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Original Research

Prognostic value of combined glucose and C-reactive protein (CRP) in cervical cancer

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Objective: In this study, we aimed to reveal the prognostic importance of glucose and C-reactive protein (CRP) together in cervical cancer, both of which play a critical role in carcinogenesis. *Methods*: A total of 243 patients who fulfilled the inclusion criteria were included in our study. The effect of fasting blood glucose (FBG) and C-reactive protein (CRP) on survival was evaluated separately as a dichotomous variable by finding the optimal cutoff value. *Results*: While 31.3% of the patients were in the early stage, 68.7% were in the locally advanced stage. The median follow-up time was 70.2 months (min: 0.57–max: 231). When the locally advanced stage and all stages were included in the analysis, there was a statistically significant difference between the 4 groups in both progression free survival (PFS) and overall survival (OS) (p: 0.026, p: 0.005, p: 0.001 and p: 0.0001, respectively). The HgLc [High fasting blood glucose (FBG) ($\geq$94.5 mg/dL), Low C-reactive protein (CRP) ($<$0.9585 mg/dL)], HgHc [High FBG ($\geq$94.5 mg/dL) and High CRP ($\geq$0.9585 mg/dL)] groups were found to be independent prognostic risk factors for OS, compared to the LgLc [(Low FBG ($<$94.5 mg/dL) and Low CRP ($<$0.9585 mg/dL)], in locally advanced stage (HR (Hazard Ratio): 2.95 (95% CI; 1.04–8.40), p: 0.042 and HR: 3.63 (95% CI; 1.39–9.47), p: 0.008, respectively). In the multivariate analysis performed for all stages, among the four groups, only the HgHc group was found to be an independent prognostic risk factor for OS (HR for HgHc group: 2.34 (95% CI; 1.14–4.78), p: 0.019). *Conclusions*: We found that combined high serum fasting blood glucose (FBG) and C-reactive protein (CRP) levels in cervical cancer, especially in the locally advanced stage, negatively affect the progression free and overall survival, and are independent prognostic risk factors affecting survival. The pre-treatment serum FBG and CRP levels should be carefully evaluated together for each cervical cancer patient. The vital importance of preoperative strict glycemic control for these patients should be considered.

Keywords

Cervical cancer; Serum fasting blood glucose (FBG) level; Serum C-reactive protein (CRP) level; Locally advanced stage; Survival

1. Introduction

When the 2018 GLOBOCAN data in terms of cervical cancer were examined, 569,847 new cases and 311,365 new deaths were reported worldwide. Cervical cancer ranks fourth among female cancers with an incidence rate of 6.6% and a mortality rate of 7.5% [1]. Pathologically, 75% of cervical cancers comprise squamous cell carcinoma (SCC), 25% comprise adenocarcinoma and very few comprise rare types. Surgical treatment is more prominent in early-stage cervical cancer and radiotherapy or chemoradiotherapy is given as adjuvant therapy according to pathological risk factors. Simultaneous chemoradiotherapy is the standard treatment approach in locally advanced cervical cancer [2]. When recurrence occurs, it has a poor prognosis in patients with cervical cancer, since there are not many treatment alternatives in clinical practice. Therefore, various methods and biochemical tumor markers have been continuously investigated to predict cancer recurrence and improve the disease prognosis. Some of these tumor markers are cancer antigen 125 (CA 125), cytokeratin 19 fragment antigen, sugar chain antigen and squamous cell carcinoma antigen (SCC Ag) [3]. However, these have not achieved the desired level of success in clinical practice.

Since human papillomavirus (HPV) triggers the inflammatory microenvironment in the pathogenesis of cervical cancer, it seems wise that inflammatory markers are the focus of attention in cervical cancer. As the relationship between inflammation, innate immunity and cancer has been widely accepted recently, scientists have focused on inflammatory markers. One of these is the acute phase reactant C-reactive protein (CRP), which plays a critical role in acute and chronic inflammation [4]. It is produced extensively in hepatocytes [4]. In addition to its role in the inflammatory response, CRP has been shown to be effective at an important stage in carcinogenesis, such as cell death, since with the inflammatory process, DNA damage occurs, angiogenesis is stimulated, apoptosis is inhibited, and cell proliferation and carcinogenesis occur [5]. Many proinflammatory cytokines such as IL-1, IL-6, tumor necrosis factor-alpha, interferon-gamma and tumor growth factor increase the CRP, which leads to survival, growth, mutation, proliferation, differentiation and migration in tumor cells [6, 7]. It has been shown that the serum CRP increases in parallel with carcinogenesis as a reaction of innate immunity [4]. When we look at the literature, CRP has been investigated in various cancers both as a risk factor and as a prognostic factor. High serum CRP levels have been shown to cause a poor prognosis among

myeloma [8], esophageal [9], hepatocellular [10], colorectal [11], renal, and lung [12] cancers. After the use of CRP in this way was revealed, its effect on gynecological malignancies was investigated and similar to the above studies, it was revealed that it negatively affects the survival in cancers of the endometrium [13], ovary [14] and the cervix [15, 16] and is an independent prognostic risk factor.

It is known that factors associated with glucose metabolism also play a role in carcinogenesis. When the literature is examined, a relationship has been shown between the glucose level or the glycemic index and colorectal [17], breast, stomach [18], ovary [19, 20], endometrium [19, 20] and cervical cancer [21]. After the indisputable importance of CRP in cancer prognosis was revealed, the effects of CRP/albumin ratio [22] (also known as Glasgow Prognostic Score (GPS)) or LDH and CRP [23] on gynecological malignancies were investigated, and it was emphasized that they had a negative effect on the prognosis.

In this study, we aimed to reveal the prognostic importance of two biochemical markers, combined glucose and CRP, which play a critical role in carcinogenesis in cervical cancer.

2. Material and methods

The data of patients with histopathologically diagnosed uterine cervical cancer, who had presented to our clinic between January 2002 and December 2020, were retrospectively collected from the electronic archive system of our hospital. The study was evaluated by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was approved with the decision numbered KAEK-110 dated 23 February 2021. Informed consent forms were obtained from all patients. The inclusion criteria for the study were as follows: Patients over the age of 18, who had a histopathologically diagnosed cervical cancer of Stage IA-IVA according to the 2018 FIGO (The International Federation of Gynecology and Obstetrics) Staging [24] and with a definitive treatment. The exclusion criteria from the study were: patients with Stage IVB cervical cancer, those who had a second primary cancer together with cervical cancer, patients whose full information was not available, those who had undergone fertility-sparing surgery, those who had prior chemotherapy or radiotherapy treatment, patients with diabetes mellitus, those with hematological and rheumatological diseases, those who had received steroid treatment and patients with signs and symptoms of infection. The histopathological diagnosis of all patients was established by the experienced gynecopathologists of our hospital. After a detailed systemic and gynecological examination of each patient, they were examined radiologically for metastasis. The diagnoses were made, and the treatments of these patients were arranged by the gynecological oncology specialists. Stage IA1 patients were treated with conization or simple hysterectomy. Patients with early stages (FIGO stage IA2, IB1, IB2, IIA) underwent radical hysterectomy $\pm$ bilateral salpingo-oophorectomy and pelvic-para-aortic lymph node dissection. According to the histopathological risk factors, these patients were given either adjuvant radiotherapy alone or chemoradiotherapy treatment by the multidisciplinary oncology council. Patients in the locally advanced stage (FIGO Stage IB3, IIB–IVA) received concurrent definitive chemoradiotherapy treatment. The limits for extended radiotherapy were determined by performing laparoscopic para-aortic lymph node dissection in selected patients with radiologically suspected para-aortic lymph nodes.

The biochemical tests of all patients were routinely performed before treatment. Tests were performed on blood samples obtained from the forearm peripheral venous vessels. For fasting blood glucose (FBG) (mg/dL) levels, blood samples were obtained from the patients at 7:00–7:30 AM (to avoid circadian rhythm) after 8 hours of fasting, without taking caloric food. FBG measurements were made using the glucose oxidase method. Patients with a FBG value of 126 mg/dL and above were not included in the study. The CRP (mg/dL) test was performed in all patients before treatment. The CRP serum levels were measured by a modified latex-enhanced immunoturbidimetric assay using a CRP Latex kit (Olympus Life and Material Science Europe) according to the manufacturer's instructions. Serum levels of 0–0.5 mg/dL were defined as normal. The manufacturer claims an intraassay variability between 1.64% and 3.34%. The ROC (receiver operating characteristic) curve analysis was performed for optimal cut-off values of the FBG and the CRP levels. While the optimal cut-off value for FBG was 94.5 mg/dL, the value of 0.9585 mg/dL was found to be the optimal value for CRP. The FBG and CRP levels were divided into four groups in two groups, and the effects of FBG and CRP on survival were examined in detail. These groups were: (1) LgLc: Low FBG ($<$94.5 mg/dL) and Low CRP ($<$0.9585 mg/dL); (2) LgHc: Low FBG ($<$94.5 mg/dL) and High CRP ($\geq$0.9585 mg/dL), (3) HgLc: High FBG ($\geq$94.5 mg/dL) and Low CRP ($<$0.9585 mg/dL), and (4) HgHc; High FBG ($\geq$94.5 mg/dL) and High CRP ($\geq$0.9585 mg/dL).

In our study, variables such as age, body mass index (BMI), smoking status (pack year), stage (early stage, locally advanced), histology (SCC (squamous cell carcinoma), (non-SCC), grade (1–2 and 3), lymph node involvement (yes, no), deep stromal invasion (yes, no), parametrial involvement (yes, no), LVSI (Lymphovascular space invasion) status, surgical margin involvement (yes, no), treatment modality, recurrence (yes, no) and death (yes, no), were used. Cervical cytology, physical examination and pelvic examinations were performed every 3 months in the first 2 years after the treatment, and then every 6 months for the next 3 years and annually after 5 years. During the follow-up, pelvic examination, transvaginal or transabdominal ultrasonography were performed in all cases, and evaluation of serum tumor markers and radiological evaluations (CT and/or Pet CT) when recurrence was suspected. A diagnosis of recurrence was made by biopsies from the suspicious areas, clinically or radiologically.

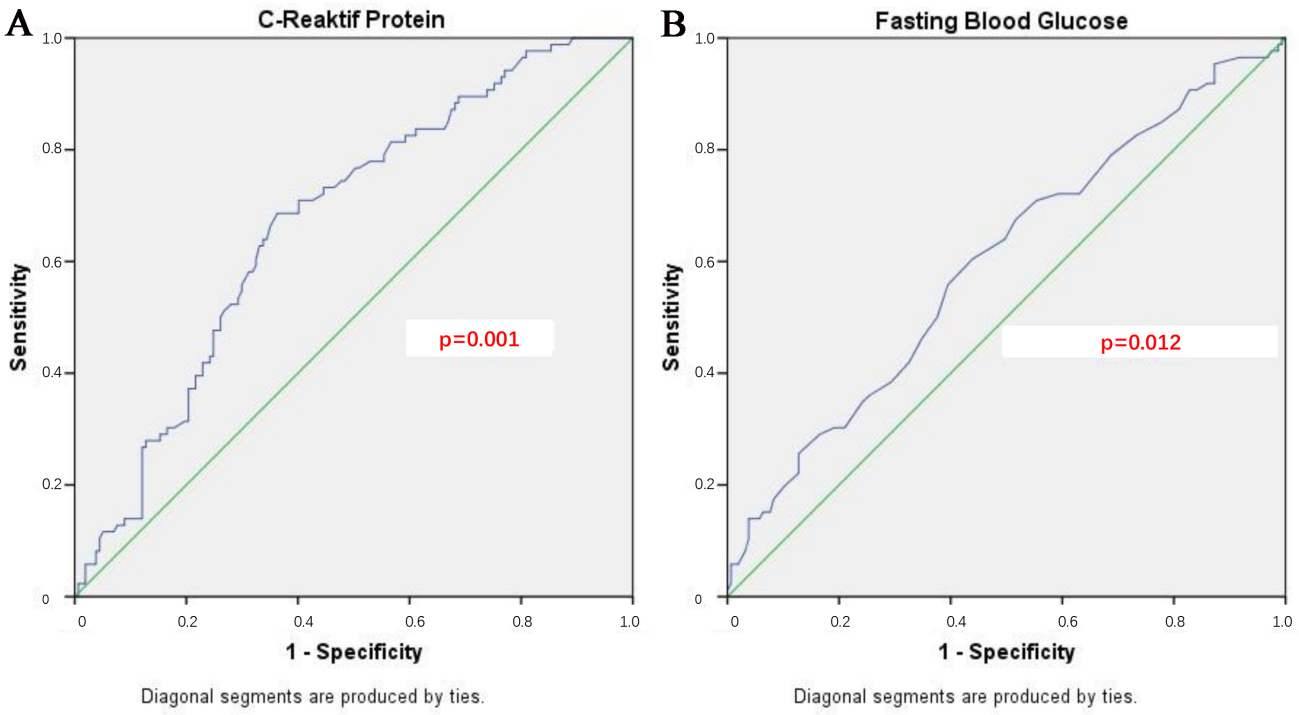

Fig. 1. ROC curve analysis for optimal cutoff values of C-reactive protein and fasting blood glucose. (A) ROC curve analysis for optimal cutoff value of C-reactive protein. (B) ROC curve analysis for optimal cutoff value of Fastin blood glucose.

Table 1. ROC curve analysis for optimal cut off value of FBG and CRP.

	AUC	Confidence Interval (95%)		Cut off (mm)	*p* value	YI	Sensitivity	Specificity
		Lower	Upper					
FBG	0.598	0.523	0.672	94.5	0.12	0.165	60.5%	56.1%
CRP	0.672	0.603	0.740	0.9585	0.001	0.323	68.6%	63.7%

YI, Youden index; AUC, Area Under Curve; FBG, Fasting Blood Glucose; CRP, C-Reactive Protein.

Progression free survival (PFS) was defined as the time from treatment initiation until appearance of recurrence or death. Overall survival (OS) was defined as the time from treatment initiation until last contact with the patient or death.

3. Statistics

For the descriptive statistics, the mean, standard deviation, median, min-max values and frequencies were used by looking at whether there was a normal distribution or not. The statistical significance between categorical variables was determined by the Chi-Square (χ^2) test. The normal distribution for the numerical data was analyzed using the Kolmogorov-Smirnov test. For the numerical data, parametric (Student *t* test) or non-parametric (Mann-Whitney U test) tests were used according to the normal distribution status. Spearman correlation test was used for the relationship between FBG and CRP. The ROC curve analysis was performed to determine the cut-off value of FBG and CRP. The maximum Youden Index was used to find the optimal cut-off value. The effect of FBG and CRP binary groups on both PFS and OS was measured separately using the Kaplan-Meier log-rank test in the early stage, locally advanced and all stages. Post-hoc analysis and Bonferroni correction were performed for multiple comparisons in survival curves. In order to evaluate the prognostic effect of FBG and CRP alone and in combination on surveillance, the univariate Cox proportional hazards model was used on the early stage, locally advanced and all stages separately. The multivariate analysis was performed for data with *p* value of <0.05 in the univariate analysis. For the multivariate analysis, the variables of age, grade and histology were used in the locally advanced stage, while age, grade, histology, body mass index and stage variables were used in all stages. Statistical analyses were performed using the 23rd version of SPSS (IBM Corp., Armonk, NY, USA). The *p* values in all tests were two-sided, and *p* values less than 0.05 were considered to be statistically significant.

4. Results

A total of 243 patients who fulfilled the inclusion criteria were included in our study. While 31.3% of the patients were in the early stage, 68.7% were in the locally advanced

stage. The median follow-up time was 70.2 months (16 days to 17.6 years). Median FBG was 94 mg/dL (min–max; 67–125), while the median CRP was 0.93 mg/dL (min–max; 0.01–14.50). In the ROC curve analysis for FBG (Table 1), the AUC (Area Under Curve) was 0.598 mg/dL (95% CI (Confidence Interval); 0.523–0.672), the optimal cut-off level was 94.5 mg/dL (p: 0.012), the sensitivity was 60.5%, and the specificity was 56.1% (Fig. 1A). For CRP, the AUC was 0.672 mg/dL (95% CI: 0.603–0.740), the optimal cut-off level was 0.9585 mg/dL (p: 0.001), the sensitivity was 68.6% and the specificity was 63.7% (Fig. 1B). According to the determined optimal cut-off values, FBG was divided into two groups as $<$94.5 mg/dL and $\geq$94.5 mg/dL, and CRP as $<$0.9585 mg/dL and $\geq$0.9585 mg/dL. There was a weak but statistically significant relationship in the correlation analysis between FBG and CRP (rho; 0.171 and p: 0.001) (**Supplementary Fig. 1**). It was found that there was no difference in age, BMI and the smoking status between the groups. The relationship of the patients' clinical and pathological risk factors with FBG and CRP has been presented in Table 2. There was a statistically significant difference between high FBG and high CRP groups and early stage and locally advanced stage (p: 0.014 and p: 0.001, respectively). There was a statistically significant difference between high FBG and lymph node involvement, high CRP and grade and LVSI (p: 0.003, p: 0.003 and p: 0.032, respectively). Recurrence occurred in 117 (48.1%) patients. It was observed that patients with recurrence were in the high FBG and high CRP groups (p: 0.025 and p: 0.001, respectively). Death occurred in 86 (35.4%) of the patients. A statistically significant difference was determined between the high FBG and high CRP groups and death (p: 0.014 and p: 0.0001, respectively).

In the Kaplan-Meier survival analysis, there was no difference for the four groups of FBG and CRP (1. LgLc, 2. LgHc, 3. HgLc, and 4. HgHc) with regard to PFS and OS at early stage (p: 0.494 and p: 0.641, respectively) (Fig. 2A,B). There was a statistically significant difference in both PFS and OS between the 4 groups at the locally advanced stage (p: 0.026 and p: 0.005, respectively) (Fig. 2C,D). However, in the post-hoc Bonferroni analysis performed between the four groups, there was a statistically significant difference between the LgLc - LgHc groups (p: 0.015), between the LgLc - HgLc groups (p: 0.008), and between the LgLc - HgHc groups (p: 0.003), for PFS. For OS, there was a statistically significant difference between the LgLc - LgHc groups and the LgLc - HgHc groups (p: 0.007 and p: 0.0001, respectively) (**Supplementary Table 1**). When all stages were included, there was a significant difference between the four groups in both PFS and OS (p: 0.001 and p: 0.0001, respectively) (Fig. 2E,F). In the post-hoc Bonferroni analysis, there was a statistically significant difference between the LgLc - LgHc groups (p: 0.0001), between the LgLc - HgLc groups (p: 0.015), between the LgLc - HgHc groups (p: 0.0001) and the HgLc - HgHc groups (p: 0.030) for PFS. For OS, there was a statistically significant difference between the LgLc - LgHc groups, the LgLc - HgHc groups and the HgLc - HgLc groups (p: 0.001, p: 0.0001 and p: 0.001, respectively) (**Supplementary Table 1**).

In the Cox proportional hazard model analysis, it was found that both high FBG (94.5 mg/dL) and high CRP ($\geq$0.9585 mg/dL) levels as dichotomous variables did not significantly affect the survival for both PFS and OS at the early stage (p: 0.662, p: 0.182, p: 0.682 and p: 0.586, respectively) (Tables 3 and 4). In addition, when we took the LgLc group as the reference group, there was no difference in PFS and OS at the early stage. However, for PFS in the locally advanced stage, the HR (Hazard Ratio) for high FBG levels was 1.53, (95% CI: 1.03–2.27) (p: 0.035). In the univariate analysis for the four groups, it was found that other groups significantly adversely affected the surveillance compared to the reference group. In the multivariable analysis performed by adding the age, grade (1–2 or 3) and histology (SCC or non-SCC) variables, there was a statistically significant difference in the other groups compared to the reference group (Table 3). When all patients were included in the analysis, it was found that the high FBG and high CRP levels significantly worsened the surveillance for PFS (HR: 1.76 (95% CI; 1.14–2.71), p: 0.010 and HR: 2.38 (95% CI; 1.63–3.47), p: 0.0001, respectively). In the univariate analysis among the four groups, other groups were found to significantly worsen the survival compared to the reference group: HR for LgHc: 3.26 (95% CI; 1.81–5.87), p: 0.0001, HR for HgLc: 2.12 (95% CI; 1.15–3.91), p: 0.016 and HR for HgHc: 3.72 (95% CI; 2.11–6.55), p: 0.0001. As a result of the multivariable analysis performed by adding the variables of age, BMI, stage (early or locally advanced), grade (1–2 or 3) and histology (SCC or non-SCC), the other groups were found to be independent prognostic risk factors on PFS compared to the reference group (Table 3).

In the univariate analysis carried out for OS in the locally advanced stage, it was found that the high FBG and high CRP levels had a negative effect on OS. The same effect was found when all stages were included in the analysis (Table 4). The HgHc group was found to have the worst effect on OS in the locally advanced stage (HR: 4.68 (95% CI; 1.83–11.98), p: 0.0001). In the multivariable analysis, the HgHc group also had the worst results for OS (HR: 3.63 (95% CI; 1.39–9.47), p: 0.008 (Table 4). When all stages were included in the analysis for OS, it was found that the LgHc and HgHc groups adversely affected the survival compared to the reference group in the univariate analysis (HR: 3.19 (95% CI; 1.54–6.50), p: 0.002 and HR: 4.78 (95% CI: 2.43–9.41), p: 0.0001, respectively). In the multivariate analysis performed for all stages (by adding age (continuous), BMI (continuous), stage (early or locally advanced), grade (1–2 or 3), histology (SCC or non-SCC) variables), only the HgHc group was found to be an independent prognostic risk factor (HR: 2.34 (95% CI; 1.14–4.78), p: 0.019).

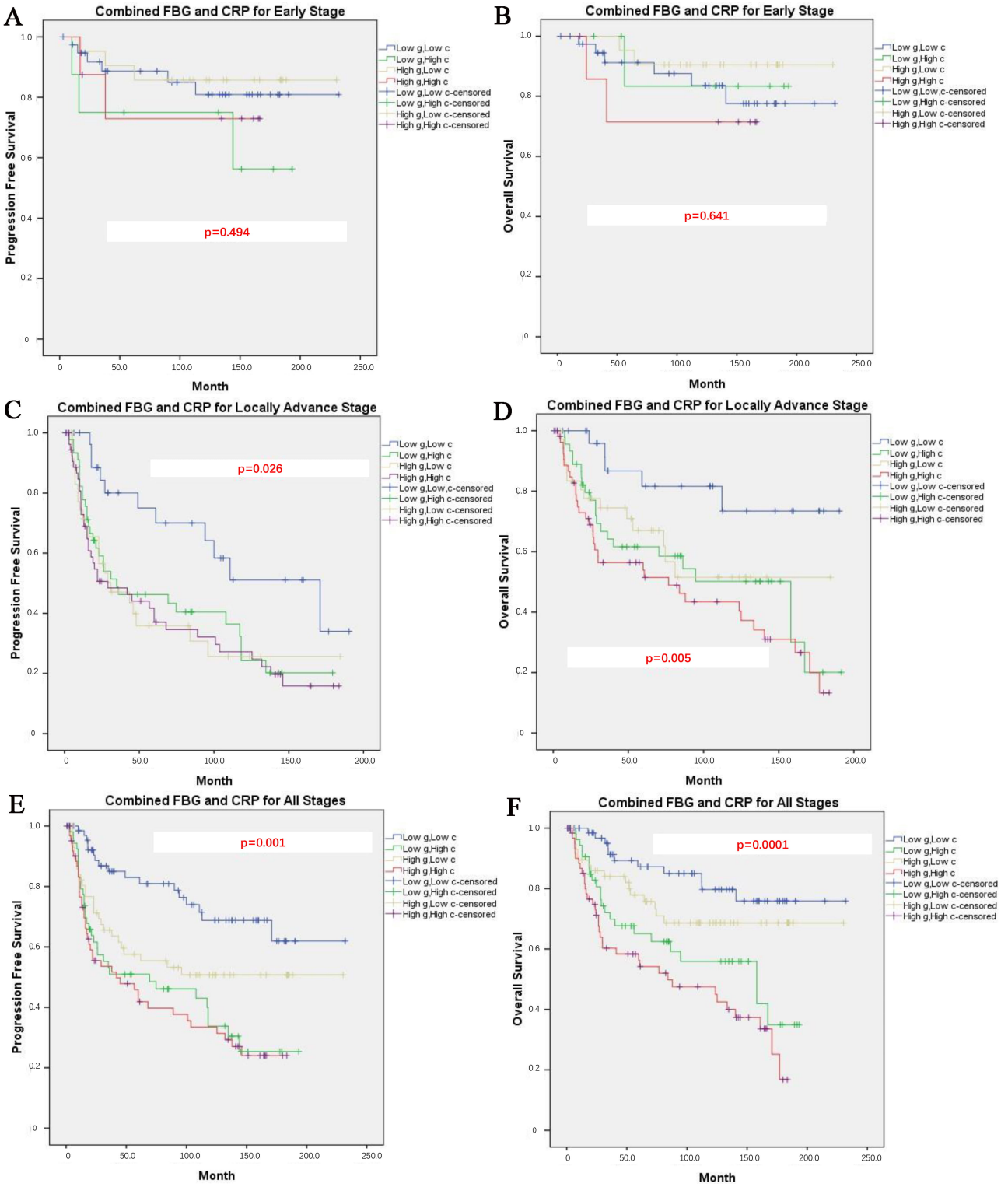

Fig. 2. Kaplan Meier's survival analysis for combined FBG and CRP groups in cervical cancer according to stages. (A) Progression-free survival analysis of combined FBG and CRP groups in patients with early stage cervical cancer. (B) Overall survival analysis of combined FBG and CRP groups in patients with early stage cervical cancer. (C) Progression-free survival analysis of combined FBG and CRP groups in patients with locally advance stage cervical cancer. (D) Overall survival analysis of combined FBG and CRP groups in patients with locally advance stage cervical cancer. (E) Progression-free survival analysis of combined FBG and CRP groups in patients with all stage cervical cancer. (F) Overall survival analysis of combined FBG and CRP groups in patients with all stage cervical cancer.

Table 2. Clinical and pathological characteristics of the cases.

			FBG (mg/dL)			CRP (mg/dL)		
		n	<94.5	≥94.5	*p* value	<0.9585	≥0.9585	*p* value
Age			48 (28–84)	51 (27–83)	0.124	48 (28–84)	51.5 (27–85)	0.161
BMI			23.08 (17.3–48.6)	23.3 (17.3–42.8)	0.514	23.5 (18.1–48.6)	23.1 (17.3–42.8)	0.809
Smoking (pack year)			12 (0–45)	12 (0–40)	0.656	12 (0–45)	12.5 (0–40)	0.502
Stage								
	Early	76 (31.3%)	47 (19.3%)	29 (11.9%)	**0.014**	60 (24.7%)	16 (6.6%)	**0.001**
	Locally advance	167 (68.7)	75 (30.9%)	92 (37.9%)		67 (27.6%)	100 (41.2%)	
Histology								
	Scc	183 (75.3%)	97 (39.9%)	86 (35.4%)	0.127	95 (39.1%)	88 (36.2%)	0.848
	Non Scc	60 (24.7%)	25 (10.3%)	35 (14.4%)		32 (13.2%)	28 (11.5%)	
Grade								
	1–2	198 (81.5%)	102 (42%)	96 (39.5%)	0.392	113 (46.5%)	85 (35%)	**0.003**
	3	45 (18.5%)	20 (8.2%)	25 (10.3%)		14 (5.8%)	31 (12.8%)	
Lymph node involvement								
	Yes	27 (21.6)	7 (5.6%)	20 (16%)	**0.003**	12 (9.6%)	15 (12%)	0.081
	No	98 (78.4)	59 (47.2%)	39 (31.2%)		64 (51.2%)	34 (27.2%)	
Deep invasion								
	Yes	31 (27.7%)	14 (12.5%)	17 (15.2%)	0.170	19 (17%)	12 (10.7%)	0.755
	No	81 (72.3%)	50 (44.6%)	31 (27.7%)		54 (48.2%)	27 (24.1%)	
LVSI								
	Yes	87 (47.3%)	42 (22.8%)	45 (24.5%)	0.388	41 (22.3%)	46 (25%)	**0.032**
	No	97 (52.7%)	53 (28.8%)	44 (23.9%)		61 (33.2%)	36 (19.6%)	
Parametrial involvement								
	Yes	15 (13.4%)	6 (5.4%)	9 (8%)	0.246	8 (7.1%)	7 (6.3%)	0.457
	No	97 (86.6%)	58 (51.8%)	39 (34.8%)		65 (58%)	32 (28.6%)	
Surgical margin								
	Yes	6 (5.4%)	3 (2.7%)	3 (2.7%)	1.000	3 (2.7%)	3 (2.7%)	0.418
	No	106 (94.6%)	60 (53.6%)	46 (41.1%)		70 (62.5%)	36 (32.1%)	
Treatment								
	Surgery	40 (16.5%)	27 (11.1%)	13 (5.3%)	0.160	29 (11.9%)	11 (4.5%)	**0.011**
	Surgery + adj RT	31 (12.8%)	16 (6.6%)	15 (6.2%)		18 (7.4%)	13 (5.3%)	
	Surgery + adj CRT	63 (25.9%)	31 (12.8%)	32 (13.2%)		34 (14%)	29 (11.9%)	
	Pr. CRT	103 (42.4%)	45 (18.5%)	58 (23.9%)		45 (18.5%)	58 (23.9%)	
	Pr. CT	6 (2.5%)	3 (1.2%)	3 (1.2%)		1 (0.4%)	5 (2.1%)	
Recurrence								
	Yes	117 (48.1%)	50 (20.6%)	67 (27.6%)	**0.025**	43 (17.7%)	74 (30.5%)	**0.0001**
	No	126 (51.9%)	72 (29.6%)	54 (22.2%)		84 (34.6%)	42 (17.3%)	
Death								
	Yes	86 (35.4%)	34 (14.0%)	52 (21.4%)	**0.014**	27 (11.1%)	59 (24.3%)	**0.0001**
	No	157 (64.6%)	88 (36.2%)	69 (28.4%)		100 (41.2%)	57 (23.5%)	
Follow up (month)		70.2 (0.57–231)						
Median (min–max)								

FBG, Fasting blood glucose; BMI, Body Mass Index; LVSI, Lymphovascular Space Invasion; Scc, Squamous cell carcinoma; Adj RT, Adjuvant Radiotherapy; Adj CRT, Adjuvant Chemoradiotherapy; Pr. CRT, Primery Chemoradiotherapy; Pr. CT, Primery Chemotherapy.

Note: Statistically significant *p* values are numbered in bold.

Table 3. The effect of only FBG, only CRP and combined FBG and CRP on progression free survival according to the cox proportional hazard model.

	Progression free survival										
	Early stage				Locally advance stage				All stage			
	Univariate	*p* value	Multivariate	*p* value	Univariate	*p* value	Multivariate[a]	*p* value	Univariate	*p* value	Multivariate[b]	*p* value
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
FBG (≥94.5)	0.78 (0.26–2.34)	0.662			1.53 (1.03–2.27)	**0.035**			1.76 (1.14–2.71)	**0.010**		
CRP (≥0.9585)	2.10 (0.70–6.30)	0.182			1.45 (0.96–2.18)	0.077			2.38 (1.63–3.47)	**0.0001**		
LgLc	1				1		1		1		1	
LgHc	2.37 (0.59–9.52)	0.222			2.29 (1.14–4.59)	**0.019**	2.18 (1.07–4.45)	**0.031**	3.26 (1.81–5.87)	**0.0001**	1.89 (1.02–3.49)	**0.040**
HgLc	0.78 (0.19–3.14)	0.733			2.57 (1.24–5.29)	**0.010**	2.86 (1.37–6.1)	**0.005**	2.12 (1.15–391)	**0.016**	2.05 (1.10–3.82)	**0.023**
HgHc	1.50 (0.30–7.48)	0.615			2.63 (1.34–5.14)	**0.005**	2.26 (1.14–4.48)	**0.019**	3.72 (2.11–6.55)	**0.0001**	1.91 (1.05–3.46)	**0.032**

Abbreviations: FBG, fasting blood glucose; CI, confidence interval; HR, hazard ratio; LgLc, Low FBG ve Low CRP; LgHc, Low FBG ve High CRP; HgLc, High FBG ve Low CRP; HgHc, High FBG ve High CRP.

a: For progression free survival, age, grade (1–2 or 3) and histology (Scc or non Scc) were used in multivariate analysis at the local advance stage; **b**: Age, BMI, stage (early or locally advance), grade (1–2 or 3), histology (Scc or non Scc) were used in multivariate analysis for overal survival in all stages.

Note: Statistically significant p values are numbered in bold.

Table 4. The effect of only FBG, only CRP and combined FBG and CRP on overall survival according to the cox proportional hazard model.

	Overall survival										
	Early stage				Locally advance stage				All stage			
	Univariate	*p* value	Multivariate	*p* value	Univariate	*p* value	Multivariate[a]	*p* value	Univariate	*p* value	Multivariate[b]	*p* value
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
FBG (≥94.5)	0.77 (0.22–2.64)	0.682			1.72 (1.07–2.76)	**0.024**			1.72 (1.11–2.63)	**0.015**		
CRP (≥0.9585)	1.44 (0.38–5.46)	0.586			2.06 (1.22–3.47)	**0.006**			2.92 (1.85–4.61)	**0.0001**		
LgLc	1				1		1		1		1	
LgHc	0.72 (0.08–5.98)	0.762			3.35 (1.26–8.86)	**0.015**	2.65 (0.98–7.16)	0.054	3.19 (1.54–6.50)	**0.002**	1.66 (0.78–3.55)	0.187
HgLc	0.47 (0.09–2.35)	0.363			2.99 (1.07–8.35)	**0.036**	2.95 (1.04–8.40)	**0.042**	1.82 (0.84–3.93)	0.125	1.56 (0.71–3.40)	0.262
HgHc	1.59 (0.32–7.90)	0.569			4.68 (1.83–11.98)	**0.001**	3.63 (1.39–9.47)	**0.008**	4.78 (2.43–9.41)	**0.0001**	2.34 (1.14–4.78)	**0.019**

Abbreviations: CI, confidence interval; FBG, fasting blood glucose; HR, hazard ratio; LgLc, Low FBG ve Low CRP; LgHc, Low FBG ve High CRP; HgLc, High FBG ve Low CRP; HgHc, High FBG ve High CRP.

a: For overall survival, age, grade (1–2 or 3) and histology (Scc or non Scc) were used in multivariate analysis at the local advance stage; **b**: Age, BMI, stage (early or locally advance), grade (1–2 or 3), histology (Scc or non Scc) were used in multivariate analysis for overal survival in all stages.

Note: Statistically significant *p* values are numbered in bold.

5. Discussion

In this first study in the literature in which FBG and CRP, two biochemical markers known to have an important role in cancer pathogenesis, were evaluated together, and it was found that the combined high FBG ($\geq$94.5 mg/dL) and high CRP ($\geq$0.9585) levels in patients with cervical cancer significantly negatively affected the PFS and OS, especially in locally advanced stage disease. We also found that the high FBG and high CRP levels were independent prognostic risk factors for cervical cancer for both PFS and OS, compared to low FBG and CRP levels.

Recently, the importance of glucose and CRP levels in gynecological cancers has increased in the literature, and it has been observed that a large number of articles have been published in the last two decades. After examining glucose and CRP alone, they were evaluated together with different biochemical markers and it has been attempted to find prognostic markers with practical and prognostic value in cervical cancer for clinicians. For example, the combination of CRP and LDH (Lactate Dehydrogenase) in cervical cancer [23], the effect of CRP and albumin combination on gynecological cancers [22] and the prognostic value of glucose and SCCA (squamous cell carcinoma antigen) together in cervical cancer [25] can lead to a better prognosis prediction. In the light of the above studies, our thought of predicting the prognosis of cervical cancer with the combination of FBG and CRP may be a reasonable assumption, because we think that these two biochemical markers, which are routinely requested in clinical practice every day and which are ubiquitous and do not require advanced laboratory support, can help clinicians in cervical cancer. However, although there are many studies stating that glucose has a negative effect on the prognosis of cervical cancer, there are also studies stating the opposite. For example, in diabetic patients with poor glycemic control (hemoglobin A1c [HbA1c] $\geq$7.0%) before radical hysterectomy, the recurrence and mortality rates have been shown to be high and it has been emphasized that it is an independent prognostic risk factor [26]. In another cervical cancer study in which FBG (cut-off; 5.1 mmol/L = 91.9 mg/dL) and SCCA (squamous cell carcinoma antigen) were evaluated together, it was observed that the rates of recurrence and death were higher in the groups with high values [25]. In another study, it has been shown that the response rate to neoadjuvant chemotherapy is worse in patients with early-stage cervical cancer with bulky tumor, with FBG above 100 mg/dL [27]. In addition, in another study, it was stated that glucose values above 102 mg/dL in non-diabetic patients that were randomly measured from randomly obtained blood samples indicated a bad prognosis in locally advanced cervical cancer [28]. However, Choi *et al.* [29] stated that glucose was not a poor prognostic risk factor in cervical cancer. Therefore, the role of glucose in the pathogenesis of cervical cancer is still being investigated. The hypotheses put forth for this are as follows: First, glucose uptake is vital for cancer cells. In cervical cancer cells, both *in vivo* and *in vitro*, hexokinase 2 (HK2) has been shown to cause proliferation and tumor formation in cancer cells as a result of a series of events that occur with activation in a high glucose environment [30]. Second, tumor cells use glycolysis for energy as a result of the expression of glycolytic enzymes with the activation of the hypoxia-inducible factor (HIF) instead of mitochondrial oxidative phosphorylation. Therefore, high glucose levels create excess resources and cause rapid proliferation in cancer cells [31]. Third, high glucose levels cause proliferation in cancer cells due to the increase in glucose transporters (GLUTs) and glycosylation in the cell membrane [31, 32]. Fourth, the epithelial-mesenchymal transition (EMT) phenotype, a multi-faceted process critical for the acquisition of migration, invasiveness and pluripotent stem cell-like behaviors, can be induced by hyperglycemia [33]. Fifth, high insulin and insulin-like growth factors support metastasis formation by inhibiting apoptosis in cancer cells with high glucose levels [34].

It is seen that different values are used for glucose in the literature. In our study, we found that when we took the FBG cut-off value of 94.5 mg/dL, it adversely affected the survival (both PFS and OS) in locally advanced stage, and this adverse effect continued when all stages were evaluated together. These results are similar to previously published results. When we evaluated FBG and CRP in combination, we found that high levels of both (HgHc group) caused approximately a five-fold worse prognosis, especially in OS, compared to the LgLc group. It has been clearly demonstrated that using glucose and CRP together rather than using them alone is a very good predictor of the prognostic risk factor in cervical cancer.

Today, human papillomavirus (HPV) infection is seen in almost all patients with cervical cancer, and as a result of this chronic inflammation, inflammatory mediators are thought to increase in cervical cells, creating a suitable microenvironment for the proliferation, survival, transformation, invasion and metastasis of malignant cells [35]. Different cytokines produced by the tumor cause neutrophils to accumulate in the environment and increase the synthesis of cytokines and cytotoxic mediators such as interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), transforming growth factor-_β (TGF-_β), and with stimulation of CRP production, result in growth and migration of tumor cells [36]. High CRP levels are associated with increased serum vascular endothelial growth factor (VEGF) levels, and it has been shown that they contribute to neoangiogenesis and invasion by contributing to the immunosuppression of the tumor microenvironment [37]. Although CRP is mainly produced in hepatocytes, it has also been shown to be produced in malignant tumor cells. This has been proven by showing the relationship between the tumor size and advanced tumor stage and high CRP levels [38]. With the increasing clarification of the etiopathogenesis of inflammation and tumorigenesis, studies on the use of CRP, one of the inflammation markers, to determine the prognosis in human cancers, have increased in number.

On examination of all of the studies published thus far, it is seen in that high CRP is a poor prognostic risk factor in gynecological cancers [8–16, 22, 23]. There is no study that proves the opposite of this situation. In some previous studies, the cut-off value of CRP was determined as 0.5 mg/dL or 1 mg/dL [13, 14]. In our study, 0.9585 mg/dL was taken as the cut-off value, and high CRP levels were found to affect survival approximately three times worse in patients with cervical cancer (p: 0.0001). When we examined the effectiveness of FBG and CRP levels as a group of four, we found that high FBG and high CRP levels for locally advanced disease and disease at all stages were independent prognostic risk factors for OS, compared to low FBG and low CRP levels. As clearly stated in our study, the use of both FBG and CRP in combination is associated with advanced tumor stage and poor survival. Therefore, drugs such as metformin that neutralize the adverse effects of glucose in tissues and been shown to decrease proliferation in cancerous cells [39] need to be studied further. Here, the question arises whether after these results, metformin should be given concurrently with treatment, particularly to patients with locally advanced cervical cancer? At the same time, anti-inflammatory drugs have been shown to prevent cancer formation, especially COX (Cyclooxygenase) inhibitors have been shown to be successful against colorectal cancer [40]. The effect of anti-inflammatory agents can also be investigated in locally advanced cervical cancer, which is a chronic inflammatory process. Multi-center randomized controlled studies are needed to answer these questions.

Considering the limitations of our study, a bias can naturally be seen in patient selection since the study had a retrospective design. In addition, the fact that it was a single-center study, and the relatively low number of patients were other limitations of our study. Another limitation is that there are no randomized controlled studies on this subject.

6. Conclusions

In conclusion, we proved that combined high serum FBG and CRP levels in cervical cancer, especially in locally advanced stage, negatively affect the PFS and OS and are independent prognostic risk factors affecting survival. For each cervical cancer patient, the pre-treatment serum FBG and CRP levels should be carefully evaluated together. The vital importance of strict preoperative glycemic control for these patients should be considered.

Author contributions

MSB and ÖB conceived and designed the study; MSB, ÖB and HAT performed the study; MSB, SD and TS analyzed the data; HAT, SD and TS contributed materials and evaluation; MSB wrote the paper.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Akdeniz University Faculty of Medicine Clinical Research (approval number: KAEK 110).

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ejgo.imrpress.com/EN/10.31083/j.ejgo4206180.

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