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Dendritic Cells as Adjuvant Therapy to Decrease Mortality for Glioblastoma Patients: Meta-Analysis

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ABSTRACT

Introduction: Glioblastoma multiforme (GBM) is a primary neoplasm of the central nervous system with a low survival rate, requiring more effective treatment to improve long-term survival. Dendritic cell (DC) therapy is expected to reduce tumor progressivity. **Obective:** The purpose of this meta-analysis was to analyze the administration of DC in reducing mortality in GBM patients. **Methods:** A systematic literature search was conducted using the PRISMA method through the Embase database, PubMed, and the Cochrane Controlled Trials Register for relevant studies between giving DC to GBM patients with conventional therapy on the number of living patients compared to controls. Article quality was assessed using the Newcastle-Ottawa Scale and statistically analyzed using RevMan 5.4. **Results:** Of the 14 articles, the rates of reduction in the probability of death during the first three years after initiation of therapy were 26%, 36%, and 38%, respectively [1st-y HR: 0.74 (0.57-0.95), I^2: 15%, p=0.02; 2nd-y HR: 0.64 (0.51-0.81), I^2: 14%, p=0.0002; 3rd-y HR: 0.62 (0.48-0.81), I^2: 0%, p=0.0004]. However, there was no difference after 5 years [HR 0.81 (0.62-1.06), I^2: 0%, p=0.13]. **Conclusion:** The DC vaccine reduces the likelihood of death in the early years of therapy but has not been proven for long-term therapy.

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INTRODUCTION

Glioblastoma multiforme (GBM) is one of the deadliest adult cancers in the world. It is the most malignant primary brain tumor of the central nervous system (CNS).[1] GBM accounted for 45.6% of all primary malignant brain tumors, with a mean incidence of 3.1 cases per 100,000, and the highest peak incidence occurred at >75 years of age, reaching 15.03/100,000.[2]

Currently, the standard first-line treatment for GBM is maximum surgical resection followed by chemotherapy with temozolomide (TMZ) and radiotherapy.[3] The median OS of glioblastoma patients after complete resection was reported to have increased to 15.5 months, compared with 11.7 months for those who underwent subtotal resection and 5.9 months for those without resection.[4] Despite using multimodal treatment, the prognosis of newly diagnosed GBM patients remains low, with a mean OS time of around 15–17 months and a 5-year survival rate of even <2%.[1,4] This is because tumor cells, especially brain tumors, can evade immune cells through different mechanisms, such as antigenic modulation, decreased immunogenicity, and immune suppression.[5]

So new treatment strategies are needed, one of which is immunotherapy, which is currently being studied. A dendritic cell (DC)-based vaccine is undergoing clinical testing as an immunotherapy strategy.[3] Dendritic cells act as regulators of the initial immune response by releasing cytokines that activate cytotoxic lymphocytes and NK cells and then represent antigens to a subset of B and T lymphocytes.[6] Thus, DCs can modulate the patient's immune system against tumors, thereby inducing immunological memory related to long-term anti-tumor protection,[7] so this therapy is expected to provide the prospect of high OS values in GBM patients. Several studies of DC administration in the scope of GBM therapy in the last decade have been carried out quite a lot in the last decade. However, the research that has been done has varying parameters and results. Thus, a study is needed to analyze the overall effect of giving DC on the mortality rate of GBM patients.

OBJECTIVE

This meta-analysis study aimed to see whether these dendritic cells have a positive effect, especially in reducing the mortality rate of GBM patients.

METHODS

a. Selection and Screening

The authors conducted a systematic search of the experimental literature using the PRISMA methodology in PubMed, EMBASE, and the Cochrane Controlled Trial Register with categories of dendritic cell therapy, glioblastoma, and mortality from the inception of the database until July 2022. Downloaded articles were identified as duplicate publications and then reviewed.

b. Eligibility Criteria

The inclusion criteria for this study were as follows: (a) published articles describing survival and measurable numbers in patients with GBM by administration of DC; (b) the DC intervention performed will be compared with the control or placebo group, namely the group of GBM patients who were given conventional therapy, either surgery, chemotherapy, or radiotherapy; (c) clinical trials; (d) the article has a complete publication format; and (e) the literature was published in English. However, we excluded studies that met any of the following conditions: (a) data could not be assessed; (b) duplication; (c) not the original experimental study.

c. Data Quality Analysis

The Newcastle-Ottawa Scale (NOS) for the cohort study was used to rate the quality of the included articles.[8]

d. Data analysis

Review Manager 5.4 software was used to analyze the data. Calculate the Hazard Ratio (HR) with the inverse variance method for the random effect model. We used generic inverse variance data with a 95% confidence interval (CI). The heterogeneity of clinical trial data will be tested using I2. The results were considered significant if $p < 0.05$.

RESULTS

A systematic search through PubMed, EMBASE, and the Cochrane Controlled Trials Register yielded 256 articles, which were then subjected to a duplication screening process, including reading titles and abstracts, as well as the suitability of the number of living patients as a result of giving DC to GBM patients and data completeness, so that 14 studies were included in this meta-analysis study. The flow is depicted in Figure 1.

All of the studies chosen have a variety of assessments and parameters that vary; with a total sample size of 826, the average age was between 14 and 70 years. The types of DC vaccine used vary with the method of administration (intracutaneous,

subcutaneous, or intratumor). Each study has a different benchmark for administration time and dose. Then for the treatment, the control group was given conventional therapy through operative methods and/or chemotherapy. All of these characteristics are reported in detail in Table 1.

The articles were then evaluated for quality using the Newcastle-Ottawa scale, with a result range of 7-9, indicating high publication quality. These results are shown in Table 2.

We analyzed the hazard ratio (HR) in the first, second, third, and fifth years using data from all 14 studies that included the number of living patients in each group. In the first year, we included data from 12 articles on the number of living GBM patients: 173/260 in the DC group and 234/414 in the control group. These results showed that DC administration significantly decreased the mortality rate of GBM patients [HR 0.74 (0.57–0.95), I2: 15%, p = 0.02]. (Figure 1)

In the second year, there were 12 studies stating the number of living patients with DC administration was 85/190, while conventional therapy was 62/389. The comparison value significantly decreased [HR 0.64 (0.51-0.81), I2: 14%, p = 0.0002]. (Figure 2) Even in the third year of evaluation of the number of living patients in the eight articles, DC showed an increased protective ability with HR 0.62 (0.48–0.81), I2: 0%, p = 0.0004. Thus, for the first three years after initiation of therapy, the rates of reduction in the probability of death were 26%, 36%, and 38%, respectively. However, in the fifth year, the administration of DC compared to conventional did not show a significant difference [HR 0.81 (0.62–1.06), I2: 0%, p = 0.13]. These results are shown in the forest plot shown in Figure 3 and Figure 4.

DISCUSSION

Pathologically, in the case of brain tumors, there is an increase in the reactivity of CD8+ T cells that acts systemically to eliminate malignant cells.[9,10] Most clinicians use standard therapy modalities carried out continuously and intersecting, such as subtotal and total tumor resection, radiotherapy, and chemotherapy.[11] Currently, immune therapy is being developed to increase the effectiveness of treatment, one of which is dendritic cells (DC).

The therapeutic collaboration between radiotherapy, chemotherapy, and DC positively interacts. Radiotherapy and chemotherapy are known to decrease CD4+ cell activity globally, which has an effect on increasing other immune responses.[12] Local radiotherapy also reduces suppressor T cells that enhance effective T cell stimulation. DC becomes the most potent antigen-presenting cell (APC) in the immune system to activate the immune response against tumors.[7,13] Dendritic cells become active as strong immune stimulators by releasing interleukin (IL)-12 when bound to pathogenic molecules such as lipopolysaccharide (LPS), which triggers the response of type 1 T-helper (Th1) lymphocytes and tumor antigen cytotoxic T cells to be eliminated.[9,10,14] The mechanism of this protective effect increases chemotherapy sensitivity in the remaining tumor cells to cytotoxic activity.[15] Jie *et al*. discovered that in the DC group there was a significant increase in CD3+, CD3+/CD4+, CD4+/CD8+ ratio, NK cell percentage, and serum levels of IL-2, IL-12, and IFN-U, indicating that DCs can induce Th1 immune responses as an antitumor.[16,17] Furthermore, the ability to induce B and T cells can theoretically increase long-term antitumor protection.[7]

The mortality of GBM patients who got DC was, according to the findings of our meta-analysis, significantly better than controls in the first year, decreased considerably in the second year, and rose to a peak in the third year. This indicates that DC therapy's effectiveness is being delayed. A meta-analysis that examined the short-term impact of DC on the survival rate of GBM patients showed a non-significant result at six months.[6] This delay in therapeutic activity was caused by the inhibition of DC transfer to lymph nodes, thereby reducing efficacy.[18] On the other hand, the generation of an immune response after DC administration may undergo sensitization, wherein the proliferative intensification of mononuclear cells and a significant increase in the leukocyte migration index occur after the third to sixth injection.[1] In addition, several factors influence disease progression and pre-vaccination immune status.[19] A study that looked at pre-vaccination immune status with Th1 indicators, IFNγ, CD8+ cells, and monocytes discovered that patients with high immunity had a higher survival rate.[3,20] The lower the tumor grade, the better the prognosis.[16]

In the fifth year, the DC administration showed no significant results compared to the control. This is thought to be due to limited studies assessing long-term protective effects. In addition, antigenic proteins introduced, processed, and presented by DCs are likely to be mutated so that they are recognized as non-malignant.[9] GBM tumor cells have a strong ability to inhibit the immune system so that it affects proliferation and immune function, and necrosis around the lesion reduces the ability to circulate T cells to reach the site.[21] In addition, the hematotoxic effect of TMZ chemotherapy also inhibits the multiplication of effector T cells, which function to reduce tumor immune tolerance.[9]

The dose and interval between administrations are two critical factors in the success of DC as adjuvant therapy.[13] However, a study by Chang *et al*.,

which used relatively higher DC doses with short administration intervals, showed a non-significant effect in the first year.[10] In subsequent years, it consistently provided good protective results. However, it is necessary to pay attention to doses that can cause dangerous side effects, such as liver failure or delayed hypersensitivity, fever, and gastrointestinal complaints.[10]

In addition, the initiation of therapy is expected to be as early as possible.[11] In most relapse cases, DC will be given earlier because no re-operation or radiotherapy is performed.[13] Newly diagnosed GBM patients often experience recurrence at the start of immunotherapy due to the formation of clones of mutant GBM cells by radiotherapy induction with changes in the antigenicity of the original GBM cells used for vaccine preparation.[10] It is necessary to conduct a study to see the feasibility of starting DC therapy as soon as possible after surgery and without waiting for radiotherapy.[22]

Another factor is the patient's age (patients under 50 years old have a higher survival rate)[23] and the volume of the resected tumor.[14] Surgical tumor removal is carried out as safely as possible, with minimal residuals.[24] It has been proven that postoperative chemotherapy has a large positive effect on GBM patients.[23] However, Ardon *et al*. stated that there was no significant difference between total and subtotal resection. This is because some samples from subtotal resection have lower RPA values and have the promoter of the O6-methylguanine-DNA methyltransferase (MGMT) gene in tumor cells, which are generally more sensitive to chemotherapy reagents.[15] Patients with a methylated promoter of the MGMT gene have a better prognosis.[23]

The different methods of producing DC therapy (such as induction methods with LPS, IFN, etc.) result in different results for the procedure.[9] This has made it difficult for several studies to apply the standardization of antitumor immune monitoring to date, which is necessary to prevent bias in various immune therapies, especially when using whole tumor cell lysates as antigens.[15] Cho *et al*. used DC-induced intact tumor cells that died from gamma radiotherapy to provide a more heterogeneous protein antigen matrix than lysates, peptides, DNA, and mRNA to minimize the potential for tumor immune escape.[13] Moreover, tumor lysates have advantages: they produce a more specific antigen immune response, minimal HLA restriction, and are easy to personalize for each patient.[20,25]

Future studies are anticipated to explore more enhancement of anti-tumor immune reactions, for instance by combining DC vaccination with other immunotherapy, as several studies have not been able to explain the immunological pathways involved (checkpoint inhibitors, anti-PDI).[26] In addition, the relatively small number of GBM patients with a a poor prognosis makes the clinical trials into studies that do not represented mass efficacy.

CONCLUSION

The DC vaccine has been shown to reduce mortality in the early years of therapy but is not significant for long-term treatment. As a result, more research on the standardization of DC administration in GBM patients with a larger sample size is needed to assess the efficacy of therapy. However, several factors must be considered, including age, severity, tumor resection volume, dose, and timing of administration.

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Author contributions
AR contributed to conceptualization, drafting, data extraction, editing, and administration. EM performed all data processing, editing, reviewing, and monitoring. All authors read and approved the final draft.

Conflict of Interest
The authors have no conflicts of interest to disclose for this report.

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TABLES AND FIGURES

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Table 1. Study characteristics

Author, year	Sample	Age	Outcome	DCV Type	Method	Time	Dose
Batich 2017[26]	34	55	PFS, OS, IFN-γ, MRI Changes, Treg respond, CD8 CD8+	pp65 lysosome-associated membrane glycoprotein mRNA-pulsed DCs	IC	During CX-RT	early: $2x10^7$. follow up : 10^7/month until 10x
Batich 2020[27]	34	56-57	OS, migration rate	pp65 RNA-pulsed DCs	IC	NA	NA
Buchroithner 2013[11]	40	NA	PFS, OS	Tumor lysate-charged autologous DCs	NA	After RT-CX	10x administration
Cho 2012[13]	52	14-70	OS, PFS; 1-, 2-, and 3-year survival rates, QoL	Whole-tumor lysate pulsed DCs	SC	During CX-RT	$2–5 \times 10^7$
Jan 2018[21]	47	51.8	CCRT, PD-1+, OS, PFS, CD45+, CD4+, CD8+, PD-L1	Autologous dendritic cell/tumor antigen vaccine	NA	Before CX-RT	$2–5 \times 10^7$ total 14-16x
Jie 2012[16]	25	43.1	cd3+; cd3+ cd4+; CD3+ CD8+; CD4+ CD8+, NK, IL2,IL12, IFN, CR, NC, PD, PR partial response	Autologous glioblastoma-DCs	SC	Before CX-RT	10^6 total 6x
Leplina 2006[24]	119	42.6	IFN-γ, TNF-α, IL-13, IL-10, Antigen-Specific Response, Patient Survival	Interferon-induced DCs	SC	After surgery	$10x10^6$ total 6x
Vik-mo 2013[18]	84	NA	TSL, hTERT, size tumor, AE, OS, PFS	autolog DC based cancer stem cell-mRNA	IC	After surgery-RT until CX	107 total 9-18x
Wheeler 2004[28]	36	55	CTL, volume tumor by MRI, OS	autologous tumor freeze-thaw lysate	SC	After surgery	$10 – 40x\ 10^6$
Wen 2019[29]	124	59.2	PFS, OS, AE,HLA-A2 antigens, HLA-A1 antigens, immune response	DCs pulsed with six synthetic peptide epitopes targeting GBM tumor	IC	During CX-RT	1.1×10^7 1x/month during CX
Yamanka 2005[30]	45	48.9	hypersensitivity, OS, IFN-g ELISPOT assay, radiological findings	Peripheral blood DCs pulsed with autologous tumor lysate	IC / intratumor	Before CX-RT	$1x10^7$
Yu 2004[31]	34	44.7	OS, AE, IFN-γ, HER-2 CTLs, gp100-specific CTLs, MAGE-1-specific CTLs	autologous DCs pulsed with tumor lysate	IC	Before surgery	2×10^5.

Notes : PFS= Progression Free Survival; IFN= Interferon; CX= Chemotherapy; RT= Radiotherapy; RNA= Ribonucleic Acid; SC= Subcutan; IC= Intracutan; AE= Adverse Effect; NA= Not Available; QoL= Quality of Life; CR= Complete Response; DC= Dendritic Cells; NC= No Change; PD= Progressive Disease; PR= Partial Response; IL= Interleukin;

Table 2. Data quality assessment

Article	Selection	Comparability	Outcome	Total Score
Batich 2017	***	**	***	8
Batich 2020	***	**	***	8
Buchroithner 2013	***	**	**	7
Buchroithner 2018	***	**	***	8
Chang 2011	****	**	***	9
Cho 2012	****	**	***	9
Jan 2018	****	**	***	9
Jie 2012	****	**	***	9
Leplina 2006	****	**	***	9
Muller 2015	****	**	***	9
Vik-Mo 2013	****	**	***	9
Wen 2019	****	**	***	9
Wheeler 2004	****	**	***	9
Yamanka 2005	****	**	***	9
Yu 2004	****	**	***	9

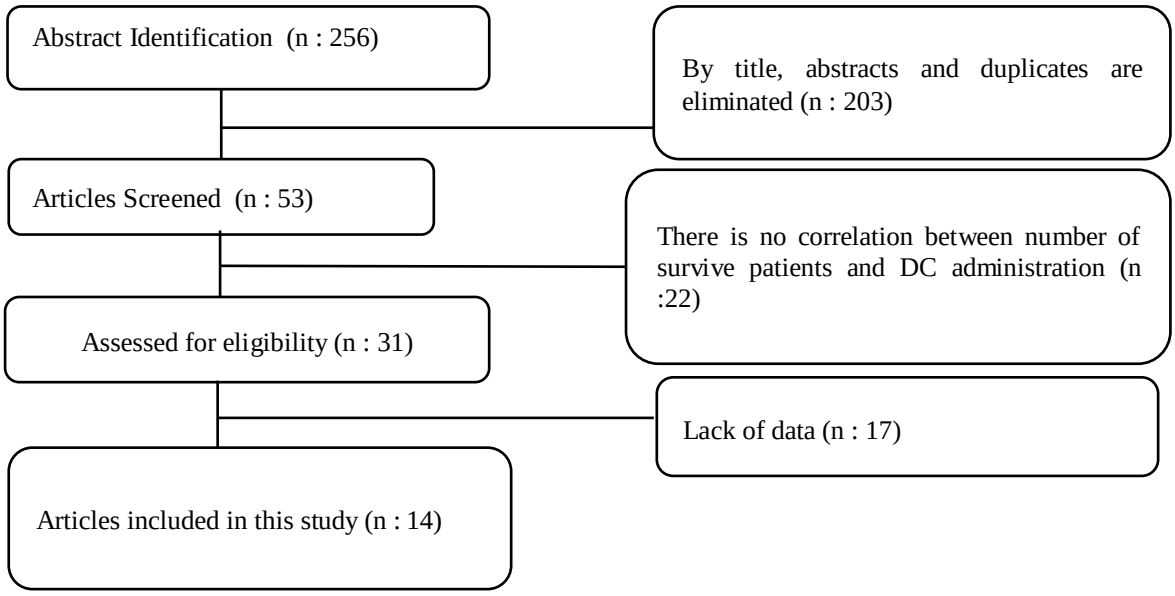

Figure 1. Flow diagram of study selection with PRISMA Method

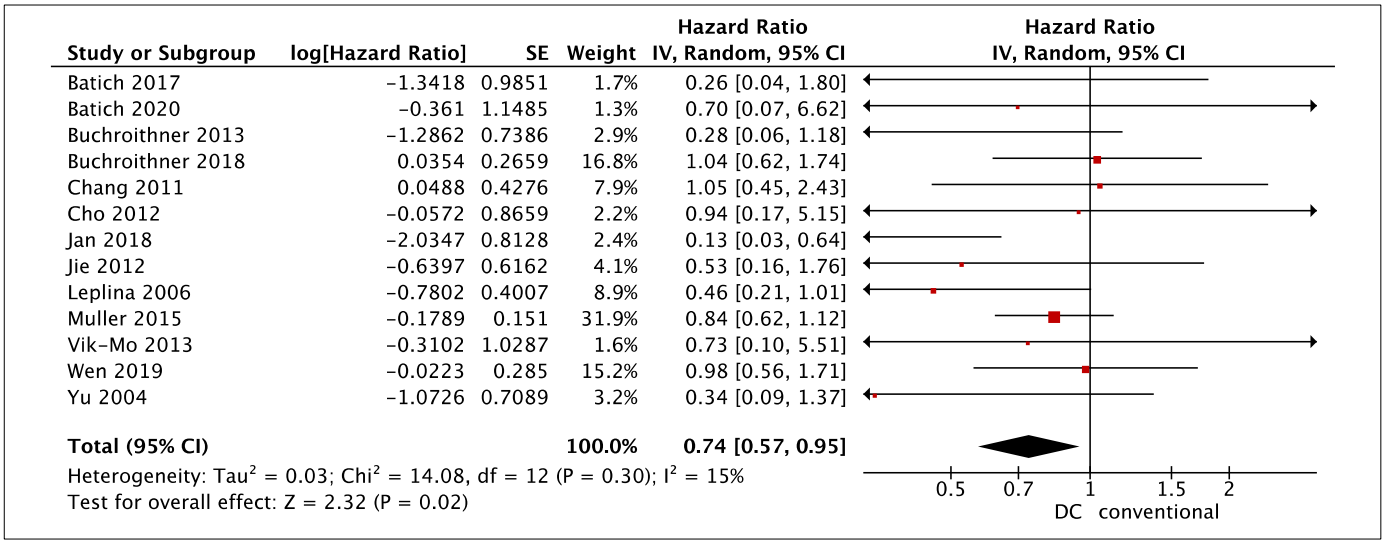

Figure 2. Forest Plot of Hazard Ratio in the First Year

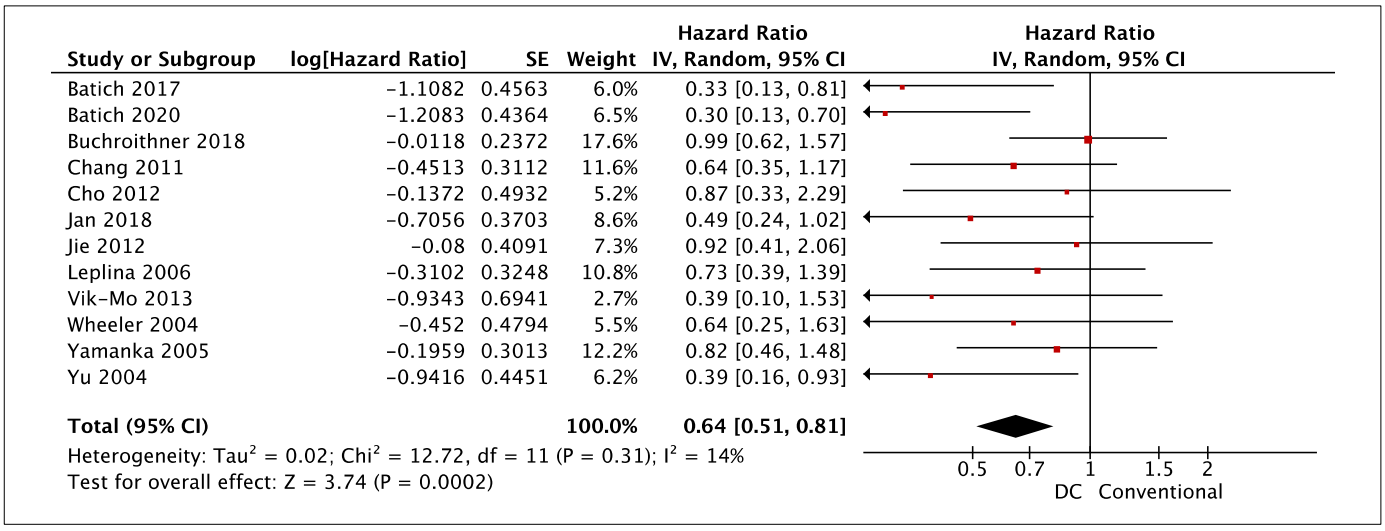

Figure 3. Forest Plot of Hazard Ratio in the Second Year

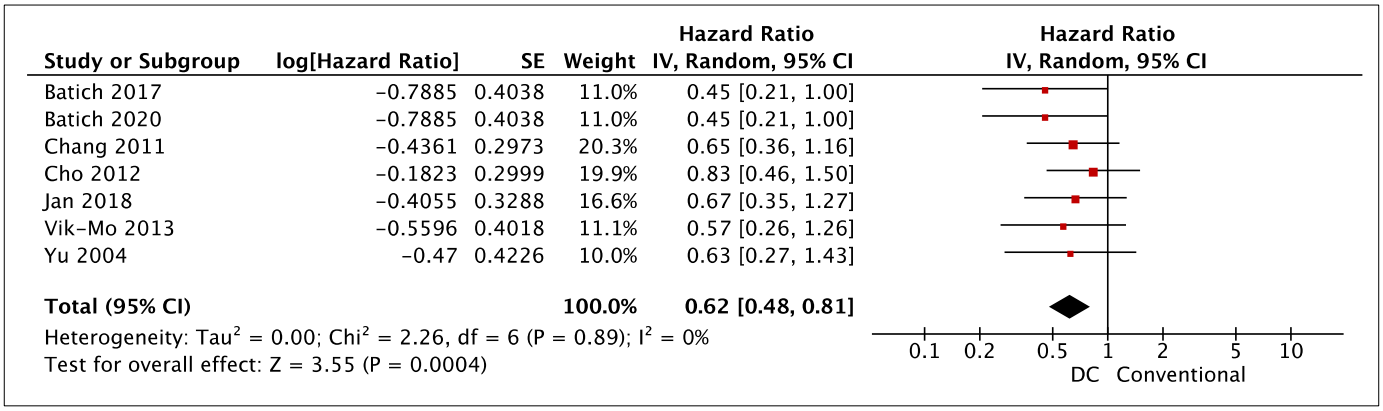

Figure 4. Forest Plot of Hazard Ratio in the Third Year

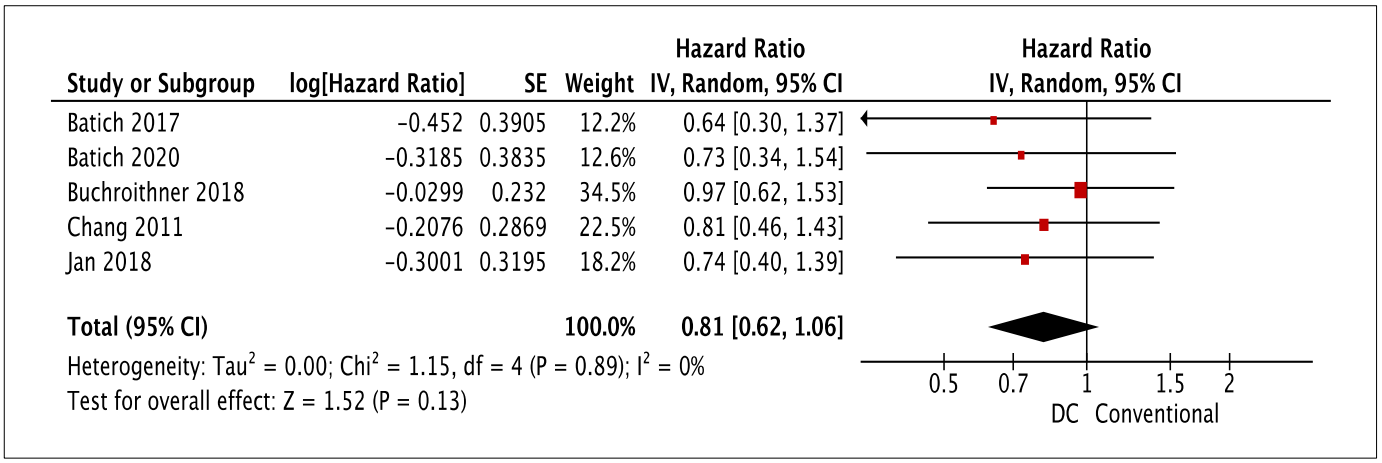

Figure 5. Forest Plot of Hazard Ratio in the Fifth Year