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Original Article

Correlation Between Risk of Febrile Neutropenia Based on Rondinelli Score with Clinical Outcomes in Acute Lymphoblastic Leukemia Patients

Dianira Hanum Febia Alifadiningrat¹, Dwiyantri Puspitasari^{2*}, Yetti Hernaningsih³

¹ Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

² Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

³ Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

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ABSTRACT

Febrile neutropenia (FN) is the most severe complication in patients with blood cancer and chemotherapy. Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children and the most common cause of febrile neutropenia. The low number of neutrophils in ALL patients due to lymphoblast cancer cells and the toxicity of chemotherapy makes patients susceptible to infection which, if not treated immediately, can lead to death. Early risk assessment for infectious complications in FN patients is needed to increase clinician awareness in high-risk patients and eliminate unnecessary therapy for low-risk patients. The Rondinelli scoring system is a reasonably good instrument for predicting severe infectious complications in pediatric patients with ALL who have febrile neutropenia. This study aims to determine the relationship between the risk category for febrile neutropenia (FN) based on the Rondinelli score with clinical outcomes in FN patients with acute lymphoblastic leukemia (ALL) in the Hematology-Oncology division of the child health department of RSUD Dr. Soetomo. This analytic observational study used secondary data FN patients with acute lymphoblastic leukemia (ALL) implementing a total sampling. From 30 samples of pediatric ALL patients with febrile neutropenia at Dr. Soetomo Hospital for June 2018-June 2020 it was found 17 patients (56.7%) had a moderate risk score category, and 13 others were in a low-risk category (43.3%). Patients were dominated by moderate and severe severity of neutropenia respectively, 43.3%, had neutropenia for 1-7 days (50%), fever less than seven days (66.7%), had a length of stay of 8-14 days, and 15-30 days 33.3% each. Conclusion from this research is that there was a significant relationship between the Rondinelli score category in pediatric ALL patients with FN with the severity of neutropenia ($p=0.037$; $R=0.383$), duration of neutropenia ($p=0.021$; $R=0.420$), duration of fever ($p=0.000$; $R=0.618$), and length of stay (p -value 0.005; $R=0.496$).

Keywords: Febrile neutropenia; acute leukemia lymphoblastic; cancer; Rondinelli score; infection

ABSTRAK

Demam neutropenia (DN) merupakan komplikasi terberat pada pasien kanker darah dan kemoterapi. Leukemia limfoblastik akut (LLA) adalah jenis kanker yang paling umum pada anak-anak dan penyebab tersering dari demam neutropenia. Rendahnya jumlah neutrofil pada pasien LLA yang diakibatkan sel kanker maupun toksisitas kemoterapi, mengakibatkan pasien mudah terinfeksi yang apabila tidak segera ditangani dapat menyebabkan kematian. Penilaian risiko dini untuk komplikasi infeksi pada pasien DN diperlukan untuk meningkatkan kewaspadaan klinisi pada pasien berisiko tinggi dan mengeliminasi terapi yang tidak perlu untuk pasien berisiko rendah. Sistem penilaian Rondinelli adalah instrumen yang cukup baik untuk memprediksi komplikasi infeksi berat pada pasien anak dengan LLA yang mengalami demam neutropenia. Penelitian ini bertujuan untuk mengetahui hubungan antara kategori risiko demam neutropenia (DN) berdasarkan skor Rondinelli dengan luaran klinis pada pasien leukemia limfoblastik akut (LLA) di divisi Hematologi-Onkologi departemen kesehatan anak RSUD Dr. Soetomo. Penelitian observasional analitik ini menggunakan data sekunder pasien DN dengan leukemia limfoblastik akut (LLA) yang dilakukan secara total sampling. Dari 30 sampel pasien LLA anak dengan demam neutropenia di RSUD Dr Soetomo Juni 2018-Juni

* Corresponding Author:
dwiyantri-p@fk.unair.ac.id

2020 didapatkan 17 pasien (56.7%) memiliki kategori skor risiko sedang, dan 13 lainnya berada dalam kategori risiko rendah (43.3%). Pasien didominasi oleh neutropenia derajat sedang dan berat masing-masing 43.3%, mengalami neutropenia selama 1-7 hari (50%), demam kurang dari tujuh hari (66.7%), memiliki lama rawat 8-14 hari, dan 15-30 hari masing-masing 33.3%. Kesimpulan dari penelitian ini ada hubungan yang bermakna antara kategori skor Rondinelli pada pasien ALL pediatrik dengan FN dengan keparahan neutropenia ($p=0.037$; $R=0.383$), lama neutropenia ($p=0.021$; $R=0.420$), lama demam ($p=0.000$; $R=0.618$), dan lama rawat inap ($p=0.005$; $R=0.496$).

Kata kunci: Demam neutropenia; leukemia limfoblastik akut; kanker; skor Rondinelli; infeksi

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INTRODUCTION

Febrile neutropenia (FN) is when axillary temperature $>38^{\circ}\text{C}$ persists for more than two hours or axillary temperature $>39^{\circ}\text{C}$ on one measurement with neutrophils <1000 cells/microliter.¹ Febrile neutropenia is the most severe complication that accounts for 50%-70% of deaths in patients with hematological malignancies and chemotherapy.² Acute lymphoblastic leukemia is the most common type of acute leukemia in children. At RSUD Dr. Soetomo Surabaya, acute leukemia was in the first rank of malignancy patients in children within a period of 10 years (1991-2000) which is 59% of all malignancies in children.³ ALL is also the most common cause of FN cases in Sanglah Hospital, which is 33.3%.⁴ In leukemia patients without chemotherapy, neutrophils will actually decrease significantly by themselves through the direct interaction of cancer with hematopoiesis. However, if the patient is undergoing chemotherapy, the interaction of several cancer drugs also has a myelosuppressive effect that interferes with the formation of neutrophils.² This makes ALL patients very susceptible to febrile neutropenia due to systemic bacterial infection or severe sepsis, which can be life-threatening.⁵

The life-threatening nature of febrile neutropenia (FN) makes an initial risk assessment necessary to increase clinicians' alertness.² For patients with low risk, this risk stratification

can provide benefits in the form of improving quality of life, reducing the risk of exposure to nosocomial infections in hospitals, and can also reduce the burden of treatment costs.⁶ The Rondinelli scoring system is a reasonably good instrument for predicting severe infectious complications in pediatric patients with ALL who have febrile neutropenia.⁷ FN patients will be categorized into low risk, medium risk, or high risk using several parameters: age, hemoglobin, central venous catheter access, location of focal infection, fever temperature, and the emergence of upper respiratory tract infection (URTI).⁸

Clinical outcomes in the form of the severity of neutropenia, duration of neutropenia, duration of fever, and length of stay were recorded to see clinical improvement in FN patients after empiric antibiotic therapy. This study aims to determine the relationship between the risk category for febrile neutropenia (FN) based on the Rondinelli score with clinical outcomes in FN patients with acute lymphoblastic leukemia (ALL) in the Hematology-Oncology division of the child health department of RSUD Dr. Soetomo.

MATERIALS AND METHODS

Materials

The collected data is processed and grouped according to the Rondinelli scoring criteria as shown in Table 1.

Table 1. Rondinelli Scoring Criteria

Clinical Variables	Score
Age ≤ 5 years	1
Age > 5 years	0
Central venous catheter	2
Without central venous catheter	0
Focal infection	4,5
Without focal infection	0
Fever ≥ 38,5 °C	1
Fever < 38,5 °C	0
Hemoglobin ≤ 7 g/dl	1
Hemoglobin >7 g/dl	0
Without URTI	0
URTI	2,5

Patients are categorized as low risk if the total score is <5.5, moderate risk if the score is 5.5 to 9, and more than 9 is high risk.¹

Methods

This study is a retrospective observational analytic study using secondary data of FN patients with acute lymphoblastic leukemia (ALL) in the Hematology-Oncology division of the child health department of RSUD Dr. Soetomo June 2018-June 2020. This research has met the requirements of ethical feasibility by the Ethics Committee RSUD Dr. Soetomo, Surabaya (0333/LOE/301.4.2/II/2021). Sampling is done by total sampling. The inclusion criteria for this study were medical records of pediatric patients (0-18 years) with ALL who were diagnosed with complications of febrile neutropenia in the complete daily records of the doctor in charge of hematology-oncology. Incomplete medical record data were excluded from this study. This research analysis uses the IBM SPSS STATISTICS version 24 application using the Crosstabs technique and Spearman's test for non-parametric data.

RESULTS AND DISCUSSION

There is no FN ICD (The International Classification of Diseases) in the electronic data center, so the authors selected the inclusion

data in two stages. The first stage, looking for medical record numbers with ICD ALL and ICD neutropenia at the electronic medical record data center, obtained 90 medical records. In the second stage, from the 90 medical records, data were taken with the diagnosis of FN complications in printed medical records, and obtained 30 medical record data.

Sample Characteristic FN Patients with LLA

Table 2. Sample Characteristic

Variables	Category	N=30	Percentage (%)
Gender	Male	17	56.7
	Female	13	43.3
Age (year)	>5	17	56.7
	≤5	13	43.3
Hemoglobin (g/dL)	>7	29	96.7
	≤7	1	3.3
Central venous catheter	No	30	100.0
	Yes	0	0.00
Focal infection	No	10	33.3
	Yes	20	66.7
Temperature (°C)	<38.5	21	70
	≥38.5	9	30
URTI	No	23	76.7
	Yes	7	23.3
Rondinelli score category	Low	13	43.3
	Moderate	17	56.7
	High	0	0

From Table 2, Pediatric ALL patients with febrile neutropenia were 17 male (56.7%) and 13 female (43.3%). This study were similar to previous studies that pediatric ALL patients with febrile neutropenia were predominantly male.^{1,7,8,9} Most patients aged over five years, as many as 17 people (56.7%) in line with the previous study that patients aged above 5 years more in number than under 5 years,^{1,8} but the proportion is almost the same.⁷ This study is similar to the previous studies in that patient's hemoglobin level was predominantly above 7

g/dL.^{1,8} From table 2, similar to the previous findings that none of the pediatric ALL patients who had FN used a central venous catheter.^{1,7} This study found most patients have a specific focus of infection same like previous studies.^{1,8} In this study, most patients had a subfebrile temperature that was below 38.5°C with a percentage similar to the results of Rondinelli et al.⁸, which was 70% vs 65%. However, other studies show the opposite, the patient's temperature is mostly above 38.5°C with a percentage of more than 60%.¹ Some febrile neutropenic patients whose temperature was recorded as normal in this study may be due to the author's error in entering the data, namely choosing which fever temperature corresponds to the time when the patient was diagnosed with febrile neutropenia. Another cause was that the patient had no fever when he checked his vital signs by a hematologist-oncologist. From this study, patients were found to have upper respiratory tract infections (URTI) only about 10%-20%.^{1,8}

Based on the calculation rules of the Rondinelli score system from Table 2, pediatric patients who experienced neutropenic fever at Dr. Soetomo Hospital for the period June 2018-June 2020, 17 patients (56.7%) had a moderate risk score category, and 13 others had a low-risk category (43.3 %). This study is different from previous studies because there were no high-risk patients (score > 9.0). According to the research conducted by Andrieanta et al.¹ at Dr. Cipto Mangunkusumo Hospital, Jakarta of the 96 samples of patients with febrile neutropenia, 52% had a low category, 48% had a high category, and none had a moderate category.¹ In another study conducted by Hidayat et al. of 30 samples, 73.33% had low risk (score <5.5), and the rest (score 5.5) as many as 26.67% had moderate and high risk.⁷ Previous studies have shown varied results regarding the distribution of the risk level of FN patients with Rondinelli scores. So it can be concluded that there is no absolute prevalence rate related to the risk of FN patients based on the Rondinelli score, depending on the situation in each hospital, and further research is needed to find out this.

Clinical Outcome FN Patients with LLA

Table 3. Result Of Clinical Outcome

Variables	Category	N=30	Percentage (%)
Severity of neutropenia	Low	4	13.3
	Moderate	13	43.3
	Severe	13	43.3
Length of neutropenia (days)	1-7	15	50
	8-14	9	30
	15-25	6	20
Length of fever (days)	≤7	20	66.7
	>7	10	33.3
Length of hospitalization (days)	1-3	1	3.3
	4-7	7	23.3
	8-14	10	33.3
	15-30	10	33.3
	>30	2	6.7

Based on Table 3 the findings of this study were dominated by the severity of moderate and severe neutropenia, respectively 43.3%. Similar to the previous study, which found that malignancy patients with FN were dominated by the severity of severe neutropenia as much as 55.55%.¹⁰ This study found that the duration of ALL patients with FN was in line with the previous finding, which was dominated by the duration of neutropenia of less than 7 days.⁹

The results of this study also showed that most febrile neutropenic patients had fever for less than seven days, which was 66.7%, almost the same as the previous study, which was 80.8%.¹¹ Based on Table 3, patients mostly had duration of hospitalization for 8-14 days and 15-30 days, respectively 33.3%. This is in line with previous studies which found that the longest duration of hospitalization for patients was 15-30 days.⁹

Table 4. Correlation Rondinelli Score with Clinical Outcomes

Risk Category	p-value	R
Length of Hospitalization	.005	.496**
Length of Fever	.000	.618**
Length of Neutropenia	.021	.420*
Severity of Neutropenia	.037	.383*

Bivariate analysis using Spearman's test

Correlation Rondinelli Score with Severity of Neutropenia

Based on Table 4, there is a moderate, positive, and significant correlation between the FN risk score category and the severity of neutropenia with $p=0.037$ ($p<0.05$) and $R=0.383$, which means that the higher the Rondinelli score, the greater the risk of FN patients experiencing infectious disease complications, the more severe the severity of neutropenia will be. In cases of neutropenia with infectious complications, especially mucositis, and gastrointestinal infections, the patients' ANC showed a significantly lower ANC.¹² This is in line with the findings of Badiei et al. that ANC <100 is one of five variables that have a significant correlation with the incidence of life-threatening infections.¹³ The other four predictor variables were fever, mucositis, platelet count, and abnormal lung temperature. This variable is very similar to the component of the Rondinelli score that assesses the risk of infectious complications in febrile neutropenic patients.¹³ Furthermore, from another study, the high risk group with the MASCC score that had an ANC <500 showed a larger number of patients, namely 55% compared to low risk patients, which was only 45%.¹⁴ Another study showed that the incidence of infection in the ANC count <500 was much higher than the ANC between 500-1000, which was 71.4% compared to 28.6%.¹⁵ Thus, it can be concluded that there is a significant relationship between the Rondinelli score category and the severity of neutropenia, related to the incidence of infection. This is because neutrophils are cells that fight and destroy pathogens that cause infection once they are in circulation.¹⁶

Correlation Rondinelli Score with Length of Neutropenia

Based on Table 4, there is a moderate and unidirectional significant relationship between the FN risk score category and the duration of neutropenia with $p=0.021$ ($p<0.05$) and $R=0.420$, which means that the higher the Rondinelli score, the greater the risk of FN patients experiencing infectious complications, the longer the duration

of neutropenia. The same result was obtained from another study in that there was a significant relationship ($p = 0.046$) between the duration of neutropenia and the risk level of pediatric patients with FN.¹⁷ Likewise from Alexander et al. who said that high-risk FN patients had a significantly longer duration of neutropenia than low-risk patients. This is because the longer the patient experiences neutropenia, the higher the risk of the patient experiencing infection due to the weakening of the patient's body defenses against infectious agents.¹⁸ The Guidelines of the Infectious Diseases Working Party, Germany has previously classified the risk of infection based on the duration of the patient experiencing neutropenia. It is said to be low risk if the duration of neutropenia is less than five days, intermediate risk if the duration of neutropenia is 6-9 days, and high risk if the duration of neutropenia is at least 10, days.¹⁹

Correlation pf Rondinelli Score with Length of Fever

Based on Table 4, there is a strong, positive, and significant correlation between the FN risk score category and the duration of fever with $p=0.000$ ($p<0.0001$) and $R=0.618$. It means that the higher the Rondinelli score, the greater the risk of FN patients experiencing infectious complications, the longer the duration of the patient's fever. The results of this study are in line with previous findings which stated that the high risk group of pediatric patients with febrile neutropenia had a significantly longer duration of fever ($p < 0.001$) than the low risk group.¹⁷ Another study said that the median duration of fever in pediatric patients with FN in the group with blood stream infection was significantly greater than in the group without infection.²⁰ This is because fever is an indication of infection, which accounts for a mortality rate of 1%-3% in pediatric patients with all who are undergoing chemotherapy.²¹ In 20-30% of pediatric cancer patients with febrile neutropenia due to bacterial infection, other causes are viral infections, blood product transfusions, cytostatic drugs, malignancy itself, and mucositis.¹⁷

Correlation Rondinelli Score with Length of Hospitalization

Based on Table 4, there is a fairly strong and unidirectional significant relationship between the FN risk score category and the length of stay with $p=0.005$ ($p<0.05$) and $R=0.496$, which means that the higher the Rondinelli score, the greater the risk of FN patients experiencing infectious complications, the longer the duration of patient care. In line with another study using the Clinical Index of Stable Febrile Neutropenia (CISNE) score, it was said that the increase in the risk category of FN patients was directly proportional to the duration of hospital stay ($p < 0.001$).¹⁴ Likewise, the Multinational Association for Supportive Care in Cancer (MASCC) score system shows a longer average duration of care in the high risk group than the low risk group.²² Longer duration of hospitalization in pediatric patients with high-risk FN was also found in another study.²³ Complications such as bacteremia/sepsis, pneumonia, bacterial or fungal infections significantly increase the duration of hospitalization for pediatric patients with FN.²⁴ Another study also showed that the median duration of stay of patients with blood stream infection (BSI) was found to be longer than that of patients without an identified pathogen (19 days versus 10 days).²⁵ Likewise, patients with MDI (microbiologically documented infection) were said to be 4.5 times more likely to have a prolonged duration of stay.²⁶ The duration of hospitalization for pediatric FN patients also had a significant relationship with the incidence of septicemia ($p < 0.0001$).²⁷

CONCLUSIONS

This study found that pediatric ALL patients who experienced febrile neutropenia in the Hematology-Oncology division of the child health department of RSUD Dr. Soetomo most of them have medium risk category and the rest are low risk. There is a fairly strong and direct significant relationship between the Rondinelli score category and the severity of neutropenia, duration of neutropenia, and length of stay. There

is also a strong and direct significant relationship between the Rondinelli score category and the duration of fever. Thus it can be concluded that the higher the Rondinelli score, the more severe the severity of the patient's neutropenia, the longer the patient's duration of treatment, the longer the patient's fever, and the longer the patient's neutropenia.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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