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Simple predictors of the re-occurrence of severe febrile neutropenia episode: a single-center retrospective cohort study in pediatric patients with malignant diseases

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Aim To identify the risk factors of a repeated episode of severe febrile neutropenia (FN) and to build an accurate and easy-to-use predictive model.

Methods This single-center retrospective cohort study conducted at the Clinical Hospital Center Children's Hospital Rijeka from January 1, 2008 to December 31, 2016 included pediatric patients with malignant diseases who experienced at least one FN episode. The association of the second severe FN episode appearance with relevant clinical and laboratory data was analyzed by logistic regression.

Results Out of 45 patients with one FN episode, 25 (56%) had severe FN and 11 (24%) had repeated severe FNs. Significant predictors of a repeated severe FN episode were the first FN episode duration of 9 or more days and red blood cells $\leq 3.0 \times 10^{12}$/L. The predictive model constructed by crossing these two indicators had the accuracy of 87% (95% confidence interval [CI] 73%-94%), sensitivity of 82% (95% CI 53%-97%), and specificity of 88% (95% CI 79%-93%).

Conclusion The first FN episode duration and anemia are significantly associated with the risk for severe FN re-occurrence. These factors may be useful in the identification of children with cancer who are at high risk for adverse outcome at any future fever onset and may benefit from early intensive treatment.

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The majority of pediatric malignances are treated by systemic combined chemotherapy, and approximately 80% of children are cured. Antineoplastic therapy adversely affects myelopoiesis and damages the integrity of gastrointestinal mucous membrane, leading to the invasion of colonizing bacteria and the development of a dangerous, quickly progressing systemic infection (1). Febrile neutropenia (FN) is the leading cause of immediate hospitalization in children with cancer and the most frequent complication of chemotherapy. It increases the morbidity and mortality due to serious infections (2-7).

In children with cancer, the beginning phase of a systemic bacterial infection, requiring early antibiotics treatment, has to be immediately differentiated from viral respiratory infections (8). However, the routine laboratory tests are not sensitive and specific enough for early detection of systemic inflammation. Some of these tests are also often time-consuming, such as blood cultures and antimicrobial susceptibility testing, which is still the gold standard for diagnostics and targeted therapy in systemic infections (9,10). Systems of prediction known as clinical decision rules (CDRs), on the other hand, do not include patient's individual characteristics into risk calculation and have not undergone external validation necessary for a wider clinical use (3,8). Monthly cycling antibiotic therapy emerged as a potential solution, but it needs to be further researched (11,12). The predictive value of serum concentrations of interleukin (IL)-6, IL-8, IL-10, and procalcitonin has also been analyzed, but the problem of early risk stratification has not been resolved (13-15). Data on predictive value of hemoglobin concentrations or red blood cell (RBC) count, known as indicators of myelosuppression, are similarly conflicting (16).

The overall outcome in children with malignant diseases can be improved by the reliable identification of individuals at high risk of systemic infections development at the time of fever onset (8,9,17). The International Consensus Statement for Core Outcomes and Definitions for Pediatric Fever and Neutropenia was agreed upon in 2015 to further develop this field but there are still no clear treatment algorithms (18). As the previously tested predictive models for any FN episode in children with cancer did not show clear clinical usefulness, we hypothesize that the focus should be on the prediction of repeated FN, and especially on repeated severe FN. Our aim was to determine which of the first FN episode clinical features could predict severe FN re-occurrence and facilitate clinical decision-making on early intensive antibiotic therapy in the next fever onset.

MATERIALS AND METHODS

Patients and study design

This retrospective single-center cohort study was conducted at the Clinical Hospital Center Rijeka, Location Kantrida, Department of Hematology and Oncology, Clinical Hospital Center Children's Hospital Rijeka, Croatia. Data were collected from the hospital electronic records for patients treated from January 1, 2008 to December 31, 2016.

The inclusion criterion was the first episode of FN, while the exclusion criterion were incomplete data in medical history. We analyzed the medical records of 225 children with malignant diseases, while the final sample included 45 (20%) children who experienced at least one FN episode. Zero time was the time point of the beginning of the first FN episode.

The key outcome was a repeated episode of severe FN. The criteria for severe FN diagnosis were the absolute neutrophil count (ANC)≤500/mm^3, the temperature ≥38.5°C (≥101.30°F), and duration longer than two days. Observed predictors were from three large groups of data: social, demographic and vitality, laboratory, and clinical data (18-21). The study protocol was approved by the Clinical Hospital Center Rijeka Ethics Committee and the University of Rijeka School of Medicine Ethics Committee (No 19-03-0-013).

Statistical analysis

Normality of data distribution was tested with the Kolmogorov-Smirnoff test. Data are presented as median and interquartile ranges. The predictive model was constructed in three steps. In the first step, the association of all variables with a severe FN repeated episode was assessed by univariate/unadjusted binary logistic regression. The variables that were significantly associated ($P<0.05$) were included into the second step, when their association with severe FN repeated episode was analyzed by multivariate adjusted binary logistic regression. In the third step, two variables that showed significant partial/adjusted association with the criterion were combined into the final model. In predictive value analysis of the new model we calculated the overall accuracy, sensitivity, specificity, positive and negative likelihood ratios, and predictive values. The level of statistical significance was set to $P<0.05$, and all confidence intervals were given on this level. The analyses were carried out using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Confidence intervals for proportions were

determined using Statistics Calculator 3.0 (Stat Pac Inc., Bloomington, MN, USA). Measures of predictive value were calculated by John C. Pezzullo online calculator (http://statpages.org/ctab2x2.html).

RESULTS

Thirty-eight of 45 patients (84%) experienced a repeated FN, and the median number of FN episodes was 2 (range, 1-5). Twenty-five patients (55%) experienced severe FN and 11 (24%) experienced a second severe episode (Table 1).

In the first step of the univariate unadjusted binary logistic regression, six parameters were significantly associated with the severe repeated FN episode: lowest ANC≤300/mm^3; duration of the first episode of 9 or more days; bone marrow suppression; RBC≤3.0×10^{12}; hematocrit ≤0.25 (25%); and platelets ≤100×10^9 (Table 2).

TABLE 1. Patients' characteristics (N = 45)*

Sociodemographic and vital parameters	N (%) or median (25-75)
Sex	
male	25 (55.6)
female	20 (44.4)
Age at the diagnosis, years	5.0 (5.0-13.0)
BMI at first FN episode	16.0 (14.5-18.0)
Type of malignant disease	
acute lymphoblastic leukemia	17 (37.8)
neuroblastoma	5 (11.1)
non-Hodgkin's lymphoma	5 (11.1)
other diagnosis†	18 (40.0)
Solid tumor	26 (57.8)
Metastatic disease	7 (15.6)
Bone marrow involvement	15 (33.3)
Broviac catheter	29 (64.4)
Duration of hospitalization in days	43 (23-77)
Febrile neutropenia (FN)	
at least one repeated episode	38 (84.4)
average number of episodes	2 (1-5)
severe FN	25 (55)
Repeated FN episode	
ANC	282 (17-500)
ANC≤500/mm^3	27 (60.0)
temperature in °C	39.4 (38.8-39.8)
duration in days	2.5 (2.0-4.5)
duration ≥3 days	19 (42.2)
severe second FN episode	11 (24.4)

*FN – febrile neutropenia; ANC – absolute neutrophil count.
†Other diagnosis, two patients each: acute myeloid leukemia, aggressive fibromatosis, Ewing's sarcoma, hepatoblastoma, Hodgkin lymphoma, medulloblastoma, Yolk sac tumor. Other diagnosis, one patient each: ganglioneuroblastoma, nephroblastoma, osteosarcoma, rhabdomyosarcoma.

Two final significant predictors in the multiple regression were duration of the first episode of 9 or more days and RBC≤3.0×10^{12} (Table 2). These two variables combined accounted for approximately Nagelkerke R^2 = 58% of the repeated severe FN episode variance. The final, simplified predictive model was constructed by crossing these two indicators (Table 3). High risk of severe FN repeated episode was indicated either by duration of the first episode of 9 or more days or by RBC≤3.0×10^{12}, while low risk was indicated by the opposite values: duration of the first episode ≤8 days and RBC>3.0×10^{12}. The new constructed predictor was significantly associated with the severity of repeated FN episode (Fisher exact test, P < 0.001) (Table 3). The overall accuracy of the model was 87% (95% CI 73%-94%), with the sensitivity of 82% (53%-97%) and the specificity of 88% (79%-93%). Positive likelihood ratio for repeated FN episode was 7.0 (95% CI 2.52-13.73). Negative likelihood ratio was 0.21 (95% CI 0.04-0.56).

DISCUSSION

This study showed two predictors of the re-occurrence of repeated severe FN: duration of the first FN episode of 9 or more days and RBC≤3.0×10^{12}. Our model based on two predictors showed very good specificity, sensitivity, and negative predictive value and could be useful in clinical practice. To the best of our knowledge, these factors have not previously been shown to be significant predictors for severe FN. The duration of the first episode of 9 or more days could indicate slower hematopoietic recovery, while the lower RBC count can be a consequence of myelosuppression or bone marrow infiltration. As the pathophysiology of FN is multifactorial, other possible causes have also to be taken into consideration (15).

Considerable evidence has been published on different single and combined predictors for severe FN. C reactive protein ≥90 mg/L, hypotension, platelet number ≤50 000 /mm^3, relapsed leukemia, and chemotherapy in the last 7 days were shown to be the predictors for severe bacterial infection (19), while intensive chemotherapy, shorter time-to-diagnosis, presence of CVC and previous FN were shown to be predictors for development of FN and FN with bacteremia (20).

Our study found several significant univariate predictors. ANC≤300/mm^3 was a good predictor of severe FN epi-

TABLE 2. Predictors associated ($P < 0.05$) with repeated episode of severe febrile neutropenia (FN) (N = 45)

	Severe FN repeated episode				
N (%)	yes	no	total	OR_{uni} (95% CI)	OR_{multi} (95% CI)
Lowest ANC at first FN episode					
ANC≤300/mm^3	10 (38.5)	16 (61.5)	26 (100)	11.3 (1.21-261.6)	4.3 (0.26-71.59)
ANC>300/mm^3	1 (5.3)	18 (94.7)	19 (100)		
Duration of the first FN episode					
≥9 days	6 (66.7)	3 (33.3)	9 (100)	12.4 (2.32-66.35)	30.4 (1.94-476.49)
≤8 days	5 (13.9)	31 (86.1)	36 (100)		
Bone marrow involvement					
yes	7 (46.7)	8 (53.3)	15 (100)	5.7 (1.32-24.54)	1.5 (0.16-13.69)
no	4 (13.3)	26 (86.7)	30 (100)		
Red blood cells					
$\leq 3.0 \times 10^{12}$	4 (80.0)	1 (20.0)	5 (100)	18.3 (1.76-189.63)	130.6 (1.3-13011)
$>3.0 \times 10^{12}$	7 (17.9)	32 (82.1)	39 (100)		
Hematocrit					
≤0.25	5 (71.4)	2 (28.6)	7 (100)	13.3 (2.08-85.41)	0.3 (0.00-9.77)
>0.25	6 (15.8)	32 (84.2)	38 (100)		
Platelets					
$\leq 100 \times 10^9$	5 (50.0)	5 (50.0)	10 (100)	4.8 (1.06-22.09)	1.0 (0.08-12.73)
$>100 \times 10^9$	6 (17.1)	29 (82.9)	35 (100)		

*OR_{uni} – univariate odds ratio for severe FN; OR_{adj} – multivariate, binary logistic regression adjusted odds ratio for severe FN; 95% CI – 95% confidence interval of odds ratio.

TABLE 3. Predictive validity for a repeated episode of febrile neutropenia (FN) (n = 45)

	Repeated episode of FN			
Estimated risk	yes	no	total	
High*	9 (69.2)	4 (30.8)	13 (100)	positive predictive value 69% (45%-82%)†
Low	2 (6.3)	30 (93.8)	32 (100)	negative predictive value 94% (94%-99%)†
	sensitivity 82% (53%-97%)†	specificity 88% (79%-93%)†		

*High risk of FN repeated episode was indicated either by duration of the first episode ≥9 days or by RBC$\leq 3.0 \times 10^{12}$.
†Values in parentheses represent 95% confidence intervals.

sodes, which is consistent with the results by Ammann et al (15). Also, hematocrit ≤0.25 was a good predictor, pointing toward bone marrow suppression or bone marrow infiltration as a possible explanation for FN susceptibility. Bone marrow involvement in malignant disease was also univariately significant, while in other studies it demonstrated multivariate significance (15,20). Platelet count $\leq 100 \times 10^9$/L was a good univariate predictor in our study, as well as in other studies (20), even in multivariate models (19,22). Other parameters investigated in this study were found to be non-significant by other authors (19,22).

Disease-specific factors depending on the type of malignant disease, type and dose of chemotherapy, comorbidities, early complications, and other patients' characteristics make the risk assessment by general score systems problematic (23-25). Only one of the available CDRs is methodologically suitable, however, it was developed and validated in South America, making its application in other parts of the world questionable (26). Also, while the greatest part of CDRs identify children at low risk of severe infection, only one of them aims at diagnosing severe bacterial infection (26-29). Better risk-stratification of patients based on our model could lead to a less intensive treatment in low-risk patients, which carries a lower risk of side effects and hospital acquired infections, lower toxicity risk and the risk of antibiotic resistance development, better quality of life for the child and the family, as well as lower costs. However, identifying children at low risk cannot have the advantage over the identifying children at high risk who can be successfully cured by an early intensive antimicrobial therapy.

Our proposal is oriented toward the general risk assessment and includes both of these groups. Also,

our results seem to be more appropriate for severe FN prediction in pediatric oncologic patients than the Systemic Inflammatory Response Syndrome (30), which is used for sepsis diagnosis but is generally questionable in oncologic patients, since it was based on studies that did not include a considerable number of patients with tumors and neutropenia. MASCC risk score by the Association for Supportive Care in Cancer, which assesses the risk of adverse outcome in oncologic patients, is also not suitable for children with tumors, since it shows gaps in evidence and requires numerous tests to be made (CRP, procalcitonin, venous blood lactate, proteinemia and phosphatemia evaluation, blood lactate, antithrombin, and VIIa factor levels, and chest x-ray) (31).

The results of this study need to be validated on larger patient populations. Also, the number of our patients did not allow sub-analyses according to malignant disease type, phase, chemotherapy type, and chemotherapy intensity. Long time period in which the study was conducted could have influenced the final results, and data on the time-to-antibiotic administration were not available.

In conclusion, we propose a predictive model for the second FN episode based on a new combination of two easily accessible risk factors. This model could be used for risk assessment in different malignant diseases, chemotherapy types, and chemotherapy intensities. Our approach might represent a step toward an individually tailored FN therapy and the prediction of repeated severe FN episode in pediatric oncology, facilitating decision-making on inpatient vs outpatient management.

Oxford Centre for Evidence-based Medicine level of evidence 2b.

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Declaration of authorship all authors conceived and designed the study; SS acquired the data; AR, DD, KB, and JR analyzed and interpreted the data; SS drafted the manuscript; all authors critically revised the manuscript for important intellectual content; all authors gave approval of the version to be submitted; all authors agree to be accountable for all aspects of the work.

Competing interests AR is a member of the Managerial Board of the *Croatian Medical Journal* and KB is the journal's Research Integrity editor. To ensure that any possible conflict of interest relevant to the journal has been addressed, this article was reviewed according to best practice guidelines of international editorial organizations. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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