# Risk Stratification in Febrile Neutropenic Episodes in Adolescent / Young Adult Patients with Cancer

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## Abstract

Background. Risk stratified management of febrile neutropenia (FN) allows intensive management of high-risk cases and early discharge of low-risk cases. Most risk stratification systems predicting severe infection from admission variables have been derived from childhood or adult populations and consequently their value in adolescents/young adults (AYA) may vary. Our objective was to determine their value in this population.

Methods. Data from the “Predicting Infectious ComplicatioNs In Children with Cancer” (PICNICC) individual participant data collaboration were used to evaluate six previously described risk stratification schema in the AYA population. Complete case analyses were undertaken for 5 ‘paediatric’ rules, with imputation for specific missing variables of the ‘adult’ rule. The rules predictive performance for the outcome microbiologically defined infection (sensitivity, specificity and predictive values) were compared.

Results. Among the 5,127 episodes of FN in 3,504 patients in the PICNICC collaboration data set, 603 episodes of FN from 478 patients in 20 studies were of patients 16-25 years old. The six rules demonstrated variable sensitivity (33% to 96%) and specificity (13% to 83). Their overall discriminatory ability was poor (area under the receiver operator curve estimates 0.514 to 0.593).

Conclusions. Both paediatric and adult FN risk stratification schema perform poorly in AYA with cancer. An alternative rule or clinical recognition of their limitations is required.

Graphical abstract image:

## Introduction

Teenage and young adult patients with cancer have distinct physiological, psychological and social issues from older adults and young children.(1) They are frequently exposed to intensive chemotherapy to treat their life-threatening illnesses, and are subject to more toxicity and side effects than either children receiving similar treatments (2) or adults with similar diseases receiving less intensive therapies.(3) They will often suffer the complication of fever during neutropenia, and they have been identified as a group at higher risk of death than others.(4)

The advancement of risk-adapted therapies for fever and neutropenia (FN) has been ongoing for a number of years, both in adults (5) and children.(6) In both areas of practice, a minority of patients have been teenagers/young adults, and to date no work has specifically examined whether a risk adaptive approach is appropriate in this subset of patients with FN.

An international collaboration (PICNICC) has been formed to undertake an individual patient data (IPD) meta-analysis of risk prediction in children and young people (0 to 25 years old), including 22 separate data sets. (7, 8) This collaboration has used the pooled data to undertake an analysis of patients aged 16 years and older, with the objective of examining the validity of previously proposed clinical decision rules for FN management in this group of patients.

## Materials and Methods

The PICNICC IPD protocol was published prior to commencement of any analysis. (7) The primary aim of the IPD analysis was to quantify the risk of poor FN outcomes according to clinical variables recorded in children and young people (0 – 25 years old) undergoing treatment for malignant disease at the onset of an episode of FN and to develop a new risk prediction model(8). For this paper, we used data from patients aged 16 – 25 years old. The secondary aim was to assess existing clinical prediction rules which have been validated in ‘child’ or ‘adult’ populations. The ‘child’ rules were selected as described in prior systematic reviews (9), with rules produced by Rackoff (10), Alexander (11), the Chilean paediatric oncology collaborative (12), the Swiss paediatric oncology group (13), and Ammann (14) (see Table 1). The ‘adult’ rule was selected as the most widely used schema, validated in previous studies and recommended in European and North American clinical practice guidelines (4, 5) .

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Rackoff** | **Alexander** | **PINDA** | **SPOG** | **Ammann** | **MASCC** |
| Outcome predicted | Bacteraemia | Serious medical complication | Invasive bacterial infection | Adverse FN outcome | Significant infection | Serious medical complication |
| Derivation population | 115 episodes, range 9m to 18y | 188 episodes, mean 8.9y (standard deviation 5.7y) | 263 episodes, mean 7y (range 7m to 17y) | 423 episodes, 6.9y (IQR 3.8 to 11.6y) | 285 episodes, median 6.3y (IQR 3.2y to 12.1y) | 756 episodes, 52y (range 16y to 91y) |
| Derivation setting | Indianapolis, USA, 1994 - 1995 | Boston, USA, 1994 - 1995 | 6 centres in Santiago, Chile, 1999 - 2000 | 6 centres in Switzerland & Germany, Europe, 2004-2007 | Bern, Switzerland, 1993 - 2001 | 20 institutions (in 15 countries),  December 1994 to November 1997 |
| Background factors | None | AML, Burkitt lymphoma, induction ALL, progressive disease, relapsed with marrow involvement | Relapsed leukaemia | 4 points for chemotherapy more intensive than ALL maintenance | Bone marrow involvement, central venous catheter, pre-B-cell leukemia | Solid tumor/lymphoma with no previous fungal infection  Age <60 years 2 |
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| Episode specific factors | Absolute monocyte count | Hypotension, tachypnea/hypoxia <94%, new CXR changes, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, other clinical reason for in-patient treatment | Chemotherapy within 7 days of episode, CRP ≥90 mg/L, hypotension, platelets ≤50,000/uL | 5 points for haemoglobin > 9 g/dL, 3 points each for white blood cell count <300/uL, platelet < 50,000/uL | Absence of clinical signs of viral infection, CRP >50 mg/dL, white blood cell count <500/uL, haemoglobin >10g/dL | Burden of illness: no or mild symptoms: 5, moderate symptoms 3 severe symptoms 0  Outpatient status (at onset of fever) 3  No hypotension (systolic BP >90 mmHg) 5  No chronic obstructive pulmonary disease 5  No dehydration 4 |
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| Low risk group | Absolute monocyte count > 100/uL | Absence of any risk factor | Zero risk factors or only low platelets or only <7 days from chemotherapy | Total score <9 | Three or fewer risk factors | Total score >21 |

TABLE 1: Composition of the selected clinical decision rules

IQR = interquartile range, y = years, uL = microlitres

### Collaboration development

The PICNICC collaboration was formed from international clinical and methodological experts, parent representatives and healthcare researchers, identified during preliminary systematic reviews(6, 15), in response to oral presentations at oncology conferences, and web-based invitations. Parents/carers were approached via UK parent support organisations. Ethical approval for the study was granted in the UK and individual members were advised to contact their local ethics board to determine the need for further approval (7) (16).

### Data acquisition

The authors of studies of FN who are members of the PICNICC working group supplied episode-by-episode, de-identified individual-level data from their studies of new-onset episodes of FN. These included patient-level variables measured on admission: patient age at, and date of, each episode of FN; underlying malignancy type; remission status; chemotherapy type and date of last cycle; type of central venous line; in/out-patient status; maximum temperature; clinical observations including global assessment of illness severity and mucositis; blood count parameters; inflammatory biomarkers; and empirical antibiotics used. The outcome used in this analysis was of microbiologically defined infection (MDI). We permitted any definition described in the original study and did not insist on the Immunocompromised Host Society consensus definition.(17) This outcome was the most frequently and consistently reported clinically relevant outcome in the data available, and was highly correlated, where data were available, with the less frequently reported “serious medical complication” detailed in the recently published core outcome set.(18)

### Statistical methods

IPD from the 22 data sets were collected, collated and cleaned, and the predictive and outcome variable (microbiologically defined infection) summarised. Studies were excluded if they did not provide the outcome of interest. Episode-by-episode calculations were made from these data for each of the selected risk stratification rules. From these, the sensitivity, specificity and predictive values of the rule were calculated, along with the proportion of episodes correctly and incorrectly classified by each rule and the area under the receiver operator curve (AUC ROC, also known as the C-statistic). The R software environment(19) using the packages ‘rms’(20) and ‘pROC’(21) were used.

For the five ‘paediatric’ rules, a complete case analysis was performed, and episodes from studies used to derive the rule were excluded. For the ‘adult’ MASCC rule, data on previous fungal infection and chronic obstructive pulmonary disease (COPD) are required, but were unavailable in all data sets. We chose to model this assuming a) no patient had COPD, b) no patient without leukaemia had experienced a prior fungal infection, and c) for those patients with leukaemia, modelled both prior fungal infection and lack of prior fungal infection as the ‘upper’ and ‘lower’ estimations of this rule’s performance.

## Results

Among the 5,127 episodes of FN in 3,504 patients in the PICNICC collaboration data set, 603 episodes of fever and neutropenia were found from AYA patients. There were 478 separate patients, with a median of 1 (range 1 – 10) episodes per patient. The median age at first episode was 18.5 years (interquartile range 17.0 to 21.4 years old) and 56% (where sex was recorded) were male (n=250). They were treated for a wide variety of conditions, with the majority having an acute leukaemia (316 episodes, 52%), with approximately equal proportions of episodes in patients with lymphoma (n=126, 21%) and solid tumours (n=134, 22%), and a very small number of patients with other conditions, for example, undergoing haematopoietic stem cell transplant for non-malignant disease (n=19, 3%) or brain tumours (n=8, 1%). Microbiologically defined infection was recorded in 160 (28%) of episodes, and there were thirteen deaths (2.2%, significantly higher than in children up to 16 years: 1.1%; p=0.039). The varied collection of data from the different groups of the PICNICC collaboration meant that a different number of complete cases were available for testing each rule.

The discriminatory accuracy of each of the six rules to determine microbiologically defined infection is given in Table 2, and illustrated in ROC space in Figure 1.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Rule** | **N episodes** | **Sensitivity** | **Specificity** | **AUC ROC** | **p value** |
| **(95% CI)** | **(95% CI)** | **(95% CI)** |  |
| Rackoff rule (low risk group) | 79 | 0.59  (0.35 to 0.83) | 0.23  (0.13 to 0.33) | 0.593  (0.46 to 0.72) | 0.17 |
| Alexander | 196 | 0.96  (0.91 to 1) | 0.13  (0.07 to 0.19) | 0.547  (0.51 to 0.59) | 0.01 |
| PINDA | 17 | 0.8  (0.41 to 1) | 0.33  (0.05 to 0.61) | 0.567  (0.33 to 0.81) | 0.59 |
| SPOG | 30 | 0.73  (0.45 to 1) | 0.21  (0.02 to 0.4) | 0.531  (0.36 to 0.70) | 0.72 |
| Ammann | 18 | 0.33  (0 to 0.74) | 0.83  (0.61 to 1) | 0.583  (0.35 to 0.82) | 0.49 |
| MASCC (upper) | 113 | 0.73  (0.56 to 0.9) | 0.36  (0.26 to 0.46) | 0.544  (0.44 to 0.65) | 0.41 |
| MASCC (lower) | 113 | 0.38  (0.19 to 0.57) | 0.64  (0.54 to 0.74) | 0.514  (0.40 to 0.62) | 0.81 |

TABLE 2: DISCRIMINATORY VALUES

95% CI = 95% confidence interval, p-value uses hypothesis test H0 AUC ROC = 0.5 (no discriminatory value)

The predictive ability of the rules, outlining the proportion of episodes classified as low risk, and the proportion of correct classifications of low-risk episodes, are detailed in Table 3.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Number of episodes available for analysis | Proportion of episodes with MDI | Number and proportion of episodes classified as low risk | Number and proportion of low risk patients classified incorrectly |
| Rackoff rule (low risk) | 79 | 17 (22%) | 21 (27%) | 7 (33%) |
| Alexander | 196 | 52 (27%) | 21 (11%) | 2 (10%) |
| PINDA | 17 | 5 (29%) | 5 (29%) | 1 (20%) |
| SPOG | 30 | 11 (37%) | 7 (23%) | 3 (43%) |
| Ammann | 18 | 6 (33%) | 14 (78%) | 4 (29%) |
| MASCC(upper) | 113 | 26 (23%) | 38 (34%) | 7 (18%) |
| MASCC(lower) | 113 | 26 (23%) | 72 (64%) | 16 (22%) |

TABLE 3: PREDICTIVE VALUES

MDI = microbiologically defined infection

All rules perform poorly in discriminating AYA patients at low and high risk of microbiologically defined infection (AUC ROC estimates all below <0.6), and data for only one rule (Alexander) are strong enough to support this rule demonstrating greater discrimination than chance (AUC ROC >0.5, p=0.01).

## Discussion

This study sought to assess the validity of previously proposed clinical decision rules for prediction of MDI in 603 episodes of FN in patients aged between 16 and 25 years old, using individual participant data collected by the PICNICC collaborative. The six rules evaluated have been validated in similar age populations to their derivation (five in children, and one in adults) but not in the AYA age group.

The rules varied in either being very sensitive but poorly specific (e.g. the Alexander rule), or poorly sensitive but moderately specific (e.g. the Ammann rule), where sensitivity is the proportion of people with MDI correctly identified, and specificity is the proportion of people without MDI identified correctly. To some extent this difference could be expected as different cut-offs may be selected for different clinical purposes. Rules to send patients home early will be designed with a high sensitivity, to produce fewer ‘false negatives’ i.e. patients with MDI who have been discharged and specificity will be sacrificed. If the rule were intended to select patients for prophylactic transfer to an intensive care unit, the specificity would be valued more highly than sensitivity. However, these rules were all designed for selecting groups for out-patient or low-intensity management, and so were produced to reasonably maximise sensitivity.

When assessed using AUC ROC, each rule demonstrated poor discrimination, with values consistently <0.6. As a rule of thumb, AUC ROC values 0.5-0.6 are considered poor, 0.6-0.7 moderate, 0.7-0.8 fair, 0.8-0.9 good and values >0.9 excellent. While the uncertainty associated with these values was large, as each rule was assessable in only a relatively small number of episodes, there is little support for their immediate use in the AYA group. This finding mirrors a failure to validate decision rules between South American and European populations(9) and to a lesser extent between different European countries(22).

The potential explanations for this lack of discriminatory ability include the different but clinically similar outcomes sought in the original rules, for example the MASCC rule predicts ‘serious medical complications’ rather than MDI (23); a different pattern of clinical presentation to health services, with longer time to contact; different physiological responses(24); or true overoptimistic initial evaluations of the validity of the rules. Further research should benefit from a consistent set of recorded outcomes, with comparable definitions, following the publication of a suggested core outcome set(18).

As many AYA with cancer are cared for in an environment run under the auspices of either paediatric or adult physicians the practical implementation of a different care pathway for children younger than 16, AYA between 16 and 25, and adults 26 years and older may be very challenging. This does not argue for either the abandonment of risk-stratified care or the imposition of unsuitable rules, but instead engagement from both paediatric and adult parties to discuss the uncertainties surrounding those presenting with FN in the AYA age range. For example, with appropriate discussion and shared responsibility, AYA patients may chose a ‘low risk’ management approach with an awareness that their risk of mis-attribution, with consequent need to return for increased intensity care, would be greater than younger or older patients assessed on the same schema. Further research, both in the predictive value of such rules and the views of those patients in whom they would be used, needs to consider AYA with cancer as a subset with unique properties and requiring specific study.

## Figure Heading

Figure 1. Test accuracy of the rules plotted in receiver-operator characteristic (ROC) space with their 95% confidence intervals. The 45o line shows indicated non-discriminatory tests.

## Conflicts of Interest

No author has any financial or non-financial conflict of interest relevant to the contents of this study.

## The Collaboration

The PICNICC collaboration is formed by those who have contributed data, or for patient/carer partners, significantly developed the project. The members are currently: the Authors, Gabrielle M Haeusler (Australia), Tiene Bauters & Geneviève Laureys (Belgium), Maria Spassova (Bulgaria), Robert Klaassen & Sarah Alexander (Canada), Pamela Silva & Juan Tordecilla (Chile), Marianne Paesmans & J Peter Donnelly (EORTC), Arne Simon (Germany), Ian M Hann, Neil Ranasinghe, Richard D. Riley, Julia Chisholm, Daniel Yeomanson, Alex J Sutton & Rachel Dommett (GB), Ajay Gupta (India), Elio Castagnola & Ricarrdo Haupt (Italy), Karin Meidema (Netherlands), Thomas Kuehne , Lidija Kitanovski (Slovenia), Felix Niggli & David Nadal (Switzerland), Gulsun Tezcan (Turkey), Hana Hakim & Glen Stryjewski (US)

## Keywords

adolescent/young adult oncology; supportive care; infectious complications; neutropenic sepsis

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