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

Victor M. Lu\(^a,b,c,^*\), Anshit Goyal\(^c\), Lachlin S. Vaughan\(^b\), Kerrie L. McDonald\(^b,b\)

\(^a\) Cure Brain Cancer Neuro-oncology Laboratory, Prince of Wales Clinical School, University of New South Wales, Sydney, Australia
\(^b\) Prince of Wales Clinical School, University of New South Wales, Sydney, Australia
\(^c\) Mayo Clinic Neuro-Informatics Laboratory, Mayo Clinic, Rochester, MN, USA

**A R T I C L E   I N F O**

**Keywords:**
Glioblastoma
Hyperglycemia
Survival
Prognosis
Blood glucose

**A B S T R A C T**

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 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
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 (CCRT), 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 analyses, 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. I² 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 I² < 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.
with significance set at \( p < 0.05 \). Statistical analyses were conducted with STATA 14.1 (StataCorp, College Station, Texas).

### 3. Results

#### 3.1. Literature search

The search strategy identified a total of 1475 studies (Fig. 1). After removal of 410 duplicate studies, inclusion and exclusion criteria were applied to titles and abstracts of the 1065 articles. This yielded 31 studies that underwent full-text analysis. Six retrospective observational studies [9,17,18,20,21] demonstrating significant prognostic effect following their own multivariate analysis (Table 2).

#### 3.2. Demographics

The overall cohort of included studies consisted of 1481 GBM patients in which respective definitions of hyperglycemia were applied over a period of observation (Table 1). Where reported, hyperglycemia was observed in 36% of the overall cohort, with a median age at presentation of 56 years and 59% of the male gender. The proportion of patients with pre-diagnosis DM ranged from 5% to 12% across the studies.

#### 3.3. Clinical features

The definition of hyperglycemia was study dependent in terms of diagnostic threshold and frequency (Table 2). All cohorts except one [18] reported GBM patients following a primary management regime of surgery, chemotherapy and radiation.

#### 3.4. Prognostic effect of hyperglycemia

The 10 cohorts reported a pooled HR of 1.671 (95% CI, 1.401–1.993; \( p < 0.001 \); \( \chi^2 = 40.5\% \)) by RE model for OS for hyperglycemia observed during GBM management (Fig. 2). Individual HRs ranged from 1.09 to 2.44, with seven individual cohorts in five studies [9,17,18,20,21] demonstrating significant prognostic effect following their own multivariate analysis (Table 2).

Linear regression of individual study HRs did not detect any significant modifying trend with respect to study year (EC, 1.013; 95% CI, 0.944–1.088; \( p = 0.678 \)), study size (EC, 1.001; 95% CI, 0.998–1.004; \( p = 0.477 \)) or proportion of cohort with pre-diagnosis DM (EC, 1.065; 95% CI, 0.968–1.172; \( p = 0.156 \)).

#### 3.5. Study bias assessment

The assessment of bias risk by the MOOSE criteria and modified NOS of each included study, and the generated funnel plot, did not implicate any obvious heterogeneous bias risk (Supplementary).

### 4. Discussion

This study investigated the prognostic role of hyperglycemia in GBM. Within all included studies and their cohorts, a trend towards worse prognosis with hyperglycemia was consistently reported. Pooled HRs of all studies demonstrated a statistically significant poorer OS prognosis in GBM patients who experience hyperglycemia independent to other prognostic factors (HR, 1.671; \( p < 0.001 \)). There was no

---

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Study Period</th>
<th>Size (n)</th>
<th>Median age (yr)</th>
<th>Males (%)</th>
<th>Pre-diagnosis diabetes (%)</th>
<th>Overall</th>
<th>Cohorts (n, % Overall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenberg et al. 2016 [17]</td>
<td>Germany</td>
<td>R, OS (1)</td>
<td>2008-2011</td>
<td>262</td>
<td>63</td>
<td>62%</td>
<td>12%</td>
<td>125, 48%</td>
<td>137, 52%</td>
</tr>
<tr>
<td>Tieu et al. 2015 [21]</td>
<td>Canada</td>
<td>R, OS (1)</td>
<td>2004-2011</td>
<td>393</td>
<td>54</td>
<td>64%</td>
<td>9%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Total/Average (where available)</td>
<td></td>
<td></td>
<td></td>
<td>1481</td>
<td>56</td>
<td>59%</td>
<td>9%</td>
<td>36%</td>
<td>64%</td>
</tr>
</tbody>
</table>

* Number of institutions in brackets.

---

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Hyperglycemia classification (glucose)</th>
<th>Observation period (months)</th>
<th>Most common GBM management</th>
<th>Prognostic HR from multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenberg et al. 2016</td>
<td>I</td>
<td>180-299 mg/dL, ( \geq 3 ) episodes</td>
<td>6 weeks after radiation to progression</td>
<td>S/C/R</td>
<td>2.15</td>
</tr>
</tbody>
</table>
| Derr et al. 2009 | II | \( 

---

* Derr et al. report glycemic quartiles. The highest quartile was defined as the hyperglycemic group.

† This value was derived from the median value of studied cohort.

§ Managed in pre-temozolomide era with noncytotoxic therapies.
significant modifying effect based on study year (p = 0.678), study size (p = 0.477) or proportion of cohort with pre-diagnostic DM (p = 0.156). These findings highlight the clinical relevance of blood glucose in GBM management.

The primary concern in prognosticating GBM is the prolongation of OS. While not quantifiable by meta-analysis due to lack of statistical reporting, anecdotal single study data implies that hyperglycemia is associated with significantly shorter OS. In their cohort of 367 cases, McGirt et al. observed median OS of 5 and 11 months (p < 0.001) for patients persistently hyperglycemic (>3 episodes) and euglycemic respectively [20]. In their cohort of 106 patients, Mayer et al. observed median OS of 8.8 and 16.7 months (p = 0.001) for those patients who had and had not experienced at least one hyperglycemic episode respectively [9]. Interestingly, McGirt et al. reported a non-significant prognostic effect (HR, 1.28; p = 0.710) in patients who experienced only one hyperglycemic episode, which may indicate a threshold for prognostic effect [20].

Biologically, there exists many possible mechanisms by which hyperglycemia can confer a worse prognosis in GBM. Hyperglycemia may be directly linked to tumor progression, with glucose a major metabolic substrate in the preferred anaerobic glycolysis that generates cellular adenosine triphosphate (ATP) [22]. It has been shown in glioma models that intraparenchymal glucose bolus minimally effects intracerebral glucose levels, but increases intratumoral glucose up to 2.5 times [23]. Also, in response to hyperglycemia, reactive hyperinsulinemia, with the subsequent increase in insulin-like growth factors (IGFs), has the potential to also stimulate tumor growth via tyrosine kinase signaling cascade [24]. Finally, hyperglycemia may contribute to undesirable radioreistance by dysregulating anti-oxidant and apoptotic protection systems within the tumor microenvironment [25]. While unlikely to affect progression in isolation, these mechanisms require further validation at a cellular level to elucidate their biological significance in GBM.

Clinically, hyperglycemia remains a relevant concern in GBM because of the routine use of corticosteroids for management of clinical neurological symptoms and cerebral edema following intervention therapies [26]. However, corticosteroids also raise blood glucose via direct inhibition of the glucose transport system, independent to GBM diagnosis [27]. This is particularly relevant, for 75% of persistent hyperglycemia in GBM patients observed by McGirt et al. were attributable to dexamethasone use, the most common corticosteroid used in this context [20]. Unfortunately, consensus is currently lacking regarding the prognostic significance of steroid use itself across the course of GBM management, with significant [17] and non-significant [19,20] findings trending towards worse prognosis reported within the included studies. Future investigation is required clearly to assess the role of corticosteroid regimes in GBM management. Nonetheless, as prolonged duration and high dosage of corticosteroids have been shown to significantly predict hyperglycemia in hospitalized patients, modification to management protocols are executable which is encouraging [28].

Another potential cause of hyperglycemia to consider is pre-diagnostic DM. However, it appears unlikely that hyperglycemia observed in GBM patients with pre-diagnostic DM possesses any different OS risk. Linear regression did not detect a significant modifying effect within the included studies. In a cross-sectional case-control study of 1144 GBM cases by Barami et al., no significant OS trend was found when evaluating DM (HR, 1.1; p = 0.29) [4]. They posited that glycemic control may be a more important factor in influencing GBM OS than the presence of DM alone, with a significant difference in OS between patients with HbA1c levels greater and less than 6.9 (HR, 1.8; p = 0.05). Furthermore, Adeberg et al. noted that in their series of 276 GBM cases, diabetic patients with metformin therapy demonstrated prolonged progression-free intervals [29]. In vitro evidence has highlighted the potential anticancer effects of metformin in GBM, and will provide further insight into the biology of the hyperglycemic effect in GBM patients as more is discovered [30].

4.1. Strengths and limitations

In its synthesis, this systematic review and meta-analysis adhered to PRISMA guidelines and its selection criteria. By pooling HRs derived from multivariate regression analysis only, it augments confidence in the final result that prognostication by the detection of hyperglycemia in GBM patients is independent to potential confounding by other prognostic factors. Linear regression was performed to identify potential modifying factors of the observed trend. This includes the year in which the study was conducted, thereby, accounting for the improvement in survival due to introduction of new and improvement treatment regimens (e.g. the commencement of the TMZ-era). Studies which did not report complete statistical data or perform adjustment in analysis were excluded, improving the validity of the pooled finding. However, it will have admittedly reduced statistical power.

It should be noted that the definition of hyperglycemia varied numerically between studies. Two based their definition of hyperglycemia to occur above the median [21] or a particular quartile [18] of the cohort rather than an absolute value. This may have its own advantage in accounting for intra-cohort variability, but complicate inter-cohort comparability. We note that individual exclusion of the two aforementioned studies in leave-one-out analysis did not affect the overall trend or its significance reported in this study. Although statistically other prognostic factors such as extent of surgical resection, performance score, age of diagnosis, immunohistochemical classifications, and response to treatment theoretically have no confounding effect on these multivariate HRs, it is conceded that there will be a degree of

![Fig. 2. A forest plot of the pooled hazard ratios (HRs) and their corresponding 95% confidence intervals (95% CIs) of all cohorts investigating prognostication by hyperglycemia. The weighted HR, the 95% CI, and the relative weightings are represented by the middle of the square, the horizontal line, and the relative size of the square respectively.](image-url)
inter-cohort variability between included studies nonetheless. Thus, the
RE model represents the more realistic model to utilize in this study in
order to minimize the impact of the clinical heterogeneity in in-
vestigating this topic.

The number of hyperglycemic episodes were broadly defined, and
also the period in which they were measured. It is impossible to be
certain that no unrecorded isolated episodes occurred between mea-
urements, or indeed after the observation period which. This is a bias
in both observation and selection, which can affect the observed HR of
a study. Yet, this is difficult to control for in retrospectively and all
included studies were performed as such. In future studies, observation
in prospect, as well as more frequent blood glucose monitoring will
allow for greater representation of hyperglycemic events in GBM pa-
tients. This will assist in modelling the true HR of hyperglycemia in
GBM. Furthermore, randomization between standard and more rig-
orous blood sugar monitoring may provide the most reliable avenue
to validate the clinical benefit of the findings from this study.

5. Conclusion

The incidence of hyperglycemia in the clinical course of GBM is
important to recognize as a prognostic factor in terms of OS. There is a
clear consensus in the current literature regarding the trend direction of
hyperglycemia in terms of worse prognosis. When pooled together by
meta-analysis, this trend was statistically signa-

Disclosures

The authors report no funding sources or conflict of interest con-
cerning the materials or methods used in this study or the findings
specified in this paper.

Approval

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

References

897–906.
with glioblastoma: recursive partitioning analysis, Neuro-Oncology 6 (3) (2004)
227–235.
Preventive Oncology.
[4] K. Barami, L. Lyon, C. Conell, Type 2 diabetes mellitus and glioblastoma multi-
forme-assessing risk and survival: results of a large retrospective study and
hyperglycemia on survival in advanced breast cancer patients, Exp. Diabetes Res.
cell lung cancer (NSCLC) patients, Lung Cancer (Amsterdam, Neth.). 76 (2) (2012)
242–247.
[8] T. Hosokawa, M. Kurosaki, K. Tsuchiya, et al., Hyperglycemia is a significant
prognostic factor of hepatocellular carcinoma after curative therapy, World J.
adverse prognostic impact of hyperglycemic episodes during adjuvant chemor-
adiotherapy of glioblastoma multiforme, Strahlentherap Und Onkologie : Organ.
Der Deutschen Rontgenvereinsschaft ...(Et Al) 190 (10) (2014) 933–938.
[10] D. Moher, A. Liberati, J. Tetzlaff, D. Altman, Preferred reporting items for sys-
tematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009)
e1000697.
13.
[13] X. Wan, W. Wong, J. Liu, T. Tong, Estimating the sample mean and standard de-
viation from the sample size, median, range and/or interquartile range, BMC Med.
epidemiology: a proposal for reporting. Meta-analysis of observational studies in
[15] G. Wells, B. Shea, D. O’connell, et al., The Newcastle-Occata scale (NOS) for as-
sessing the quality of nonrandomised studies in meta-analyses, Ott. (ON): Ott.
radiotherapy on survival in patients with primary glioblastoma, Acta Oncol.
between hyperglycemia and survival in patients with newly diagnosed glo-
hyperglycemia and survival in patients with glioblastoma, J. Neurosurg.
cemia is independently associated with decreased survival after primary resec-
291.
[21] M.T. Tieu, I.E. Loblom, M.G. McNamara, et al., Impact of glycemia on survival of
glioblastoma patients treated with radiation and temozolomide, J. Neuro-Oncol.
MRS pattern by induced acute hyperglycemia, NMR Biomed. 21 (3) (2008)
251–264.
between hyperglycemia and survival in patients with newly diagnosed glo-
[27] J.M. Olfekisk, Effect of dexamethasone on insulin binding, glucose transport, and
1499–1508.
[29] S. Adebeg, D. Bernhard, S. Ben Harrah, et al., Metformin influences progression in
diabetic glioblastoma patients, Strahlentherap Und Onkologie : Organ der
e1037271.