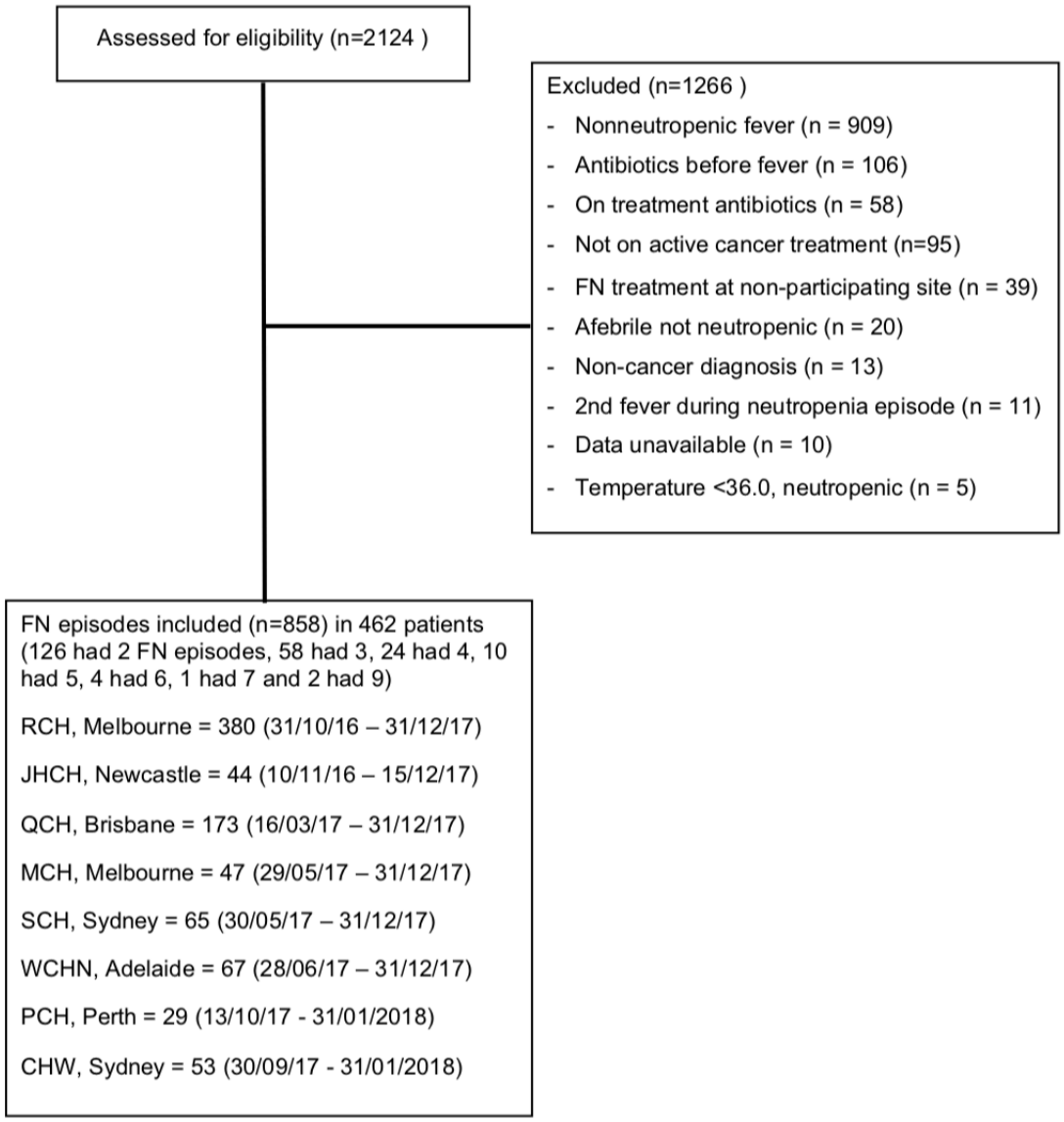
Risk stratification in children with cancer and febrile neutropenia: a national, prospective, multicentre validation of nine clinical decision rules.

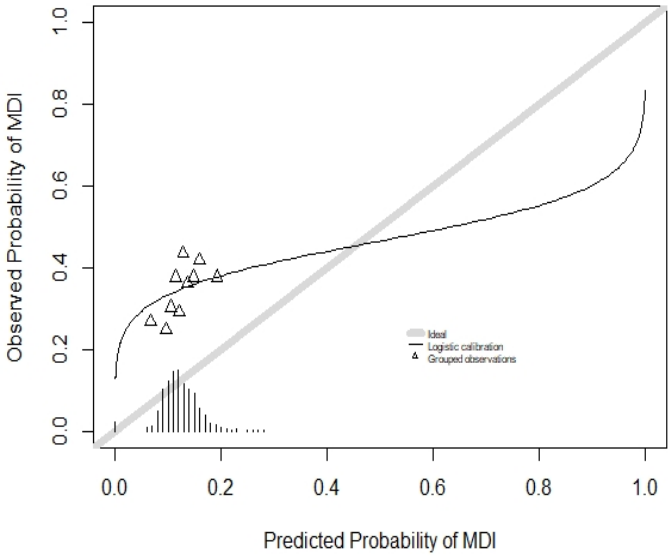
Supplementary material

Figure 1. Study flow diagram



Summary of abbreviations: RCH, Royal Children's Hospital; JHCH, John Hunter Children's Hospital; QCH, Queensland Children's Hospital; MCH, Monash Children's Hospital; SCH, Sydney Children's Hospital; WCHN, Women and Children's Hospital Network; PCH, Perth Children's Hospital; CHW, Children's Hospital at Westmead; FN, febrile neutropenia

Figure 2. Calibration curve for the Australian recalibrated PICNICC (top) and original (non-recalibrated) (bottom) score showing distribution of predicted probability points and grouped decile of these. The original calibration curve slope was 0.07.



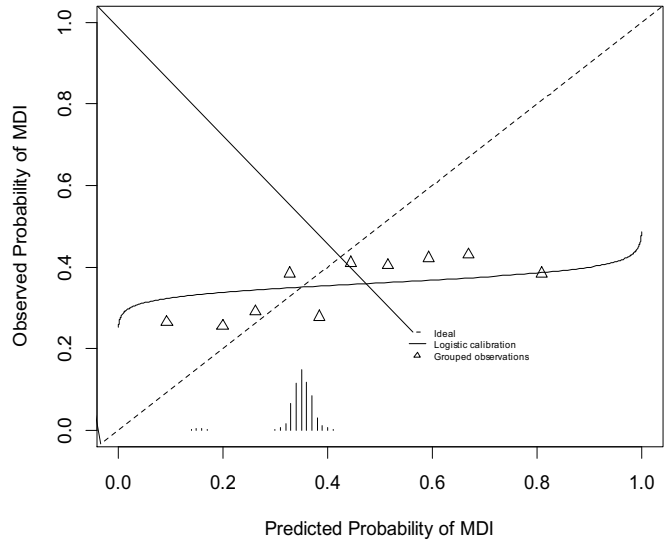


Table 1. Sensitivity, specificity, positive predictive value and negative predictive value of derivation study (d) and entire prospective validation cohort (Pv all) and the outpatient onset FN cohort (OP)

Rule	Epi-sodes	Out-come n (%)	Low risk n (%)	Sensitivity		Specificity		PPV, % (95% CI)	NPV,% (95% CI)	LR
				% (95% CI	Dif from deriv. % (p value)	% (95% CI)	Dif from deriv. % (p value)			
Rules predicting MDI										
d-PICNICC[1]	909	236 (26.0)	163 (17.9)	91.5 (87.3-94.4)	-	21.2 (18.3-24.5)	-	29 (25.8-32.2)	87.7 (81.8-91.9)	1.16
Pv-PICNICC (all)	858	296 (34.5)	155 (18.1)	87.2 (82.9-90.5)	4.3 (0.12)	20.8 (17.7-24.4)	0.4 (0.89)	36.7 (33.2-40.3)	75.5 (68.2-81.6)	1.10
Pv-PICNICC (OP)	689	236 (34.3)	140 (20.3)	86.0 (81.0-89.9)^	5.5 (0.8)	23.6 (19.9-27.7)^	2.4 (0.38)	37.0 (33.0-41.1)	76.4 (68.8-82.7)	1.13
Rules predicting adverse outcome										
d-SPOG AE[2]	423	122 (28.2)	165 (39)	91.8* (85.6-95.5)	-	51.5 (45.9-57.1)	-	43.3 (37.5-49.5)	93.9 (89.2-96.7)	1.89
Pv-SPOG AE (all)	858	320 (37.3)	329 (38.3)	72.2* (67.0-76.8)	19.6 (<0.001)	44.6 (40.5-48.8)	6.9 (0.07)	43.7 (39.5-47.9)	73.0 (67.9-77.5)	1.30
Pv-SPOG AE (OP)	689	252 (36.6)	268 (38.9)	71.0* (65.2-76.3)^	20.8 (<0.001)	44.6 (40.0-49.3)^	6.9 (0.07)	42.5 (37.9-47.3)	72.8 (67.1-77.7)	1.28
d-Hakim[3]	323	47 (14.6)	223 (69)	74.5 (60.5-84.7)	-	76.4 (71.1-81.1)	-	35.0 (26.4-44.7)	94.6 (90.8-96.9)	3.16
Pv-Hakim (all)	858	151 (17.6)	693 (80.8)	41.7 (34.2-49.7)	32.8 (<0.001)	85.6 (82.8-88.0)	9.1 (<0.001)	38.2 (31.1-45.8)	87.3 (84.6-89.6)	2.89
Pv-Hakim (OP)	689	103 (14.9)	589 (85.5)	36.9 (28.2-46.5)^	37.6 (<0.001)	89.4 (86.7-91.7)	13.0 (<0.001)	38.0 (29.1-47.8)	89.0 (86.2-91.2)	3.49
d-Alexander[4]	104	22 (21.2)	55 (53)	90.9 (72.2-98.4)	-	64.6 (53.8-74.1)	-	40.8 (28.2-54.8)	96.4 (87.7-99.4)	2.57
Pv-Alexander (all)	858	306 (35.7)	354 (41.3)	63.7 (58.2-68.9)	27.2 (<0.01)	44.0 (39.9-48.2)	20.6 (<0.001)	38.7 (34.5-43.0)	68.6 (63.6-73.2)	1.14
Pv-Alexander (OP)	689	239 (34.7)	354 (51.4)	53.6 (47.2-59.8)	37.3 (<0.001)	54.0 (49.4-58.6)	10.6 (0.09)	38.2 (33.2-43.5)	68.6 (63.6-73.3)	1.16
d-Klaassen[5]	227	43 (18.9)	83 (36.6)	83.7 (70-91.9)	-	41.5 (34.6-48.8)	-	25.3 (18.8-32.9)	91.6 (83.6-95.9)	1.43
Pv-Klaassen (all)	858	135 (15.7)	207 (24.1)	85.2 (78.2-90.2)	1.5 (0.81)	25.9 (22.8-29.2)	15.7 (<0.001)	17.7 (14.9-20.8)	90.3 (85.6-93.7)	1.15
Pv-Klaassen (OP)	689	97 (14.1)	187 (27.1)	81.4 (72.6-87.9)^	2.3 (0.82)	28.6 (25.1-32.3)^	12.9 (<0.001)	15.7 (12.8-19.2)	90.4 (85.3-93.8)	1.14

d-Baorto[6]	1171	189 (16.1)	164 (14)	94.7 (90.5-97.1)	NA	15.7 (13.5-18.1)	NA	17.8 (15.5-20.3)	93.9 (89.1-96.7)	1.12
Pv-Baorto (all)	858	111 (12.9)	148 (17.2)	93.7 (87.6-96.9)	1.0 (0.80)	18.9 (16.2-21.8)	3.2 (0.08)	14.6 (12.2-17.4)	95.3 (90.5-97.7)	1.16
Pv-Baorto (OP)	689	75 (10.9)	135 (19.6)	92.0 (83.6-96.3)^	2.7 (0.40)	21.0 (18.0-24.4)^	5.3 (<0.01)	12.5 (10.0-15.5)	95.6 (90.6-15.5)	1.17
d-Rackoff[7]	115	24 (20.9)	94 (81.7)	41.7 (24.5-61.2)	-	87.9 (79.6-93.1)	-	47.6 (28.3-67.6)	85.1 (76.5-90.9)	3.45
Pv-Rackoff** (all)	858	111 (12.9)	691 (80.5)	35.1 (26.9-44.4)	6.5 (0.64)	82.9 (80.0-85.4)	5.0 (0.30)	23.4 (17.6-30.3)	89.6 (87.1-91.6)	2.05
Pv-Rackoff** (OP)	689	75 (10.9)	547 (79.4)	40.0 (29.7-51.3)^	1.7 (>0.99)	81.8 (78.5-84.6)^	6.1 (0.18)	21.1 (15.2-28.6)	91.8 (89.2-93.8)	2.19
d-Ammann[8]	348	85 (24)	100 (28.7)	95.3 (88.5-98.2)	-	36.5 (30.9-42.5)	-	3.7 (27.1-38.7)	96.0 (90.2-98.4)	1.50
Pv-Ammann (all)	858	111 (12.9)	139 (16.2)	95.5 (89.9-98.1)	0.2 (>0.99)	17.9 (15.4-20.9)	18.6 (<0.001)	14.7 (12.3-17.5)	96.4 (91.9-98.5)	1.16
Pv-Ammann (OP)	689	75 (10.9)	139	93.3 (85.3-97.1)^	0.2 (>0.99)	21.8 (18.7-25.3)^	14.7 (<0.001)	12.7 (10.2-15.8)	96.4 (91.9-98.5)	1.19
d-SPOG bacteraemia [9]	423	67 (15.8)	54 (12.8)	100* (94.6-100)	-	15.2 (11.8-19.3)	-	18.2 (14.6-22.4)	100 (93.4-100)	1.18
Pv-SPOG bacteraemia (all)	858	111 (12.9)	133 (15.5)	94.6* (88.7-97.5)	5.4 (0.8)	17.1 (14.6-20.0)	1.9 (0.44)	14.5 (12.1-17.3)	95.5 (90.6-97.9)	1.14
Pv-SPOG bacteraemia (OP)	689	75 (10.9)	134	92.0* (83.6-96.3)^	8.0 (0.03)	20.9 (17.8-24.2)^	5.7 (0.03)	12.4 (9.9-15.4)	95.5 (90.6-97.9)	1.16

d, derivation study; Pv, prospective validation; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; Dif, difference.
*includes episodes with adverse event known at reassessment;
**Rule stratifies patients into 3 groups (ie, low, intermediate and high risk) - intermediate and low risk combined into a single low-risk group.
^no significant difference between outpatient onset FN (n=689) and full FN cohort (n=858)

Table 2. Discrimination and clinical utility of the PICNICC rule for the prediction of bacteraemia (with 95% confidence intervals)

Outcome	AUC-ROC	Outcome, n (%)	Low-risk, n (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR
Bacteraemia (all-858)	0.70 (0.63- 0.75)	111 (12.9)	155 (18.1)	92.8 (86.4-96.3)	19.7 (17.0-22.7)	14.7 (12.2-17.5)	94.8 (90.2-97.4)	1.16
Bacteraemia (OP-689)	0.69 (0.64- 0.75)	75 (10.9)	140 (20.3)	90.7 (82.0-95.4)	21.7 (18.6-25.1)	12.4 (9.9-15.4)	95.0 (90.0-97.6)	1.16

AUC-ROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value

Table 3. Odds ratio and 95% confidence interval for the individual variables of the PICNICC rule.[1]

	Odds ratio	lower	upper
(Intercept)	0.30	-	-
Tumour – Acute lymphoblastic leukaemia	1.00	referent	-
Tumour – Acute myeloid leukaemia	0.54	0.30	0.95
Tumour – Ewing's sarcoma	0.34	0.18	0.64
Tumour – High grade brain	0.79	0.40	1.50
Tumour – Hodgkin lymphoma	0.11	0.01	0.63
Tumour – High risk neuroblastoma	0.51	0.24	1.04
Tumour – low grade brain	0.63	0.19	1.75
Tumour – low risk neuroblastoma	0.62	0.03	6.54
Tumour – Non-hodgkin lymphoma	0.61	0.32	1.11
Tumour – Osteosarcoma	0.48	0.24	0.93
Tumour – Other	0.59	0.29	1.15
Tumour – Relapsed acute leukaemia	1.14	0.61	2.12
Tumour - retinoblastoma	1.62E-06	NA	1.98E+19
Tumour – Rhabdomyosarcoma	0.55	0.26	1.09
Tumour – Wilm's	0.36	0.10	1.03
Temperature (centred at 37°C)	1.53	1.18	1.99
Severely unwell	1.00	0.57	1.71
Haemoglobin	0.99	0.92	1.06
White cell count (natural log)	0.93	0.76	1.14
Absolute monocyte count (natural log)	0.94	0.85	1.05

Table 4. Details of missed bacteraemia episodes, known after Day 2 assessment, in outpatient onset FN episodes

Rule (no. missed bacteraemia)	Pathogens
Rules predicting MDI	
PICNICC (n=5)	Gram positive: Coagulase negative staphylococci (CoNS) (n=2), oral viridans streptococci (OVS) Gram negative: *Capnocytophaga sputigena* Fungal: *Candida albicans*
Rules predicting adverse outcome	
SPOG-AE (n=17)*	Gram positive: *Staphylococcus aureus*, *Enterococcus* spp (n=2), CoNS (n=3), OVS (n=2), *Bacillus* spp, *Clostridium septicum* Gram negative: *Escherichia coli* (n=2), *Klebsiella pneumoniae*, *Neisseria* spp, *C. sputigena, Acinetobacter baumanii, Pseudonomas* spp, *Moroxella* spp, *Enterobacter cloacae* Fungal: *C. alibicans*,
Hakim (n=28)**	Gram positive: CoNS (n=5), *S. aureus* (n=2), OVS (n=5), *Enterococcus* spp (n=2), *C. septicum, Bacillus* spp, *Abiotrophia defectiva* Gram negative: *E. coli* (n=4), *K. pneumoniae* (n=2), *Neisseria* spp (n=2), *Capnocytophagia sputigena*, *Pseudomonas* spp., *S. paucimobilis, E. cloacae* Fungal: *C. albicans* (n=2)
Alexander (n=13)	Gram positive: CoNS (n=3), OVS, *S. aureus*, *Bacillus* spp, Gram negative: *Neisseria* spp (n=2), *Klebsiella* spp (n=2), *E. coli* (n=2), *S. paucimobilis*
Klaassen (n=4)	Gram positive: CoNS, OVS, *Abiotrophia* spp Gram negative: *C. sputigena*
Rules predicting bacteraemia	
SPOG-bact (n=6)	Gram positive*:* CoNS (n=2), *S. aureus, E. faecalis* Gram negative: *C. sputigena, Pseudomonas* spp
Ammann (n=3)	Gram positive: CoNS, OVS Fungal: *C. albicans*
Baorto (n=3)	Gram positive: CoNS, OVS, *Abiotrophia* spp
Rackoff (n=25)*	Gram positive: CoNS (n=4), OVS (n=4), *S. aureus* (n=2), *Enterococcus* spp, *Bacillus* spp, *Abiotrophia* spp, *C. septicum* Gram negative: *E. coli* (n=2), *Neisseria* spp (n=3) *K. pneumoniae* (n=2), *Pseudomonas* spp (n=2) *C. sputigena, S. paucimobilis, E. cloacae* Fungal: *C. albicans* (n=2)

* includes n=4 low risk and n=21 intermediate risk episodes; **1 episode had 2 pathogens and 1 had 3 pathogens

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