Research Article

Çiğdem Damla Deniz*, Mehmet Gürbilek and Mehmet Koç

Effects of chemoradiotherapy on acute-phase protein levels in glioblastoma multiforme and locally advanced non-small cell lung cancer

Glioblastoma multiforme ve lokal ileri evre küçük hücreli dışı akciğer kanserinde kemoradyoterapinin akut faz protein seviyelerine etkisi

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Abstract

Objective: Chemoradiotherapy (CRT) is a commonly used therapeutic modality. We investigated CRT effects on acute phase reactants (APRs). The aim of this study was to assess possible changes in APR levels during radiotherapy and to determine the usefulness of APRs as prognostic factors in patients with non-small cell lung cancer (NSCLC) and glioblastoma multiforme (GBM).
Methods: We prospectively evaluated 30 patients and 30 healthy controls. Plasma levels of APRs were measured. Post-CRT and pre-CRT levels were compared. Survival of patients were also followed up for a period of 3 years.
Results: In NSCLC patients, post-CRT albumin, transferrin (Trf), and ceruloplasmin (Cp) levels were significantly lower, and post-CRT ferritin (FER) levels were significantly higher, than their pre-CRT levels. In GBM patients, post-CRT Trf and prealbumin (Prealb) levels were significantly higher than pre-CRT levels. Pre-CRT C-reactive protein (CRP) and FER levels in NSCLC patients and Cp levels in GBM patients were associated with patient survival.
Conclusion: This study suggests that APRs may be useful for monitoring response to treatment during CRT in NSCLC and GBM patients. Bearing in mind their accessibility and clinical value, plasma CRP and FER in NSCLC patients and Cp in GBM patients can be considered candidate prognostic factors.

Keywords: Acute-phase proteins; Survival; Chemoradiotherapy; Non-small cell lung cancer; Glioblastoma multiforme.

Özet

Amaç: Kemoradyoterapi (KRT) sık kullanılan bir tedavi yöntemidir. KRT'nin akut faz reaktanları (AFR) üzerindeki etkilerini araştırdık. Bu çalışmanın amacı, radyoterapi sırasında AFR düzeylerindeki olası değişiklikleri değerlendirmek ve küçük hücreli dışı akciğer kanseri (KHDAK) ve glioblastoma multiforme (GBM) hastalarında prognostik faktör olarak AFR'lerin kullanılabilirliğini belirlemektir.
Metod: Prospektif olarak 30 hasta ve 30 sağlıklı kontrol değerlendirildi. AFR'lerin plazma seviyeleri ölçüldü. Post-KRT ve pre-KRT seviyeleri karşılaştırıldı. Hastaların sağkalımı da 3 yıllık bir süre boyunca takip edildi.
Bulgular: KHDAK hastalarında; pre-KRT seviyeleri ile karşılaştırıldığında post-KRT albümin, transferrin (Trf), ve seruloplasmin (Cp) düzeyleri anlamlı derecede düşük ve post-KRT ferritin (FER) düzeyleri anlamlı derecede yüksek bulunmuşdur. GBM hastalarında; Post-KRT Trf ve prealbümin (Prealb) düzeyleri KRT öncesi düzeyler ile kıyaslandığında anlamlı derecede yüksekti. KHDAK hastalarında pre-KRT C-reaktif protein (CRP) ve FER düzeyleri ve GBM hastalarında Cp düzeyleri hasta sağkalımı ile ilişkilendirildi.
Sonuç: Bu çalışma, AFR'larının KHDAK ve GBM'li hastalarda KRT sırasında tedaviye yanıtın izlenmesi için yararlı olabileceğini düşündürmektedir. Erişilebilirlik ve klinik değeri göz önüne alındığında, KHDAK hastalarında plazma CRP ve FER, GBM hastalarında Cp aday prognostik faktörler olarak düşünülebilir.

***Corresponding author: Çiğdem Damla Deniz,** MD, Department of Medical Biochemistry, Meram School of Medicine, Necmettin Erbakan University, 42080, Konya, Turkey,
Phone: +90 332 223 60 00, Fax: +90 332 223 6181,
e-mail: c.d.cetinkaya@gmail.com
Mehmet Gürbilek: Department of Medical Biochemistry, Meram School of Medicine, Necmettin Erbakan University, 42080, Konya, Turkey, e-mail: gurbil@yahoo.com
Mehmet Koç: Department of Radiation Oncology, Meram School of Medicine, Necmettin Erbakan University, 42080, Konya, Turkey, e-mail: m_koc42@yahoo.com

Anahtar kelimeler: Akut faz proteinleri; Sağkalım; Kemoradyoterapi; Küçük hücreli dışı akciğer kanseri; Glioblastoma multiforme.

Introduction

Lung cancer is the most common cause of cancer-related deaths. Non-small cell lung cancer (NSCLC) is responsible for more than 85% of lung cancer cases [1]. Standard treatment for patients with good performance status and inoperable stage III NSCLC is combined chemoradiotherapy (CRT) [2, 3].

Glioblastoma multiforme (GBM) is one of the most malignant neoplasms in humans [4]. Apart from other mechanisms, inflammatory cell-driven micro-environment, composed of a variety of cytokines, chemokines and enzymes, may lead to tumor initiation and promotion [5]. Despite standard treatment of surgery combined with radiotherapy (RT) and temozolomide, survival of GBM patients varies significantly, even among those who received the same treatment [6].

During RT, a series of proteins is produced that induce inflammation and oxidative stress. Acute-phase proteins (APPs) are a family of proteins synthesized by liver. In response to injury, levels of some APPs, such as C-reactive protein (CRP), ferritin (FER) and ceruloplasmin (Cp), increase. In contrast, levels of others, such as albumin (Alb), prealbumin (Prealb) and transferrin (Trf), fall [7].

CRP is measured as a direct, quantitative indicator of acute phase reaction, and because of its fast kinetics, provides adequate information on the situation. Its relationship with cytokines and its possible functional role add to its clinical value as a parameter of inflammatory activity [8].

FER is a primary iron-storage protein. It is a 24-mer, hollow "nano cage" capable of sequestering iron in a nontoxic, bio-available form [9]. In patients with lung cancer, FER levels are elevated [10]. Due to the prevailing paradigm of FER as a housekeeping iron-storage protein and a non-specific acute phase reactant (APR), the functional significance of this elevation has been ignored consistently [9]. Increased levels of FER are due to inflammation rather than to increased ferrum concentration [11].

Cp, a plasma glycoprotein, is the body's main copper carrier [12]. Cp permits incorporation of iron (Fe) into Trf without formation of toxic Fe products [13, 14].

Cp acts as an antioxidant by several mechanisms: inhibiting iron-dependent lipid peroxidation (Lp) and formation of HO from hydrogen peroxide (H_2O_2) via its ferroxidase activity, reacting with and scavenging H_2O_2 and superoxide anion radicals, and inhibiting copper-induced Lp by binding copper ions [15–17].

Serum Alb is an indicator of splanchnic protein function [18]. Prealb has a half-life much shorter than that of Alb. Therefore, Prealb is more sensitive to changes in protein-energy status than is Alb [19].

To investigate prognostic utility of CRP, Trf, Cp, FER, Alb and Prealb during CRT in cancer patients, the present study evaluated plasma levels of APRs before and after completion of CRT by patients suffering from locally advanced NSCLC and GBM.

Materials and methods

Study design and ethical guidelines

Patients in our study were selected from those admitted to Department of Radiation Oncology, Meram Medical School, Necmettin Erbakan University, Konya, Turkey. All participants provided written informed consent. Approval for this study was obtained from Meram Medical Faculty Ethics Committee, on 01.03.2013 in decision number: 2013/366.

Selection of cases and controls

NSCLC patients who were in inoperable stage III and GBM patients who had postoperative residual tumors are recruited. None of the patients had previously undergone CT or RT. Heparinized blood samples were taken from 20 NSCLC, 10 GBM patients, and 30 healthy volunteers for data measurements. Samples were taken before and after 6 weeks of RT and CT (temozolomide 75 mg/m^2 in GBM and paclitaxel 40–50 mg/m^2, etoposide 100–120 mg/m^2, carboplatin AUC 2 in NSCLC) from patients while one blood sample are taken from each of the controls. Chemotherapeutics were used only for radiosensitization not for curative treatment. Control group did not receive CRT during the study. Survival of patients were followed up for a period of 3 years. Follow-up information are retrieved from hospital records or by telephone contacts. Dates of deaths are recorded for patients who died during follow-up.

Inclusion and exclusion criteria

The inclusion criteria were (1) histologically confirmed GBM and stage III cases of NSCLC, (2) aged between 40 and 70 years with a Karnofsky performance status score

≥70, and (3) being from similar ethnicity. Exclusion criteria included cases of (1) previous CT or RT experience, (2) a secondary malignancy, (3) history of any drug addiction, chronic smoking habit, or alcohol addiction, (4) any metabolic or endocrine disorders, and (5) any chronic inflammatory condition.

Biochemical analysis

Plasma was separated by centrifugation at 1500*g* for 10 min. Plasma samples were stored at −80°C until analysis. APR measurements in control and patient groups were studied at the Department of Biochemistry, Meram Medical Faculty. Trf, Cp, CRP and Prealb plasma levels underwent immunoturbidimetric analysis, Alb was analyzed by bromocresol green method and FER by chemiluminescence process. All were evaluated on routine auto-analyzers. APR levels were compared before and after CRT. CRP, Trf, Cp, Alb and Prealb were analyzed with Abbott Kits (Abbott Laboratories, Chicago, IL, USA), [intra-assay coefficient of variations were (CV): <4.5%, <1.7%, <1.86%, <1.7%, <0.6% and <2.6%, respectively] manufactured for use with Architect c16000 Auto-Analyzer. FER was analyzed with Siemens Kits (Siemens Diagnostic Solutions, Tarrytown, NY, USA), (intra-assay CV < 3% and inter-assay CV < 5.4%) by Siemens ADVIA analyzer.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (IBM-SPSS, Chicago, IL, USA). Linear models are used to compare APP levels. Associations between survival and APPs were evaluated by a backward likelihood ratio (LR) Cox regression model. A p-value less than 0.05 was considered statistically significant.

Results

Patients diagnosed with NSCLC and GBM had lower Alb levels before CRT (3.31 ± 0.57 and 3.53 ± 0.32 g/dL, respectively) and after CRT (3 ± 0.63 and 3.48 ± 0.5 g/dL, respectively) compared to healty control group (4.2 ± 0.38 g/dL, $p < 0.05$) (Table 1) (Figure 1). When post-CRT and pre-CRT Alb levels were compared, there was a significant difference in NSCLC patients, but not in GBM patients.

In both patient groups, there was an increase in Prealb during CRT. Although there was no significant difference between Prealb levels before and after CRT in NSCLC group (5.26 ± 4.21 and 6.86 ± 6.22 mg/dL, respectively; $p > 0.05$), there was a significant difference in GBM group (10.8 ± 9.24; 19.4 ± 9.09 mg/dL;, respectively, $p < 0.001$) (Table 1).

Table 1: Pre-chemoradiotherapy and post-chemoradiotherapy levels of C-reactive protein, ferritin, transferrin, ceruloplasmin, albumin and prealbumin in the control group, non-small cell lung cancer patients, and glioblastoma multiforme patients.

	Pre-CRT (mean ± SD)	Post-CRT (mean ± SD)	Control
Albumin (g/dL)			
NSCLC	3.31 ± 0.57[a]	3 ± 0.63[a,b]	4.2 ± 0.38
GBM	3.53 ± 0.32[a]	3.48 ± 0.5[a]	
Prealbumin (mg/dL)			
NSCLC	5.26 ± 4.21[a]	6.86 ± 6.22[a,c]	21 ± 5.72
GBM	10.8 ± 9.24[a]	19.4 ± 9.09[d,b]	
Transferrin (mg/dL)			
NSCLC	175.26 ± 49.48[a]	156.53 ± 45.17[a,b]	249.73 ± 32.5
GBM	169.5 ± 50.07[a]	193.8 ± 51.09[a,b]	
Ceruloplasmin (mg/dL)			
NSCLC	28.06 ± 4.9[a,c]	25.06 ± 4.44[b]	22.23 ± 2.59
GBM	34.4 ± 3.56[a,d]	26.7 ± 5.88[a,b]	
C-reactive protein (mg/L)			
NSCLC	39.32 ± 49.86[a]	29.54 ± 31.17[a]	5.47 ± 23.53
GBM	39.18 ± 33.43[a]	16.42 ± 19.05[b]	
Ferritin (ng/mL)			
NSCLC	174.23 ± 115.42	382.99 ± 297.09[a,b]	51.52 ± 42.04
GBM	297.93 ± 433.96[a]	244.87 ± 449.88	

CRT, Chemoradiotherapy; NSCLC, non-small cell lung cancer; GBM, glioblastoma multiforme; SD, standard deviation. [a]Significantly different when compared with control group ($p < 0.05$). [b]Significantly different when compared with pre-CRT ($p < 0.05$). [c]Significantly different when compared with GBM group ($p < 0.05$). [d]Significantly different when compared with NSCLC group ($p < 0.05$).

In both patient groups, Trf levels both before and after treatment were significantly lower than those of control group ($p < 0.001$) (Figure 1). In addition, both patient groups presented significant differences in terms of Trf levels when pre-CRT and post-CRT levels compared ($p < 0.01$) (Table 1).

In both patient groups, Cp levels were significantly lower after CRT than they had been before CRT ($p < 0.01$) (Table 1) (Figure 1).

Patients diagnosed with NSCLC and GBM had higher CRP levels before CRT [median 27.28 (range 2.34–190.73 mg/L) and median 34.57 (range 1.62–105.21 mg/L), respectively] compared to control group (median 1.15, range 0.1–130 mg/L; $p < 0.05$). In the NSCLC group, CRP levels decreased with CRT but still were significantly higher than that of control group CRT [median 14.79 (range 0.9–87.73 mg/L) and median 1.15 (range 0.1–130 mg/L), respectively; $p < 0.05$].

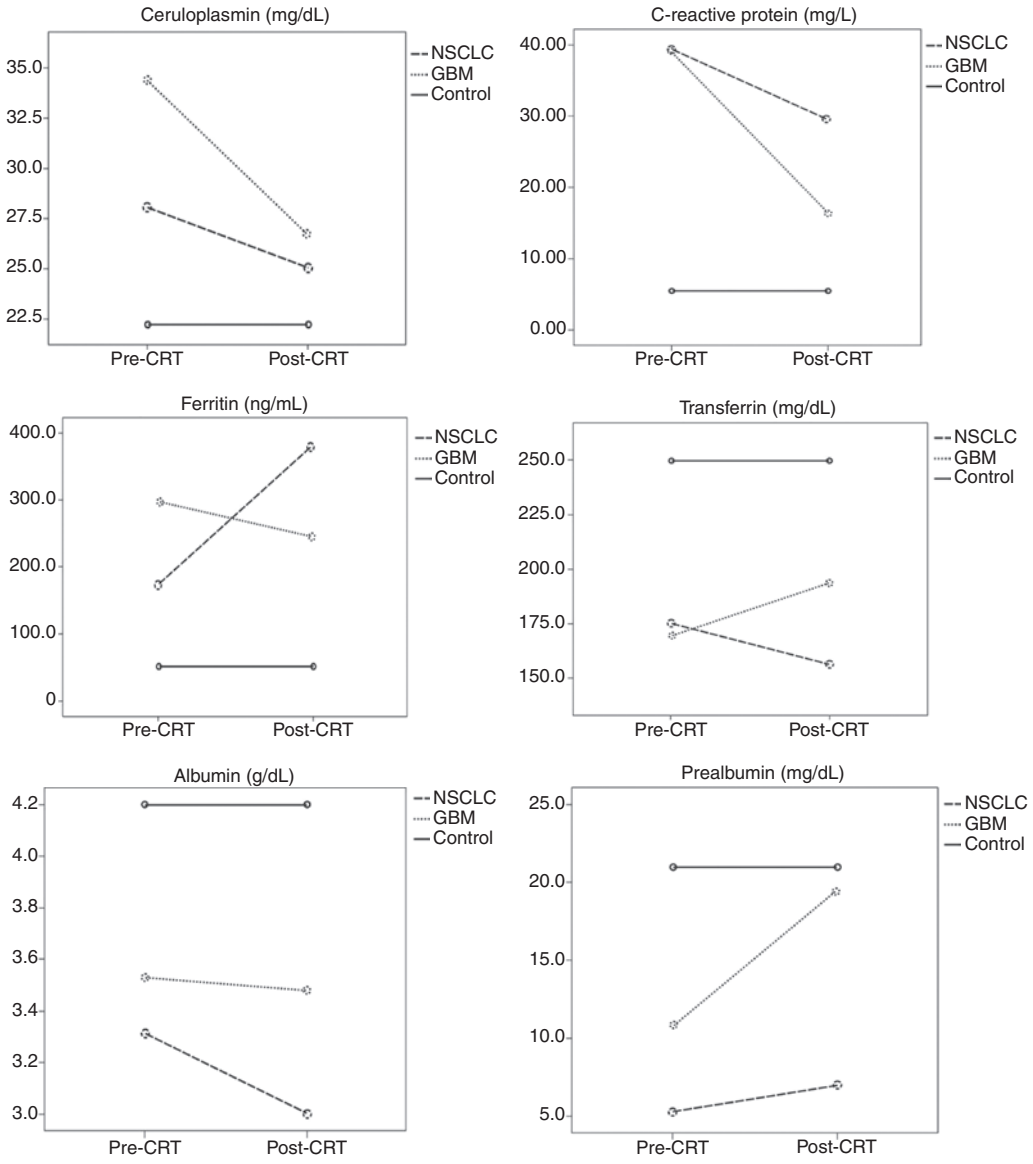

Figure 1: APR levels in non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), and healthy control groups.
However, just for NSCLC and GBM groups, it is before and after treatment. In both the NSCLC and GBM groups, albumin (Alb) and transferrin values both before and after chemoradiotherapy (CRT) were significantly lower than in the control group ($p < 0.001$). In NSCLC patients, post-CRT Alb and ferritin levels differed significantly from pre-CRT levels ($p < 0.05$). In both patient groups, ceruloplasmin significantly decreased during CRT. In GBM patients, post-CRT prealbumin and C-reactive protein levels differed significantly from pre-CRT levels ($p < 0.05$).

In both patient groups, FER levels before and after CRT were higher than that of control group (Figure 1). In GBM patients, pre-CRT FER levels were significantly higher than control group [median 216.15 (range 8.7–1500 mg/L) and median 31.45 (range 8.6–137.4 mg/L), respectively]. In NSCLC patients, post-CRT FER levels were significantly different than those of control group [median 334.35 (range 22.5–1188.3 mg/L) and median 31.45 (range 8.6–137.4 mg/L), respectively; $p < 0.001$]. In addition, in NSCLC patients, a statistically significant difference was detected between pre-CRT and post-CRT levels of FER [median 151.3 (range 5.4–1500 mg/L) and median 334.35 (range 22.5–1188.3 mg/L), respectively; $p < 0.001$].

Survival times [mean ± SD (median)] in patients with NSCLC and GBM were 287.8 ± 193.8 (290.5) days and 466.7 ± 377.46 (303) days, respectively. LR Cox regression analysis revealed an association between pre-CRT FER levels and NSCLC survival [hazard ratio (HR) = 1.007; $p = 0.023$; 95% CI; 1.001–1.013] (Table 2). LR Cox regression analysis also detected that high levels of pre-CRT CRP were associated with worse outcomes for NSCLC patients (HR = 1.017; 95% CI; 1.001–1.032; $p = 0.035$) (Figure 2).

Table 2: Relationship between survival and pre-chemoradiotherapy acute phase reactant levels in non-small cell lung cancer and glioblastoma multiforme patients.

	p-Value	HR	95.0% CI Lower-upper
Pre-CRT ferritin			
NSCLC	0.023[a]	1.007	1.001–1.013
GBM	0.514	0.996	0.986–1.007
Pre-CRT ceruloplasmin			
NSCLC	0.163	1.115	0.957–1.298
GBM	0.028[a]	2.784	1.114–6.958
Pre-CRT CRP			
NSCLC	0.035[a]	1.017	1.001–1.032
GBM	0.642	1.007	0.977–1.038
Pre-CRT albumin			
NSCLC	0.408	0.671	0.261–1.728
GBM	0.944	0.908	0.062–13.292
Pre-CRT prealbumin			
NSCLC	0.077	0.835	0.684–1.020
GBM	0.962	1.002	0.916–1.096
Pre-CRT transferrin			
NSCLC	0.330	0.994	0.982–1.006
GBM	0.248	0.985	0.961–1.010

HR, Hazard ratio; CI, confidence ınterval; CRT, chemoradiotherapy; NSCLC, non-small cell lung cancer; GBM, glioblastoma multiforme; CRP, C-reactive protein. [a]Significant correlation was found when compared with survival ($p < 0.05$). Pre-CRT CRP and ferritin in NSCLC patients and ceruloplasmin in GBM patients were associated with survival.

Before CRT, GBM patients had higher mean values of Cp than NSCLC patients had (34.4 ± 3.56 and 27.88 ± 4.62 mg/dL, respectively; $p < 0.001$). LR Cox regression analysis revealed that pre-CRT Cp was associated with GBM survival (HR = 2.784; p = 0.028; 95% CI; 1.114–6.958) (Table 2) (Figure 2). Alb, Prealb and Trf levels were not associated with patient survival. In addition, no relationships were detected between post-CRT parameter values and survival.

Discussion

Identification of prognostic factors is pivotal for cancer patients and can guide clinical treatment. To stage cancer and predict prognosis, measuring levels of several cytokines, APR and DNA content (except APR), is difficult and expensive [20]. The present study reveals that before CRT higher Cp, CRP, FER and lower Alb, Prealb, Trf levels were observed in both patient groups compared to control group.

In inflammation, "negative" APPs, such as Alb, Prealb and Trf, decrease [18]. Trf, Alb and Prealb levels both before and after CRT were lower in patients with NSCLC and GBM than those of control group. But the same was not true of RT responses. RT reduced Alb, while it increased Prealb. The mechanism by which serum Alb levels predict cancer's clinical outcome is complex, not only because Alb is a nutritional indicator, but also because of its role in the inflammatory response [21]. In the present study, Alb decreased significantly only in NSCLC group during CRT.

Prealb acts as a transport protein in the body. It has a shorter half-life, 2–3 days, and there is less of it in the body. Therefore, Prealb is a good marker of visceral protein status, and in addition, Prealb is affected earlier by acute variations in protein balance [22]. In GBM group, post-CRT Prealb levels were found to be higher than pre-CRT Prealb levels.

Maretty-Nielsen [23] found that pre-treatment Alb levels were correlated independently with soft tissue sarcoma-specific mortality. Trf, Alb and Prealb levels may be crucial to identifying patients who might benefit from more aggressive treatment. But in our study; Alb, Prealb and Trf levels were not found associated with patient survival.

Iron, an essential element, participates in redox-reactions, leading to production of free radicals that increase oxidative stress and the risk of damaging processes. To protect against oxidative damage, living organisms have an efficient mechanism to regulate iron absorption in response to their iron levels [24].

During radiation or CT treatment, high serum iron and Trf saturation levels can contribute to production of free radicals, leading to endothelial cell damage or membrane lipid peroxidation, which can harm the patient [20]. In the present study, RT significantly decreased Trf levels in NSCLC patients but increased Trf levels in GBM patients. Using medulloblastoma and glioblastoma cell lines, Kim et al. [25] reported varying effects inTrf receptors depending of the time after single-dose exposure to 5 Gy.

Since free iron is toxic to cells, FER serves to store iron in a nontoxic form [26]. Shi et al. [27] reported that higher serum FER levels in advanced NSCLC patients, revealing a relationship between expression levels of FER and tumor progression, as well as the efficacy of platinum-based therapies. In their study, FER increased significantly during CRT in NSCLC patients. The present study found FER levels increased significantly in NSCLC patients after CRT. This may explain the role of FER in protecting from oxidative stress.

As in the present study, Milman and Pedersen [28] found a clinically relevant relationship between serum FER concentrations and prognosis in patients with primary lung cancer. In the present study, plasma FER

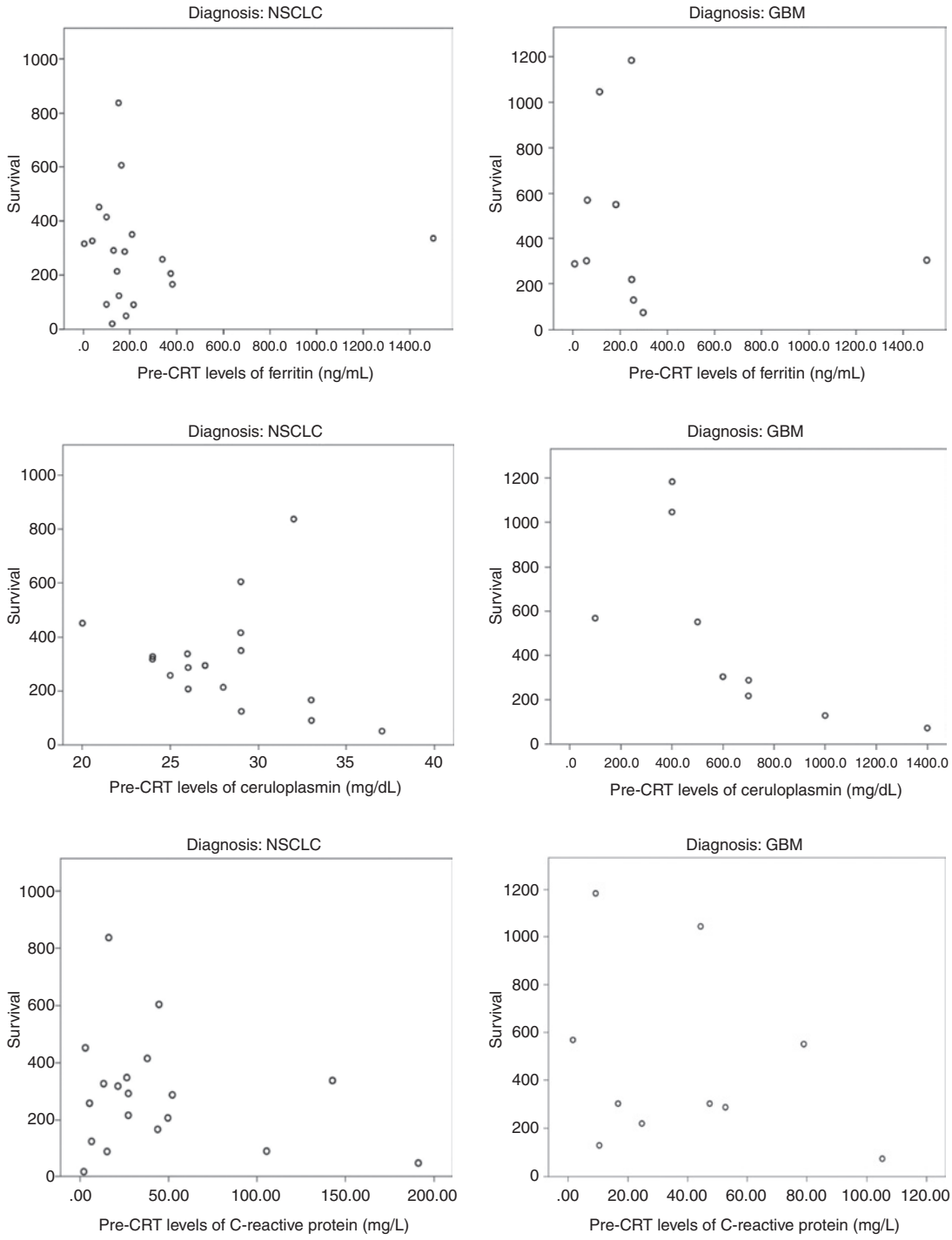

Figure 2: Scatter-plot graphs of correlation between survival and ferritin, C-reactive protein, and ceruloplasmin levels in non-small cell lung cancer (NSCLC) and glioblastoma multiforme (GBM) patients.

levels associated negatively with NSCLC patient survival, so plasma FER could be a useful biomarker to indicate prognosis (Figure 2) (Table 2). Elevated FER is the result of inflammation rather than body iron overload.

Onizuka et al. [29] suggested that a more significant decrease of serum Cp level after treatment is linked with a better response to therapy, as these alterations may influence disease outcome. In accordance with that study, we detected a relationship between pre-CRT Cp values and survival.

In another study, patients with breast cancer without remission were found to have significantly higher levels

of CA 15-3 and Cp. For detecting active breast cancer, the highest sensitivity of Cp was obtained by combined use of tumor markers [30]. In the present study, before CRT, plasma Cp levels were higher in both GBM and NSCLC patients than that of controls. Cp levels decreased with CRT in both patient groups. But Cp levels in only patients with GBM were still higher than those of controls after CRT. Decreased Cp levels may be explained by the response to CRT, which may cause a decrease in antioxidants and an increase in oxidants.

As an APR, CRP is a nonspecific protein reacting to acute inflammation, infection, and tissue damage [31]. Zeng et al. [32] aimed to evaluate association of CRP with prognosis in patients with nasopharyngeal carcinoma (NPC) treated with CRT. They found that elevated serum CRP before treatment predicted poor prognosis among NPC patients. In the present study, patients' CRP levels were significantly higher than those of the controls before RT. Normalized CRP levels after CRT could be a prognostic factor in patients.

In the present study, pre-CRT CRP was associated with worse outcomes for NSCLC patients. Results of Fiola et al.'s study are in accordance with our findings. Monitoring CRP levels, which is simple and easy, should be considered a routine clinical practice in follow-up of NSCLC patients [33].

In conclusion, the present study found decreased Alb, Cp and CRP levels during irradiation period in both NSCLC and GBM patients, in contrary to increased Prealb levels. In addition, responses of Trf and FER levels to RT differed in NSCLC and GBM patients. Pre-CRT CRP and FER levels in NSCLC patients and Cp levels in GBM patients all were associated with patient survival. Therefore, bearing in mind their accessibility and clinical value, plasma CRP and FER in NSCLC patients and Cp in GBM patients can be considered useful markers. To better understand values of those above-mentioned markers including other APRs on prognostic utility, further studies should be conducted on larger samples of cancer patients undergoing CRT.

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