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Title

Prevalence and predictors of poor outcome in children with febrile neutropaenia presenting to the Emergency Department.

Short title

Prognostication in children with febrile neutropaenia.

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Contributorship statement
Associate Professors Long and Haeusler, and Professor Babl had the original study idea. Associate Professor Haeusler wrote the protocol and obtained ethics approval. Associate Professor Long conducted the initial analysis and wrote the first draft of the resulting paper. Professor Babl, Dr N Phillips, Professor Craig, Dr Zhang, Dr Kochar, Dr McCaskill, Professor Borland, Professor Slavin, Professor R Phillips, Mr Lourenco, Professor Michinaud, Professor Thursky, and Associate Professor Haeusler critically reviewed and revised the manuscript for critical intellectual content. All authors contributed to the study concept and design; acquisition, analysis, and interpretation of data; drafting and revising the manuscript; and agree to be accountable for the accuracy and integrity of the work.

List of key words
Febrile neutropaenia; child; cancer; multiple organ failure; sepsis; Emergency Services, Hospital

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Abbreviations:

ANC	absolute neutrophil count
AUROC	area under the receiver operating characteristics curve
BP	blood pressure
CRT	capillary refill time
ECLS	extra-corporeal life support
ED	Emergency Department
FN	fever and neutropaenia
GCS	Glasgow Coma Scale
HR	heart rate
ICU	Intensive Care Unit
IQR	inter-quartile range
LOS	length of stay
MV	mechanical ventilation
PICNICC	Predicting Infectious Complications in Children with Cancer
qPELOD-2	quick Pediatric Logistic Organ Dysfunction-2
qSOFA	quick Sequential Organ Failure Assessment
REDCap	Research Electronic Data Capture
RR	respiratory rate
RRT	renal replacement therapy
ScvO2	central venous oxygen saturations
SIRS	Systemic Inflammatory Response Syndrome

Abstract

Background: Children with acquired neutropaenia due to cancer chemotherapy are at high risk of severe infection. This study aims to describe the prevalence and predictors of poor outcomes in children with fever and neutropaenia (FN).

Methods: A multi-center, prospective observational study in tertiary Australian Emergency Departments. Cancer patients with FN were included. Fever was defined as a single temperature ≥38ºC, and neutropaenia was defined as an absolute neutrophil count <1000/mm^3. The primary outcome was the intensive care unit (ICU) admission for organ support therapy (inotropic support, mechanical ventilation, renal replacement therapy, extra-corporeal life support). Secondary outcomes were: ICU admission, ICU length of stay (LOS) ≥3 days, proven or probable bacterial infection, hospital LOS ≥7 days, and 28-day mortality. Initial vital signs, biomarkers (including lactate), and clinical sepsis scores including: Systemic Inflammatory Response Syndrome (SIRS), quick Sequential Organ Failure Assessment (qSOFA), and quick Pediatric Logistic Organ Dysfunction-2 (qPELOD-2) were evaluated as predictors of poor outcomes.

Results: Between December 2016 and January 2018, 2124 episodes of fever in children with cancer were screened, 547 episodes in 334 children met inclusion criteria. Four episodes resulted in ICU admission for organ support therapy, nine episodes required ICU admission, ICU LOS was ≥3 days in four, hospital LOS was ≥7 days in 153, and two patients died within 28 days.

Vital signs, blood tests, and clinical sepsis scores, including SIRS, qSOFA, and qPELOD-2, performed poorly as predictors of these outcomes (AUROC <0.6).

Conclusions: Very few patients with FN required ICU-level care. Vital signs, biomarkers, and clinical sepsis scores for the prediction of poor outcomes are of limited utility in children with FN.

Section 1. What is already known on this topic

1. Children with fever and neutropaenia are thought to be at high risk of severe infection and poor outcome.

2. Risk prediction tools to date have focused on identifying those at low risk of microbiologically diagnosed infection who may be suitable for outpatient management.

Section 2. What this study adds

1. This large prospective observational study describes the low prevalence of multiple poor outcomes in children with fever and neutropaenia, and the poor predictive performance of biomarkers and sepsis scores for these outcomes.

2. Future directions may include redirecting low-risk prediction rules to address clinical rather than microbiological outcomes.

Introduction

Children with chemotherapy-induced neutropaenia are at risk of developing invasive infections and infection related complications[1]. As a result, guidelines for the treatment of febrile neutropaenia (FN) in children recommend universal early administration of broad-spectrum antimicrobial therapy, regardless of the clinical severity of disease[2]. Yet children with FN are a heterogenous group, with varying risk of invasive infection and resulting complications. The degree of bone marrow suppression, features of inflammation, and clinical judgement predict the presence of invasive bacterial infection in children with FN across multiple studies, including the prospective Australian Predicting Infectious ComplicatioNs in Children with Cancer (PICNICC) study[3]. Prediction of severity of disease, however, has focused on identifying those at *low* risk of infection who may benefit from reduced intensity, home-based treatment[4]. Few studies have focused on identifying those at *high* risk for severe infection, clinical deterioration, and poor outcome[5-7].

In the non-neutropaenic general paediatric population, early markers of severe infection have been evaluated as predictors of clinical deterioration and poor outcome, including: vital signs, biomarkers (including lactate), and clinical sepsis scores[8-10]. These parameters may have clinical applicability in differentiating patients at high risk of clinical deterioration and poor outcome from those at low risk. Early differentiation allows targeted therapy and appropriate resource allocation, and has been shown to improve outcomes in non-neutropenic children[11], and adults with cancer[12]. Despite the frequency with which these parameters are utilised in the ED to triage and risk stratify the general paediatric population, they have not been specifically evaluated in children with FN.

The aim of this study was to evaluate the prevalence of poor outcomes, and the performance of paediatric sepsis scores, vital signs, and commonly used biomarkers to predict poor outcomes in children with cancer and FN.

Methods

This was a secondary analysis of the Australian PICNICC dataset, a prospective, multicentre, non-interventional FN study enrolling participants from all eight Australian tertiary paediatric hospitals (Australian and New Zealand Clinical Trials Registry 12616001440415)[4]. The primary objective of the PICNICC study was to validate existing paediatric FN clinical decision rules designed to predict infection or adverse events[4]. As such, the study prospectively collected outcome data according to international consensus paediatric FN definitions, including intensive care unit (ICU) admission, organ support therapies, length of stay (LOS), and infection diagnosis[13].

Children with leukaemia or solid organ cancer with chemotherapy induced neutropenia and fever who presented to the ED were eligible for inclusion in this secondary analysis. Demographic, clinical, and outcome data were prospectively collected by site research assistants, and de-identified data was entered into a Research Electronic Data Capture (REDCap) database. Data accuracy was verified by the site investigator (oncology or infectious disease physician). Clinical management was not influenced by study procedures and followed local FN guidelines.

For this analysis, the primary outcome was the prevalence of ICU admission for organ support therapy at any time during the FN episode. Secondary outcomes evaluated were the prevalence of any ICU admission, ICU length of stay (LOS) ≥3 days, individual organ support therapies, proven or probable bacterial infection, hospital LOS ≥7 days, and 28-day mortality[14-16]. These outcomes have been identified as important to children, carers, and clinicians[15, 17]. All outcome data were collected at the end of the FN episode, and on day 30 following ED presentation.

Clinical variables, routinely used in the ED setting, were evaluated as predictors of poor outcome, including: initial vital signs (heart rate (HR), respiratory rate (RR), blood pressure (BP), capillary refill time (CRT), and Glasgow Coma Scale score (GCS)), biomarkers (serum lactate, creatinine, and central venous oxygen saturations (ScvO2)). Three paediatric sepsis scores (Systemic Inflammatory Response Syndrome (SIRS), quick Sequential Organ Failure Assessment (qSOFA), and quick Pediatric Logistic Organ Dysfunction-2 (qPELOD-2) were also evaluated (Table 1)[9, 18, 19]. Clinical data, including vital signs and pathology results, were obtained between 0-4 hours from the time of ED presentation. The worst recorded values over this time-period were used. Sepsis management, including time to first antibiotic and fluid resuscitation, were also obtained between 0-4 hours from the time of ED presentation. Vital signs and pathology results that were not recorded were assumed to be normal, in keeping with prior validation studies[9].

Definitions:

Fever was defined as a single temperature ≥38^{o}C, and *neutropaenia* was defined as an absolute neutrophil count (ANC) <1000/mm^{3} [4].

Organ support therapy was defined as the requirement for inotropic support, mechanical ventilation (MV), renal replacement therapy (RRT), or extra-corporeal life support (ECLS).

End of febrile neutropaenia episode was defined as: no fever for >48hours, recovery of ANC beyond nadir, and cessation of antibiotic therapy[4].

Blood stream infection was defined as a recognised pathogen (including organisms associated with mucosal barrier injury in the setting of mucositis or neutropaenia) from ≥1 blood culture set or common commensals from ≥2 blood culture sets drawn on separate occasions[13].

Proven or probable bacterial infection was defined as: any infection with a microbiologically documented bacterial cause or that was clinically documented in categories typically attributed to bacterial infection, including pneumonia, skin and soft-tissue infection, osteomyelitis or myositis, enterocolitis, otitis media or externa, sinusitis, epididymo-orchitis, central venous catheter pocket or tunnel infection, pharyngitis, peri-anal abscess or cellulitis, peritonitis, lymphadenitis, or culture negative sepsis[3].

Tachycardia, tachypnoea, abnormal CRT, and *hypotension* were defined as per age-adjusted international consensus criteria[8].

Decreased conscious state was defined as GCS score <11[9].

Serum lactate was evaluated for levels ≥2 and ≥4mmol/L due to variability in the definition of hyperlactaemia[18].

Abnormal creatinine was defined according to PELOD-2 criteria[9].

Abnormal ScvO2 was defined as ≤70%[20].

Prolonged hospitalisation was defined as ≥7 days[16].

SIRS criteria, qSOFA criteria, and qPELOD-2 criteria were defined as per Table 1.

Analysis: Continuous data were presented as median and interquartile range (IQR). The sensitivity, specificity, positive and negative predictive value and area under the receiver operating characteristics curve (AUROC) for each clinical variable and each sepsis score were calculated. AUROC values <0.60 were considered poorly predictive[21]. Statistical analysis was performed using Stata 14 (StataCorp. 2015. *Stata Statistical Software:Release 14*. College Station, TX: StataCorp LP).

The study had national and site-specific Human Research Ethics Committee approval and informed patient consent was obtained (HREC #16RCHM108).

Results

Over a 13-month period (December 2016 – January 2018), 2124 episodes of fever in children with cancer were screened, in whom 858 episodes in 462 patients met inclusion criteria for the original study[4]. Five-hundred and forty-seven of these episodes in 334 patients presented to the ED and were included in this analysis (figure 1). Demographic data were available for all patients.

Median age of included patients was 5.7 years (IQR 3.6 – 10.6 years), and 154 (46.1%) were female. Underlying oncological diagnosis was acute leukaemia in 161 (48.2%), lymphoma in 27 (8.2%), and solid tumour in 146 (43.7%). The ANC was <500/mm^3 in 482 episodes (88.1%), and <300/mm^3 in 439 (80.3%). Three-hundred and twenty-nine (98.5%) had a central venous access device. No episodes were receiving antibacterial prophylaxis with a fluoroquinolone or equivalent. Fluid bolus' were administered in 66 (12.1%) episodes: ≤10ml/kg in 35 (6.4%), 11-

20 ml/kg in 23 (4.2%), 21-30 ml/kg in 4 (0.7%), 31- 40 ml/kg in 2 (0.4%), and >40ml/kg in 2 (<0.4%).

Fifty-five (10.1%) episodes had a proven bacterial bloodstream infection, 37 (6.8%) had a proven or probable other bacterial infection, and 306 (55.9%) had fever of unknown origin as the documented cause of their presentation (Table 2).

Prevalence of clinical variables: Full blood count, heart rate, RR, and GCS score were recorded for all episodes. Blood pressure was recorded in 544 episodes, CRT in 360, creatinine in 540, lactate in 357, and ScvO2 in 347. The most common vital sign abnormality was tachypnoea in 518 (94.7%), followed by hypotension in 311 (56.9%) and tachycardia in 299 (54.7%). Decreased conscious state was observed in 4 (0.7%). Sixty episodes (10.9%) were associated with a serum lactate ≥2mmol/L, and six (1.1%) had a serum lactate ≥4mmol/L. Serum creatinine was elevated in six episodes (1.1%), while ScvO2 was ≤70 in 209 (38.2%). Two-hundred and seventy-three (49.9%) of episodes met SIRS criteria, four (0.7%) met qSOFA criteria, and only one (0.2%) met qPELOD-2 criteria(Table 2).

Primary outcome: Four episodes (0.7%) resulted in ICU admission for organ support therapy, including inotropic support in three, MV in two, and both therapies in one episode. No patients were commenced on RRT or ECLS.

Secondary outcomes: Nine episodes (1.6%) resulted in ICU admission, including five that did not require any organ support. Overall median ICU LOS was 36.6 hours (IQR 18.9-83.8 hours),

and was ≥3 days in four (0.7%) patients. Median hospital LOS was 4.6 days (IQR 2.7-7.6 days), and was ≥7 days in 153 patients (28.0%). All-cause 28-day mortality was two (0.4%), neither of which were attributed to infection (Table 2).

Performance of clinical variables and sepsis scores: For the calculation of SIRS, qSOFA, and qPELOD-2, there were no missing data. For the calculation of qPELOD-2, crt data were missing in 7/547 (1.2%), and lactate data were missing in 190/547 (34.7%) and assumed to be normal. Overall, vital signs and sepsis scores performed poorly for the prediction of the primary (Table 3) and secondary outcomes (Supplementary Tables 1-7), with most AUROCs <0.6. While the presence of tachycardia, hypotension or SIRS criteria had a sensitivity of 100% and an AUROC between 0.70 and 0.75 for the prediction of ICU admission for organ support, specificity was poor (Table 3). Of the 60 episodes with a raised serum lactate (≥2mmol/L), only 13 had a proven or probable bacterial infection documented, and only one was subsequently admitted to ICU for organ support (Table 3). Similarly, all variables performed very poorly for prediction of proven or probable bacterial infection or prolonged hospital LOS with AUROC all <0.55 (Supplementary Tables 1-7).

Discussion

In this multi-centred, prospective observational study, we found that our primary outcome (ICU admission for organ support therapy) was infrequent in children with FN presenting to the ED. Vital signs, blood biomarkers, and existing paediatric sepsis scores were non-discriminatory in this population. Out of a total of 547 episodes of care, only nine required ICU admission, and fewer still required organ support therapy. Children with cancer and fever require rapid access to

high quality care to promote good outcomes, this study supports the continued application of existing highly functional care pathways. The proportion of episodes with the primary and most of the secondary outcomes was low, limiting conclusions that could be drawn. Nevertheless, the lack of association between vital signs or biomarkers routinely used the ED to differentiate well from unwell children is striking, particularly in this population of children considered to be at high risk of severe infection and poor outcome.

The low prevalence of secondary outcomes was similar to that observed in non-neutropenic children presenting to the ED with suspected bacterial infection[16]. ICU LOS was ≥3 days in only four (0.7%) episodes, and 28-day mortality was rare, with two deaths (0.4%). While hospital LOS ≥7 days occurred in 153 (28.0%) episodes, and considered a sign of poor outcome in the non-cancer population[16], this may be influenced by some patients remaining in-hospital beyond the end of FN episode to received other cancer-directed treatment such as chemotherapy. We also showed that vital signs and clinical biomarkers, such as lactate, creatinine, and ScvO2, though used in clinical practice and recommended in the paediatric surviving sepsis guidelines to identify severely unwell children at risk of clinical deterioration[22], individually were also non-discriminatory.

Tachycardia, tachypnoea, and hypotension were common in the study population, and in isolation did not confer an increased risk of clinical deterioration. Similarly, in a study of children with undifferentiated fever presenting to the ED, where abnormal vital signs meeting sepsis criteria were observed in >90% of children, the majority were discharged home without antibiotics[23]. Defining hypotension in children is problematic and age-based thresholds for blood

pressure have not been validated in this population[24], and are not included in most paediatric sepsis definitions[8]. Nevertheless, hypotension is regarded a late sign of circulatory failure, indicative of imminent cardiovascular collapse[25]. In this population of children with FN, hypotension was observed in 311 (56.9%) episodes, yet the majority did not go on to require inotropic support or ICU admission. This may have resulted from adequate circulatory supportive care in the form of fluid bolus therapy, though this was administered in only 12.1% of episodes. Blood pressure values used to define hypotension may not have been used by clinicians, in isolation, when making treatment decisions. Previously published data from the Australian PICNICC study identified that more subjective and global assessment of being 'clinically unwell' was predictive of a proven or probable bacterial infection[3].

Decreased conscious state was observed in very few children (four, <1%). This may have been due to the infrequency of primary neurological disease in the study population, and the infrequency of severe derangements in circulatory or respiratory vital signs that may have secondarily affected conscious state. Nevertheless, altered conscious state did not predict clinical deterioration.

Elevated venous lactate was not a good predictor of clinical deterioration in the study population. In addition, the risk of ICU admission did not increase with increasing lactate levels. This stands in contrast to studies in non-neutropenic children with suspected invasive bacterial infection, where higher venous lactate levels have been associated with higher risk of organ dysfunction and death[18]. In keeping with the results of our study, van Nassau found that the inclusion of venous lactate >2mmol/L to a sepsis scoring tool did not improve its predictive performance for

prolonged hospital LOS[16]. Elevated initial serum creatinine was similarly not associated with poor outcome in our study, despite its validation as an early predictor of mortality in the overall PICU population[9]. This may have resulted from the infrequency of early infection-related acute kidney injury in the study population, where only six (1.1%) had elevated initial serum creatinine.

Children with FN have central venous access in the majority of cases. This allows a unique opportunity to evaluate ScvO2 as a marker of the balance between oxygen delivery and oxygen extraction / consumption. Central venous oxygen saturation >70% formed part of the early goal directed therapy strategy for adult sepsis[26], and has been used in the paediatric post-operative cardiac setting to predict major adverse events[20]. In the population of children with FN, however, ScvO2≤70% was not demonstrated to be a good predictor of clinical deterioration.

Clinical sepsis scores, based on combinations of abnormal vital signs, had poor test characteristics for predicting clinical deterioration in the study population. While all children requiring organ support therapy did meet SIRS criteria, almost 50% of those episodes that did not experience clinical deterioration also met SIRS criteria. In addition, meeting SIRS criteria did not significantly increase the odds of hospital LOS ≥7 days. The qSOFA and qPELOD-2 scores were not predictive of the need to organ support therapy or ICU LOS ≥3 days, and were poorly predictive of hospital LOS ≥7 days. Beyond the potential limitations of each score outlined in Table 1 when applied to children with FN, several other factors may explain these findings. Notably, these scores have only been validated in the ICU population, where there is a higher pre-test probability of clinical deterioration. In a study evaluating clinical scores as

predictors of clinical deterioration in immunocompetent children with suspected bacterial infection in the ED, SIRS, qSOFA, and qPELOD-2 were poorly predictive of hospital LOS≥7 days (AUROC SIRS 0.49, qSOFA 0.53, qPELOD-2 0.51), and only moderately predictive of ICU admission or death (AUROC SIRS 0.64, qSOFA 0.72, qPELOD-2 0.60)[16]. Finally, immune suppression in children with FN may attenuate the normal physiological response to infection, making scores based on this physiological response less useful.

While our study is the first of its kind to explore performance of paediatric sepsis scores in children with cancer and FN, the results are limited by the infrequency of clinical deterioration in this population. This resulted in poor performance of all predictive tests and scores, and wide confidence intervals for AUROC values. As a non-interventional study, the impact of early supportive therapies and antibiotic administration is unknown, though may have contributed to the low number of poor outcomes. As a post-hoc analysis of a prospectively collected database, some data were missing, further limiting the conclusions that can be drawn. Vital signs and blood tests were assumed to be normal if not recorded, this may have been an incorrect assumption. This was unlikely to have a significant impact on the use of vital signs or sepsis scores (SIRS, qSOFA, qPELOD-2) to predict poor outcome in this population, as these data were available in the vast majority of episodes. The impact of missing data on qPELOD-2 may have been greater, as lactate data was missing for one third of episodes.

Conclusion

Clinical deterioration requiring ICU-level care was very uncommon in children presenting to the ED with FN. Vital signs, biomarkers, and clinical sepsis scores all had limited ability to predict

clinical deterioration in this patient group. Future studies may focus on early identification of children with FN at *low* risk for clinical deterioration.

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Figure 1. Study enrolment diagram.

Table 1. Characteristics of clinical scores used to predict clinical deterioration in children with severe infections.

Score	Clinical variables used to calculate score	Outcomes measured	Setting	Limitations in febrile neutropenia
Systemic Inflammatory Response Syndrome (SIRS)[8]	2 of: Fever >38·5ºC Tachycardia Tachypnoea Leukopenia or leukocytosis (must include either fever or leukocytosis)	Diagnosis of sepsis, severe sepsis, and septic shock	ED	Corticosteroids may dampen fever response. Physiological response to infection / leukocyte count may be altered by chemotherapy.
Quick Sequential Organ Failure Assessment (qSOFA)[10]	3 of: Tachypnoea GCS score <11 Hypotension	Death or ICU admission / LOS ≥3 days or Hospital LOS ≥7 days	ED ICU	Physiological response to infection may be altered by chemotherapy Underlying disease may alter baseline Glasgow Coma Scale score
Quick Pediatric Logistic Organ Dysfunction-2 (qPELOD-2)[19]	3 of: Tachycardia GCS score <11 Hypotension	Death or ICU admission / LOS ≥3 days or Hospital LOS ≥7 days	ED ICU	Physiological response to infection may be altered by chemotherapy Underlying disease may alter baseline GCS score
Pediatric Logistic Organ Dysfunction-2 (PELOD-2)[9]	Any of: GCS score <11 Hypotension Elevated lactate Elevated creatinine Invasive ventilation Leukopenia Thrombocytopenia	Death	ICU	Physiological response to infection may be altered by chemotherapy Organ dysfunction may be due to underlying disease or chemotherapy

ED=Emergency Department, ICU=Intensive Care Unit, LOS=length of stay, GCS=Glasgow Coma Scale

Table 2. Clinical, and outcome data for episodes of febrile neutropenia presenting to the Emergency Department[α].

Variable	Number of episodes (n=547)
Clinical Variables	
Vital signs	
Tachypnoea	518 (94.7%)
Glasgow Coma Scale score≤11	4 (0.7%)
Capillary refill time>2sec	59 (10.8%)
Tachycardia	299 (54.7%)
Hypotension	311 (56.9%)
Blood tests	
Lactate ≥2mmol/L	60 (10.9%)
Lactate ≥4mmol/L	6 (1.1%)
Elevated creatinine	6 (1.1%)
ScvO2 ≤70%	209 (38.2%)
Sepsis Scores	
SIRS	273 (49.9%)
qSOFA	4 (0.7%)
qPELOD-2	1 (0.2%)
Outcome Variables	
PICU admission for organ support	4 (0.7%)
PICU admission	9 (1.6%)
Inotropic support*	3 (0.5%)
Mechanical ventilation*	2 (0.4%)
Renal replacement therapy	0 (0%)
Extracorporeal life support	0 (0%)
Proven or suspected bacterial infection	115 (21.0%)
28-day mortality	2 (0.4%)
PICU LOS ≥3 days	4 (0.7%)
Hospital LOS ≥7 days	153 (28.0%)
Microbiological Diagnosis	
Proven bacterial bloodstream infection	55 (10.1%)
Proven other bacterial infection	37 (6.8%)
Probable bacterial infection	23 (4.2%)
Proven / probable fungal infection	7 (1.3%)
Proven / probable viral infection	119 (21.8%)
Fever of unknown origin	306 (55.9%)

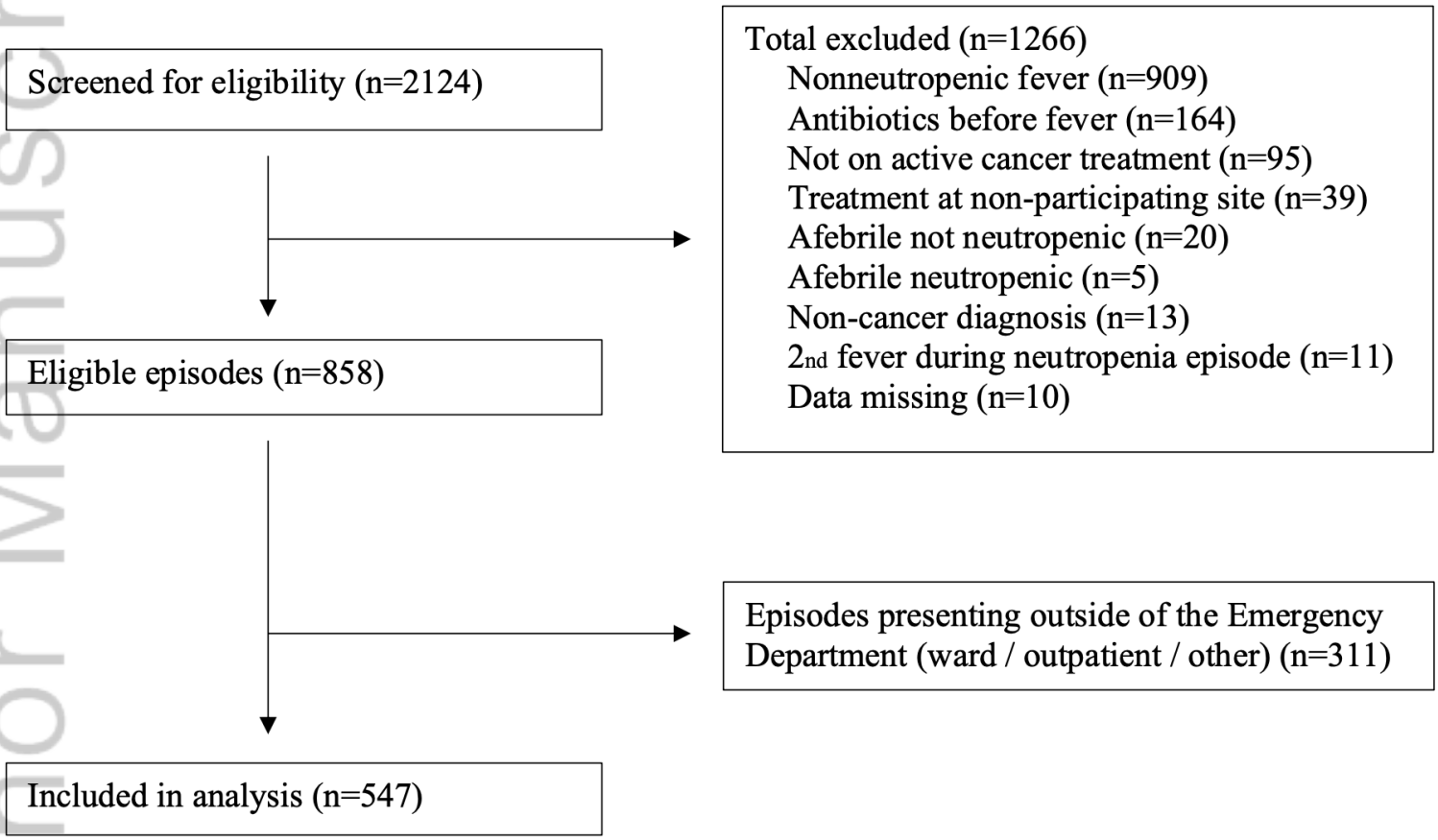
IQR=interquartile range, ScvO2=central venous oxygen saturation, SIRS=systemic Inflammatory Response Syndrome, qSOFA=quick Sequential Organ Failure Assessment, qPELOD-2=quick Pediatric Logistic Organ Dysfunction-2, PICU=pediatric intensive care unit, LOS=length of stay, *one patient required both inotropic support and mechanical ventilation.
[α]Data were missing for capillary refill time in 187 episodes, for blood pressure in 3 episodes, for

lactate in 190 episodes, for creatinine in 7 episodes, and ScvO2 in 200. Missing data were assumed to be normal.

Table 3. Test characteristics of initial vital signs, blood tests, and sepsis scores for predicting ICU admission for organ support therapy (n=4)*.

Variable (frequency)	TP	FP	FN	TN	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUROC (95% CI)
Vital Signs:									
Tachypnoea (n=518)	4	514	0	29	100	5.3	0.8	100	0.53 (0.52-0.54)
GCS ≤11 (n=4)	0	4	4	539	0	99.3	0	99.3	0.50 (0.42-0.67)
CR>2sec (n=59)	1	58	3	485	25.0	89.3	1.7	99.4	0.57 (0.30-0.63)
Tachycardia (n=299)	4	295	0	248	100	45.7	1.3	100	0.73 (0.16-0.79)
Hypotension (n=311)	4	307	0	236	100	43.5	1.3	100	0.72 (0.16-0.83)
Blood Tests:									
Lactate ≥2mmol/L (n=60)	1	59	3	484	25.0	89.1	1.7	99.4	0.57 (0.42-0.62)
Lactate ≥4mmol/L (n=6)	0	6	4	537	0	98.9	0	99.3	0.50 (0.39-0.68)
Elevated creatinine (n=6)	0	6	4	537	0	98.9	0	99.3	0.50 (0.39-0.68)
ScvO2 <70 (n=209)	1	208	3	335	25.0	61.7	0.5	99.1	0.43 (0.30-0.87)
Sepsis Scores:									
SIRS (n=273)	4	269	0	274	100	50.5	1.5	100	0.75 (0.35-0.83)
qSOFA (n=4)	0	4	4	539	0	99.3	0	99.3	0.50 (0.39-0.65)
qPELOD-2 (n=1)	0	1	4	542	0	99.8	0	99.3	0.50 (0.42-0.59)

ICU=intensive care unit, GCS=Glasgow Coma Scale score, ScvO2=central venous oxygen saturations, SIRS=Systemic Inflammatory Response Syndrome, PELOD=Pediatric Logistic Organ Dysfunction Score, TP=true positive, FP=false positive, TN=true negative, FN=false negative, Sens=sensitivity, Spec=specificity, AUROC=area under the receiver operating characteristics curve, CI=confidence interval. *Data were missing for CR in 187 episodes, for blood pressure in 3 episodes, for lactate in 190 episodes, for creatinine in 7 episodes, and ScvO2 in 200. Missing data were assumed to be normal.



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