Circulating Brain Injury Biomarkers: A Novel Method for Quantification of the Impact on the Brain After Tumor Surgery

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ABSTRACT

Background: Clinical methods to quantify brain injury related to neurosurgery are scarce. Circulating brain injury biomarkers have recently gained increased interest as new ultrasensitive measurement techniques have enabled quantification of brain injury through blood sampling.

Objective: To establish the time profile of the increase in the circulating brain injury biomarkers, glial fibrillary acidic protein (GFAP), tau, and neurofilament light (NfL), after glioma surgery and to explore possible relationships between these biomarkers and outcome in

terms of volume of ischemic injury identified with postoperative MRI and new neurological deficits.

Methods: In this prospective study, 34 adult patients scheduled for glioma surgery were included. Plasma concentrations of brain injury biomarkers were measured the day before surgery, immediately after surgery, and on postoperative Days 1, 3, 5, and 10.

Results: Circulating brain injury biomarkers displayed a postoperative increase in the levels of GFAP (P <.001), tau (P <.001), and NfL (P <.001) on Day 1 and a later, even higher, peak of NFL at Day 10 (P = .028). We found a correlation between the increased levels of GFAP, tau, and NfL on Day 1 after surgery and the volume of the ischemic brain tissue on postoperative MRI. Patients with new neurological deficits after surgery had higher levels of GFAP and NFL on Day 1 compared to those without new neurological deficits.

Conclusion: Measuring circulating brain injury biomarkers could be a useful method for quantification of the impact on the brain after tumor surgery, or neurosurgery in general.

Running Title: Biomarkers for Quantifying Brain Injury after Surgery

Keywords: Biomarkers, Brain injury, GFAP, NfL, Tau, Neurosurgery, Glioma, Outcome

Abbreviations: 2D, 2-dimensional; **3D**, 3-dimensional; **ADC,** apparent diffusion coefficient; **ELISA**, enzyme-linked immunosorbent assay; **FLAIR**, fluid-attenuated inversion recovery; **GBM**, glioblastoma multiforme; **GFAP**, glial fibrillary acidic protein; **GS**, gliosarcoma; **IDH**, isocitrate dehydrogenase; **IQR**, interquartile range; **MRI**, magnetic resonance imaging; **NfL**, neurofilament light; **SD**, standard deviation; **Simoa**, single molecule array; **T1w**, T1-weighted; **T2w**, T2-weighted; **WHO**, World Health Organization.

INTRODUCTION

Even in technically successful brain tumor surgery, some degree of brain injury is unavoidable. Depending on the type of surgery, this may range from slight brain retraction and manipulation to a surgical trajectory through normal brain tissue to reach a deep-seated tumor.

Today, postoperative magnetic resonance imaging (MRI) is used to determine the presence of residual tumor and also to detect surgical complications such as hematoma or ischemia.[1]

However, despite anatomical integrity and no demonstrated collateral damage on MRI, some patients have long-standing and non-focal neurological and neurocognitive symptoms following surgery.[2,3] Quantification of injury to the brain may prove useful to identify patients at high-risk for developing these symptoms.[4,5] An objective evaluation of brain injury following surgery may also allow comparison of surgical approaches with respect to invasiveness. There are no methods in clinical use for the identification and measurement of presumed diffuse brain injury related to surgery. Measurement of brain injury biomarkers has recently gained increased interest as new ultrasensitive measurement techniques, including the single molecule array (Simoa) technology, have enabled accurate quantification of such proteins in blood samples. These techniques have been used in a large number of neurological diseases[6] and traumatic brain injury,[7] and results correlate with both outcome and structural brain injury.[8-11] We have recently shown that circulating brain injury biomarkers increase after transsphenoidal surgery for pituitary tumors in a similar temporal pattern as described after traumatic brain injury and that increased levels of the biomarker tau immediately after surgery correlates with fatigue 6 months after surgery.[12] However, the release pattern of circulating brain injury biomarkers after intra-axial brain surgery is unknown.

Gliomas are the most common malignant primary brain tumor and are associated with high morbidity and mortality. They are often treated with a multimodal approach including surgical resection, when feasible, followed by chemotherapy and radiotherapy.[13]

Given the direct and predictable trauma induced by intra-axial glioma surgery, the aim of the present study was to establish the time profile of the increase in the circulating brain injury biomarkers glial fibrillary acidic protein (GFAP), tau, and neurofilament light (NfL) after intra-axial surgery. We further explored possible relationships between these biomarkers and outcome defined as the volume of ischemic injury identified with postoperative MRI and as new neurological deficits.

METHODS

Patients

The study was approved by the Ethical Review Board in Gothenburg (Dnr: 071-18), Sweden, and complied the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to any intervention.

In this prospective study, 41 adult patients (≥18 years of age) scheduled for glioma surgery at Sahlgrenska University Hospital were included between November 2018 and February 2020. Inclusion criteria were the presence of a suspected glioma based on preoperative MRI and planned tumor resection. Information about the duration of surgery was collected from patient records. The outcome variable "neurological deficit" was defined as any new neurological deficit after surgery, transient or persistent at 30 days after surgery. Data was retrieved from the Swedish Quality Registry for Primary Brain Tumors which is a national registry containing clinical characteristics, patterns of care, and outcome data for adult patients with primary brain tumors. Tumor subclassification was performed according to the 2016 WHO Classification of Tumors of the Central Nervous System.[14]

Anesthesia and Surgical Techniques

General anesthesia was induced with propofol in all patients and maintained with volatile anesthesia (sevoflurane) and remifentanil/fentanyl or remifentanil only (Table 1). In general, gliomas were operated upon with microsurgical techniques, although technique and tools used could differ and were at the discretion of the surgeons. Tools such as neuronavigation, 2D B-mode ultrasound, intraoperative 3T MRI, 5-aminolevulinic acid tumor visualization, and intraoperative monitoring/mapping were available and used when found appropriate by the treating surgeon.

Analysis of Biomarkers

Blood samples were collected the day before surgery, immediately after surgery, and at Days 1 and 3 postoperatively. Patients living close to the hospital were also offered a visit to the outpatient clinic for blood samples on Days 5 and 10. Blood samples (approximately 4 mL) were collected in vacutainer tubes, which were centrifuged for 10 min at 2300 g; then, 0.5-mL plasma aliquots were pipetted into cryotubes and stored at −70°C before analysis at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital. Plasma GFAP and tau concentrations were measured using commercially available digital enzyme-linked immunosorbent assay (ELISA) reagents with a Simoa HD-1 Analyzer (Quanterix, Billerica, MA). Plasma NfL concentration was measured using in-house digital ELISA reagents on the Simoa platform, as previously detailed.[15] All measurements were performed by board-certified

laboratory technicians blind to clinical information. The intra-assay coefficients of variation were <10% for all biomarkers.

Radiology

All patients underwent MRI examinations before surgery. Relevant for this study, examinations included 3D T1-weighted (T1w) MRI scans with and without gadolinium contrast media, 3D T2-weighted (T2w), and 3D fluid-attenuated inversion recovery (FLAIR) images with a minimum resolution of 1.0 mm^3. Tumor location assessment was performed by a neuroradiologist (ML). Preoperative tumor volume was evaluated by segmentation of the MRI images performed with the open-source software 3D Slicer, version 4.11.0 by neurosurgical resident (I.M.). For the segmentation of tumor volume, we used the tools LevelTracingEffect and DrawEffect in the Editor module when appropriate. 3D T2w or 3D FLAIR sequences were used for gliomas with no or only focal contrast enhancement. In tumors with significant contrast enhancement (i.e., a presumed glioblastoma) 3D T1w gadolinium images were used for tumor volume segmentation as per usual practice.[16,17] Both the contrast-enhancing rim and the central non-enhancing tumor were included in the total tumor volume. Postoperatively, patients were examined using MRI within 72 h after surgery including structural imaging as above and diffusion-weighted imaging (B-values 0 s/mm^2 and 1000 s/mm^2, apparent diffusion coefficient [ADC] maps). The volume of postoperative ischemic brain injury was assessed by quantification of brain parenchyma with restricted diffusion (high signal on high B-value images and low signal on ADC maps).

Statistics

Data was analyzed using IBM SPSS, version 28 (IBM Corp., Armonk, NY) and were visualized using GraphPad Prism version 8 (GraphPad Software, San Diego, CA) and R version 4.1.3 (R Core Team, 2022) with the package plot 3D, version 1.4. Categorical data is presented as number (%) and normally distributed variables as mean (± standard deviation [SD] and range), while non-normally distributed variables are presented as median (interquartile range [IQR]). The preoperative (baseline) and postoperative levels of the biomarkers assumed a skewed distribution. Hence, non-parametric tests were used for statistical analyses. For paired longitudinal data, the Wilcoxon signed-rank test was used and for correlation between

continuous variables Spearman's correlation was used. The Mann-Whitney *U*-test was used for comparison between groups. For all tests, a *P*-value of ≤.05 was considered significant (two-sided).

RESULTS

Patient Characteristics

Of the original 41 patients, two were excluded due to technical failure with samples and five patients due to non-glioma diagnosis after pathological anatomical diagnosis (4 metastases and 1 inflammatory lesion). Thirty-four patients (20 men and 14 women) with mean age 57 (range, 24-76) age were included in the study. Twenty-five (74%) patients were diagnosed with glioblastoma multiforme (GBM) or gliosarcoma (GS), six (17%) with mutant-IDH grade II-III glioma, two (6%) with wild-type IDH grade II-III glioma, and one (3%) with grade I ganglioglioma. Patient characteristics are presented in Table 1.

GFAP

Preoperative GFAP levels correlated with age (P = .013) but not with gender or tumor volume. Median (IQR) GFAP level in patients with GBM/GS was significantly higher compared to those with IDH-mutant grade II-III glioma (4.4 [1.4-7.9] vs 0.2 [0.1-0.3] ng/mL, P <.001) (Figure 1). GFAP levels were significantly increased on postoperative Days 1 and 3 compared to preoperative levels (Figure 2 and Table 2). Peak GFAP levels (Day 1) were used for further statistical analysis. Both the absolute levels of GFAP on Day 1 and the increase of GFAP on Day 1 compared to baseline showed a correlation with the volume of the ischemic brain tissue measured on postoperative MRI (Figure 3). Median (IQR) absolute levels of GFAP on Day 1 were higher in patients with new neurological deficits after surgery compared to those without deficits (112.6 [29.7-166.4] vs 36.3 [12.2-58.0] ng/mL, P = .048). There was no significant difference between patients with new neurological deficits compared to those without deficits for the median (IQR) GFAP increase from baseline to Day 1 (96.6 [21.3-96.6] vs 31.5 [11.3-53.0] ng/mL, P = .061).

Tau

Preoperative tau levels were not correlated with age, gender, or tumor volume. Preoperative tau levels did not differ significantly between the glioma subgroups (Figure 1). Tau levels were significantly increased on Days 1 and 3 compared to preoperative levels (Figure 2 and Table 2). Peak tau levels (Day 1) were used for further statistical analysis. Both the absolute levels of tau on Day 1 and the increase of tau on Day 1 compared to baseline showed a correlation with the volume of the ischemic brain tissue measured on postoperative MRI (Figure 3). There were no differences for the absolute levels of tau on Day 1 or the increase of tau on Day 1 comparing patients with new neurological deficits after surgery and those without deficits.

NfL

Preoperative NfL levels were correlated with age (P <.001) but not with gender or tumor volume. Median (IQR) NfL level in patients with GBM/GS was significantly higher compared to those with IDH-mutant grade II-III glioma (43.0 [28.2-124.5] vs 6 [5.9-7.7] pg/mL, P <.001) (Figure 1). NfL values were significantly decreased immediately after surgery and on Days 1 and 10 compared to preoperative levels (Figure 2 and Table 2). There was no significant increase in NfL values on Day 3 compared to preoperative levels. There were only two samples on Day 5 and relatively few samples on Day 10 (n = 11) due to the high dropout rate: for this reason, NfL levels on Day 1 were used for further statistical analysis. Both the absolute levels of NfL on Day 1 and the increase of NfL on Day 1 compared to baseline showed a correlation with the volume of the ischemic brain tissue measured on the postoperative MRI (Figure 3). Median (IQR) absolute NfL levels on Day 1 were higher in patients with new neurological deficits after surgery compared to those without deficits (86.2 [44.1-238.5] vs 52.2 [28.1-73.0] pg/mL, P = .043). There was no difference for the increase of NfL from baseline comparing patients with new neurological deficits after surgery compared to those without deficits.

Correlation of Biomarkers with Ischemic Damage

To facilitate analysis of the relationship between biomarker levels and volume of ischemic tissue measured on postoperative MRI, a 3D plot of the levels of biomarkers on Day 1 was created (Figure 5). This method demonstrated a clustering of patients with no or small postoperative ischemic tissue volumes in the lower right corner of the 3D plot, representing low levels of biomarkers. However, one patient was found with high levels of all three biomarkers

but with only a small ischemic tissue volume on postoperative MRI: this patient had undergone surgery due to GBM in the thalamus using a transcallosal approach. The retraction of the frontal lobe, surgical trajectory through the corpus callosum, and tumor resection in the thalamus resulted in a significant degree of brain tissue damage compared to surgery of a lesion located closer to the cortical surface.

DISCUSSION

In this prospective exploratory study of 34 patients who underwent surgery for glioma, we found a postoperative release pattern of circulating brain injury biomarkers similar to that described after traumatic brain injury, with an almost immediate increase in the levels of GFAP, tau, and NfL and a later, even higher, peak of NfL.[18,19] We found a correlation between the increased levels of GFAP, tau, and NfL on Day 1 after surgery and the volume of the ischemic brain tissue on postoperative MRI. Patients with new neurological deficits after surgery had higher levels of GFAP and NfL on Day 1 compared to those without new neurological deficits.

Preoperative Levels of Brain Injury Biomarkers

The protein GFAP is a major component of the cytoskeleton in astrocytes.[20] We found a correlation between preoperative GFAP levels and increased age, which has been shown previously.[21] We noted higher GFAP levels in patients with GBM/GS compared to those with IDH-mutant grade II-III glioma. The possibility of using GFAP as a biomarker for malignancy in gliomas has been previously discussed and higher GFAP levels have been found in patients with GBM compared to those with other space-occupying lesions in the brain.[22] The reasons for the elevated levels are not completely understood but might be caused by a release of GFAP from the glioma tumor cells as well as increased leakage due to the damaged blood-brain barrier.[22,23]

NfL is a neuron-specific intermediate filament and is mostly found in large-caliber myelinated axons[18]. In our study, preoperative NfL levels were also correlated with age and were higher in patients with GBM/GS. Although we had a limited number of patients in each subgroup, it was interesting to note that NfL levels discriminated completely between patients with GBM/GS and those with IDH-mutant grade II-III glioma, i.e., NfL levels did not overlap between these glioma types.

Tau is a protein expressed in the thin, non-myelinated axons of cortical interneurons.[24,25] Increased blood tau levels have been found in a variety of diseases including neurodegenerative diseases[26] and head trauma.[27] However, in our study, there was no significant difference between tumor types regarding preoperative tau levels and there was no correlation with age.

Temporal Profile of the Postoperative Biomarkers Increase

We noted a postoperative increase of the studied brain injury biomarkers after surgery. GFAP and tau had a monophasic release pattern with a peak value on Day 1. Similar temporal profiles of these biomarkers have been shown in a number of studies of patients with traumatic brain injuries[28] and also in patients with ischemic stroke.[29]

The postoperative NfL increase showed a tendency towards a biphasic pattern with a first peak on Day 1 and a later, even higher, peak on Day 10. Since no later blood samples were taken, it is unclear whether NfL continues to increase over a sustained period of time. A study of patients with traumatic brain injuries showed increased NfL levels several months after the trauma.[10] Also, in patients with anterior circulation stroke, high levels were observed 3 months after the stroke.[29] In another study of patients who underwent of intraventricular catheter implantation, serum NfL peaked 1 month after surgery and returned to preoperative levels 6-9 months after surgery.[30] The prolonged increased levels are thought to be caused by Wallerian degeneration triggered after the surgical trauma to neuronal bodies and axons.[31]

Biomarkers and Prediction of Outcome

The increased levels of GFAP, tau, and NfL on Day 1 after surgery correlated with the volume of the ischemic brain tissue on postoperative MRI. These biomarkers have previously been shown to correlate with the volume of infarctions in patients with stroke in the anterior circulation.[29] We also observed that patients with new neurological deficits after surgery had higher levels of GFAP and NfL on Day 1 compared to those without new neurological impairment. It should be noted that one patient with a small ischemic lesion on postoperative MRI (Figure 5) had relatively high levels of biomarkers, which we relate to the surgical trauma itself. Due to the deep location of the lesion, the surgical approach involved a trajectory through the corpus callosum and significant retraction of the frontal lobe as well as tumor resection in the thalamus, which resulted in a significant degree of brain tissue damage. An interesting aspect of

this finding is that this presumed brain injury was not apparent on the MRI as an ischemic lesion, suggesting that biomarkers could identify damage which is not readily identifiable on postoperative MRI.

Measurement of brain injury biomarkers is used in many neurological diseases to describe severity and to predict outcome. In traumatic brain injury, the levels of GFAP and, especially, NfL have shown correlation with clinical outcome and MRI brain atrophy, indicating that NfL is a biomarker of traumatic axonal injury.[10] In patients with spinal cord injury, NfL has been shown to be a biomarker of injury severity and outcome.[32] Both tau and NfL have been shown to increase during and after cardiac surgery, especially in patients on extracorporeal circulation, who are considered to be at higher risk for brain injuries during cardiac surgery.[33] These brain injury biomarkers may also mark disease severity and predict outcome in neurological diseases such as Alzheimer's disease,[34] brain injury after cardiac arrest,[35] and multiple sclerosis.[36]

To our knowledge, only few studies of brain injury biomarkers after elective brain surgery have been published. Increased levels of the biomarker S100B after meningioma surgery correlated with postoperative deterioration[37,38] and brain damage.[39] Elevated levels of GFAP after glioma surgery have been previously described but no outcome data was presented[23,40]

Possible Future Use of Circulating Biomarkers in Neurosurgery

The improvement in microsurgical techniques and the development of technical aids for planning and performing surgery have led to prolonged progression-free survival as well as a decrease in neurological deficits after surgery for brain tumors such as meningiomas and low-grade gliomas.[41] This has led to an increased focus on cognitive outcome and health-related quality of life after brain surgery.[42]

Although our study is exploratory, with a limited number of patients, the results indicate that measuring circulating brain injury biomarkers could add valuable information on the severity of the brain damage caused by the surgery. Blood biomarkers to monitor neurosurgery outcomes will become even more clinically relevant when analyses such as NfL and GFAP are available on random access fully automated laboratory analyzers with very short turn-around times (<1 h). More studies will be needed, but the use of biomarkers may be useful for prediction of long-term problems, i.e., fatigue and cognitive impairment, after surgery for both gliomas and benign tumors such as meningiomas.

Biomarkers could also be used as an objective measure of the trauma caused by the surgical technique used and, on group basis, used to compare different surgical techniques and approaches. This might facilitate the development of new neurosurgical methods which minimize brain injury.

Limitations

This is an explorative study with a relatively small number of observations, not allowing for appropriate multivariate analysis. The fact that a majority of patients in the cohort received postoperative radiation made long-term follow-up unfeasible due to the potential release of brain injury biomarkers by radiotherapy itself.

CONCLUSION

In the present prospective exploratory study, we describe the temporal release pattern of brain injury biomarkers (GFAP, tau, and NfL) after glioma brain surgery. We conclude that the release patterns mimic those described after traumatic brain injury and that the biomarker levels were related to the brain injury caused by surgery.

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FIGURE LEGENDS

FIGURE 1. *Preoperative plasma concentrations of (A) glial fibrillary acidic protein (GFAP), (B) tau, and (C) neurofilament light (NfL) for glioma subtypes. Circles represent individual values, and error bars medians and interquartile range (IQR). The difference between IDH-mutant grade II-III glioma and glioblastoma multiforme/gliosarcoma was calculated using Mann-Whitney U-test.*

FIGURE 2. *Temporal profiles of plasma brain injury biomarkers after neurosurgery. Median change from baseline (preoperative) (IQR) for (A) glial fibrillary acidic protein (GFAP), (B) tau, and (C) neurofilament light (NfL).*

FIGURE 3. *Correlations between volume of postoperative ischemic brain tissue measured on MRI and postoperative levels of brain injury biomarkers. Outliers are excluded in the graph but included in the presented statistical analysis. Correlations were calculated by Spearman's correlation coefficient. Graphs including the outliers are provided as Supplemental Digital Content, Figure S1.*

FIGURE 4. *Comparison of postoperative levels of brain injury biomarkers for (A) glial fibrillary acidic protein (GFAP), (B) tau, and (C) neurofilament light (NfL) between patients with and without new neurological deficits after surgery. Differences were calculated using Mann-Whitney U-test.*

FIGURE 5. *(A) 3D plot where each sphere represents the postoperative values of glial fibrillary protein (GFAP), tau, and neurofilament light (NfL) for each patient on Day 1 . The levels of the biomarkers have been log transformed to enhance visualization. Color coding represents the volume of ischemia measured on the postoperative MRI: black represents a volume over the median value of all patients and red a volume below the median ischemic volume. Note the clustering of red spheres in the lower right corner with low values of brain injury biomarkers. Note also the red sphere marked with * with high levels of brain injury biomarkers but small ischemic volume. (B) Preoperative and (C) postoperative FLAIR MRI from the patient marked*

*with * and with a GBM located in the thalamus. The latter patient underwent surgery using a transcallosal approach. Although only a small postoperative ischemic lesion (not shown) was detected, the retraction of the frontal lobe, surgical trajectory through the corpus callosum and the tumor resection in the thalamus resulted in a significant degree of brain tissue damage.*

Figure 1

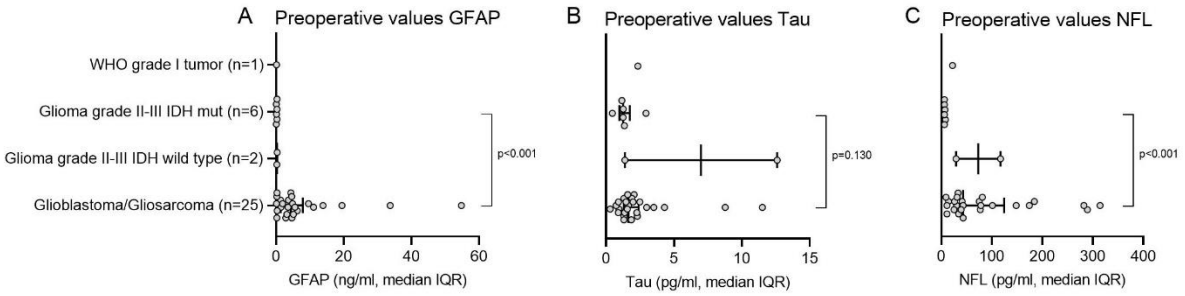
A
Preoperative values GFAP
WHO grade I tumor (n=1)
Glioma grade II-III IDH mut (n=6)
Glioma grade II-III IDH wild type (n=2)
Glioblastoma/Gliosarcoma (n=25)
p<0.001
0
20
40
60
GFAP (ng/ml, median IQR)
B
Preoperative values Tau
p=0.130
0
5
10
15
Tau (pg/ml, median IQR)
C
Preoperative values NFL
p<0.001
0
100
200
300
400
NFL (pg/ml, median IQR)

Figure 2

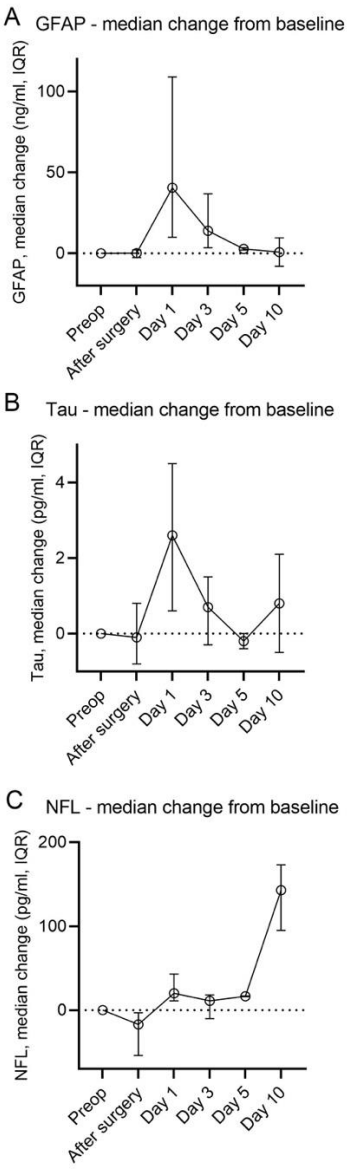
A
GFAP - median change from baseline
GFAP, median change (ng/ml, IQR)
100
50
0
Preop
After surgery
Day 1
Day 3
Day 5
Day 10
B
Tau - median change from baseline
Tau, median change (pg/ml, IQR)
4
2
0
Preop
After surgery
Day 1
Day 3
Day 5
Day 10
C
NFL - median change from baseline
NFL, median change (pg/ml, IQR)
200
100
0
Preop
After surgery
Day 1
Day 3
Day 5
Day 10

Figure 3

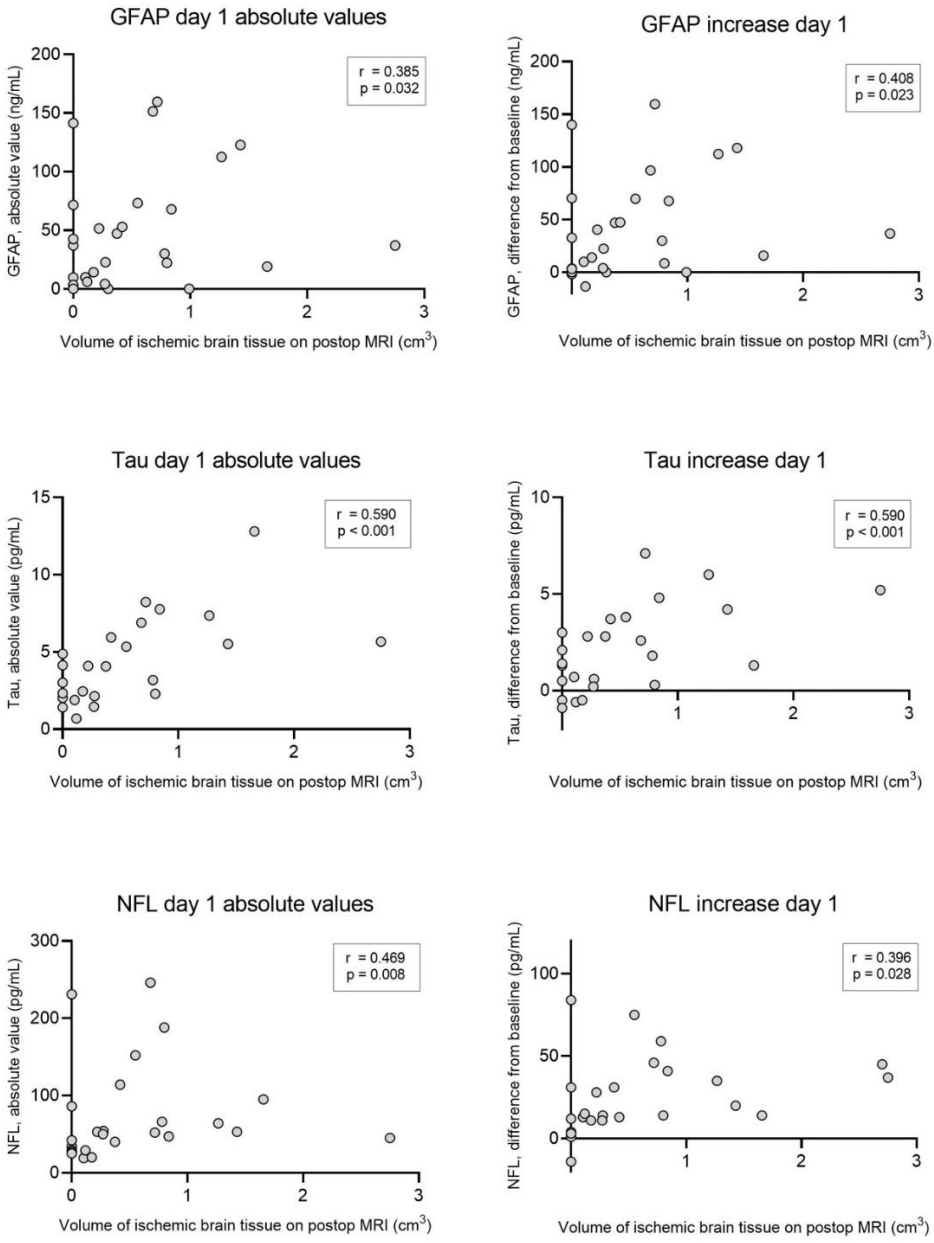
GFAP day 1 absolute values
r = 0.385
p = 0.032
GFAP, absolute value (ng/mL)
Volume of ischemic brain tissue on postop MRI (cm3)
GFAP increase day 1
r = 0.408
p = 0.023
GFAP, difference from baseline (ng/mL)
Volume of ischemic brain tissue on postop MRI (cm3)
Tau day 1 absolute values
r = 0.590
p < 0.001
Tau, absolute value (pg/mL)
Volume of ischemic brain tissue on postop MRI (cm3)
Tau increase day 1
r = 0.590
p < 0.001
Tau, difference from baseline (pg/mL)
Volume of ischemic brain tissue on postop MRI (cm3)
NFL day 1 absolute values
r = 0.469
p = 0.008
NFL, absolute value (pg/mL)
Volume of ischemic brain tissue on postop MRI (cm3)
NFL increase day 1
r = 0.396
p = 0.028
NFL, difference from baseline (pg/mL)
Volume of ischemic brain tissue on postop MRI (cm3)

Figure 4

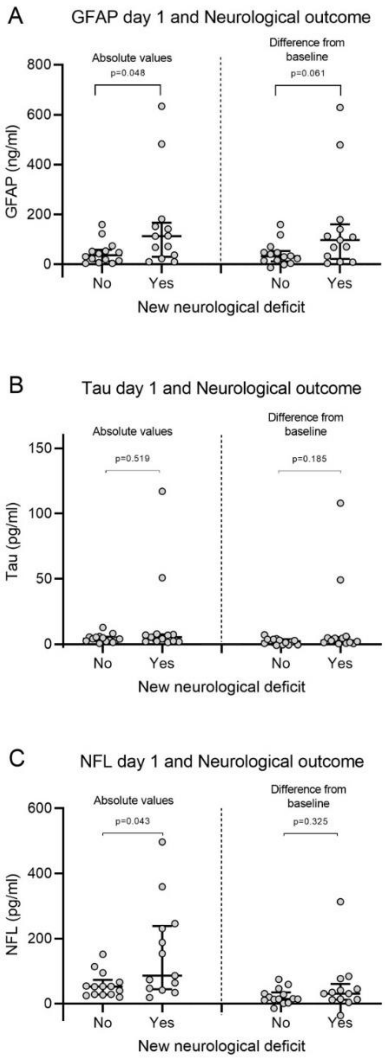
A
GFAP day 1 and Neurological outcome
Absolute values
p=0.048
Difference from baseline
p=0.061
GFAP (ng/ml)
800
600
400
200
0
No
Yes
No
Yes
New neurological deficit
B
Tau day 1 and Neurological outcome
Absolute values
p=0.519
Difference from baseline
p=0.185
Tau (pg/ml)
150
100
50
0
No
Yes
No
Yes
New neurological deficit
C
NFL day 1 and Neurological outcome
Absolute values
p=0.043
Difference from baseline
p=0.325
NFL (pg/ml)
600
400
200
0
No
Yes
No
Yes
New neurological deficit

Figure 5