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Review Article

Diagnostic and Differential Effects of CRP and PCT on Respiratory Virus and Mycoplasma Pneumoniae Infections in Children with Respiratory Tract Infections: A Meta-Analysis

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Abstract

Background: This study aimed to investigate the differential diagnostic value of CRP and PCT in distinguishing viral and Mycoplasma pneumonia infections in children with respiratory tract infections.

Methods: A total of 13 relevant articles (12 of relatively high quality) were included after quality evaluation, through a literature search. Meta-analysis and SROC curve evaluation were performed.

Results: The pooled sensitivity and specificity of CRP diagnosis were 0.91 (95% CI: 0.893-0.937) and 0.4815 (95% CI: 0.440-0.523), respectively, and the area under the SROC curve was 0.699. The pooled sensitivity and specificity of PCT were 68.92% (95% CI: 64.9%-72.7%) and 50.00% (95% CI: 45.6%-54.4%), respectively, and the area under the curve was 0.595.

Conclusion: CRP demonstrated higher sensitivity, while PCT showed relatively better specificity. Using both together could improve diagnostic performance.

Keywords: Respiratory tract infection; Respiratory virus; Mycoplasma infection

Introduction

Respiratory tract infection is the general term for infection of nasal cavity, throat, trachea and subordinate bronchi. The disease is characterized by its prevalence, high incidence rate, long latency period, acute symptoms at onset, and rapid progression. The detection rate of respiratory tract infection in children varies in different age groups. The highest incidence rate is among those over 3 years old, followed by those aged 1-3 (1). The main cause of the disease is bacterial, viral, and mycoplasma pneumonia infections. In children's respiratory tract infections, viral infections are usually more common than bacterial infections. Common viral infections include adenoviruses, influenza viruses, etc. Viral infections cannot usually be treated with antibiotics. The main way to ensure that the child has sufficient rest is through symptomatic treatment. Treatment plans for bacterial infections, such as pneumococcal infections, must be selected based on antibiotic resistance and the patient's specific situation. Mycoplasma pneumonia infection is a microbial infection between bacteria and viruses, usually treated with antibiotics. The ability to ac-

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curately identify the types of pathogens causing respiratory tract infections is crucial for doctors. It helps them determine the cause of an infection. This is important because it affects the treatment methods chosen for patients and their prognosis (2).

At present, microbiological detection of pathogens is an important standard for clinical diagnosis of respiratory tract infections. However, the microbiological detection of pathogens is time-consuming and requires highly skilled inspectors, who are subject to certain limitations (3). Accurately identifying the types of pathogens causing respiratory tract infections helps doctors determine the cause. This is important for selecting treatment methods and the prognosis of patients. Serological indicator testing refers to a method of assisting in diagnosing and evaluating the severity of a disease by detecting specific biomarkers in the patient's blood. Compared to pathogen microbiological testing, serological testing has a shorter detection time and can provide results faster, facilitating early treatment. It can also be repeated in the short term, and changes in indicators can be observed as treatment progresses to determine treatment effectiveness (4).

Serum procalcitonin (PCT) is a protein that can be induced and secreted by mycoplasma. It has good stability both in vivo and in vitro. The body can induce the secretion of serum PCT after being infected with mycoplasma. When its concentration is ≥ 40mg/L, it has diagnostic value for predicting severe infections. Previous studies have examined the diagnostic value of serum PCT in distinguishing between bacterial and non-bacterial pulmonary infections. PCT can improve the early diagnosis rate of non-bacterial pulmonary infections by about 15% (5). Serum C-reactive protein (CRP) is a protein with lower concentrations in healthy human serum. This protein binds to endotoxins during bacterial or mycoplasma infections. It forms C-polysaccharide complexes and activates immune cells, such as macrophages and monocytes. This process can cause inflammatory reactions. When these inflammatory cells cause damage to the alveolar epithelium in the respiratory tract, it may lead to worsening of pulmonary inflammation and symptom (6). There is a large amount of literature on the application of CRP and PCT. This literature is on the differential diagnosis of bacterial and non-bacterial infections. However, there is relatively little research on the application of CRP and PCT in the differential diagnosis of respiratory virus and mycoplasma pneumonia (7). This systematic review uses meta-analysis to comprehensively evaluate the differential diagnostic value of CRP and PCT in respiratory virus infection and mycoplasma pneumonia infection.

Materials and Methods

Retrieval strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines. Two researchers independently screened the retrieved literature based on the inclusion criteria of the review. The search databases included PubMed, EMBase, full-text Chinese journals, China Wanfang, and China National Knowledge Infrastructure. The search period was from the establishment of the database to Mar 2023. Chinese search terms: English search terms: pediatric pneumonia, respiratory virus infection, mycoplasma pneumonia infection, CRP, PCT, and diagnostic differentiation.

Inclusion and exclusion criteria for literature

(a)The included group was children aged 0-14 years old with respiratory virus infections and mycoplasma pneumonia infections. (b) True and false positive, true and false negative values forth differential diagnosis of CRP or PCT could be obtained directly or at a reduced price. (c) Positive thresholds for CRP and PCT were indicated in the literature. Exclusion criteria: (a) The study subjects only included children with respiratory virus infection or mycoplasma pneumonia infection. (b) The literature could not obtain relevant data for differential diagnosis using CRP and PCT.(c) The diagnostic criteria described in the literature did not align with the criteria for respir-

atory tract infections or mycoplasma pneumonia. (d) Literature on the differential diagnosis of respiratory virus and mycoplasma pneumonia infections using CRP or PCT alone. (e) Review, conference abstract, basic research, case studies, and reissued literature.

Data extraction and literature quality evaluation

The literature extraction data included the first author's name, publication year, nationality, sample size, CRP and PCT diagnostic methods, as well as true positive, false positive, false negative, and true negative values. The included studies were evaluated for quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS), which included a total of 17 items. The evaluation results were categorized as "yes", "unclear," or "no". GRADE evaluation was used for publication bias. Quality evaluation required two researchers to complete the evaluation independently. In case of disagreement, the opinion of a third researcher must be sought.

Statistical analysis

Meta-analysis was performed using RevMan 5.4.1. Cochran Q test and heterogeneity test were utilized, when $p>0.1$ and $I^2<50\%$, a fixed effects model was used for analysis, otherwise a random effects model was used for analysis. Count data were expressed using relative risk (RR) and 95% confidence interval (95% CI), while measure data were expressed using mean difference (MD) and 95% CI. A funnel plot was used to represent publication bias. Test level $\alpha=0.05$.

Results

According to the inclusion and exclusion criteria of the literature, 13 articles were ultimately included. The literature screening process was detailed in Fig. 1.

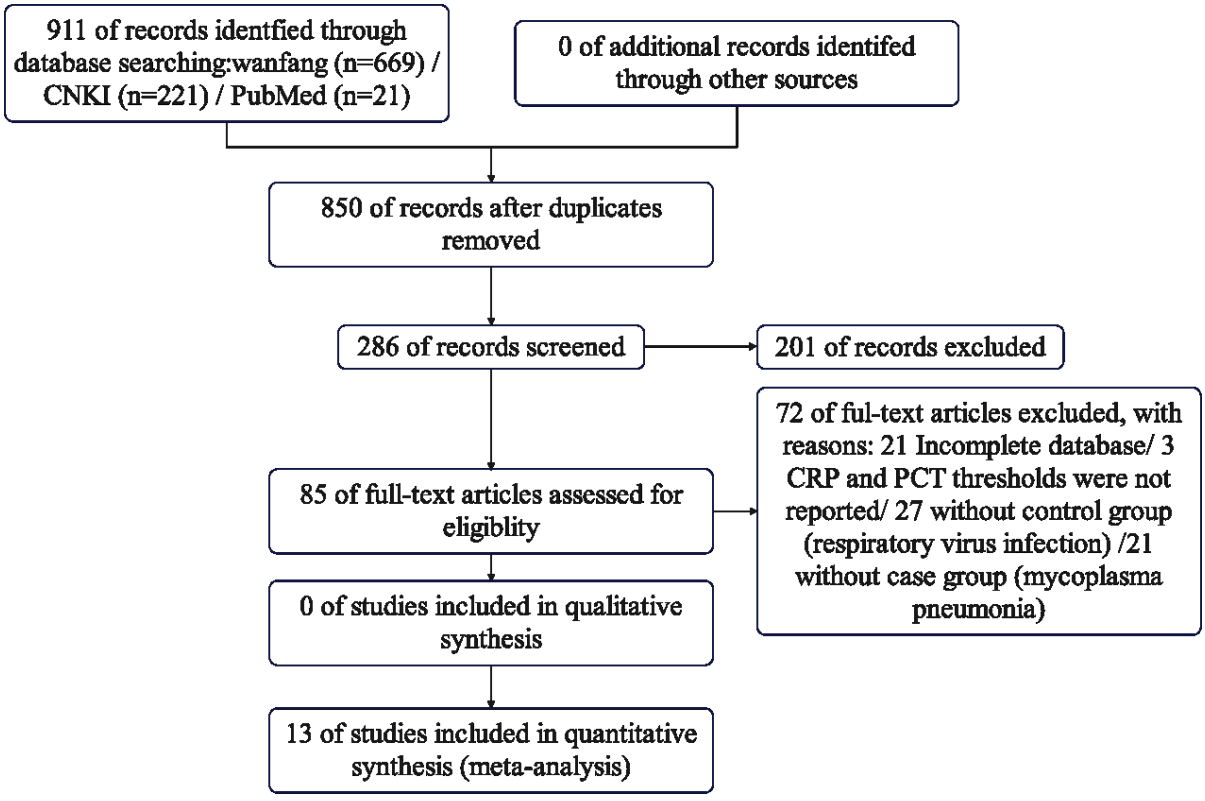

Fig. 1: Literature screening process

0 of additional records identified through other sources
850 of records after duplicates removed
286of records screened
201 of records excluded
85 of full-text articles assessed for eligibility
A total of 72 full-text articles were excluded for the following reasons: 21 were incomplete databases, three did not report CRP and PCT thresholds, 27 lacked a control group for respiratory virus infections, and 21 lacked a case group for mycoplasma pneumonia.
0 of studies included in qualitative synthesis
13 of studies included in quantitative synthesis (meta-analysis)

Basic characteristics of included literature

This systematic review included a total of 13 articles, 12 of which were domestic and one of which was foreign, published from 2014 to 2022.A total of 2,214 patients between the ages of three and 14 were included in the analysis. Four articles described the diagnostic value of CRP and PCT in children with pneumonia, while other articles (8-19) described changes in CRP and PCT indicators in children with pneumonia, as shown in Tables 1 and 2.

Table 1: Basic characteristics of literature with CRP detection method

Authors	Country	Year	Research object	Test method	True positive	False positive	False negative	True negative
Li HW(8)	China	2022	Child patient	CRP	24	20	5	13
Li Y(9)	China	2021	Child patient	CRP	36	18	5	26
Zhou ZQ(10)	China	2022	Child patient	CRP	52	13	2	25
Liu SJ(11)	China	2021	Child patient	CRP	33	22	7	14
Liu XQ(12)	China	2017	Child patient	CRP	42	15	5	28
Alcoba G(13)	America	2017	Child patient	CRP	40	19	8	23
Zhang MH(14)	China	2016	Child patient	CRP	37	12	5	11
Huang XS(15)	China	2015	Child patient	CRP	67	16	2	28
Gao JH(16)	China	2015	Child patient	CRP	65	28	2	15
Lin YR(17)	China	2014	Child patient	CRP	34	18	2	28
Zhang RL(18)	China	2015	Child patient	CRP	35	16	5	25
Zhang HL(19)	China	2016	Child patient	CRP	56	26	2	26
Gu YM(20)	China	2019	Child patient	CRP	54	71	2	13

Table 2: Basic characteristics of literature with PCT detection method

Authors	Country	Year	Research object	Test method	True positive	False positive	False negative
Li HW(8)	China	2022	Child patient	PCT	46	12	16
Li Y(9)	China	2021	Child patient	PCT	21	13	12
Zhou ZQ(10)	China	2022	Child patient	PCT	26	11	12
Liu SJ(11)	China	2021	Child patient	PCT	16	10	13
Liu XQ2(12)	China	2017	Child patient	PCT	29	11	16
Alcoba G(13)	America	2017	Child patient	PCT	22	19	15
Zhang MH(14)	China	2016	Child patient	PCT	28	18	17
Huang XS(15)	China	2015	Child patient	PCT	28	14	11
Gao JH(16)	China	2015	Child patient	PCT	60	15	10
Lin YR(17)	China	2014	Child patient	PCT	48	11	14
Zhang RL(18)	China	2015	Child patient	PCT	12	13	16
Zhang HL(19)	China	2016	Child patient	PCT	25	24	7
Gu YM(20)	China	2019	Child patient	PCT	27	13	16

Quality evaluation of literature QUADAS

Among the 13 included literature, 11 were Chinese and 2 were English. The quality of the retrieved literature was evaluated using QUADAS. The results of the literature quality evaluation were detailed in Table 3 and Fig. 2. In all the literature, the evaluation results for item 9 are mostly "no"or "unclear". The analysis reasons may be related to the fact that clinical testing standards do not require a special description, which does not affect the results.

The sensitivity and specificity of CRP and PCT in diagnosing respiratory tract infections were graded using GRADE, as shown in Tables 4 and 5.

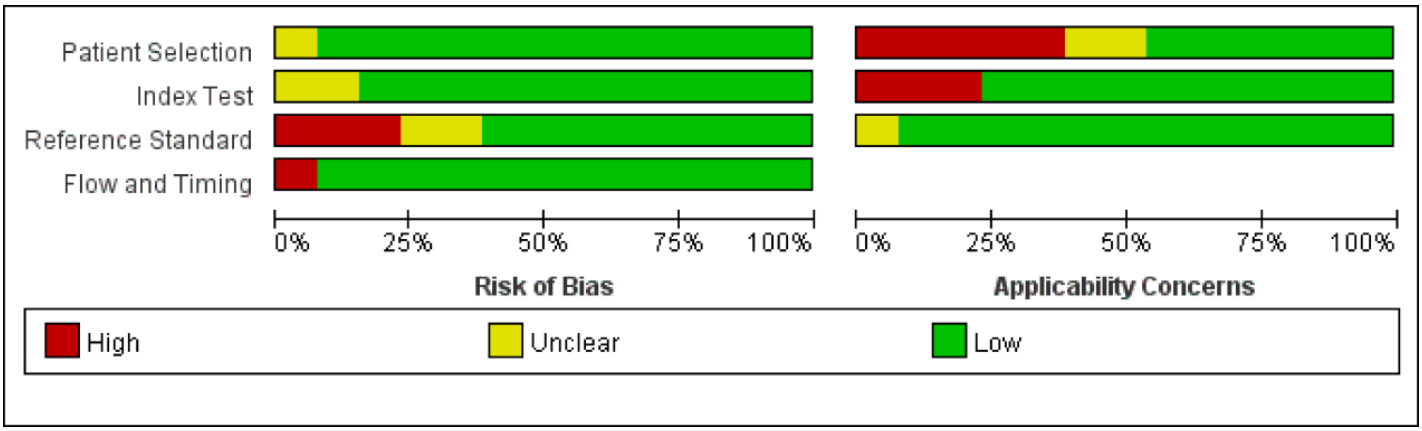

Fig. 2: Literature quality evaluation chart

Note: Red represents high risk. Yellow represents unknown risks. Green represents low risk

Table 3: Quality evaluation of literature QUADAS

Author	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17
Li HW(8)	Yes	No	Yes	No	No	No	Yes	No	Unclear	Yes	No	No	Unclear	Yes	No	No
Li Y(9)	Yes	No	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	No	No
Zhou ZQ(10)	Yes	No	Yes	No	No	No	Unclear	No	No	Yes	No	No	No	No	No	No
Liu SJ(11)	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes	No	No	No
Liu XQ(12)	Yes	No	Yes	No	Unclear	No	Yes	No	Unclear	Yes	No	No	Yes	No	No	No
Alcoba G(13)	Yes	No	Yes	No	No	No	Yes	No	No	Yes	No	No	No	No	Unclear	No
Zhang MH(14)	Yes	Unclear	Yes	No	No	No	Yes	No	Unclear	Yes	No	No	Yes	Unclear	No	No
Huang XS(15)	Yes	No	Yes	Unclear	No	No	Yes	No	No	Yes	No	No	Yes	Yes	Unclear	No
Gao JH(16)	Yes	No	Yes	No	Unclear	No	Yes	No	Unclear	Yes	No	No	Unclear	No	No	No
Lin YR(17)	Yes	No	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	No	No
Zhang RL(18)	Yes	No	Yes	Unclear	No	No	Yes	No	Unclear	Yes	No	No	Yes	No	No	Unclear
Zhang HL(19)	Yes	No	Yes	No	No	No	Unclear	No	No	Yes	No	No	Yes	Unclear	No	No
Gu YM(20)	Yes	No	Yes	No	No	No	Yes	No	Unclear	Yes	No	No	Unclear	No	No	No

Table 4: Sensitivity and specificity of CRP in diagnosing respiratory tract infections GRADE grading

Out-comes indicators	Number of in-cluded samples (total number of sam-ples)	Re-search design	Factors that reduce the quality of evidence					Total quality of evi-dence
			Risk of bias	Indirec-tion	Inconsisten-cy	Inaccura-cy	Publica-tion bias	
True posi-tive	13(848)	Cross-sectional study	Down-grade one level	Not down-grade	Not down-grade	Not down-grade	Not down-grade	B
False posi-tive								
True posi-tive	13(848)	Cross-sectional study	Down-grade one level	Not down-grade	Not down-grade	Not down-grade	Not down-grade	B
False posi-tive								

Table 5: Sensitivity and specificity of PCT in diagnosing respiratory tract infections GRADE grading

Outcomes indicators	Number of included samples (total number of samples)	Research design	Factors that reduce the quality of evidence					Total quality of evidence
			Risk of bias	Indirection	Inconsistency	Inaccuracy	Publication bias	
True positive	13(652)	Cross-sectional study	Downgrade one level	Not downgrade	Not downgrade	Not downgrade	Downgrade one level	B
False positive							Downgrade one level	
True positive	13(652)	Cross-sectional study	Downgrade one level	Not downgrade	Not downgrade	Not downgrade	Downgrade one level	B
False positive								

Meat analysis results

The combined sensitivity of CRP for diagnosing respiratory virus and mycoplasma pneumoniae infections was 0.91, with a 95% CI of 0.893-0.937. The combined specificity was 0.4815, with a 95% CI of 0.440-0.523. The area under the SROC curve was 0.699. The combined sensitivity of PCT for diagnosing respiratory virus and mycoplasma pneumoniae infections was 68.92%, with a 95% CI of 64.9%-72.7%. The combined specificity was 50.00%, with a 95% CI of 45.6%-54.4%. The area under the SROC curve was 0.595,as shown in Fig. 3.

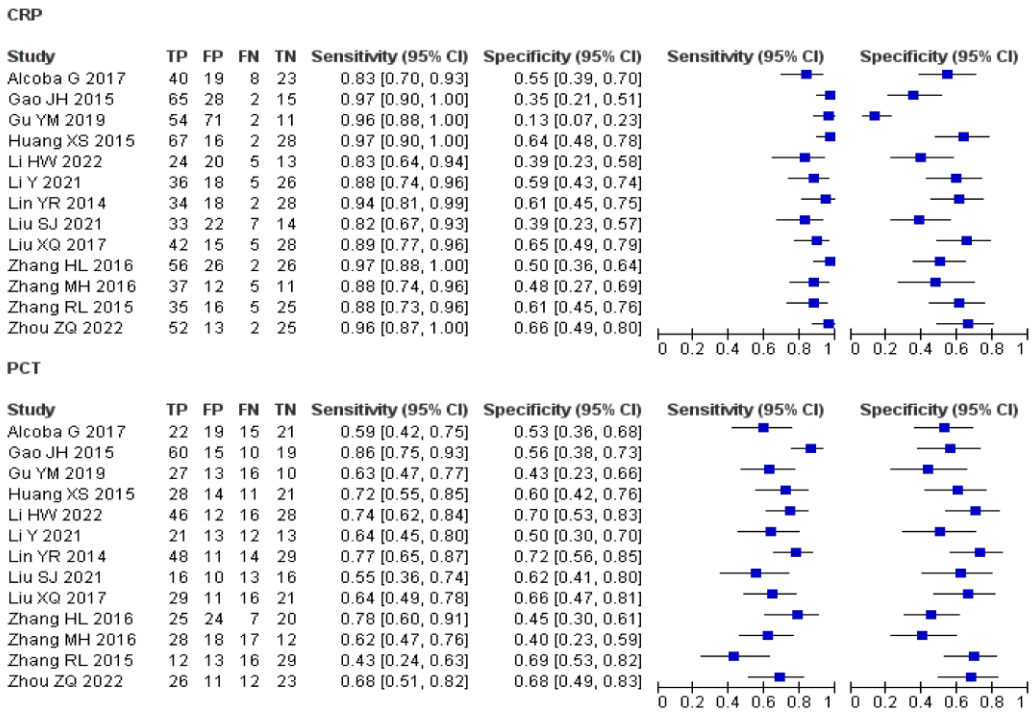

Fig. 3: Meta-analysis results of differential diagnosis between respiratory virus and mycoplasma pneumonia using CRP and PCT
Note: The sensitivity and specificity of differential diagnosis between respiratory virus and mycoplasma pneumonia using CRP and PCT were 95% confidence intervals for each horizontal line.

Discussion

During the growth process, children's immune systems are not fully developed and their respiratory mucosal barriers are weak. The influence of the external environment makes it easy for bacteria and viruses to enter the body, leading to respiratory tract infections. This study adopted the meta-analysis manner to comprehensively and quantitatively assess the diagnostic value of CRP and PCT in distinguishing respiratory virus infection from mycoplasma pneumonia infection. Some studies revealed that the majority of respiratory tract infections in children were mainly caused by mycoplasma pneumonia infection (21). Other studies revealed that the positivity rate for mycoplasma pneumonia in pathogen testing for children with chronic cough could be as high as 46.3%. This suggested that mycoplasma pneumonia might be the primary microorganism causing respiratory tract infections in children (22). The prognosis of children with respiratory tract infection depended on whether they could identify the types of pathogens in the early stage and apply anti-infection treatment in a timely manner. Children with respiratory tract infections could not form antibodies in the early stages of infection. Additionally, the time required for antibody detection was long. Therefore, antibody detection could not provide important references for selecting later treatment methods (23-24).

White blood cells are important immune cells that have the function of phagocytizing invading pathogens. When the body experiences acute infection, white blood cells in the blood can play a phagocytic role. The white blood cell count is influenced by physiological conditions and the body's physical and mental state. Additionally, some cytokines and cell-stimulating factors can cause changes in white blood cell count. A simple white blood cell count is not very effective in diagnosing respiratory tract infections. CRP is a non-specific inflammatory marker. After pathogens invade the body, the liver synthesizes CRP. This plays a role in activating complement. It also assists phagocytic function. Furthermore, it clears damaged necrotic tissue and foreign pathogens. As an important role in the body's natural immune barrier, CRP belongs to one of the items in clinical immunology examination. It consists of five basic units, forming a circular symmetric structure. When the body experiences acute inflammation, the synthesis of CRP rapidly increases within 4-6 hours of infection. By eight hours, there is a multiple increase, with a positive rate of up to 96% (25). A high level of CRP indicates acute, immune-related reactions in the body. It is the preferred indicator for judging the degree of acute tissue inflammation and the effectiveness of treatment. In bacterial infections, CRP can reach as high as 150-350mg/L, which can accurately reflect the body's infection situation.

It is used clinically to distinguish between bacterial and viral infections. However, there is little research related to PCT in the differential diagnosis of mycoplasma and respiratory virus infections. PCT is secreted by thyroid C cells under normal physiological conditions. Pro-inflammatory responses stimulate organs, which can directly induce intracellular signal transduction or indirectly mediate the host cell's immune response through pro-inflammatory factors, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These factors are secreted by pathogenic microorganisms and act as toxins, such as endotoxin. In addition, when the body experiences inflammatory reactions or pathogenic microbial infections, peripheral blood leukocytes and vascular endothelial cells, such as monocytes, neutrophils, and macrophages, synthesize and release a large amount of PCT. This results in an increase in PCT levels in plasma. PCT is also released by parenchymal tissues outside the thyroid gland, such as the heart, liver, spleen, and fat. PCT plasma levels can be detected in the plasma 4 hours after systemic bacterial infection, with a sharp increase at 6 hours and a maintenance level at 6-24 hours. It is not affected by hormone levels in the body and has good stability. In healthy individuals, the level is relatively low and cannot even be detected. The level of increase is signifi-

cantly higher when bacterial infection causes systemic reactions, and the degree of increase is proportional to the severity of the infection (26). At present, the amount of blood collected for PCT testing is relatively small. From the perspective of timely infection prediction and patient reduction, PCT has high clinical value as a predictor of bacterial infection. However, compared with CRP, relatively little research has been conducted on its application in the differential diagnosis of respiratory virus and mycoplasma pneumonia infections. Additionally, the sample size is small (27). Heterogeneity testing is a necessary task before meta-analysis.

This study established strict criteria for inclusion and exclusion of literature to minimize the sources of heterogeneity. This study used QUADAS to evaluate the quality of literature. The quality of the literature included in this study was relatively high overall. However, the evaluation results for item 9, "Is it concerned about the repeatability of indicator testing, its operation, or interpretation?", were "unclear" or "no". This could be related to the fact that the clinical testing process become standardized and did not require a detailed description. The meta-analysis results showed that compared with PCT, the sensitivity of CRP was significantly higher than that of PCT detection diagnosis, and the specificity of PCT was relatively higher than CRP. The area under the curve of CRP combined with SROC was 0.699, and the area under the curve of PCT combined with SROC was 0.595. The closer the area under the SROC curve was to 1, the higher the diagnostic efficacy, indicating that CRP had a higher diagnostic efficacy for pathogen pneumonia than PCT. CRP and PCT were significantly elevated in mycoplasma pneumonia infection, indicating that CRP and PCT could be involved in the occurrence and development of mycoplasma pneumonia. CRP and PCT could provide reference for the diagnosis of mycoplasma pneumonia. The publication bias test indicated the presence of publication bias in the diagnosis of PCT in this study. This could be due to significant heterogeneity in indicator selection and sampling methods. The fundamental reason could be the limited amount of included literature. Further design of such diagnostic tests was needed to verify the authenticity and reliability of the results.

Conclusion

The existing research literature indicated that, compared with PCT, CRP was highly sensitive in distinguishing respiratory virus, and mycoplasma pneumonia infections. Compared with CRP, PCT had a relatively high specificity in distinguishing between respiratory virus and mycoplasma pneumonia. To obtain higher diagnostic differentiation capabilities, CRP and PCT could be combined for diagnosis. The advantage of this study lied in the inclusion of a large sample size. The sample sizes for children with respiratory virus infections and mycoplasma pneumonia infections were sufficient. The results of the sensitivity analysis showed that there was no significant difference in the overall results of a single study in the literature. The evaluation results had good stability.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Availability of data and materials

The datasets of the current study are available from the corresponding author on a reasonable request.

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Not applicable

Conflict of interest

The authors declare that there is no conflict of interests.

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