Research Article

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Area of Expertise: Infectious Diseases

Title: Evaluation of c-reactive protein and procalcitonin as a mortality indicator in febrile neutropenic patients.

Short title: C-reactive protein and procalcitonin in FN.

Abstract

Purpose: Febrile neutropenia (FN) develops as a side effect of chemotherapeutics in cancer patients. It causes complications, increased cost, and mortality. Microbiological agents can be detected in 30-50% of FN. Therefore, specific, highly effective, and rapid markers that can indicate infection are needed. Various biomarkers are under investigation and are still in use today. In this study, it was aimed to evaluate their effectiveness in early detection of infection and mortality by comparing quantitative C-reactive protein (CRP) and procalcitonin values at the beginning of FN and during treatment.

Material and methods: This research is a retrospective, case-control study. The study included 572 FN patients who were followed up in the Hematology Clinic, Bone Marrow Transplantation Unit and Medical Oncology Clinic between 3 September 2018 and 25 May 2022. 748 FN attacks developed in these patients. The hospital information management system was analysed, and the data of the patients were recorded in the pre-prepared form. Data were analysed using 'The Package for Social Sciences 26.0' statistical program.

Results: 49.1% of FN cases were female and 50.9% male. Hematological malignancy was detected in 60.8% of the patients. Mortality developed in 118 (20.6%) patients. The rate of bacteremia in FN attacks was 36.5%. The most common causative microorganism was *Escherichia coli*. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were more common in patients with mortality. CRP and procalcitonin values in the first five days of treatment were higher in patients with bacteremia and mortality. Prolonged neutropenia and bloodstream infection were found to be risk factors for mortality.

Conclusion: It has been observed that CRP and procalcitonin values can be used both prognostically and diagnostically. It was found that resistant Gram-negative bacteria growth was higher in blood cultures of patients with mortality. More studies are needed to develop new treatment algorithms.

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

Makale başlığı: Febril nötropenik hastalarda c-reaktif protein ve prokalsitoninin mortalite göstergesi olarak değerlendirilmesi.

Kısa başlık: Febril nötropenide c-reaktive protein ve prokalsitonin.

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.

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 oranu %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.

Introduction

Intensive and high-dose chemotherapy causes infectious complications in cancer patients. These infections emerge as difficult problems to solve. The cause of morbidity and mortality is usually bacterial and fungal infections [1, 2]. Inflammation and infection progress with subtle clinical signs and symptoms. Fever is often the only manifestation of infection in neutropenic patients.

While the cause of fever in 30-50% of the patients is infections defined as clinical or microbiological, the causative agent cannot be determined in the remainder. Therefore, there is a need for specific, highly effective and rapid markers to detect infection early.

Therefore, CRP is used frequently. It is an important indicator of the inflammatory response to infection [3-5]. It has been reported that procalcitonin can also be used in the detection of bacterial infections in neutropenic patients [6].

In this study, it was aimed to evaluate their effectiveness in early detection of infection and mortality by comparing quantitative CRP and procalcitonin values at the onset of febrile neutropenia (FN) and during treatment.

Materials and methods

572 patients who were followed up in Hematology Clinic and Bone Marrow Transplantation Unit and Medical Oncology Clinic between 3 September 2018 and 25 May 2022 due to FN were included in the study. A total of 748 FN attacks developed in these patients.

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

Patients with a single measurement body temperature ≥38.3°C or a body temperature ≥38.0°C for more than one hour and whose neutrophil count is expected to be ≤500 cells/mm^3 or below 500 cells/mm^3 within 24-48 hours are to be included in the study with the diagnosis of FN were taken.

The data of the patients were recorded in the form by scanning the hospital information management system. In the format; name-surname, age, gender (female, male), underlying malignancy [hematological malignancy, solid organ tumor (with/without metastasis)], comorbid disease (present or absent), comorbid disease [diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), chronic kidney failure (CKD), chronic obstructive pulmonary disease (COPD)], mortality (yes, no), 0^{th}, 3^{rd}, 5^{th}, 7^{th}, 10^{th}, 14^{th} CRP and procalcitonin values on days 1 and 21, fever value, duration of fever, duration

of neutropenia, duration of treatment, antibiotic use in the last three months (yes, no), growth in blood culture (yes, no), pathogens grown 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 conformity of the data to the normal distribution was evaluated with Kolmogorov-Smirnov or Shapiro-Wilks tests. Mean and standard deviation for data specified by measurement in descriptive analyses; Number and percentage were used for qualitative variables. The Mann-Whitney U test was used when the parametric test assumptions were not met in the evaluation of the data specified by the measurement. Pearson chi-square, Fisher Exact or Fisher-Freeman-Halton tests were used to compare the counted data between groups.

The study employed advanced statistical and machine learning methods to evaluate mortality predictors in febrile neutropenia patients. Key predictors, including fever duration, CRP change rate, neutropenia duration, and additional clinical variables such as blood culture results and comorbidities, were analyzed for their association with mortality.

Statistical tests, including boxplots and histograms, illustrated significant differences in the distribution of these predictors between mortality and non-mortality groups. Machine learning models, such as Gradient Boosting and XGBoost, were compared for predictive performance, with the Random Forest model achieving the highest ROC-AUC score (0.86). Analyses were performed using Python, with $p<0.05$, $p<0.05$, $p<0.05$ set as the threshold for statistical significance.

Results

572 patients were included in the study. Hematological malignancy was found in 348 (60.8%) patients, and solid organ tumor was detected in 224 (39.2%) patients. Of the patients with hematological malignancy, 155 (44.5%) were female and 193 (55.5%) were male. Of the patients with solid organ tumors, 126 (56.25%) were female and 98 (43.75%) were male. A total of 748 FN attacks developed in five hundred and seventy-two patients. Among the patients with hematological malignancy, the most FN attacks were detected in patients with acute leukemia.

Mortality developed in 118 (20.6%) patients during FN attack. Patients were compared as FN group with mortality and FN group without mortality. There was no significant difference between the groups in terms of age, underlying malignancy, presence of comorbidity, DM, HT and COPD (Table 1).

The normal distribution of variables measured numerically, such as CRP, procalcitonin, age, fever, fever duration, duration of neutropenia, febrile neutropenia duration, and IV antibiotic therapy duration, was evaluated in both mortality and non-mortality groups using the Kolmogorov-Smirnov or Shapiro-Wilk test. If the sample size was above 50, the Kolmogorov-Smirnov test was used; if below 50, the Shapiro-Wilk test was used. Additionally, CRP and procalcitonin values were similarly evaluated for normality in groups with positive and negative blood cultures. The analysis results indicated that the significance value (p) of all numerically measured variables mentioned above was below 0.05 in at least one group, indicating that the data did not show normal distribution. Therefore, non-parametric tests (Mann-Whitney U) were used (Table 7, 8).

To perform logistic regression analysis, including CRP and procalcitonin values on days 7, 10, 14, and 21 in mortality and non-mortality groups, multiple imputation was used to estimate missing values and calculate standardized equivalents of all values, as these values were missing in half of the sample. 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 was found to be CRP on days 3, 10, 14, and 21 and procalcitonin on days 0, 5, 10, and 21. The *p*-value of the obtained model was <0.001, explaining 53.4% of the sample (R-squared=0.534).

The male sex ratio was found to be significantly higher in the mortality group than in the non-mortality group (χ^2=4.425, *p*=0.035). The presence of metastases in patients with solid organ malignancy in the mortality group was significantly higher than in the non-mortality group (χ^2=7.308, *p*=0.007). The rates of chronic arterial disease (CAD) and chronic renal failure (CRF) in the mortality group were found to be significantly higher than in the non-mortality group (*p*<0.05) (Table 1).

CRP and procalcitonin values at days 0, 3, 5, 7, 10, 14 and 21 were found to be significantly higher in the mortality group than in the non-mortality group (*p*<0.001) (Table 2).

Fever value, duration of fever and duration of neutropenia were found to be significantly higher in the mortality group than in the non-mortality group (*p*<0.001). There was no significant difference between the groups in terms of treatment duration (*p*>0.050) (Table 3).

Antibiotic use in the last three months was found to be significantly higher in the mortality group than in the non-mortality group (χ^2=42.174, *p*<0.001) (Table 3).

FN patients were divided into two groups as those with and without growth in blood culture. These groups were compared in terms of CRP and procalcitonin levels on days 0, 3, 5, 7, 10, 14 and 21. CRP values at 0, 3, 5, 10 and 14 days were found to be significantly

higher in the FN group with growth in blood culture than in the FN group without growth in blood culture (p<0.050). When the CRP values on the seventh and 21st days were compared, no significant difference was found between the groups (p>0.050) (Table 4).

Procalcitonin values at 0, 3, 5 and 7 days were found to be significantly higher in the FN group with growth in blood culture than in the group without growth in blood culture (p<0.050). There was no significant difference between the groups in terms of CRP values on the tenth, 14th and 21st days (p>0.050) (Table 4).

When the factors reproduced in the blood culture were compared, the rates of *Pseudomonas aeruginosa, Acinetobacter baumannii*, coagulase negative staphylococci, *Enterococcus faecium* and *Candida albicans* were found to be significantly higher in the FN group with mortality compared to the FN group without mortality (χ^2=51,334, p<0.001) (Table 5).

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

The Random Forest algorithm was used to determine the relative importance of variables. Fever duration (25%), CRP change rate (15%), and neutropenia duration (13%) were identified as the top predictors of mortality. 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%) showed relatively lower but consistent contributions to mortality prediction (Table 7, Figure 1).

Discussion

20.6% (118) of all patients died due to FN. 16.5% (37) of patients with solid organ tumors and 23.3% (81) of patients with hematological malignancies died due to FN. In a multicenter study by Kuderer et al. [7], the mortality rate was reported as 11% in 55,276 FN patients. In a study by Ghosh et al. [8], the mortality rate due to FN was found to be 19.5% in patients with hematological malignancies. In a study by Du et al. [9], the mortality rate was found to be 4.6%. In a study by Hatamabadi et al. [10], in which patients with solid organ tumors were weighted, the mortality rate was found to be 5.3%. In this study and in the literature, it is thought that the varying mortality rates vary depending on the types of malignancy, chemotherapy regimens given, comorbid diseases, and microorganisms grown in culture.

In this study, male gender, CAD and CRF were found to be significant in terms of FN-related mortality. In a study by Hatamabadi et al. [10], advanced age and the presence of

additional comorbidities were found to be associated with mortality, but not with gender. In the study of Kuderer et al. [7], it was reported that comorbidity increased mortality by 2.8%. In a study by Lyman et al. [11] including 5,990 FN patients, being over 65 years old and the presence of comorbidity were found to be significant in terms of mortality. In a study by Hosmer et al. [12], patients were over 65 years of age and the presence of CAD, CRF and COPD was found to be significant in terms of mortality]. Comorbidity alone does not affect mortality. In this study, it was thought that comorbidity was associated with mortality in elderly patients.

In the study, it was determined that CRP and procalcitonin values were high on all days in the FN group with mortality. In a study by Mondragon et al. [13], it was stated that a procalcitonin value higher than 0.46 ng/mL was effective in predicting septic shock and mortality. In a study, CRP was found to be an important prognostic marker in FN patients [14]. In a study investigating the etiology of fever in patients with hematological malignancies in northern India, it was reported that high CRP was a better predictor than procalcitonin in predicting fever of malignancy [15]. In a study conducted in patients admitted to the emergency department with FN, it was reported that procalcitonin was a better predictor of mortality than CRP [16]. Similarly, in this study, CRP and procalcitonin values were found to be higher in the FN group with mortality.

Prolongation of neutropenia in FN attacks increases the risk of complications. The mean duration of neutropenia was found to be 12 days in cases with mortality in one of the two studies and 15 days in the other [17, 18]. In this study, the mean duration of neutropenia in the mortality group was found to be nine days. In a study, the mean duration of neutropenia was 3.3 days in the group with mortality [19]. Prolongation of neutropenia was found to be associated with mortality [19]. In this study, the duration of neutropenia was found to be longer in the FN group with mortality.

In a study by Mert et al. [17], prolonged antibiotic therapy was not found to be significant in terms of mortality, but antibiotic use in the last three months was found to be significantly higher. In this study, the duration of antibiotic therapy was not found to be significant in terms of mortality. Antibiotic use in the last three months was found to be significantly higher in the FN group with mortality.

In this study, it was found to be significantly higher in FN patients with reproductive mortality in blood culture. In a study involving 85 patients with bone marrow transplantation, bloodstream infection was found to be significant in terms of mortality [20]. In a study covering 177 FN attacks between 1995 and 2001 in Lebanon, it was reported that the risk of mortality was higher in patients with growth in blood culture [21]. In one study, it was stated that the mortality rate was higher in those with proven bloodstream infections [22].

In a study by Feld et al. [23], it was stated that the mortality rate is high in patients with bloodstream infections and that new treatments are needed.

In this study, the CRP value was 0th, 3rd, 5th. It was found to be higher in the group with growth in blood culture on days. The procalcitonin value was found to be higher in the group with growth in blood culture on the 0^{th}, 3^{rd}, 5^{th} and 7^{th} days. In a study by Ruokonen et al. [6], it was reported that procalcitonin is specific in febrile neutropenic attacks, but it is not a sensitive marker of infection.

In a study, it was reported that serum CRP levels were more sensitive than procalcitonin in demonstrating bacteremia, but its specificity was low [24]. In another study, it was reported that the CRP value was higher than procalcitonin in neutropenic fever of unknown origin [15]. In another study, it was reported that the use of procalcitonin together with lectin-binding protein may have a diagnostic value in demonstrating bacteremia [25]. In this study, the fact that CRP and procalcitonin values were higher in patients with bacteremia in the first days of FN attack suggested that they could be used diagnostically in predicting bacteremia.

Escherichia coli was the most abundant pathogen in blood cultures. This was followed by *Klebsiella pneumoniae*. The rates of *P. aeruginosa*, *A. baumannii* and *C. albicans* were found to be significantly higher in the mortality group. In a study by Wang et al. [20] in which FN attacks were examined, *E. coli* grew the most in blood cultures. In a study conducted with FN patients, the most abundant microorganism in blood culture was *E. coli* [26]. In another study, *A. baumannii*, *Enterococcus* spp. and *C. albicans* have been reported to have a higher mortality rate [27]. In a multicenter study, it was reported that *P. aeruginosa* bacteremia caused the highest number of deaths in patients with hematological malignancies and had a poor prognosis [28]. In another study, it was reported that *E. coli* was the most reproducing microorganism in blood culture in FN attacks of 589 acute leukemia patients [29]. *P. aeruginosa* and *Enterococcus* spp. mortality was found to be higher in patients who reproduced [29].

In this study, the rate of resistance to carbapenem group and other antibiotics was found to be high in all microorganisms grown in blood culture. Therefore, treatment failure and mortality rates were found to be high in the group with resistant bacteria in blood culture.

This study provides important insights into the predictors of mortality in febrile neutropenia patients, 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 durations indicating poor infection control and increased risk (1, 7). Similarly, CRP change rate was found to be an important marker of treatment response, with slower reductions or increases in CRP levels strongly associated with mortality (4, 6). Regular monitoring of CRP levels may enhance early identification of high-risk patients (3, 5).

Neutropenia duration, reflecting ongoing immunosuppression, was another key predictor. Longer durations were associated with higher complications and mortality, highlighting 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, emphasizing the importance of targeted antibiotic therapies based on local microbiological profiles (20, 21).

Comorbidities such as diabetes and chronic kidney disease, along with prior antibiotic use within the last three months, further increased mortality risk (11, 19). Age and male sex were also identified as moderate predictors, supporting their inclusion in risk assessment models (12, 22).

The Random Forest model demonstrated superior performance, with balanced predictions and a clear ranking of variable importance, compared to other models (2, 9). This study underscores the potential of machine learning models to integrate clinical and microbiological variables to improve mortality prediction in febrile neutropenia patients. However, validation through larger datasets and prospective studies is essential to ensure generalizability and accuracy.

Strengths and weaknesses of the study

One of the strengths of the study is the sample size. A total of 748 FN attacks were examined. CRP and procalcitonin values, fever value and duration, duration of neutropenia, duration of treatment and blood cultures of the patients on days 0, 3, 5, 7, 14 and 21 were evaluated.

The most important limitation of the study is that it is retrospective. It could not be determined on which day of the FN attacks mortality occurred in the patients. More consistent and generalizable results will be obtained by evaluating mortality times with prospective studies in this area.

In conclusion this study, CRP and procalcitonin values were found to be statistically higher in the first five days of FN attacks in the mortality group. This suggests that CRP and procalcitonin can be used as prognostic markers.

It is not considered likely that CRP and procalcitonin will provide a specific value in predicting mortality. However, the reduction in consecutive days after treatment is useful

for evaluating treatment continuity. CRP and procalcitonin levels that remain at the same level or increase in the following days of treatment may be useful in predicting mortality. In the study, it was shown that CRP and procalcitonin may have diagnostic value in addition to their prognostic value in FN attacks. CRP and procalcitonin values measured in the first five days were found to be significantly higher in demonstrating bacteremia.

In the study, the rate of bacteremia was 36.5% and the most reproduced microorganism was *E. coli. P. aeruginosa* and *A. baumannii* were grown in the blood cultures of the patients in the mortality group. Multi-drug resistance was found in all these pathogens. An increase in the frequency of Gram-negative bacterial infections was detected in FN attacks. In order to better manage the treatment, each center should know its own microorganism profiles and antibiotic susceptibility and update the empirical antibiotic therapy options accordingly.

Identification of risk factors for mortality in FN attacks will contribute to the development of treatment protocols. More studies are needed to update treatment protocols according to variable clinical conditions, agent and antibiogram spectrum.

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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 (%)			4.425[2]	0.035
Female	46 (39.0%)	312 (49.5%)		
Male	72 (61.0%)	318 (50.5%)		
Malignancy, n (%)			0.124[2]	0.724
Hematological malignancy	81 (68.6%)	422 (67.0%)		
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

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

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 (^{0}C), 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 (%)			42.174[2]	<0.001
Yes	92 (78%)	286 (45.4%)		
No	26 (22%)	344 (54.6%)		

FN: febrile neutropenia, 1 Mann Whitney U, 2 Pearson Chi-Square

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

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%)	51.334	<0.001
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%)		
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

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

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

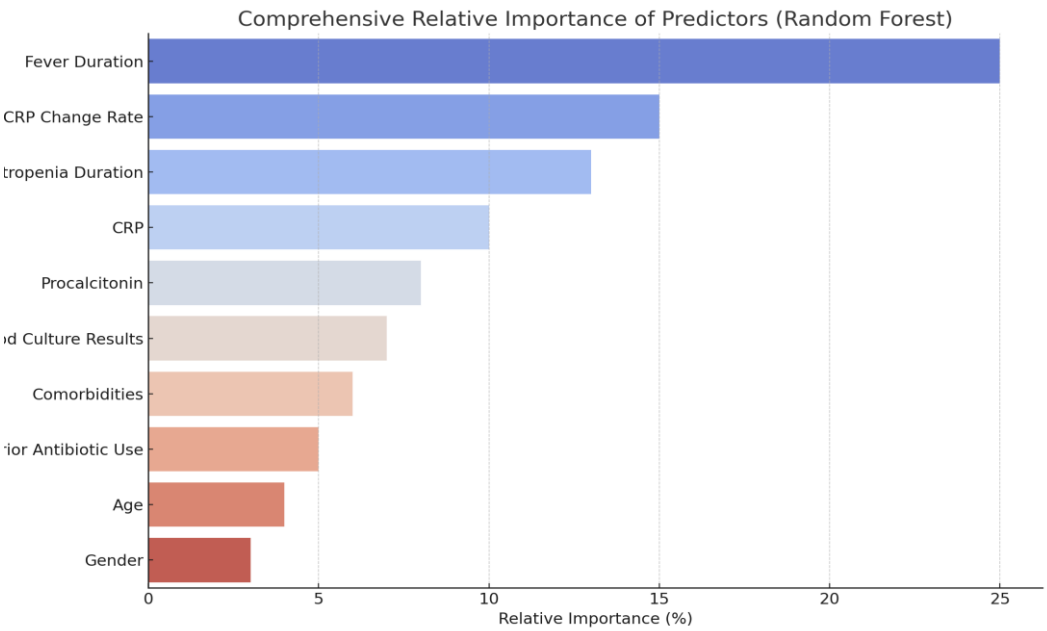

Figure 1. Relative Importance of Predictors (Random Forest)

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