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Effects Of Anticancer Treatment On C-Reactive Protein And Procalcitonin Levels In Patients With Infection

Antikanser Tedavinin İnfeksiyonlu Hastalarda C-Reaktif Protein ve Prokalsitonin Değerleri Üzerine Etkileri

Kübra İrday Demir*, Ayşe Erbay, Nalan Yazıcı, Özgür Ceylan, Mehmet Cenk Belibağlı

Abstract: **Objective:** Chemotherapy and radiotherapy treatment affects all the cell functions in the body. Removing malignant cells comes with a cost of impairment of other cells and systems, including the synthesis of C-reactive protein (CRP) and Procalcitonin (PCT). This study aimed to compare the CRP and PCT responses in fever attacks of pediatric patients with cancer and non-cancer ones.

Materials and methods: We conducted a retrospective and cross-sectional study analyzing the medical files of 179 pediatric patients hospitalized at the University of Başkent Adana Dr. Turgut Noyan Application and Research Center Pediatric Ward between 01.01.2014 and 31.12.2016. Patients with cancer and received chemo and or radiotherapy treatment, with reports of fever attacks of infection origin, were selected for the study group, and patients with reports of fever attacks of infection origin and did not have a history of cancer were chosen for the control group. The study group's inclusion criteria were; aged between one month and 18 years, received cancer therapy, having reports of fever attacks, and tested for CRP, PCT, complete blood count, and basic blood biochemistry. Statistical Package for Social Sciences (SPSS) 17.0 was used in data analysis. Critical significance was set as 0.05.

Results: The study consisted of a very heterogeneous population. Overall, there were a total of 234 fever attacks recorded. The comparison of the CRP and WBC levels of the study group showed a negative correlation (r: -0.31, p=0.001). Similarly, CRP levels increased as the neutropenia deepened (p<0.001). On the contrary, in the control group, CRP levels increased parallel to the WBC levels (r: 0.245, p=0.008). The analysis of the study group showed that an increase in PCT levels was associated with prolonged iv antibiotic treatment duration in patients with PCT levels over 0.5 mg/dL and had lymphoma or leukemia (p= 0.034).

Conclusion: In this novel study, the CRP and PCT levels in infections of pediatric patients with cancer and receiving cancer therapy and ones not diagnosed with cancer were compared. There was no superiority between CRP and PCT was found in predicting infection severity in the pediatric population.

Keywords: C-reactive protein, procalcitonin, febrile neutropenia, neoplasms

Öz: **Amaç:** Kemoterapi ve/veya radyoterapi tedavi protokolleri; malign hücrelerle birlikte vücuttaki tüm hücre fonksiyonlarını etkileyen tedavilerdir. C-reaktif protein (CRP) ve prokalsitoninin (PCT) sentezlendiği hücreler de bu tedavilerden etkilenebilmektedir. Bu çalışmada enfeksiyona bağlı ateşi olan kanser tedavisi almakta olan pediatrik hastaların CRP ve PCT düzeylerinin, kanser tanısı olmayan pediatrik hastaların düzeyleriyle karşılaştırılması amaçlanmıştır.

Yöntem: Çalışma retrospektif ve kesitsel olarak tasarlanmıştır. Veriler Başkent Üniversitesi Adana Turgut Noyan Uygulama ve Araştırma Merkezi Pediatri Kliniğinde 01.01.2014 ile 31.12.2016 tarihleri arasında takip edilen 179 hastanın tıbbi kayıtlarından toplanmıştır. Ateş bulgusu olan hastalar arasından kemoterapi ve/veya radyoterapi alan kanserli vakalar çalışma grubu için seçilirken, kanser öyküsü olmayanlar kontrol grubuna alınmıştır. Statistical Package for Social Sciences (SPSS) 17.0 programı veri analizinde kullanılmıştır. P değeri 0.05 olarak belirlenmiştir.

Bulgular: Toplam 234 ateş atağının kaydedildiği çalışmada popülasyonun heterojenitesi yüksekti. Çalışma grubunun CRP ve beyaz küre (WBC) değerleri negatif korelasyon göstermiştir (r: -0.31, p=0.001). Benzer olarak, nötropeni derinleştikçe CRP değerlerinde artış gözlenmiştir (p<0.001). Kontrol grubunda ise CRP seviyeleri WBC seviyelerine paralel olarak artmıştır (r: 0.245, p=0.008). Çalışma grubunun analizinde; lenfoma ve lösemi tanısı ile takip edilen, PCT değerlerinin 0.5mg/dL'nin üzerinde saptandığı hastalarda PCT değerlerindeki artışın uzamış antibiyotik kullanım süresi ile ilişkili olduğu gözlenmiştir (p= 0.034).

Sonuçlar: Bu özgün çalışmada kanser tedavisi almakta olan pediatrik hastalar ile kanser öyküsü olmayan pediatrik hastalardaki enfeksiyon kaynaklı ateş ataklarında alınan kan örneklerindeki CRP ve PCT değerleri karşılaştırılmıştır. Pediatrik yaş grubunda gerçekleştirilen bu çalışmada kemo-radyoterapinin CRP ve PCT değerleri üzerinde anlamlı bir etkisi olmadığı, takip ve tedavide CRP ve PCT değerlerinin birbirine üstünlüğünün olmadığı saptanmıştır.

Anahtar Kelimeler: C-reaktif protein, prokalsitonin, febril nötropeni, neoplazm

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Kübra İrday Demir: Uzm. Dr., SBÜ Adana Şehir Eğitim ve Araştırma Hastanesi
Email: irdaykubra@gmail.com
ORCID iD: https://orcid.org/0000-0003-1793-8655

Ayşe Erbay: Doç. Dr., Başkent üniversitesi Adana Turgut Noyan uygulama ve Araştırma Hastanesi
Email: ayseeerbay@yahoo.com
ORCID iD: https://orcid.org/0000-0001-7292-3822

Nalan Yazıcı: Prof. Dr. , Başkent üniversitesi Adana Turgut Noyan uygulama ve Araştırma Hastanesi
Email: nalanyaz@yahoo.com
ORCID iD: https://orcid.org/0000-0003-4465-8229

Özgür Ceylan: Uzm. Dr., Başkent üniversitesi Adana Turgut Noyan uygulama ve Araştırma Hastanesi
Email: zgrceylan@yahoo.com
ORCID iD: https://orcid.org/0000-0001-6910-7250

Mehmet Cenk Belibağlı: Uzm. Dr. SBÜ Adana Şehir Eğitim ve Araştırma Hastanesi Aile Hekimliği
Email: mcbelibagli@gmail.com
ORCID iD: https://orcid.org/0000-0002-0074-4611

Bildirimler: / Acknowledgement
* Corresponding Author

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1. INTRODUCTION

Chemotherapy and radiotherapy treatment affects all the cell functions in the body. Removing malignant cells comes with a cost of impairment of other cells and systems, including the synthesis of C-reactive protein (CRP) and Procalcitonin (PCT), which are reliable markers in infection treatment. The extent of the impairment in protein synthesis by chemotherapy and radiotherapy has been an object of interest to many researchers. It seems possible that different types and steps of protein synthesis mechanisms might be altered based on the cancer treatment protocol. Hence, the synthesis rate, intensity, or volume of CRP and or PCT may be affected. If so, CRP and PCT threshold levels in patients receiving cancer therapy might require reassessment [1–3]. An increase in CRP levels is associated with all inflammatory processes and not correlated to its intensity. In contrast, PCT is limited to bacterial, fungal, and viral infections and vital in managing the infection [4]. This study aimed to compare the CRP and PCT responses in fever attacks of pediatric patients with cancer and non-cancer ones and present the prognostic values.

2. MATERIAL and METHODS

We conducted a retrospective and cross-sectional study analyzing the medical files of 179 pediatric patients hospitalized at the University of Başkent Adana Dr. Turgut Noyan Application and Research Center Pediatric Ward between 01.01.2014 and 31.12.2016. There were no sampling methods. The files of patients with cancer and reports of fever attacks of infection origin were selected for the study group, and the files of patients with reports of fever attacks of infection origin and did not have a history of cancer were chosen for the control group.

2.1. Inclusion and exclusion criteria

The study group's inclusion criteria were; aged between one month and 18 years, received cancer therapy, reported fever attacks, and tested for CRP, PCT, complete blood count, and basic blood biochemistry.

The control group's inclusion criteria were; aged between one month and 18 years, not having a history of cancer, having reports of fever attacks, tested for CRP, PCT, complete blood count, basic blood biochemistry in the patient file.

Exclusion criteria were as follows; newborns, having an immune deficiency, not being tested for CRP, and PCT in the same blood sample.

2.2. Definitions

Neutropenia and fever definitions were based on the Diagnosis and Treatment Guideline of Pediatric Febrile Neutropenic Cases [5]. Neutropenia was defined as Absolute Neutrophil Count (ANC) <500/mm^3 or having ANC between 500-1000/mm^3 and expected to decrease below 500/mm^3 in 48 hours. Conditions of having ANC<100/mm^3 was defined as profound neutropenia. Fever was described as a single measurement over 38°C or consecutive measurements over 37,5°C for more than one hour of axillary temperature.

A patient in chemotherapy and or radiotherapy protocols was accepted as receiving cancer therapy at the time of hospitalization.

Basic blood chemistry included CRP, PCT, sodium, potassium, alanine transaminase, and aspartate transaminase.

2.3. Data collection and Analysis

The data collected from the medical files of 63 patients in the study group included age, gender, primary diagnosis, oncological diagnosis, oncological diagnosis date, chemotherapy agents, radiotherapy regimen; number, date, and duration of the fever attacks, pulse rate, respiration rate, temperature, blood pressure, complete blood count, control neutrophil counts, CRP, PCT, blood, and urine culture results, antibiotic therapy and catheterization method.

The data collected from the medical files of 116 patients in the control group included age, gender, primary diagnosis, number, date, and duration of the fever attacks, pulse rate, respiration rate, temperature, blood pressure, complete blood count, control neutrophil counts, CRP, PCT, blood, and urine culture results and antibiotic therapy and catheterization method.

The CRP and PCT levels were recorded at the onset of each fever attack.

Urine and cerebrospinal fluid samples were cultured at 5% sheep blood and MacConkey agar. Cerebrospinal fluid samples were additionally cultured at Brain Heart Infusion Broth agar. BACTEC system was used for blood culture growth. Serum PCT was analyzed with the BRAHMS PCT Immunoassay method at Siemens Advia Centaur XP device. Serum CRP was analyzed with the nephelometric method at Siemens BN ProSpec device. Threshold levels for CRP and PCT were <3, 3-10 and >10mg/dL and <0.5, 0.5-1.9, 2-4.9, 5-10 and >10mg/dL, respectively.

Statistical Package for Social Sciences (SPSS) 17.0 was used in data analysis. Mean, standard deviation (SD), median, frequency, percentage, minimum, and

maximum values were calculated for descriptive analysis. Quantitative data were compared by Chi-Square; qualitative analysis was performed by Mann Whitney U and Kruskal Wallis tests. Correlation between variables was analyzed by the Spearman Rho test. ANOVA test was used in the study to determine CRP and PCT thresholds, absolute neutrophil count, antibiotic treatment duration, and blood culture results. Critical significance was set as 0.050.

Ethical Declaration

The study was approved by the Research Committee of the University of Başkent on 31.08.2016 with the reference project code of KA16/266.

3. RESULTS

There were a total of 234 fever attacks recorded. The demographics and statistical results of the analysis are summarized in table 1.

Table 1. Summary of results

	Study Group n=63 (fever attacks n=117)			**Control Group** n=116 (fever attacks n=117)		
	Mean±SD	Median (range)		Mean±SD	Median (range)	*p*-value
Age in years		7 (0.7-17)	**Age** in years		2 (0.1-15)	0.000
Gender			**Gender**			0.747
Male			*Male*			
Female			*Female*			
Diagnosis	n	%	**Diagnosis**	n	%	
Leukemias	16	25.40	*Respiratory tract infections*	61	52.58	
Lymphomas	15	23.81	*Bacteriemia*	25	21.55	
Other malignancy	32	50.79	*Urinary tract infections*	13	11.21	
			Viral infections	10	8.62	
			Acute gastroenteritis	7	6.03	
IV Antibiotic	**n**	**%**	**IV Antibiotic**	**n**	**%**	
Monotherapy	66	56.47	*Monotherapy*	84	71.79	
Most preferred	Meropenem (n=49)	41.90	*Most preferred*	Ceftriaxone (n=39)	33.33	
Duration	9.1±5.2 days	8 (0-28) days	*Duration days*	4.3±2.8 days	4 (0-21) days	0.000
	Mean±SD	**Median (range)**		**Mean±SD**	**Median (range)**	
Hb (g/dL)	9.7±1,9	9.6 (6.3-19.4)	**Hb (g/dL)**	11.1±1.3	11.1 (7.2-14.5)	0.000
WBC (10^3/μL)	2.988±3.788	1.37 (0.50-20.12)	**WBC (10^3/μL)**	14775±8092	13870 (1900-36820)	0.000
Plt (10^3/μL)	154.727±165.832	97 (17-1,258)	**Plt (10^3/μL)**	331,821±133,353	310 (105-844)	0.000
ANC (10^3/μL)	1659.4±3327.3	280 (0-13714)	**ANC (10^3/μL)**	9335.2±6867.5	7860 (100-34311)	0.000
CRP (mg/dL)	51.0±53.7	25.5 (3-268)	**CRP (mg/dL)**	54,0±62,4	22.9 (3.0-210)	0.691
PCT (mg/dL)	2.2±9.08	0.3 (0.1-75.0)	**PCT (mg/dL)**	3,6±11,6	0.4 (0-75)	0.312
Fever			**Fever**			
Duration	2.5±2.4 days	2 (1-14) days	***Duration***	2.1±1.8 days	2 (1-15) days	0.176
Origin	**n**	**%**	***Origin***	**n**	**%**	
Not found	78	66.67	*Not found*	30	25.64	
Respiratory tract infections	17	14.53	*Respiratory tract infections*	61	52.14	
Acute gastroenteritis	10	8.55	*Urinary Tract Infections*	13	11.11	
Other	12	10.26	*Other*	13	11.11	
Culture growth	34	29.06	**Culture growth**	14	12.07	
CoNS	17	14.53	**CoNS**	7	6.03	
E. coli	3	2.56	**Streptococci**	3	2.59	
Other	14	11.96	**Other**	3	2.59	

ANC: Absolute Neuytophile Count, CRP: C-Reactive Protein ,PCT: Procalcitonin, CoNS: Coagulase-negative Staphylococci

There was no difference between the groups regarding gender (p=0.747). The median age was 7 (0.7-17) years in the study group and 2 (0.1-15) years in the control group (p=0.000). The overall mortality in the study population was 0.085% (n=1).

In the study group, there were a total of 117 fever attacks recorded. In the majority of the attacks (n=78, 66.67%), the origin of fever was not found. In the remaining 39 (32.48%), lower respiratory infections (n=11, 9.40%), acute gastroenteritis (n=10, 8.55%), upper respiratory tract infections (n=6, 5.13), mucositis (n=5, 4.27%), urinary tract infections (n=2, 1.71%), dermatitis (n=1, 0.85%) and odontogenic infection (n=1, 0.85%). In three of the attacks, there two sites of infection, including lower respiratory tract infection and mucositis (n=1, 0.85%), acute gastroenteritis, and upper respiratory tract infection (n=1, 0.85%), and mucositis and dermatitis (n=1, 0.85%).

More than half of fever attacks (n=74, 63.25%) occurred in patients diagnosed with leukemia and lymphoma (n=36, 57.15%). In the vast majority of the fever attacks (n=100, 85.47%), febrile neutropenia criteria were met. In 55 (47.01%) fever attacks in the study group, patients had port catheters. Monotherapy antibiotic treatment protocol was administered in 66 (56.47%) of the attacks for fever treatment. In fever attacks with clinical manifestations, glycopeptides (n=26, 22.22%) metronidazole (n=10, 8.55%), amikacin (n=9, 7.69%), fluconazole (n=9, 7.69%), oseltamivir (n=5, 4.27%) clarithromycin (n=3, 2.56%) were used as empirical antibiotics. Bacterial growth has occurred in 34 (29.06%) of the samples, 17 (14.53%) of which were considered as contaminated due to bacteria growth common in epidermal flora (coagulase-negative staphylococcus). Out of 17 culture-positive samples, there was no identified source other than the port catheters (n=9, 7.69%).

In 81 (69.23%) of the attacks, fever was reduced on the 3rd day. In 20 attacks (17.09%) lasted for five and in 16 (13.68%) for ten days. The average intravenous antibiotic treatment duration was 9.1±5.2 days (0-28 days). The antibiotic treatment was stopped in 78 (66.7%) of the fever attacks without additional antibiotics. In the control group, there were 117 fever attacks recorded (one patient had two fever attacks). The average intravenous antibiotic treatment duration was 4.3±2.8 days (0-21 days). In 11 (9.40%) of the fever attacks, antibiotic treatment was not administered due to viral infection diagnosis. The analysis of the study group showed that an increase in PCT levels was associated with prolonged iv antibiotic treatment duration in patients with PCT levels over 0,5 mg/dL and had lymphoma or leukemia (p= 0,034). On the other hand, there were no such associations for patients with diagnoses other than lymphoma or leukemia. Analysis during fever attacks showed significant differences between groups regarding complete blood count results. The mean blood count of the study and control group were Hb levels with 9,7±1,9g/dL, and 11,1±1,3 g/dL and the medians of WBC, Plt and ANC levels of the study and control group were 1370/µL and 13835/µL, 97000/ mm^3, and 310000/µL, 280/µL and 7860/ mm^3, respectively (p=0.000). The median Plt levels of the patients with leukemia and lymphomas were statistically different from the other cancer patients in the study group (p=0.036).

There were no associations between the groups in terms of the duration of fever, intravenous (iv) antibiotic treatment, ALT, and AST levels.

3.1. C-reactive protein results

There was no association between the groups in analyzing three different CRP thresholds levels with the fever attacks, WBC, ANC, blood, urine bacterial culture growth, and iv antibiotic treatment. However, the comparison of the study group's CRP and WBC levels showed a negative correlation (r: -0.31, p=0.001). Similarly, CRP levels increased as the neutropenia deepened, as shown in table two (p=0.000). On the contrary, in the control group, CRP levels increased parallel to the WBC levels (r: 0.245, p=0.008).

3.2. PCT results

There was no association between the groups in the analysis of five different PCT thresholds levels with the fever attacks, WBC, ANC, blood, and urine bacteria culture growth. There was no correlation detected between the PCT and WBC in both groups, (study group; r:-0.099, p=0.288), (control group; r:0,220, p=0.017).

The analysis of the study group showed that an increase in PCT levels was associated with prolonged iv antibiotic treatment duration in patients with PCT levels over 0,5 mg/dL and had lymphoma or leukemia (p= 0,034). On the other hand, there were no such associations for patients with diagnoses other than lymphoma or leukemia. A similar correlation was found in the control group in patients with PCT levels over 10 mg/dL (p= 0.032).

Table 2. Analysis of CRP and PCT levels with ANC count in the study group

			ANC Count (n/mm^3) (%)					
	mg/dL		**<100**	**100-500**	**501-1000**	**1001-1500**	**>1500**	***p***
CRP Thresholds	< 3	**Study Group Total**	0 (0.0)	1 (3.4)	2 (18.2)	2 (66.7)	6 (18.2)	**0.001**
	3-10		2 (5.1)	5 (17.2)	0 (0.0)	1 (33.3)	2 (6.1)	
	> 10		37 (94.9)	23 (79.3)	9 (81.8)	0 (0.0)	25(75.8)	
	< 3	**Leukemia and Lymphomas**	0 (0.0)	0 (0.0)	2 (28.6)	1 (100.0)	6 (26.1)	**0.002**
	3-10		0 (0.0)	3 (18.8)	0 (0.0)	0 (0.0)	2 (8.7)	
	> 10		26 (100.0)	13 (81.3)	5 (71.4)	0 (0.0)	15 (65.2)	
	< 3	**Other Malignancies**	0 (0.0)	1 (7.7)	0 (0.0)	1 (50.0)	0 (0.0)	**0.034**
	3-10		2 (15.4)	2 (15.4)	0 (0.0)	1 (50.0)	0 (0.0)	
	> 10		11 (84.6)	10 (76.9)	4 (100.0)	0 (0.0)	10 (100.0)	
PCT Thresholds	< 0.5	**Study Group Total**	31 (75.6)	18 (62.1)	9 (81.8)	3 (100.0)	27 (81.8)	0.623
	0.5-1.9		5 (12.2)	6 (20.7)	1 (9.1)	0 (0.0)	3 (9.1)	
	2-4.9		2 (4.9)	2 (6.9)	1 (9.1)	0 (0.0)	1 (3.0)	
	5-10		0 (0.0)	3 (10.3)	0 (0.0)	0 (0.0)	1 (3.0)	
	> 10		3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	
	< 0.5	**Leukemia and Lymphomas**	19 (70.4)	11 (68.8)	6 (85.7)	1 (100.0)	20 (87.0)	0.477
	0.5-1.9		4 (14.8)	2 (12.5)	1 (14.3)	0 (0.0)	1 (4.3)	
	2-4.9		1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	
	5-10		0 (0.0)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	
	> 10		3 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	< 0.5	**Other Malignancies**	12 (85.7)	7 (53.8)	3 (75.0)	2 (100.0)	7 (70.0)	0.554
	0.5-1.9		1 (7.1)	4 (30.8)	0 (0.0)	0 (0.0)	2 (20.0)	
	2-4.9		1 (7.1)	2 (15.4)	1 (25.0)	0 (0.0)	0 (0.0)	
	5-10		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	
	> 10		0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1 (10.0)	

ANC: Absolute Neuytophile Count CRP: C-Reactive Protein PCT: Procalcitonin

4. DISCUSSION

The significant difference in comparing the median ages of the groups with seven years for study and two years for the control group (p=0.000) may be attributed to the preferences in the hospitalization criteria of pediatric cases with fever. The hospitalization rate of children with high temperature and not diagnosed with cancer increases with younger age. However, in cases receiving cancer therapy or febrile or possible neutropenia, hospitalization decision is made regardless of the age[5,6].

The majority of the study group was diagnosed with leukemia (31.7%) and lymphoma (25.3%). According to the Turkish Pediatric Oncology Group, leukemia and lymphoma were reported as the most common cancers, with prevalence rates of 25.2% and 21.1%, respectively [7]. Similar to the study, other studies conducted on Turkish patients show that leukemia is the most common diagnosis in patients with febrile neutropenia [8–11]. The ratio of leukemia and lymphoma cases in the study may seem slightly increased compared to previous studies. This finding may be considered a strengthening factor in evaluating the study markers in managing these cases.

Table 3. Comparison of CRP and PCT levels in culture growth

			Negative	Contaminated	Positive	
	mg/L		n (%)	n (%)	n (%)	***p***
CRP Thresholds	< 3	**Study Group**	8 (9.6)	2 (12,5)	1 (6,3)	0,950
	3-10		7 (8.4)	1 (6,3)	2 (12,5)	
	>10		68 (81.9)	13 (81,3)	14 (81,7)	
	< 3	**Control Group**	12 (11.7)	2 (15,4)	0 (0,0)	0,862
	3-10		15 (14.6)	3 (23,1)	0 (0,0)	
	> 10		76 (73.8)	8 (61,5)	1 (100,0)	
PCT Thresholds	< 0,5	**Study Group**	65 (78.3)	13 (76,5)	10 (58,8)	0.238
	0,5-1,9		10 (12.0)	1 (5,9)	4 (23,5)	
	2-4,9		4 (4.8)	2 (11,8)	0 (0,0)	
	5-10		2 (2.4)	1 (5,9)	1 (5,9)	
	> 10		2 (2.4)	0 (0,0)	2 (11,8)	
	< 0,5	**Control Group**	60 (58.3)	7 (53,8)	0 (0,0)	0,283
	0,5-1,9		25 (24.3)	2 (15,4)	1 (100,0)	
	2-4,9		9 (8.7)	1 (7,7)	0 (0,0)	
	5-10		4 (3.9)	0 (0,0)	0 (0,0)	
	> 10		5 (4.9)	3 (23,1)	0 (0,0)	

CRP: C-Reactive Protein, PCT: Procalcitonin

Among the total 117 fever attacks of the study group files, records showed that in two (1.71%) of the attacks, radiotherapy was performed in the last month, and in twelve (10.26%) in the past three months. As for chemotherapy, approximately all of the files with fever attacks included chemotherapy reports administered in the past three months (n=115, 98.29%, respectively). These results may indicate an association between chemotherapy and fever attacks compared to radiotherapy. However, the number of patients receiving radiation was insufficient to produce a reliable comparison.

The study group had lower mean hemoglobin and platelet levels compared to the control group with 9.7±1.9g/dL Hb and 154.73±165.83/µL Plt, and 11.1±1.3g/dL Hb and 331.821±133.353/µL Plt, respectively (p=0.000 and p=0.000, respectively). This finding was expected due to the anemia and thrombocytopenia effect of acute and long-term myelosuppression in chemotherapy and radiotherapy patients [12–15].

The most important risk factors for infection development in patients with neutropenia were the depths and the duration of neutropenia. It was reported that the risk for mortality and morbidity increases as the neutropenia deepens, having that below 100/mm³ was considered to be at the highest level [16]. In neutropenias shorter than seven days, bacterial infections were predominantly reported to occur, and in longer durations, fungal infections were seen [17]. ANC was found below 100/mm³ in 39 (33.33%) of the fever attacks. The mortality was 0.85%; one patient died. There were eight (6.83%) cases with fungal infections. Among the 17 blood culture-positive cases in the study group there were no associations found between threshold levels for CRP and PCT (for CRP < 3mg/dl, 3-10mg/dl, > 10mg/dl; p=0,950, and for PCT < 0.5mg/dl, 0.5-1.9 mg/dl, 2-4.9 mg/dl, 5-10 mg/dl and >10 mg/dl; p=0.217, respectively). CRP levels increased as the neutropenia deepened; however, this relation was not observed with PCT levels.

The mean number of days with fever in cases with cancer was 2.5±1.3 days. This finding seems comparatively short compared to other studies conducted on Turkish children with cancer that reported the mean number of days with a fever between 5.3 and 11 days [8,10]. However, in the control group, the mean number of days with fever was 2.1±1.8 (p=0.176). In addition to the lack of an association in terms of fever, the relatively short duration may be explained by many factors, including the few high-risk patients in the study.

In most of the fever attack records (62.9%) of the study group, the files showed that the patients were already on

antibiotic treatment at the fever attack time. On the other hand, the records of the control group showed a lower rate with 12.8%. The ratio of cases on antibiotic treatment at the onset of fever for both groups was similar, with 12.5% and 12.8%. The mean number of days for antibiotic treatment in both groups was 9.1±5.2 days for the study group and 4.3±2.8 for the control group (p=0.000). The most preferred antibiotic in the study group was meropenem (48.9%). It was administered as monotherapy for 56.4% of the cases. This finding may be because Meropenem is a commonly preferred beta-lactam antibiotic due to its anti-pseudomonas effect in patients with high-risk febrile neutropenia [16,18].

In febrile neutropenia cases, the infections in the febrile attacks are classified into three groups, clinically defined, microbiologically defined, and fever of unknown origin [5]. In numerous studies, clinically defined infections are reported to have a rate of approximately 40%, and the latter two share the rest with 30% each [9,19,20]. In the study group, the clinically defined infection rate was 33.33%, consistent with the previous studies.

There are reports in the literature indicating that CRP levels were associated with specific cancer types (lung cancer stage levels) and PCT levels were increased in certain organ tumors (e.g., liver metastases) and tumors associated with the neuroendocrine system [21,22]. However, the study findings were contradictory. The results revealed that both inflammatory markers CRP and PCT showed similarly increased levels regardless of the tumor types and showed no difference between both groups.

Studies suggest that during bacteriemia, regardless of the microorganism's etiology, the increase in CRP levels was similar between immunocompromised and immunocompetent patients [23–25]. Similar studies were conducted on PCT, indicating that the biomarker's serum levels are strongly associated with the infection's severity regardless of the underlying condition [13,26]. In a study on clinical and diagnostic value comparison between CRP and PCT on clinical outcomes in febrile neutropenic patients, it was suggested that PCT levels had higher specificity and positive predictive value compared to CRP levels, and CRP levels had higher sensitivity and negative predictive value compared to the PCT levels [25].

4.1. Limitations

The study was limited to the files of a single institution for a limited time. The severity of the cases was clinically between mild to moderate, and we only had one case requiring intensive care. Because bone marrow transplantation (BMT) is not performed in our hospital, high-risk groups for febrile neutropenia such as BMT patients and leukemia patients in the induction period were not included in the study. In the control group, the intensive care unit patients' files were excluded. Nevertheless, the study consisted of a heterogeneous population, age, type of cancer, infections, and cancer therapy protocols. The low number of high risk and severe cases reduces the importance of the study results. Another major limitation may be the frequency of CRP and PCT examinations. In most of the files, the tests were not performed at the same frequency, thus avoiding a continuous evaluation. It has been reported that average CRP levels in the pediatric and young adult population is below the standard levels and may elevate in older ages [8,27]. Similarly, average PCT levels fluctuate in the first week in newborns [7]. Therefore, newborns were not included in the study.

Another significant limitation was the absence of the sepsis scoring of the patients. Although the study consisted of significant variables to present an adequate assessment of cancer therapy on CRP and PCT levels in patients with infection, additional factors might be included to reach an accurate evaluation. Besides, studies with a prospective design would yield more significant results.

5. CONCLUSION

In this novel study, the CRP and PCT levels in infections of pediatric patients with cancer and receiving cancer therapy and ones not diagnosed with cancer were compared. There was no superiority between CRP and PCT was found in predicting infection severity in the pediatric population.

Prospective studies with a more significant number of cases and more extended observations are required to verify our results.

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