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REVIEW

Updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment and management of fever during neutropenia in children with cancer

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Abstract

Routinely measurable biomarkers as predictors for adverse outcomes in febrile neutropenia could improve management through risk stratification. This systematic review assesses the predictive role of biomarkers in identifying events such as bacteraemia, clinically documented infections, microbiologically documented infection, severe sepsis requiring intensive care or high dependency care and death. This review collates 8319 episodes from 4843 patients. C-reactive protein (CRP), interleukin (IL)-6, IL-8 and procalcitonin (PCT) consistently predict bacteraemia and severe sepsis; other outcomes have highly heterogeneous results. Performance of the biomarkers at admission using different thresholds demonstrates that PCT > 0.5 ng/mL offers the best compromise between sensitivity and specificity: sensitivity 0.67 (confidence interval [CI] 0.53-0.79) specificity 0.73 (CI 0.66-0.77). Seventeen studies describe the use of serial biomarkers, with PCT having the greatest discriminatory role. Biomarkers, potentially with serial measurements, may predict adverse outcomes in paediatric febrile neutropenia and their role in risk stratification is promising.

KEYWORDS

biomarker, children, febrile neutropenia, sensitivity, specificity

1 | INTRODUCTION

Neutropenic sepsis, or febrile neutropenia (FN), remains a serious complication of childhood cancer therapy with an incidence of bacteraemia in 11-24% cases, paediatric intensive care unit (PICU) admissions in 0.9-11% cases, and fatality in 0.2-3% cases.[1–8] For this reason, children receiving anticancer treatment are frequently required to present to hospital if they have a fever. Subsequently, they experience long hospital admissions for treatment of FN despite data supporting safe and effective use of risk-stratified early discharge.[9–11]

There are at least 25 different paediatric clinical decision rules for the assessment of FN. These require local calibration before implementation, and lack of discriminatory value in the adolescents and young adult (AYA) group suggests this group may need its own risk prediction model.[12–14]

Biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) have been used to fortify adult risk systems successfully.[15,16] Three paediatric clinical decision rules have utilised biomarkers to guide risk stratification (CRP in two rules and PCT in one[17–19]). The International Pediatric Fever and Neutropenia Guideline Panel and the National Institute of Clinical Excellence (NICE) have recommended further research in the use of biomarkers for differentiating between low-, standard- or high-risk episodes and guide on-going treatment.[20,21]

Abbreviations: CDI, clinically documented infection; CI, confidence interval; CRP, C-reactive protein; FN, febrile neutropenia; FUO, fever of unknown origin; HSCT, hematopoietic stem cell transplant; IL, interleukin; LOS, length of stay; MDI, microbiologically documented infection; PCT, procalcitonin; PICU, paediatric intensive care unit; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies; ROC, receiver operating characteristic.

Two previous systematic reviews have assessed the use of biomarkers in predicting adverse outcomes in febrile neutropenic episodes in children and young people with cancer.[22,23] These reviews showed marked variation in terms of the quality of individual studies, biomarkers used and outcomes measured, which made it difficult to make comparisons between the biomarkers. Further studies have been published since the last review in 2011, necessitating an updated systematic review to evaluate the sensitivity and specificity of serum biomarkers in predicting adverse outcomes in paediatric FN.

2 | MATERIALS AND METHODS

This is an update of two preceding systematic reviews of the predictive value of serum biomarkers in the assessment and management of fever during neutropenia in children with cancer.[22,23] The review protocol was registered with the International register of systematic reviews (PROSPERO) database of systematic reviews: CRD42016036350 in March 2016 (https://www.crd.york.ac.uk/prospero/).

2.1 | Search strategy and selection criteria

The update search strategy mirrored the preceding reviews. It was undertaken in April 2016 and further updated in November 2018 in MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, Web of Science Conference Proceedings Citation Index–Science and Literatura Latinoamericana e do Caribe em Ciencias da Saude (LILACS). The full electronic search strategy for the MEDLINE database is provided in Supporting Information S1. Reference lists of systematic reviews were examined for further relevant studies. Published and unpublished studies were included. Language restrictions were not applied and relevant non-English language studies were translated. Authors were contacted where further details were required about study conduct or data.

The titles and abstracts of studies were screened by two independent reviewers (TA and AH). Disagreements were resolved through consensus or recourse to a third reviewer (RSP).

Studies deemed eligible for the systemic review included diagnostic cohort studies of patients receiving anticancer treatment for solid, brain or haematological malignancies between the ages of 0 and 24 years, who presented to hospital or community settings with FN, assessed a biomarker and its value in predicting an adverse outcome of the FN episode.

The adverse outcomes considered included death, PICU/HDU (high dependency unit) admission, single organ impairment, invasive bacterial or fungal infection, presence of microbiologically documented infection (MDI) and presence of radiologically confirmed infection. Studies with combined adult and children populations were excluded if the outcome data for children or young people (0–24 years) could not be reported separately.

2.2 | Data extraction and risk of bias assessment

Data were extracted by one reviewer using a standardised data extraction form, which had been used in the preceding systematic reviews, and checked for accuracy independently by a second reviewer.

General data items extracted from the studies included demographics, geographical location, participant inclusion/exclusion criteria, clinical characteristics and treatment course. Data were extracted for the index tests (serum biomarker values) and adverse outcomes (e.g. survival, intensive/high dependency care admission, sepsis, bacteraemia). Biomarker data for different cutoff values as well as different or serial time points were obtained.

Studies were included if data could be extracted by either a 2×2 tables comparing dichotomized test results against the study adverse outcome or by a measure of central tendency plus spread (e.g. mean and standard deviation or median with range). If only the latter data were available, it was converted using the assumption of normality and 2×2 tables derived for cut-offs reported in other studies.

Risk of bias was assessed using an adapted Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, which had been used in the preceding reviews. The quality item 'time between index test and reference test were appropriate' was considered indiscriminate because the index test (biomarker) and reference test (clinical outcome) are always examined within a single episode of FN; the 'intermediate results' outcome was deemed irrelevant as biomarker values were required, so the 'positive', 'intermediate' and negative' categories were obsolete.

2.3 | Methods of data synthesis

Quantitative pooling was performed for the commonest biomarkers if there was sufficient data for meta-analysis, where the same biomarker for equivalent clinical outcomes was available. Where possible, the groups were analysed for sources of heterogeneity. The MADA package was used in R to undertake the data pooling. The results are displayed using cross-hairs plots in receiver operating characteristic (ROC) space. This graphical approach combines the forest plot with the ROC curve, showing study weight, the bivariate relationship of sensitivity and specificity, and the confidence intervals around each individual study as well as the overall pooled estimate.

3 | RESULTS

The search strategy identified 509 articles, of which 38 new articles were included. Sixteen studies were excluded because data were not extractable either by a 2×2 table of dichotomized data or by a measure of central tendency plus spread. Twenty-two remaining studies with suitable quantitative data were combined with 21 studies from the preceding two systematic reviews (Figure 1). Two further studies were excluded before quantitative synthesis because there were insufficient studies looking at similar outcomes using interleukin (IL)-10[24] or insufficient numbers examining adrenomedullin.[25]

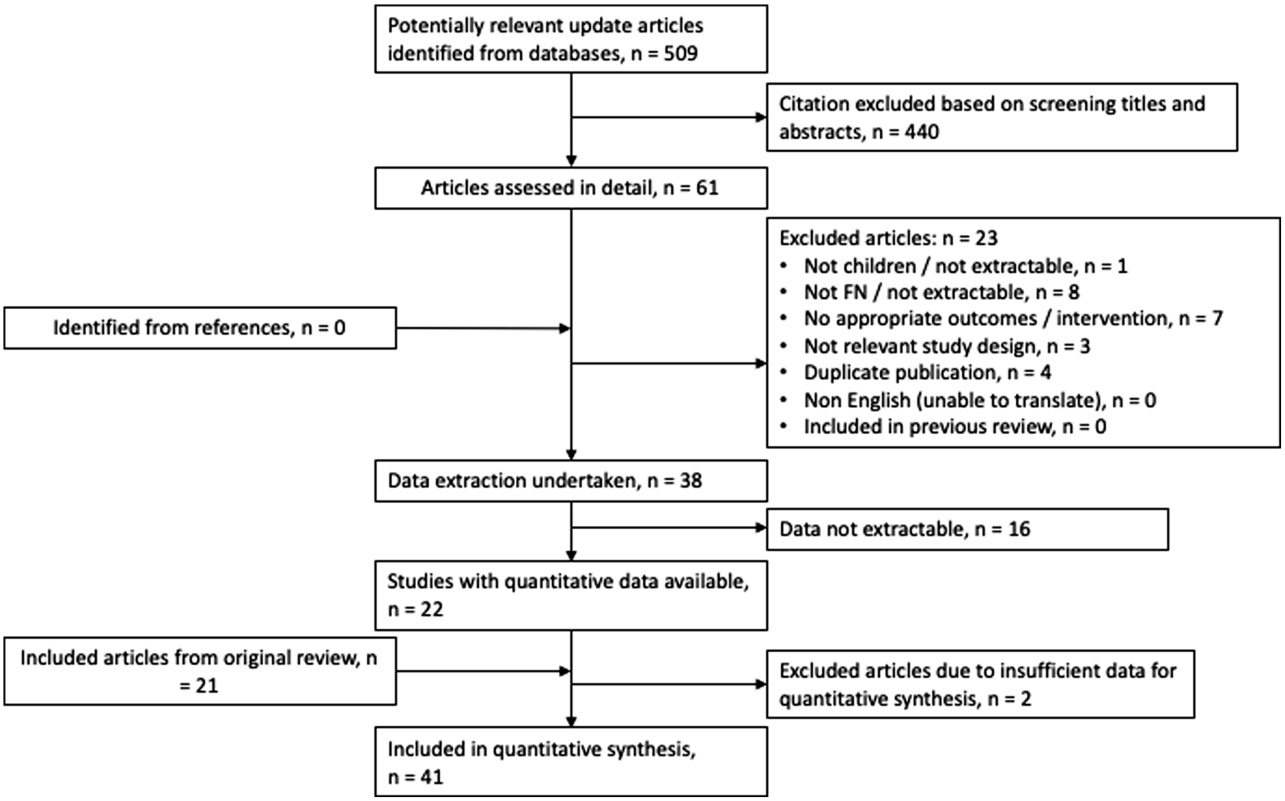

FIGURE 1 Flowchart of study selection process

3.1 | Study and population characteristics

Twenty-two new studies with quantitative data were identified in this update comprising of 1851 patients and 3060 episodes. The new studies were geographically diverse (11 different countries) with an appropriate range of paediatric malignant diagnoses (Table 1). The mean age of the patients within these studies was 6.7 years with an age range between 0.3 and 23 years. One study did not provide data on patient age.[26] Hematopoietic stem cell transplant (HSCT) patients were not represented in this population. The population characteristics of these 22 studies mirrored the population of the studies in the previous reviews in terms of malignant diagnoses, age range, and lack of HSCT patients.

Many biomarkers have been used to predict adverse outcomes in paediatric FN but CRP, PCT, IL-6, and IL-8 remain the mostly commonly studied (13 studies, eight studies, eight studies and eight studies, respectively). Fourteen studies assessed more than one biomarker in their populations, and seven studies assessed more than two biomarkers. Biomarkers were tested at serial time points in 12 out of 22 studies.

The outcomes measures reported were infections (microbiological or clinical), PICU, length of stay (LOS) in hospital, death and fever of unknown origin (FUO). Infections were described as MDIs, clinically documented infections (CDIs), bacteraemia, blood stream infection, severe infection, sepsis, severe sepsis and systemic infection. The most commonly reported outcomes were bacteraemia, CDI, MDI and FUO.

3.2 | Risk of bias assessment

The summarised QUADAS-2 assessment of the 22 new studies is shown in Figure 2; the quality assessment of individual studies is provided in Supporting Information S2.

The selection process was inadequately described in 12 (55%) studies and three included studies were not cohort designed. Two of these studies were case-control[40,44] and one was a clinical trial.[38] FN data relating to biomarkers and outcomes were extractable from these studies but case-control studies have been shown to exaggerate diagnostic accuracy estimates[48] and the clinical trial data introduced bias through non-blinding of the index test (biomarkers), using different index tests in separate groups, and using the result of the index test to define groups within the study.

FN was defined clearly within a study but varied between studies. This review found 17 definitions of FN including 16 for fever and four for neutropenia. All studies, except one, included definitions of fever to include a threshold of above 38°C as a solitary (four studies) or sustained (11 studies) temperature. One study differed by defining fever as a solitary temperature over 38.5°C. Twenty studies defined neutropenia as a count below 0.5×10^9/L, although 'falling counts' under 1.0×10^9/L was accepted within six of these definitions. The other two studies used falling counts under 0.75×10^9/L[34] and under 1.0×10^9/L[26] as definitions of neutropenia.

Descriptions of how multiple episodes were included in a study is poorly described in most studies, as is whether the index test was blindly interpreted without knowledge of the outcome. Descriptions

TABLE 1 Population and study characteristics of 22 new studies in updated systematic review

Citation	Mean age, years (range, years)	Underlying conditions (*n*)	Markers studied [and time point(s)]	Number of patients	Number of episodes	Endpoints studied	Comments on endpoints
Aggarwal et al[27]	6 (2-13)	ALL (40), NHL (6), AML (2)	IL-5, IL-6, IL-8, TNF-α [within 24 h]	48	52	CDI, MDI, FN related death	Group 1 = No focus of infection (low risk), Group 2 = clinical or radiological documented focus of infection (high risk), Group 3 = microbiologically proven infection or FN related death (high risk)
Aquino et al[28]	7.6 ($\pm$ 3.3)	ALL (36), AML (6), Solid (16)	ESR, CRP, protein C level, IFN-G, IL-1B, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, MIP-1a, MIP-1b, MCP-1, exotoxin [admission]	47	58	Bacteraemia LOS	
Badurdeen et al[26]	Not stated	ALL (22), AML (10), Lymphoma (4), Bone sarcomas (5), soft tissue sarcomas (6), CNS (6), other malignancies (2)	IL-1, IL-5, IL-6, IL-8, IL-10, IL-12p70, CRP [timing unclear]	44	55	Bacteraemia	
Chaudhary et al[29]	6 (1-23)	ALL/AML (20), RMS (2), HL (1), ATRT (1), immature teratoma (1), NBL (1)	IL-6, CRP [days 1 and 3]	26	57	CDI, MDI, FUO	MDI = $\geq$1 blood culture positive, other positive culture
Cost et al[30]	Median 6.8 (no range)	ALL (66), AML (9), CNS (13), lymphoma (4), sarcomas (11), other (13)	IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, CRP, GMCSF, IFN-G, TNF-α [<24 h]	116	195	Bacteraemia PICU, death	PICU admission, fluid resus, and death commented on but no data available with biomarkers
Delebarre et al[31]	7.6 ($\pm$5.1)	ALL (54), AML (21), lymphoma (19), bone (25), RMS (16), brain (8), NBL (5), nephroblastoma (5), others (6)	CRP, PCT [timing unclear]	160	372	Severe infection	'Severe infection' defined as bacteraemia, positive culture of a normally sterile body fluid, invasive fungal infection, localized infection at risk of extension
Demirkaya et al[32]	7.5 (1-18)	Leukaemias (27), solid (7), lymphoma (3)	Adrenomedullin, CRP, PCT [days 0, 3, 7–10]	37	50	CDI, MDI, sepsis, severe sepsis, Death, FUO	Sepsis-SIRS in presence of suspected/proven infection. Severe sepsis-sepsis and cardiac or ARDS, or two more organ dysfunction
Hazan et al[33]	9.5 ($\pm$5.9)	Solid (75), nonsolid (120)	CRP [admission, daily during hospitalization]	73	195	Blood stream infection (BSI)	Positive blood culture at admission, or $\geq$10 days after BSI episode, followed by disappearance of first pathogen (three blood cultures), CONS $\geq$ 2 separate occasions
Hemming et al[34]	Median 5.2 (1.3-18)	Solid (14), lymphomas (4), leukaemias (9)	PCT [admission, days 2 and 3]	27	48	Severe infection Non-severe infection	Severe and non-severe infection as per PICNICC collaboration definition[35]
Kar et al[36]	Median 3.41 (5.75-11.9)	ALL (50), AML (8), NHL (7), Hodgkin (1), NBL (1), Wilms (1)	CRP [admission]	68	200	CDI, MDI, fever of unknown origin (FUO)	
Kesik et al[25]	Median 10 (1.66-16)	PNET (2), Ewings (3), HL (2), NBL (3), NHL (2), osteosarcoma (1), ependymoma (1)	Adrenomedullin [0 h, 24 h, 48 h, 7 days]	14	36	Culture positive Culture negative	Culture positive—microorganism identified in blood or urine
Mian et al[37]	Median 12 (2-21)	ALL (10), AML (5), NHL (1), bone (6), RMS (3), CNS (4), NBL (4), others (3)	Hs-CRP, PCT, IL-1α, IL-1β, IL-1Ra, IL-2, sIL-2Ra, IL-3, 4, 5, 6, 7, 8, 9, 10, IL-12, TNF-α, and TNF-β [days 1 and 2]	36	89	High risk Low risk	High risk: micropositive blood culture, prolonged hospital stay (>7 days), admission to PICU. Low risk; none of high-risk outcomes (negative blood culture, pneumonia, colitis, cellulitis)

(Continues)

TABLE 1 (Continued)

Citation	Mean age, years (range, years)	Underlying conditions (*n*)	Markers studied [and time point(s)]	Number of patients	Number of episodes	Endpoints studied	Comments on endpoints
Miedema et al[38]	Median 1 (1-6)	ALL (58), AML (13), lymphoma (12), solid (42), brain (13), other (3)	IL-8, CRP [admission and at 12-24 h]	141	233	Safety Bacteraemia, LOS	Clinical trial primary outcome = safety (blood culture positive, recurrent fever). Secondary outcome = bacteraemia, duration of fever, LOS, or complications (PICU admission/death). IL-8 used to group low-risk and medium-risk episodes
Oberoi et al[39]	Median 5 (4-7)	ALL only	CRP [admission]	176	320	Complications (yes or no)	Definition of complication; septic shock, pneumonia (requiring invasive/non-invasive support), renal failure, neutropenic enterocolitis, encephalopathy, congestive cardiac failure, mucosal bleeds, other complications that were considered serious and clinically significant
Penagos-Paniagua et al[40]	9.3 (± 3.9)	ALL (49), AML (11), NHL (10), soft tissue sarcomas (11), HL (2), NBL (1), retinoblastoma (1), other (6)	CRP [admission]	127	98	CDI, MDI, FUO	
Reitman et al[41]	8.6	Not stated	PCT [admission and 12-24 h]	70	89	Bacteraemia	Not defined
Santolaya et al[42]	9.2 (no range)	Leukemia (303), lymphoma (27), solid (117) [episode data]	CRP, IL-8 [admission and 24 h]	403	447	Severe sepsis	'Severe sepsis' as per international definition[43]
Schroder and Lodahl[44]	5.7 (0.3-15)	Haematological cancer (45), solid (40)	PCT, CRP [admission and serial samples within 48 h, timings unclear)	85	230	Systemic infection (SI) Non-systemic infection (NSI)	SI—culture positive bacteraemia. NSI—all other causes of fever
Urbonas et al[45]	7 (1-18)	Haematological and non-haematological cancers (numbers unclear)	IL-6, IL-8 [days 1 and 2]	37	61	Bacteraemia/sepsis group, FUO group	Bacteraemia/sepsis: positive blood culture, clinically documented sepsis. FUO-negative blood culture, absence of clinical/microbiological signs of infection
Urbonas et al[24]	3 (1-17)	ALL (16), AML (2), NHL (1), non-haematological cancer (5)	IL-10 [day 1]	24	36	Septic group, FUO group	Septic: positive blood culture, clinically documented sepsis
Urbonas et al[46]	Median 6 (range 1–17)	ALL (28), AML (2), NHL (1), non-haematological cancer (6)	PCT, IL-2R, sHLA-G, prespsin [day 1]	37	62	Bacteraemia/sepsis group, FUO group	Bacteraemia/sepsis: positive blood culture, clinically documented sepsis
van der Galien et al[47]	Median 6.3 (0.8-18.8)	Hematologic (44), solid (26), brain (7)	IL-6, PCT [admission, 12-24 h]	55	77	Bacterial infection No bacterial infection	Bacterial infection; blood culture, or culture of fluid from otherwise sterile site, or radiologically documented infection

Abbreviations: ALL, acute lymphoblastic leukemia; NHL, non-Hodgkins lymphoma; AML, acute myeloid leukemia; CNS, central nervous system tumors; RMS, rhabdomyosarcomas; HL, Hodgkins lymphoma; ATRT, atypical teratoid rhabdoid tumors; NB, neuroblastoma; PNET, primitive neuroectodermal tumors; IL, interleukin; ESR, erythrocyte sedimentation rate; IFN-γ, interferon-gamma; MIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; GMCSF, granulocyte macrophage colony stimulating factor; sHLA-G, soluble human leukocyte antigen G.

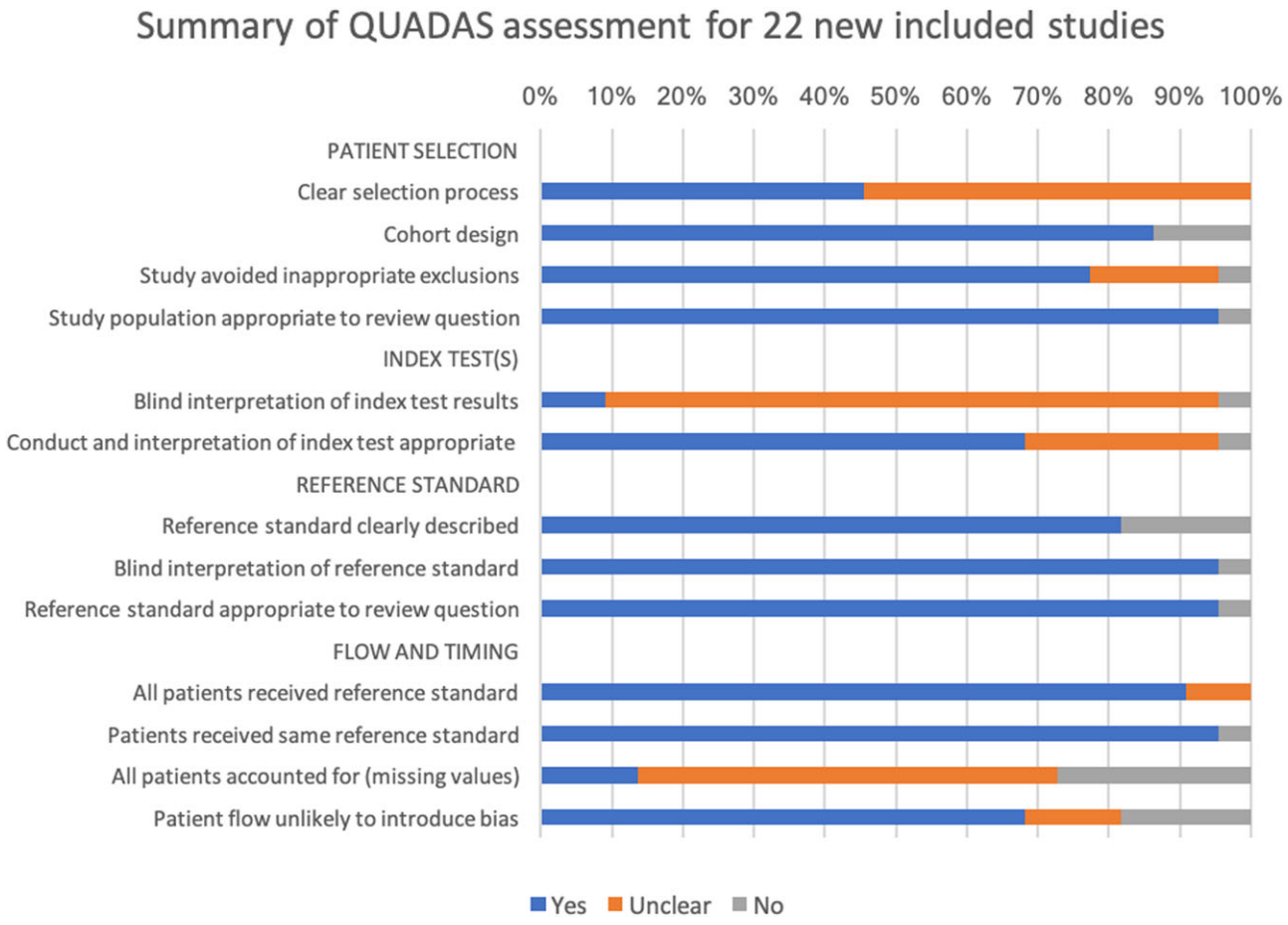

FIGURE 2 Overall summary of the quality of 22 new studies included in this updated review

of outcomes (reference standards) were explained well within studies but descriptions of the same outcome, such as bacteraemia, sepsis and severe infection, differed between studies. Definitions of MDI, CDI and FUO were similar between studies. Although measures of LOS, PICU admission and death were reported, data were usually not presented in context of biomarker levels against these outcome measures.

The timings of tests were not given in two studies.[19,26] 'Admission' samples were reported as taken before the commencement of treatment. When serial biomarkers were used, timings varied between studies and missing values were unclear if mean results were given.

3.3 | Quantitative synthesis

This updated review now collates 8315 FN episodes from 4822 patients evaluating 30 different biomarkers. The most common biomarkers reported are CRP (42 studies), PCT (22 studies), IL-6 (20 studies) and IL-8 (13 studies). The next most frequently studied biomarkers are tumour necrosis factor-alpha/-RII (TNF-α /-RII) with nine studies, IL-5 with eight studies, and IL-10 and IL-2 with seven studies each. The aggregate number of studies looking at other biomarkers is shown in Supporting Information S3. Quantitative synthesis was performed on the four most common biomarkers due to the availability of sufficient data on biomarker and similar outcomes.

Quantitative synthesis was possible for CRP and clinical bacterial infections, bacteraemia, serious bacterial infections and severe sepsis; PCT and clinical bacterial infections, bacteraemia, microbiologically defined infections and serious bacterial infections; IL-6 and clinical bacterial infections, bacteraemia, and serious bacterial infections; and finally, IL-8 and clinical bacterial infections, bacteraemia, serious bacterial infections and severe sepsis. There were insufficient data to provide quantitative synthesis of outcomes such as LOS, PICU admissions and death. The analyses per-outcome can be seen in Supporting Information S4. The pooled sensitivity (pSn) and specificity (pSp) for the biomarkers to detect any adverse outcome is CRP pSn 40% (95% confidence interval [CI] 20-75%), pSp 65% (95%CI 30-85%); PCT pSn 60% (95% CI 35-80%), pSp 75% (95%CI 50-90%); IL-6 pSn 65% (95% CI 20-85%), pSp 70% (95%CI 30-90%); and IL-8 pSn 70% (95% CI 40-90%), pSp 60% (95%CI 25-80%).

Bivariate meta-analysis of the biomarkers at different cutoff levels reiterates the expected relationship found in the previous reviews; low biomarker cutoff levels predict adverse outcomes with great sensitivity but poor specificity, and high biomarker cutoff levels predict adverse outcomes with poor sensitivity but good specificity (Table 2).

The cross-hairs ROC plots (Figure 3A–D) displaying the predictive ability of the biomarkers at commonly reported cutoff points illustrates imprecision within each study as well as between study heterogeneity.

TABLE 2 Bivariate meta-analysis of CRP, PCT, IL-6, and IL-8 at different cutoff levels to detect any adverse outcome

Marker and cutoff threshold	Number of studies	Number of FN episodes	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
CRP > 20 mg/L	4	321	0.82 (0.58-0.94)	0.24 (0.15-0.35)
CRP > 50 mg/L	9	1148	0.58 (0.37-0.77)	0.71 (0.64-0.78)
CRP > 90 mg/L	9	1801	0.56 (0.40-0.70)	0.75 (0.58-0.87)
PCT > 0.2 ng/mL	8	661	0.80 (0.56-0.93)	0.60 (0.33-0.82)
PCT > 0.5 ng/mL	10	1204	0.67 (0.53-0.79)	0.73 (0.66-0.77)
PCT > 1.0 ng/mL	5	880	0.35 (0.21-0.52)	0.88 (0.65-0.87)
IL-6 > 100 pg/mL	7	379	0.63 (0.52-0.72)	0.56 (0.34-0.75)
IL-6 > 235 pg/mL	5	570	0.66 (0.29-0.90)	0.88 (0.73-0.95)
IL-6 > 1000 pg/mL	4	502	0.15 (0.05-0.41)	0.97 (0.86-0.99)
IL-8 > 100 pg/mL	8	660	0.80 (0.71-0.86)	0.48 (0.31-0.66)
IL-8 > 320 pg/mL	6	952	0.47 (0.22-0.73)	0.81 (0.55-0.94)
IL-8 > 500 pg/mL	3	455	0.22 (0.02-0.83)	0.90 (0.45-0.99)
IL-8 > 1000 pg/mL	1	193	0.22 (0.02-0.83)	0.90 (0.45-0.99)

3.4 | Comparison of biomarkers

Thirteen studies in this review used more than one biomarker and gave comparative descriptions of performance.[26–32,37,38,42,44,45,47] Three out of the four studies comparing the performance of CRP and PCT[31,32,37,44] found the latter to be better at predicting adverse outcomes. Such comparisons can be affected by the choice of cutoff, but the following are consistent across thresholds. PCT appeared to be more discriminatory at admission, whereas CRP was more discriminatory after 48 h. In one of these comparative studies, CRP was more sensitive but not more specific than PCT. CRP was also found to be more sensitive but less specific in a study where its performance was compared with IL8.[42] There were seven studies evaluating CRP and IL-8 or IL-6[26,28–30,37,38,42] but only two compared their predictive capacities, finding that the ILs added greater predictive value than CRP.[29,30] Five studies explored the predictive role of IL-6 and IL-8: one found IL8 to perform better,[30] one found them to be equivalent,[45] and the other three did not make any comparisons.[26,27,37] There were no direct comparisons of PCT with IL-8 but one study compared the predictive value of PCT to IL-6,[47] finding that IL-6 demonstrated better discriminatory power at admission and at 12-24 h of admission but particularly at admission. The authors also found combining PCT (>0.25 ng/L) with IL-6 (>60 ng/L), which significantly increased the likelihood of identifying a bacterial infection at both time points.

3.5 | Use of serial biomarkers

Eleven new studies in this systematic review assessed the four commonest biomarkers at more than one time point. Serial CRP levels were evaluated in seven studies, PCT in six studies, IL-8 in four studies and IL-6 in four studies (Table 3). The description of the timings was often unclear or varied; for example, studies describe the timing of the initial biomarker as 'admission', 'day 0′ or 'day 1′. Meta-analysis was not possible due to varying time points and outcome measures, and insufficient data.

Four of seven studies evaluating serial CRPs described a better predictive value after 48 h than at admission, echoing five out of six studies showing serial PCTs were likely to be more useful than single PCTs. The claimed benefit of serial IL-8 levels was inconsistent, and two of the four IL-6 studies showed no benefit in serial assessment.

4 | DISCUSSION

This systematic review includes 8315 FN episodes from 4822 patients from 11 different countries. The age of patients represented in this systematic review characterise the general paediatric oncology patient population well. However, HSCT population is poorly represented in these studies. This group is subject to more intense systemic anticancer treatment, so there should be caution in extrapolating the results of this review to HSCT patients.

The number of biomarkers being explored has doubled from 14 in the original 2011 review to 30 in the 2018 update. Laboratory techniques allow panels of multiple biomarkers to be explored simultaneously but small study numbers prevent meaningful quantitative synthesis of such biomarkers. Interestingly, lactate was not explored as a biomarker in any of these studies despite its incorporation in national and international sepsis guidelines.[49]

The overall quality of studies included in this systematic review was good with the greatest difficulties found in reporting whether the biomarkers were interpreted without knowledge of the outcome. Variation in the definition of FN has decreased in the updated 22 studies, this update with more consistency for fever to be defined as a temperature over 38°C and neutropenia as below 0.5×10^9/L. The majority of studies did not clarify how multiple FN episodes in the same patient would be defined. This could have affected the quality of their study if the episodes occurred within a short period of time (i.e. biomarker had not returned to baseline levels) or there was overrepresentation of patients with genetic predisposition to

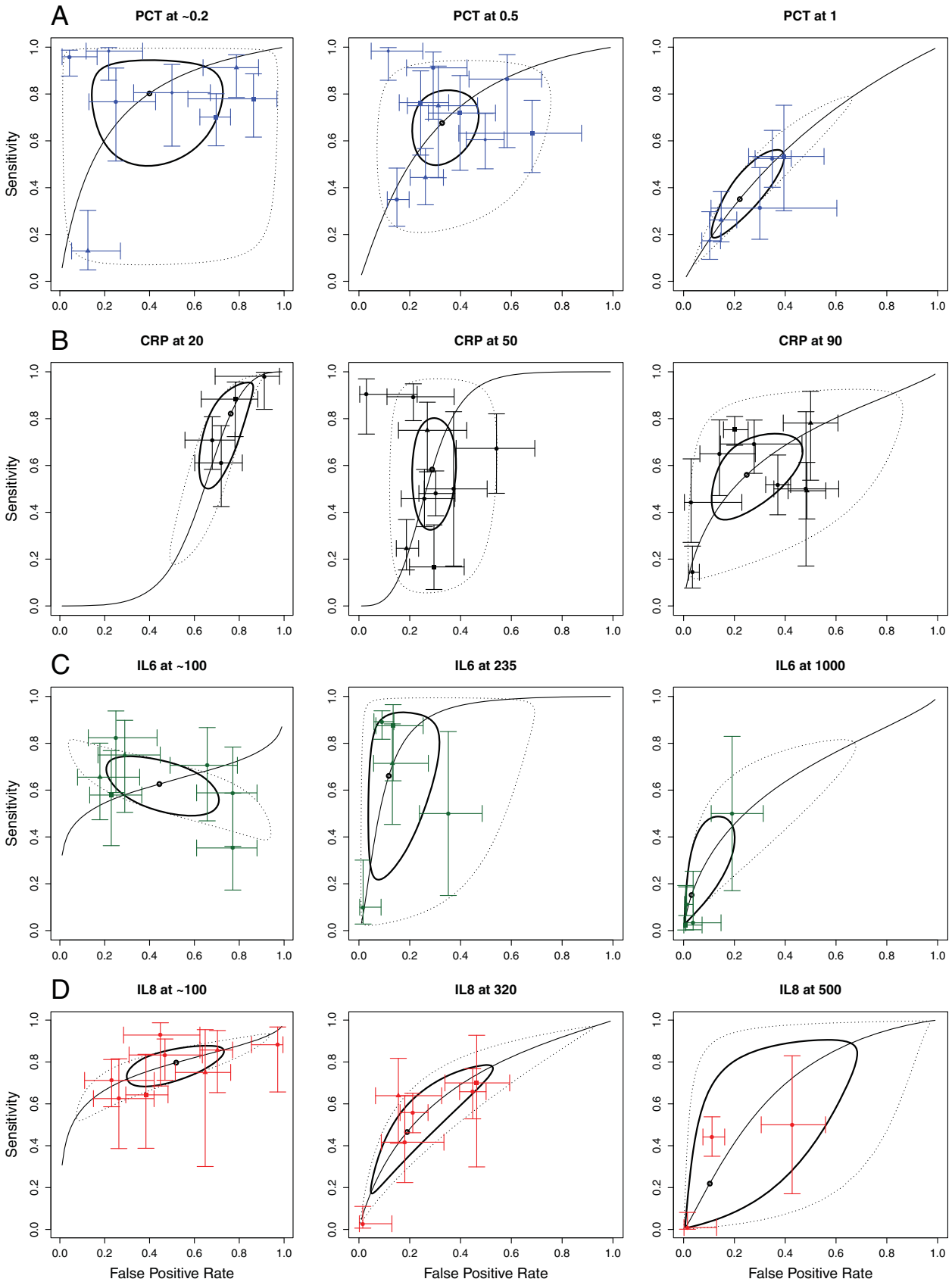

FIGURE 3 Cross-hairs ROC plot showing relationship of sensitivity and specificity at different cutoff levels of (A) PCT, (B) CRP, (C) IL-6, and (D) IL-8. Crosses = individual studies; centre of cross = predictive value, length of cross = CIs within the study. Small circle = pooled predictive value of marker, solid ellipse 95% confidence region, dashed ellipse 95% prediction region

TABLE 3 Serial biomarker studies in updated review describing time points for biomarker analysis, outcomes assessed, and study findings

Biomarker	Study	Time points (days)	Outcomes assessed	Reported findings
CRP	Chaudhary et al[29]	1, 3	MDI, CDI	Statistically significantly higher on 3 versus 1 for MDI (not CDI)
CRP	Demirkaya et al[32]	0, 3, 7-10	MDI, CDI, sepsis, death	Statistically significantly higher on 3 versus 0. No difference 7-10.
CRP	Hazan et al[33]	A, daily	Bacteraemia	Statistically significantly higher on A and 5-8 for bacteraemia
CRP	Mian et al[37]	1, 2	Bacteraemia, LOS, ICU	No statistical difference
CRP	Miedema et al[38]	A, 0.5-1	Bacteraemia, LOS, PICU, death	Clinical trial, levels predetermined
CRP	Santolaya et al[42]	A, 1	Severe sepsis	Increase >100 mg/L at 24 h risks severe sepsis
CRP	Schroder and Lodahl[44]	A, unclear (within 2)	Bacteraemia	Description; discriminatory power better after 2 than A
PCT	Demirkaya et al[32]	0, 3, 7-10	MDI, CDI, sepsis, death	Statistically significantly lower on 3 versus 7-10. 0 versus 3 showed no difference
PCT	Hemming et al[34]	0, 2, 3	SBI	Description; rose on 2 versus 0 in three out of three cases of SBI
PCT	Mian et al[37]	1, 2	Bacteraemia, LOS, PICU	No statistical difference
PCT	Reitman et al[41]	A, 0.5-1	Bacteraemia	Serial PCT is better than single PCT
PCT	Schroder and Lodahl[44]	A, unclear (within 2)	Bacteraemia	Description; discriminatory power rises over time
PCT	Van der Galien et al[47]	A, 0.5-1	Bacterial infection	Significantly higher at both time points and discriminatory power increases with time
IL-8	Mian et al[37]	1, 2	Bacteraemia, LOS, PICU	Statistically significantly lower on 2 versus 1
IL-8	Miedema et al[38]	A, 0.5-1	Bacteraemia, LOS, PICU, death	Clinical trial, levels predetermined
IL-8	Santolaya et al[42]	A, 1	Severe sepsis	Increase >300 pg/mL at 24 h risks severe sepsis
IL-8	Urbonas et al[45]	1, 2	Bacteraemia	No benefit in doing serial IL-8
IL-6	Chaudhary et al[29]	1, 3	MDI, CDI	Not statistically significantly different between days 1 and 3
IL-6	Mian et al[37]	1, 2	Bacteraemia, LOS, ICU	Statistically significantly lower on 2 versus 1
IL-6	Urbonas et al[24]	1, 2	Bacteraemia	No benefit in doing serial IL-8
IL-6	Van der Galien et al[47]	A, 0.5-1	Bacterial infection	Significantly higher at both time points and discriminatory power decreases with time

Abbreviation: A, admission time-point.

infections, in their biomarker response, or fever without adverse outcome.[50]

Episodes were not described in context of clinical features (e.g. haemodynamic parameters, maximum/duration of temperature, etc.) or patient-specific features (e.g. type of cancer, intensity of anticancer regimen, trisomy 21) that would normally be used in clinical decision rules. Therefore, associations between biomarker and clinical outcomes found in this review do not account for the complexity of multiple factors in an FN episode. The PICNICC (Predicting Infectious Complications of Neutropenic sepsis In Children with Cancer) collaboration has collected data on 20 variables within FN episodes including patient-specific clinical features and laboratory variables.[51] The influence of these multiple variables in predicting FN outcomes can be better explored in such individual patient data meta-analyses.

The outcomes explored in individual studies were relevant but when grouping the outcomes of all the studies, there was considerable overlap, for example, MDI and bacteraemia, CDI and sepsis, bacteraemia and sepsis, or severe infection and bacteraemia. This could explain the marked heterogeneity seen in the cross-hair plot of biomarkers predicting different outcome groups (Supporting Information S4). Better collaboration in future research is required to provide consistency in outcome definitions.[52] This review did not find adequate data to perform meta-analyses on LOS in hospital or community-based treatment (i.e. treatment duration) but the available data for such outcomes are likely to be confounded by centre-specific FN policy.

The biomarkers predictive ability decreased in sensitivity and increased in specificity as the cutoff level increased. The potential use of different biomarker assays between studies for a given threshold may impact the reliability of the pSn and pSp results obtained, especially where fewer studies contributed to the pSp/pSn of a threshold. The trade between an acceptable level of sensitivity and specificity is a clinical decision and factors such as study/episode numbers and heterogeneity of data should be considered when deciding upon which threshold to use in clinical practice.

Comparative descriptions of the biomarkers found CRP to be the poorest performing biomarker. The ILs possibly have a predictive role within 24 h of admission but greater patient numbers and studies are required to strengthen this finding. PCT is more discriminatory at admission and performs better than CRP but its performance against the ILs has only been explored in one study against IL-6.

The update found 12 out of 22 studies evaluated biomarkers at serial time points. The previous systematic review[23] identified only six serial biomarker studies. Serial PCT studies in this review supported the findings of the previous review showing a better discriminatory power over time with a rise interval of 24-48 h and then a fall. The serial CRP results appear to show higher levels after 48-72 h, which probably reflects its slower kinetic activity compared to PCT[53] implying CRP is not clinically useful in making decisions about early de-escalation or cessation of treatment. This review found no strong predictive role of serial IL-6 and IL-8. Inconsistencies in methodology and reporting of outcomes would not allow meta-analyses of these biomarkers to be performed. However, the descriptive findings of these studies suggest encouraging results for the predictive use of serial PCT and further studies using consistent methodological and reporting approaches should focus in this area.

5 | CONCLUSIONS

Biomarkers have been used to fortify existing clinical decision rules in the management of FN. The choice of biomarker for predicting an adverse outcome and the choice of optimal threshold remain inconclusive due to the variability within and between studies. However, based on this review, PCT at a threshold of 0.5 ng/mL appears the most suitable admission biomarker to predict adverse outcomes. There may be additional benefit in using serial PCT measurements. This needs to be validated through a larger multicentre study, using consistent biomarker timings, assays and outcome definitions, before widespread clinical recommendation and use.

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CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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