

# Electrolyte and renal disorders in patients with newly diagnosed glioblastoma

**Daniela Pierscianek** (✉ [daniela.pierscianek@uk-essen.de](mailto:daniela.pierscianek@uk-essen.de))

University Hospital Essen Department of Neurosurgery: Universitätsklinikum Essen Klinik für Neurochirurgie und Wirbelsäulenchirurgie <https://orcid.org/0000-0003-0980-7444>

**Marvin Darkwah Oppong**

University Hospital Essen Department of Neurosurgery: Universitätsklinikum Essen Klinik für Neurochirurgie und Wirbelsäulenchirurgie

**Yahya Ahmadipour**

University Hospital Essen Department of Neurosurgery: Universitätsklinikum Essen Klinik für Neurochirurgie und Wirbelsäulenchirurgie

**Laurèl Rauschenbach**

University Hospital Essen Department of Neurosurgery and Spinal Surgery: Universitätsklinikum Essen Klinik für Neurochirurgie und Wirbelsäulenchirurgie

**Anna Michel**

University Hospital Essen Department of Neurosurgery and Spinal Surgery: Universitätsklinikum Essen Klinik für Neurochirurgie und Wirbelsäulenchirurgie

**Sied Kebir**

University Hospital Essen, Department of Neurology

**Philipp Dammann**

University Hospital Essen Department of Neurosurgery and Spinal Surgery: Universitätsklinikum Essen Klinik für Neurochirurgie und Wirbelsäulenchirurgie

**Karsten H. Wrede**

University Hospital Essen Department of Neurosurgery and Spinal Surgery: Universitätsklinikum Essen Klinik für Neurochirurgie und Wirbelsäulenchirurgie

**Martin Glas**

University Hospital Essen, Department of Neurology

**Jörg Hense**

University Hospital Essen, Department of Medical Oncology

**Christoph Pöttgen**

University Hospital Essen, Department of Radiotherapy

**Ulrich Sure**

University Hospital Essen Department of Neurosurgery: Universitätsklinikum Essen Klinik für Neurochirurgie und Wirbelsäulenchirurgie

**Ramazan Jabbarli**

## Research

**Keywords:** glioblastoma, hypochloremia, kidney function, electrolytes, routine laboratory parameters

**Posted Date:** October 6th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-84298/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

**Version of Record:** A version of this preprint was published at Future Oncology on October 21st, 2021. See the published version at <https://doi.org/10.2217/fo-2020-1312>.

# Abstract

## Background

Electrolyte disturbances and altered renal function have been linked to the prognosis of critically ill patients and recently also of cancer patients. Little is known about the prevalence and prognostic impact of electrolyte and renal disorders in patients with glioblastoma (GBM), the most frequent malignant primary brain tumor. This study aimed to assess electrolyte and renal disorders in GBM patients and evaluate their effect on patients' outcome.

## Methods

Patients treated for newly diagnosed GBM between 2005 and 2018 were included. Electrolytes and renal function parameters were assessed preoperatively. Medical records of patients were retrospectively reviewed for demographic and clinical parameters, as well as patients' survival.

## Results

Electrolyte and renal disorders at admission were present in 275 (30.6%) and 544 (60.4%) of 900 GBM patients respectively and were more common in patients with higher age, previous comorbidities and poor initial clinical performance status. In univariate analysis and Kaplan-Meier survival plots, presence of hyponatremia, hypochloremia, hypocalcemia, hyperuricemia and low glomerular filtration rate were associated with poorer survival. Multivariate analysis revealed hypochloremia as an independent prognostic factor for overall ( $p=0.004$ ) and 1-year ( $p=0.021$ ) survival.

## Conclusions

Preoperative electrolyte and renal disorders are common in GBM patients. Of them, only hypochloremia showed a strong association with GBM prognosis, independently of age, sex, extent of resection, clinical performance status, postoperative therapy, and molecular status. Further studies are needed to evaluate the impact of hypochloremia on GBM survival.

## 1. Introduction

Glioblastoma (GBM) is the most frequent primary malignant brain tumor in adults. Prognosis remains poor with a median survival of 17–25 months despite multimodal therapies (1). Still, survival varies significantly among individuals and estimation of patients' prognosis evolves into a highly relevant aspect in the treatment of patients with GBM. Therapies comprise tumor resection or stereotactic biopsy followed by combined radio-/chemotherapy or solely one of both adjuvant modalities, according to the patients' clinical status, age, etc. Several prognostic factors have been identified in GBM, like patients' age, clinical performance status, methylation of O6-methylguanine-DNA-methyltransferase gene promoter (MGMT), or mutation of the isocitrate-dehydrogenase gene 1 (IDH1) (2–5). These parameters allow an early estimation of patients' prognosis after GBM diagnosis. However, the identification of other relevant survival markers,

particularly of those assessable prior to surgery, is of eminent clinical importance and might be helpful during initial treatment planning.

Electrolyte disorders and altered renal function have long been linked to patients' prognosis in various diseases. Aberrations in serum electrolyte levels were shown to be associated with a higher mortality in intensive care units in critically ill adult patients (6, 7). Several recent studies additionally suggest that electrolyte disorders might be associated with a worse prognosis in a variety of malignancies (8), e.g. in colorectal cancer (9), lung cancer (10) and lymphoma (11, 12). To date, data on prevalence and eventual clinical impact of preoperative disturbances in serum electrolytes and renal parameters in GBM patients is scarce.

This study aimed to assess routinely investigated electrolytes and renal parameters in GBM patients at admission and to evaluate the impact of electrolyte and renal disorders on patients' survival.

## **2. Patients And Methods**

### **2.1. Study population**

In this retrospective longitudinal cohort study all patients (aged  $\geq 18$  years) with newly diagnosed and histologically confirmed GBM, that were treated between July 2005 and December 2018 in the University Hospital Essen were included. After surgery (microsurgical tumor resection or tumor biopsy), patients were transferred to adjuvant therapies (chemotherapy, radiation), or in accordance with patients' willingness, to best supportive care. The study was approved by the Institutional Ethics Committee.

### **2.2. Data management**

The primary objective of the study was to evaluate the association between routinely analyzed electrolytes and kidney function parameters with initial demographic/clinical characteristics and survival of GBM patients. As outcome endpoints, overall survival (OS) and 1-year survival (1-YS) were assessed. Preoperative serum blood samples were routinely collected 1–2 days prior to surgery. For electrolytes, sodium, chloride, potassium, and calcium were investigated. Kidney function was assessed using creatinine, urea, and glomerular filtration rate (GFR) GFR was estimated according to the Modification of Diet in Renal Disease (MDRD) equation. Default laboratory cutoff values were used to define aberrations in serum values. Medical records were reviewed for patients' age at diagnosis, sex, preoperative clinical status (Karnofsky Performance Scale [KPS]), treatment modalities (microsurgical tumor resection, tumor biopsy, radiation and chemotherapy), MGMT and IDH1 status.

### **2.3. Statistical analysis**

Statistical analysis was performed using SPSS (version 26, SPSS Inc., IBM, Chicago, IL, USA) and PRISM (version 5.0, GraphPad Software Inc., San Diego, CA, USA). First, all assessed variables were investigated in univariate analyses. Continuous, non-normally distributed data were presented as median with the corresponding interquartile range (IR, 25. – 75. percentile) whereas categorical data were reported as absolute numbers and their percentages. For categorical data, Fisher's exact or chi-square test was used, as

applicable. The Mann-Whitney-U test was performed for continuous variables. Differences with a P value  $\leq$  0.05 were considered statistically significant. All laboratory variables, that reached significance in the univariate analyses were then evaluated in multivariate analyses adjusted for patients' age, preoperative clinical condition, treatment modalities, and molecular aberrations. Multivariate binary logistic regression analyses were performed for 1-YS and Cox-Regression analysis was applied for evaluation of OS. Missing values were replaced using multiple imputation. Kaplan-Meier curves and log-rank test were used for survival analysis.

## **3. Results**

### **3.1. Patients' characteristics**

This cohort comprised 900 patients with newly diagnosed and histologically confirmed GBM. The median age was 65.1 years (IR 55.8–72.3 years). 524 patients were male (58.2%). Microsurgical resection was performed in 70.9% of patients and 72.6% of patients received combined radio- and chemotherapy postoperatively. The median overall survival was 8.93 months (IR 3.5–16.4 months). One-year survival rate was 41.1%. Detailed patients' characteristics are summarized in Table 1.

### **3.2. Electrolytes and kidney function in GBM**

In this cohort of GBM, electrolyte disorders occurred in 275 (30.6%) of GBM patients, whereas renal disorders were more frequent, affecting 544 patients (60.4%). In 74 patients (8.2%), more than one electrolyte parameter was deranged. The most frequent electrolyte disorder was hyperchloremia (13%), followed by hyponatremia (6.7%). A restricted GFR occurred in 29% of patients, whereas hyperuricemia was present in 48% of patients. Frequencies of electrolyte and renal disorders are shown in Fig. 1.

Associations of each electrolyte disorder with patients' baseline parameters were tested. Here, frequent associations with patients' age, preoperative clinical performance, and previous comorbidities were detected. For electrolyte disorders, no significant association with renal disorders were found. Detailed information on associations of electrolyte and renal disorders with the above-mentioned parameters are presented in Table 2.

### **3.3. Association of electrolyte disorders with GBM outcome**

#### **3.3.1. Univariate and survival analysis**

In univariate analysis, there was a significant association between hyponatremia ( $p < 0.001/p = 0.001$ ), hypochloremia ( $p < 0.001/p < 0.001$ ) and hypocalcemia ( $p < 0.001/p = 0.005$ ) with OS and 1-YS respectively. Patients with hyponatremia, hypochloremia or hypocalcemia had a shorter OS and survived less frequently one year. All results of univariate analyses are shown in Table 3. Survival analyses using Kaplan-Meier curves and the log-rank test confirmed poorer survival in GBM patients with hypochloremia ( $p < 0.001$ ), hyponatremia ( $p = 0.026$ ) and hypocalcemia ( $p < 0.001$ ). The Kaplan-Meier curves are shown in Fig. 2A-C.

Moreover, the impact of the number of electrolyte disorders on OS was also investigated. Here, a significant association between the number of electrolyte disorders and OS was found ( $p < 0.001$ ). This association is further supported by Kaplan-Meier analysis (log-rank test  $p < 0.001$ ) as shown in Fig. 2D.

### 3.3.2. Multivariate analysis

In multivariate analysis, only hypochloremia was found to be predictive for 1-YIS, independently of age, sex, extent of resection, clinical performance status, postoperative therapy and molecular alterations (adjusted odds ratio [aOR] = 0.33 [95% CI: 0.13–0.84],  $p = 0.021$ ). For OS, cox regression analysis showed a significantly poorer survival in patients with hypochloremia (hazard ratio [HR] = 1.59 [95% CI: 1.16–2.18],  $p = 0.004$ ), independently of covariates. Hyponatremia ( $p = 0.2$ ) and hypocalcemia ( $p = 0.39$ ) showed no association with OS in multivariate analysis. The results of multivariate analyses are listed in Table 4.

## 3.4. Association of kidney function with GBM outcome

### 3.4.1. Univariate and survival analyses

Patients with an urea serum level  $> 20$  mg/dl showed a significantly shorter median OS than patients with an urea level  $\leq 20$  mg/dl ( $p < 0.001$ , 7.3 vs. 10.6 months). A GFR  $< 60$  ml/min/1.73 m<sup>2</sup> was also associated with a shorter median OS ( $p < 0.001$ , 6.7 vs. 10.2 months). Additionally, patients with a GFR  $< 60$  ml/min/1.73 m<sup>2</sup> showed less frequently a survival of more than 1 year ( $p = 0.001$ ). This association was also found in patients with a urea serum level  $> 20$  mg/dl ( $p < 0.001$ ). Altered creatinine levels were not associated with OS or 1YS.

Survival analyses applying the log-rank test and Kaplan-Meier curves revealed a significantly worse survival in patients with a serum urea level  $> 20$  mg/dl ( $p < 0.001$ ) and in patients with a GFR  $< 60$  ml/min/1.73 m<sup>2</sup> ( $p < 0.001$ ) (see Supplemental Figure S1).

### 3.4.2. Multivariate analysis

Multivariate analyses did not reveal a serum urea level  $> 20$  mg/dl or a restricted GFR as independent predictive factors for 1-YIS and OS in binary logistic and Cox regression analyses respectively (see Supplemental Table S1).

## 4. Discussion

In cancer patients, electrolyte and acid-base disorders are reported in more than 50% (8). Moreover, kidney function and electrolyte homeostasis have been linked to patients' prognosis for several types of cancer (8, 10, 11). This study identified hypochloremia in GBM as an independent prognostic marker for 1-YIS and OS, whereas all other investigated electrolytes and parameters of kidney function failed to display a consistent relation to patients' outcome.

Chloride is the main anion in plasma and interstitial fluid and carries a significant role in maintaining serum osmolarity and acid-balance. There are several possible causes for hypochloremia in patients, like chloride

loss via vomiting or diarrhea, use of diuretics, or excess water gain due to infusion of hypotonic solutions. During the last years, chloride serum levels gained increasing attention in the intensive care of critically ill patients and also in cancer patients (13). In intensive care units, hypochloremia occurs in up to one-third of all individuals (14–16). This study found hypochloremia in 6.3% of patients with GBM in the preoperative routine investigation of electrolytes. This study cohort mainly comprises patients that are admitted to hospital for elective surgery of intracranial lesions, whereas the studies mentioned-above investigated critically ill patients in intensive care units. This might explain the higher rate of hypochloremia in the studies that were mainly conducted on patient collectives in intensive care units.

Several studies additionally addressed the association between hypochloremia and patients' outcome. Kimura et al. detected a significantly higher mortality in patients with hypochloremia after elective thoracic or abdominal surgery (16). Similar results revealed a study of 106,505 adult patients undergoing noncardiac surgery. Here, patients with preoperative hypochloremia showed a significant increased 90-days mortality compared to patients with normochloremia. Patients with hypochloremia also had a higher risk of postoperative acute kidney injury (17). These results are in agreement with several investigations reporting a poorer outcome for patients with hypochloremia (14, 18–20) whereas Thongprayoon et al. only found hospital-acquired hyperchloremia in 39,298 patients to be associated with increased in-hospital mortality (21). There is only sparse evidence for the influence of hypochloremia on the outcome of cancer patients. One recent study retrospectively collected clinical data and electrolytes parameters from all cancer patients treated over one year. In 25,881 patients, hypochloremia occurred in 24.5% of patients. The authors found a higher in-hospital mortality in patients with electrolyte disorders compared to patients with normal electrolytes (8). In another investigation among 5,089 patients with colorectal cancer, hypochloremia was associated with a worse overall survival and shorter disease-free survival (9). This study detected hypochloremia to be an independent prognostic factor for OS and 1-YS in GBM patients and is well in line with previous results. So far, there are no investigations that specifically address hypochloremia and its prognostic impact on GBM survival. One recent study analyzed the predictive value of hyponatremia in 200 GBM patients. Similar to the results of this study, the authors could not demonstrate an association between hyponatremia and patients' outcome (22). In this cohort of GBM patients, arterial hypertension, diabetes, a higher age, and a poor preoperative clinical status characterized the cohort of patients with hypochloremia. This observation is in line with previous studies, that also reported renal dysfunction, hypertension, and diabetes as risk factors for electrolyte disorders (8).

Hypochloremia might be a surrogate marker for patients with a specific risk profile that is associated with a poorer outcome. Petnak et al. investigated chloride levels of adult patients at discharge and found both hypochloremia and hyperchloremia to be associated with an increased risk of one-year mortality (23). In 18,825 critically ill adult patients, a fluctuation of chloride serum levels during the first 72 hours after admission to the intensive care unit was associated with increased 30-day mortality (6). So far, there are no studies on patients with GBM that included the evaluation of hypochloremia during the course of the disease and the influence of an early correction of hypochloremia on patients' outcome.

## 5. Limitations

The limitations of this study are mainly due to its retrospective design. The interpretation of the results is limited due to in part incomplete data, that carry the risk of inaccuracy. Furthermore, treatment strategies in our cohort were heterogenous and several factors, that might influence patients' renal function and electrolytes could not be incorporated in the analysis, e.g. medication at admission, repetitive vomiting, etc.

## 6. Conclusion

Despite the limitations mentioned above, this study is based on a large cohort of GBM patients and their corresponding serum laboratory parameters at admission. Hypochloremia was identified as an independent prognostic factor making serum chloride levels a promising preoperative biomarker in GBM. The results of this study will have to be confirmed in a prospective study including multiple centers. Additionally, the role of hypochloremia during the adjuvant therapies and the effect of adjustment of chloride serum levels on survival should be elucidated.

## Abbreviations

GBM: glioblastoma

MGMT: O6-methylguanin-DNA-methyltransferase gene promotor

IDH1: isocitrate-dehydrogenase gene 1

OS: overall survival

1-YS: 1- year survival

GFR: glomerular filtration rate

MDRD: Modification of Diet in Renal Disease

KPS: Karnofsky Performance Scale

aOR: adjusted odds ratio

HR: hazard ratio

## Declarations

### Ethical approval

The study was approved by the Institutional Ethics Committee, University of Essen (15-6504-BO and 15-6505-BO). As this is an retrospective analysis, consent on participation is not applicable.

### Consent for publication

The manuscript does not contain any individual person's data.

### **Availability of data**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### **Competing interests**

The authors state that there are no conflicts of interest, ethical adherence or any financial disclosures.

### **Funding**

none

### **Authors contributions**

All authors gave their final approval of the manuscript to be published and agreed to be accountable for all aspects of the work.

Daniela Pierscianek: Conception of the work, Data acquisition, analysis and interpretation, Drafting the work

Marvin Darkwah Oppong: Data acquisition and analysis, Drafting the work

Yahya Ahmadipour: Data acquisition, Revising the Manuscript

Laurèl Rauschenbach: Data acquisition, Revising the Manuscript

Anna Michel: Data acquisition, Revising the Manuscript

Sied Kebir: Data acquisition, Revising the Manuscript

Philipp Dammann: Data analysis and interpretation, Revising the Manuscript

Karsten H. Wrede: Data analysis and interpretation, Revising the Manuscript

Martin Glas: Data analysis and interpretation, Revising the Manuscript

Jörg Hense: Data analysis and interpretation, Revising the Manuscript

Christoph Pöttgen: Data analysis and interpretation, Revising the Manuscript

Ulrich Sure: Conception of the work, Data interpretation, Revising the Manuscript

Ramazan Jabbarli: Conception of the work, Data interpretation, Revising the Manuscript

### **Acknowledgements**

not applicable

## References

1. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. *JAMA*. 2017;318(23):2306–16.
2. Pierscianek D, Ahmadipour Y, Kaier K, Darkwah Oppong M, Michel A, Kebir S, et al. The SHORT Score for Preoperative Assessment of the Risk for Short-Term Survival in Glioblastoma. *World Neurosurg*. 2020.
3. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10):997–1003.
4. Nobusawa S, Watanabe T, Kleihues P, Ohgaki H. IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. *Clin Cancer Res*. 2009;15(19):6002–7.
5. Pierscianek D, Ahmadipour Y, Michel A, Chihi M, Oppong MD, Kebir S, et al. Preoperative Survival Prediction in Patients With Glioblastoma by Routine Inflammatory Laboratory Parameters. *Anticancer Res*. 2020;40(2):1161–6.
6. Kim HJ, Oh TK, Song IA, Lee JH. Association between fluctuations in serum chloride levels and 30-day mortality among critically ill patients: a retrospective analysis. *BMC Anesthesiol*. 2019;19(1):79.
7. Oh HJ, Kim SJ, Kim YC, Kim EJ, Jung IY, Oh DH, et al. An increased chloride level in hyponatremia is associated with decreased mortality in patients with severe sepsis or septic shock. *Sci Rep*. 2017;7(1):15883.
8. Li Y, Chen X, Shen Z, Wang Y, Hu J, Xu J, et al. Electrolyte and acid-base disorders in cancer patients and its impact on clinical outcomes: evidence from a real-world study in China. *Ren Fail*. 2020;42(1):234–43.
9. Li Q, Dai W, Jia H, Li Y, Xu Y, Li X, et al. Prognostic Impact of Hyponatremia in Patients With Stage I to III Colorectal Cancer After Radical Resection. *Dis Colon Rectum*. 2018;61(11):1273–80.
10. Li W, Chen X, Wang L, Wang Y, Huang C, Wang G, et al. The prognostic effects of hyponatremia and hyperchloremia on postoperative NSCLC patients. *Curr Probl Cancer*. 2019;43(5):402–10.
11. Castillo JJ, Glezerman IG, Boklage SH, Chiodo J 3rd, Tidwell BA, Lamerato LE, et al. The occurrence of hyponatremia and its importance as a prognostic factor in a cross-section of cancer patients. *BMC Cancer*. 2016;16:564.
12. Cheungpasitporn W, Thongprayoon C, Qian Q. Dymagnesemia in Hospitalized Patients: Prevalence and Prognostic Importance. *Mayo Clin Proc*. 2015;90(8):1001-10.
13. Bandak G, Kashani KB. Chloride in intensive care units: a key electrolyte. *F1000Res*. 2017;6:1930.
14. Shao M, Li G, Sarvottam K, Wang S, Thongprayoon C, Dong Y, et al. Dyschloremia Is a Risk Factor for the Development of Acute Kidney Injury in Critically Ill Patients. *PloS one*. 2016;11(8):e0160322.

15. Van Regenmortel N, Verbrugghe W, Van den Wyngaert T, Jorens PG. Impact of chloride and strong ion difference on ICU and hospital mortality in a mixed intensive care population. *Ann Intensive Care*. 2016;6(1):91.
16. Kimura S, Matsumoto S, Muto N, Yamanoi T, Higashi T, Nakamura K, et al. Association of serum chloride concentration with outcomes in postoperative critically ill patients: a retrospective observational study. *J Intensive Care*. 2014;2(1):39.
17. Oh TK, Do SH, Jeon YT, Kim J, Na HS, Hwang JW. Association of Preoperative Serum Chloride Levels With Mortality and Morbidity After Noncardiac Surgery: A Retrospective Cohort Study. *Anesth Analg*. 2019;129(6):1494–501.
18. Li Z, Xing C, Li T, Du L, Wang N. Hypochloremia is associated with increased risk of all-cause mortality in patients in the coronary care unit: A cohort study. *J Int Med Res*. 2020;48(4):300060520911500.
19. Ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, et al. Hypochloremia, Diuretic Resistance, and Outcome in Patients With Acute Heart Failure. *Circ Heart Fail*. 2016;9(8).
20. Prins KW, Kalra R, Rose L, Assad TR, Archer SL, Bajaj NS, et al. Hypochloremia Is a Noninvasive Predictor of Mortality in Pulmonary Arterial Hypertension. *J Am Heart Assoc*. 2020;9(5):e015221.
21. Thongprayoon C, Cheungpasitporn W, Petnak T, Mao MA, Chewcharat A, Qureshi F, et al. Hospital-Acquired Serum Chloride Derangements and Associated In-Hospital Mortality. *Medicines (Basel)*. 2020;7(7).
22. Mrowczynski OD, Bourcier AJ, Liao J, Langan ST, Specht CS, Rizk EB. The predictive potential of hyponatremia for glioblastoma patient survival. *J Neurooncol*. 2018;138(1):99–104.
23. Petnak T, Thongprayoon C, Cheungpasitporn W, Bathini T, Vallabhajosyula S, Chewcharat A, et al. Serum Chloride Levels at Hospital Discharge and One-Year Mortality among Hospitalized Patients. *Med Sci (Basel)*. 2020;8(2).

## Tables

**Table 1. Patients' characteristics.**

<b>Parameter</b>	<b>Value</b>
Number of patients, <i>n</i>	900
Age in years, median (IR)	65.14 (55.8 – 72.3)
Sex (female), <i>n</i> (%)	376 (41.8 %)
Tumor resection, <i>n</i> (%)	638 (70.9 %)
IDH1-mut. (R132H), <i>n</i> (%)	17 (3.0 %)
MGMT-meth., <i>n</i> (%)	311 (41.3 %)
KPS preop < 80%	239 (28.1 %)
arterial hypertension	452 (54.3%)
diabetes mellitus	153 (18.3%)
hypothyroidism	107 (11.9%)
Overall survival in months, median (IR)	8.93 (3.5 – 16.4)
1-Year survival	361 (41.1 %)

Abbreviations: IDH1-mut.: IDH1-Mutation; MGMT-meth.: O6-Methylguanin-DNA-Methyltransferase Promotor-Methylation; KPS: Karnofsky Performance Scale; preop: preoperatively; CTX: Chemotherapy; RTX: radiotherapy; IR: interquartile range

**Table 2. Univariate analyses of electrolyte and renal parameters and patients' characteristics and comorbidities.**

Laboratory parameter	age <sup>#</sup> (in years)	sex <sup>*</sup>	KPS <sup>#</sup>	aHTN <sup>*</sup>	DM <sup>*</sup>	Hypo-thyreodism <sup>*</sup>	BMI <sup>#</sup> (kg/m <sup>2</sup> )
Hypernatremia	<i>p</i> =0.590	<i>p</i> =0.867	<b><i>p</i>=0.034</b>	<i>p</i> =0.383	<i>p</i> =0.372	<i>p</i> =0.426	<i>p</i> =0.953
Hyponatremia	<b><i>p</i>=0.008</b>	<i>p</i> =0.491	<b><i>p</i>=0.012</b>	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>&lt;0.001</b>	<i>p</i> =0.098	<i>p</i> =0.591
Hyperkalemia	<b><i>p</i>=0.031</b>	<i>p</i> =0.848	<i>p</i> =0.165	<i>p</i> =0.178	<i>p</i> =1.00	<i>p</i> =0.379	<i>p</i> =0.145
Hypokalemia	<b><i>p</i>&lt;0.001</b>	<i>p</i> =0.254	<i>p</i> =0.368	<b><i>p</i>=0.001</b>	<i>p</i> =0.076	<b><i>p</i>=0.024</b>	<i>p</i> =0.077
Hyperchloremia	<i>p</i> =0.343	<b><i>p</i>=0.017</b>	<i>p</i> =0.993	<b><i>p</i>=0.011</b>	<i>p</i> =1.00	<b><i>p</i>=0.002</b>	<i>p</i> =0.093
Hypochloremia	<b><i>p</i>=0.008</b>	<i>p</i> =0.202	<b><i>p</i>=0.003</b>	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>&lt;0.001</b>	<i>p</i> =1.00	<i>p</i> =0.124
Hypercalcemia	<i>p</i> =0.496	<i>p</i> =0.912	<i>p</i> =0.130	<i>p</i> =0.187	<i>p</i> =0.781	<i>p</i> =0.787	<i>p</i> =0.057
Hypocalcemia	<b><i>p</i>&lt;0.001</b>	<i>p</i> =0.333	<b><i>p</i>=0.006</b>	<b><i>p</i>=0.002</b>	<i>p</i> =0.296	<i>p</i> =0.473	<i>p</i> =0.153
Hyperuricemia	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>=0.002</b>	<b><i>p</i>=0.003</b>	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>=0.036</b>	<i>p</i> =0.249	<i>p</i> =0.114
Creatinine >1.1mg/dl	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>&lt;0.001</b>	<i>p</i> =0.207	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>=0.001</b>	<b><i>p</i>=0.047</b>	<b><i>p</i>=0.007</b>
GFR < 60ml/min/1.73m <sup>2</sup>	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>&lt;0.001</b>	<i>p</i> =0.795	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>&lt;0.001</b>	<b><i>p</i>=0.012</b>	<b><i>p</i>=0.032</b>

Abbreviations: KPS: Karnofsky Performance Scale; aHTN: arterial hypertension, DM: Diabetes mellitus; BMI: Body Mass Index; Na<sup>+</sup>: Natrium; K<sup>+</sup>: potassium; Cl<sup>-</sup>: Chloride; Ca<sup>2+</sup>: Calcium; GFR: glomerular filtration rate.

#: continuous data, Mann-Whitney U test; \*: categorical data, fishers' exact test/chi-square

**Table 3. Univariate analysis of serum electrolytes and kidney function parameters and patients' outcome.**

Parameter	Overall survival (median)	1-year survival (%)
Na <sup>+</sup> >145mmol/L vs. ≤145 mmol/L	7.1 vs. 8.8 months; <i>p</i> =0.134	36.8% vs. 40.5%; <i>p</i> =0.736
Na <sup>+</sup> <135mmol/L vs. ≥135 mmol/L	3.5 vs. 9.2 months; <b><i>p</i>&lt;0.001</b>	19.3% vs. 41.9%; <b><i>p</i>=0.001</b>
Cl <sup>-</sup> >107mmol/L vs. ≤107 mmol/L	8.9 vs. 8.7 months; <i>p</i> =0.813	38.7% vs. 40.7%; <i>p</i> =0.751
Cl <sup>-</sup> <98mmol/L vs. ≥98 mmol/L	3.5 vs. 9.4 months; <b><i>p</i>&lt;0.001</b>	13.2% vs. 42.3%; <b><i>p</i>&lt;0.001</b>
K <sup>+</sup> >5.0mmol/L vs. ≤5.0 mmol/L	5.7 vs. 8.8 months; <i>p</i> =0.171	27.6% vs. 40.8%; <i>p</i> =0.180
K <sup>+</sup> <3.5mmol/L vs. ≥3.5 mmol/L	7.0 vs. 8.8 months; <i>p</i> =0.297	31.6% vs. 40.5%; <i>p</i> =0.487
Ca <sup>2+</sup> >2.65mmol/L vs. ≤2.65 mmol/L	14.2 vs. 8.7 months; <i>p</i> =0.321	60.0% vs. 39.2%; <i>p</i> =0.205
Ca <sup>2+</sup> <2.08mmol/L vs. ≥2.08 mmol/L	2.7 vs. 9.2 months; <b><i>p</i>&lt;0.001</b>	19.0% vs. 40.9%; <b><i>p</i>=0.005</b>
Creatinine >1.1mg/dl vs. ≤1.1 mg/dl	8.3 vs. 9.3 months; <i>p</i> =0.192	36.8% vs. 42.4%; <i>p</i> =0.121
Urea >20mg/dl vs. ≤20mg/dl	7.3 vs. 10.6 months; <b><i>p</i>&lt;0.001</b>	32.4% vs. 47.9%; <b><i>p</i>&lt;0.001</b>
GFR <60ml/min/1.73qm vs. ≥60ml/min/1.73qm	6.7 vs. 10.2 months; <b><i>p</i>&lt;0.001</b>	30.4% vs. 44.8%; <b><i>p</i>=0.001</b>

#### Abbreviations

Na<sup>+</sup>: Natrium; Cl<sup>-</sup>: Chloride; K<sup>+</sup>: potassium, Ca<sup>2+</sup>: Calcium; GFR: glomerular filtration rate

**Table 4. Multivariate analysis for OS and 1-YS using Cox and binary regression analysis respectively.**

Parameters	OS predictors			1-YS predictors		
	<i>aHR</i>	<i>95% CI</i>	<i>p-value</i>	<i>aOR</i>	<i>95% CI</i>	<i>p-value</i>
Sex (female)	1.02	0.88 – 1.17	0.816	1.15	0.81 – 1.61	0.438
Age (continuous)	1.03	1.02 – 1.04	<0.001	0.96	0.95 – 0.98	<0.001
Surgical resection	0.45	0.38 – 0.53	<0.001	4.95	3.25 – 7.53	<0.001
KPS <80%	1.47	1.22 – 1.78	<0.001	0.54	0.34 – 0.87	0.012
MGMT (methylated)	0.70	0.59 – 0.83	<0.001	1.76	1.22 – 2.54	0.003
IDH1 (mutated)	0.83	0.59 – 1.16	0.262	2.13	0.80 – 5.62	0.119
RTX/CTX	0.44	0.35 – 0.55	<0.001	5.07	2.71 – 9.48	<0.001
Hyponatremia	1.23	0.89 – 1.69	0.2	0.49	0.23 – 1.05	0.068

Parameters	OS predictors			1-YS predictors		
	<i>aHR</i>	<i>95% CI</i>	<i>p-value</i>	<i>aOR</i>	<i>95% CI</i>	<i>p-value</i>
Sex (female)	1.02	0.88 – 1.17	0.838	1.13	0.81 – 1.59	0.475
Age (continuous)	1.03	1.03 – 1.03	<0.001	0.96	0.95 – 0.98	<0.001
Surgical resection	0.44	0.38 – 0.52	<0.001	4.89	3.20 – 7.46	<0.001
KPS <80%	1.44	1.20 – 1.71	<0.001	0.55	0.35 – 0.88	0.013
MGMT (methylated)	0.70	0.59 – 0.83	<0.001	1.76	1.22 – 2.56	0.003
IDH1 (mutated)	0.82	0.57 – 1.18	0.271	2.19	0.76 – 6.32	0.132
RTX/CTX	0.45	0.36 – 0.55	<0.001	5.05	2.69 – 9.48	<0.001
Hypochloremia	1.59	1.16 – 2.18	0.004	0.33	0.13 – 0.84	0.021

Parameters	OS predictors			1-YS predictors		
	<i>aHR</i>	95% CI	<i>p-value</i>	<i>aOR</i>	95% CI	<i>p-value</i>
Sex (female)	1.01	0.88 – 1.17	0.858	1.14	0.81 – 1.61	0.446
Age (continuous)	1.03	1.02 – 1.03	<0.001	0.96	0.95 – 0.98	<0.001
Surgical resection	0.44	0.37 – 0.52	<0.001	4.98	3.26 – 7.61	<0.001
KPS <80%	1.46	1.21 – 1.76	<0.001	0.54	0.34 – 0.87	0.011
MGMT (methylated)	0.70	0.60 – 0.83	<0.001	1.73	1.21 – 2.48	0.003
IDH1 (mutated)	0.83	0.60 – 1.16	0.262	2.07	0.78 – 5.51	0.132
RTX/CTX	0.44	0.35 – 0.54	<0.001	5.23	2.82 – 9.70	<0.001
Hypocalcemia	1.16	0.82 – 1.64	0.388	0.92	0.40 – 2.13	0.847

Abbreviations: aOR: adjusted Odds Ratio; aHR: adjusted Hazard Ratio; 95% CI: 95% Confidence Interval; KPS: Karnofsky Performance Scale; RTX/CTX: combined Radio- and Chemotherapy; OS: overall survival; 1YS: 1-year survival;

## Figures

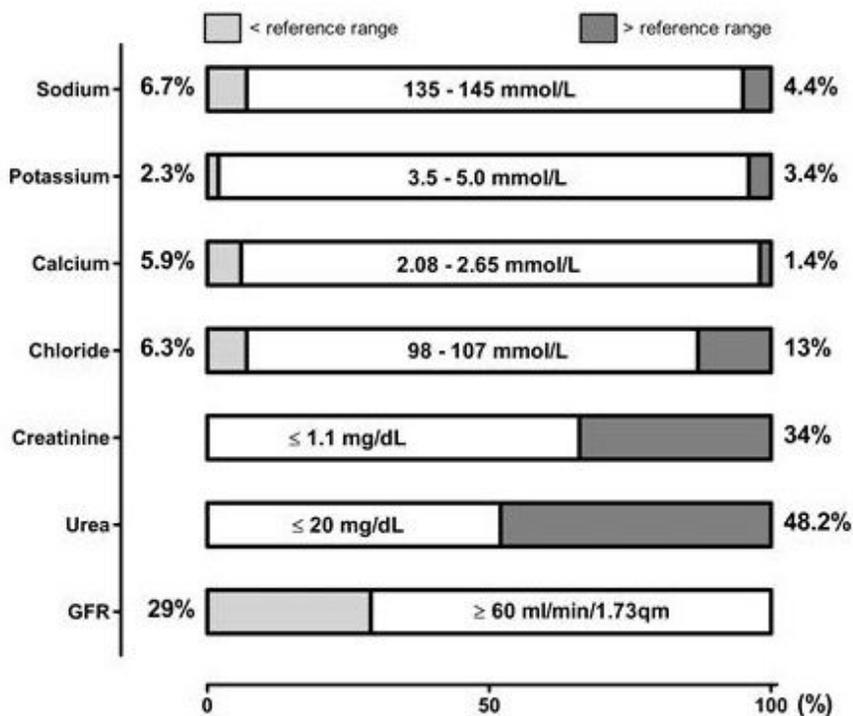


Figure 1

Prevalence of electrolyte and renal disorders in the analyzed GBM cohort. Preoperative serum lab values were available for: sodium, potassium and creatinine in 860 patients; chloride and urea in 857 patients; calcium in 717 and glomerular filtration rate (GFR) in 645 patients. Reference ranges with appropriate units are shown in white bars. The prevalence of aberrations below (light grey bars) and above (dark grey bars) the range limits is reported in percentages.

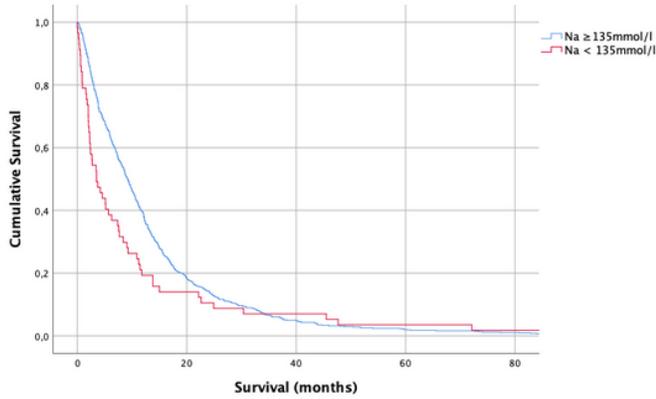


Figure 2A.

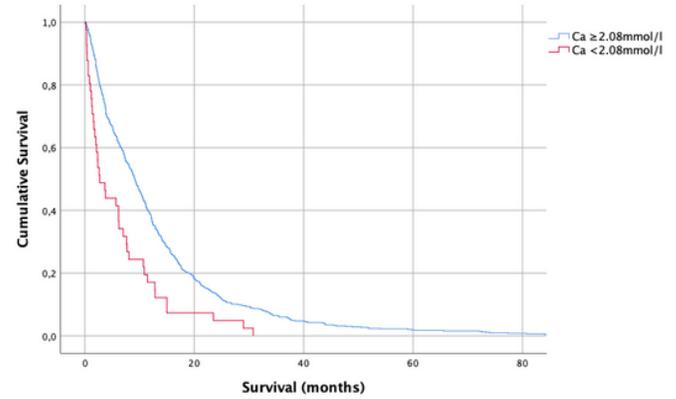


Figure 2C.

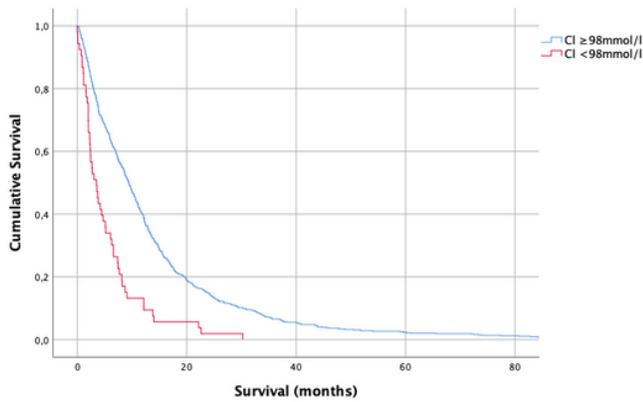


Figure 2B.

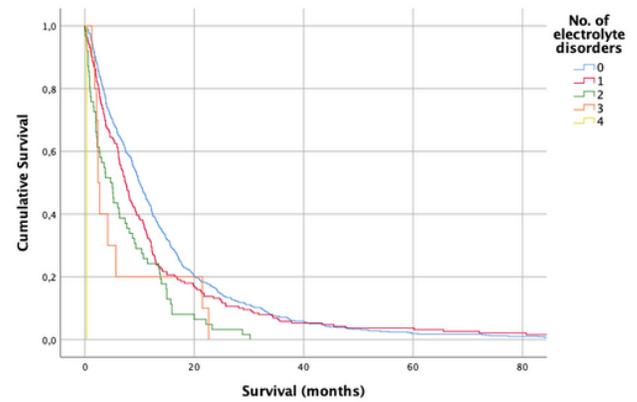


Figure 2D.

## Figure 2

Survival analysis using Kaplan-Meier curves for hyponatremia (A), hypochloremia (B) and hypocalcaemia (C). Figure 2D shows survival analysis for combined electrolyte disorders.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableS1.docx](#)
- [FigureS1.docx](#)