Research Article

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Evaluation of C-reactive protein and procalcitonin as a mortality indicator in febrile neutropenic patients

Febril nötropenik hastalarda C-reaktif protein ve prokalsitoninin mortalite göstergesi olarak değerlendirilmesi

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Abstract

Purpose: Febrile neutropenia (FN) is a common side effect of chemotherapy in cancer patients, leading to complications, increased healthcare costs, and mortality. Microbiological agents can be identified in 30-50% of FN cases. Therefore, there is a need for specific, highly effective, and rapid markers to indicate infection. Various biomarkers are currently under investigation and in clinical use. This study aims to evaluate their effectiveness in the early detection of infection and mortality by comparing quantitative C-reactive protein (CRP) and procalcitonin levels at the onset of FN and during treatment.

Material and methods: This study is a retrospective case-control study. It included 572 patients with febrile neutropenia (FN) who were followed up in the Hematology Clinic, Bone Marrow Transplantation Unit, and Medical Oncology Clinic between September 3, 2018, and May 25, 2022. A total of 748 FN episodes were recorded in these patients. Data were retrieved from the hospital information management system and documented using a pre-prepared form. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 26.0 software.

Results: Of the febrile neutropenia (FN) patients included in the study, 118 experienced mortality, whereas 630 survived. The mean age was 51.6 years in the mortality group and 50.5 years in the non-mortality group. Females constituted 47.9% of the cohort, while males accounted for 52.1%. Hematological malignancies were present in 67.2% of all patients. Bacteremia was identified in 36.5% of FN episodes. Although E. coli was the most frequently isolated microorganism, P. aeruginosa and A. baumannii were more commonly detected in patients who succumbed to the illness. Elevated C-reactive protein (CRP) and procalcitonin levels within the first five days of treatment were significantly associated with both mortality and the presence of bacteremia. Neither leukocyte count nor absolute neutrophil count at the time of diagnosis showed a significant association with mortality. However, prolonged duration of neutropenia, bloodstream infections, catheter-related bloodstream infections, and the presence of pneumonia emerged as significant risk factors for mortality.

Conclusion: CRP and procalcitonin levels were observed to have both prognostic and diagnostic value. Additionally, resistant Gram-negative bacterial growth was more frequently detected in the blood cultures of patients who did not survive. Further studies are needed to develop new treatment algorithms.

Keywords: Febrile neutropenia, C-reactive protein, procalcitonin, mortality.

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Öz

Giriş: FN, kemoterapötiklerin komplikasyonlara, maliyet artışı ve mortaliteye yol açabilen yan etkisidir. Enfeksiyon hastalıklarının sadece %30-50'sinde ateşin kaynağı ve mikrobiyolojik etkenler saptanabilmektedir. Bu nedenle enfeksiyonu gösterebilecek, spesifik, yüksek etkinlikli ve hızlı belirteçlere ihtiyaç duyulmaktadır. Bu nedenle çeşitli biyomarkerlar araştırılmakta ve günümüzde halen kullanılmaktadır. Çalışmamızda da nötropenik ateşte CRP ve prokalsitoninin tanısal, prognostik kullanılabileceği ve FN ataklarının klinik, laboratuvar özelliklerinin, kültürde üreyen mikroorganizmaların araştırılması amaçlanmıştır.

Gereç ve yöntem: Retrospektif, vaka – kontrol çalışması olarak yürütülen bu çalışma 3 Eylül 2018-25 Mayıs 2022 tarihleri arasında hematoloji, kemik iliği transplantasyon ve tıbbi onkoloji kliniğinde FN sebebiyle tedavi gören 18 yaş ve üstü hastalarda gelişen 748 FN atağı irdelendi. Hastane bilgi yönetim sistemi taranarak uygun olan hastalar veri formuna kaydedilerek The Package for Social Sciences 26.0 (SPSS 26.0) aracılığıyla analiz edildi.

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Bulgular: Çalışmaya dahil edilen FN hastalarından 118 tanesinde mortalite gelişmişken, 630 tanesinde mortalite gelişmemiştir. Mortalite grubunda yaş ortalaması 51,6, mortalite olmayan grupta ise 50,5 bulunmuştur. Hastaların %47,9'unu kadın, %52,1'ini erkek hastalar oluşturmaktadır. Hastaların %67,2'sinin hematolojik malignitesi mevcuttu. FN ataklarında bakteriyemi oranı %36,5 bulundu ve en sık saptanan mikroorganizma E. coli olmasına rağmen P. aeruginosa ve A. baumannii üremesi olanlar mortalitesi olanlarda daha yüksek saptanmıştır. Tedavinin ilk beş gününde bakılan CRP ve prokalsitonin değeri mortalite ve bakteriyemisi olan hastalarda yüksek bulunmuştur. Tanı anında lökosit ve nötrofil sayısının mortaliteye etkisi olmadığı saptandı. Nötropeni süresi uzaması, kandolaşım enfeksiyonu, kateter ilişkili kandolaşım enfeksiyonu ve pnömoni varlığı mortalite açısından risk faktörü olarak saptanmıştır.
Sonuç: CRP ve prokalsitonin değerlerinin mortalite göstergesi olarak değerlendirildiği çalışmamızda hem prognostik hem de tanısal olarak kullanılabileceği öngörülmüştür. Mortalitesi olan hastalarda dirençli gram-negatif mikroorganizmaların daha hakim olduğu saptanmış olup yeni tedavi algoritmalarının geliştirilmesi için daha çok çalışmaya gereksinim duyulmaktadır.

Anahtar kelimeler: Febril nötropeni, C-reaktif protein, prokalsitonin, mortalite.

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Introduction

Intensive and high-dose chemotherapy leads to infectious complications in cancer patients, posing significant challenges in clinical management. Bacterial and fungal infections are the primary causes of morbidity and mortality in these patients [1, 2]. Inflammation and infection often progress with subtle clinical signs and symptoms, making early detection difficult. In neutropenic patients, fever is frequently the sole manifestation of infection.

In 30-50% of patients, fever is attributed to infections classified as clinical or microbiological; however, the causative agent remains unidentified in the remaining cases. Therefore, there is a need for specific, highly effective, and rapid markers for early infection detection.

C-reactive protein (CRP) is frequently used for this purpose, as it serves as a key indicator of the inflammatory response to infection [3-5]. Additionally, procalcitonin has been reported to be useful in detecting bacterial infections in neutropenic patients [6].

This study aimed to assess the effectiveness of CRP and procalcitonin in the early detection of infection and mortality by comparing their quantitative values at the onset of febrile neutropenia (FN) and during treatment.

Materials and methods

A total of 572 patients who were followed up in the Hematology Clinic, Bone Marrow Transplantation Unit, and Medical Oncology Clinic for febrile neutropenia (FN) between September 3, 2018, and May 25, 2022, were included in the study. These patients experienced a total of 748 FN episodes.

This study was reviewed and approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (approval date: 24.02.2021, approval number: 2021-02/1045).

Patients with a single body temperature measurement of ≥38.3°C or a body temperature of ≥38.0°C persisting for more than one hour, along with an expected neutrophil count of ≤500 cells/mm³ or a neutrophil count falling below 500 cells/mm³ within 24-48 hours, were included in the study with a diagnosis of febrile neutropenia (FN).

Patient data were collected by reviewing the hospital information management system and recorded in a standardized form. The form included the following variables: name and surname, age, gender (female or male), underlying malignancy [hematological malignancy or solid organ tumor (with/without metastasis)], presence of comorbid diseases, specific comorbid conditions [diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD)], mortality status (yes or no), CRP and procalcitonin levels on days 0, 3, 5, 7, 10, 14, and 21, fever measurement, fever duration, duration of neutropenia, treatment duration, history of antibiotic use in the past three months (yes or no), blood culture growth (yes or no), identified pathogens in blood culture, and antibiogram results.

Statistical analysis

Statistical analyses were performed using the Statistical Program for Social Sciences (IBM SPSS Statistics 26.0) package program.

The normality of the data distribution was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk tests. In descriptive analyses, mean and standard deviation were used for continuous variables, while categorical variables were presented as frequencies and percentages. When parametric test assumptions were not met, the Mann-Whitney U test was applied for continuous data comparisons. For categorical data, Pearson's chi-square, Fisher's exact, or Fisher-Freeman-Halton tests were used to compare groups.

This study utilized advanced statistical and machine learning methods to identify predictors of mortality in patients with febrile neutropenia. Key variables, including fever duration, CRP change rate, neutropenia duration, and additional clinical factors such as blood culture results and comorbidities, were analyzed for their association with mortality. To conduct logistic regression analysis, CRP and procalcitonin values on days 7, 10, 14, and 21 were included for both mortality and non-mortality groups. Multiple imputation was applied to estimate missing values and standardize all measurements, as approximately half of the sample had missing data for these variables.

Statistical analyses, including boxplots and histograms, revealed significant differences in the distribution of key predictors between mortality and non-mortality groups. Machine learning models, such as Gradient Boosting and XGBoost, were evaluated for predictive performance, with the Random Forest model achieving the highest ROC-AUC score (0.86). All analyses were conducted using Python, with a significance threshold set at $p<0.05$.

Results

A total of 572 patients were included in the study. Hematological malignancies were identified in 348 patients (60.8%), while solid organ tumors were detected in 224 patients (39.2%). Among patients with hematological malignancies, 155 (44.5%) were female, and 193 (55.5%) were male. In the solid organ tumor group, 126 (56.25%) were female, and 98 (43.75%) were male.

In total, 748 febrile neutropenia (FN) episodes occurred among the 572 patients. Among those with hematological malignancies, the highest number of FN episodes was observed in patients with acute leukemia.

Mortality occurred in 118 patients (20.6%) during a febrile neutropenia (FN) episode. Patients were categorized into two groups: FN with mortality and FN without mortality. No significant differences were observed between the groups regarding age, underlying malignancy, presence of comorbidities, diabetes mellitus (DM), hypertension (HT), or chronic obstructive pulmonary disease (COPD) (Table 1).

The proportion of male patients was significantly higher in the mortality group than in the non-mortality group ($\chi^2=4.425$, $p=0.035$). Additionally, the presence of metastases in patients with solid organ malignancies was significantly more common in the mortality group compared to the non-mortality group ($\chi^2=7.308$, $p=0.007$). The prevalence of coronary artery disease (CAD) ($p<0.001$) and chronic renal failure (CRF) ($p=0.007$) was also significantly higher in the mortality group (Table 1).

CRP and procalcitonin values on days 0, 3, 5, 7, 10, 14, and 21 were significantly higher in the mortality group compared to the non-mortality group ($p<0.001$ for all) (Table 2).

Fever levels, fever duration, and neutropenia duration were significantly higher in the mortality group compared to the non-mortality group ($p<0.001$ for all). However, there was no significant difference between the groups in terms of treatment duration ($p=0.900$) (Table 3).

The rate of antibiotic use in the past three months was significantly higher in the mortality group than in the non-mortality group ($\chi^2=42.174$, $p<0.001$) (Table 3).

FN patients were categorized into two groups based on the presence or absence of bacterial growth in blood cultures. These groups were compared in terms of CRP and procalcitonin levels on days 0, 3, 5, 7, 10, 14, and 21.

Table 1. Comparison of socio-demographic characteristics and underlying diseases between groups

	FN group with mortality (N=118)	Non-mortality FN group (N=630)	Statistics	
			χ^2 or U	*p*
Age, mean (SD)	51.6 (16.8)	50.5 (16.3)	3601.0[1]	0.590
Gender, n (%)				
Female	46 (39.0%)	312 (49.5%)	4.425[2]	0.035*
Male	72 (61.0%)	318 (50.5%)		
Malignancy, n (%)				
Hematological malignancy	81 (68.6%)	422 (67.0%)	0.124[2]	0.724
Solid organ tumor	37 (31.4%)	208 (33.0%)		
With metastases	26 (22.0%)	96 (15.2%)	7.308[2]	0.007*
Without Metastases	11 (9.3%)	112 (17.7%)		
Comorbidity, n (%)	49 (41.5%)	235 (37.3%)	0.753[2]	0.386
Diagnosis of DM	31 (26.3%)	143 (22.7%)	0.711[2]	0.399
Diagnosis of HT	25 (21.2%)	150 (23.8%)	0.382[2]	0.537
Diagnosis of CAD	23 (19.5%)	45 (7.1%)	18.338[2]	<0.001*
Diagnosis of CRF	9 (7.6%)	15 (2.4%)	-[3]	0.007*
Diagnosis of COPD	5 (4.2%)	20 (3.2%)	-[3]	0.575
None	69 (58.5%)	395 (62.7%)		

FN: febrile neutropenia, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease CRF: chronic renal failure COPD: chronic obstructive pulmonary disease, 1- Mann-Whitney U, 2- Pearson Chi-Square, 3 Fisher Exact Test; *p<0.05

Table 2. Comparison of CRP and procalcitonin values between groups

	FN group with mortality	Non-mortality FN group	Statistics	
	Mean. (SD)		U[1]	*p*
CRP (mg/L)				
(n=118-630)	201.3 (118.5)	149.5 (89.9)	27548.5	<0.001*
Day 3 (n=103-622)	204.3 (108.8)	115.6 (83.4)	16291.5	<0.001*
Day 5 (n=87-543)	187.4 (72.4)	76.5 (72.4)	8748.0	<0.001*
Day 7 (n=75-462)	187.9 (106.0)	56.5 (63.8)	4752.0	<0.001*
Day 10 (n=60-333)	214.0 (121.0)	45.6 (60.0)	1862.5	<0.001*
Day 14 (n=43-175)	216.6 (121.6)	39.8 (55.6)	491.0	<0.001*
Day 21 (n=25-32)	216.5 (80.7)	32.1 (30.3)	6.0	<0.001*
Procalsitonin (mcg/L)				
Day 0 (n=106-489)	15.4 (25.7)	6.4 (15.0)	17817.0	<0.001*
Day 3 (n=77-409)	19.1 (32.2)	4.5 (12.5)	8236.5	<0.001*
Day 5 (n=68-339)	11.3 (21.6)	2.2 (7.7)	5698.5	<0.001*
Day 7 (n=59-293)	13.8 (25.0)	0.6 (1.5)	3160.5	<0.001*
Day 10. (n=45-187)	19.8 (42.5)	0.3 (1.1)	889.5	<0.001*
Day 14 (n=37-112)	12.5 (20.9)	0.3 (1.3)	173.0	<0.001*
Day 21 (n=22-19)	21.9 (26.3)	0.1 (0.1)	0.0	<0.001*

FN: febrile neutropenia, CRP: C-reactive protein, 1- Mann-Whitney U; *p<0.05

Table 3. Comparison of the groups in terms of fever value, duration of fever, duration of neutropenia, duration of treatment and antibiotic use in the last three months

	FN group with mortality	Non-mortality FN group	Statistic	
			χ^2 veya U	*p*
Fever (ºC), mean. (SD)	39.1 (0.4)	38.7 (0.3)	20923.0[1]	<0.001*
Duration of fever (days), mean. (SD)	6.7 (5.7)	2.2 (1.6)	12421.5[1]	<0.001*
Neutropenia duration, mean. (SD)	9.0 (7.4)	4.4 (3.8)	22433.5[1]	<0.001*
Duration of treatment, mean. (SD)	11.4 (7.9)	10.4 (4.8)	36902.0[1]	0.900
Antibiotic use in the last three months, n (%)				
Yes	92 (78%)	286 (45.4%)	42.174[2]	<0.001*
No	26 (22%)	344 (54.6%)		

FN: febrile neutropenia, 1- Mann Whitney U, 2- Pearson Chi-Square; *p<0.05

CRP values were significantly higher in the FN group with blood culture growth compared to the FN group without growth on days 0 (p<0.001), 3 (p<0.001), 5 (p<0.001), 10 (p=0.037), and 14 (p=0.022). However, no significant difference was observed between the groups for CRP values on days 7 (p=0.129) and 21 (p=0.598) (Table 4).

Procalcitonin values were significantly higher in the FN group with blood culture growth compared to the group without growth on days 0 (p<0.001), 3 (p<0.001), 5 (p<0.001), 7 (p=0.001), and 21 (p=0.047). However, no significant difference was observed between the groups in terms of CRP values on days 10 (p=0.617) and 14 (p=0.332) (Table 4).

When comparing microorganisms identified in blood cultures, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, coagulase-negative *Staphylococci*, *Enterococcus faecium*, and *Candida albicans* were found at significantly higher rates in the FN group with mortality than in the FN group without mortality (χ^2=51.334, p<0.001) (Table 5).

The presence of at least one antibiotic-resistant microorganism in blood cultures was significantly higher in the FN group with mortality compared to the FN group without mortality (χ^2=4.093, p=0.043) (Table 6).

Subsequently, CRP and procalcitonin values on days 0, 3, 7, 14, and 21, which significantly predicted mortality, were analyzed using the backward conditional method. The most significant model identified CRP on days 3, 10, 14, and 21, and procalcitonin on days 0, 5, 10, and 21 as key predictors. The obtained model was statistically significant (p<0.001) and explained 53.4% of the variance in mortality outcomes (R^2=0.534).

The Random Forest algorithm was used to determine the relative importance of variables in predicting mortality. The top predictors identified were fever duration (25%), CRP change rate (15%), and neutropenia duration (13%). Additional variables, including CRP levels, procalcitonin levels, blood culture results indicating resistant Gram-negative bacteria (7%), comorbidities (6%), and prior antibiotic use (5%), also demonstrated significant associations with increased mortality risk. Age (4%) and male sex (3%) contributed relatively less but remained consistent predictors of mortality (Table 7, Figure 1).

Table 4. Comparison of CRP and procalcitonin values according to the growth status in blood culture of the groups

	FN group with growth in blood culture	FN group without growth in blood culture	Statistic	
	Mean. (SD)		U[1]	*p*
CRP (mg/L)				
Day 0 (n=475-273)	175.5 (90.5)	147.5 (98.9)	50689.0	<0.001*
Day 3 (n=461-264)	157.0 (98.4)	111.7 (85.2)	43194.5	<0.001*
Day 5 (n=385-245)	110.5 (95.3)	79.9 (80.2)	36285.5	<0.001*
Day 7 (n=306-231)	77.5 (84.9)	72.7 (83.8)	32637.5	0.129
Day 10. (n=205-188)	66.0 (96.5)	76.2 (92.6)	16929.5	0.037*
Day 14 (n=109-109)	66.1 (99.3)	83.2 (103.5)	4873.0	0.022*
Day 21 (n=29-28)	123.8 (115.2)	102.3 (103.1)	373.0	0.598
Procalcitonin (mcg/L)				
Day 0 (n=354-241)	13.5 (22.8)	4.3 (11.8)	25694.5	<0.001*
Day 3 (n=281-205)	11.0 (23.5)	3.7 (11.6)	17285.0	<0.001*
Day 5 (n=236-171)	5.2 (13.7)	2.6 (10.0)	14445.5	<0.001*
Day 7 (n=188-164)	4.2 (15.1)	1.6 (6.4)	12232.0	0.001*
Day 10 (n=118-114)	6.2 (27.1)	2.1 (9.0)	6470.5	0.617
Day 14 (n=72-77)	2.9 (9.1)	3.8 (13.9)	2516.5	0.332
Day 21 (n=19-22)	19.4 (27.7)	3.0 (5.1)	133.0	0.047*

FN: febrile neutropenia, CRP: C-reactive protein,1- Mann Whitney U; *p<0.05

Table 5. Comparison of pathogens grown in blood culture between groups

Blood culture	FN group with mortality (N=66)	Non-mortality FN group (N=207)	Statistic	
	n (%)		(χ^2)[1]	*p*
Escherichia coli	23 (34.8%)	100 (48.3%)		
Klebsiella pneumoniae	14 (21.2%)	29 (14.0%)		
Pseudomonas aeruginosa	9 (13.6%)	6 (2.9%)		
Acinetobacter baumannii	6 (9.1%)	2 (1.0%)		
Stenotrophomonas maltophilia	0 (0.0%)	1 (1.5%)		
Coagulase negative staphylococci	4 (6.1%)	53 (25.6%)		
Staphylococcus aureus	2 (3.0%)	6 (2.9%)	51.334	<0.001*
Enterococcus faecium	3 (4.5%)	1 (0.5%)		
Streptococcus pyogenes	0 (0.0%)	1 (0.5%)		
Candida albicans	3 (4.5%)	0 (0.0%)		
Candida krusei	1 (1.5%)	1 (0.5%)		
Burkholderia cepacia	0 (0.0%)	1 (0.5%)		
Enterobacter cloacae	0 (0.0%)	6 (2.9%)		

FN: febrile neutropenia, 1 Fisher-Freeman-Halton Test; *p<0.05

Table 6. Comparison of the presence of resistant microorganisms in blood culture between groups

	FN group with mortality	Non-mortality FN group	Statistic	
	n (%)		$(\chi^2)^1$	*p*
Resistant microorganism in blood culture	41 (62.1%)	99 (47.8%)	4.093	0.043*

FN: febrile neutropenia, 1 Pearson Chi-Square; *: $p<0.05$

Table 7. Comprehensive predictor summary table for mortality

Predictor	Impact on Mortality	Relative Importance (Random Forest)
Fever Duration	Longer fever duration is associated with higher mortality risk	25
CRP Change Rate	Slower reductions or increases in CRP levels indicate higher mortality risk	15
Neutropenia Duration	Prolonged neutropenia duration increases the risk of mortality	13
CRP	Elevated CRP levels are associated with higher mortality	10
Procalcitonin	Higher procalcitonin levels are linked to severe infections and mortality	8
Blood Culture Results	Presence of resistant Gram-negative bacteria increases mortality risk	7
Comorbidities	Chronic comorbidities, such as diabetes or chronic kidney disease, are associated with higher mortality	6
Prior Antibiotic Use	Prior antibiotic use within three months increases the likelihood of resistant infections and mortality	5
Age	Older age is associated with higher mortality risk	4
Gender	Male sex is linked to increased mortality risk	3

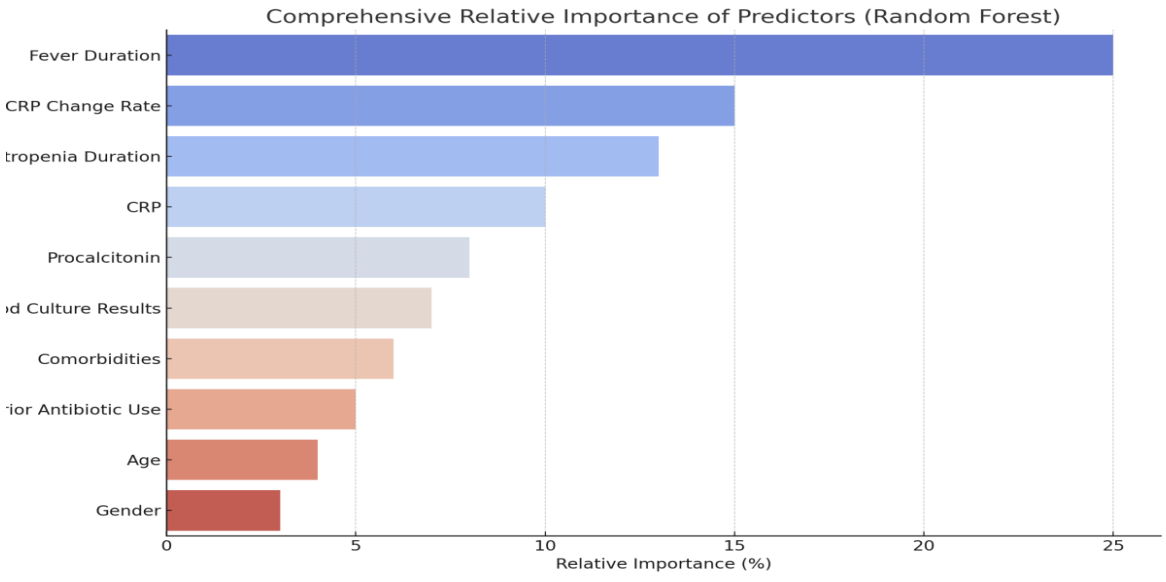

Figure 1. Relative importance of predictors (Random Forest)

Discussion

Among all patients, 20.6% (118) died due to FN. The mortality rate was 16.5% (37) among patients with solid organ tumors and 23.3% (81) among those with hematological malignancies.

In a multicenter study by Kuderer et al. [7], the mortality rate was reported as 11% among 55,276 FN patients. Similarly, Ghosh et al. [8] found an FN-related mortality rate of 19.5% in patients with hematological malignancies. In contrast, Du et al. [9] reported a lower mortality rate of 4.6%, while Hatamabadi et al. [10], in a study focusing on patients with solid organ tumors, found a mortality rate of 5.3%. The variability in mortality rates observed in this study and the literature is likely influenced by factors such as malignancy type, chemotherapy regimens, comorbid conditions, and the specific microorganisms identified in culture.

In this study, male gender, coronary artery disease (CAD), and chronic renal failure (CRF) were found to be significant predictors of FN-related mortality. In a study by Hatamabadi et al. [10], advanced age and the presence of additional comorbidities were associated with increased mortality; however, gender was not found to be a significant factor. Kuderer et al. [7] reported that the presence of comorbidities increased mortality by 2.8%. Similarly, in a study by Lyman et al. [11] involving 5,990 FN patients, being over 65 years of age and having comorbid conditions were significant predictors of mortality. Additionally, Hosmer et al. [12] found that age over 65, as well as the presence of CAD, CRF, and COPD, were associated with increased mortality risk. While comorbidities alone may not directly impact mortality, the findings of this study suggest that they are strongly associated with mortality in elderly patients.

This study found that CRP and procalcitonin levels were consistently elevated on all measured days in the FN group with mortality. In a study by Reyes Mondragon et al. [13], a procalcitonin level above 0.46 ng/mL was identified as an effective predictor of septic shock and mortality. Additionally, CRP has been recognized as an important prognostic marker in FN patients [14]. A study investigating the etiology of fever in patients with hematological malignancies in northern India reported that elevated CRP was a better predictor than procalcitonin for malignancy-related fever [15]. Conversely, in a study conducted on FN patients admitted to the emergency department, procalcitonin was found to be a superior predictor of mortality compared to CRP [16]. Similarly, the findings of this study indicate that both CRP and procalcitonin levels were significantly higher in the FN group with mortality, reinforcing their prognostic value.

Prolonged neutropenia in FN episodes increases the risk of complications. In previous studies, the mean duration of neutropenia was reported as 12 days in FN cases with mortality in one study and 15 days in another [17, 18]. In this study, the mean duration of neutropenia in the mortality group was found to be nine days. In contrast, one study reported a shorter mean neutropenia duration of 3.3 days in the mortality group [19]. However, the same study found that prolonged neutropenia was significantly associated with increased mortality risk [19]. Similarly, in this study, the duration of neutropenia was longer in the FN group with mortality, reinforcing its role as a critical factor in patient outcomes.

In a study by Mert et al. [17], prolonged antibiotic therapy was not found to be a significant factor in mortality; however, antibiotic use in the last three months was significantly higher in the mortality group. Similarly, in this study, the duration of antibiotic therapy was not associated with mortality, whereas prior antibiotic use in the last three months was significantly more common in the FN group with mortality.

In this study, the presence of bloodstream infections was significantly higher in FN patients who did not survive. Similarly, a study involving 85 patients who underwent bone marrow transplantation found bloodstream infections to be a significant predictor of mortality [20]. In a study conducted in Lebanon covering 177 FN episodes between 1995 and 2001, the risk of mortality was reported to be higher in patients with positive blood culture results [21]. Another study also indicated that mortality rates were elevated in patients with confirmed bloodstream infections [22]. Additionally, Feld et al. [23] highlighted the high mortality rate associated with bloodstream infections and emphasized the need for new treatment strategies.

In this study, CRP levels measured on days 0, 3, and 5 were found to be higher in the group with positive blood culture growth. Similarly, procalcitonin levels were significantly elevated in the same group on days 0, 3, 5, and 7. In a study by Ruokonen et al. [6], procalcitonin was reported to be a specific marker in febrile neutropenic episodes; however, it was not considered a highly sensitive marker for detecting infections.

One study reported that serum CRP levels were more sensitive than procalcitonin in detecting bacteremia; however, its specificity was low [24]. Another study found that CRP levels were higher than procalcitonin in cases of neutropenic fever of unknown origin [15]. Additionally, a separate study suggested that the combined use of procalcitonin and lectin-binding protein may have diagnostic value in detecting bacteremia [25]. In this study, the observation that CRP and procalcitonin levels were elevated in patients with bacteremia during the early days of FN episodes suggests their potential diagnostic utility in predicting bacteremia.

Escherichia coli was the most frequently isolated pathogen in blood cultures, followed by *Klebsiella pneumoniae*. The prevalence of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Candida albicans* was significantly higher in the mortality group. Similarly, in a study by Wang et al. [20] investigating FN episodes, *E. coli* was the most commonly identified pathogen in blood cultures. Another study conducted in FN patients also reported *E. coli* as the most abundant microorganism [26]. Additionally, a separate study found that *A. baumannii*, *Enterococcus* spp., and *C. albicans* were associated with higher mortality rates [27]. In a multicenter study, *P. aeruginosa* bacteremia was reported to have the highest mortality rate among patients with hematological malignancies and was linked to poor prognosis [28]. Furthermore, in a study examining FN episodes in 589 acute leukemia patients, *E. coli* was the most frequently detected pathogen in blood cultures [29]. The same study also found that *P. aeruginosa* and *Enterococcus* spp. were associated with higher mortality rates [29].

In this study, high resistance rates to carbapenem and other antibiotic groups were observed among all microorganisms isolated from blood cultures. Consequently, treatment failure and mortality rates were significantly higher in patients with resistant bacterial infections.

This study provides valuable insights into the predictors of mortality in febrile neutropenia patients by integrating machine learning methods with clinical variables. The Random Forest model identified fever duration, CRP change rate, and neutropenia duration as the most significant factors in mortality risk stratification [4, 7].

Fever duration emerged as the strongest predictor of mortality, with prolonged fever indicating poor infection control and an increased risk of adverse outcomes [1, 7]. Similarly, the CRP change rate was identified as a crucial marker of treatment response, with slower reductions or persistent increases in CRP levels being strongly associated with mortality [4, 6]. Regular monitoring of CRP levels may facilitate the early identification of high-risk patients, allowing for timely intervention [3, 5].

Neutropenia duration, as an indicator of ongoing immunosuppression, was identified as another key predictor of mortality. Longer durations were associated with increased complications and mortality, underscoring the need for targeted interventions in high-risk patients [8, 13]. Additionally, blood culture results-particularly the presence of resistant Gram-negative bacteria-were strongly linked to mortality. This finding highlights the critical importance of implementing targeted antibiotic therapies based on local microbiological profiles to improve patient outcomes [20, 21].

Comorbidities such as diabetes and chronic kidney disease, along with prior antibiotic use within the last three months, were associated with an increased risk of mortality [11, 19]. Additionally, age and male sex were identified as moderate predictors, supporting their inclusion in risk assessment models [12, 22].

The Random Forest model demonstrated superior performance compared to other models, providing balanced predictions and

a clear ranking of variable importance [2, 9]. This study highlights the potential of machine learning models in integrating clinical and microbiological variables to enhance mortality prediction in febrile neutropenia patients. However, validation through larger datasets and prospective studies is essential to ensure the generalizability and accuracy of these findings.

Strengths and limitations of the study

One of the key strengths of this study is its large sample size, with a total of 748 FN episodes analyzed. CRP and procalcitonin levels, fever measurements and duration, neutropenia duration, treatment duration, and blood culture results were systematically evaluated on days 0, 3, 5, 7, 14, and 21.

The primary limitation of this study is its retrospective design, which prevented precise determination of the exact day of mortality during FN episodes. More consistent and generalizable findings could be achieved through prospective studies that specifically assess mortality timing in this context.

In conclusion, CRP and procalcitonin levels were found to be significantly higher during the first five days of FN episodes in the mortality group, suggesting their potential utility as prognostic markers. However, their specific predictive value for mortality remains uncertain. Instead, their sequential decline following treatment may serve as an indicator of treatment response, while persistently elevated or increasing levels in the following days may help predict mortality.

Additionally, CRP and procalcitonin demonstrated diagnostic value in FN episodes, beyond their prognostic role. Notably, CRP and procalcitonin levels measured within the first five days were significantly higher in cases of bacteremia, further supporting their use in clinical decision-making.

In this study, the bacteremia rate was 36.5%, with *Escherichia coli* being the most frequently isolated microorganism. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were identified in the blood cultures of patients in the mortality group, all exhibiting multidrug resistance. A notable increase in Gram-negative bacterial infections was observed during FN episodes.

To optimize treatment strategies, healthcare facilities should routinely monitor local microorganism profiles and antibiotic resistance patterns, ensuring that empirical antibiotic therapy is updated accordingly. Identifying risk factors for mortality in FN episodes will contribute to the development of more effective treatment protocols. Further studies are needed to refine these protocols based on evolving clinical conditions, pathogen profiles, and antibiogram patterns.

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