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SYSTEMATIC REVIEW

Dendritic Cell Vaccines for Glioblastoma: A Systematic Review and Meta-Analysis Comparing New-Onset and Recurrent Cases

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Abstract: ***Introduction*:** Glioblastoma (GBM), an aggressive and highly recurrent brain tumor, remains a significant challenge despite advancements in treatment. With a median survival of only 15 months and recurrence often occurring within a year despite aggressive initial therapy, there is an urgent need for more effective therapeutic strategies. The interplay of intrinsic and extrinsic factors, such as genetic mutations and alterations in the tumor microenvironment, drives recurrence, highlighting the importance of targeted approaches. Emerging therapies, particularly dendritic cell (DC)-based immunotherapies, show promise in enhancing anti-tumor immune responses. This study aimed to compare the effectiveness of DC-based immunotherapy in improving survival outcomes for patients with newly diagnosed or recurrent GBM.

***Methods*:** We conducted a comprehensive search across four electronic databases (Cochrane Central Register of Controlled Trials, PubMed, Scopus, and Web of Science) up to March 2024 to identify pertinent studies evaluating the efficacy of DC vaccines in the treatment of both newly diagnosed and recurrent GBM. The quality of evidence from trials was assessed using the Cochrane risk-of-bias version 1 (RoB1) tool. Data from the included studies were extracted into a standardized online sheet and analyzed using Review Manager (RevMan) 5.4.

***Results*:** Our search identified three records with a total of 355 patients. The results of the meta-analysis showed that DC-based immunotherapy had a greater impact on recurrent GBM than on newly diagnosed GBM. However, overall survival favored newly diagnosed cases, demonstrating a more protective effect (HR = 0.62, 95% confidence intervals (CI) (0.46,0.84), $p = 0.002$) with no significant heterogeneity ($p = 0.97$, $I^2 = 0\%$). A similar trend was observed for progression-free survival, favoring newly diagnosed cases over recurrent ones (HR = 0.56, 95% CI (0.31,1.00), $p = 0.05$), with no significant heterogeneity ($p = 0.48$, $I^2 = 0\%$). Moreover, comparable results were observed for survival at both 12 and 24 months.

***Conclusion*:** Dendritic cell-based immunotherapy can enhance survival outcomes in GBM patients. The results showed DC-based immunotherapy to be more effective in newly diagnosed GBM than in recurrent cases.

Keywords: Dendritic cells, glioblastoma, recurrence, immune therapy, brain tumor, cell vaccine.

1. INTRODUCTION

Glioblastoma (GBM) is one of the most challenging central nervous system (CNS) malignancies to treat due to its aggressive nature and high recurrence rate. According to Ostrom and colleagues, GBM is the most common malignant CNS tumor, accounting for 48.3% of all malignant CNS tumors and 14.6% of all CNS tumors [1], with an estimated average incidence rate of 3.2 per 100,000 [2]. Despite advances in therapeutic modalities, GBM remains an incurable condition, with a median survival of only 15 months [3] and only 5.5% of patients surviving beyond 5 years after diagnosis [4]. This poor prognosis is attributed to tumor's invasive nature and high recurrence rate [5]. Initially, GBMs were believed to originate exclusively from glial cells; however, later evidence suggests that they may arise from various cell types with neural stem cell-like characteristics. These cells exhibit diverse stages of development, ranging from stem cells to neurons to glial cells [6].

The recurrence of GBM is a complex process. Despite maximal initial resection and multimodality therapy, approximately 70% of GBM patients experience disease progression within one year of diagnosis [5, 7]. The recurrence of GBM is influenced by multiple factors, including alterations in the tumor microenvironment, genetic mutations, and treatment effects [8]. Although patients may initially respond well to therapy, such as radiation and concomitant temozolomide, recurrent GBM often exhibits increased aggressiveness and resistance to treatments [9]. This recurrence suggests the presence of a resilient population of tumor cells capable of evading therapeutic effects, or alternatively, that radio-chemotherapy may induce senescence from which tumor cells recover and continue proliferation. The interaction between GBM cells and their microenvironment plays a crucial role in tumor progression and recur-

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rence, emphasizing the need for treatment strategies that target both intrinsic and extrinsic factors.

The CNS maintains a tightly regulated immune surveillance system, which involves the circulation of various immune cell types [10]. Dendritic cells (DCs) specialize in capturing, processing, and presenting antigens to T and B cells, thereby initiating adaptive immune responses or promoting immunological tolerance [11]. Many immunotherapy approaches focus on enhancing the function of cytotoxic CD8 T cells, including chimeric antigen receptor (CAR) T cells, checkpoint inhibitors, and adoptive T-cell therapy [12,13]. However, these treatments are less effective in GBMs due to the low baseline anti-tumor T-cell response and the absence of tumor-infiltrating lymphocytes (TILs) [14], as well as a potential lack of sufficient neoantigens. DC therapies offer a unique advantage by stimulating anti-tumor T-cell responses and increasing tumor immunogenicity through their antigen-presenting capabilities, effectively bridging innate and adaptive immunity [15]. By targeting the immune response early, DC-based therapies can enhance subsequent anti-tumor activity and generate cytotoxic responses against various tumor antigens more efficiently than CAR-T-cell therapy. As a result, there is a growing interest in developing GBM treatments that specifically target DCs due to their critical role in both innate and adaptive immunity.

Advances in understanding the molecular landscape of GBM recurrence have led to the identification of potential therapeutic targets aimed at preventing tumor regrowth and improving patient outcomes. Expedited sequencing technologies have revealed recurrent genetic alterations and signaling pathways involved in GBM progression. This knowledge is being utilized to explore new targeted therapies and immunotherapies to overcome treatment resistance and reduce recurrence rates. Innovative treatments, like tumor-treating fields (TTFields), have shown promise in extending progression-free survival for patients with recurrent GBM without requiring invasive procedures [16].

While previous reviews, such as that of Lv *et al*. [17], have examined the overall efficacy and safety of DC vaccines for GBM patients, in this systematic review and meta-analysis, we aimed to evaluate the existing evidence on the utilization of DC-based immunotherapy in GBM. Specifically, we sought to determine whether this approach can lead to improved survival outcomes in patients with recurrent or newly diagnosed GBM.

2. METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18] and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [19]. This study was registered with PROSPERO (CRD42024558448).

2.1. Database Search

We searched the Cochrane Central Register of Controlled Trials, PubMed, Scopus, and Web of Science databases for relevant articles up to March 2024. The following search terms were used in combination: (vaccine OR vaccination OR “dendritic cell vaccine” OR “dendritic vaccine”) AND (glioblastoma OR glioma), with no time constraints applied.

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria

For the quantitative assessment, we included all randomized controlled trials (RCTs) involving adult patients with a confirmed diagnosis of GBM, including both newly diagnosed and recurrent cases. RCTs evaluating survival analysis were included in this study.

2.2.2. Exclusion Criteria

Articles with designs other than RCTs, such as reviews, letters to editors, abstracts, opinion articles, and non-human studies, were excluded from the meta-analysis. Trials that used drugs other than DC-based therapy, included additional interventional drugs, or had comparators other than both types of GBM, were also excluded. Additionally, we excluded articles published in languages other than English.

2.3. Study Selection and Data Extraction

Search results were exported to EndNote version 20 [20], where duplicates were screened and removed. The remaining records were then imported into Rayyan [21] for an initial independent review of titles and abstracts by two authors to assess study eligibility. Any disagreements between the reviewers were resolved through discussion. If disagreements persisted, a third reviewer made the final decision. Full-text screening was conducted for eligible articles that met the inclusion criteria. Additionally, the references of the included studies were reviewed to identify any potential studies that may have been missed in the initial search. Data from the final records, including the year of publication, target population, baseline characteristics, study locations, and outcomes, were manually extracted from the articles into a Google Sheet by two independent reviewers.

2.4. Efficacy Outcomes

2.4.1. Primary Outcomes

The primary outcomes of this study were overall survival and progression-free survival. Overall survival is a measure used to describe the prognosis of a disease, while progression-free survival refers to the period during which a patient lives without disease progression.

2.4.2. Secondary Outcomes

The secondary outcome of interest was survival at 12 months after treatment, as well as survival at 24 months.

2.5. Risk of Bias Assessment

The risk of bias in the included clinical trials was assessed using the Cochrane risk-of-bias version 1 (RoB 1) tool for interventional studies, as outlined in the guidelines. The tool evaluates various domains, including selection bias, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, missing outcome data, selective reporting, and other potential sources of bias. Each domain was rated as having a low or unclear risk by two authors independently [22].

2.6. Statistical Analysis

Meta-analysis was conducted when at least two included studies provided available data for assessed outcomes, using RevMan 5.4.1 [23]. For time-to-event outcomes, including overall survival (OS) and progression-free survival (PFS), data were pooled as hazard ratios (HR) with 95% confidence intervals (CI). Since survival data were only presented in Kaplan-Meier curves, the PlotDigitizer online app [24] was used to extract the data. A reconstructed meta-analysis was then performed, with the corresponding HR and 95% CI estimated using a validated method obtained from the study by Tierney *et al*. [25]. The level of statistical significance was set at $p < 0.05$. A random-effects model (inverse variance method) was used instead of a fixed-effects model to provide a more conservative estimate of the pooled effect and improve the generalizability of results [19]. To assess the presence and degree of heterogeneity, we used the Chi-square and I-square (I2) tests, following the guidelines of the Cochrane Handbook (chapter 9) [19]. The I2 test, which

quantifies the proportion of variability across studies due to heterogeneity rather than chance, was interpreted as follows: 0–40% (insignificant), 30–60% (moderate), and more than 50% (substantial) [26]. Heterogeneity was considered statistically significant if the alpha level for the Chi-square test was below 0.1. Additionally, we could not assess publication bias using funnel plots due to the limited number of included studies.

3. RESULTS

3.1. Study Selection

A systematic literature search identified 1,919 potentially relevant records from multiple databases, including PubMed, Cochrane Central, Scopus, and Web of Science. Endnote [20] was used to remove 492 duplicate records. After screening the titles and abstracts of the remaining 1,427 records, 72 articles met the eligibility criteria for our research question. The final step involved full-text assessment, resulting in the exclusion of 69 records for various reasons. Consequently, three studies were included in both the qualitative synthesis and the meta-analysis: Liau (2022) [27], Hu (2022) [28], and Rudnick (2020) [29]. The search process, along with the number of included and excluded studies, is shown in Fig. (**1**).

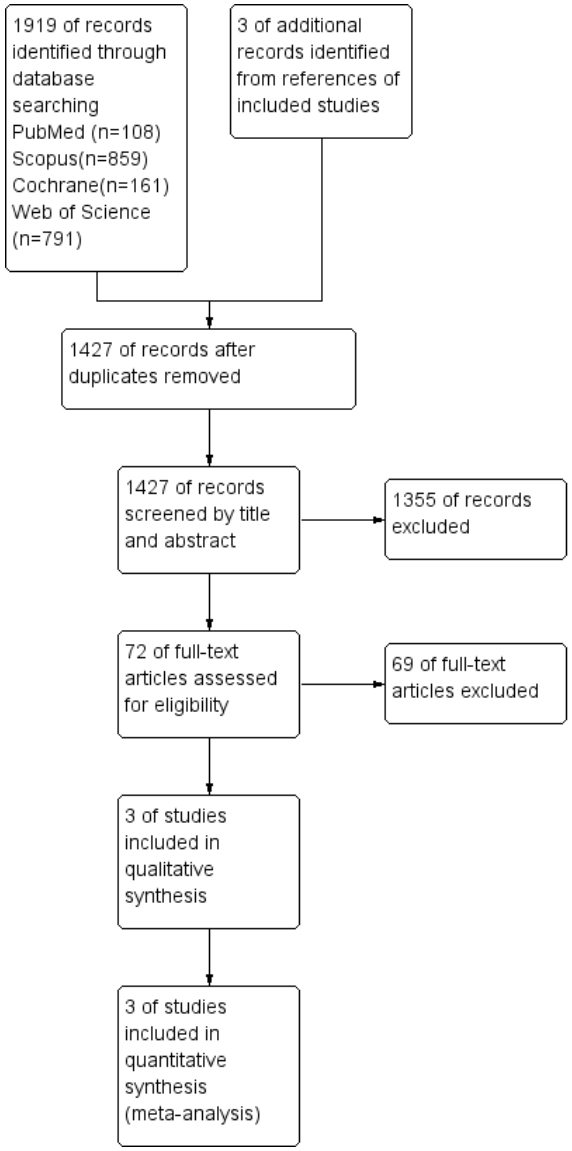

Fig. (1). Showing PRISM flow diagram of selection process.

3.2. Characteristics of the Studies

This analysis included the three clinical trials [27-29] published between 2020 and 2022, all of which evaluated the effectiveness of DC vaccination in patients with GBM. The studies involved a total of 355 patients, with follow-up periods ranging from 40 to 60 months. Among these, two studies [28, 29] were conducted in the USA, while that of Liau [27] was a multicenter trial spanning the USA, the UK, Canada, and Germany. Further details on these studies can be found in Table **1**, while patient baseline characteristics are presented in Table **2**.

3.3. Risk of Bias and Quality Assessment

We evaluated the potential for bias in the included RCTs using the RoB 1 tool. This evaluation identified one study as high risk of bias. The study by Hu (2022) [28] was classified as high risk due to concerns regarding detection bias (as outcome assessors were not blinded) and performance bias (as patients and personnel were not blinded). Figs. (**2** and **3**) present the risk of bias graph and risk of bias summary for the included studies.

3.4. Primary Outcomes

Overall survival: A comprehensive analysis of three studies, including those of Hu (2022) [28], Liau (2022) [27], and Rudnick (2020) [29], revealed that patients with newly diagnosed GBM experienced more favorable overall survival outcomes compared to those with recurrent cases. This finding was supported by a lower HR [HR = 0.62, 95% CI (0.46, 0.84)] and a statistically significant *p*-value of 0.002. Notably, no heterogeneity was observed among the studies, as indicated by a *p*-value of 0.97 and I2 = 0%. The forest plot illustrating the meta-analysis results is presented in Fig. (**4**).

Progression-free survival: A thorough examination of three studies, including those of Hu (2022) [28], Liau (2022) [27], and Rudnick (2020) [29], revealed that individuals with newly diagnosed GBM had better progression-free survival outcomes compared to those with recurrent cases. This conclusion was supported by a lower HR [HR = 0.56, 95% CI (0.31,1.00)] and a statistically significant *p*-value of 0.05. Importantly, no heterogeneity was detected among the studies, as evidenced by a *p*-value of 0.48 and I2 = 0%. The forest plot illustrating the meta-analysis results is presented in Fig. (**5**).

3.5. Secondary Outcomes

Survival at 12 months: A detailed analysis of three studies, including those of Hu (2022) [28], Liau (2022) [27], and Rudnick (2020) [29], found that patients with newly diagnosed GBM exhibited better survival outcomes at 12 months compared to those with recurrent cases. This conclusion was supported by a lower HR [HR = 0.41, 95% CI (0.26, 0.65)] and a statistically significant *p*-value of 0.05. Notably, no heterogeneity was identified among the studies (P = 0.96, I2 = 0%). The forest plot illustrating the meta-analysis results is presented in Fig. (**6**).

Survival at 24 months: A comprehensive analysis of three studies, including those of Hu (2022) [28], Liau (2022) [27], and Rudnick (2020) [29], revealed that patients with newly diagnosed GBM had better survival outcomes at 24 months compared to those with recurrent cases. This finding was supported by a lower HR [HR = 0.61, 95% CI (0.44,0.85)] and a statistically significant *p*-value of 0.03. Notably, no heterogeneity was detected among the studies (p = 0.97, I2 = 0%). The forest plot summarizing the meta-analysis results is presented in Fig. (**7**).

4. DISCUSSION

Glioblastoma (GBM) is a highly aggressive and malignant primary brain tumor with limited treatment options and poor prognosis

Table 1. Summary of included studies in the systematic review.

Study ID	Registration Number	Study Phase	Location	Follow-up (Months)	Vaccine	Newly Diagnosed GBM (n)	Recurrent GBM (n)
Hu 2022	NCT02010606	Phase I Clinical Trial	USA	54	Autologous dendritic cell vaccine pulsed with allogeneic stem-like cell line lysate	11	25
Liau 2022	NCT00045968	Phase III (Crossover) Randomized Trial	USA, Canada, UK, Germany	60	Autologous tumor lysate-loaded dendritic cell vaccine (DCVax-L)	232	64
Rudnick 2020	Not reported	Phase I Non-Randomized Clinical Trial	USA	40	Dendritic cell-based tumor vaccination	8	15

Abbreviation: GBM = glioblastoma multiforme.

Table 2. Characteristics of patients in included studies.

Study ID	Study Arm	Sample Size	Age (Mean ± SD)	Sex, Male n (%)	KPS (Mean ± SD)	MGMT Methylation n (%)	MGMT Non-Methylated n (%)	MGMT Missing	Hispanic n (%)	Non-Hispanic n (%)	Others n (%)
Hu 2022	Newly diagnosed GBM	11	55.9 ± 18.2	8 (72.7%)	85 ± 6.6	4 (36.4%)	–	–	–	10 (90.9%)	1 (9.1%)
	Recurrent GBM	25	52.3 ± 14.2	14 (56.0%)	80 ± 9.0	4 (16.0%)	9 (36.0%)	12 (48.0%)	–	4 (30.8%)	8 (69.2%)
Liau 2022	Newly diagnosed GBM	232	–	–	–	–	–	–	–	–	–
	Recurrent GBM	64	–	–	–	–	–	–	–	–	–
Rudnick 2020	Newly diagnosed GBM	8	60.6 ± 8.5	0 (0%) †	87.5 ± 6.6	–	–	–	–	–	–
	Recurrent GBM	15	51.9 ± 11.5	9 (60.0%)	88.0 ± 9.8	–	–	–	–	–	–

† All patients were female.
Abbreviations: GBM = glioblastoma; KPS = Karnofsky Performance Status; MGMT = O6-methylguanine-DNA methyltransferase.

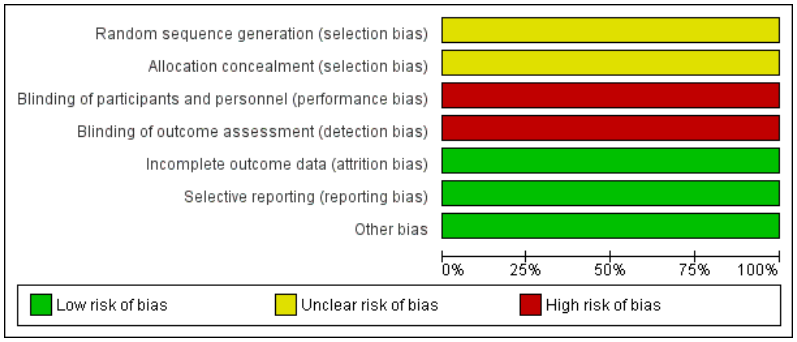

Fig. (2). Showing risk of bias graph. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

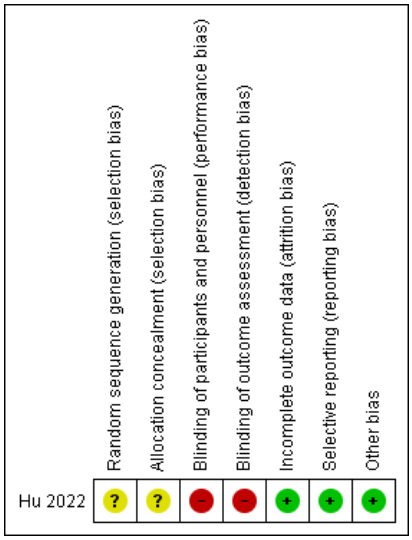

Fig. (3). Showing risk of bias summary. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

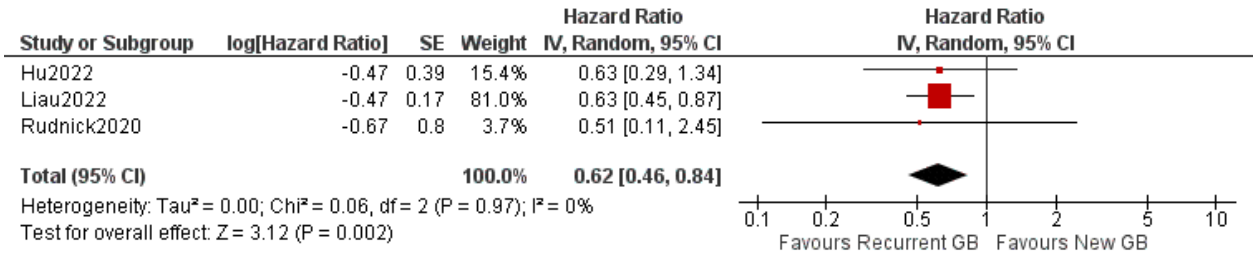

Fig. (4). Showing forest plot of overall survival outcome. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

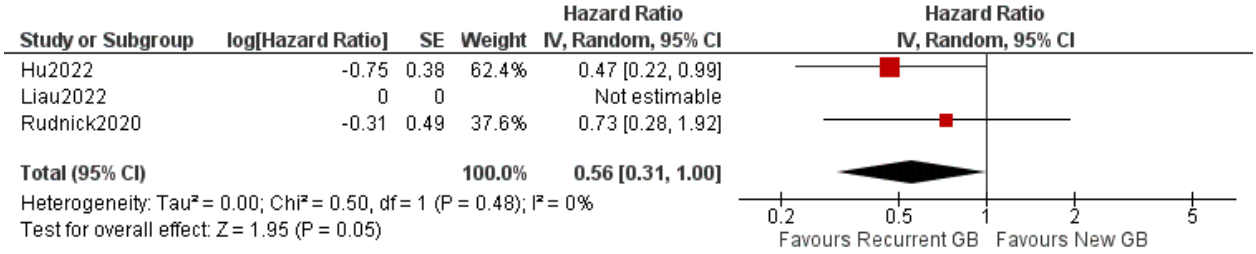

Fig. (5). Showing forest plot of progression free survival outcome. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

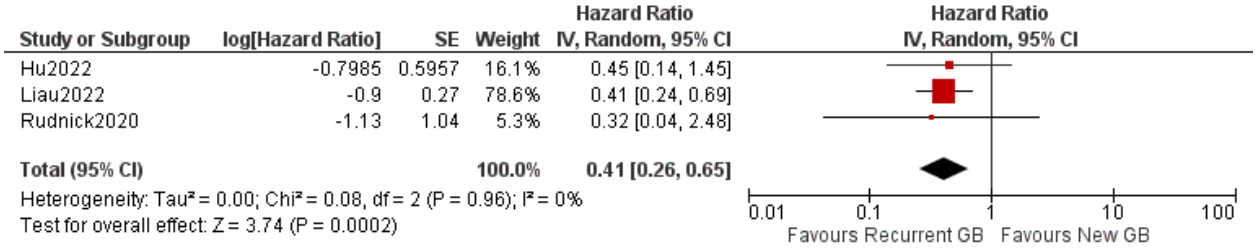

Fig. (6). Showing overall survival after 12 months. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

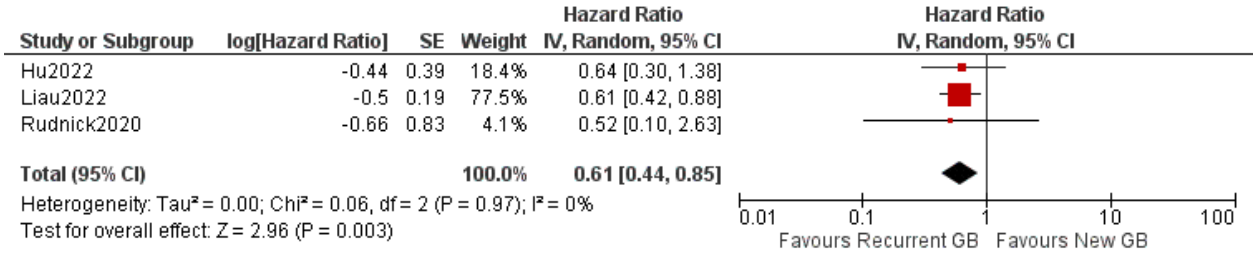

Fig. (7). Showing overall survival after 24 months. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

[30, 31]. Traditional therapies, such as surgery, radiation, and chemotherapy, have shown limited success in improving patient survival and quality of life [32,33]. Given these challenges, there is an urgent need to explore novel therapeutic approaches for GBM management.

Dendritic cell (DC) vaccines have emerged as a promising strategy for cancer immunotherapy due to their ability to stimulate and activate the immune system's response to tumor antigens [34,35]. As professional antigen-presenting cells, DCs efficiently process and present tumor-associated antigens (TAAs) to T cells, triggering a targeted immune response against cancer cells [36].

4.1. Main Findings

A comprehensive meta-analysis demonstrated that patients with newly diagnosed GBM had significantly better outcomes compared to those with recurrent cases. This conclusion was supported by a lower HR, indicating improved survival prospects for newly diagnosed patients. Notably, no heterogeneity was observed among the included studies, reinforcing the reliability and consistency of the results across different research settings. Furthermore, the analysis revealed that individuals with newly diagnosed GBM had better progression-free survival outcomes compared to those with recurrent cases. Additionally, secondary outcomes, including survival at 12 and 24 months, showed similar trends, with newly diagnosed patients experiencing better survival rates in both time frames. These findings further support the evidence that DC vaccination yields more favorable results in newly diagnosed GBM, highlighting its potential as an effective therapeutic approach in improving patient outcomes.

LIMITATIONS

Notably, there were some limitations to consider when interpreting these findings. First, our results were based on a limited number of RCTs [3], all with small sample sizes, highlighting the need for further high-quality RCTs with larger cohorts to validate the results in the future. Although there was no heterogeneity (I2 =

0), variations in the vaccine preparation, dosage, number of administrations, treatment durations, and initiation timing could introduce biases and potentially influence the pooled outcomes. Consequently, more RCTs are needed to determine whether study characteristics influence the effects of DC vaccinations on survival outcomes. Additionally, standardized preparation protocols and the most effective regimens for DC vaccines in GBM patients are yet to be established. It is also important to note that this meta-analysis focused on comparing DC vaccination outcomes between newly diagnosed and recurrent GBM, and therefore, a direct comparison of DC vaccination against conventional standard-of-care therapies was not feasible within the scope of this study due to data heterogeneity across the included trials. MGMT (O6-methylguanine-DNA methyltransferase) gene promoter methylation status is a critical prognostic and predictive biomarker in glioblastoma, influencing response to temozolomide chemotherapy. Finally, conducting a subgroup analysis based on MGMT status and assessing publication bias were not feasible due to the limited number of included studies.

CONCLUSION

This meta-analysis has been the first to compare the effectiveness of DC-based therapy in newly diagnosed versus recurrent GBM. The findings suggested that DC-based immunotherapy may improve survival rates of GBM patients, with greater efficacy observed in newly diagnosed cases.

AUTHORS' CONTRIBUTIONS

All authors substantially contributed to the study, including drafting of the manuscript, conducting the literature search, analyzing data, critically reviewing the manuscript, and approving the final version for publication.

LIST OF ABBREVIATIONS

CAR	=	Chimeric Antigen Receptor
CI	=	Confidence Interval
CNS	=	Central Nervous System
DC	=	Dendritic Cell
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TILs	=	Tumor-Infiltrating Lymphocytes

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study will be made available by the corresponding author on request.

STANDARDS OF REPORTING

PRISMA guidelines were followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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