PATIENT BLOOD MANAGEMENT

Original article

Red blood cell transfusion in patients undergoing elective primary glioblastoma resection

Vanessa Neef[1*], Sven König[2*], Hendrik Becker[1], Daniel Dubinski[2,3], Armin Flinspach[1], Florian J. Raimann[1], Katharina Weber[4], Michael W. Ronellenfitsch[4], Juergen Konczalla[2], Elke Hattingen[6], Marcus Czabanka[2], Christian Senft[7], Kai Zacharowski[1], Peter Baumgarten[2,7]

***Vanessa Neef and Sven König contributed equally as co-first Authors**

[1]*Goethe University Frankfurt, University Hospital, Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, Frankfurt, Germany;*
[2]*Goethe University Frankfurt, Department of Neurosurgery, University Hospital Frankfurt, Frankfurt, Germany;*
[3]*Department of Neurosurgery, University Medicine Rostock, Rostock, Germany;*
[4]*Goethe University Frankfurt, Neurological Institute, Edinger Institute, Neuropathology, Frankfurt, Germany;*
[5]*Goethe University Frankfurt, Dr. Senckenberg Institute of Neurooncology, University Hospital Frankfurt, Frankfurt, Germany;*
[6]*Goethe University Frankfurt, Department of Neuroradiology, University Hospital Frankfurt, Frankfurt, Germany;*
[7]*Friedrich Schiller University Jena, Department of Neurosurgery, University Hospital Jena, Jena, Germany*

Background - Red blood cell (RBC) transfusion in patients undergoing major elective cranial surgery is associated with increased postoperative morbidity and mortality. This study aims to identify the clinical outcome of transfused glioblastoma patients undergoing primary surgical tumor resection and identify risk factors for RBC transfusion.

Material and methods - Between 2009 and 2019, 406 patients underwent elective primary glioblastoma resection. For multivariate analysis to assess risk factors for RBC transfusion, logistic regression was conducted. The impact of RBC transfusion on overall survival was assessed using Kaplan-Meier analysis.

Results - In total, 36 (8.9%) patients received RBC transfusion. Preoperative anemia rate was significantly higher in transfused patients compared to patients without RBC transfusion (33.3 *vs* 6.5%; p<0.0001). Postoperative complications as well as hospital length of stay (LOS) (p<0.0001) were significantly increased in transfused patients compared to non-transfused patients. After multivariate analysis, risk factors for RBC transfusion were preoperative anemia (p<0.0001), intraoperative blood loss (p<0.0001), female gender (p=0.0056) and radiation (p=0.0064). Kaplan-Meier curves revealed that RBC transfusion and being elderly (age ≥75 years) were relevant for overall survival.

Discussion - RBC transfusion is associated with increased postoperative morbidity and mortality in patients undergoing elective primary glioblastoma resection. Preoperative anemia and intraoperative blood loss are major risk factors for RBC transfusion. Preoperative anemia management and blood conservation strategies are crucial in patients undergoing elective primary glioblastoma resection.

Keywords: *red blood cells, anemia, blood transfusion, glioblastoma.*

INTRODUCTION

Preoperative anemia is common in patients undergoing major surgery, with a prevalence up to 50%[1]. A study of patients undergoing various non-neurosurgical procedures revealed that preoperative anemia is an independent risk factor for peri-operative morbidity and mortality, including prolonged hospital length of stay (LOS) and an increased risk of red blood cell (RBC) transfusion[2]. However, the administration of allogeneic RBC often

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Correspondence: Vanessa.Neef
e-mail: neef@med.uni-frankfurt.de

remains the main treatment for an existing anemia[3]. Focusing on the clinical outcomes of patients undergoing elective cranial surgery, the administration of RBCs is associated with prolonged hospital LOS, an increased complication rate and 30-day mortality rate[4]. A recent study in 423 patients undergoing elective primary meningioma resection revealed a RBC transfusion rate of 16.1%. In transfused patients, preoperative anemia rate, postoperative complications (e.g., pneumonia, sepsis, pulmonary embolism and postoperative seizure) as well as hospital LOS were significantly higher compared to patients without RBC transfusion[5]. Glioblastoma is the most frequent malignant brain tumor and common treatment strategies include neurosurgical tumor resection with adjuvant chemotherapy and concomitant radiotherapy[6]. According to an analysis in 2022 in patients undergoing craniotomy for resection of newly diagnosed glioblastoma, 17 out of 240 (7.0%) patients received perioperative RBC transfusions. The median overall survival of transfused patients was significantly shorter than that of patients who did not receive RBC (7 *vs* 18 months, p<0.0001). The authors of the study concluded that perioperative RBC transfusion compromises survival in patients with glioblastoma, so the use of RBC transfusion needs to be reduced[7]. Despite this study, there are no data on surgery-related postoperative complications affecting patients' morbidity in association with perioperative blood transfusions in a large population of patients with glioblastoma. Thus, this retrospective study aimed to identify the clinical outcome of patients undergoing elective glioblastoma resection who receive RBC transfusions.

MATERIALS AND METHODS

Patients

We retrospectively analyzed patients who underwent primary glioblastoma resection at the University Hospital Frankfurt between September 2009 and October 2019. The study protocol was approved by the ethics committee of the University Hospital Frankfurt (Ref. 274/18) and the requirement for written informed consent by patients was waived. All patients analyzed received standard perioperative care. The diagnosis of the patients in the cohort studied corresponded to the updated 2016 World Health Organization (WHO) classification of central nervous system tumour[6]. The patient-specific data extracted were age, sex, body mass index, the American Society of Anesthesiologists physical status score, comorbidities and preoperative Karnofsky performance scale (KPS) value. A cut-off of 60% was used for all KPS, since values above that mean independence of help for daily living. Extracted tumor-relevant data were tumor localization, WHO grade, conduction of radiotherapy and chemotherapy, Methylguanine-DNA methyltransferase promotor methylation status and histology.

Surgical parameters included intraoperative blood loss and duration of surgery. Postoperatively extracted data were hospital LOS, LOS in the intensive care unit (ICU), and postoperative complications (acute renal failure, pneumonia, sepsis, pulmonary embolism, myocardial infarction, stroke and seizures). Hematological and transfusion-related parameters recorded were hemoglobin value at admission to hospital, postoperatively and at discharge from hospital, as well as the perioperative transfusion rate of RBC, platelets, fresh-frozen plasma, fibrinogen and prothrombin complex concentrate. RBC transfusions were administered in accordance with the German transfusion guidelines. The patients' follow-up was conducted in the neuro-oncology department or by external oncologists at least every three months, depending on the course of the disease.

Classification of anemia

In this study, anemia was defined, according to the WHO definition of anemia, as a hemoglobin concentration of <12 g/dL in women and <13 g/dL in men[8].

Endpoints

The primary endpoints of this study were the prevalence of preoperative anemia and perioperative RBC transfusion rate. Secondary endpoints were hospital LOS and ICU LOS, postoperative complications, anemia rate at hospital discharge and perioperative rate of transfusion of other blood products (platelets, fresh-frozen plasma, fibrinogen and prothrombin complex concentrate).

Statistical analysis

Statistical analysis was performed using JMP 17.1.0 software (SAS Institute, Cary, NC, USA) and GraphPad Prism 9 (GraphPad Software Inc., La Jolla, CA, USA). Descriptive statistical methods, i.e., mean (± standard deviation [SD]) or median and interquartile range (IQR,

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25%-75%) were used to analyze data. The Shapiro-Wilk test was used to assess normality of continuous variables. Normally distributed continuous variables (hemoglobin value at hospital discharge) were compared with the two-sided *t*-test. Non-normally distributed continuous variables were compared with the Mood's median test. Categorical variables were compared with Pearson's c^2 test. For multivariate analysis, logistic regression was conducted. Survival analyses were performed using Kaplan-Meier analyses. To compare the survival curves, we used Wilcoxon and log-rank tests for censored data. A p-value <0.05 was considered statistically significant.

RESULTS

Patients

Between 2009 and 2019, a total of 1,121 patients underwent any surgical procedure for glioblastoma disease. Of these, 413 patients were scheduled for biopsy only, 204 patients had recurrent tumors and in clinical data were missing for 98 patients who were, therefore, excluded from further evaluation. The remaining 406 patients were included in the final analysis (**Figure 1**). The median follow-up period in this study cohort was 14 months (mean: 20.6 months, IQR: 6-25 months, range, 0-128 months).

Patients' characteristics in the RBC transfusion and non-RBC transfusion group

In total, 36 out of 406 (8.9%) patients received perioperative RBC transfusions and 370 out of 406 (91.1%) patients did not receive RBCs. There was no significant difference in age and any comorbidity analyzed between the RBC transfusion group and the non-RBC transfusion group.

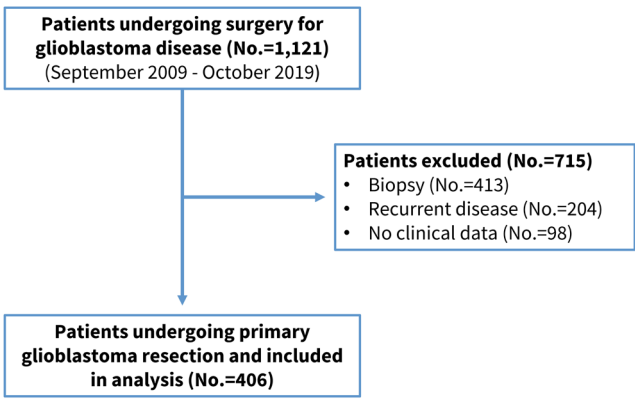


Figure 1 - Overview of the study population

The rate of cases with a preoperative KPS ≤60% was significantly higher in patients in the RBC transfusion group than in those in the non-RBC transfusion group (33.3 *vs* 13.1%; p=0.0007) (Table I).

Transfusion characteristics, anemia and postoperative complications in the RBC transfusion and non-RBC transfusion group

The median [IQR] duration of surgery was significantly longer in patients in the RBC transfusion group (282 [242-299] min) than in patients who did receive RBC transfusion (238 [190-277] min; p=0.0001). In addition, patients requiring allogeneic RBC transfusion had significantly greater median blood loss (1,016 [500-1,300] mL) compared to patients not requiring RBC transfusion (479 [200-600] mL); p=0.0001) (**Table I**).

In all patients analyzed, the overall rate of preoperative anemia was 8.9% (36 out of 406 patients) whereas 91.1% (370 out of 406) patients did not have preoperative anemia. The rate of anemia at hospital admission was significantly higher in the RBC transfusion group than in the non-RBC transfusion group (33.3 *vs* 6.5%; p<0.0001). Regarding the transfusion rates of other blood products, the transfusion rate of platelets (11.1 *vs* 0.3%; p<0.0001), fresh-frozen plasma (8.3 *vs* 0.0%; p<0.0001), fibrinogen (8.3 *vs* 1.9%; p=0.0173) and platelet complex concentrate (16.7 *vs* 3.0%; p<0.0001) differed significantly between the RBC-transfusion group and the non-RBC transfusion group, respectively.

Regarding postoperative complications, median hospital LOS was significantly longer in transfused patients (19.3 [11-27] days) than in non-transfused patients (12.7 [8-16] days; p=0.0039). The complication rates were significantly higher in patients who received RBC transfusions than in those who did not for pneumonia (p<0.0001), sepsis (p=0.0013), pulmonary embolism (p=0.0061) and seizures (p<0.0001). Finally, all (100.0%) transfused patients were anemic at discharge from hospital compared to 75.5% of patients not transfused with RBC (p=0.0008) (**Table II**).

Timing of perioperative red blood cell transfusions

The majority of RBC units (No.=29; 80.6%) were transfused between the day of surgery (day 0) until 3 days after surgery. Secondly, 11.1% of all RBC were transfused >10 days after surgery. Between days 4-6 and days 7-10 after surgery, one (2.8%) and one (2.8%) RBC units were transfused, respectively. In total seven (19.4%), 19 (52.8%),

Table I - *Patient and tumor characteristics between the RBC transfusion and non-RBC transfusion group*

Characteristics	RBC transfusion, No. (%) 36 (8.9%)	Non-RBC transfusion, No. (%) 370 (91.1%)	p-value
Patients` characteristics			
Male/female	15 (41.7%)/21 (58.3%)	228 (61.6%)/142 (38.4%)	**0.0197**
Age (years)*	59 (54;70)	59 (51;68)	0.7782
Elderly (≥75 years)	2 (5.6%)	37 (10.0%)	0.3876
Body mass index (kg/m²)*	25.8 (23.3;26.9)	26.4 (23.4;28.9)	0.9689
ASA score (I/II/III/IV)	3 (8.3%)/18 (50.0%)/15 (41.7%)/0 (0%)	22 (5.9%)/211 (57.0%)/133 (35.9%)/4 (1.1%)	0.7352
Comorbidities			
Smoking	6 (16.7%)	73 (19.7%)	0.6576
Cardiovascular disease	21 (58.3%)	190 (51.4%)	0.4234
Pulmonary disease	2 (5.6%)	31 (8.4%)	0.5541
Diabetes	4 (11.1%)	44 (11.9%)	0.8898
Endocrine disorder	15 (41.7%)	124 (33.5%)	0.3250
Chronic kidney injury	10 (27.8%)	145 (39.3%)	0.1747
Liver disorder	0 (0%)	11 (3.0%)	0.2942
Gastrointestinal disorder	1 (2.8%)	23 (6.2%)	0.4037
Coagulopathy	2 (5.6%)	9 (2.4%)	0.2705
Preoperative seizure	10 (27.8%)	139 (37.6%)	0.2447
Intake of antiplatelet medication	6 (16.7%)	42 (11.4%)	**0.0199**
Intake of direct oral anticoagulation	5 (13.9%)	18 (4.9%)	**0.0199**
Glioblastoma			
Location left/right/both sides	10 (28.6%)/25 (71.4%)/0 (0%)	145 (39.3%)/217 (58.8%)/7 (1.9%)	0.2905
MGMT methylation	20 (57.1%)	162 (44.4%)	**0.3403**
Radiation	24 (68.6%)	325 (89.5%)	**0.0003**
Chemotherapy	26 (74.3%)	310 (85.6%)	**0.0754**
Preoperative KPS ≤60%	12 (33.3%)	48 (13.1%)	**0.0007**
Surgical management			
Surgical time (min)*	282 (242;299)	238 (190;277)	**<0.0001**
Intraoperative blood loss (mL)*	1,016 (500;1,300)	479 (200;600)	**<0.0001**

*Results are expressed as median (interquartile range, 25%;75%); p-values in bold are statistically significant. RBC: red blood cell; BMI: body mass index; ASA: American Society of Anesthesiologists physical status score; KPS: Karnofsky Performance Scale; MGMT: methylguanine-methyltransferase.

four (11.1%), and six (16.7%) received one, two, three, or more than three RBC transfusions, respectively (**Table III**).

Risk factors for red blood cell transfusion

The analyzed risk factors for RBC transfusion in all patients (No.=406) are summarized in **Table IV**. Of all analyzed factors, anemia at hospital admission (p<0.0001), female gender (p=0.0197), preoperative KPS ≤60% (p=0.0011), radiotherapy (p=0.0003), duration of surgery (p<0.0001) and intraoperative blood loss (p<0.0001) were significantly associated with the risk for RBC transfusion. Multivariate analyses of all factors that showed significant influence in univariate analyses (p<0.05) were performed. After logistic regression, anemia at hospital admission (p<0.001), sex (female) (p=0.0056), radiotherapy (p=0.0064) and intraoperative blood loss (p<0.0001) remained as independent risk factors for perioperative RBC transfusion (**Table IV**).

Table II - *Postoperative complications, hemoglobin values and transfusion rates between the RBC transfusion and non-RBC transfusion group*

Characteristics	RBC transfusion, No. (%) 36 (8.9%)	Non-RBC transfusion, No. (%) 370 (91.1%)	p-value
Postoperative complications			
Acute renal failure	2 (5.6%)	66 (17.8%)	0.0596
Pneumonia	7 (19.4%)	7 (1.9%)	**<0.0001**
Sepsis	1 (2.8%)	0 (0%)	**0.0013**
Pulmonary embolism	5 (13.9%)	14 (3.8%)	**0.0061**
Stroke	0 (0%)	3 (0.8%)	0.5876
Seizure	11 (30.6%)	31 (8.4%)	**<0.0001**
Hospital LOS (days)*	19.3 (11;27)	12.7 (8;16)	**0.0039**
ICU LOS (days)*	8.3 (1;14)	1.6 (1;1)	**<0.0001**
Hb values and transfusion rates			
Hb value (admission) (g/dL)*	12.9 (11.6;14.7)	14.3 (13.4;15.3)	**0.0356**
Anemia rate at admission	12 (33.3%)	24 (6.5%)	**<0.0001**
Hb value (discharge) (g/dL)*	9.8 (8.8;10.5)	11.6 (10.5;12.7)	**<0.0001**
Anemia rate at discharge	36 (100%)	280 (75.7%)	**0.0008**
Platelet transfusion rate	4 (11.1%)	1 (0.3%)	**<0.0001**
FFP transfusion rate	3 (8.3%)	0 (0%)	**<0.0001**
Fibrinogen transfusion rate	3 (8.3%)	7 (1.9%)	**0.0173**
PCC transfusion rate	6 (16.7%)	11 (3%)	**<0.0001**

*Results are expressed as median (interquartile range, 25%;75%). p-values in bold are statistically significant. Hb: hemoglobin; RBC: red blood cell; ICU: intensive care unit; LOS: length of stay; FFP: fresh-frozen plasma; PCC: prothrombin complex concentrate.

Table III - *Day of RBC transfusion*

Day of RBC transfusion	No. (%)	Total number of RBC units No. (%)			
		1 RBC unit	2 RBC units	3 RBC units	4 RBC units
Day 0	1 (2.8%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
0-3	29 (80.6%)	5 (17.2%)	16 (55.2%)	2(6.9%)	6 (20.7%)
4-6	1 (2.8%)	0 (0%)	0 (0%)	1(100%)	0 (0%)
7-10	1 (2.8%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
>10	4 (11.1%)	1 (25%)	2 (50%)	1 (25%)	0 (0%)

Day 0: day of operation; RBC: red blood cell.

Table IV - *Risk factors for RBC transfusion*

Risk factor	Univariate analysis p-value	Multivariate analysis p-value	OR	95% CI
Anemia at admission	<0.0001	**0.0001**	10.31	−1.75; −0.58
Sex (female)	0.0197 0.0011 0.0003	**0.0056**	4.1	−1.23-; −0.18
Preoperative KPS ≤60%	-	0.0856	2.5	−0.97; 0.05
Radiation	-	**0.0064**	0.19	0.25; 1.4
Surgical time	<0.0001	0.8414	1.47	−0.01; 0.01
Intraoperative blood loss	<0.0001	**<0.0001**	1,723.67	0.00; 0.00

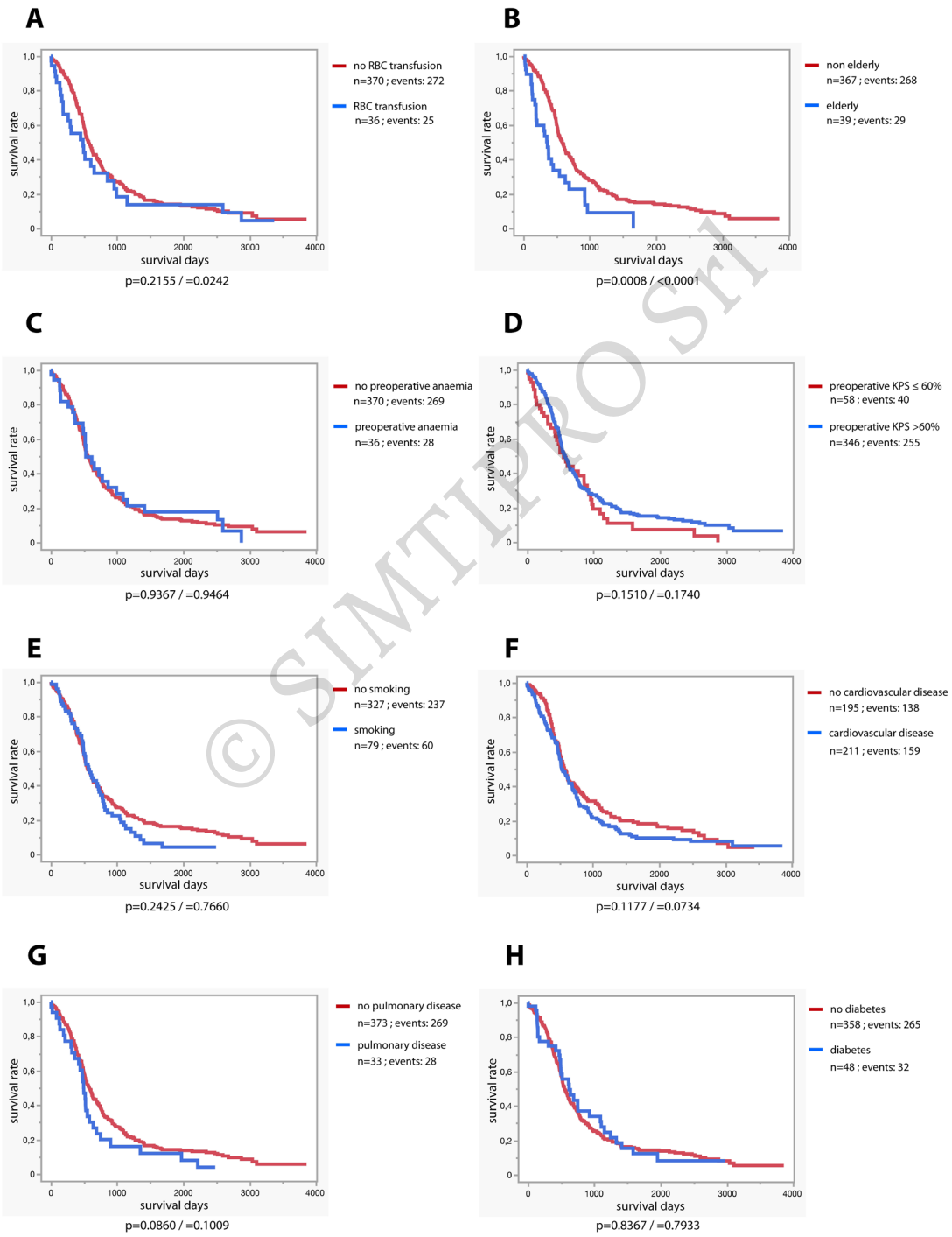
Bold p-values statistically significant in multivariate analysis; RBC: red blood cell; KPS: Karnofsky performance scale; OR: odds ratio; CI: confidence interval.

Survival

Kaplan-Meier curves revealed that RBC transfusion had a significant influence on overall survival (Wilcoxon, p=0.0242) as did age (elderly patients ≥75 years). None of the other variables analyzed had a significant influence on survival (**Figure 2**).

DISCUSSION

The present study examined the clinical outcome and risk factors for perioperative RBC transfusion in patients undergoing elective primary glioblastoma resection. Overall, 36 out of 406 (8.9%) patients received RBC transfusion. The rate of preoperative anemia was



significantly higher in the RBC transfusion group than in the non-RBC transfusion group. Furthermore, patients who were transfused with RBC had increased rates of postoperative complications, anemia at hospital discharge and prolonged hospital LOS. Multivariate analyses revealed that preoperative anemia, gender (female) and intraoperative blood loss are independent risk factors for RBC transfusion. Last, Kaplan-Meier curves revealed that RBC transfusion and age (≥75 years) had a significant influence on overall survival.

In our study the rate of anemia was rather low, being 8.9% in all patients undergoing craniotomy for

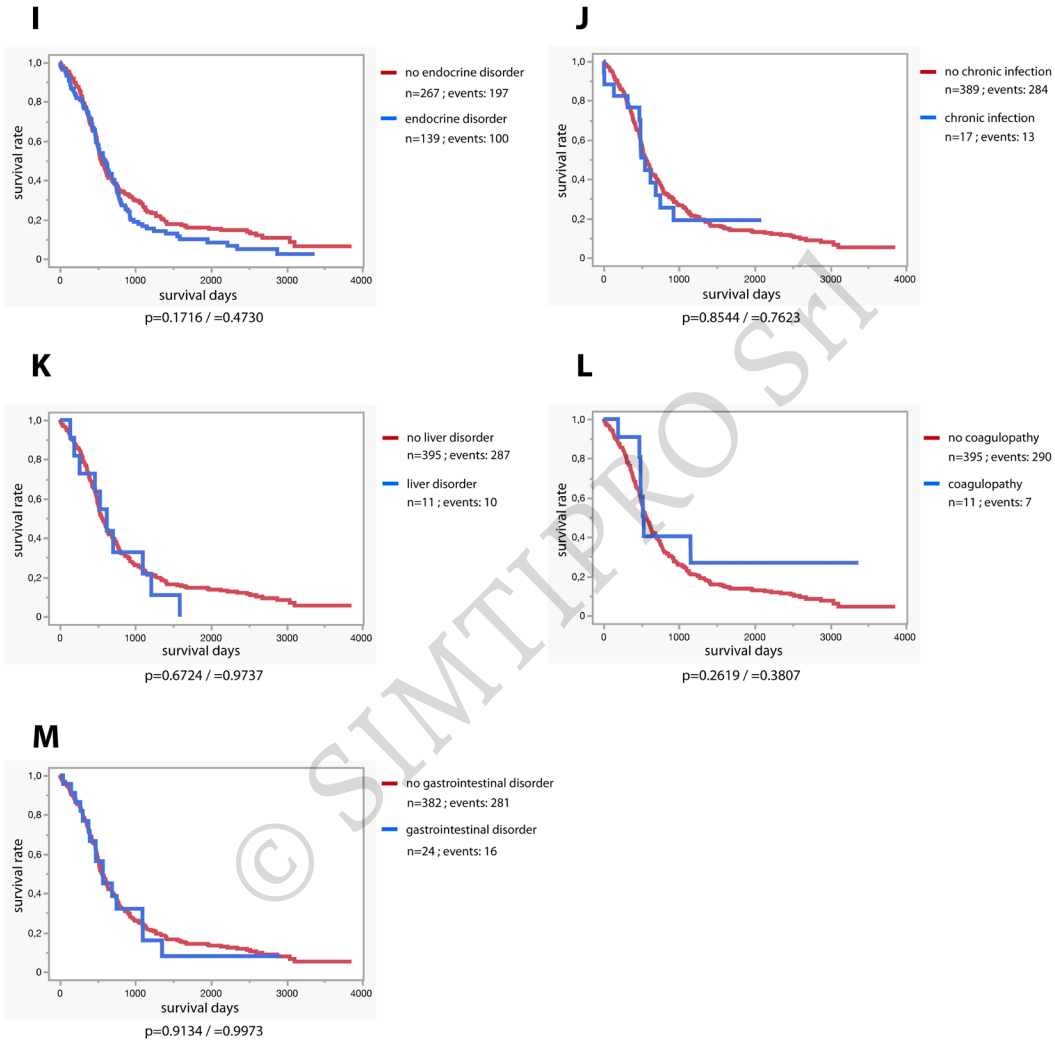


Figure 2 - Kaplan-Meier curves of overall survival of subgroups of the study population
(**A**) Kaplan-Meier curve illustrates the overall survival in the cohort divided according to whether the patients had or had not been given a red blood cell transfusion. (**B**) Overall survival according to whether the patients were elderly patients (≥75 years) or not (<75 years). (**C**) Overall survival according to whether the patients had preoperative anemia or not. (**D**) Overall survival according to whether the patients had Karnofsky performance scale value of >60% or ≤60%. (**E**) Overall survival according to whether the patients were smokers or not. (**F**) Overall survival according to whether the patients did or did not have cardiovascular disease. (**G**) Overall survival according to whether the patients had or did not have pulmonary disease. (**H**) Overall survival according to whether the patients had or did not have diabetes. (**I**) Kaplan-Meier curve illustrating the overall survival according to whether the patients had or did not have an endocrine disorder. (**J**) Overall survival according to whether the patients had or did not have a chronic infection. (**K**) Overall survival according to whether the patients did or did not have a liver disorder. **(L)** Overall survival according to whether the patients did or did not have coagulopathy. (**M**) Overall survival according to whether the patients did or did not have a gastrointestinal disorder. The p values were obtained from log-rank tests/ Wilcoxon tests.

glioblastoma resection. In comparison, a study by Bydon *et al.* documented an anemia rate of 21.4% in patients undergoing neurosurgical operation (e.g., craniotomy, surgery of intracranial arteriovenous malformation). However, patients undergoing various neurosurgical procedures and patients who had undergone surgery within the preceding 30 days were included in their study. The selection of the study population might explain the higher rate of preoperative anemia in the study by Bydon *et al.*[9].

It is worth noting that the definitions of anemia vary between studies. In some studies anemia is defined by hematocrit[9], whereas in the present study we used the WHO definition of anemia based on hemoglobin values[8]. Therefore, comparisons between studies should be conducted carefully. In a recent study of patients undergoing elective primary resection of skull base and only non-skull base meningioma, the preoperative anemia rate was comparable to this study, being 8.0% in all patients. In this study, pre-operative anemia was defined, as in ours, by hemoglobin value in accordance with the WHO definition[5].

Preoperative anemia in patients undergoing elective cranial neurosurgery is independently associated with increased 30-day morbidity and mortality compared to patients without preoperative anemia[9]. In addition, a study on 1,728 patients undergoing major surgery revealed that anemic surgical patients are transfused more frequently than non-anemic surgical patients[10].

The fact that anemic patients are at higher risk of allogeneic blood transfusion is also reflected by the results of the present study. The rate of anemia was significantly higher in transfused patients (33.3%) compared to patients without perioperative RBC transfusion (6.5%; p<0.0001).

A recent systematic review, including seven studies on RBC transfusion in brain tumor surgery demonstrated that RBC transfusion is associated with multiple postoperative major and minor complications, including longer hospital LOS, increased return to the operating room and elevated 30-day mortality[11]. In our study, transfused patients suffered from significantly more postoperative complications (e.g., pneumonia, sepsis, pulmonary embolism and seizures) as well as increased ICU LOS and hospital LOS. Transfused patients also received significantly more blood products such as platelets (p<0.0001), fresh-frozen plasma (p<0.0001), platelet complex concentrates (p<0.0001) and fibrinogen (p=0.0173). In this context, special consideration should be given to the potential complications of allogeneic RBC, which may explain the association of increased postoperative morbidity and RBC transfusion[12].

In the present study, glioblastoma patients with a perioperative need for RBC transfusion had a significantly greater intraoperative blood loss (p<0.0001) and longer surgical time (p<0.0001). In total, 80.6% of all RBC transfusion were conducted in a direct surgical context (day 0-3). It may –therefore– be assumed, that due to the greater intraoperative blood loss, optimization of oxygen supply by the transfusion of RBC was attempted. In general, patients who receive RBC transfusion are typically morbid patients with a higher number of comorbidities than those who do not receive RBC[13]. However, in the present study we did not observe a trend of a higher comorbidity burden in the group of patients who received RBC transfusion.

In our study, multivariate analyses revealed preoperative anemia (p<0.0001) and intraoperative blood loss (p<0.0001) as independent risk factors for RBC transfusion. So far, this has not been investigated in a large cohort (No.=406) of glioblastoma patients. In a study by Lagman *et al.* another risk factor for blood transfusion was a longer operative time[14].

With the aim of reducing risks associated with perioperative RBC transfusion, Patient Blood Management (PBM) has evolved within the last decade[15]. PBM is an evidence-based, patient-centered, multidisciplinary approach based on three pillars: reduction of preoperative anemia (pillar 1), minimization of iatrogenic blood loss (pillar 2) and optimization of patients` specific tolerance of anemia (pillar 3)[16]. In accordance with the results of the present study, special attention should be paid to the management of preoperative anemia and blood conservation strategies, as preoperative anemia and surgical blood loss represent independent risk factors for RBC transfusion in glioblastoma patients.

Regarding the minimization of iatrogenic blood loss, efforts should focus on optimization of coagulopathy, surgical hemostasis and management of coagulation[17]. With focus on states of anemia, preoperative anemia management should be considered in glioblastoma patients and the cause(s) of the anemia should be

addressed accordingly. Iron deficiency is a main cause of preoperative anemia and can be addressed easily with intravenous iron supplementation[18]. In the case of preoperative iron-deficiency anemia, recent studies prove that the administration of intravenous iron reduces the need for RBC transfusion and is associated with fewer postoperative complications and shorter hospital LOS[10,19,20]. The correction and avoidance of perioperative anemia are especially crucial in neurosurgical patients[21]. An existing anemia is associated with reduced cerebral oxygen delivery and thus secondary hypoxic insults to the injured brain[22].

The present study has several limitations. Data collection was conducted retrospectively and only data from one center are presented. In addition, with this database the cause of anemia remains unknown. However, iron deficiency is a potential, as well as the most common, cause of preoperative anemia in patients undergoing major surgery. Furthermore, it is noteworthy that despite 406 patients being included in the study, only 36 (8.9%) received RBC transfusion. Nonetheless, this analysis provides a first description of the outcome of a large cohort of surgical patients undergoing primary glioblastoma resection who received perioperative RBC transfusion. In the future, larger prospective multicenter studies should be conducted to increase knowledge about the association of RBC transfusion and clinical outcome in patients with glioblastoma.

CONCLUSIONS

Anemic patients were transfused more frequently than patients without preoperative anemia. In addition, RBC transfusion was associated with increased postoperative morbidity in patients undergoing elective glioblastoma resection, as demonstrated by the longer ICU and hospital LOS as well as increased postoperative complications. Identified risk factors for RBC transfusion include preoperative anemia and intraoperative blood loss. Future prospective studies need to evaluate the clinical benefit of preoperative anemia management in the context of PBM in glioblastoma patients in order to increase the safety of patients and improve their outcomes.

Institutional review board statement

The study was approved by the local Ethics Committee of the University Hospital of Frankfurt and the University Cancer Center (UCT) Frankfurt/Main (EC number UCT-65-2020, date of acceptance: January 5, 2021). Patients gave written consent to the use of blinded clinical data and tissue specimens for scientific purposes at admission to hospital. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Informed consent statement

Informed consent was obtained from all subjects involved in the study. Patients gave written consent to the use of blinded clinical data and tissue specimens for scientific purposes on admission to hospital.

Availability of data and materials

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

AUTHORSHIP CONTRIBUTIONS

PB conceived the study, curated and analyzed the data, was responsible for the investigation, methodology, project administration and supervision, and wrote the original version of the manuscript. VN conceived the study, curated and analyzed the data, was responsible for the investigation, and wrote the original version of the manuscript. SK curated and analyzed the data and wrote the original version of the manuscript. DD was responsible for the methodology of the study. EH was responsible for validation. All Authors have read, reviewed and edited the manuscript and agreed to the published version.

CONFLICTS OF INTEREST

ANF received speaker fees from P.J. Dahlhausen & Co. GmbH, Cologne, Germany and received the Sedana Medical Research Grant 2020. FJR received speaker fees from CSL Behring, King of Prussia, PA, USA, University Hospital Wuerzburg, Germany, and HELIOS clinics, Krefeld, Germany; patent funding support from LifeSystems, Moenchengladbach, Germany; publication fees from publication fund of the Goethe University, Frankfurt, Germany; and travel expenses from MCN congress organization, Nuernberg, Germany. VN has received honoraria for lectures and travel expenses from Sysmex, Pharmacosmos, MCN congress organization, and support for publication costs from Goethe University Frankfurt. KZ has received honoraria from Haemonetics and Vifor for participation in advisory board meetings and received speaker fees from CSL Behring,

Masimo, Pharmacosmos, Boston Scientific, Salus, iSEP, Edwards and GE Healthcare. He is the Principal Investigator of the EU-Horizon 2020 project ENVISION (Intelligent plug-and-play digital tool for real-time surveillance of COVID-19 patients and smart decision-making in intensive care units) and Horizon Europe 2021 project COVend (Biomarker and AI-supported FX06 therapy to prevent progression from mild and moderate to severe stages of COVID-19). KZ is Chief Executive Officer of the Christoph Lohfert Foundation as well as the Health, Patient Safety & PBM Foundation. All other Authors declare no conflicts of interest.

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