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Survival and Mortality-Associated Factors in Febrile Neutropenia Among Patients with Malignancy Receiving Empirical Ceftazidime

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ABSTRACT: Febrile neutropenia is a serious complication of cancer therapy that may rapidly progress to severe infection and death. Evidence on survival determinants among patients receiving empirical ceftazidime in Indonesia remains limited. This study evaluated survival and examined the associations of absolute neutrophil count (ANC), age, and cancer type with mortality. This single-centre retrospective cohort study included adults with cancer and febrile neutropenia admitted to Dr Wahidin Sudirohusodo Hospital, Makassar, between January 2025 and April 2026. Survival was evaluated using Kaplan-Meier analysis and the log-rank test, and factors associated with mortality were assessed using Cox proportional hazards regression. Among 90 patients, 78.9% had haematological malignancies and 25.6% had an ANC <100 cells/ μ L. During follow-up, 19 patients (21.1%) died. Survival was significantly lower in patients with an ANC <100 cells/ μ L than in those with an ANC of 100-500 cells/ μ L (log-rank $p < 0.001$), while no significant differences were observed by cancer type or age group. In multivariable analysis, an ANC <100 cells/ μ L (aHR 5.84, 95% CI 2.17-15.78; $p < 0.001$) and age ≥ 60 years (aHR 3.08, 95% CI 1.03-9.20; $p = 0.044$) were independently associated with a higher hazard of death. Severe neutropenia and older age may help identify patients requiring closer clinical monitoring.

1. INTRODUCTION

Febrile neutropenia (FN) is a serious complication of cancer treatment and is associated with severe infection, hospitalisation, and death. Its reported incidence ranges from 10% to 50% among patients with solid tumours and exceeds 80% among those with haematological malignancies. These figures indicate that FN remains a frequent clinical problem, particularly in patients receiving treatment for haematological cancer.^{1,2}

The risk of infection increases as the absolute neutrophil count (ANC) declines, particularly when the ANC falls below 500 cells/ mm^3 . At this level, patients become increasingly susceptible to bacteraemia, pneumonia, and sepsis. Mortality is highest among patients with an ANC <100 cells/ mm^3 . The duration of neutropenia also has prognostic relevance. Its median duration is approximately 3 days in patients with solid tumours but may exceed 14 days in those with haematological malignancies. Age

>60 years, neutropenia lasting >7 days, and delayed administration of empirical antibiotics have also been reported as predictors of mortality.^{3–6}

Empirical treatment for FN must provide adequate coverage against Gram-negative pathogens, particularly *Pseudomonas aeruginosa*, because delayed administration of effective antibiotics may adversely affect clinical outcomes. Antipseudomonal β -lactams are used as initial treatment in patients with high-risk FN. The choice of antibiotic is determined by the patient's clinical condition, local bacterial resistance patterns, and the institutional antibiogram. Ceftazidime is one of the empirical antibiotics used in this patient population.^{3,4,7–9}

Data on factors associated with short-term survival among patients with FN receiving empirical ceftazidime in Indonesian referral hospitals remain limited. This study therefore evaluated survival among patients with cancer and FN treated with empirical ceftazidime and examined whether the severity of neutropenia, malignancy type, and age were associated with mortality.

2. MATERIALS AND METHODS

2.1 Study design, setting, and participants

This observational analytical study used a retrospective cohort design based on medical records of patients admitted to Dr Wahidin Sudirohusodo Hospital, Makassar, between January 2025 and April 2026. Total sampling was applied, whereby all patients who met the study criteria during the specified period were included. Eligible participants were adults with cancer who had received chemotherapy, developed febrile neutropenia (FN), and received ceftazidime as empirical antibiotic therapy in accordance with the institutional protocol. FN was defined as a single body temperature measurement of $\geq 38.3^{\circ}\text{C}$ or a temperature of $\geq 38.0^{\circ}\text{C}$ sustained for at least 1 hour, accompanied by an absolute neutrophil count (ANC) < 500 cells/ mm^3 or an ANC expected to decline below 500 cells/ mm^3 within 48 hours. For this analysis, severe neutropenia was defined as ANC < 100 cells/ mm^3 , while ANC 100–500 cells/ mm^3 comprised the comparison category. Patients with septic shock or haemodynamic instability, severe kidney failure requiring dialysis, severe hepatic impairment classified as Child-Pugh class C, pregnancy, or breastfeeding were excluded. Medical records with incomplete information on the principal study variables or outcome were also excluded.

2.2 Study variables and follow-up

Information on age, malignancy type, ANC at the diagnosis of FN, and vital status was obtained through medical-record review. The ANC value used for analysis was the value documented at the diagnosis of FN. Malignancies were classified as haematological malignancies or solid tumours. The study outcome was survival time from the first administration of ceftazidime until death or the end of the observation period. All included patients received empirical ceftazidime; concomitant infections, additional antimicrobial therapy, and other supportive-care interventions were not included among the principal analysed covariates.

The institutional empirical ceftazidime regimen was 1 g administered intravenously every 8 hours.

2.3 Statistical analysis

Categorical variables were presented as frequencies and percentages. Numerical variables were reported as means with standard deviations or medians with interquartile ranges, according to their distributions. Survival probabilities were estimated using the Kaplan-Meier method. Survival differences according to ANC category, malignancy type, and age group (< 60 or ≥ 60 years) were evaluated using the log-rank test. The multivariable Cox proportional hazards model included the three study variables examined in the primary analysis: ANC category, malignancy type, and age group. Results were reported as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics. A formal assessment of the proportional hazards assumption was not documented in the available statistical output.

3. RESULTS AND DISCUSSION

3.1 Study population

A total of 147 medical records of patients with cancer were screened between January 2025 and April 2026. Fifty-seven patients were excluded because they did not meet the diagnostic criteria for FN. The remaining 90 patients fulfilled the eligibility criteria and were included in the final analysis. Their mean age was 45.89 ± 17.35 years. The sex distribution was relatively balanced, with 46 men (51.1%) and 44 women (48.9%). Most patients had haematological malignancies (78.9%), whereas 21.1% had solid tumours. Twenty-five per cent of the cohort had an ANC <100 cells/mm³. The characteristics of the study population are presented in Table 1.

Table 1. Patient characteristics and outcomes	
Characteristic	Overall (n=90)
Age (years)	45,89 $\pm$ 17,35
Sex	
Male	46 (51,1%)
Female	44 (48,9%)
Cancer type	
Hematologically malignancy	71 (78,9%)
Solid Tumour	19 (21,1%)
Vital status	
Died	19 (21,1%)
Survived	71 (78,9%)
ANC category, cells/ μ L	
< 100	23 (25,6%)
100 – 500	67 (74,4%)
Length of stay (days)	8,07 $\pm$ 4,23
Duration of Ceftazidime therapy (days)	6,37 $\pm$ 2,88

3.2 Survival according to ANC

Twenty-three patients (25.6%) had an ANC <100 cells/mm³, whereas 67 (74.4%) had an ANC of 100–500 cells/mm³. The mean ANC across the entire cohort was 209.37 ± 147.25 cells/mm³. The mean length of hospital stay was 8.07 ± 4.23 days, and the mean duration of ceftazidime therapy was 6.37 ± 2.88 days. The median duration of ceftazidime treatment was 6 days, with an interquartile range of 3.5 days. During the observation period, 19 patients (21.1%) died. The median duration of observation was 7 days, with an interquartile range of 6 days.

Mortality differed markedly according to ANC category. Death occurred in 10 of 23 patients (43.5%) with an ANC <100 cells/mm³ and in 9 of 67 patients (13.4%) with an ANC of 100–500 cells/mm³. Kaplan–Meier analysis demonstrated a significant difference in survival between the two ANC groups (log-rank $p < 0.001$). Mean survival was 6.86 ± 0.85 days in patients with an ANC <100 cells/mm³ and 14.99 ± 0.74 days in those with an ANC of 100–500 cells/mm³. Median survival was 10 and 17 days, respectively (Table 2).

Table 2. Survival by absolute neutrophil count					
ANC, cells/ μ L	Patients, n	Deaths, n	Mean survival, days	Median survival, days	Log-rank p
< 100	23	10	6,86 $\pm$ 0,85	10	<0,001
100-500	67	9	14,99 $\pm$ 0,74	17	<0,001

3.3 Survival according to malignancy type and age

Survival did not differ significantly between patients with haematological malignancies and those with solid tumours (log-rank $p = 0.355$). Among patients with haematological malignancies, 14 of 71 died. Their mean survival time was 13.80 ± 0.86 days, and median survival was 17 days. Among patients with solid tumours, 5 of 19 died, with a mean survival time of 8.58 ± 0.93 days. Median survival was not reached in the solid-tumour group during the observation period.

Kaplan–Meier analysis also showed no significant difference in survival between patients aged <60 and ≥60 years (log-rank $p=0.194$). Among the 73 patients aged <60 years, 14 died, and the mean survival time was 13.95 ± 0.81 days. Among the 17 patients aged ≥60 years, 5 died, and the mean survival time was 7.79 ± 0.84 days.

3.4 Multivariable analysis

In the multivariable Cox proportional hazards analysis, an ANC <100 cells/mm³ was independently associated with a 5.84-fold higher hazard of death compared with an ANC of 100–500 cells/mm³ (aHR 5.84; 95% CI 2.17–15.78; $p<0.001$). Age ≥60 years was also independently associated with a higher hazard of death (aHR 3.08; 95% CI 1.03–9.20; $p=0.044$). By contrast, malignancy type was not significantly associated with mortality (aHR 1.41; 95% CI 0.48–4.16; $p=0.532$). The results of the multivariable analysis are presented in Table 3.

Variable	HR	95% IK	P value
ANC < 100 cells/ μ L	5,84	2,17 - 15,78	<0,001
Solid tumor	1,41	0,48 - 4,16	0,532
Age ≥ 60 years	3,08	1,03 - 9,20	0,044

3.5 Discussion

This study evaluated survival among patients with cancer and FN who received ceftazidime as empirical therapy at Dr Wahidin Sudirohusodo Hospital, Makassar. Among the 90 patients included in the analysis, mortality during the observation period was 21.1%. An ANC <100 cells/mm³ and age ≥60 years were independently associated with a higher hazard of death, whereas malignancy type was not significantly associated with survival. The principal findings indicate that the severity of neutropenia and patient age had a greater influence on survival than the broad classification of cancer as a haematological malignancy or solid tumor.

The sex distribution was relatively balanced, with men accounting for 51.1% and women for 48.9% of the cohort. This finding is consistent with the study by Shmueli et al., in which men constituted 49.4% of patients with haematological malignancies and FN, indicating no marked predominance according to sex. The mean age in the present study was 45.89 ± 17.35 years, which was lower than the mean age of approximately 60–70 years reported in several studies from high-income countries. This difference may be related to variation in population characteristics, the distribution of malignancy types, access to healthcare, and patterns of clinical care. Although the present cohort was relatively young, older age remained clinically important because it is associated with impaired immune function, a greater burden of comorbidities, and reduced bone marrow regenerative capacity after chemotherapy.

Most patients in this study had haematological malignancies (78.9%). This proportion is consistent with previous reports showing that patients with leukaemia, lymphoma, and other haematological malignancies are particularly susceptible to FN. Their greater susceptibility is associated with the higher intensity of chemotherapy and with neutropenia that tends to be more severe and prolonged than that experienced by patients with solid tumours.¹¹ The predominance of haematological malignancies in this cohort should therefore be considered when interpreting the findings because treatment characteristics and clinical trajectories may differ between patients with haematological malignancies and those with solid tumors.

An ANC <100 cells/mm³ showed the strongest association with poorer survival. Mean survival in this group was 6.86 days, substantially shorter than the 14.99 days observed among patients with an ANC of 100–500 cells/mm³. Mortality was also higher among patients with an ANC <100 cells/mm³, at 43.5%, compared with 13.4% among those with an ANC of 100–500 cells/mm³. After adjustment for age and malignancy type, an ANC <100 cells/mm³ remained independently associated with a 5.84-fold higher hazard of death (aHR 5.84; 95% CI 2.17–15.78; $p<0.001$). This association can be explained by the central role of neutrophils in innate immunity, particularly in the phagocytosis and elimination of bacterial and fungal pathogens. When the ANC falls below 100 cells/mm³, the ability to contain pathogen invasion and dissemination is markedly impaired. This impairment increases susceptibility to bacteraemia, sepsis, septic shock, and death. The present findings support previous

evidence that the depth of neutropenia is an important marker of adverse outcomes among patients with FN.¹¹ From a clinical perspective, an ANC <100 cells/mm³ may help identify patients who require more intensive monitoring, comprehensive evaluation for a source of infection, and optimal empirical antibiotic therapy from the beginning of treatment. The strength of the observed association supports the clinical importance of recognising severe neutropenia at presentation. Nevertheless, the relatively wide confidence interval indicates uncertainty regarding the precise magnitude of risk, and the estimated association should therefore be interpreted cautiously.

Malignancy type was not significantly associated with survival in either the Kaplan–Meier analysis or the Cox regression model (aHR 1.41; 95% CI 0.48–4.16; $p=0.532$). Although patients with solid tumours had a numerically shorter mean survival time, this difference did not reach statistical significance. The finding differs from reports suggesting that patients with haematological malignancies have a greater risk of severe infection and mortality because their neutropenia is generally deeper and more prolonged. Other studies, however, indicate that age, organ function, septic shock, acute kidney injury, and the depth of neutropenia may exert a greater influence on mortality than malignancy type itself.¹²

The absence of a significant association between malignancy type and survival may partly be attributable to the relatively small number of patients with solid tumours. Only 19 patients, representing 21.1% of the cohort, belonged to this group. The imbalance in group size may have reduced the ability of the analysis to detect a genuine survival difference. In addition, the use of a uniform empirical treatment protocol across the study population may have reduced variation in outcomes between patients with haematological malignancies and those with solid tumours. The findings should therefore not be interpreted as evidence that malignancy type has no clinical relevance. Rather, its independent association with survival could not be demonstrated in this study population.

Age ≥ 60 years was not significantly associated with survival in the Kaplan–Meier analysis ($p=0.194$) but emerged as an independent factor in the multivariable Cox regression model (aHR 3.08; 95% CI 1.03–9.20; $p=0.044$). This difference between the analyses suggests that the association between age and mortality became more apparent after ANC and malignancy type were included in the multivariable model. The finding is consistent with the study by Shmueli *et al.*, which identified older age as an independent predictor of mortality among patients with haematological malignancies and FN.¹⁰

Older patients generally have lower physiological reserve, a greater burden of comorbidities, and impaired immune responses associated with immunosenescence. These conditions may reduce the patient's ability to control infection and increase susceptibility to multiorgan failure during an episode of FN.⁴ The present findings therefore support consideration of age in clinical monitoring and risk stratification.¹³ Nevertheless, this association should be interpreted carefully because the lower limit of the confidence interval was close to unity and the number of patients aged ≥ 60 years was relatively small.

The mortality rate of 21.1% observed in this study was higher than the approximately 12%–16% reported by several international studies during the first 30 days of treatment. However, it remained within the range reported among patients with haematological malignancies and severe neutropenia.¹⁰ Differences in mortality may be influenced by the severity of neutropenia, the prevalence of infections caused by multidrug-resistant organisms, the timing of empirical antibiotic administration, and the availability of supportive facilities. The high proportions of patients with haematological malignancies and an ANC <100 cells/mm³ in this cohort may also have contributed to the observed mortality.^{13,14}

This study has several limitations. Its retrospective design made the analysis dependent on the completeness and accuracy of information recorded in the medical records and introduced the possibility of selection bias. The study was conducted at a single healthcare centre with a relatively small sample, particularly in the solid-tumour and older-age subgroups, which limits precision and generalisability. Residual confounding is possible because several clinically relevant factors were not included in the analysis, including the Multinational Association for Supportive Care in Cancer score, source of infection, microbiological culture findings, comorbidities, performance status, local antimicrobial resistance patterns, concomitant infections, additional antimicrobial therapy, and supportive-care interventions. Variation in antimicrobial management and supportive care may therefore have influenced outcomes. All included patients received ceftazidime and no comparator group receiving another empirical antibiotic was included; consequently, this observational study cannot establish that empirical ceftazidime itself caused or prevented the observed survival outcomes. Larger prospective multicentre studies with more comprehensive adjustment for potential confounding factors are required to confirm these findings. In addition, a formal assessment of the proportional

hazards assumption was not documented in the available statistical output, which should be considered when interpreting the Cox regression estimates.

4. CONCLUSION

Among patients with cancer and febrile neutropenia receiving ceftazidime as empirical therapy, an ANC <100 cells/mm³ and age ≥ 60 years were independently associated with a higher hazard of death. An ANC <100 cells/mm³ showed the strongest association with poorer survival, whereas malignancy type was not significantly associated with survival. These findings support the use of neutropenia severity and patient age as considerations in risk stratification and clinical monitoring throughout hospitalisation.

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Author Contributions

Surya Hadiwijaya: Conceptualization, Investigation, Data Curation, Writing - Original Draft. Andi Fachrudin Benyamin: Supervision, Clinical Methodology, Interpretation, Writing - Review & Editing. Risna Halim Mubin: Supervision, Clinical Methodology, Interpretation, Writing - Review & Editing. Syakib Bakri: Supervision, Clinical Methodology, Interpretation, Writing - Review & Editing. Suriani Alimuddin: Supervision, Clinical Methodology, Interpretation, Writing - Review & Editing. Andi Alfian Zainuddin: Methodology, Formal Analysis, Statistical Analysis, Writing - Review & Editing. All authors reviewed and approved the final manuscript and agree to be accountable for the work.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Statement

This study was approved by the Health Research Ethics Committee of Hasanuddin University, RSPTN Universitas Hasanuddin, and Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia (Ethical Approval No. 464/UN4.6.4.5.31/PP36/2026; Protocol No. UH26030380; approval date: 6 April 2026).

Data Availability Statement

The datasets generated and/or analysed during the current study are not publicly available due to patient confidentiality and ethical restrictions but may be available from the corresponding author upon reasonable request and with appropriate institutional approval.

Generative AI and AI-assisted technologies disclosure

OpenAI ChatGPT was used for language editing and manuscript-formatting assistance. The authors reviewed and verified the accuracy and integrity of the final manuscript and remain fully responsible for its content.

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