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| RESEARCH ARTICLE

A Systematic Review of Three Biomarkers to Aid in the Assessment of Outcomes for Children and Young People with Cancer that are Febrile Neutropenic

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| ABSTRACT

For paediatric patients with cancer, febrile neutropenia (FN) is the most common complication of treatment. It requires inpatient hospitalisation and treatment with empirical broad-spectrum antibiotics. Approximately 20-30% of febrile neutropenic patients have a documented infection, thus needing antibiotics. For the rest, it is suggested that the cause of FN could be a viral or fungal infection, the malignancy itself, drug related or the result of a blood transfusion reaction as examples, therefore not requiring antibiotics. With no risk-stratification tool in use in practice to distinguish between patients who are at high or low risk of bacterial infections, recent studies have focused on identifying clinical and laboratory markers for this. This systematic review will focus on three biomarkers, C-reactive protein (CRP), presepsin (sCD14-ST) and lactate, to find their sensitivities and specificities for diagnosing bacterial infections and thus help determine the risk of poor outcomes for patients with FN. This review has systematically searched for relevant primary research papers. These studies have been critically appraised using a validated critical appraisal tool. Data from these studies were then extracted using a data extraction form, and evidence summarised. The findings have been interpreted, and the implications to practice and research are discussed. 1051 febrile neutropenic episodes from 743 children from different countries were analysed. In the majority of studies (75%), acute lymphoblastic leukaemia was the most frequent diagnosis. Eight of the studies in this review are looking at CRP. Two studies are looking at lactate, and five review presepsin. Lactate is a sensitive and specific biomarker with a lactate level ≥ 2mmol/L and >2.5mmol/L showed sensitivities of 81% and 80% and specificities of 83% and 92.1%, respectively. Presepsin and CRP had mixed results for its sensitivity and specificity. Lactate and CRP are useful biomarkers for assessing the outcomes of children with FN and could be added to a CDR. This review cannot confirm that presepsin is a useful biomarker for practice and, therefore, cannot justify adding it to a CDR.

| KEYWORDS

Systematic Review, Biomarkers, Children, Cancer, Febrile Neutropenic.

| ARTICLE INFORMATION

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1. Introduction

Around 400,000 children and young people are diagnosed with cancer each year worldwide.[Agnello et al. 2020] A diagnosis of cancer means that healthy cells in the body have become abnormal and are dividing in an uncontrolled manner.[Akcay et al. 2021] Cancer treatment can involve surgery, chemotherapy, and radiotherapy. [Baraka et al. 2018] The aim of anti-cancer treatment is to kill cancer cells, but the treatment also destroys healthy blood cells, in particular white blood cells (WBC), known as neutrophils, which assist the body in fighting infection. [Bettany-Saltikov 2012] With fewer neutrophils in the body, the ability to fight infection is reduced. [Cancer Research UK 2021] With infection being the biggest risk of mortality to children with cancer, prompt recognition and treatment can save lives. [Cancer Research UK 2021] Initial signs of infection can be fever. [Delebarre et al. 2015] Fever alongside a low neutrophil count is called FN. [Dommett et al. 2009]

FN is defined as having a temperature equal to or higher than 38ºC and a neutrophil count of 0.5 x 10^9 per litre or lower. [Dommett et al. 2009] In practice, FN is an oncological emergency and requires inpatient hospitalisation, urgent investigation, and

the administration of intravenous antibiotics within one hour. [Dommett et al. 2009] With an increased risk of sepsis, defined as a life-threatening reaction to an infection, the paediatric sepsis six tool is used by clinicians when presented with a patient with FN. [Haeusler et al. 2020, Kitanovski et al. 2014] This prompt treatment of FN can prevent mortality due to infection. [Cancer Research UK 2021]

Research suggests that not all febrile neutropenic patients require such intense treatment and can be risk-stratified into low or high-risk categories for significant complications. [Klastersky et al. 2000] This risk-stratification is not seen in the United Kingdom (UK), even with an international paediatric FN guideline suggesting that we adopt a validated risk-stratification tool to use in practice. [Kuter et al. 2018] Adopting this could have huge implications for patients and their families, including improved quality of life, reduced length of in-patient hospitalisation, reduced exposure to hospital acquired infections and a reduced risk of developing antibiotic resistance. [Lehrnbecher et al. 2017] Other benefits include reduced costs to the NHS, a reduction in nursing care hours and an increase in bed availability, which is vital in an underfunded and overstretched organisation. [Multinational Association of Supportive Care in Cancer 2021]

However, there is no single internationally agreed reliable and validated risk-stratification tool in use for paediatrics. [National Cancer Institute 2021] There is, however, in adult cancer patients with FN. This is called the multinational association for supportive care in cancer (MASCC) tool, which allows clinicians to assess whether a patient is at low-risk from complications of FN. [NHS 2020] It identifies that some adult patients can be safely treated at home. [NHS 2019] For paediatric patients to have the same opportunity, there is a need for a reliable and validated risk-stratification tool for this population.

There are at least 27 different clinical decision rules (CDR) that have been created to risk-stratify complications in paediatric patients with cancer that are febrile neutropenic. [Lehrnbecher et al. 2017] A CDR is a tool that can be used by clinicians at the patient's bedside to make clinical decisions. [NHS Foundation Trust 2014] Each CDR contains different variables, suggesting that there is no consensus on which variables should be included in a paediatric CDR.

Research suggests that using biomarkers of infection and inflammation can help predict patients who are at low-risk of complications of infection. [NHS Foundation Trust 2015] With this in mind, three biomarkers have been chosen for this systematic review. These are CRP, presepsin and lactate.

This leads to the review question, 'What is the sensitivity and specificity of C-reactive protein (CRP), presepsin (sCD14-ST) and lactate for assessing whether children and young people with cancer that are febrile neutropenic are at risk of poor outcomes?'. The aim of this systematic review is to find out the sensitivity and specificity of CRP, presepsin and lactate in determining the risk of poor outcomes for children and young people with cancer who are febrile neutropenic.

Poor outcomes can be defined as serious medical complications leading to death, admission to the intensive care unit (ITU) or other life-threatening complications due to infection. [Lehrnbecher et al 2017]

The specific objectives were to identify all relevant information on the topic area. This includes primary research papers by systematically searching electronic databases. Searching for published and unpublished papers and studies that are found from sources other than electronic databases ('Grey literature'); Hand searching bibliography of key review articles and included studies. Critically appraising the quality of all included studies. Summarising the results using an appropriate scientific methodology. Reviewing the relevance of the findings for practice and research.

2. Methods

2.1 Search strategy and selection criteria

In order to develop a comprehensive and specific review question, the PICO (Population, Intervention, Comparison and Outcome) format was used. [Olad et al. 2014]

A Simplified PICO Framework

Population - Children (0-19 years old) with cancer that are febrile neutropenic

Intervention -

Comparison - C-reactive protein, lactate and presepsin

Outcome - Sensitivity and Specificity

Searches were untaken on Cochrane Library, Campbell collaboration, emerald insight, the EPPI-centre, PubMed, TRIP, CORE and BioMed Central. No systematic reviews were found on the review question. Articles were found on Academic Search Complete, CINAHL Complete and MEDLINE using the keywords (Child* OR P? diatric* OR Teen* OR 'Young Person' OR Adolescen* OR Minor*)

and (Febrile* OR Fever* OR Temp* OR Pyre*) and (Neutrop*) and (crp* OR c-reactive protein OR 'c reactive protein' OR presepsin OR sCD14-ST OR 'soluble CD14 subtype' OR lact*). No grey literature was found from Zetoc, CADTH, The New York Academy of Medicine, EThOS, the British Library, Open Grey and BDENF. Google was searched, and reference lists of included primary research were hand searched. Only academic journals were included, and articles in all languages were included to avoid missing relevant evidence. Articles not available in full-text were included. Articles pre 2012 were excluded to ensure evidence was up to date. Journals not listed above were excluded as no articles were found.

2.2 Data extraction

Appropriate data was then extracted from the final chosen research papers. A data extraction form was developed to ensure all included studies are treated equally. Data extracted from each article includes study details, level of evidence, methodology and method, interventions, settings, participants, data analysis, key findings (Outcomes), quality, applicability to practice and comments, including quality appraisal findings. A supervisor assisted in the data extraction of one paper and the results were compared. The data extraction table can be seen in the supporting information table 1.

For each biomarker, data was extracted If available for sensitivity, specificity, Area under the ROC Curve (AUC), P (value) and confidence intervals.

3. Results

Database searches were performed on February 20, 2022, and three hundred thirty-seven articles were identified. Of these, twelve articles met the inclusion criteria. The Preferred Reporting Items for Systematic Reviews and Mata-Analyses (PRISMA) diagram showing how the articles were selected is shown in Figure 1.

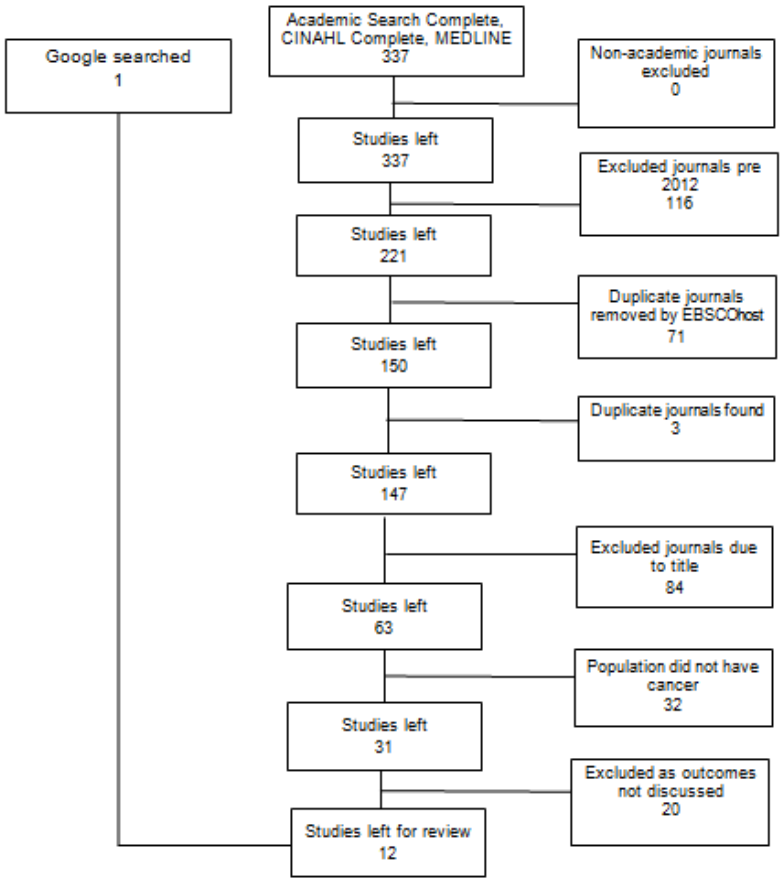

Fig.1. PRISMA Flow Diagram

3.1 Study and Population Characteristics

The quality of the final 12 articles in this review was then graded using the GRADE approach. As the 12 included studies are either observational or diagnostic in design, they all start of as low in quality. Only one study was rated down. The GRADE table can be seen in supporting information table 2.

Of the 12 articles, three are case-control studies, six prospective observational studies, two diagnostic test studies and one retrospective 2-centre cohort study. The number of febrile neutropenic episodes ranged from 29 in two studies to 372 episodes in one 2-centre cohort study. Eight of the studies in this review are looking at CRP. Two studies are looking at lactate, and five review presepsin.

Across the included studies, 1051 febrile neutropenic episodes from 743 children from different countries were analysed. The age ranged from 0-19 years. In the majority of studies (75%), acute lymphoblastic leukaemia was the most frequent diagnosis.

The definitions of fever were compared between the studies. FN is defined as having a temperature equal to or higher than 38ºC and a neutrophil count of 0.5 x 10^9/L or lower. [Dommett et al. 2009] One study uses this definition for their inclusion criteria. [Özdemir et al. 2019] One study included a higher threshold for fever of >38.5.ºC. [Pacheco-Rosas et al. 2014] Four studies define FN with a single oral temperature of >38.3°C or a temperature of ≥38.0°C over a one-four hour period. One study included children with an axillary temperature of >37.3 ºC if it persisted for more than two hours; oral temperatures were not allowed. [Phillips et al. 2020] Four studies included axillary temperatures of ≥38.5°C once or ≥38.0°C on 2 occasions over a 1-, 6- or 12-h period. [Phillips et al. 2016, Royal College of physicians 2016, Sirinoglu et al. 2016, Stiell et al. 2007] The last study defines a fever as an axillary temperature of >38.0°C on one occasion or >37.5 ºC for at least one hour.

The definitions of neutropenia were mostly consistent, defined as a neutrophil count <500 cells/microlitre at the onset of fever in 6 studies (50%). Six studies (50%) expanded on this definition to include neutrophils <1000 cells/microlitre with the expectation to drop <500 cells/microlitre within 48h-72 hours.

The heterogeneity in the blood sampling times of the biomarkers under review has been noted. Most studies discuss that blood sampling for the biomarkers was taken on the first day, within 24 hours of admission and before antibiotics were commenced. In one study, blood samples were taken on the day of admission; however, participants had a fever which started in the last 48 hours and had a much lower fever threshold of >37.3 ºC. [Phillips et al. 2020] One study evaluated presepsin at admission (T0). It is important to note that the timing of the fever detection, travel time to the hospital, and time to be reviewed and consented to will all vary between participants. It is important to note that two case-control studies included 'apparently' healthy control participants, with one study unable to obtain urine, stool and blood culture samples from their controls.

3.2 Summary of main findings:

C-reactive protein: CRP is an inflammatory marker that rises when there is a bacterial infection; however, this rise can be slow. Research suggests the disadvantages of CRP are its limited specificity and delayed increase. This is because inflammation in the body can be caused by injury or disease as well as infection.

The eight studies in this review looking at CRP had mixed results. Four of the studies found that CRP is a useful diagnostic marker of infection with high sensitivity and specificity. Three studies found that CRP was not a useful biomarker of infection with mixed sensitivities and specificities. One study found that CRP used in combination with presepsin would improve the sensitivity and specificity for bacterial infection prediction.

Serum Lactate: Lactate is a biomarker of sepsis with a high lactate level associated with mortality in patients with infection. However, it must be noted that lactate levels can rise due to the malignancy or dexamethasone.

The two studies looking at lactate both suggest that this is a good marker for sepsis, producing high sensitivities and specificities. A lactate level ≥ 2mmol/L and >2.5mmol/L showed sensitivities of 81% and 80% and specificities of 83% and 92.1%, respectively.

Presepsin: Presepsin, also known as the soluble CD14 subtype, is a biomarker that is released early in infection, and the levels rise within 2 hours of inflammation. A recent systematic review and meta-analysis found that presepsin is more accurate and has a higher sensitivity than CRP in detecting sepsis in children.

The five studies looking at Presepsin have shown mixed results. Three studies indicate that presepsin levels correlate with the severity of infection. With one study with a cut-off value ≥1014 has a sensitivity of 100% and specificity of 85.7% for presepsin. However, two studies show that presepsin has low diagnostic accuracy in predicting bacterial infection.

Outcome: In practice, CRP is a useful biomarker of infection with low levels suggestive of a viral infection. As CRP levels rise slowly it could mean that CRP would not help with making decisions about de-escalating treatment. This suggests that CRP does not belong in a CDR. However, it is important not to forget that CRP is noted as important in the diagnosis of sepsis in the sepsis 6

tool. If CRP levels are within normal range or are very low upon admission, this could still be a predictor of a patient at low-risk of FN.

The importance of lactate is clearly highlighted in the sepsis 6 tool, as a Lactate >2mmol/l is a red flag for sepsis. With all this in mind and, the fact that lactate level is quick and easy to obtain, is an indicator that this biomarker would be useful in a CDR to assess the risk of FN patients.

Presepsin is a biomarker that is not currently used in practice, and due to the mixed results and heterogeneity between all the studies, it is difficult to determine how useful presepsin is in the diagnosis of bacterial infections in the population under review.

Confidence intervals were undertaken in five studies. Confidence intervals indicate how precise the study results are. The study with the narrowest confidence interval levels of 0.935-1.000% was for CRP. The two studies looking at lactate had fairly narrow intervals with 0.725-0.977 and 0.81-0.98, respectively. The study with the widest intervals of 0.676-1.00% was for presepsin and 0.353-0.925 for CRP, suggesting there is more uncertainty in these results. In one study, the results suggested that CRP was not correlated with bacteremia/sepsis; however, as the confidence intervals are wide, there is uncertainty in these results, meaning that, in fact, there could be a correlation, but it is not shown in this study. What is interesting is that two studies looking at CRP both have the smallest sample sizes of the 12 studies included and have produced contrasting results.

The P-value in research is the probability that the results obtained in a study are due to chance. All but one study uses P-values. Seven studies have P-values of <0.05, suggesting statistically significant results for the specified biomarkers. It has been suggested that P-values are arbitrary, and in fact, a non-significant P-value could demonstrate that the sample size was too small to show an effect. The results from the 12 studies can be seen in Table 1.

3.2.1 TABLE 1: Results table

	Sensitivity	Specificity	AUC	P (value)	95% Confidence Intervals	Results
Suwanpakdee et al. (2021)	80%	92.1%	0.90	<.001	0.81-0.98	Lactate level >2.5mmol/L is a predictor for developing septic shock
Akcay et al. (2021)	100%	14%	X	0.981	X	CRP cut off of 10mg/L CRP could not distinguish between an infectious and a non-infectious inflammatory response
Agnello et al. (2020)	X	X	0.58	0.09	X	Presepsin has a low diagnostic accuracy and cannot predict blood culture positivity.
Özdemir et al. (2019)	84.6 (CRP) X Presepsin	55.9 (CRP) X Presepsin	0.758 (CRP) X Presepsin	FN group versus control: CRP <0.001 Presepsin <0.05 Culture positive:	X	CRP Cut-off 2.5mg/dl CRP is a useful marker for predicting bloodstream infections

				CRP <0.01 Presepsin >0.05 Sepsis: CRP>0.05 Presepsin >0.05		Presepsin had low significance.
Baraka and Zakaria (2018)	Presepsin 100% CRP 77.8%	Presepsin 85.7% CRP 66.7%	Presepsin 0.95 CRP 0.75	<0.001 0.01	X	Cut-off presepsin ≥ 1014 Presepsin can be used as a discriminator of infectious and non-infectious origin of fever CRP cut-off ≥ 105 Combination of CRP and presepsin may improve the sensitivity and specificity for bacterial infection prediction.
Kuter et al. (2018)	X	X	Presepsin 0.861 CRP 0.639	Presepsin 0.027 CRP 0.395	Presepsin 0.676-1.00% CRP 0.353-0.925	Presepsin is an indicator of positive hemoculture CRP not correlated to bacteremia/ sepsis
Sirinoglu et al. (2016)	93.10%	92.00%	0.972	.001	0.935-1.000%	CRP cut-off ≥8.03 CRP good diagnostic marker of infection
Delebarre et al. (2015)	14%	97%	0.61	<0.010	Sensitivity 7-25% Specificity 94-98%	CRP ≥ 90mg/L at risk of severe infection
Olad et al. (2014)	X	X	0.663	<0.05	X	Increasing levels of presepsin correlates with severity of infection Levels higher in culture positives in the absence of clinically detectable source of infection
Pacheco-Rosas et al. (2014)	81%	83%	0.851	X	0.725-0.977	A lactate level ≥ 2mmol/L is consistent with severe sepsis

Kitanovski et al. (2014)	Day 1 Sepsis 50% Day 1 Severe sepsis 37.5% Day 2 Sepsis 77.8% Day 2 severe sepsis 100%	Day 1 Sepsis 87.3% Day 1 Severe sepsis 93.8% Day 2 sepsis 100% Day 2 severe sepsis 79.7%	Day 1 0.695 Day 2 0.828	Day 1 0.01 Day 2 0.00	X	CRP has a low to intermediate diagnostic accuracy for sepsis
Penagos-Paniague et al. (2012)	94%	94%	X	<0.001	X	CRP cut- off 60mg/L CRP is a useful test for the diagnosis of bacterial infections

The four case-control studies do not explain how the control groups were chosen. In one study, the control group consisted of participants without any infection; however, blood, urine and stool cultures were not obtained, unlike in the cohort group. The results of the biomarkers from the control group could be elevated due to an unknown infection.

Heterogeneity between the inclusion and exclusion criteria of each of the studies has been noted. Two Studies do not have inclusion and exclusion criteria documented. Three studies do not have exclusion criteria stated.

Participant Outcomes: As seen, there is no consensus on how to take a temperature. Three studies measure temperatures orally, whilst five studies measure temperature by axillary. In practice, treatment should be commenced with a fever by any measurement. What is worrying about some of these definitions is the waiting time to start antibiotics. This can be seen in one study with a fever >38.0°C on multiple occasions during a 12 hour period. Antibiotics should be commenced within one hour of a documented fever; the longer the wait, the higher the risk of death. In one study, 3 participants died. Another 8 of the participants died, that being 20.5% of the total participants. Lastly, in another study, 4 participants died. It could be suggested that waiting and monitoring patient's temperatures, as seen by some of these definitions could be contributing to the outcome of these patients. This highlights that there are many variables which can impact the outcome of febrile neutropenic patients, the variables under review will not alone suffice in the assessment. Hence, the a need for a validated and reliable CDR.

4. Discussion

The population of interest in this review is unique and specific, which makes it hard for the results from this review to be generalisable to other populations. All 12 studies include children under 19 years old, both males and females with cancer. Due to the rarity of the disease in children, not all types of childhood cancers have been investigated in these studies, making it difficult to generalise these results to all childhood cancers. This is a difficult point to make as this review is not only looking for sensitive and specific biomarkers to assess the outcomes of FN in all childhood cancers, it is also looking to see if these biomarkers under review can fit into a CDR. If this review suggested that the biomarkers under review could fit into a CDR, the CDR could only be used for the types of cancers that have been investigated.

To note, none of the studies were undertaken in the UK so this could be considered a limitation. Although the studies were undertaken in paediatric oncology or haematology hospital settings, there will be cultural, socioeconomic and environmental differences which could impact the results of the study. For example, children in the UK are nursed in cubicles to protect them from infection. In other countries, due to limited funds, children are cared for in bays, increasing their chance of getting a hospital acquired infection. This shows the inequality in care for children with cancer between low and middle-income countries and high-income countries. This highlights the importance of this review because if some children who are febrile neutropenic can be at home on oral antibiotics, this treatment is cheaper and will prevent children from being in the hospital, where they can pick up further infections.

The sample size in all 12 studies is small. Cancer in children is rare, and therefore, it is inevitable that sample sizes will be small when undertaking research in rare diseases. One way to overcome this problem is for studies to undertake a power calculation. Only one study undertook a power calculation to determine the minimum sample size required.

The strengths of this review include the clear and thorough search which was undertaken to find all the relevant research for this review. Library sessions were had to ensure accurate and quality searching. This reduced bias in this review and reduced the threat to the validity and reliability of the data. Two critical appraisal tools were used to ensure a thorough analysis. To prevent data extraction bias, a supervisor assisted in the data extraction of one paper and the results were compared. A transparent and reproducible review has been produced. Limitations in this review include the date restrictions of the included articles; bias has been introduced here. Another limitation is that the library could not gain full-text access to one possibly included article. The grading of the quality of included studies was under taken by a single-reviewer, and due to its subjective nature, there is a risk of bias. A second reviewer here would have reduced this risk.

Four studies recommend further studies with larger sample sizes. As all 12 studies have small sample sizes due to the rarity of the disease, this recommendation could be difficult to achieve and time consuming. Other studies suggest using a combination of biomarkers to increase the sensitivity and specificity for predicting bacterial infections. In order for this to be used widely, including low-income countries, these tests need to be done at low cost. The added benefits need to be weighed up against the cost.

5. To conclude, this review has found that lactate has good sensitivity and specificity for assessing whether children and young people with cancer who are febrile neutropenic are at risk of poor outcomes. Although only two papers were found in the last 10 years, showing that more research is required, the fairly narrow confidence intervals provide confidence in the results. CRP has shown mixed results for sensitivity and specificity in this review; however, the papers with positive findings had narrow confidence intervals, whereas the papers that suggested no correlation had wide confidence intervals, suggesting that there could be a correlation, but it is not shown in that study. Lactate and CRP are used in practice, and the results in this review highlight that they are still useful biomarkers in practice. They are still applicable. Presepsin had mixed results for its sensitivity and specificity for the assessment of outcomes for children with FN. Only one of the five studies calculated confidence intervals, and the results were fairly wide. The small sample sizes and heterogeneity between all the studies makes it difficult to confirm that presepsin is a useful biomarker for clinical practice.

In regards to poor outcomes, it can be seen from the heterogeneity between the studies that there are many factors which can influence the outcomes of febrile neutropenic children. The definition of FN being one, as this influences the timing and commencement of antibiotics treatment. It is well known that the longer it takes to commence antibiotic treatment, the higher the risk of poor outcomes in this patient population. Secondly, the risk of poor outcomes is higher in lower and middle income countries, showing inequality in care. This review has highlighted the many benefits that could come from finding reliable biomarkers to use in practice and, thus, the production of a CDR to help risk stratify this patient population. Although this remains important, this review has found that there are other changes that need to be made. In many of these studies, children died. Therefore, there is a need for one simple universal definition for FN. The timing and commencement of antibiotics need to be immediate. And there needs to be a reduction in the gap between care in lower income countries and high income countries.

Producing a validated CDR that can be used worldwide could help close the gap between outcomes in lower and higher income countries. If children can be risk-stratified as low-risk, they could go home on oral antibiotics. This treatment is cheaper, easier to administrate, and requires less training and fewer resources than intravenous antibiotics.

Recommendations for practice include the need for a large prospective multicentre UK study looking at the sensitivity and specificity of CRP, presepsin and lactate for assessing whether children and young people with cancer who are febrile neutropenic are at risk of poor outcomes. Alongside this, other variables which are deemed important can be reviewed in order to create a CDR.

Conflict of Interest: This review was undertaken as part of my dissertation to gain a Master of Science in Children and Young People's Health. This module was funded by my place of work. Great Ormond Street Hospital. No other conflict of interest to declare.

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Glossary of terms: CDR: Clinical Decision Rule; CRP: C-reactive protein; FN: Febrile Neutropenia; sCD14-ST: Presepsin

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http://www.scielo.org.mx/pdf/bmim/v69n5/v69n5a8.pdf?_x_tr_sl=es&_x_tr_tl=en&_x_tr_hl=en&_x_tr_pto=sc&_x_tr_sch=http [Accessed 27 February 2022].
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Legends

Figure 1: PRISMA (2020) Flow Diagram. This diagram shows the number of papers found during the systematic search and how this was reduced down to the 12 included studies.

Table 1: Results. This table shows the sensitivities, specificities, AUC, P (value), confidence intervals and, thus, the results of the biomarkers under investigation from each study.

Supporting information NOT for review

Supporting table 1: Data extraction table. This form was developed to ensure all included studies were treated equally and data was extracted in a consistent and uniform manner.

Study details (Reference)	Level of evidence	Study design (Methodology and method)	Intervention/ Phenomenon of interest	Setting e.g. location	Participants (Number/ age/gender/ ethnicity/ cultural context)	Type of data analysis	Key findings	Quality (Validity/ Reliability)	Applicability to practice	Comments/ GRADE
Suwanpakdee, D., Prasertsin, W., Traivaree, C. and Rujkijyanont, P. (2021) Serum Lactate: A Predictor of Septic Shock in Childhood Cancers with Febrile	**IV**	**Prospective observational study between 1st January 2019- 31st January 2020** **Patient's demographic data and serum lactate level were collected**	**To investigate the prognostic accuracy of serum lactate level to predict the occurrence of septic shock within 48 hours after developing febrile neutropenia and**	**Division of hematology and oncology, Department of pediatrics, Phramongkutklao hospital**	**99 children** **Age 3 months-18 years** **Males and females** **Single hospital in**	**Mean, median (range), standard deviation, percentage** **Fisher's exact test**	***P*-value was undertaken** **Serum lactate level was significantly higher among patients developing septic shock**	**Small sample size** **Not UK centre** **Ethics approved** **Consent taken**	**A serum lactate level of more than 2.5mmol/L is the threshold to start pre-emptive aggressive hemodynamic monitoring and prompt**	**Very clear data presentation and rationale** **Study flow diagram useful**

Neutropenia, *Global Pediatric Health,* 8, pp. 1-10. DOI: 10.1177/2333794X211022711.		**when a febrile neutropenic episode developed, followed by the collection of clinical information over the next 48 hours.**	**which optimal cut off level of serum lactate should be established** **Secondary outcome was to determine the association between serum lactate level and mortality risk and to identify additional determinant factors associated with septic shock**		**Bangkok, Thailand** **Acute lymphoblastic leukaemia most frequent diagnosis** **63%**	**Mann-Whitney *U* test** **Receiver operating characteristic (ROC)** **Trapezoidal rule** ***P*-value**	**within 48 hours compared to those not experiencing septic shock. *P*-value <.001** **Serum lactate levels were significantly elevated in the 4 patients that died within 48 hours compared to those still alive. *P*-value** **.002** **AUC was 0.90** **A serum lactate level of 2.5mmol/L was found to be the optimal predictor for developing septic shock with a sensitivity of 80%, specificit**	**Funding bias**	**treatment to ensure adequate tissue perfusion** **Serum lactate is an effective surrogate marker for developing septic shock**	**Low**

							y of 92.1% and accuracy of 90.9%			
Akcay, A., Agaoglu, L., Ekmekci, H., Ekmekci, O. B., Saribeyoglu, E., Atay, D., Tugcu, D., Karakas, Z., Unuvar, A., Anak, S., Ozturk, G. and Deveciogl u, O. (2021) Interleuki n-8 in Febrile Neutropen ic Children with Cancers: Its Diagnostic Value for Bacteremi a/ Sepsis is Superior to that of Interleuki n-6, Mannose Binding Lectin, Procalcito nin and C-Reactive Protein, *Internatio nal Journal of Hematolo gy and Oncology,* 31 (4), pp. 230-238. DOI:	IV	A single-center prospectiv e study No time frame of the study Blood samples were obtained in two different clinical periods. Afebrile neutropeni c period after chemother apy and febrile neutropeni c period Blood samples taken included C-reactive protein.	To determine the predictive value of serum C-reactive protein levels for bacteremia /sepsis at the start of a febrile episode in children with chemother apy-induced febrile neutropeni a	Single centre in Istanbu l, Turkey	30 children with 54 febrile neutropen ic episodes Age 1-16 years Males and females Acute lymphobla stic leukaemia most frequent diagnosis 53.3%	Mean, standa rd deviati on, media n, freque ncies and percen tages Mann-Whitn ey *U* test Kruska l-Wallis test Wilcox on test Spear man's correla tion coeffic ient Receiv er operat ing charac teristic (ROC) curve	C-reactive protein levels could not distingui sh between an infectiou s and a non-infectiou s inflamma tory response. At a cut-off value of 10mg/L, C-reactive protein had a sensitivit y of 100% and a specificit y of 14% Sensitivit y decrease d, and specificit y of C-reactive protein increased as the cut-off value	Small sample size Not UK centre Ethics approved Consent taken Funding bias	C-reactive protein is used in practice, but other biomarke rs were found to be a more reliable test. Combine d use of biomarke rs can help identify patients at low-risk of bacterem ia/sepsis. Thus reducing antibiotic use and cost of treatmen t.	Low

10.4999/uhod.215278.						**Sensitivity, specificity, positive predictive value and negative predictive value** **Two-tailed *P*-value**	**increased.**			
Agnello, L., Bivona, G., Parisi, E., Lucido, G. D., Lacona, A., Ciaccio, A. M., Giglio, R. V., Ziino, O. and Ciaccio, M. (2020) Presepsin and Midregional Proadrenomedullin in Pediatric Oncologic Patients with Febrile Neutropenia, *Laboratory Medicine,* 51 (6), pp. 585-591. DOI:	**IV**	**Prospective observational study between February 2018- May 2019** **Presepsin levels were taken on admission (T0), after 24/48 hours (T1) and after 5 days (T2)** **Patients were classified into groups** **-** **Bacteremia (B)** **-Fever of unknown**	**To investigate the roles of presepsin in children with febrile neutropenia due to chemotherapy**	**Unit of pediatric onco-hematology, ARNAS Civico hospital, Palermo, Italy**	**26 children with 37 febrile neutropenic episodes** **0-17 years old** **Males and females** **Hospital in Palermo, Italy** **Acute lymphoblastic leukaemia most frequent diagnosis** **38%**	**Chen-Shapiro test** **Mean, standard deviation, median, inter-quartile range, frequencies** **Mann-Whitney *U* test** **Spearman test**	**Presepsin levels were elevated at T0 and decreased at T2.** **At T0, presepsin is a predictor of length of hospital stay but not duration of fever.** **AUC presepsin 0.58** **Presepsin is not efficient in predictin**	**Small sample size** **Not UK centre** **Ethics approved** **Consent taken** **Single centre study**	**Presepsin displays poor clinical usefulness for febrile neutropenia in oncologic children.**	**Low**

10.1093/labmed/Imaa011.		origin (FUO)				*P*-value Generalised linear models	g culture positivity			
Özdemir, Z. C., Düzenli-Kar, Y., Canik, A., Küskü-Kiraz, Z., Özen, H. and Bör, Ö. (2019) The predictive value of procalcitonin, C-reactive protein, presepsin, and soluble-triggering receptor expressed on myeloid cell levels in bloodstream infections in pediatric patients with febrile neutropenia, *The Turkish Journal of Pediatrics,* 61 (3), pp. 359-367. DOI: 10.24953/turkjped.2	IV	Between December 2015-February 2016 Blood samples were taken on admission (D1), after 24-48 hours (D2) and on day 7 (D7) Control group had one blood sample taken.	To investigate the predictive value of C-reactive protein and presepsin in bloodstream infections in children with febrile neutropenia	Does not discuss Authors work in Turkey. Suggests a hospital in Turkey	30 children with 47 febrile neutropenic episodes 27 children in control group I. MEAN AGE 8.6 ± 0.83 Males and females Acute lymphoblastic leukaemia most frequent diagnosis 56.6%	Mean, standard deviation, median and interquartile range Chi-square test Kolmogorov-Smirnov test Independent *t*-test Mann-Whitney *U* test Spearman's correlation coefficient Receiver	The median C-reactive protein and presepsin levels were significantly higher in the study group. C-reactive protein levels in the culture-positive episodes on days 1, 2 and 7 were significantly higher than culture-negative episodes. No difference between the culture-positive and culture-negative	Small sample size Not UK centre Ethics approved Consent taken Funding bias	C-reactive protein is a useful marker in predicting bloodstream infections in pediatric patients with febrile neutropenia. Presepsin proved to be of low significance	Low

019.03.007.						**operating characteristics (ROC) curve** ***P*-value**	**episodes for presepsin on days 1, 2 and 7**			
Baraka, A. and Zakaria, M. (2018) Presepsin as a diagnostic marker of bacterial infections in febrile neutropenic pediatric patients with hematological malignancies, *International Journal of Hematology*, 108 (2), pp. 184-191. DOI:10.1007/s12185-018-2447-x.	**IV**	**A case-control study** **Study population was divided into patients and control groups.** **No date range when study took place**	**To evaluate the significance of presepsin and other biomarkers for diagnosis of bacteremia in children with hematological malignancies**	**Clinical pathology and pediatric oncology departments of Zagazig university hospital**	**90 children** **60 in the patient group, 30 in the control group** **Control group healthy participants** **Age 2-15 years** **Males and females** **Egypt hospital** **Acute lymphoblastic leukaemia most frequent diagnosis** **60%**	**Student's *t* test** **One-way ANOVA test** **Kruskal-Wallis test** **Mann-Whitney and Chi-squared** ***P*-value** **Correlation co-efficient rank test** **Receiver-operat**	***P*- value was undertaken** **Presepsin levels were elevated in patients with bacterial infections.** **Presepsin had a higher sensitivity and specificity than CRP for predicting bacterial infections.** **Presepsin had 100% sensitivity and 85.7% specificity**	**Small sample size** **Not UK centre** **Ethics approved** **Control group** **Consent taken**	**The combination of presepsin and CRP may improve the sensitivity and specificity for the prediction of bacterial infection.**	**Low**

						ing charac teristic (ROC)				
Kuter, Ş., Canpolat, C. and Yılancıoğlu, K. (2018) Diagnostic Role of sCD14-Subtype as a Sepsis Biomarker in Febrile Neutropenic Pediatric Oncology Patients, II. *Acibadem University Health Sciences Journal*, 9 (4), pp. 395-400. DOI: 10.31067/0.2018.62.	IV	A prospectiv e study No date range when study took place Patients were classified into bacteremia /sepsis group or fever without origin group Serum samples of presepsin and c-reactive protein were collected once febrile neutropeni a had been confirmed	To assess the potential of presepsin as an additional diagnostic tool for the detection of bacteremia /sepsis in childhood febrile neutropeni a patients	Divisio n of pediatr ic hemat ology and oncolo gy Clinic in Turkey	24 children with 29 febrile neutropen ic episodes Males and females Age 0-14 years Acute lymphobla stic leukaemia most frequent diagnosis 29%	Mann-Whitn ey-*U* test Spear man rank test Receiv er-operat ing charac teristic (ROC) analysi s *P*-value	Medium presepsi n and c-reactive protein levels did not differ significa ntly between the bacterem ia/sepsis and fever without origin groups Medium presepsi n concentr ations was significa ntly different between patients with positive and negative hemocult ures p=0.012, whereas c-reactive protein did not differ significa ntly	Small sample size Not UK centre Ethics passed Consent taken	Presepsin might be used as an additiona l diagnosti c tool for the detection of bacterem ia/sepsis in childhoo d febrile neutrope nia patients AUC-ROC presepsin is 0.861, p=0.027	Very Low
Sirinoglu, M., Soysal, A., Karaaslan, A.,	IV	A prospectiv e case-control study	To determine the diagnostic value of C-	Marma ra Univer sity School	29 children	Descri ptive statisti cs	The mean C-reactive protein levels in	Small sample size	C-reactive protein has an outstandi	Low

Kadayifci, E. k., Cinel, I., Koc, A., Tokuc, G., Yaman, A., Haklar, G., Sirikci, O., Turan, S., Gelmez, G. A., Soyletir, G. and Bakir, M. (2016) The diagnostic value of soluble urokinase plasminogen activator receptor compared with C-reactive protein and procalcitonin in children with febrile neutropenia, *Pediatric hematology and oncology,* 33 (3), pp. 200-208. DOI: 10.3109/08880018.2016.1155100.		**between December 2013-December 2014** **Serum blood samples were taken on admission, 4th and 7 day** **Control group were patients admitted to the pediatric endocrinology outpatient clinic** **Only one blood sample was obtained from the control group**	**reactive protein in pediatric patients with febrile neutropenia**	**of Medicine Hospital**	**27 control children** **Age 1 month- 18 years** **Solid tumours and hematologic malignancies**	**Student's *t* test** **Mann-Whitney *U* test** **1-way analysis of variance (ANOVA)** **Tukey's honestly significant difference (HSD) test** **Kruskal-Wallis test** **Pearson's chi-square test** **Fischer's exact test**	**the febrile neutropenic group was significantly higher than the control group** **The mean C-reactive protein levels of the first and second samples were statistically significant** **C-reactive protein with a cutoff point of 8.03mg/L had a sensitivity of 93.10, a specificity of 92.00, a positive predictive value of 93.10 and a negative predictive value of 92.00**	**Not UK hospital** **Ethics passed** **Consent taken** **Funding bias**	**ng diagnostic value for children with febrile neutropenia**	

						Yates continuity correction test Receiver operating characteristics (ROC) curve *P*-value	ROC curve for C-reactive protein =0.972 P value for C-reactive protein= .001			
Delebarre, M., Garnier, N., Macher, E., Thebaud, E., Mazingue, F., Leblond, P., Duhamel, A., Martinot, A. and Dubos, F. (2015) Which Variables Are Useful for Predicting Severe Infection in Children With Febrile Neutropenia?, *Journal of pediatric hematolo*	IV	Retrospective 2-center cohort study between January 2005-December 2006 Data available at admission was collected from medical files Data collected included demographic, recent history, clinical data, laboratory data and	To identify the variables that could predict sever infection in children with chemotherapy-induced febrile neutropenia	Tertiary-care university hospital Pediatric oncology unit of Oscar Lambret Cancer Center or the pediatric hematology unit of the Lille University Hospital	160 children with 372 FN episodes Males and females Age 0-18 years Acute lymphoid leukemia most frequent diagnosis 34%	Descriptive analysis Shapiro-Wilk test Student t test Mann-Whitney test Receiver operating characteristic (ROC) curve χ^2 test	There are 4 factors that have shown to be significantly associated with the risk of severe infection. These are, disease with high risk of prolonged neutropenia, blood cancer, fever ≥ 38.5°C and C-reactive protein level ≥ 90mg/L AUC ROC of C-	Largest sample size Ethics approved Not UK centre Data collection was blinded Multicentre study Consent not required Age of data-limitation	C-reactive protein level ≥ 90mg/L is significantly associated with severe infection in children with febrile neutropenia This variable could be added to a new decision rule to predict low risk of severe infection in children with febrile	Low

gy/oncology, **37 (8), pp. e468-e474. DOI: 10.1097/MPH.0000000000000440**		**microbiological data**				**Fisher exact test** ***P*-value**	**reactive protein= 0.61**	**Funding not discussed**	**neutropenia, leading to the de-escalation of antimicrobial treatment or early discharge for patients at low risk**	
Olad, E., Sedighi, I., Mehrvar, A., Tashvighi, M., Fallahazad, V., Hedayatiasl, A. and Esfahani, H. (2014) Presepsin (Scd14) as a Marker of Serious Bacterial Infections in chemotherapy Induced Severe Neutropenia, *Iranian Journal of Pediatrics,* 24 (6), pp. 715-722. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4442833/	**IV**	**Prospective study between September 2012 to January 2013** **Blood cultures and serum soluble CD14 was taken on the first day of admission** **Febrile and afebrile groups**	**To determine a rapid and secure predictor of sepsis in severe neutropenic cancer children** **To investigate the utility of sCD14 level to detect serious bacterial infections in chemotherapy induced neutropenia**	**Mahak pediatric oncology center** **Hospital in Tehran, Iran**	**39 children with 78 neutropenic episodes** **18 febrile and 21 afebrile** **Age 1-19 years old** **Males and females** **Acute lymphoblastic leukaemia most frequent diagnosis** **30.8%**	**Descriptive statistics, mean** **One-way ANOVA** ***t* test** **Receiver-operating characteristic (ROC) curves** **Sensitivity and specificity**	**AUC for presepsin was 0.563 and 0.633 when excluding mixed cultures** **CD14 levels increase with fever** **CD14 levels were not significantly higher in blood culture positive cases** **Higher levels of CD14 in patients that died in the next 15 days was**	**Small sample size** **Consent taken** **Randomised into study** **Not UK centre** **Ethics not discussed** **Funding bias**	**Presepsin was not sensitive in detection of bacteremia** **In the absence of clinically detectable source of infection, presepsin was significantly higher in culture positives** **Increasing presepsin level correlates directly with the severity of infection**	**Low**

[Accessed 27 February 2022].							statistically significant			
Pacheco-Rosas, D. O., Huelgas-Plaza, A. C. and Miranda-Novales, M. G. (2014) Serum lactate as a biomarker of severe sepsis in children with cancer, neutropenia and fever, *Medical Journal of the Mexican Institute of Social Security,* 52 (S2), pp. 24-29. Available from: https://www.medigraphic.com/pdfs/imss/im-2014/ims142e.pdf [Accessed 27 February 2022].	IV	A phase II diagnostic test study between December 2011- June 2012 Lactate levels were measured on admission Neutropenic episodes were classified into 3 groups: -with sepsis -without sepsis -without fever (control)	To determine the usefulness of serum lactate as a biomarker of severe sepsis in children with cancer, fever and neutropenia	Pediatric Hospital of the XXI Century National Medical Center, Mexican Institute of Social Security	100 children with neutropenia 89 children had FN 11 children were control Age 1 month- 16 years old Males and females Solid tumour was most frequent diagnosis with 64%	Sensitivity, specificity, positive predictive value, negative predictive value Area under the curve (AUC)	A serum lactate level ≥ 2 mmol/L has a sensitivity of 81%, specificity of 83%, a positive predictive value of 48% and negative predictive value of 95% ROC for lactate was 0.851	Small sample size Ethics approved Consent taken Control group used Not UK centre	A serum lactate level ≥ 2 mmol/ L is consistent with severe sepsis in children with cancer, fever and neutropenia	Low
Kitanovski, L., Jazbec, J., Hojker, S. and Derganc, M. (2014) Diagnosti	IV	Prospective study between November 2007- March 2009	To determine the early diagnostic accuracy of CRP for predicting bacteremia	Pediatric Hemato-Oncology Department	47 or 48 children with 90 FN episodes	Sensitivity, specificity, positive predictive	The concentrations of all biomarkers were significantly	Small sample size Ethics approved	An ideal marker would be able to reliably stratify patients with	Low

c accuracy of lipopolysaccharide-binding protein for predicting bacteremia/clinical sepsis in children with febrile neutropenia: comparison with interleukin-6, procalcitonin, and C-reactive protein, *Supportive Care in Cancer,* 22 (1), pp. 269-277. DOI: 10.1007/s00520-013-1978-1.		**Febrile neutropenic episodes divided into 4 groups:** **-bacteremia and/or clinical sepsis** **-local infection** **-fever of unknown origin** **-others** **Blood samples (CRP) were taken on day 1 and 2**	**/clinical sepsis in febrile neutropenic children**	**of the University Medical Center Ljubljana** **Slovenia**	**Age 5 months-19 years old** **Males and females** **67% had a hematologic disease**	**value and negative predictive value** **Receiver operating characteristic (ROC) curves** **Mann-Whitney test** **Kruskal-Wallis non-parametric analysis of variance** **χ^2 test**	**higher in patients with bacteremia/clinical sepsis than those with non-bacteremia/clinical sepsis on both days** **LBP is less accurate for predicting bacteremia/clinical sepsis in febrile neutropenic children than CRP** **Day 2 AUC for CRP =0.828 to detect bacteremia/clinical sepsis** **Day 2 AUC for CRP= 0.911 to detect severe sepsis**	**Consent taken** **Not UK centre** **Single centre** **Funding bias**	**febrile neutropenia and consequently enable treatment of a subset of patients in outpatient settings with oral antibiotics**	

Penagos-Paniagua, M., Villasís-Keever, M. Á., Miranda-Novales, M. G., Tapia-Marcial, A., Rivera-Márquez, H., Bernaldez –Ríos, R., Aguilar, E. L. and Santos, F. S. (2012) Usefulness of C-reactive protein for the diagnosis of bacterial infection in pediatric patients with cancer, fever, and neutropenia, *Medical bulletin of the Children's Hospital of Mexico,* 69 (5), pp. 376-383. Available from: http://www.scielo.org.mx/pdf/bmim/v69n5/v69n5a8.pdf?x_tr_sl=es&_x_tr_tl=en&_x_tr_hl=en&_x	IV	Diagnostic test study No dates Neutropenic episodes divided into 4 groups: - microbiologically documented infection -clinically documented infection -fever of unknown origin -patients with neutropenia without fever Blood cultures and CRP level was taken prior to antibiotic commencement	To calculate the sensitivity, specificity, positive predictive value and negative predictive value, and likelihood ratios for C-RP in the diagnosis of bacterial infection of patients with cancer, neutropenia and fever	Pediatric Hospital of the XXI Century National Medical Centre Third-level health care centre Mexico City	98 children with 127 episodes Males and females Age 4- 13 years old Acute lymphoblastic leukaemia most frequent diagnosis 50%	Median, interquartile range Mann-Whitney *U* test Kruskal-Wallis test χ^2 test Fisher's exact test Spearman's rho test *p*-value Bayes analysis Receiver operating characteristic (ROC) curves Sensitivity,	With C-reactive protein of 60mg/L, it has a sensitivity of 94%, specificity 94%, positive predictive value 96% and negative predictive value 92%	Small sample size Ethics approved Consent taken Not UK centre Single centre Treating physician blinded	C-reactive protein is a useful and inexpensive test for the diagnosis of bacterial infection in patients with cancer, fever and neutropenia	Low

tr_pto=sc&_x_tr_sch=http [Accessed 27 February 2022].						**specificity, positive and negative predictive values**				

Supporting table 2: GRADE. Values were given to each paper to highlight their quality, i.e., good, or poor quality. This tool was chosen because it is a transparent framework with a systematic approach.

Key	
Rated up or down	✓
Not rated up or down	X

Study	**Risk of bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Publication bias**	**Large magnitude of effect**	**Exposure-response gradient**	**All residual confounding would decrease magnitude of effect**	**GRADE certainty**	**Justification**
Suwanpakdee et al. (2021)	X	X	X	X	X	X	X	X	Low	-Inclusion and exclusion criteria documented -Outcome measured accurately -Can't tell if exposure was measured accurately -Complete and adequate follow up of participants -Small sample size -Confidence intervals

										for sensitivity is wide, however narrower for specificity -Heterogeneity explained -RR & OR not calculated -Evidence is applicable
Akcay et al. (2021)	✓	X	X	X	X	X	X	X	Low	-Exclusion criteria not documented -Can't tell if exposure was measured accurately -Outcome measured accurately -Adequate follow up of participants -small sample size -Confidence intervals not discussed -Heterogeneity -Relative risk not calculated -No exposure-response gradient
Agnello et al. (2020)										-Inclusion and exclusion

	✓	X	X	X	X	X	X	X	Low	criteria documented -Outcome measured accurately -Confounding factors not adequately controlled -Measurement bias could be present -Complete and adequate follow up of participants -Small sample size -Confidence intervals not calculated -heterogeneity -Relative risk not calculated -No exposure-response gradient
Özdemir et al. (2019)	✓	X	X	X	X	X	X	X	Low	-Inclusion and exclusion criteria stated -Unsure if exposure and outcome measured accurately

										-Not all Confounding factors discussed -Participant follow up appropriate -Small sample size -Width of confidence intervals not shown -heterogeneity -Relative risk not calculated -No exposure-response gradient
Baraka and Zakaria (2017)	✓	X	X	X	X	X	X	X	Low	-Inclusion and exclusion criteria documented -Can't tell if exposure measured accurately -Confounding discussed -Follow up appropriate -Small sample size -Confidence intervals not calculated -Heterogeneity

										-Relative risk not calculated -No exposure-response gradient
Kuter et al. (2018)	✓	✓	X	X	X	X	X	X	Very low	-Inclusion and exclusion criteria not documented -Outcome measure accurately -Can't tell if exposure was measured accurately -Follow up complete enough, unsure if long enough -Wide confidence interval, small sample size -Heterogeneity -Relative risk not calculated -No exposure-response gradient
Sirinoglu et al., (2016)	✓	X	X	X	X	X	X	X	Low	-Exclusion criteria not documented -Confounding factors not adequately controlled

										-Adequate follow up, incomplete data from control group -Small sample size but narrow confidence interval - heterogeneity explained -Relative risk not calculated -No exposure-response gradient -
Delebarre et al. (2015)	X	X	X	X	X	X	X	X	Low	-Inclusion and exclusion criteria clearly documented -Outcome measured accurately, physicians blinded -adjusted odds ratio undertaken -Largest sample size of included studies -narrow confidence intervals - Heterogeneity explained -Relative risk not calculated

										- Exposure-response gradient not present
Olad et al. (2014)	✓	X	X	X	X	X	X	X	Low	-Inclusion criteria not clear enough, no exclusion criteria documented -Exposure not accurately measured -Small sample size - Confidence intervals not undertaken for sensitivity and specificity - Heterogeneity explained -Relative risk not calculated -No exposure-response gradient
Pacheco-Rosas et al. (2014)	X	X	X	X	X	X	X	X	Low	-Inclusion and exclusion criteria documented -Follow up of participants appropriate

										-Small sample size -Confidence intervals fairly narrow -Heterogeneity explained -Relative risk not calculated -No exposure-response gradient
Kitanovski et al. (2014)	✓	X	X	X	X	X	X	X	Low	-Inclusion criteria not clear but documented, exclusion criteria not documented -Exposure and outcome measured accurately -Confounding variables discussed -Participants followed up appropriately -Small sample size -Confidence intervals not calculated -Heterogeneity discussed

										- Relative risk not calculated -No exposure-response gradient
Penagos-Paniagua et al. (2012)	X	X	X	X	X	X	X	X	Low	-Inclusion and exclusion criteria documented -Chemist blinded -Small sample size -Narrow confidence intervals -heterogeneity discussed -Relative risk not calculated -No exposure-response gradient