SYSTEMATIC REVIEW

Cerebral and tumoral blood flow in adult gliomas: a systematic review of results from magnetic resonance imaging

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Objective: Blood flow is the rate of blood movement and relevant to numerous processes, though understudied in gliomas. The aim of this review was to pool blood flow metrics obtained from MRI modalities in adult supratentorial gliomas.

Methods: MEDLINE, EMBASE and the Cochrane database were queried 01/01/2000–31/12/2019. Studies measuring blood flow in adult Grade II–IV supratentorial gliomas using dynamic susceptibility contrast (DSC) MRI, dynamic contrast enhanced MRI (DCE-MRI) or arterial spin labelling (ASL) were included. Absolute and relative cerebral blood flow (CBF), peritumoral blood flow and tumoral blood flow (TBF) were reported.

Results: 34 studies were included with 1415 patients and 1460 scans. The mean age was 52.4 ± 7.3 years. Most patients had glioblastoma (n = 880, 64.6%). The most common imaging modality was ASL (n = 765, 52.4%) followed by DSC (n = 538, 36.8%). Most studies were performed pre-operatively (n = 1268, 86.8%). With increasing glioma grade (II vs IV), TBF increased (70.8 vs 145.5 ml/100 g/min, p < 0.001) and CBF decreased (85.3 vs 49.6 ml/100 g/min, p < 0.001). In Grade IV gliomas, following treatment, CBF increased in ipsilateral (24.9 ± 1.2 vs 26.1 ± 0.0 ml/100 g/min, p < 0.001) and contralateral white matter (25.6 ± 0.2 vs 26.0 ± 0.0 ml/100 g/min, p < 0.001).

Conclusion: Our findings demonstrate that increased mass effect from high-grade gliomas impairs blood flow within the surrounding brain that can improve with treatment.

Advances in knowledge: This systematic review demonstrates how mass effect from brain tumours impairs blood flow in the surrounding brain parenchyma that can improve with treatment.

INTRODUCTION

Perfusion is the process by which blood flows through tissue, provides nutrition and removes metabolic waste products. It can be quantified using imaging techniques, the gold-standard of which include radiolabelled water ([15O]-H2O)1 positron emission tomography (PET) and Xenon-enhanced CT. In these techniques, a tracer is delivered to the tissue and leaves the vasculature producing changes in signal which directly reflect blood flow and capillary exchange, producing a true measurement of perfusion.1 However, these techniques cannot be performed in routine clinical practice. Recent advances have therefore attempted to quantify perfusion metrics using MRI.

MRI-derived perfusion metrics can aid in the diagnosis of gliomas.3 They can also aid understanding of several clinically relevant processes including angiogenesis, intracranial pressure effects, drug delivery, tumour infiltration and hypoxia.3–5 To date, the most widely studied MRI-derived perfusion metrics in the glioma literature are cerebral blood volume (CBV), which is the total volume of blood moving through a tissue per unit volume of brain, and the contrast transfer constant (ktrans), which is a composite parameter reflecting both tissue blood flow and the capillary permeability surface area product.6,7 However, blood flow, representing the rate over which blood moves through a unit of tissue, is understudied though uniquely relevant to a wide range of biological processes.
MRI techniques to measure local blood flow can be split into contrast-based methods such as dynamic susceptibility contrast (DSC) and dynamic contrast enhanced (DCE) MRI, and non-contrast based methods such as arterial spin labelling (ASL).\(^1\) DSC relies on proton decay of transverse magnetisation induced by adjacent intra-arterial paramagnetic contrast media (T2* shortening effects). DCE also exploits contrast effects, but is based on recovery of proton longitudinal magnetisation (T1 shortening effects). ASL avoids exogenous contrast agent and instead, labels protons in the neck, usually by application of a 180 degree inversion radiofrequency pulse. These inverted protons subsequently flow into the region of interest and the signal differences between a pre- and post-inversion image are used to determine blood flow.\(^9\)

To date, there is limited data on MRI derived blood flow metrics in adult supratentorial gliomas. The aim of this systematic review was to quantitatively pool blood flow metrics obtained from commonly used MRI modalities in adult supratentorial gliomas.

**METHODS AND MATERIALS**

**Registration**

The study protocol was registered on the international prospective register of systematic reviews (PROSPERO) under the ID number: CRD42019111578. The review was undertaken and the manuscript composed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.

**Literature search**

The literature search strategy is outlined in Supplementary Table 1. All searches were conducted by two authors (MW and DL). MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews were queried starting from 01/01/2000 to 31/12/2019 using the NICE Healthcare Databases Advanced Search (HDAS) service. References of included studies were examined to extract potential further papers that may have been missed during the initial systematic search. Two authors (MW and DL) screened titles, abstracts and full-texts independently to identify articles meeting the inclusion criteria. Discrepancies were resolved through discussion and review by a third author (EA).

**Inclusion criteria**

Articles meeting the following criteria were included in the study, grouped as per our Participants, Interventions, Comparisons and Outcomes (PICO) strategy:

- **Participants:**
  - Adult patients (\(\geq18\) years)
  - Minimum sample size \(\geq5\)
  - Diagnosis of WHO Grade II, III or IV glioma
  - Treatment prior to imaging clearly described

- **Interventions**
  - DSC, DCE or ASL imaging

- **Comparisons**
  - Grade of glioma: results were presented separately for WHO Grade 2 (G2), Grade 3 (G3) and Grade 4 (G4) gliomas. Subgroup analysis was also performed between gliomas with an oligodendrogial component to those without.
  - Time point of imaging: pre-operative; post-treatment, where treatment refers to surgery ±radiotherapy/chemotherapy; and recurrence.
  - Type of imaging: contrast based – (DSC/DCE); and non-contrast based – (all types of ASL).

- **Outcome**
  - Absolute or relative blood flow metrics reported

**Data extraction**

For each study, data on patient characteristics, imaging modality, blood flow metrics and key confounding variables was extracted into an excel spreadsheet. Only results from study groups and subgroups with \(\geq5\) patients were analysed. Differences and subsequent bias in blood flow results can be attributed to heterogeneity in imaging modality (DSC, DCE or ASL), region of interest (ROI) analysis, reference tissue selection for measurement of relative blood flow and the time point at which imaging is performed (e.g. pre-, post-operatively or at recurrence). Data on these variables were therefore collected to account for potential bias in reported outcomes and inform our analysis. For inclusion, studies must therefore have provided data on these confounding variables to minimise bias.

**Risk of bias**

The risk of bias in each included study was assessed using the QUADAS-2 tool that is designed for diagnostic studies.\(^9\) Two authors (MW and DL) agreed a set of standards for bias assessment using this tool prior to screening, particularly those relating to selection bias (e.g. consideration of which patients were excluded) and assessment of the reference standard (e.g. correlation to histological grade). These authors then screened each included study independently using the QUADAS-2 tool. Disagreements were resolved through discussion with a third author (EA).

**Data analysis**

Data on ROIs employed by studies was used to group reported blood flow metrics and create universal definitions (Table 1). Three main groups of flow metrics were considered, including: cerebral blood flow (CBF) relating to non-tumoral brain parenchyma; peritumoral flow – relating to signal abnormality beyond the enhancing edge of the glioma; and tumoral flow – relating to the tumour itself (defined variably as the total T1-enhancing hyperintensity or T2 hyperintensity).

Data were described as categorised by the following variables that can influence blood flow metrics:

- Grade of glioma: results were presented separately for WHO Grade 2 (G2), Grade 3 (G3) and Grade 4 (G4) gliomas. Subgroup analysis was also performed between gliomas with an oligodendrogial component to those without.
- Time point of imaging: pre-operative; post-treatment, where treatment refers to surgery ±radiotherapy/chemotherapy; and recurrence.
- Type of imaging: contrast based – (DSC/DCE); and non-contrast based – (all types of ASL).
| Term | Definition |
|------|------------|
| **CBF**<br>Mean CBF overall | Mean flow in whole brain minus tumour |
| Max CBF overall | Area of maximal flow in whole brain minus tumour |
| Mean CBF white matter overall - both sides | Mean flow in white matter ipsilateral and contralateral to tumour |
| Max CBF white matter overall - both sides | Area of maximal flow in white matter ipsilateral and contralateral to tumour |
| Mean CBF white matter ipsilateral | Mean flow in white matter ipsilateral to tumour |
| Mean CBF white matter contralateral | Mean flow in white matter contralateral to tumour |
| Max CBF white matter contralateral | Area of maximal flow in white matter contralateral to tumour |
| Max CBF grey matter contralateral | Area of maximal flow in grey matter contralateral to tumour |
| **Perilesional flow**<br>Mean perilesional flow | Mean flow in non-enhancing T2 or FLAIR hyperintensity |
| Max perilesional flow | Area of maximal flow in non-enhancing T2 or FLAIR hyperintensity |
| Mean relative perilesional flow - white matter reference | Mean perilesional flow/mean flow in ipsilateral or contralateral white matter |
| Max relative perilesional flow - white matter reference | Max perilesional flow/mean flow in ipsilateral or contralateral white matter |
| **TBF**<br>Mean TBF | Mean flow in tumour |
| Max TBF | Area of maximal flow in tumour |
| Mean rTBF - all reference ROIs | Mean TBF/any reference ROI |
| Mean rTBF - white matter reference | Mean TBF/mean flow in ipsilateral or contralateral white matter |
| Mean rTBF - mixed | Mean TBF/area that includes both white matter and grey matter e.g. whole brain, contralateral mirror ROI |
| Mean rTBF - grey matter reference | Mean TBF/mean flow in ipsilateral or contralateral grey matter |
| Mean rTBF - cerebellum reference | Mean TBF/mean flow in any area of the cerebellum |
| Max rTBF - all reference ROIs | Max TBF/any reference ROI |
| Max rTBF - mixed | Max TBF/area that includes both white matter and grey matter e.g. whole brain, contralateral mirror ROI |
| Max rTBF - white matter reference | Max TBF/mean flow in ipsilateral or contralateral white matter |
| Max rTBF - grey matter reference | Max TBF/mean flow in ipsilateral or contralateral grey matter |
| Max rTBF - cerebellum reference | Max TBF/mean flow in any area of the cerebellum |

CBF, cerebral blood flow; ROI, region of interest; TBF, tumoral blood flow. Relative values were study defined and not generated.
Flow metrics in which statistical comparison was possible between the different grades are shown in Table 3 and visually represented in Figure 1a. In pre-operative studies, all tumoral flow metrics increased with increasing glioma grade as shown in Table 3. For example, max TBF increased sequentially from G2 to G3 and G4 tumours (70.8 vs 122.9 vs 145.5, ANOVA, F = 56.9, p < 0.001). Relative max peritumoral flow showed a similar pattern (1.1 vs 1.3 vs 1.7, respectively; ANOVA, F = 39.8, p < 0.001).

Meanwhile, total max CBF decreased with increasing glioma grade and this change was statistically significant between G2/ G3 and G4 tumours (85.3/80.0 vs 49.6 ml/100 g/min, ANOVA, F = 39.7, p < 0.001).

A subgroup comparison was performed between Grade II-III oligodendrogial tumors and pure astrocytic tumours, including results from those studies reporting exclusively on these tumour types. This analysis included 88 gliomas with oligodendrogial components and 60 pure astrocytic tumors. The max relative TBF with all reference ROIs was significant higher in oligodendrogial tumours (3.2 ± 2.4 vs 2.4 ± 1.1, t-t, t = 3.4, p < 0.001).

Type of imaging

Blood flow metrics were significantly different between contrast and non-contrast based MRI studies (Table 4). Where n > 30 for both imaging types (seven studies highlighted with an asterisk* in Table 4), non-contrast based methods produced significantly higher flow results for most measures (in five out of seven of these studies).

Time point of imaging

Time point comparison of blood flow metrics was only possible for G2 and G4 tumours. This analysis was limited due to the small number of studies reporting on post-treatment and recurrence blood flow metrics. In G2 tumours, only one study reported on post-treatment max relative TBF (relative to white matter), with a significant increase in this parameter compared to the pre-operative stage (2.1 ± 0.9 vs 2.6 ± 0, t-t, t = 6.8, p < 0.001).

Time point comparison for G4 tumours is shown in Table 5 and visually represented in Figure 1b. Following treatment (surgery + oncological therapy), there were marginal but statistically significant increases in mean CBF in ipsilateral (24.9 ± 1.2 vs 26.1±0.0 ml/100 g/min, t-t, t = 6.79, p < 0.001) and contralateral white matter (25.6 ± 0.2 vs 26.0±0.0 ml/100 g/min, t-t, t = 20.0, p < 0.001). This was accompanied by variable changes in TBF. There was a significant reduction in mean TBF (98.0 ± 34.5 vs 68.2±0.0 ml/100 g/min, t-t, t = 10.7, p < 0.001), but increase in relative flow values (Table 5). At recurrence, there were significant reductions in all flow metrics compared to the pre-operative stage.

Sensitivity analysis

A sensitivity analysis of max rTBF (relative to white matter) revealed a serial increase with increasing tumour grade (ANOVA, F = 286.3, p < 0.001). Changes were significant when comparing G2 and G3 (Post-hoc Bonferroni, p < 0.001), G2 and G4 (Post-hoc Bonferroni, p < 0.001) and G3 and G4 (Post-hoc Bonferroni, p < 0.001).
DISCUSSION
In this systematic review, we reported blood flow characteristics in gliomas obtained from conventional MRI sequences – DSC, DCE or ASL. Pre-operative TBF and peritumoral flow increased with increasing tumour grade and was associated with a corresponding decrease in CBF. TBF was also higher in oligodendrogliomas compared to astrocytomas. Although only a handful of studies reported post-treatment results, CBF seemed to increase

| Study                  | Imaging modality | Stage of imaging | nG2 | nG3 | nG4 |
|------------------------|-----------------|-----------------|-----|-----|-----|
| Hakyemez et al35       | DSC             | Preoperative    | 8   | 18  |     |
| Wolf et al42           | CASL            | Preoperative    | 5   | 8   | 11  |
| Bastin et al31         | DSC             | Preoperative    | 10  |     |     |
| Kim et al10            | PASL            | Preoperative    | 11  | 7   | 15  |
| Haris et al36          | DCE             | Preoperative    | 17  | 7   | 35  |
| Kim et al38            | PASL            | Preoperative    | 26  |     |     |
| Weber et al41          | PASL, DSC       | Preoperative    | 12  | 26  | 24  |
| Server et al139        | DSC             | Preoperative    | 18  | 14  | 47  |
| Thomsen et al40        | DSC             | Preoperative, post-treatment | 6   |     | 38  |
| Fellah et al33         | DSC             | Preoperative    | 24  | 26  |     |
| Artzi et al30          | DSC             | Post-treatment  |     |     | 14  |
| Falk et al32           | DSC, DCE        | Preoperative    | 18  | 7   |     |
| Furtner et al34        | PASL            | Preoperative    |     |     | 14  |
| Andre et al19          | pCASL           | Recurrence      |     |     | 18  |
| Qiao et al24           | pCASL           | Preoperative    |     |     | 53  |
| Smitha et al25         | DSC             | Preoperative    | 15  | 18  | 7   |
| Lin et al15            | pCASL           | Preoperative    |     |     | 24  |
| Petr et al32           | pCASL           | Post-treatment  | 24  |     |     |
| Puig et al23           | DSC             | Preoperative    |     |     | 15  |
| Yang et al27           | PASL            | Preoperative    | 15  | 15  | 13  |
| Ganbold et al13        | pCASL           | Preoperative    |     |     | 25  |
| Kim et al16            | pCASL           | Recurrence      |     |     | 72  |
| Lin et al10            | DSC             | Preoperative    | 18  | 15  |     |
| Zeng et al29           | pCASL           | Preoperative    | 13  | 17  | 28  |
| Brendle et al11        | DCE, PASL       | Preoperative    | 20  |     |     |
| Durmo et al14          | DSC             | Preoperative    | 10  |     |     |
| Han et al14            | pCASL           | Preoperative    |     | 92  |     |
| Khashbat et al13       | pCASL           | Preoperative    | 6   |     |     |
| Komatsu et al17        | ASL - type unspecified | Preoperative | 40  | 18  | 44  |
| Lee et al18            | DSC             | Preoperative    |     | 89  |     |
| Liu et al21            | pCASL           | Preoperative    | 22  |     |     |
| Stadlbauer et al26     | DSC             | Preoperative, post-treatment |     | 57  |     |
| You et al28            | pCASL           | Preoperative    |     |     | 93  |
| Sengupta et al43       | DCE             | Preoperative    | 15  | 12  | 26  |

CASL, Continuous arterial spin labelling; DCE, Dynamic contrast enhanced MRI; DSC, Dynamic susceptibility contrast MRI; G2, WHO grade two gliomas; G3, WHO grade three gliomas; G4, WHO grade four gliomas; PASL, Pulsed arterial spin labelling; pCASL, Pseudo continuous-continuous arterial spin labelling.

34 studies were included in the final quantitative meta-analysis. Please note that the numbers refer to the number of patients in the study. Most studies reported imaging metrics at the preoperative stage. G4 tumours were the most commonly studied.
Table 3. Comparison of pre-operative cerebral and tumoral blood flow metrics between glioma grades

|                | Grade 2 |          | Grade 3 |          | Grade 4 |          | ANOVA | Bonferroni | Factorial ANOVA |
|----------------|---------|----------|---------|----------|---------|----------|-------|------------|------------------|
|                | M ± SD  | R        | N       | M ± SD   | R        | N       |       |            |                  |
| **CBF** Max CBF overall | 85.3 (±0.0) | 1, 13 | 80.0 (±0.0) | 1, 17 | 49.6 (±20.0) | 35.2–77.0 | 2, 81 | F = 39.7 | p < 0.001 |
| **Perilesional flow** Max perilesional relative flow - white matter reference | 1.1 (±0.0) | 2, 28 | 1.3 (±0.0) | 1, 14 | 1.7 (±0.4) | 1.1–2.0 | 2, 71 | F = 39.8 | p < 0.001 |
| **TBF** Mean TBF | 34.2 (±20.2) | 4.2–51.7 | 6, 113 | 64.4 (±10.5) | 49.0–71.3 | 2, 26 | 98.0 (±34.5) | 49.0–136.5 | 7, 154 | F = 167.1 | p < 0.001 |
| Max TBF | 70.8 (±13.8) | 46.9–85.8 | 4, 46 | 122.9 (±34.9) | 73.0–146.4 | 2, 25 | 145.5 (±48.0) | 74.5–250.0 | 6, 214 | F = 56.9 | p < 0.001 |

(Continued)
### Table 3. (Continued)

|                          | Grade 2 | Grade 3 | Grade 4 | ANOVA | Bonferroni | Factorial ANOVA |
|--------------------------|---------|---------|---------|-------|------------|----------------|
| Mean rTBF - all reference ROIs | M ± SD  | R      | N       | M ± SD | R          | N              |
|                           | 1.5 (±0.6) | 0.9–1.7 | 7, 99   | 2.8 (±0.9) | 1.4–3.7 | 5, 49   |
|                           | 3.8 (±2.1) | 1.6–7.9 | 6, 188  |       |            |                |
| F = 63.9                  | p < 0.001 |         |         |       |            |                |
| two vs 3                  | p < 0.011 |         |         |       |            |                |
| two vs 4                  | p < 0.001 |         |         |       |            |                |
| three vs 4                | p < 0.001 |         |         |       |            |                |
| Mean rTBF - white matter reference | M ± SD  | R      | N       | M ± SD | R          | N              |
|                           | 1.8 (±0.5) | 1.3–2.7 | 4, 66   | 3.0 (±0.7) | 1.9–3.7 | 4, 41   |
|                           | 4.0 (±2.1) | 2.1–8.0 | 5, 177  |       |            |                |
| F = 40.2                  | p < 0.001 |         |         |       |            |                |
| two vs 3                  | p < 0.011 |         |         |       |            |                |
| two vs 4                  | p < 0.001 |         |         |       |            |                |
| three vs 4                | p < 0.007 |         |         |       |            |                |
Table 3. (Continued)

|                     | Grade 2           | Grade 3           | Grade 4           | ANOVA | Bonferroni | Factorial ANOVA |
|---------------------|-------------------|-------------------|-------------------|-------|------------|-----------------|
|                     | M ± SD R N        | M ± SD R N        | M ± SD R N        |       |            |                 |
| Max rTBF - all      | 1.9 (±0.8) 14 205 | 3.4 (±1.5) 10 138 | 5.1 (±2.5) 13 342 | F = 179.2 p < 0.001 |
| reference ROIs      | 1.0–3.5           | 1.3–5.5           | 1.6–9.5           | two vs 3 (p < 0.001) |
|                     |                   |                   |                   | two vs 4 (p < 0.001) |
|                     |                   |                   |                   | three vs 4 (p < 0.001) |
|                     |                   |                   |                   | two vs 3: MD = 1.91, p < 0.001 |
|                     |                   |                   |                   | two vs 4: MD = 3.21, p < 0.001 |
|                     |                   |                   |                   | three vs 4: MD = 3.10, p = 0.35 |
|                     |                   |                   |                   | Non-contrast based |
|                     |                   |                   |                   | two vs 3: MD = 0.42, p = 0.225 |
|                     |                   |                   |                   | two vs 4: MD = 3.53, p < 0.001 |
|                     |                   |                   |                   | three vs 4: MD = 3.11, p < 0.001 |
|                     |                   |                   |                   | Contrast based |
|                     |                   |                   |                   | two vs 3: MD = 2.34, p < 0.001 |
|                     |                   |                   |                   | two vs 4: MD = 4.13, p < 0.001 |
|                     |                   |                   |                   | three vs 4: MD = 1.80, p = 0.001 |
|                     |                   |                   |                   | Non-contrast based |
|                     |                   |                   |                   | two vs 3: MD = 0.85, p = 0.506 |
|                     |                   |                   |                   | two vs 4: MD = 4.34, p < 0.001 |
|                     |                   |                   |                   | three vs 4: MD = 3.49, p < 0.001 |
| Max rTBF - mixed    | 1.7 (±0.3) 3.46   | 3.7 (±0.8) 3.41   | 5.7 (±2.7) 5.19   | F = 60.3 p < 0.001 |
|                     | 1.3–2.0           | 2.1–4.2           | 2.3–9.5           | two vs 3 (p < 0.001) |
|                     |                   |                   |                   | two vs 4 (p < 0.001) |
|                     |                   |                   |                   | three vs 4 (p < 0.001) |
|                     |                   |                   |                   | two vs 3: MD = 2.34, p < 0.001 |
|                     |                   |                   |                   | two vs 4: MD = 4.13, p < 0.001 |
|                     |                   |                   |                   | three vs 4: MD = 1.80, p = 0.001 |
|                     |                   |                   |                   | Non-contrast based |
|                     |                   |                   |                   | two vs 3: MD = 0.85, p = 0.506 |
|                     |                   |                   |                   | two vs 4: MD = 4.34, p < 0.001 |
|                     |                   |                   |                   | three vs 4: MD = 3.49, p < 0.001 |

(Continued)
### Table 3. (Continued)

|                   | Grade 2          | Grade 3          | Grade 4          | ANOVA   | Bonferroni | Factorial ANOVA |
|-------------------|------------------|------------------|------------------|---------|------------|-----------------|
| Max rTBF - white matter reference | M ± SD  | R    | N    | M ± SD | R    | N    | F  | p       | two vs 3 (p < 0.001) | two vs 4 (p < 0.001) | three vs 4 (p < 0.001) |
|                   | 2.1 (±0.9) | 1.0–3.5 | 8, 118 | 3.9 (±1.6) | 1.3–5.5 | 5, 69 | 4.8 (±1.9) | 1.6–7.3 | 6, 118 | Contrast based |
|                   | F = 100.5     | p < 0.001       |                | two vs 3: MD = 1.69, p < 0.001 |
|                   |                 |                  |                | two vs 4: MD = 2.81, p < 0.001 |
|                   |                 |                  |                | three vs 4: MD = 1.13, p < 0.001 |
|                   |                 |                  |                | Non-contrast based |
|                   |                 |                  |                | two vs 3: MD = 0.15, p = 0.756 |
|                   |                 |                  |                | two vs 4: MD = 0.50, p = 0.167 |
|                   |                 |                  |                | three vs 4: MD = 0.35, p = 0.519 |
| Max rTBF - grey matter reference | M ± SD | R    | N    | M ± SD | R    | N    | F  | p       | two vs 3 (p = 0.002) | two vs 4 (p < 0.001) | three vs 4 (p < 0.001) |
|                   | 1.2 (±0.4) | 0.6–1.5 | 3, 47 | 1.4 (±0.3) | 1.0–1.8 | 3, 43 | 2.1 (±0.3) | 1.7–2.7 | 3, 52 | Contrast based |
|                   | F = 96.3       | p < 0.001       |                | two vs 3: MD = 0.43, p < 0.001 |
|                   |                 |                  |                | two vs 4: MD = 1.14, p < 0.001 |
|                   |                 |                  |                | three vs 4: MD = 0.71, p < 0.001 |
|                   |                 |                  |                | Non-contrast based |
|                   |                 |                  |                | two vs 3: MD = 0.28, p < 0.001 |
|                   |                 |                  |                | two vs 4: MD = 0.98, p < 0.001 |
|                   |                 |                  |                | three vs 4: MD = 0.69, p < 0.001 |

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marginally, with variable changes reported for relative and absolute TBF. Non-contrast based imaging modalities (ASL) tended to produce higher flow results.

We found that TBF increases with increasing glioma grade. In contrast to normal brain vasculature, glioma vessels have increased total vessel surface area, branch points and vessel length, but reduced diameter and branch length. They can also aggregate to form complex glomeruloid structures, with increased gap between endothelial cells to facilitate vascular leak. These characteristics transition from less to more frequent with increasing glioma grade. However, the net effect of these vascular changes is increased flow with increasing glioma grade, despite some features producing increased resistance to flow (increased branch points, increased permeability) and decreased local flow (increased vessel length, decreased vessel diameter). Presumably, the net effect of increased total vessel surface area outweighs that of the other factors.

The higher TBF in oligodendrogliomas versus astrocytomas corresponds to prior reports of a higher cerebral blood volumes (CBVs). The exact reasoning for this is unclear. One explanation relates to oligodendroglioma vasculature, often described as a network of regular fine branching capillaries, resulting in a “chicken wire” appearance on imaging. Oligodendrogliomas vessels also have a larger mean vessel size to facilitate greater flow. Another explanation relates to the preferentially cortical location of oligodendrogliomas, arising mostly in grey matter, which has a higher flow rate than white matter.

Absolute flow metrics were sparsely reported. In Grade IV gliomas, absolute pre-operative CBV values were 30–50 ml/100 g/min overall, 20–30 ml/100 g/min in white matter, and 70 ml/100 g/min in grey matter. These values are similar, but not completely homologous, to those reported in healthy volunteers. Therefore, relative flow metrics such as rTBF are less useful than absolute metrics, as they assume normality in normal appearing tissue, whereas our data suggest this is not a valid assumption. There is also variation in perfusion metrics across normal tissue such that their mean value is not a useful reference marker. Tumour-related raised intracranial pressure may also impact relative flow metrics more so than absolute values in the setting of impaired autoregulation, which is found in a high proportion of brain tumour patients.

Non-contrast based imaging modalities tended to produce higher results. Prior studies comparing ASL to quantitative [15O]-H2O PET in healthy volunteers have also reported a tendency for the former to overestimate flow values. However, evidence to the contrary also exists, and in one study comparing ASL and DSC in the ischaemic penumbra of cerebral infarcts, ASL tended to underestimate true blood flow compared to DSC, producing in turn a higher total hypoperfusive tissue volume. Studies using ASL have highlighted the importance of a long enough post-labelling delay to produce robust results. Limitations of ASL techniques include their relatively low signal-to-noise ratio in comparison to DSC/DCE, sensitivity to motion due to reliance on image subtraction, and potential for discrepant results in elderly patients due to prolonged arterial transit.
There are important limitations of contrast-based imaging techniques that could limit interpretation of our results, given that most data were derived from these techniques. The spatial resolution of both DSC and DCE is limited. In DSC, the main sources of error are: susceptibility artefacts around air-bone interfaces, especially at the skull base; tissue contrast leakage effects as a result of blood-brain-barrier breakdown and strong relaxation effects on T2*; and systematic errors from the assumption of uniform tissue relaxivity and blood haematocrit.57–59 In DCE, errors can arise from these same factors and in addition: motion artefacts resulting from a longer data acquisition time; differences in contrast timing and dose; and the kinetic model used for data analysis.60–63

Blood flow can be measured using imaging modalities not included in this review. MRI-based modalities include diffusion-weighted MRI using intravoxel incoherent motion and phase contrast angiography.64,65 Non-MRI modalities include CT perfusion, Xenon enhanced CT, Single Photon Emission CT (SPECT) and [15O]-H2O PET. Studies using these techniques have similarly reported increasing TBF with glioma grade.65–68

Table 4. Comparison of pre-operative flow metrics obtained by contrast and non-contrast MRI studies

|                          | Contrast-based | Non-contrast-based | T-test       |
|--------------------------|----------------|--------------------|--------------|
|                          | M ± SD         | R                  | N            | M ± SD         | R                  | N            |              |
| Max perilesional flow    | 23.7 ± 0.0     | 1, 15              | 26.4 ± 0.5    | 26.2–27.4      | 2, 117            | t = 60.0, p < 0.001|
| Max perilesional relative flow - white matter reference | 1.6 ± 0.4     | 1.1–2.0            | 1.1 ± 0.0    | t = 10.1, p < 0.001 |
| Mean TBF*                | 42.6 ± 25.0    | 4.2–63.9           | 79.1 ± 41.5  | 46.9–250.0     | 11, 223           | t = 9.0, p < 0.001 |
| Max TBF                  | 151.6 ± 0.0    | 1, 15              | 130.4 ± 52.3 | 12.1–136.5     | 26.2–27.4        | 11, 270     | t = 6.7, p < 0.001 |
| Mean rTBF - all reference ROIs* | 2.9 ± 2.0 | 1.5–7.9            | 3.1 ± 1.9    | 0.9–5.7        | 6.144            | t = 0.59, p = 0.56 |
| Mean rTBF - white matter reference* | 2.9 ± 2.0 | 1.5–7.9            | 3.1 ± 1.9    | 0.9–5.7        | 6.144            | t = 0.59, p = 0.56 |
| Max rTBF - all reference ROIs* | 4.0 ± 1.8 | 1.0–7.3            | 3.5 ± 2.9    | 1.0–9.5        | 17, 330          | t = 3.0, p = 0.003 |
| Max rTBF - mixed*        | 3.8 ± 1.7      | 1.7–5.9            | 5.3 ± 3.0    | 1.3–9.5        | 6.169            | t = 5.1, p < 0.001 |
| Max rTBF - white matter reference* | 4.1 ± 1.8 | 1.0–7.3            | 1.3 ± 0.2    | 1.1–1.6        | 4.59             | t = 24.2, p < 0.001 |
| Max rTBF - grey matter reference* | 1.2 ± 0.5 | 0.6–1.7            | 1.8 ± 0.5    | 1.0–2.7        | 6.96             | t = 6.6, p < 0.001 |

ANOVA, One way analysis of variance; CBF, Cerebral blood flow; M ± SD, Mean ± standard deviation; N, Number of studies followed by number of patients between studies; N/A, Current statistical test could not be performed; R, Range; ROI, Region of interest; TBF, Tumoral blood flow; rTBF, Relative tumoral blood flow.

This table shows blood flow metrics that were comparable between contrast and non-contrast based MRI studies. Where n > 30 for both imaging types (*), there was a trend for non-contrast based methods to produce higher flow results. All absolute flow metrics are in ml/100 g/min and all relative flow values are unitless.
Table 5. Serial comparison of cerebral and tumoral blood flow metrics at different time points in patients with glioblastoma

|                      | Pre-op | Post-treatment | Recurrence | Pre-op vs Post-treatment | Pre-op vs Recurrence | ANOVA (all stages) | Bonferroni |
|----------------------|--------|----------------|------------|--------------------------|-----------------------|--------------------|-------------|
|                      | M ± SD | R | N | M ± SD | R | N | M ± SD | R | N | t | p |
| Max CBF overall      | 49.6 ± 20.0 | 35.2–77.0 | 2, 81 | 35.0 ± 0.0 | 1, 18 | t = 11.0 | p < 0.001 |
| Mean CBF white matter (ipsilateral) | 24.9 ± 1.2 | 23.7–26.1 | 2, 49 | 26.1 ± 0.0 | 1, 32 | t = 6.79 | p < 0.001 |
| Mean CBF white matter (contralateral) | 25.6 ± 0.2 | 25.4–25.7 | 2, 49 | 26.0 ± 0.0 | 1, 32 | t = 20.0 | p < 0.001 |
| Mean perilesional flow | 15.5 ± 3.3 | 13.5–20.6 | 2, 35 | 18.8 ± 0.0 | 1, 32 | t = 5.9 | p < 0.001 |
| Mean TBF             | 98.0 ± 34.5 | 49.0–136.5 | 7, 154 | 68.2 ± 0.0 | 1, 32 | t = 10.7 | p < 0.001 |
| Max TBF              | 145.5 ± 48.0 | 74.5–250.0 | 6, 214 | 75.0 ± 15.1 | 45.0–82.5 | 2, 90 | t = 16.5 | p < 0.001 |
| Max rTBF - all reference ROIs | 5.1 ± 2.5 | 1.6–9.5 | 13, 342 | 5.4 ± 0.0 | 1, 26 | 2.5 ± 0.0 | 1, 72 | t = 2.6 | p = 0.009 |
|                       | F = 15.4 | p < 0.001 | Pre-op vs Post-op, p = 0.016 | Pre-op vs first recurrence, p < 0.001 | Post-op vs first recurrence, p < 0.001 |
| Max rTBF - white matter reference | 4.8 ± 1.9 | 1.6–7.3 | 6, 118 | 5.4 ± 0.0 | 1, 26 | 2.5 ± 0.0 | 1, 72 | t = 3.23 | p = 0.002 |
|                       | F = 23.0 | p < 0.001 | Pre-op vs Post-op, p < 0.001 | Pre-op vs first recurrence, p < 0.001 | Post-op vs first recurrence, p < 0.001 |

ANOVA, One way analysis of variance; CBF, Cerebral blood flow; M ± SD, Mean±standard deviation; N, Number of studies followed by number of patients between studies; N/A, Current statistical test could not be performed; R, Range; ROI, Region of interest; TBF, Tumoral blood flow; rTBF, Relative tumoral blood flow.

Results were compared at three different time points: preoperatively, post-treatment (after surgery ± adjuvant treatment) and at recurrence. Comparisons were made using independent t-tests or one-way analysis of variance with post-hoc Bonferroni tests, as required. There was a marginal but significant increase in CBF following treatment. Changes in TBF were more variable, with a reduction in absolute mean TBF, but increase in rTBF. All absolute flow metrics are in ml/100g/min and all relative flow values are unitless.
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A better understanding of glioma perfusion has several applications. Blood flow metrics could aid in selecting patients for antivascular endothelial growth factor (VEGF) treatment. Knowledge of blood flow in addition to other perfusion metrics, could guide treatment planning and chemotherapy dose adjustment, and serve as a marker of treatment response. Blood flow metrics could help to better define the tumour edge to aid operative resection. They could also provide an indication of cerebral perfusion pressure, which in turn could help determine the urgency of surgical intervention.

Limitations of the current review include the fact that different software packages/analytical processing methods to extract blood flow metrics, were not accounted for, this is especially relevant for ASL, for which several processing models exist. This includes quality control measures during measurement of blood flow to avoid extreme values (e.g. excluding necrotic areas, major vessels within the regions of interest). Different imaging protocols between studies were also not considered. However, arguably, attempting to adjust for these factors would have reduced the overall number of results that could be aggregated and made our methodology overly complex. The majority of studies presented results at the pre-operative stage such that interpretation of flow metrics at other time points - post-treatment and recurrence, was limited by study size and number. There was a lack of data on glioma genomics and how they relate to blood flow.

CONCLUSION
This study represents the first systematic review of MRI derived blood flow metrics in adult supratentorial gliomas. Pooling data from 3 MRI sequences – DSC, DCE and ASL, we reported blood flow metrics related to the tumor, peritumoral area and normal surrounding brain parenchyma. Pre-operative TBF and peritumoral flow increased with increasing tumour grade and was accompanied by a corresponding decrease in CBF. TBF was higher in oligodendrogliomas compared to astrocytomas. After treatment, there were marginal increases in CBF, presumably relating to relief of mass effect. ASL techniques tended to overestimate flow metrics in comparison to DSC/DCE. Our results have a number of potential applications and aid understanding of perfusion in adult gliomas.

CONTRIBUTORS
Conception and supervision of study: DC, AJ. Registration and protocol design: MW, DL, EA. Database searching and results: MW, DL, EA. Screening results for inclusion: MW, DL, EA, DC. Data extraction: MW, DC. Data analysis: MW, DL, MG. Preparation of first manuscript draft: MW, DL, EA, MG, DC, AJ. Revision and approval of final manuscript draft: EA, DC, AJ.

AVAILABILITY OF DATA AND MATERIAL
Supplementary material can be found online.

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