 (24-80)	NR	NR	NR	NR	IHQ	Clone 2-18C9 (monoclonal)	1:40 Overnight 4°C	Membrane	Labelling index (intensity + cell count)	150 (84.27)
de Andrade et al.	2015	Brazil	English	Retrospective	NR	NR	45	NR	NR	Buccal mucosa Gingiva Oropharynx Palate Retromolar trigone Tongue	NR	NR	NR	IHQ	Clone SP9 (monoclonal)	1:200 60 min Room Temperature	Membrane	51	36 (80)
Gupta et al.	2015	India	English	Retrospective	2009-2011	NR (NR-24)	120	M: 96 (80) F: 24 (20)	49.48 ± 12.19 (20-67)	Buccal mucosa Gingiva Hard palate Lip Retromolar trigone Tongue	NR	NR	NR	IHQ	Clone EP-22 (monoclonal)	NR Overnight 4°C	Membrane Cytoplasm	50	87 (72.5)
Gröbe et al.	2014	Germany	English	Retrospective	1998-2008	NR (NR-120)	206	M: 150 (72.82) F: 56 (27.18)	56 (20-93)	Buccal mucosa Floor of mouth Tongue Maxilla	NR	NR	NR	IHQ	Clone 2-18C9 (monoclonal)	0 NR NR	Membrane Cytoplasm Nuclear	Labelling index (intensity x cell count)	196 (95.15)
Monteiro et al.	2014	Portugal	English	Retrospective	2000-2006	39.6 ± 33.1 (1-142)	74 Missing= 1	M:55 (74.32) F:19 (25.68)	62.3 ± 15.6 (25-96)	Buccal mucosa Floor of mouth Gingiva Hard palate Lip Retromolar trigone Tongue	NR	NR	NR	IHQ	Clone 25 (monoclonal)	1:100 60min Room Temperature	Membrane	Labelling index (intensity x cell count)	68 (93.15)
Silva et al.	2014	Brazil	English	Retrospective	NR	120	82	M:70 (85.37) F:12 (14.63)	54.8 (38-78)	NR	67 (92.1)	63 (87.5)	NR	IHQ	NR	1:400 Overnight 4°C	Membrane	Labelling index (intensity x cell count)	38 (50)

Bernardes et al.	2013	Brazil	English	Retrospective	NR	6	52	M:12 (23.08) F: 40 (76.92)	56.3	Buccal mucosa Floor of mouth Gingiva Palate Tongue	24	27	NR	IHQ	Clone 31G7 (monoclonal)	1:100 60 min Room temperature	Membrane	10%	29 (55.77)
Perisanidis et al.	2013	Austria	English	Retrospective	2000-2009	55.2	113	M:83 (73.45) F:30 (26.55)	Median 58 (24-79)	Oral cavity Oropharynx	94	83	NR	IHQ	NR	NR	Membrane	Labelling index (cell count x cell count)	112 (99.12)
Dadfarnia et al.	2012	United States	English	Retrospective	1992-2009	NR	16	M:11 (68.75) F:5 (31.25)	56.2 (40-73)	Floor of mouth Palate Retromolar trigone Tongue Tonsil	NR	NR	NR	IHQ	Clone H11 (monoclonal)	1:200 NR NR	Membrane	10%	3 (18.75)
Dragomir et al.	2012	Romania	English	Retrospective	2008-2011	NR	44	NR	NR	Lip Palate Tongue	NR	NR	NR	IHQ	NR	NR	Membrane Cytoplasm	0	33 (75)
Hanabata et al.	2012	Japan	English	Retrospective	NR	NR	52	M:35 (67.31) F:17 (32.69)	56.75 (23-84)	Tongue	NR	NR	NR	IHQ	sc-03 (polyclonal)	1:100 NR NR	NR	Labelling index (intensity x cell count)	46 (88.46)
Monteiro et al.	2012	Spain	English	Retrospective	1995-2003	NR	63 Missing= 4	M:52 (77.6) F: 15 (22.4)	59 ± 12.6 (31-85)	Buccal mucosa Floor of mouth Gingiva Hard palate Retromolar trigone Tongue	NR	NR	NR	IHQ	Clone 2-18C9 (monoclonal)	NR 30 min Room temperature	Membrane Cytoplasm	10	50 (79.37)
Won et al.	2012	South Korea	English	Retrospective	1995-2009	NR	60	M: 38 (63.3) F: 22 (36.7)	56.3 ± 12.1	Buccal mucosa Floor of mouth Palate Oropharynx Tongue Tonsil	36 (60)	NR	NR	IHQ	NR	NR	Membrane	Labelling index (intensity x cell count)	46 (76.67)
Nakata et al.	2011	Japan	English	Retrospective	1999-2009	NR (NR-128.5)	89	M:62 (69.66) F:27 (30.34)	NR	Tongue	40	29	NR	IHQ	Clone 31G7 (monoclonal)	1:50 NR NR	Membrane	50	73 (82.02)
Ryott et al.	2009	Sweedden	English	Retrospective	200-2004	36	78	M:45 (57.69) F:33 (42.31)	NR	Tongue	40	NR	NR	IHQ	Clone 31G7 (monoclonal)	NR	Membrane	Labelling index (intensity x cell count)	74 (94.87)
Shah et al.	2009	India	English	Retrospective	2000-2003	NR (24-NR)	135	M:101 (74.81) F:34 (25.19)	45 (28-75)	Buccal mucosa Tongue	110	NR	NR	IHQ	Clone 111.6 (monoclonal)	1:50 Overnight 4°C	Membrane Cytoplasm	10	81 (60)
Sheu et al.	2009	China	English	Retrospective	NR	60	115	NR	50.27 ± 11.38 (30-78)	Buccal mucosa Floor of mouth Gingiva Palate Tongue	106 (92.2)	69 (60)	101 (87.8)	IHQ	Clone 31G7 (monoclonal)	1:10 NR NR	NR	Labelling index (intensity)	29 (25.22)
Agra et al.	2008	Brazil	English	Retrospective	1990-2004	Median 11.94 (0.8-140.9)	111 Missing= 6	M:81 (72.97) F:30 (27.03)	Median 56 (31-90)	Buccal mucosa Floor of mouth Gingiva Lip Palate Retromolar trigone Tongue Tonsil	NR	NR	NR	IHQ	NR	NR	Membrane	0	82 (77.36)
Diniz-Freitas	2007	Spain	English	Retrospective	1995-2000	Median 37.80 (6-108)	47	M:39 (82.98) F:8 (17.02)	57.68 (31-85)	Buccal mucosa Floor of mouth Hard palate Retromolar trigone Tongue	NR	NR	NR	IHQ	Clone 2-18C9 (monoclonal)	NR 30 min NR	Membrane	Labelling index (intensity x cell count)	35 (74.47)

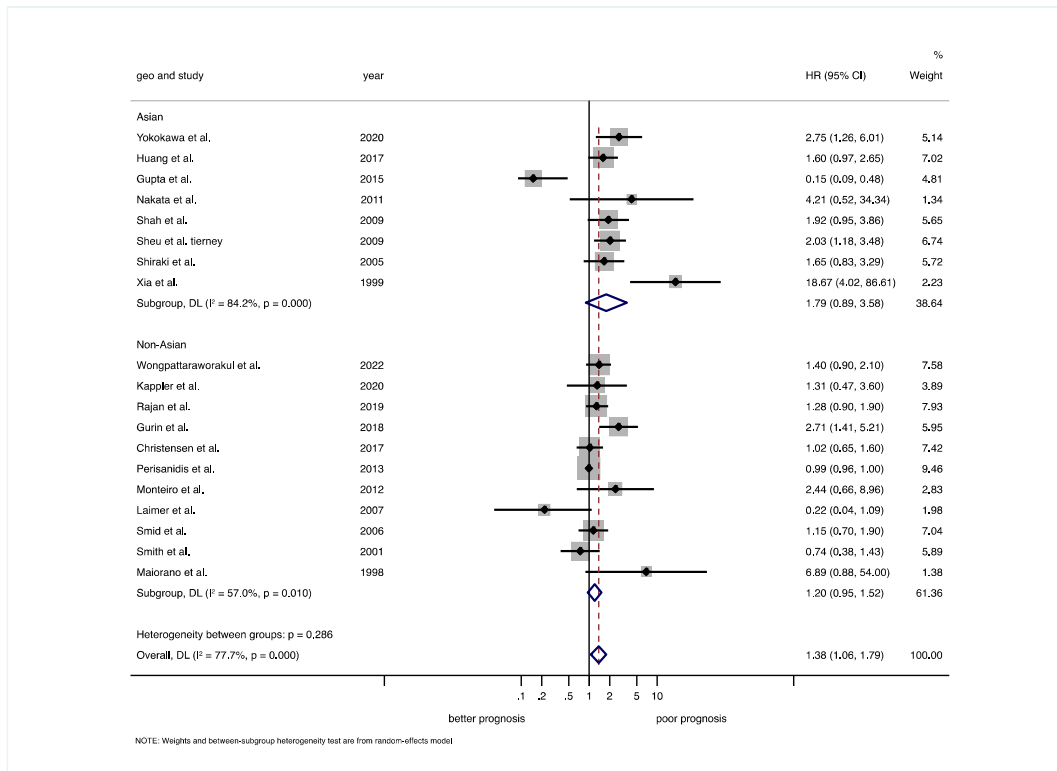
Laimer et al.	2007	Austria	English	Retrospective	1980-1997	NR (NR-88)	109	M: 83 (76.15) F: 26 (23.85)	Median 63.2 (25.6–86.8)	NR	NR	NR	NR	IHQ	NR	NR	Membrane	Labelling index (intensity x cell count)	100 (91.74)
Nestor et al.	2007	Sweedeen	English	Retrospective	NR	NR	9	NR	NR	Buccal mucosa Gingiva Tongue	NR	NR	NR	IHQ	Clone 31G7 (monoclonal)	1:40 NR 4°C	Membrane	Labelling index (intensity x cell count)	9 (100)
Hiraishi et al.	2006	Japan	English	Retrospective	1990-2002	NR	52	M:33 (63.46) F:19 (36.54)	67.5 (49-91)	Floor of mouth Gingiva Hard palate Maxillary sinus Oropharynx Tongue	NR	NR	NR	IHQ	NR	1:200 Overnight 4°C	NR	>0%	48 (92.31)
Smid et al.	2006	The Netherlands	English	Retrospective	1985-2000	NR (24-60)	165	M: 109 (66.06) F: 56 (33.94)	Median 58 (25–89)	NR	NR	NR	NR	IHQ	NR	1:20 Overnight NR	Membrane	Labelling index intensity	132 (80)
Ekberg et al.	2005	Sweedeen	English	Retrospective	1996-2002	NR	19	M:8 (42.1) F:11 (57.9)	65.4	Floor of mouth Gingiva Palate Tongue	NR	NR	NR	IHQ	Clone 31G7 (monoclonal)	1 :30 960 min 4°C	Membrane	Labelling index (cell count x intensity)	18 (94.74)
Shiraki et al.	2005	Japan	English	Retrospective	1986-1998	Median 66 (5-134)	140	M:98 (70) F:42 (30)	59 (26-85)	Buccal mucosa Floor of mouth Gingiva Tongue	NR	NR	NR	IHQ	sc-03 (polyclonal)	1:40 Overnight 4°C	Membrane Cytoplasm	Labelling index (cell count x intensity)	54 (38.57)
Smith et al.	2001	United States	English	Retrospective	1981-1992	73	56	M:46 (82.14) F:10 (17.86)	NR	Oral cavity Oropharynx	NR	NR	NR	IHQ	E30	NR Overnight 4°C	Membrane	Labelling index (index)	36 (64.29)
Ibrahim et al.	1999	Norway	English	Retrospective	1991-1993	NR	26 Missing= 1	M:18 (69.23) F:8 (30.77)	65.5± 12.83 (24-82)	Floor of mouth. Gingiva. hard palate. tongue	18	10	NR	IHQ	RPN 513	1:20 60 min NR	Membrane Cytoplasm	10	23 (92)
Xia et al.	1999	China	English	Retrospective	1989-1991	NR (NR-74)	111	M:74 (66.6) F: 37 (33.3)	Median 51 (13-76)	Floor of mouth Gingiva Tongue Others	NR	NR	NR	IHQ	sc-003 (polyclonal)	1:200 180 min Room Temperature	Membrane Cytoplasm	20	41 (36.94)
Maiorano et al.	1998	Italy	English	Retrospective	NR	46.8 (5-140)	100	M:79 (79) F:21 (21)	63.4 (28-93)	Buccal mucosa Floor of mouth Gingiva Lip Palate Retromolar trigone Tongue	NR	NR	NR	IHQ	Clone 29.1	1:400 NR NR	Membrane Cytoplasm	10	36
Takes et al.	1998	The Netherlands	English	Retrospective	1990-1995	NR	35 Missing= 1	M:22 (61.1) F:14 (38.9)	60 (34-87)	NR	NR	NR	NR	IHQ	Ab-4	1:20 NR NR	Membrane	>0	18 (51.43)
Kusukawa et al.	1996	Japan	English	Retrospective	NR	NR	65	M:40 (61.54) F:25 (38.46)	60.2 ± 15.2 (27-89)	Floor of mouth Gingiva Lip Mandible Tongue	NR	NR	NR	IHQ	Ab-1	1:400 720 min 4°C	Cytoplasm	NR	20 (30.77)
Storkel et al.	1993	Germany	English	Retrospective	NR	60	100	NR	NR	NR	NR	NR	NR	IHQ	NR	1:50 NR NR	Membrane	Labelling index (cell count x intensity)	74 (74)
Partridge et al.	1988	United Kingdom	English	Retrospective	NR	NR	20	NR	NR	NR	NR	NR	NR	IHQ	NR	NR 60 min NR	NR	Labelling index	18 (90)

Abbreviations: n, number; m, months; y, years; SD, standard deviation; IHQ, immunohistochemical; NR, not reported; OSCC, oral squamous cell carcinoma.

3. Meta-analysis on the EGFR overexpression and overall survival in OSCC

3.1 Subgroup meta-analysis by geographical area

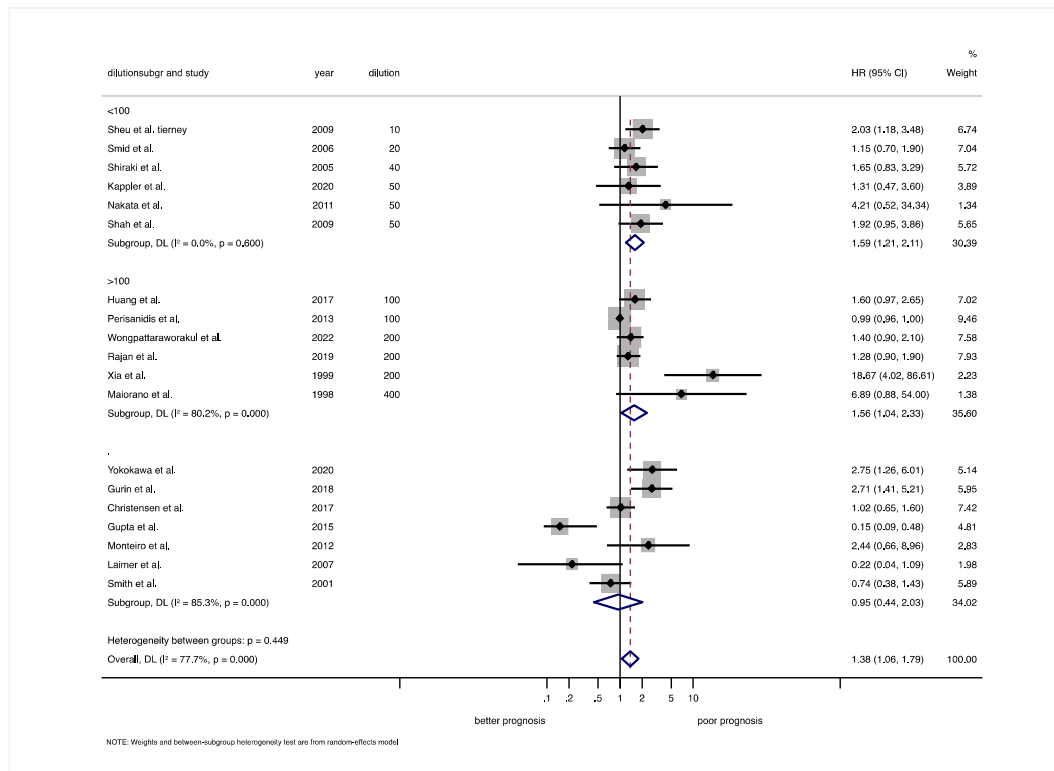
Figure S1. Forest plot graphically representing the stratified analysis by geographical area on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A HR > 1 suggests that the EGFR overexpression is associated with poor overall survival. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

3.2 Subgroup meta-analysis by anti-EGFR antibody dilution

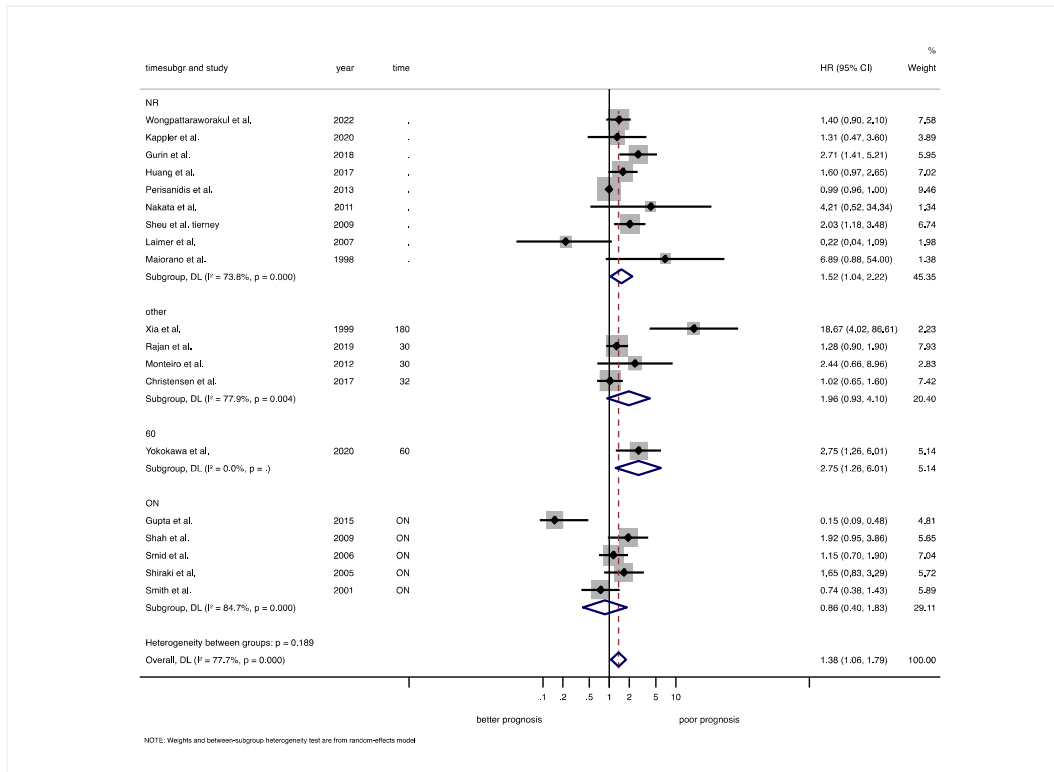
Figure S2. Forest plot graphically representing the stratified analysis by anti-EGFR antibody dilution on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A HR > 1 suggests that EGFR overexpression is associated with poor overall survival. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

3.3 Subgroup meta-analysis by anti-EGFR antibody incubation time

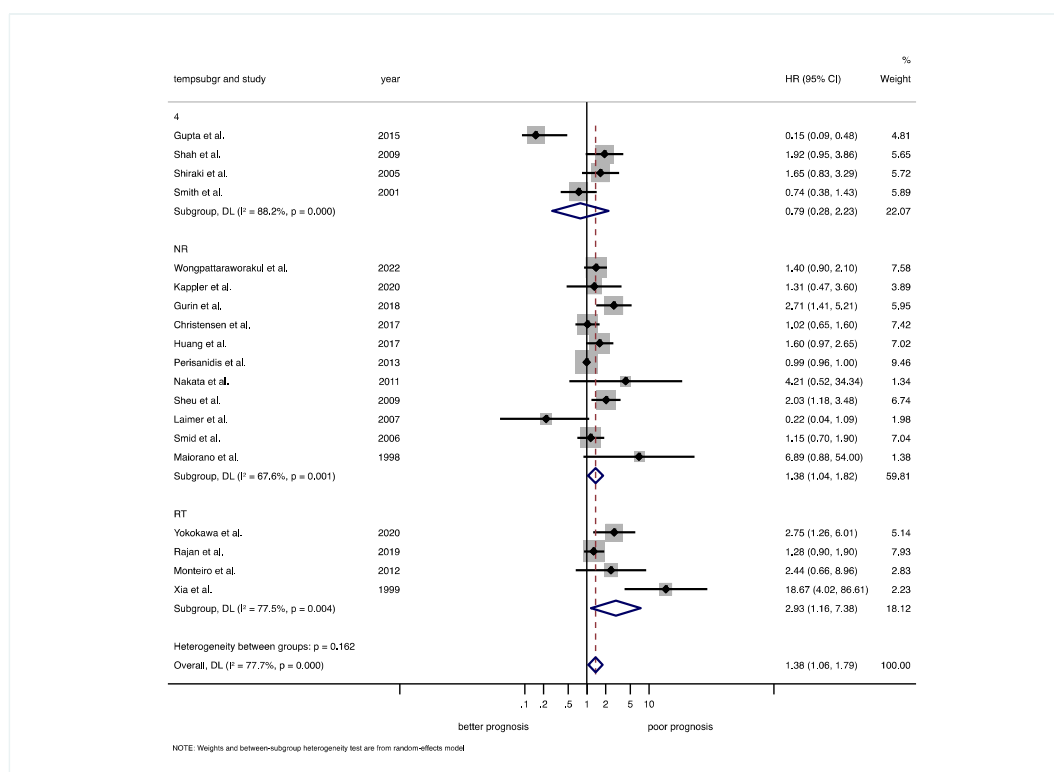
Figure S3. Forest plot graphically representing the stratified analysis by anti-EGFR antibody incubation time on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A $HR > 1$ suggests that EGFR overexpression is associated with poor overall survival. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

3.4 Subgroup meta-analysis by anti-EGFR antibody incubation temperature

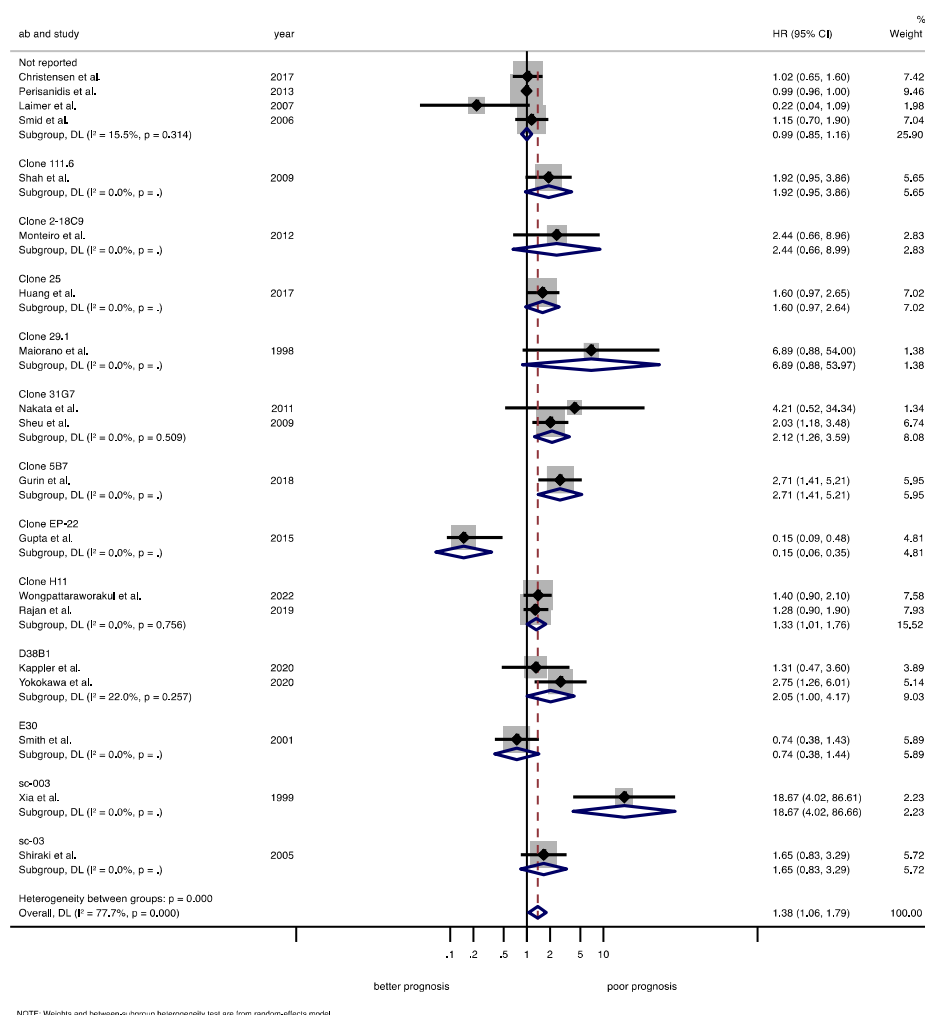
Figure S4. Forest plot graphically representing the stratified analysis by anti-EGFR antibody incubation temperature on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A HR > 1 suggests that EGFR overexpression is associated with poor overall survival. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

3.5 Subgroup meta-analysis by antibody

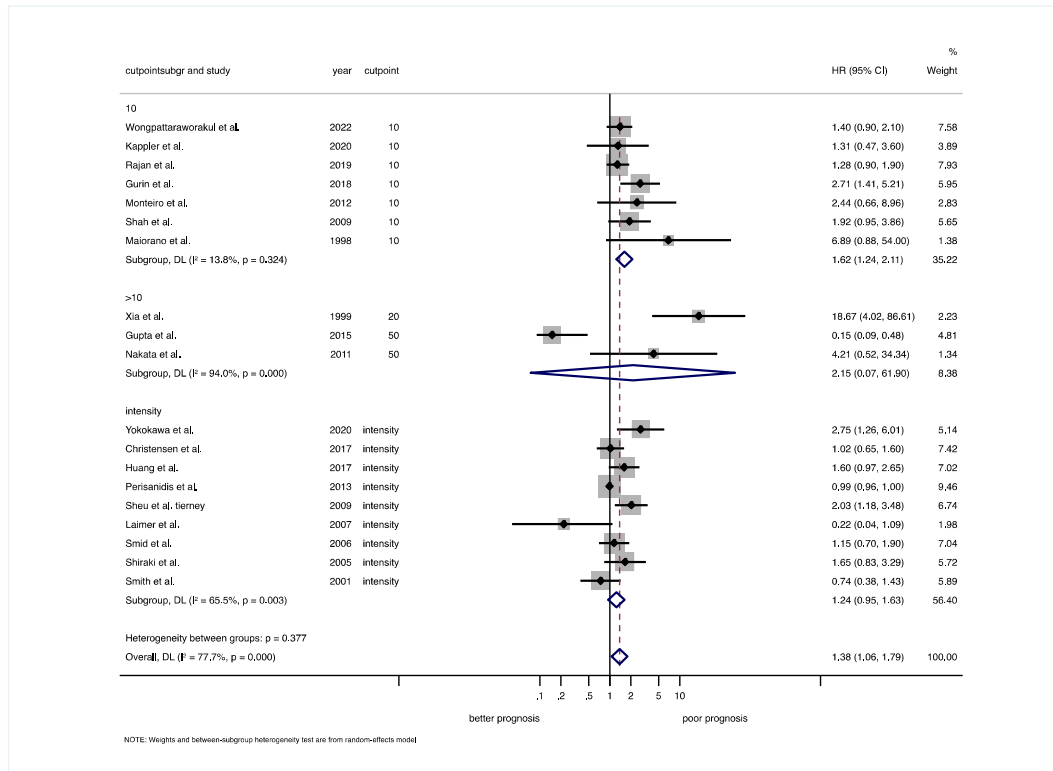
Figure S5. Forest plot graphically representing the stratified analysis by antibody on the association EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A HR > 1 suggests EGFR overexpression is associated with poor overall survival. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

3.6 Subgroup meta-analysis by cut-off point

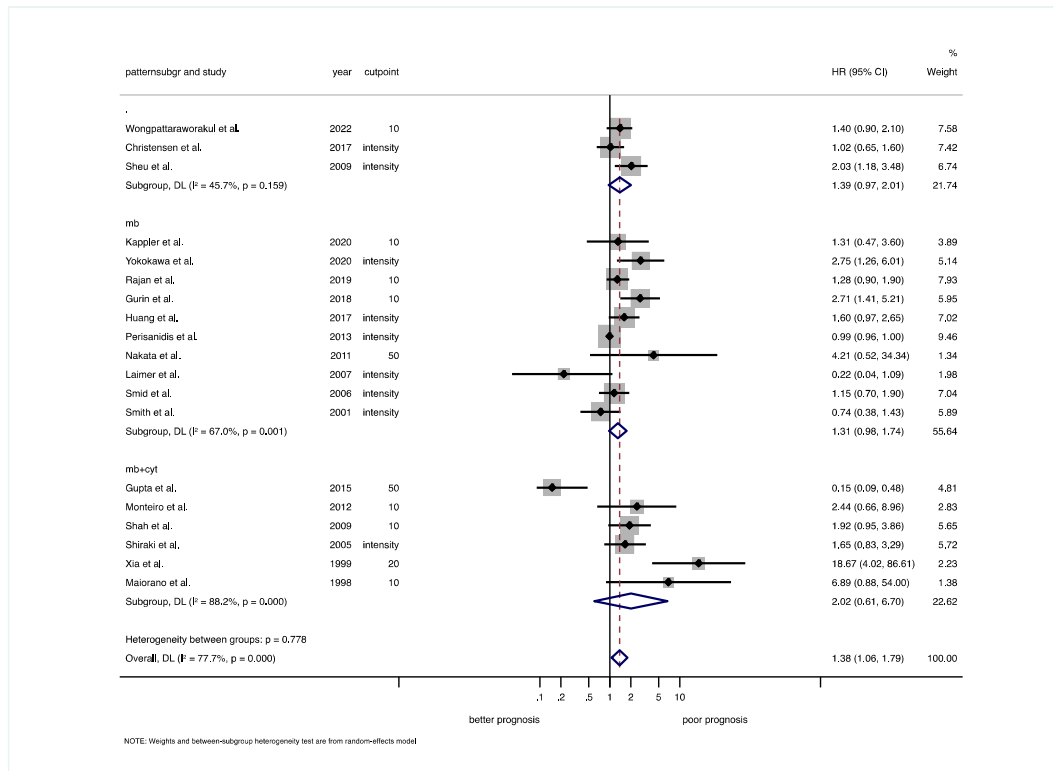
Figure S6. Forest plot graphically representing the stratified analysis by cut-off point on the association EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A $HR > 1$ suggests EGFR overexpression is associated with poor overall survival. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

3.7 Subgroup meta-analysis by immunohistochemical staining pattern

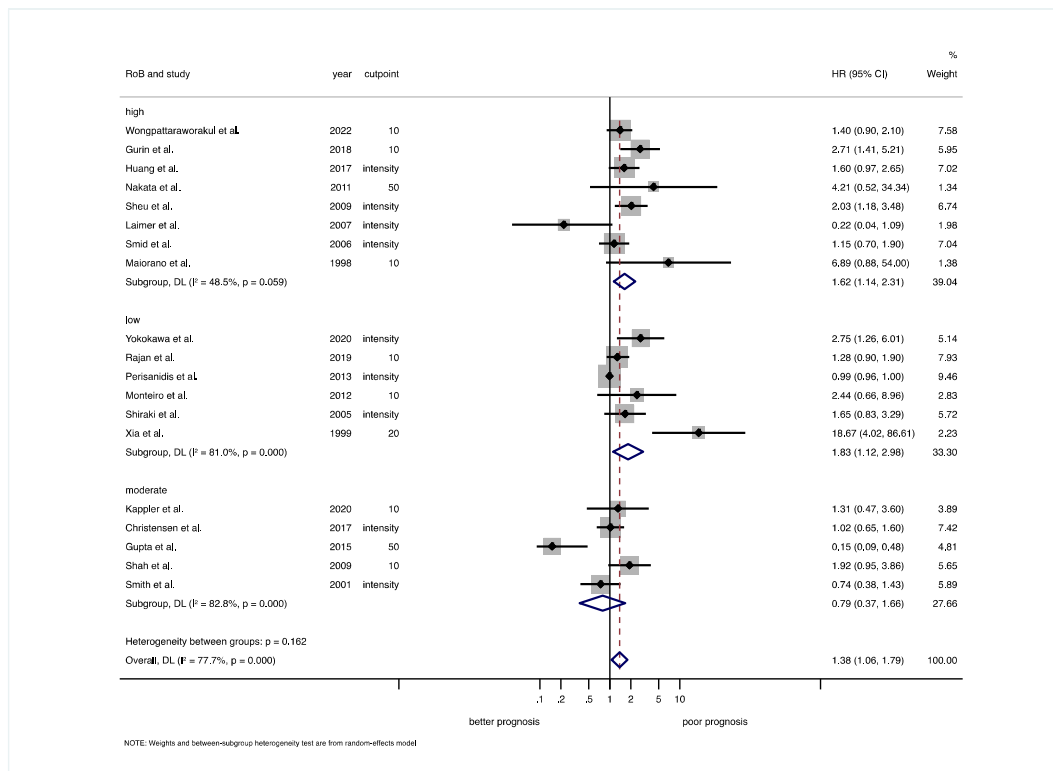
Figure S7. Forest plot graphically representing the stratified analysis by immunohistochemical staining pattern on the association between EGFR overexpression and overall survival in patient with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals; mb, membrane; mb+cyt, membrane and cytoplasm. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A HR > 1 suggests that EGFR overexpression is associated with poor overall survival. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

3.8 Subgroup meta-analysis by overall risk of bias in primary-level studies

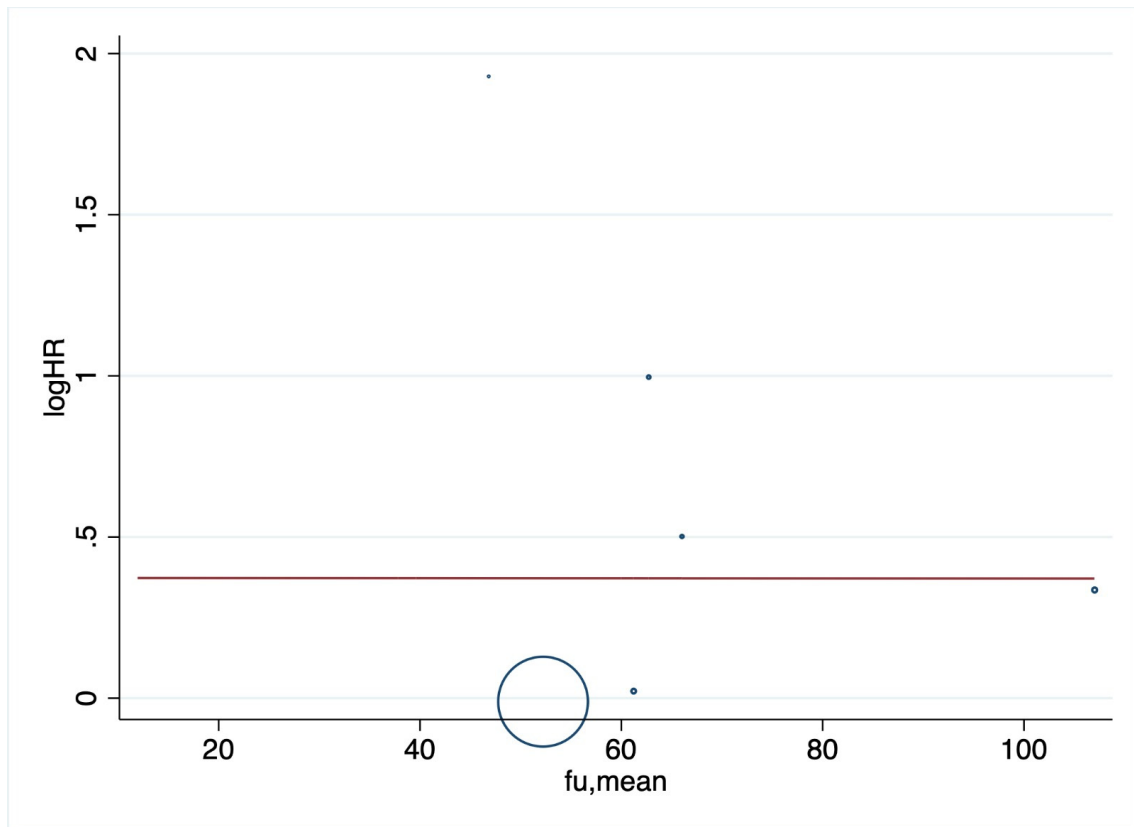
Figure S8. Forest plot graphically representing the stratified analysis by overall EGFR in primary-level studies, on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; RoB, risk of bias; HR, hazard ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A HR > 1 suggests that EGFR overexpression is associated with poor overall survival. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

3.9 Univariable meta-regression on the effect of follow up

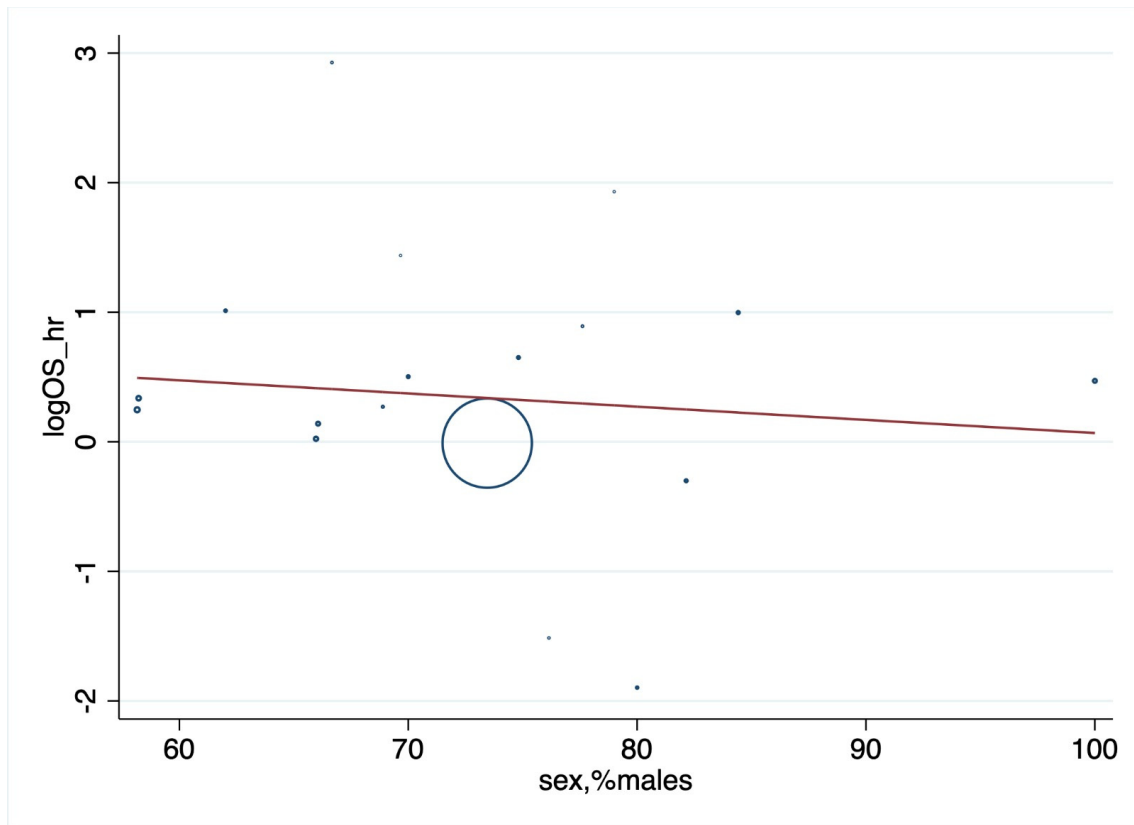
Figure S9. Bubble plot graphically representing the univariable meta-regression analysis of the potential effect of follow up period (expressed in months, in x-axis) on the association between EGFR overexpression and overall survival in patients with OSCC (using HR as effect size measure, in y-axis).



OSCC, oral squamous cell carcinoma; HR, hazard ratio; log, natural logarithm (i.e., log base e). The red line exhibits the fitted regression line together with blue circles representing the estimates from each individual study, sized according to the precision of each estimate (the inverse of its within-study variance).

3.10 Univariable meta-regression on the effect of sex

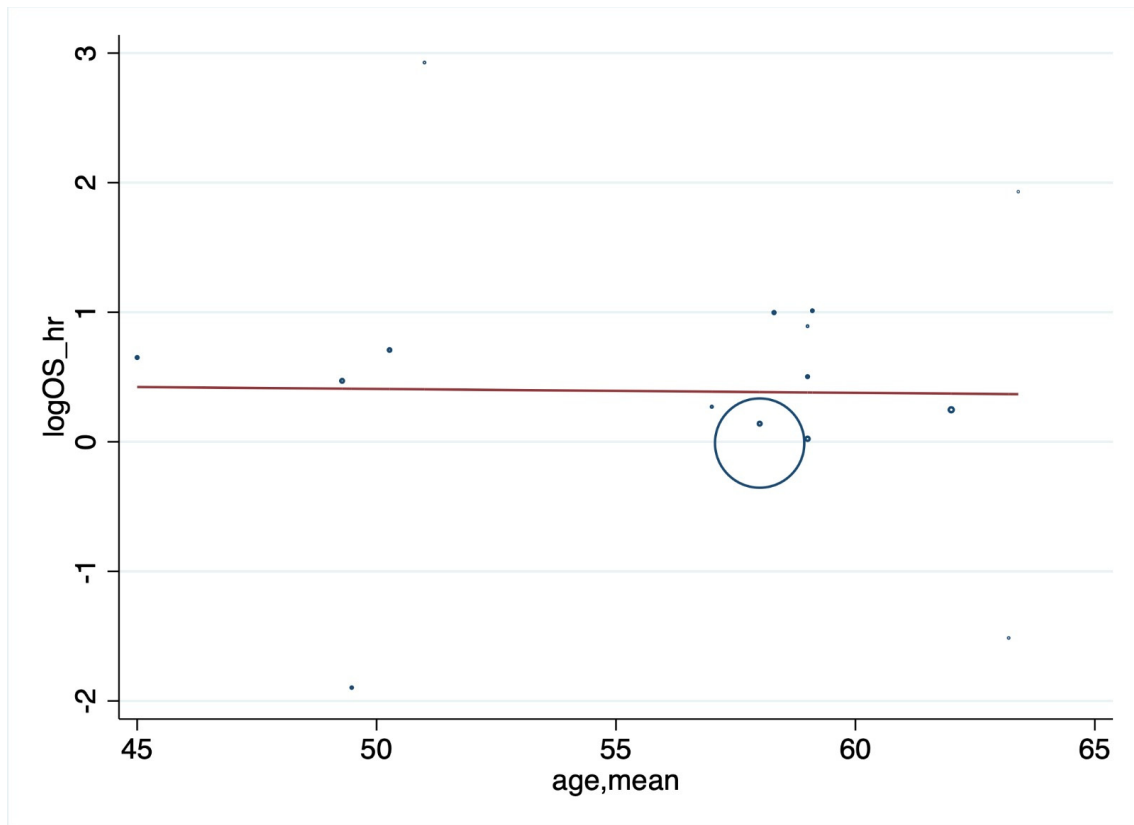
Figure S10. Bubble plot graphically representing the univariable meta-regression analysis of the potential effect of sex (% of males) on the association EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; log, natural logarithm (i.e., log base e). The red line exhibits the fitted regression line together with blue circles representing the estimates from each individual study, sized according to the precision of each estimate (the inverse of its within-study variance).

3.11 Univariable meta-regression on the effect of age

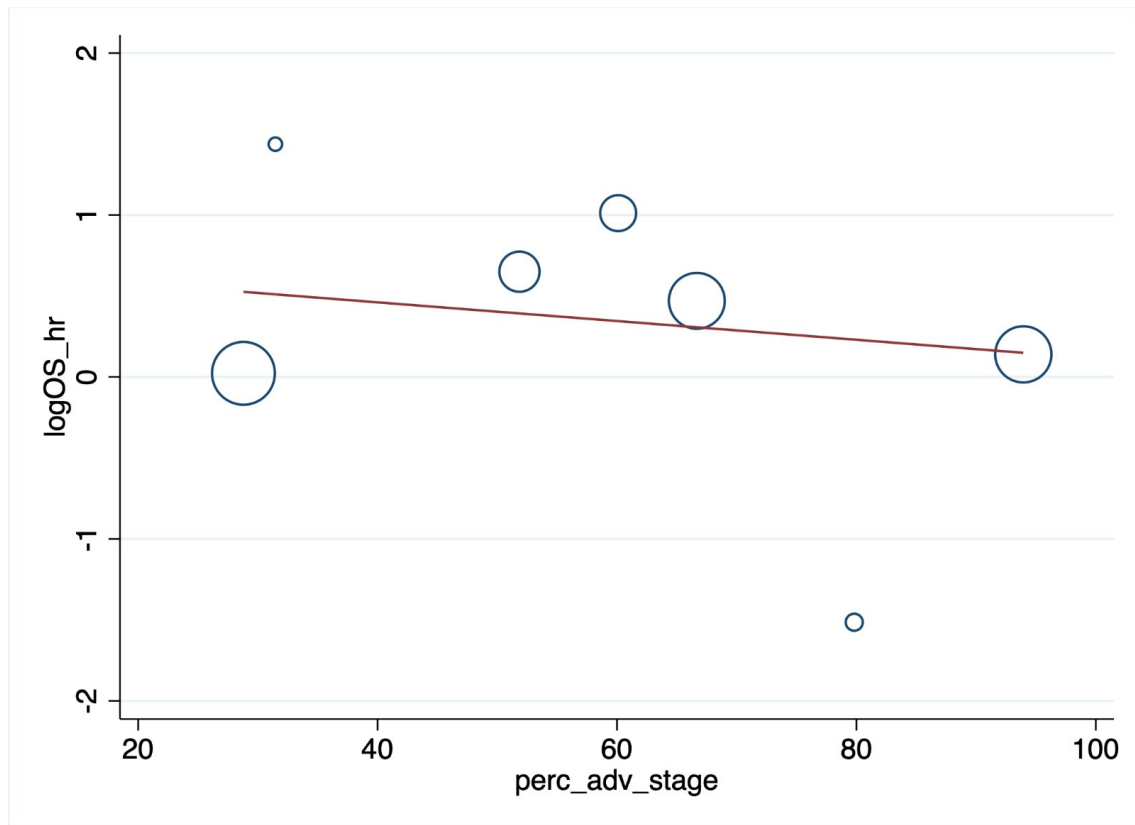
Figure S11. Bubble plot graphically representing the univariable meta-regression analysis of the potential effect of age (mean age of patients, expressed in years) on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; log, natural logarithm (i.e., log base e). The red line exhibits the fitted regression line together with blue circles representing the estimates from each individual study, sized according to the precision of each estimate (the inverse of its within-study variance).

3.12 Univariable meta-regression on the effect of stage

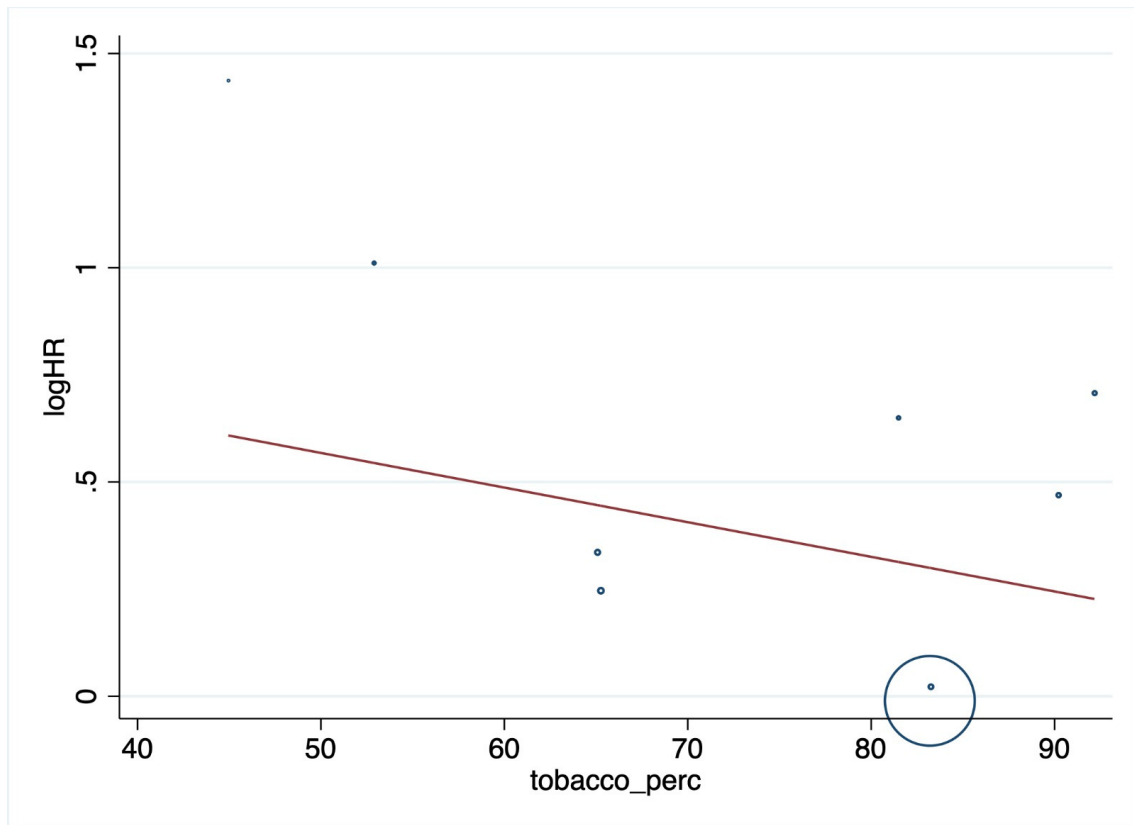
Figure S12. Bubble plot graphically representing the univariable meta-regression analysis of the potential effect of stage (expressed in percentage, in x-axis) on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; log, natural logarithm (i.e., log base e). The red line exhibits the fitted regression line together with blue circles representing the estimates from each individual study, sized according to the precision of each estimate (the inverse of its within-study variance).

3.13 Univariable meta-regression on the effect of tobacco

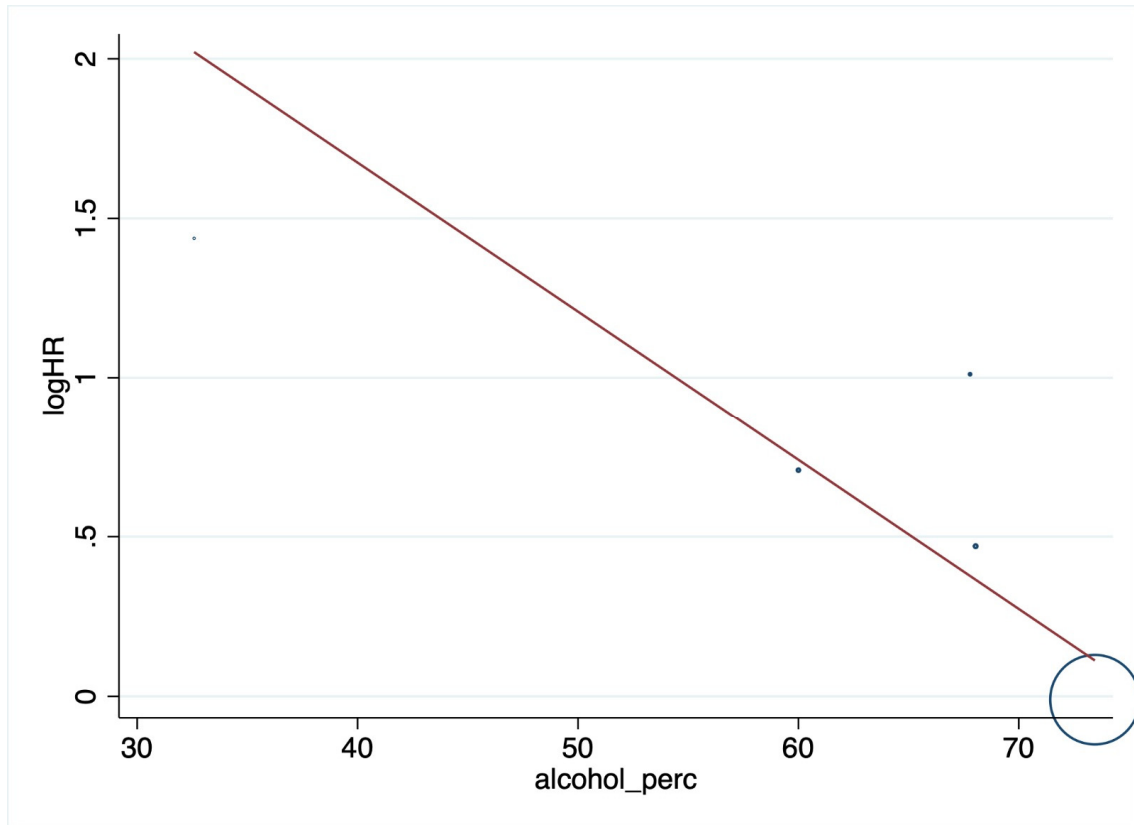
Figure S13. Bubble plot graphically representing the univariable meta-regression analysis of the potential effect of tobacco (percentage of smokers, expressed in x-axis) on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; log, natural logarithm (i.e., log base e). The red line exhibits the fitted regression line together with blue circles representing the estimates from each individual study, sized according to the precision of each estimate (the inverse of its within-study variance).

3.14 Univariable meta-regression on the effect of alcohol

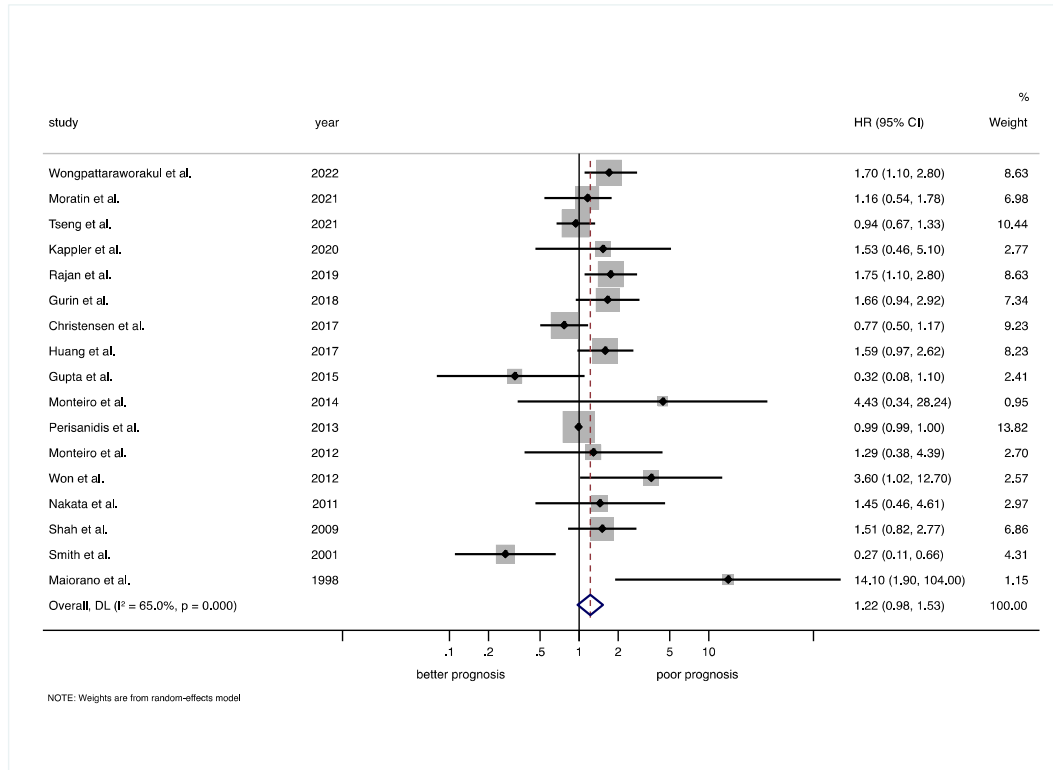
Figure S14. Bubble plot graphically representing the univariable meta-regression analysis of the potential effect of alcohol (percentage of drinkers, expressed in x-axis) on the association between EGFR overexpression and overall survival in patients with OSCC.



OSCC, oral squamous cell carcinoma; HR, hazard ratio; log, natural logarithm (i.e., log base e). The red line exhibits the fitted regression line together with blue circles representing the estimates from each individual study, sized according to the precision of each estimate (the inverse of its within-study variance).

4. Meta-analysis on EGFR overexpression and DFS in OSCC

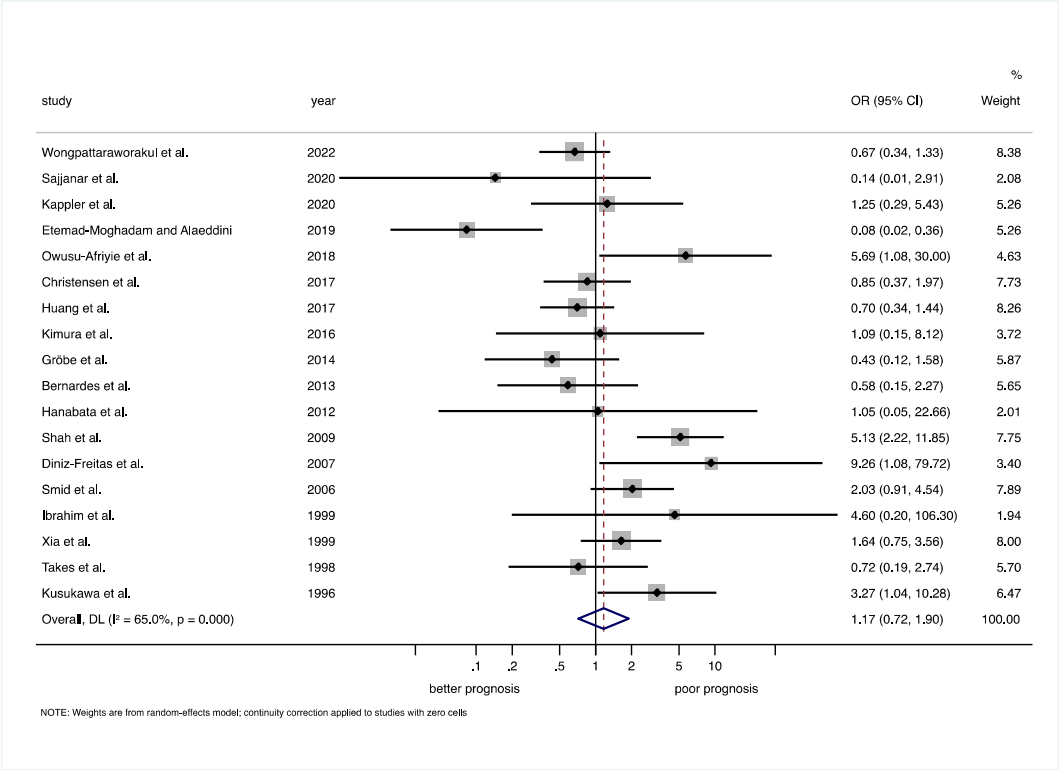
Figure S15. Forest plot graphically representing the meta-analysis on the association between EGFR overexpression and DFS in patients with OSCC.



DFS, disease-free survival; OSCC, oral squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A HR > 1 suggests that EGFR overexpression is associated with poor DFS. Diamonds indicate the pooled HRs with their corresponding 95% CIs.

5. Meta-analysis on EGFR overexpression and T status in OSCC

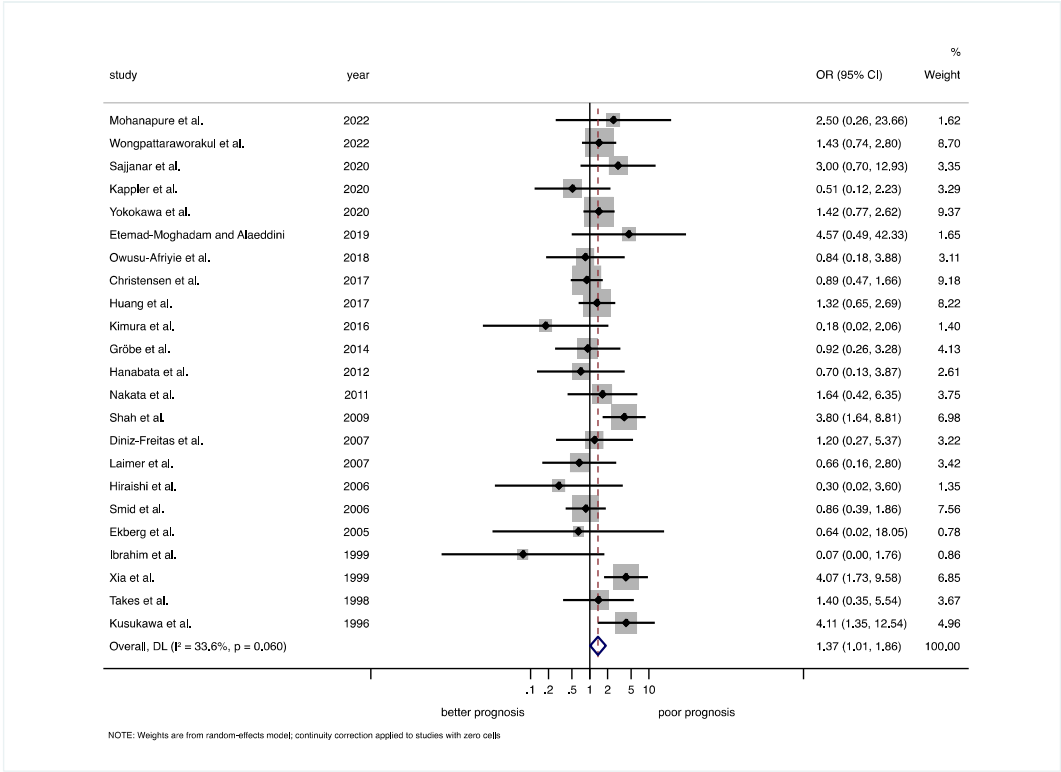
Figure S16. Forest plot graphically representing the meta-analysis on the association between EGFR overexpression and T status (T3/T4 vs. T1/T2) in patients with OSCC.



OSCC, oral squamous cell carcinoma; OR, odds ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A OR > 1 suggests EGFR overexpression is associated with a higher T status. Diamonds indicate the pooled ORs with their corresponding 95% CIs.

6. Meta-analysis on EGFR overexpression and N status in OSCC

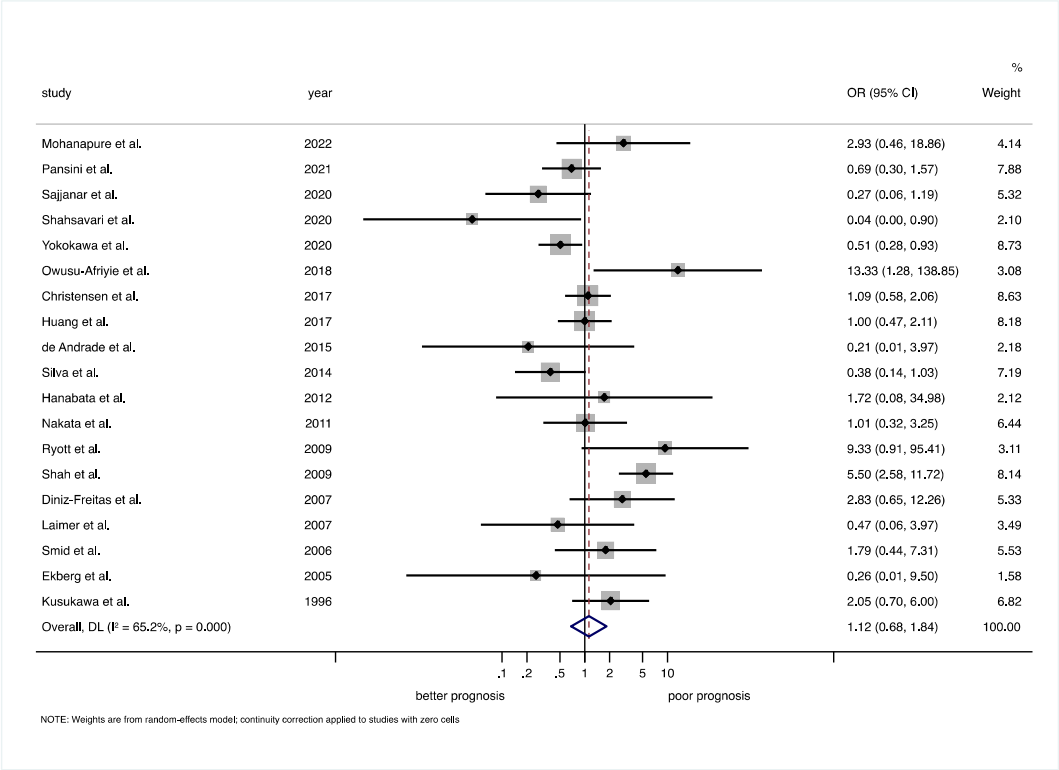
Figure S17. Forest plot graphically representing the meta-analysis on the association between EGFR overexpression and N status (positive metastatic lymph nodes vs. negative) in patients with OSCC.



OSCC, oral squamous cell carcinoma; OR, odds ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A OR > 1 suggests that EGFR overexpression is associated with positive N status. Diamonds indicate the pooled ORs with their corresponding 95% CIs.

7. Meta-analysis on EGFR overexpression and clinical stage in OSCC

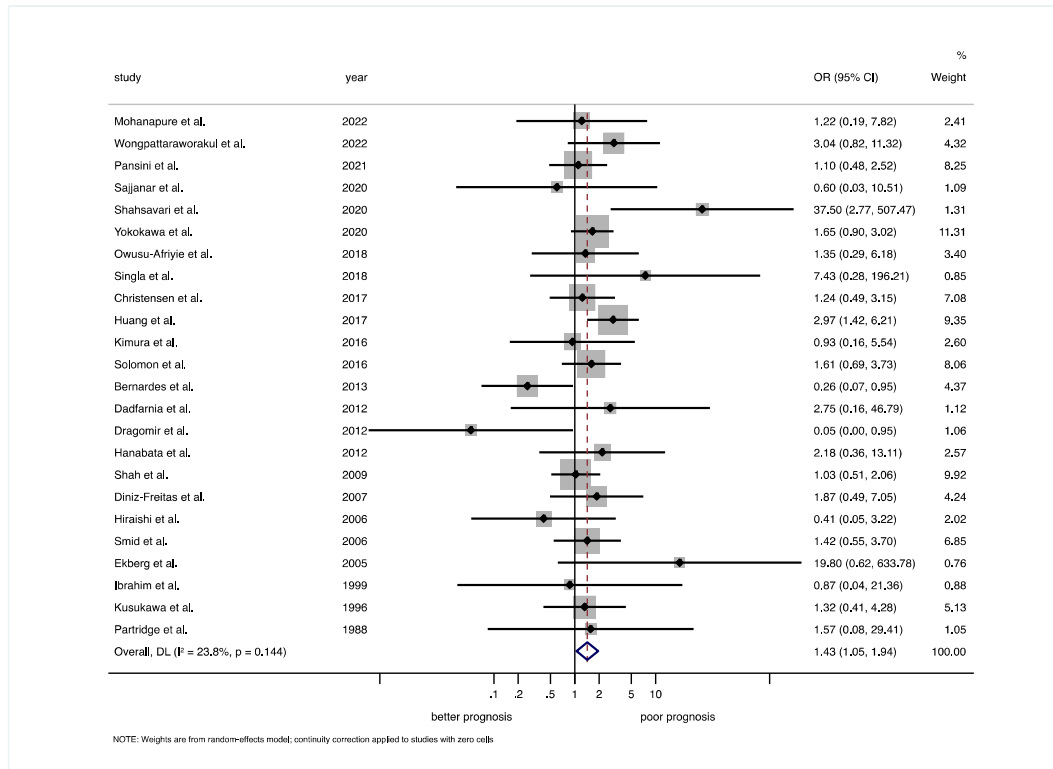
Figure S18. Forest plot graphically representing the meta-analysis on the association between EGFR expression and clinical stage (III/IV vs. I/II) in patients with OSCC.



OSCC, oral squamous cell carcinoma; OR, odds ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A OR > 1 suggests that EGFR overexpression is associated with a higher stage. Diamonds indicate the pooled ORs with their corresponding 95% CIs.

8. Meta-analysis on EGFR overexpression and histological grade in OSCC

Figure S19. Forest plot graphically representing the meta-analysis on the association between EGFR overexpression and histological grade (poorly-moderate vs. well-differentiated carcinomas) in patients with OSCC.

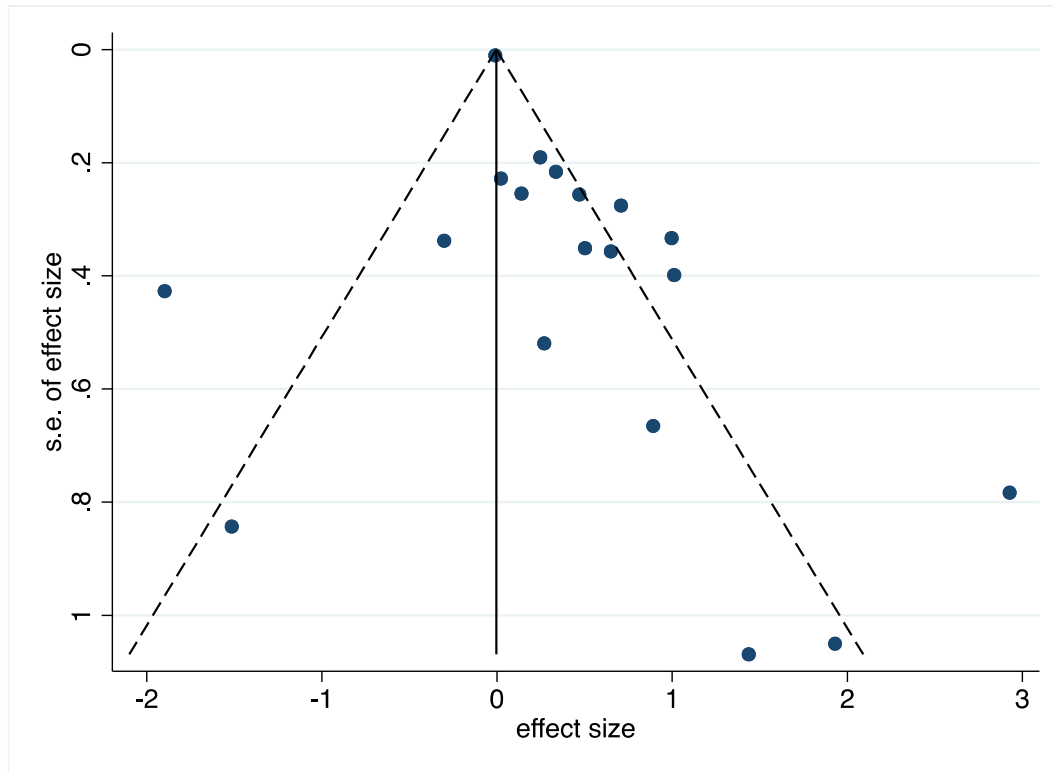


OSCC, oral squamous cell carcinoma; OR, odds ratio; CI, confidence intervals. Random-effects model, inverse-variance weighting (based on the DerSimonian and Laird method). A $OR > 1$ suggests that EGFR overexpression is associated with a higher grade. Diamonds indicate the pooled ORs with their corresponding 95% CIs.

9. Analysis of small-study effects

9.1 EGFR overexpression and overall survival in OSCC

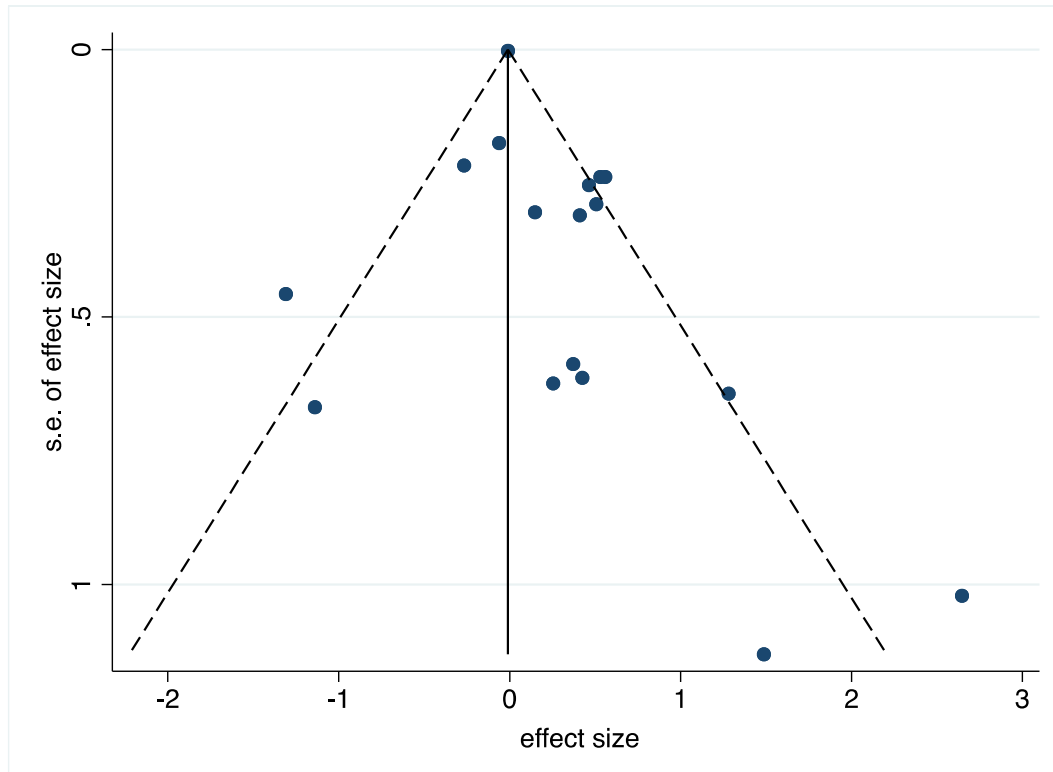
Figure S20. A funnel plot of estimated effect size against their standard errors, graphically representing the analysis of small-study effects on the association between EGFR overexpression and overall survival in OSCC.



s.e., standard error. The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

9.2 EGFR overexpression and DFS in OSCC

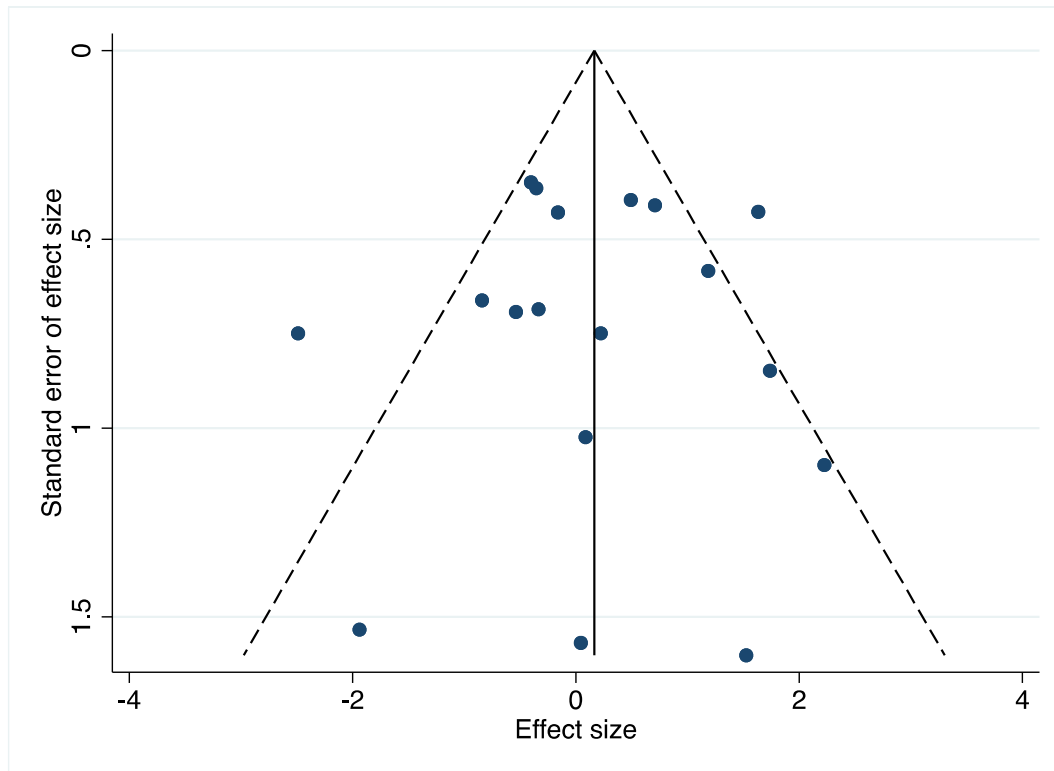
Figure S21. A funnel plot of estimated effect size against their standard errors, graphically representing the analysis of small-study effects on the association between EGFR overexpression and DFS in OSCC.



DFS, disease-free survival; s.e., standard error; HR, hazard ratio; log, natural logarithm (i.e., log base e). The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

9.3 EGFR overexpression and T status in OSCC

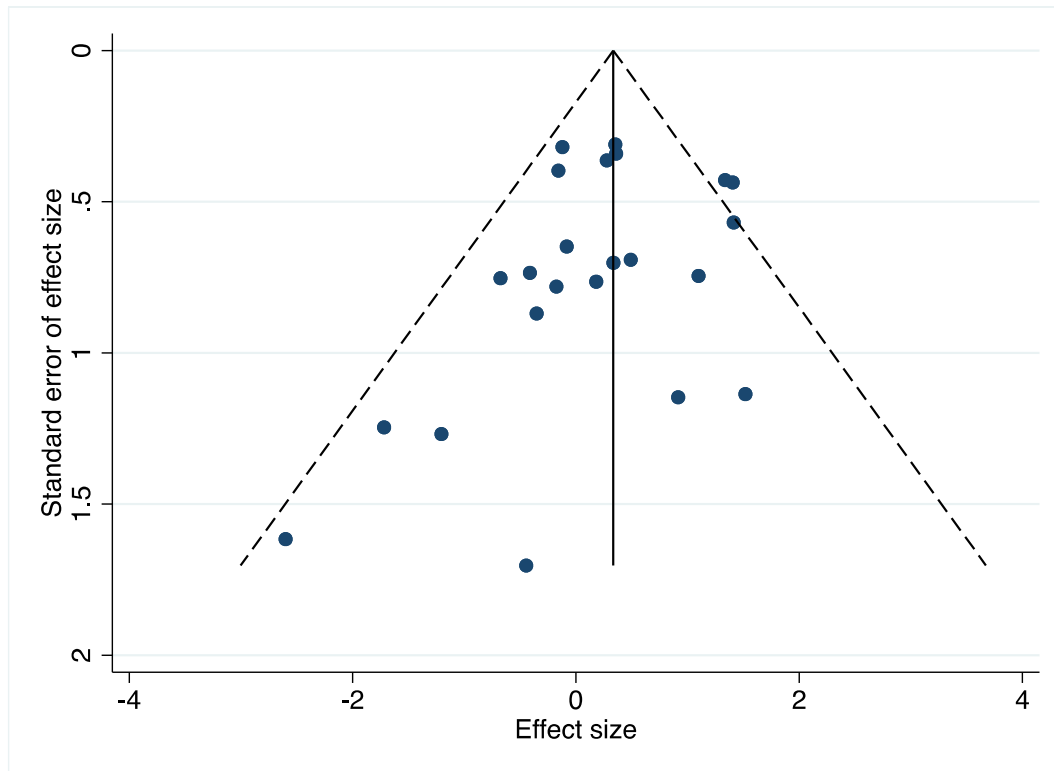
Figure S22. A funnel plot of estimated effect size against their standard errors, graphically representing the analysis of small-study effects on the association between EGFR overexpression and T status in OSCC.



SE, standard error. The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

9.4 EGFR overexpression and N status in OSCC

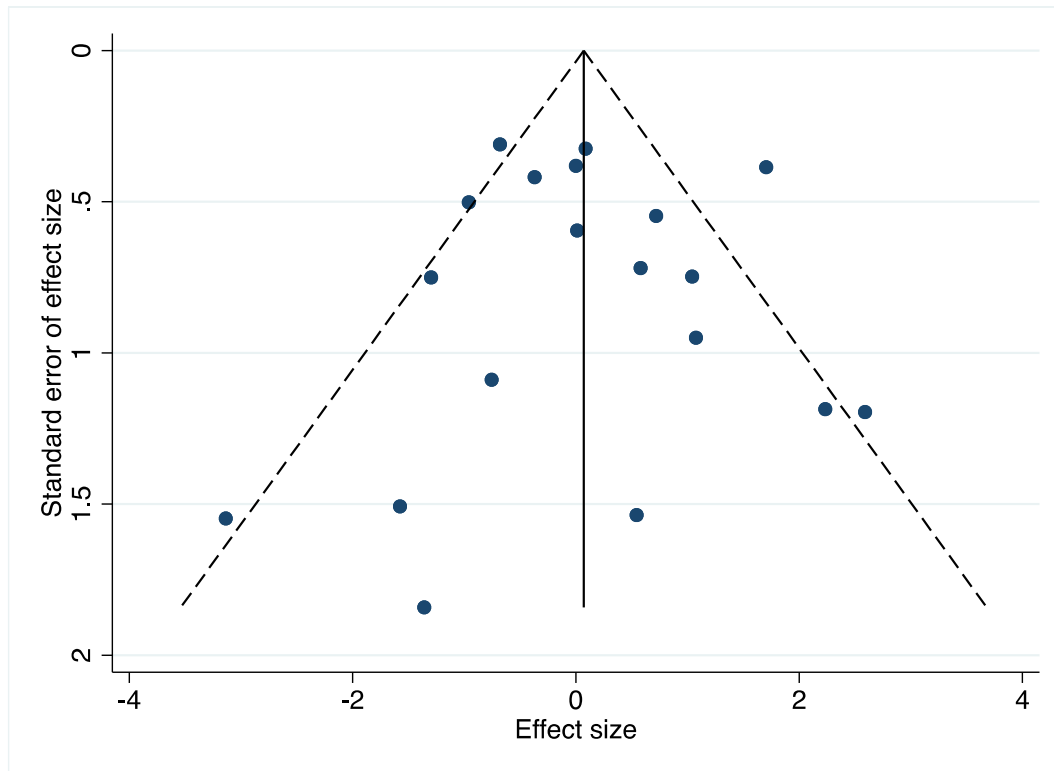
Figure S23. A funnel plot of estimated effect size against their standard errors, graphically representing the analysis of small-study effects on the association between EGFR overexpression and N status in OSCC.



SE, standard error. The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

9.5 EGFR overexpression and clinical stage in OSCC

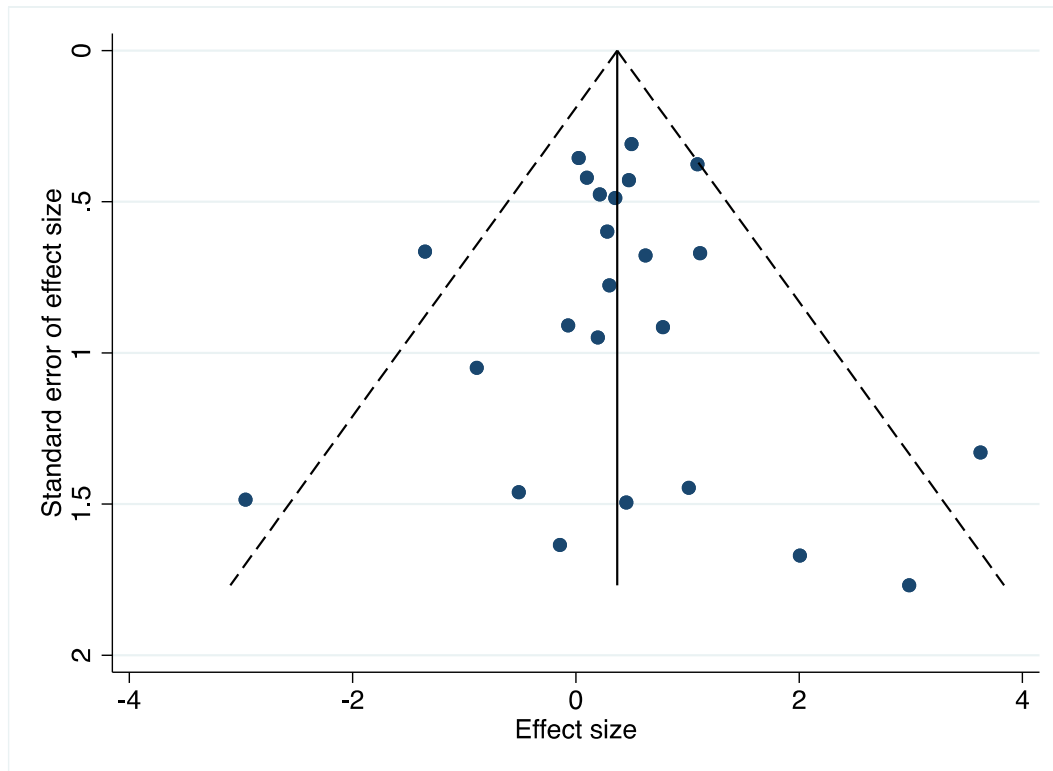
Figure S24. A funnel plot of estimated effect size against their standard errors, graphically representing the analysis of small-study effects on the association between EGFR overexpression and clinical stage in OSCC.



SE, standard error. The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

9.6 EGFR overexpression and histological grade in OSCC

Figure S25. A funnel plot of effect size against their standard errors, graphically representing the analysis of small-study effects on the association between EGFR overexpression and histological grade in OSCC.



SE, standard error. The black vertical line corresponds to the pooled estimated prevalence. The two diagonal intermittent lines represent the pseudo-95% confidence interval. The blue circles represent the estimates from primary-level studies.

10. List of full-text articles excluded with reasons

Lack of essential data (n = 91) [1-91]:

1. Adduri R Sr, Kotapalli V, Gupta NA, Gowrishankar S, Srinivasulu M, Ali MM, Rao S, Uppin SG, Nayak UK, Dhagam S, Chigurupati MV, Bashyam MD. P53 nuclear stabilization is associated with FHIT loss and younger age of onset in squamous cell carcinoma of oral tongue. *BMC Clin Pathol*. 2014 Aug 9;14:37. doi: 10.1186/1472-6890-14-37. PMID: 25152695; PMCID: PMC4141988.
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- Oral Lichen Planus. *Adv Pharm Bull.* 2015 Dec;5(Suppl 1):649-52. doi: 10.15171/apb.2015.088. Epub 2015 Dec 31. PMID: 26793611; PMCID: PMC4708036.
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