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Clinicopathological and Prognostic Significance of Epidermal Growth Factor-Like Domain 7 (EGFL7) Overexpression in Primary Central Nervous System Tumor: A Meta-Analysis

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Abstract

Background: Central nervous system (CNS) tumors are associated with high rates of progression and mortality. Several biomarkers have been identified and investigated for their role in tumor progression, including Epidermal Growth Factor-Like Domain 7 (EGFL7). This study aims to evaluate the clinicopathological and prognostic significance of EGFL7 overexpression in CNS tumor.

Methods: The literature search was conducted using PubMed, ScienceDirect, and Web of Science. Studies were selected according to PRISMA guidelines and analyzed using Review Manager 5.4 (Cochrane Collaboration, UK).

Results: A total of 313 patients with CNS tumors from six eligible studies were included in this meta-analysis. EGFL7 overexpression was significantly associated with tumor grade and Karnofsky Performance Status (KPS) score (OR, 6.86; 95% CI, 2.41 – 19.57; p, 0.0003; and OR, 2.92; 95% CI, 1.52 – 5.59; p, 0.001 respectively). Furthermore, EGFL7 overexpression was significantly associated with the poorer overall survival (HR, 1.64; 95% CI, 1.02 – 2.63; p, 0.04).

Conclusions: EGFL7 overexpression is associated with clinicopathologic characteristics and patient prognosis in CNS tumors. This highlights the potential of the marker as a valuable tool for diagnosis and disease risk assessment, contributing to enhanced personalization of treatment strategies and cancer monitoring.

Keyword: biomarker; glioblastoma; immunohistochemistry; molecular pathology; oncology

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Клинико-патологическое и прогностическое значение повышенной экспрессии EGFL7 при первичных опухолях центральной нервной системы: метаанализ

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Резюме

Цель: Опухоли центральной нервной системы (ЦНС) отличаются высокой частотой прогрессирования и значительной смертностью среди онкологических заболеваний. За последнее десятилетие было обнаружено и исследовано большое количество биомаркеров, влияющих на развитие новообразований, включая эпидермальный фактор роста типа 7 (EGFL7). Основная цель настоящей статьи заключается в оценке клинической, патоморфологической и прогностической роли гиперэкспрессии EGFL7 при опухолевых заболеваниях ЦНС.

Методы: Для анализа доступной научной литературы применялись базы данных PubMed, ScienceDirect и Web of Science. Отбор публикаций соответствовал критериям рекомендаций PRISMA, а статистический анализ выполнялся с использованием программного обеспечения Review Manager версии 5.4 (The Cochrane Collaboration, Великобритания).

Результаты: Метаанализ охватил выборку из 313 пациентов с опухолями ЦНС, основанную на результатах шести соответствующих научных исследований. Установлено, что избыточная экспрессия EGFL7 ассоциирована с повышенной степенью злокачественности новообразования и снижением индекса функционального состояния больного по шкале Карновского (Karnofsky Performance Scale, KPS): коэффициент отношения шансов составил 6,86 (95%-й доверительный интервал 2,41–19,57; p=0,0003), а также 2,92 (95%-й ДИ 1,52–5,59; p=0,001) соответственно. Кроме того, наличие высокого уровня экспрессии EGFL7 отрицательно влияет на общую продолжительность жизни больных: отношение рисков составило 1,64 (95%-ДИ 1,02–2,63; p=0,04).

Заключение: Избыточное накопление EGFL7 тесно связано с неблагоприятными клиническими проявлениями и ухудшением прогноза у пациентов с опухолью ЦНС. Это делает данный маркер потенциально важным инструментом диагностики и оценки риска течения болезни, способствующим улучшению персонализации подхода к лечению и мониторингу онкозаболевания.

Ключевые слова: биомаркер, глиобластома, иммуногистохимия, молекулярная патология, онкология

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Introduction

Primary central nervous system (CNS) tumors comprise a diverse group of tumors that can be either benign or malignant and originate from cells within the brain. These tumors significantly consciousness, brain capacity, and cognitive function.[1] Over the past few years, the incidence of primary CNS tumors has remained relatively stable, with some variations observed across different age groups and tumor subtypes. The prevalence of primary brain tumors varies according to histologic type, age at diagnosis, sex, and race/ethnicity. According to the Global Cancer Observatory (GLOBOCAN) an estimated 392,914 cases of primary CNS tumors were reported worldwide over a 5-year period in 2012 , with Asia and Europe reporting the highest number of cases (186,866 and 57,132 respectively).[2] The 5-year relative survival rate for patients with malignant primary CNS tumors was 32.1 %, compared with 90.8% for those with nonmalignant tumors.[3]

Tumorigenesis of primary CNS tumors involves complex processes. Epidermal Growth Factor (EGF) expression plays a major role in these processes. EGF is a transmembrane protein with tyrosine kinase activity that regulates mitosis in early CNS development and progressively declines with CNS maturation. Nonetheless, EGF expression reoccurs in brain cells following brain injure and decline in neural function, which is linked to the etiology of brain cancers.[4,5] Abnormal expression of EGF receptor (EGFR) in primary CNS tumors has been associated with poorer survival and adverse clinicopathological features.[6–8]

Since the effect of EGFR expression on CNS tumor is widely known, Epidermal growth factor-like domain 7 (EGFL7), which belongs to the EGF-like protein family, is anticipated as a novel factor for prognosis and clinicopathological features of CNS tumors. EGFL7 has been linked to poor clinicopathology features and prognosis in various cancers, including colorectal cancer, pancreatic cancer, hepatocellular carcinoma, osteosarcoma, breast cancer, cervical cancer, and ovarian cancer.[9–14] EGFL7 is currently known to act as an angiogenic factor that accelerates malignancy progression in these cancers.[15] However, the role of EGFL7 in clinicopathological features and prognosis of primary CNS tumors remains unclear. Therefore, we performed a meta-analysis to assess the clinicopathological and prognostic significance of EGFL7 in primary CNS tumors.

Methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline, as outlined in Figure 1.

Data Sources and Search

A literature search was performed in PubMed, ScienceDirect, and The Cochrane Library from January 2025 to March 2025 using multiple search terms: “EGFL7 AND (Central Nervous System OR Brain OR Spinal Cord) AND (Cancer OR Tumor)”. Boolean operators “AND” or “OR” were used to refine the search.

Eligibility Criteria

Study eligibility was determined based on inclusion and exclusion criteria. Inclusion criteria were: (1) articles published in English; (2) human studies; (3) studies including patients with central nervous system tumors; (4) studies describing the association between EGFL7 overexpression

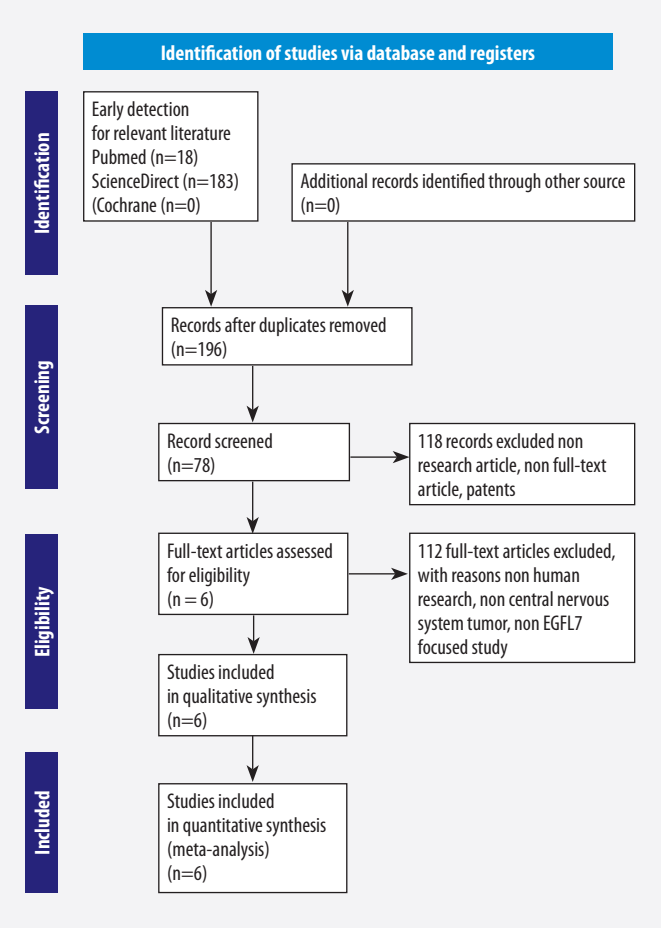

Figure 1. PRISMA flowchart
Рисунок 1. Блок-схема PRISMA

and CNS tumors. Exclusion criteria included: (1) incomplete studies at the time of the search; (2) studies inaccessible in full text. Included study designs were cohort and case-control studies. Study quality and risk of bias were evaluated using the Newcastle Ottawa Scale (NOS) for cohort and cross-sectional studies.

Data extraction

Data extraction was performed based on variables reported in the included studies. The following data were collected: (1) baseline study information including author, year of publication, country, type of malignancy, number of patients, detection method for EGFL7 expression, and criteria for EGFL7 overexpression; (2) clinicopathological data including sex, tumor grade, patient age, tumor location, and SOX2 expression in primary and recurrent tumors; (3) prognostic data, including overall survival and p-values.

Data analysis

The effects of EGFL7 overexpression on clinicopathological features were analyzed using Review Manager 5.4 (Cochrane Collaboration, UK). Publication bias was qualitatively assessed using Begg's Funnel Plot. Quantitative assessment of publication bias was conducted using the Egger and the Begg tests (MedCalc).

Results

The general characteristics of each studies included in this meta-analysis are summarized in Table 1. This meta-analysis comprised 6 quantitative studies with a total 313 patients. The majority of the study populations were Asian (4 of 6 studies). Methods used to detect SOX2 overexpression included immunohistochemical staining (5 of 6 studies) and Semi-quantitative PCR (1 of 6 studies). The included studies had NOS scores between 7 and 9, indicating good quality.

Association Between EGFL7 Overexpression and Clinicopathological Features

The association between EGFL7 overexpression with clinicopathological features of CNS tumor was analyzed several variables, including grade, gender, Karnofsky Performance Status Scale (KPS), tumor location, and patient age. The analysis revealed that EGFL7 overexpression was significantly associated with higher tumor grade and lower KPS with an odds ratio of 6.81 (95% CI, 2.38-19.51; I^2 0%; p = 0.0004) and 2.91 (95% CI, 1.52-5.56; I^2 0%; p = 0.001). No significant associations were observed gender, tumor location, or age (Figure 2).

Association Between EGFL7 Overexpression and Overall Survival

Prognostic analysis evaluated the association between EGFL7 overexpression and overall survival in patients with CNS. The analysis showed a statistically significant result, with a hazard ratio of 1.64 (95% CI, 1.02-2.36; I^2 0%; p = 0.04), that is pooled using a Fixed-Effect Model, as shown in Figure 3.

Publication Bias Analysis

Qualitative analysis of publication bias was performed using Begg's Funnel Plot. This analysis demonstrated a relatively symmetrical distribution of the studies included in the meta-analysis, indicating no evidence of publication bias (Figure 4). Quantitative analysis was conducted using Egger's test, which showed possible publication bias (p < 0.0001) for grade, location, and overall survival analyses (Table 2).

Discussion

Primary CNS tumors were diverse group of tumors that originate within the brain and its surrounding tissue. Despite advances in treatment, the prognosis for these tumors remains poor. A better understanding of prognostic factors is important for identifying molecular variations, as it may prolong survival and improve quality of life.[16] EGFL7 expression contributes to the diversity of molecular characteristics of primary CNS tumors. Our meta-analysis examined the association between EGFL7 expression and the clinicopathology features and prognosis of primary CNS tumors. Along with other research by Luo et al[10], we observed that EGFL7 overexpression is associated with tumor stage progression in primary CNS tumors. This may correlate to EGFL7's role as an angiogenic factor. Physiologically, EGFL7 is expressed in activated vascular endothelial cells. Under pathological conditions such as malignancy, the increased demand for nutrients is supported

Table 1. **Characteristics of The Study**
Таблица 1. **Характеристики исследования**

Study	Source	Type of Malignancy	Number of Patients	Method	Expression Criteria	NOS Score
Brunhara, 2020.[21]	Brazil	Pilocytic Astrocytomas	64	IHC staining	Summed IHC score >3	9
da Costa, 2022.[19]	Brazil	Glioblastoma	74	IHC staining	Summed IHC score >3	7
Huang, 2010.[29]	China	Malignant Glioma	36	Sq-PCR	Positive expression	8
Huang, 2014.[30]	China	Malignant Glioma	45	IHC	IHC >50%	9
Wang, 2016.[31]	China	Glioma	46	IHC	IHC score >25%	8
Wang, 2017.[20]	China	Pituitary Adenomas	48	IHC	H-score: >80.5	8

Immunohistochemistry (IHC). IHC Score= 0: negative, 1: <25%; 2: 25-50%, 3: >50%. H-score = (% cells 1+) + 2(% cells 2+) + 3(% cells 3+)

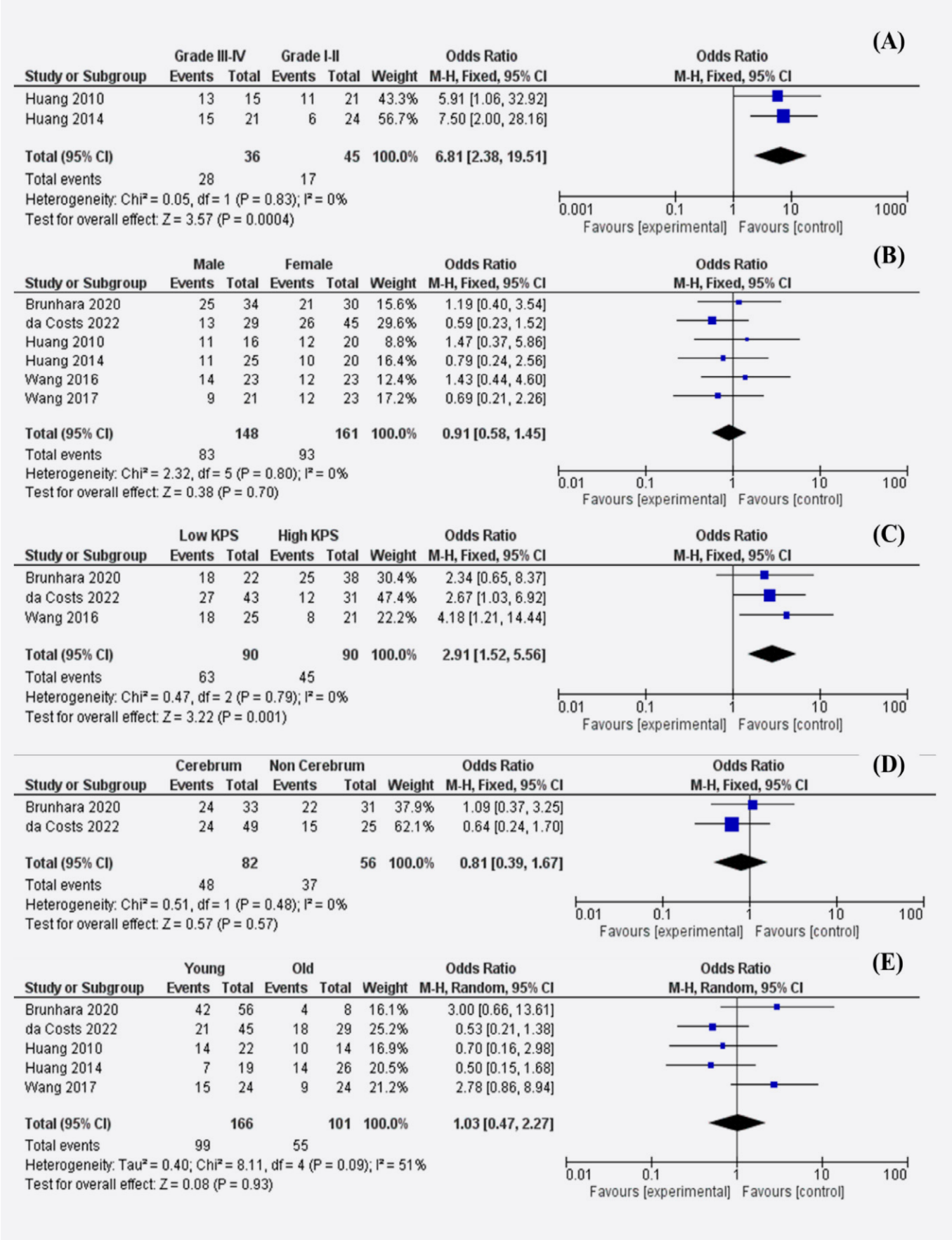

Figure 2. Forest Plot Result of Clinicopathological Significance of EGFL7 Overexpression in Central Nervous System Tumors (A-Grade; B-Gender C-KPS; D-Location; E-Age

Рисунок 2. График клинико-патологической значимости сверхэкспрессии EGFL7 при опухолях ЦНС (А-степень злокачественности; В-пол; С-шкала Карновского; D-локализация; Е-возраст)

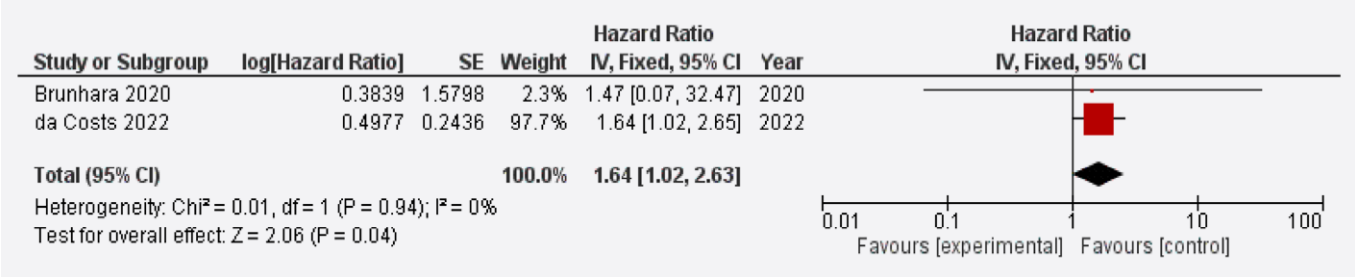

Figure 3. Forest Plot Result of Prognostic Significance of EGFL7 Overexpression with Overall Survival of Central Nervous System Tumors Patients.
Рисунок 3. График прогностической значимости сверхэкспрессии EGFL7 для общей выживаемости пациентов с опухолями ЦНС

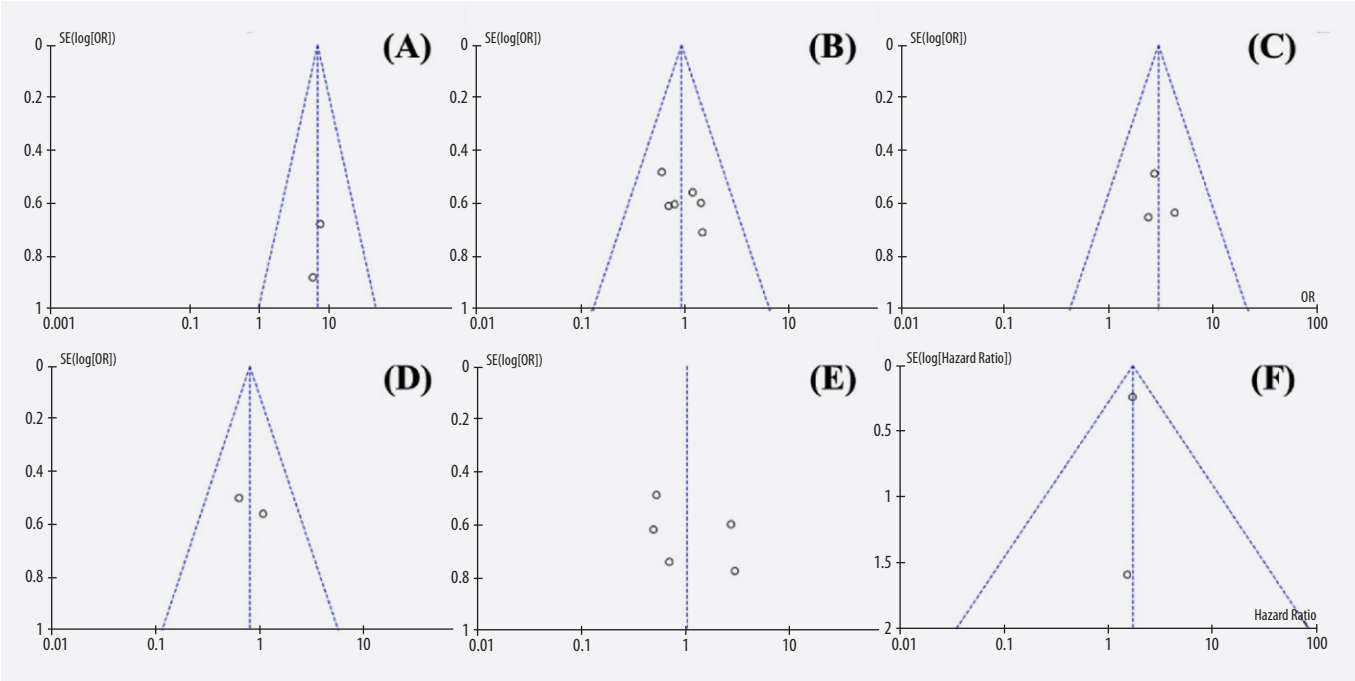

Figure 4. Funnel Plot of Publication Bias. SE(log[OR]) = Standard error multiplied log scale of odd ratio; SE(log(HazardRatio) = Standard error multiplied log scale of hazard ratio (A – Grade, B – Gender, C – KPS, D – Location. E – Age, F – Overall Survival).
Рисунок 4. График для оценки публикационного смещения. SE(log[OR]) – стандартная ошибка логарифма отношения шансов; SE(log(HazardRatio) – стандартная ошибка логарифма отношения рисков (A – степень злокачественности, B – пол, C – шкала Карновского, D – локализация опухоли, E – возраст, F – общая выживаемость)

by increased pro-angiogenic gene expression. Research by Huang et al[17] confirmed that EGFL7 expression was upregulated in malignant glioma compared to normal brain tissue. Current evidence suggests that angiogenesis induction by EGFL7 is associated with its role in interfering with Notch signaling. One of the EGF-like domains on the EGFL7 structure comprises a region that similar to a ligand of the Notch receptor, the Delta–Serrate–LAG-2 domain.[18–20] This shared characteristic allows EGFL7 to interact with Notch4, Notch1, and DLL4. Research by Wang et al, found that specifically in the CNS tumors, EGFL7 promotes proliferation and invasiveness of pituitary adenoma by interfering Notch2/DLL3 pathway.[20] Furthermore, previous studies propose that EGFL7 upregulation is triggered by β-catenin/transcription factor-4 (TCF-4) as a result of MAPK pathway overactivation, leading to increased tumor progression by paracrine signaling to adjacent vascular endothelial cells.[21]

We also found that the prognosis and KPS scores in patients with primary CNS tumors were negatively affected by EGFL7 overexpression. Those findings align with previous studies reporting that poor outcomes are associated with EGFL7 overexpression in pancreatic, ovarian, and laryngeal cancer.[11,13,22,23] As mentioned above, EGFL7 overexpression accelerates angiogenesis which is crucial in malignancy progression. In addition, EGFL7 overexpression has been associated with an increased incidence of metastasis and invasiveness through several mechanisms. The first involves the enhancement

Table 2. **Summary of Heterogeneity and Publication Bias Analysis of Each Group Analysis**
Таблица 2. **Сводка анализа гетерогенности и публикационного смещения для каждого группового анализа**

Clinicopathological Characteristic Group Analysis										
Analysis	**NS**	**Model**	**Status**	**PN**	**TN**	**OR**	**95% CI**	**pH**	**pE**	**pB**
Grade	2	Fixed	III-IV	28	36	6.81	2.38-19.51	0.83	<0.0001	0.317
			I-II	17	45					
Gender	6	Fixed	Male	83	148	0.91	0.58-1.45	0.80	0.169	0.573
			Female	93	161					
KPS	3	Fixed	Low	63	90	2.91	1.52-5.56	0.79	0.815	0.602
			High	45	90					
Location	2	Fixed	Cerebrum	48	82	0.81	0.39-1.67	0.48	<0.0001	0.317
			Non-Cerebrum	37	56					
Age	5	Random	Young	99	166	1.03	0.47-2.27	0.09	0.4364	0.327
			Old	55	101					
Analysis	**NS**	**Model**	**Hazard Ratio (HR)**				**95% CI**	**pH**	**pE**	**pB**
Overall Survival	2	Fixed	1.64				1.02-2.63	0.94	<0.0001	0.317

Note: NS – Number of Sample, PN – Positive Number of Sample, TN – Total Number of Sample, OR – Odds Ratio, CI – Confident Interval, pH – p Heterogeneity, pE – p Egger's Test, pB – p Begg's Test

Прим.: NS – количество образцов, PN – количество положительных образцов, TN – общее количество образцов, OR – отношение шансов, CI – доверительныый интервал, pH – p гетерогенность, pE – тест Эггера, pB – тест Бегга

of epithelial-to-mesenchymal transition in certain cancer.[14,24] The second mechanism entails the promotion of cell motility, thereby intensifying invasion and migration. This metaplastic process is driven by phosphorylation of focal adhesion kinase via the EGF-receptor-like domain.[25]

Regarding the patient age, gender, and tumor location, we found a non-significant correlation between these characteristics and EGFL7 overexpression in primary CNS tumors. The association between these two variables has also been reported in other studies, suggesting that EFGL7 overexpression is independent of age and sex.[17,19] This phenomenon is also observed with other frequently mutated genes in primary CNS tumors, such as Isocitrate dehydrogenase 1 (IDH1) mutation and O6-methylguanine-DNA methyltransferase (MGMT) methylation.[26–28] Based on tumor location, current evidence for EGFL7 overexpression in different regions of CNS remains limited. One study reported that EGFL7 was highly expressed in pituitary gland cells that had transformed into growth hormone-secreting pituitary adenomas.[20]

Since our meta-analysis is the first to specifically evaluate the clinicopathological and prognostic significance of EGFL7 in primary CNS tumors, several limitations remain. The was still an insufficient number of references to yield accurate results in meta-analysis. Furthermore, the analysis did not specify types of primary CNS tumors, which may compromise the reliability of the findings due to the considerable variability in origin, clinical features, and molecular characteristics. The extraction of HR also requires further validation due to the limited number of references and the potential for error during the conversion of the survival data into HR.

Conclusions

This meta-analysis demonstrated that EGFL7 overexpression significantly associated with tumor grade, overall survival, and KPS, but not with patient age, sex, or tumor location. These results suggest that EGFL7 may represent an important factor affecting primary CNS tumors and should be detected through genetic and histologic assessment.

Author contributions

Concept and design: Sasmana, Supadmanaba, Wihandani
Acquisition, analysis, or interpretation of data: Sasmana, Wiranata, Wihandani
Manuscript drafting and revising: Sasmana, Kusuma, Wihandani
Statistical analysis: Sasmana, Wihandani
Final approval of the version to be published: Sasmana, Wiranata, Kusuma, Supadmanaba, Wihandani

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