INTRODUCTION

Tumors in the central nervous system have become a global concern with incidence and prevalence rates increasing every year and contributing to various complaints and increased mortality. The global incidence rate of tumors in the central nervous system reaches 8.5 per 100,000 adult population and is the sixth leading cause of death from cancer. Most of the benign tumors of the central nervous system are non-malignant meningioma (40.1%) while the most common malignancy is glioblastoma (15.2%). Central nervous system tumor has a 5-year survival rate of just 36%, so it is referred to as one of the most progressive cancers. In addition, tumors of the central nervous system are the most common cause of cancer death in the pediatric population. Many cases of tumors in the central nervous system are quite difficult to detect and sometimes asymptomatic at an early stage thus it caused delayed treatment which worsens the prognosis. These conditions have led to the development of various approaches in terms of detection, monitoring, and treatment of malignancy. Several specific biomarkers in tumors of the central nervous system have been developed. Some of them such as detection of CD133, IDH1/2, TP53, BRAF, SOX2, NANOG, and so on. SRY (Sex determining region Y)-box transcription factor 2 (SOX2) is a gene that plays an important role in the regulation of cancer in humans. This gene is included in stem cell genes which, if dysregulated, will cause abnormalities in tissue growth and differentiation. The interaction between SOX2 and signal transducer and activator of transcription 3 (STAT3) induces the formation of various types of cancer, one of which is glioblastoma (GBM) in the central nervous system. SOX2 has roles in increasing the growth and metastasis of cancer cells while on the other hand can suppress tumor cells. This process is regulated by miRNA and lncRNA factors via the STAT3 and WNT/β-catenin signaling pathways. Several
previous studies have found the increased expression of SOX2 in tumors in the central nervous system whose expression is also influenced by several factors, such as age, gender, tumor location, ethnicity, and so on. SOX2 expression was also found to affect tumor progression so that it can be used as a marker to assess patient prognosis. Therefore, this review aims to provide an up-to-date summary evaluating the clinicopathological and prognostic significance of SOX2 overexpression in central nervous system tumors.

MATERIAL AND METHODS
This literature was created using a literature review method based on Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (7) in Figure 1.

Data Sources and Search
The author conducted a literature search through several search engines, including PubMed, ScienceDirect, and the Cochrane Library from January 2023 to February 2023 using several search keywords, including “SOX2”, “Tumor”, “Cancer”, and “Central Nervous System”. The literature search also used the Boolean Operator approach including “AND” and “OR”.

Study Eligibility Criteria
Study eligibility was assessed based on several inclusion and exclusion criteria. The inclusion criteria include: (1) English literature; (2) human research; (3) included central nervous system tumor patient’s sample; (4) explaining the association of SOX2 overexpression with clinicopathology and/or prognostic features of central nervous system tumors. While the exclusion criteria of the study, include: (1) unfinished studies at the time of the search; (2) studies that cannot be accessed completely. The selected studies were cohort and case-control studies; thus, the study quality and risk of bias were assessed using The Newcastle Ottawa Scale (NOS) for cohort and cross-sectional research.

Data Extraction
The data extraction process was carried out based on the variables available in the study. Systematic extraction of each study characteristic data including (1) literature base information (author and year of publication, nation, types of malignancies, number of patients, method of detecting SOX2 expression, and criteria of SOX2 overexpression); (2) clinicopathological data (gender, tumor grade, patient age, tumor location, SOX2 expression in primary and recurrent tumors); (3) prognostic value data, including the hazard ratio of overall survival and p-value. Prognostic data were taken directly from the literature and some were analyzed based on time-to-event outcome data using the method by Tierney et al (8).

Data Analysis
The effect of SOX2 overexpression on clinicopathological characteristics was analyzed using Review Manager 5.4 (Cochrane Collaboration, Oxford, UK). The results of the analysis will be presented in a Fixed Effect Model (FEM) on variables with a low level of heterogeneity (I^2<50%) and will be presented in a Random Effect Model (REM) on high heterogeneity (I^2>50%). The standardized mean difference was used to determine the effect size, with a 95% confidence interval with a value of p<0.05 indicating a statistically significant association and Odds Ratio >2 indicating a clinically significant association. Quantitative assessment of publication bias analysis involved Egger’s test and Begg’s test (MedCalc). A value of p<0.05 indicates the possibility of publication bias.

RESULTS
Characteristic and Research Outcome for Each Study
The characteristic details of each study are shown in Table 1. The selection of studies according to the flowchart according to Figure 1 resulted in 10 suitable study groups which were then followed up with qualitative and quantitative analysis. The study involved 466 patients with tumors in the central nervous system, mostly from Asian populations (5/10).
Most of the tumor types in the qualitative assessment of the study were gliomas (astrocytoma, oligodendrogliomas, oligoastrocytomas, glioblastomas) and some were meningiomas (3/10). Most of the SOX2 expression assessment in samples (9/10) was carried out on tumor tissue samples using the immunohistochemistry (IHC) method, while some used tumor cell samples using the immunofluorescence staining method and some used additional tests in the form of reverse transcription-quantitative polymerase chain reaction (RT-qPCR). The criteria for overexpression vary from 5% to 50% of the examination results. The NOS score of each study ranged from 6 to 9 indicating fair and good study quality. Each risk of bias analysis was showed in Supp Table 1.

### Association Between SOX2 Overexpression and Clinicopathological Features of Central Nervous System Tumors

SOX2 overexpression was found significantly correlate in females compared to the male population (OR 2.08; 95% CI: 0.64 to 7.05; p = 0.0002) that is pooled in a fixed effect model with low heterogeneity (I² = 13%). The association was also found clinically significant in tumor grade (III-IV vs I-II) and statistically significant in SOX2 expression in primary vs. recurrent tumors with Odds Ratios (ORs) of 7.05 (95% CI: 2.83 to 17.53; p< 0.0001) and 4.31 (95% CI: 1.41 to 13.14; p = 0.01) respectively.

On the other side, the analysis of age (>50 vs ≤50) and tumor location (supratentorial vs non-supratentorial) was found not significant with OR of 1.48 (95% CI: 0.71 to 3.08; p: 0.29) and 1.81 (95% CI: 0.64 to 5.09; p: 0.26) respectively that were pooled on the fixed-effect model (FEM). The analysis of each variable has been shown in Figure 2.

### Subgroup Analysis of SOX2 Overexpression Association with Clinicopathological Features of Central Nervous System Tumors

Based on the data extracted, the subgroup analysis was done in gender variables (in Asian and Non-Asian populations) and tumor grade (in glioma and meningioma). Our subgroup analysis showed a significant association of SOX2 overexpression with females in the non-Asian population (OR 5.31; 95% CI: 2.20 to 12.84; I² = 0.0002).

While the subgroup analysis of tumor grade with SOX2 overexpression was found clinically significant in glioma (OR 6.81; 95% CI: 2.26 to 20.54; I² = 65%; p: 0.0007) and meningioma (OR 8.41; 95% CI: 1.17 to 60.43; I² = 36%; p: 0.03) that were pooled in the random-effect model. The overall subgroup analysis result was shown in Figure 3.
Heterogeneity and Publication Bias Analysis

The analysis of heterogeneity found that the assessment of overall grade, grade in glioma, and overall survival from RevMan analysis confirmed by MedCal Meta-Analysis had significant heterogeneity data. The confirmation from the quantitative analysis showed that the analysis of SOX2 expression in primary vs. recurrent tumor had the possibility of publication bias (Egger’s test score: <0.001) (Table 2).

DISCUSSION

Central nervous system tumors are conditions with high mortality. Some cases are still very difficult to detect, especially in the early stages, and very difficult to monitor and cure. Various approaches from molecular biology have been developed to predict the progress of CNS tumors so that they can determine the current condition, predict the prognosis, and take appropriate treatment actions based on the patient’s condition. One of them is the detection of SOX2, a tumor biomarker that has been detected to have overexpression in central nervous system tumors, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, and so on.

The current meta-analysis shows that overexpression of SOX2 is strongly associated with a higher histopathological grade of CNS tumors. This shows that cancer with SOX2 overexpression has a higher progression. These results are similar to the previous meta-analysis conducted by Zhang, et al (2015) which showed SOX2 overexpression was related to breast cancer grade (OR=2.28, 95% CI=1.72-3.03) (19). SOX2 plays a major role in the development of tumors, including CNS tumors, especially because of its role as a stem cell gene involved in neurogenesis and tumorigenesis (20,21). Overexpression of SOX2 in tumor cells will induce pro-survival autophagy to prevent cell damage. This process is regulated by miRNA and lncRNA factors via the STAT3 and WNT/β-catenin signaling pathways. The WNT/β-catenin pathway will activate the GLI1/2 transactivator, then signal transduction occurs from the GPCR-s receptors and LRPS/LRP6 coreceptors thereby increasing the stabilization and accumulation of β-catenin, undergoing translocation to the nucleus which ends in increased proliferation. The increasingly massive proliferation causes an aplastic histopathological picture and leads to a tumor with a higher grade. It was also shown in a previous study that evaluated SOX2 expression in glioma samples and related to the grade of malignancy that amplification of the gene was found in neurospheres, glioblastomas, and aplastic oligodendromas.

Previous research by Zhang, et al did not find a significant relationship between SOX2 expression and age and gender, whereas the current meta-analysis found a significant relationship where SOX2 is expressed more in women but not related to age.

SOX2 is a gene that has emerged from the early stages of neurogenesis in the neural tube whose expression will decrease over time in the subventricular zone and dentate gyrus. This gene regulates the
In the process of metastasis, there is a relationship between epithelial-mesenchymal transition (EMT) and autophagy, while autophagy can be antagonistic to EMT and autophagy degradation can stimulate EMT. The SOX2 gene will activate EMT, downregulate E-Cadherin and increase N-Cadherin so that tumor cell motility also increases. In addition, cancer metastasis also involves mesenchymal factors such as TGF-β and increased ZEB. Metastases can continue and amplify because SOX2 undergoes nuclear translocation from β-catenin thereby increasing Beclin-1 expression, re-inducing autophagy which will stimulate EMT.

Therefore, SOX2 is also related to metastasis and tumor staging. The prognosis of central nervous system tumors is also determined by SOX2 expression on several sides of the cancer pathway. The prognosis of CNS tumors is correlated with advanced stage, life survival, and distant metastases, but is not affected by age and sex which have been evaluated in several tumor cell types. In this case, SOX2 plays a role in increasing the grade and size of the tumor as mentioned above. Meta-analysis of 13 different cancer types in 20 studies showed a reduction in overall survival (OS) (HR = 1.65, 95% CI: 1.34-2.04, P < 0.001) similar to the current meta-analysis, accompanied by a reduction in disease-free survival (DFS) (HR = 1.54, 95%CI: 1.14-2.08, P = 0.005).

**CONCLUSION**

This meta-analysis suggests that overexpression of SOX2 in central nervous system tumors clinically has a significant correlation with higher tumor grade both in gliomas and meningiomas, higher in females than in males especially in the non-Asian population, while statistically significant high in primary tumor tissue compared to recurrent tumor tissue. SOX2 overexpression is not significantly associated with patient age, tumor location, and gender difference in the Asian population. While the prognostic value shows insignificant results with SOX2 overexpression.

**ACKNOWLEDGMENTS**
Table 2. Summary of Heterogeneity and Publication Bias Analysis of Each Group and Subgroup Analysis

Clinicopathological Characteristic Group Analysis

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<tr>
<th>Analysis</th>
<th>NS</th>
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Clinicopathological Characteristic Subgroup Analysis

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<th>TN</th>
<th>OR</th>
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Prognostic Characteristic Group Analysis

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Abbreviations: NS: Number of Sample; PN: Positive Number of Sample; TN: Total Number of Sample; OR: Odds Ratio; HR: Hazard Ratio; CI: Confidence Interval; pH: p Heterogeneity; pE: p Egger’s Test; pB: p Begg’s Test

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DISCLOSURE

The author declares there is no conflict of interest in this meta-analysis.

REFERENCES


