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The impact of hyperglycemia on survival in glioblastoma: A systematic review and meta-analysis

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ABSTRACT

In the management of glioblastoma (GBM), there is a considerable predisposition to hyperglycemia due to significant integration of corticosteroid therapy to treat predictable clinical sequelae following diagnosis and treatment. The aim of this study was to quantify effect of hyperglycemia during the management of GBM on overall survival (OS). Searches of seven electronic databases from inception to January 2018 were conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. There were 1475 articles identified for screening. Prognostic hazard ratios (HRs) derived from multivariate regression analysis were extracted, and analyzed using meta-analysis of proportions and linear regression. Six observational studies reporting prognostic HRs in 10 cohorts were included. They described 1481 GBM diagnoses, all surveyed for hyperglycemia during management. Hyperglycemia was found to confer a statistically significant poorer OS outcome (HR, 1.671; $p < 0.001$). This trend and its significance was not modified by study year, size or proportion of pre-diagnostic diabetes mellitus. Hyperglycemia in GBM is an independent poor prognostic factor for OS. Heterogeneity in clinical course limits inter-study comparability. Future, prospective, randomized studies will validate the findings of this study, and ascertain the potential benefit of more rigorous monitoring for hyperglycemia and glycemic control.

1. Introduction

The median survival in patients with glioblastoma (GBM) is 14 months following a standard treatment regimen of surgery, chemotherapy and radiation [1]. While attempts to significantly prolong overall survival (OS) have yet to come to fruition, a number of prognostic factors have been established to improve interpretation of clinical presentation. These include age at diagnosis, superior Karnofsky Performance Scale (KPS) score, and extent of surgical resection [2,3]. It has been recently suggested by a large cohort study [4] that hyperglycemia may also be prognostic in GBM.

The potential for hyperglycemia to possess prognostic potential is not novel in oncology. In 1924, Otto Warburg noted tumor cells preferentially perform anaerobic glycolysis for metabolism and thus division, a process which requires glucose to produce cellular energy [5]. A negative association between hyperglycemia and OS has been observed in multiple solid cancers, including breast [6], lung [7] and liver [8]. However, particular relevance to GBM derives from the high disposition by which hyperglycemia-inducing corticosteroids are administered in the standard treatment of care of GBM – primarily to manage common edematous swelling after treatment, as well as provide symptomatic relief for elevated intracranial pressures [9].

Given the heterogeneous clinical course of GBM, the reported influence of hyperglycemia on overall survival (OS) can be subject to confounding by other, established prognostic factors. A hazard ratio (HR) is a prognostic statistic derived from regression analysis to infer the effect of a particular indication. When obtained in a multivariate setting, it stands as an independent factor to other potential prognostic factors. The aim of this study was to search the current literature for HRs obtained from multivariate analyses only to investigate the independent prognostic effect of hyperglycemia upon GBM OS by means of meta-analysis.

2. Methods

2.1. Search strategy

The strategy was designed around the PICO question format – Do GBM patients (Population) who experience hyperglycemia (Indication) compared to those who do not (Comparator) have a superior OS

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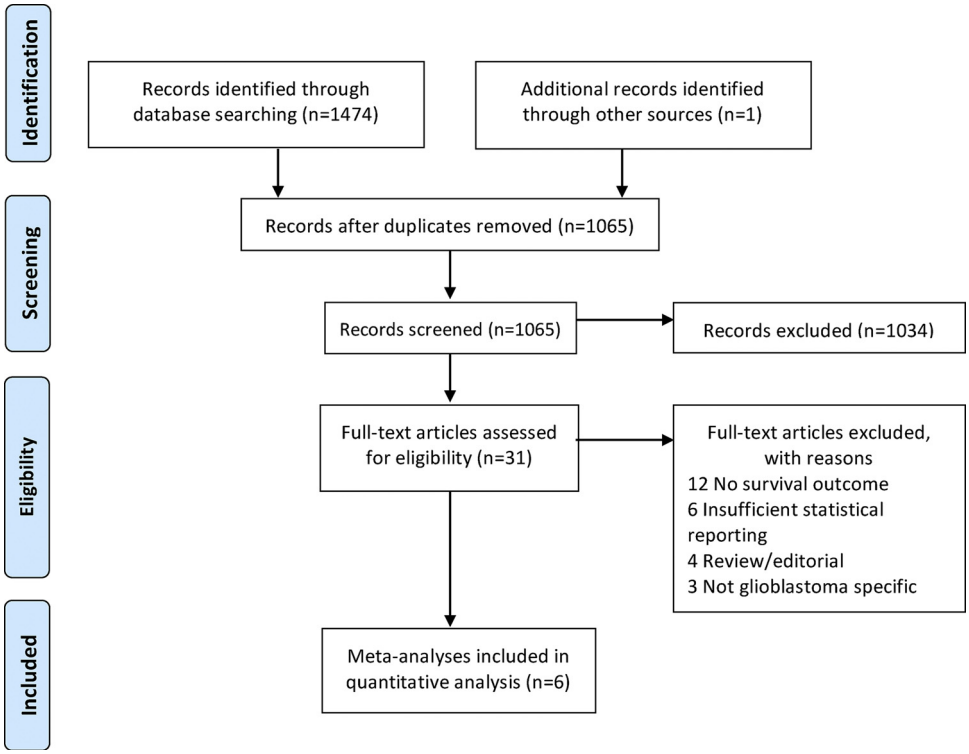

Fig. 1. The results of the search strategy as performed by under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

(Outcome)? The present review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations [10]. However, we did not produce a predefined study protocol. Electronic searches were performed using Ovid Embase, PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to January 2018. The literature involving all comparative studies were searched by using the following string of MeSH terms: (glioblastoma OR glioma) AND (hyperglycemia/hyperglycaemia OR diabetes), with the PubMed string provided in the Supplementary. All identified articles were then systematically assessed against the inclusion and exclusion criteria independently by two investigators (V.M.L. and A.G.).

2.2. Selection criteria

The inclusion criteria used to screen all identified articles were 1) confirmed histopathological cases of GBM, 2) with a clinical definition of hyperglycemia, 3) summarized by a comparative prognostic hazard ratio (HR) statistic accompanied by estimation of error (i.e. 95% CI, confidence interval), from adjusted Cox multivariate regression analysis, 4) in cohorts of patients > 18 years. The exclusion criteria applied to all identified articles were 1) low grade glioma, and 2) cohorts of patients < 18 years. When institutions published duplicate studies involving overlapping patients or increased lengths of follow-up, and when studies reported multiple time courses of the same treated cohort, the most complete reports were included for quantitative assessment. All publications were limited to those involving human subjects and in the English language. Reviews, abstracts, case reports, conference presentations, editorials and expert opinions were excluded to minimize potential publication bias and duplication of results.

2.3. Data extraction and critical appraisal

All data were extracted from article texts, tables and figures with any estimates made based on the presented data and figures. This includes variance estimations based on established statistical methodologies when appropriate [11–13]. The clinical outcome of interest was prognostic effect of hyperglycemia as inferred by a HR and its respective 95% CI. Two investigators (V.M.L. and A.G.) independently reviewed each included article with any discrepancy resolved by discussion to reach consensus. All attempts were made to contact study authors for data clarification if needed. Because quality scoring is controversial in meta-analyses of observational studies, each article included in our analysis was appraised according to a modified version of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria [14] and assessed by a modified Newcastle-Ottawa Scale (NOS) [15].

2.4. Meta-analysis

The HRs of each included study were pooled together by meta-analysis of proportions via a logit transformation to provide the overall summary statistic. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity [16]. A random-effect (RE) model was tested, and in the case of $I^2 < 50\%$, a fixed-effect (FE) model was also considered if suspicion was low for possible clinical diversity and methodological variation between studies. Linear regression was performed to analyze for potential modifying trends by study year, size, and proportion of pre-diagnostic diabetes mellitus (DM). The effect coefficient (EC) is reported for each analysis to identify the direction of modifying trend when non-zero.

Publication bias was assessed through the generation of funnel plots for all outcomes and assessed for asymmetry. The final inclusion of any outlying study was reconsidered in the context of overall trend direction and significance upon their exclusion. All p values were 2-sided