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A STUDY TO ASSESS THE RISK PREDICTORS ASSOCIATED WITH ADVERSE OUTCOMES IN CHILDREN WITH FEBRILE NEUTROPENIA AT A TERTIARY CARE CENTRE.

Paediatric Medicine

Dr. Chitra Marmat Pediatric resident Pediatrics MGMMC Indore,
Dr. Prachi Choudhary Associate Professor Pediatrics MGMMC Indore,
Dr. Dharmanshu Chaube Assistant Professor Pediatrics MGMMC Indore,
Dr. Urvashi Channa* Assistant Professor Pediatrics MGMMC Indore. *Corresponding Author

ABSTRACT

Background: Risk stratification of patients with febrile neutropenia (FN) into those at "High Risk" and "Low Risk" of developing adverse outcomes helps in making decisions regarding optimal treatment, such as whether to treat as inpatient or outpatient and how long to treat the patient. **Methods:** It was a prospective observational study. All patients with Febrile Neutropenia under age of 18 years were enrolled sequentially during the study period. Their detailed clinical history and thorough clinical examination based on a pre-structured proforma were noted. Lab investigations and radiological evaluation were performed to assess risk factors associated with adverse outcomes in these patients according to unit's protocol. **Results:** A total of 11 risk factors were assessed with respect to 5 Adverse outcomes included in our study. History of previous ICU admission in last 6 months(p value <0.05) and higher duration for defervescence of fever(p value<0.05) were a common significant risk factor for all the adverse outcomes. While chemotherapy was a significant risk factor for 4 out of 5 adverse outcomes. **Conclusion:** In conclusion, there is significant association between risk factors and adverse outcomes considered in our study, in patients of febrile neutropenia, accounting for great morbidity and mortality, requiring high degree of clinical suspicion and recognizing and stratifying patients who might require intensive care and treatment, vigilant monitoring and prognostication.

KEYWORDS

Febrile Neutropenia, Adverse Outcomes, Risk Predictors

INTRODUCTION:

Febrile neutropenia (FN) is the development of fever, often with other signs of infection, in a patient with neutropenia, an abnormally low number of neutrophil granulocytes defined as an Absolute Neutrophil Count (ANC) of 1500/MM3

Febrile neutropenia (FN) can be because of transient marrow suppression due viral illnesses is a common and dangerous consequence of myelosuppressive chemotherapy but can occur as part of the disease processes. Risk stratification of patients with febrile neutropenia (FN) into those at "High Risk" and "Low Risk" of developing complications helps in making decisions regarding optimal treatment.

There is a paucity of data on risk predictors for Febrile Neutropenia in a resource limited country like India and therefore we designed and undertook the present study with an aim to assess the risk predictors associated with adverse outcomes in children with Febrile Neutropenia

METHOD:

This prospective observational study was conducted at PICU of Department of Paediatrics MYH and CNBC, Indore (M.P) a tertiary care centre catering population of central India with a pediatric haemat-oncologic unit, chemotherapy day care and bone marrow transplant unit on children presenting with febrile neutropenia and satisfying the inclusion and exclusion criteria after approval from institutional ethics committee.

Inclusion Criteria:

Children from age 1 month- 18 years of age presenting with fever >38.3 c and neutropenia (ANC<1500/mm3) were included for the purpose of this study.

Exclusion Criteria:

Patients who presented with neutropenia without fever and patients who took LAMA during the course of hospitalization were excluded from the study.

Detailed clinical history and thorough clinical examination of the patient was conducted and all the baseline data was recorded on a proforma. After due consent, blood sample of the patient was drawn for routine hematological and other relevant investigations on case-to-case basis as per unit's protocol.. The risk predictors associated with adverse outcomes in children with Febrile Neutropenia were assessed.

We compared 11 risk factors with 5 adverse outcomes, namely, Pts. with Underlying Malignancy, Pts. undergoing chemotherapy, pts. with h/o febrile neutropenia in past 6 months, pts. with h/o previous ICU admission, duration of fever, culture status, defervesence of fever, CRP status, packed cell transfusion, platelet transfusion, ANC on admission.

We analysed the following adverse effects with respect to the above mentioned risk factors, which included 1. Serious medical complication (Morbidities) a).Prolonged ICU Stay(>7 Days) b.)Prolonged Antibiotic Use (>14 Days) c.)Prolonged Ventilator Requirement(>7 Days) d.)Prolonged Ionotropic Requirement(>7 Days) 2.)Death.

The data was collected and entered in Microsoft Excel 2010 (Microsoft corp.) and analyzed using the SPSS version 20.0 operating on Windows 10. All the descriptive data were presented as mean, standard deviation, frequency and percentages represented as the pie charts and bar diagrams. The continuous data were analyzed using student t-test for mean difference and the strength of association between the variable using the Pearson's correlation was calculated. A P value of <0.05 was considered statistically significant.

RESULTS:

A total of 100 patients with Febrile neutropenia were enrolled during a period of one year. A higher preponderance of males was observed with 59 males and 41 females . Maximum number(N=48) of patients were in the age group of 6-10 years (48%) . Fever was the most common symptom found in all patients, followed by diarrhea (47%), Bleeding manifestation (43%), Abdominal pain (35%), Vomiting (33 %), Cutaneous manifestations (27%) and Cough in 26 % patients, while only 1 patient had Peri-anal excoriation. The most common sign found was temperature above 100.9°F (100 %), followed by tachypnea (72%) and tachycardia (52%). Organomegaly was observed in 43% of patients, followed by hypotension (38 %). 30% patients were dehydrated, 21% patients had sick/toxic look, 21% patients also had cutaneous manifestations like petechiae/purpura and 20% had dyspnea, 3 patients had neck rigidity on examination. The most common (36%) underlying condition noted was Infection(N=36) including septicemia (17%), second most common underlying condition in our study population was Malignancy (33%), among which majority had B Cell ALL (23 %), followed by AML (5%), T Cell ALL (4%) and only 1 patient with HL. Most common focus of infection was noted to be Septicemia (50%) [TABLE 2]. Majority of the patients in our study group had anemia (Hb<10 gm%), 26%

patients in our study had severe neutropenia (ANC 0-500), 30% patients had thrombocytopenia, blood culture came positive in 41% patients, whereas CRP was positive in 53% patients. 40% patients required packed cell transfusion whereas 36% required platelet transfusion.

51 patients with FN (i.e) 51% in our study had requirement of Prolonged ICU care, for whom risk factors that were found to be significant were history of ICU admission in past 6 months(N=24, p value<0.05), patients with positive culture(N=40, p value<0.05), lower ANC below<500(N=27, p value<0.05)patients on chemotherapy(N=14, p value<0.05), patients with higher duration for defervescence of fever (N=19, p value<0.05).

58 patients required prolonged Antibiotic administration, risk factors like previous history of ICU admission(N=24, p value<0.05), lower ANC below<500(N=31, p value<0.05), positive culture profile(N=44, p value<0.05) higher duration for defervescence of fever(N=22, p value<0.05), and patients needing platelet transfusion(N=27, p value<0.05) were found to be statistically significant.

17% patients required prolonged Ventilator support, In our study the significant risk factor associated with this adverse outcome were previous history of ICU admission(N=17, p value<0.05) positive culture profile(N=13, p value<0.05), higher duration for defervescence of fever(N=10, p value<0.05), patients on chemotherapy(N=11, p value<0.05), patients requiring platelet transfusion(N=16, p value<0.05), patients requiring packed cell transfusion(N=11, p value<0.05),and patients with underlying malignancy(N=11, p value<0.05). were the risk factors which were significantly associated (p value < 0.05) with patients requiring prololonged ventilatory support 17

18% patients required prolonged ionotropic support, this was significantly associated with risk factors like previous history of ICU admission(N=18, p value<0.05),s positive culture profile(N=14, p value<0.05), higher duration for defervescence of fever(N=10, p value<0.05,) patients on chemotherapy(N=12, p value<0.05) patients needing platelet transfusion(N=16, p value<0.05), patients requiring packed cell transfusion(N=11, p value<0.05) and patients with underlying malignancy(N=12, p value<0.05)

There was 14% mortality in our study group, and the risk factors that were found to be statistically significant were previous history of ICU admission(N=13, p value<0.05), higher duration for defervescence of fever(N=9, p value<0.05), those with underlying malignancy(N=8, p value<0.05), patients on chemotherapy(N=8, p value<0.05) and patients requiring platelet transfusion(N=13, p value<0.05).

- History of previous ICU admission in last 6 months and higher duration for defervescence of fever was a common significant risk factor for all the adverse outcomes.
- Whereas, patients with positive blood cultures, receiving chemotherapy and requiring platelet transfusion were significant risk factors in four out of five adverse outcomes in our study.

Table 1 Signs And Symptoms In Patients With Febrile Neutropenia

	Variable	Frequencyn	Percentage%
Symptoms	Fever	100	100
	Abdominal Pain	35	35
	Cough	26	26
	Sore Throat	13	13
	Headache	5	5
	Altered Sensorium	2	2
	Diarrhea	47	47
	Vomiting	33	33
	Burning Micturition	10	10
	Malena	14	14
	Hematemesis	04	04
	Petechiae/Purpura	25	25
	Peri-Anal Excoriation	01	01
Signs	Temperature	100	100
	Hypotension	38	38
	Tachypnea	72	72
	Tachycardia	20	20
	Dyspnea	20	20
	Dehydration	30	30
	Sick/Toxic Look	21	21
	Organomegaly	43	43
	Petechiae/Purpura	21	21
	Neck Rigidity	03	03

Table 2 Focus Of Infection In Patients With Febrile Neutropenia

	Variable	Frequency	Percentage %
Focus Of Infection	Sepsis(Culture Proven)	50	50
	Respiratory Tract	27	27
	Sinus/Oral Cavity	25	25
	Skin/Soft Tissue	15	15
	Gastro-Intestinal Tract	15	15
	Urinary Tract	13	13
	Multi Organ	08	08

Table 3 Lab Profile Of Patients With Febrile Neutropenia

LAB PARAMETER	N	COLUMN N %
HAEMOGLOBIN		
<5	05	05%
5-10	83	83%
>10	12	12%
TOTAL WBC COUNTS		
0-1000	5	05%
1000-3000	63	63%
3000-5000	12	12%
ANC ON ADMISSION		
0-200	26	26%
200-500	20	20%
500-1000	54	54%
PLATELET COUNT		
<50,000	30	30%
50,000- 1 lacs	20	20%
>1 lacs	50	50%
CRP		
POSITIVE	53	53%
NEGATIVE	47	47%
LAB PARAMETER	**N**	**COLUMN N %**
BLOOD CULTURE		
POSITIVE	41	41%
URINE CULTURE		
POSITIVE	09	09%

Table 4 Association Of Risk Factors With Adverse Outcomes

Risk Factors	Adverse Effect				
	Prolonged Icu Care N=51	Prolonged Antibiotic Use N=58	Prolonged Ventilator CareN=17	Prolonged Inotropic UseN=18	Death N=14
H/O F.N. In Past	Non Sig	Non Sig	Non Sig	Non Sig	Non Sig
H/O Prev. Icu Admission P Value	(N=24) <0.05	(N=24) <0.05	(N=17) <0.05	(N=18) <0.05	(N=13) <0.05
Anc- On Admission	(N=27) <0.05	(N=31) <0.05	Non Sig	Non Sig	Non Sig
Crp	Non Sig	Non Sig	Non Sig	Non Sig	Non Sig
Packed Cell Transfution	Non Sig	Non Sig	(N=11) <0.05	(N=11) <0.05	Non Sig
Platelet Transfusion	Non Sig	(N=27) <0.05	(N=16) <0.05	(N=16) <0.05	(N=13) <0.05
On Chemo therapy	(N=14) <0.05	Non Sig	(N=11) <0.05	(N=12) <0.05	(N=8) <0.05
Culture	(N=40) <0.05	(N=44) <0.05	(N=13) <0.05	(N=14) <0.05	Non Sig
Duration Of Fever	Non Sig	Non Sig	Non Sig	Non Sig	Non Sig
Time For Defervescens e Of Fever	(N=19) <0.05	(N=22) <0.05	(N=10) <0.05	(N=10) <0.05	(N=9) <0.05
Malignancy	Non Sig	Non Sig	(N=11) <0.05	(N=12) <0.05	(N=8) <0.05

DISCUSSION:

This prospective observational study was conducted over a period of 1 year to assess the risk predictors associated with adverse outcomes in children presenting with Febrile Neutropenia(fever more than 38.3 °c and neutropenia (ANC<1500) at our Centre. In general, fever is defined as a single oral temperature of at least 38.3°C or a temperature of at least 38.0°C for 1 h. Severe Neutropenia is defined as an absolute neutrophil count of 500 cells/μL or less.[1]

In resource limited settings, there are many logistical issues in the treatment of FN: Constraints in the form of limited hospital beds and manpower; the higher costs resulting from prolonged hospital stays and intravenous (IV) antibiotics; and disruption of the quality of life of patient and family.

Many anecdotal studies have attempted to define risk factors for complications in pediatric FN, and to develop a protocol defining the clinical risk decision rules and risk prediction models factors for adverse outcome in pediatric FN.[2-8]

However, these studies have used various definitions of adverse outcome, and the risk prediction variables across these studies have not been consistent. To date, few pediatric models have undergone multinational prospective validation, and there is no single accepted score in pediatric FN.[9-13]

The main objective of risk stratification is to identify a subset of children in who FN can be managed on an outpatient basis, thereby reducing the cost and workload on the hospital.[13] In India, this approach has been proposed by centres of excellence with high patient load.[14]

The demographic variables showed a higher preponderance of males i.e., 59(59%) over females 41(41%). This was in concurrence with study done by Prasad M et al.21[15] , who observed a Male: female ratio of 2.2:1 in their study. In our study, Maximum number(N=48) of patients were in the age group of 6-10 years (48%) followed by 40(40%) patients in the age group 0-5 years and least number of patients belonged to 11-18 years of age- 12 (12%). Similar prevalence was observed by **Prasad M et al.**[15], in their study with median age being 6 years (range 0.5-15 years).

In our study, we found that the most common underlying condition presenting with febrile neutropenia was Infections (36%), among which majority of the patients i.e., 17/36 had Septicemia and Respiratory Infections (17%) as the leading causes followed by Urinary tract infections (13 %), Dengue fever (10 %) and Enteric fever (06 %). Second most common underlying condition in our study population was Malignancy (33%), among which majority had B Cell ALL (23 %), followed by AML (5%), T Cell ALL (4%) and only 1 patient with HLH.

A similar study by **Prasad M et al**[15]., 21 reported that amongst 183 patients evaluated ALL was seen in 79 (43%) patients and AML in 27 (14.7%) patients.

In our study, For System involvement, most common focus of infection was noted to be Septicemia (50%), followed by Respiratory tract infections (27%), Sinus/oral cavity infections (25%), Gastro-intestinal tract and Skin/soft tissue infections comprises 15 % focus of infection of the total patient population, followed by Urinary tract infection in (13%) of patients, whereas only 8 % and 5% patients had involvement of Multi organ systems and CNS respectively.

The Laboratory profile of pt. with febrile neutropenia was studied in the present study and the results showed that Majority of the patients in our study group had Anemia i.e, Hemoglobin in the range of 5 – 10 gm% (83%), 63 % patients had Total WBC count in the range 1000-3000/µL, similarly on admission On admission ANC of maximum(54%) patients lied in the range of 500-1000, 26 patients had severe neutropenia with ANC in the range of 0-500 and only 20 patients had ANC in the range of 200 -500. Platelet count of 30% patients was below 50,000. CRP came positive in 53% patients, 53% patients had positive Culture (Blood, Urine and CSF). Deranged RFT was observed in 30%, similarly 42% patients had deranged Liver function tests

Culture profile of patients in our study showed that Staphylococcus (13%) and Pseudomonas (12%) were found to be the most common organism that were isolated from blood culture followed by E. coli (9%), Klebsiella (6%) and only 1 % were positive for Enterococcus. As stated by **Cennamo F et al**[16]. The principal agents responsible of bacteremia in febrile neutropenia were Gram-negative bacteria (GNB), mainly Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa. . As suggested by Kar YD et al.22[17], & Gupta S et al.24[18] , blood culture is by far the most contributory test in any child with FN, albeit its low yield of 20–30%. **Oberoi et al.**[19] pointed out that *Staphylococcus aureus* and *E. coli* were the most common Gram-positive and Gram-negative identified bacteria in children with febrile neutropenia, respectively. Instead, **Jeddi et al.**[20] found that *K. pneumoniae* and *S. aureus* were the predominant Gram-negative and Gram-positive bacteria, respectively. Over the past decade, drug-resistant human fungal infection has been emerging as a serious concern.[21]

Gary H et al.95[22] , in their study suggested that it is important to identify which patients are at high risk for developing FN so that patients can receive optimal chemotherapy while their risk for FN is appropriately managed. A systematic review of the literature was performed to gain a comprehensive and updated understanding of FN risk factors. Older age, poor performance status, advanced disease, certain comorbidities, low baseline blood cell counts, and treatment with myelosuppressive chemotherapies. The factors identified by early studies, including anticipated depth and duration of neutropenia[23] and absence of comorbidities[24], may be among the most practical and robust predictors of a low-risk population.

The clinical prediction rule set by **Rackoff et al.**[25] which had the criteria of AMC and high temperature to exclude bacteremia has been assessed across multiple data sets. History of a previously documented infection diagnosed in the past 6 months of treatment, (either during an episode of FN or otherwise) was also an independent predictor of adverse outcome, and has also been described earlier.

In a study done by **Sulviani, R et al,**[26] they identified whether age, type of malignancy, phase & dose of chemotherapy, nutritional status, and absolute neutrophil count are risk factors for febrile neutropenia In a study done by **Prasad et. al.**[15] , the strongest independent predictor on multivariate analysis (OR - 18) was the presence of a significant focus of infection at presentation or during the course of FN - this has been reported in earlier studies**.**

In our study we considered total of five adverse outcomes and compared them with eleven risk factors.

51 patients with FN (i.e) 51% in our study had requirement of Prolonged ICU care, for whom risk factors that were found to be significant were history of ICU admission in past 6 months, patients with positive culture, lower ANC below<500, patients on chemotherapy, patients with higher duration for defervescence of fever.

58 patients required prolonged Antibiotic administration, risk factors like previous history of ICU admission, lower ANC below<500, positive culture profile,higher duration for defervescence of fever, and patients needing platelet transfusion were found to be statistically significant.

17% patients required prolonged Ventilator support, significant risk factor associated with it were previous history of ICU admission, positive culture profile, higher duration for defervescence of fever, patients on chemotherapy, patients requiring platelet transfusion, patients requiring packed cell transfusion and patients with underlying malignancy **were the risk factors which were significantly associated with patients requiring prolonged ventilatory support.**

risk factors like previous history of ICU admission, positive culture profile, higher duration for defervescence of fever, patients on chemotherapy, patients needing platelet transfusion, patients requiring packed cell transfusion and patients with underlying malignancy were associated significantly with prolonged ionotropic requirement in 18% patients with FN

There was 14% mortality in our study group, and the risk factors that were found to be statistically significant were previous history of ICU admission, higher duration for defervescence of fever, those with underlying malignancy, patients on chemotherapy and patients requiring platelet transfusion.

Our study highlights the association of various risk factors with morbidity and mortality in patients with malignancy as well as patients who did not have any malignant condition with FN . Significant contributory **factors that led to adverse outcomes were Prolonged ICU care, longer defervescence of fever.** In the past, majority of studies on febrile neutropenia were conducted in patients with

malignancy receiving chemotherapy, our study considered malignant as well as non-malignant conditions. Our study is one of the few prospective studies done in a tertiary care Centre, which has assessed the risk factors predictive of adverse outcome in pediatric patients with FN including both Malignant as well as Non-malignant patients. Although this model would need validation across other resource limited settings, it should have risk factors that are pertinent to the local population as well.

CONCLUSION

Our study emphasizes the need for timely initiation of antibiotics based on high-risk patients. A stepwise approach to treatment will avoid over treatment and achieve the best possible outcome. Sufficient attention must be given to the additional challenges encountered in neutropenic children in resource-poor countries. In the past, majority of studies on febrile neutropenia were conducted in patients with malignancy receiving chemotherapy, our study considered malignant as well as non malignant conditions.

Hence, it is hoped that the information gained from this study will help in formulating a risk prediction model which is easy to use, would help in risk stratification of patients, also in vigilant monitoring of At risk patients, laying down SOPs, developing a systematic approach towards patient management and formulating unit protocols for better management of these patients and rationalizing use of antibiotics.

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