C-Reactive Protein or Procalcitonin Combined with Rhinorrhea for Discrimination of Viral from Bacterial Infection in Hospitalized Adults of Non-Intensive Care Medical with Lower Respiratory Tract Infection

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Research

Keywords: C-reactive protein, procalcitonin, clinical characteristics, rhinorrhea, lower respiratorytract infection

Posted Date: June 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-539293/v1

Abstract

Background: Whether procalcitonin (PCT) or C-reactive protein (CRP) combined with some clinical characteristics can better distinguish viral from bacterial infection is not clear. The aim was to assess the ability of PCT or CRP combined with clinical characteristics to distinguish between viral and bacterial infections in hospitalized non-intensive care unit (ICU) adults with lower respiratory tract infection (LRTI).

Methods: This was a post-hoc analysis of a randomized clinical trial previously conducted among LRTI patients. The ability of PCT, CRP, and PCT or CRP combined with clinical characteristics to discriminate between viral and bacterial infection were estimated by portraying receiver operating characteristic (ROC) curves among patients with only vial or typical bacterial infection .

Results: In total, 209 patients (virus 69%, bacteria 31%) were included in this study. When using CRP or PCT to discriminate between viral and bacterial LRTI, the optimal cut-off point were 22mg/L and 0.18ng/ml, respectively. When the optimal cut-off for CRP (≤22ml/L) or PCT (≤0.18ng/ml) combined with rhinorrhea was used to discriminate viral from bacterial LRTI, the AUCs were 0.81 (95% CI, 0.75–0.87) and 0.80 (95% CI, 0.74–0.86), respectively. When CRP≤22ml/L, PCT≤0.18ng/ml and rhinorrhea were combined, the AUC was 0.86 (95% CI, 0.80–0.91), which was statistically significant higher than that when CRP(≤22mg/L) or PCT (≤0.18ng/mL) was combined with rhinorrhea (p=0.0107 and p=0.0205).

Conclusions: Either CRP≤22mg/L or PCT≤0.18ng/mL combined with rhinorrhea could help distinguish viral from bacterial infection in hospitalized non-ICU adults with LRTI. When rhinorrhea was combined together, discrimination ability can be further improved.

Background

Lower respiratory tract infection (LRTI) is the most common infectious disease that may cause death, with about 3.0 million deaths worldwide in 2020.[1] Viral infection is one of the most important causes of LRTI. Identifying the pathogens involved timely is essential for antibiotics treatment, as detection delay may potentially result in antimicrobial resistance. Antimicrobial resistance can cause corresponding financial burden and environmental pollution, especially when antibiotics are inappropriately prescribed to patients with viral infection.[2]

Although some novel molecular diagnostic or culture-independent assays offer enhanced opportunities to identify respiratory pathogens, researchers are still pursuing much simpler, faster, and cheaper ways to identify different pathogens. Serum markers such as C-reactive protein (CRP) and procalcitonin (PCT), which can help guide antibiotic use in LRTI patients, have been studied most often.[3], [4] But whether PCT or CRP could distinguish viral or bacterial infection is a controversial issue.[5], [6], [7], [8] Furthermore, most of the studies have been hampered by an incomplete etiologic approach, because only a limited number of infectious agents have been assessed or techniques with low sensitivity have been used.[9], [10] Consequently, those studies have not reported reliable information on the use of biomarkers for differentiating bacterial from viral LRTI.

Though some overlaps exist in symptoms and clinical presentation between bacterial and viral infection, viral infection has its own characteristic, such as headache, generalized muscle pain and rhinorrhea. One recently

study showed that combination of clinical symptoms and blood biomarkers can distinguish bacterial from viral community-acquired pneumonia in children.[11] However, few studies have been conducted among adult LRTI so far.

The aim of this study was to assess whether PCT or CRP combined with clinical characteristics could distinguish between viral and bacterial infections using comprehensive and sensitive methods of etiologic classification in hospitalized non-intensive care unit (ICU) adults with LRTI.

Methods

This was a post-hoc analysis of a randomized controlled trial (RCT) that had been published previously.[12] The RCT took place between October 2017 and July 2018 in the China-Japan Friendship Hospital (CJFH), Beijing, China (clinicaltrials.gov identifier: NCT03391076). The study was approved by the ethics committee of CJFH (2017-29). Written informed consent was obtained from each participant after meeting the inclusion criteria.

Study Population

The inclusion criteria of the RCT study were as follows: hospitalized patients aged ≥ 18 years who were preliminarily diagnosed as having radiographically confirmed community acquired pneumonia (CAP), acute exacerbation of chronic obstructive pulmonary disease (AECOPD), or acute exacerbation of bronchiectasis were recruited on the day of hospitalization. Patients were excluded if they were < 18 years old, pregnant, had hospital acquired pneumonia, or lung tuberculosis. We also excluded immunosuppressive patients. In addition, patients with any other condition that may have increased serum PCT levels were also excluded. For this post-hoc analysis, Patients who did at least one bacterial and one viral test could be recruited in this study.

patients without CRP or PCT testing results, or without bacterial or viral pathogens detected were further excluded.

PCT and CRP Measurement

PCT or CRP concentrations were measured in the clinical laboratory of CJFH within 24 hours of admission. CRP was measured using the high sensitive-CRP Kit (i-Reader, China). The upper and lower detection limits were 200 mg/L and 1 mg/L, respectively. PCT was measured by use of the PCT Kit (i-Reader, China), with a detection limit of 0.01 ng/mL.

Pathogen Testing

Bacterial testing included qualified sputum (defined as squamous cells < 10 per low-power field; polymorphonuclear leukocytes > 25 per low-power field, or the ratio between the 2 < 1:2.5), lower respiratory tract samples and histological biopsy samples such as endotracheal aspiration, bronchoalveolar lavage fluid, and protected specimen brush or pleural fluid samples culture; blood culture; Streptococcus detected by urinary antigen (BinaxNOW, Alere). Atypical bacteria testing for Mycoplasma pneumoniae (MP) and Chlamydophila pneumoniae (CP) included reverse transcriptase polymerase chain reaction (RT-PCR) of sputum or other lower respiratory tract specimen samples; nasopharyngeal swabs used FilmArray Respiratory Panel for MP and CP; Urinary antigen for Legionella pneumophila (BinaxNOW, Alere). Mycobacterial testing included acid-fast bacillus

culture and mycobacteria nucleic acid detection (Xpert MTB/RIF). Samples included Sputum, endotracheal aspiration, bronchoalveolar lavage fluid and protected specimen brush; blood, pleural effusion, bronchial mucosa biopsy; lung biopsy. Fungal testing included cultures of blood or other sterile samples such as pleural effusion, lung biopsy tissue samples, etc.

Viral testing included FilmArray Respiratory Panel of nasopharyngeal swabs for influenza A (H1 and H3) virus, influenza B virus, respiratory syncytial virus, rhinovirus or enterovirus, human metapneumovirus, parainfluenza virus types 1–4, coronaviruses (OC43, 229E, HKU1, and NL63), and adenovirus; RT-PCR of sputum, nasopharyngeal swabs, or other lower respiratory tract specimen samples for influenza A (H1N1, H7N9) virus, influenza B virus, respiratory syncytial virus, parainfluenza virus, adenovirus, EpsteineBarr virus, herpes simplex virus, and human cytomegalovirus; rapid antigen assay of influenza virus (BinaxNOW, Alere) in oropharyngeal or nasopharyngeal swabs, or qualified lower respiratory tract.

Statistical Analysis

Patients were divided into two groups according to pathogen detection results. Those with bacteria detected and negative mycobacterial/fungal tests results, regardless of viral or atypical bacteria results, were classified into bacteria group. The other patients only with viruses detected were classified into virus group.

Baseline characteristics were expressed as number (proportion) or median (interquartile range) respectively and compared by $\chi 2$ test or Mann-Whitney U test where appropriate. We then assessed the predictive performance of CRP, PCT and PCT combined with CRP for discriminating viral from bacterial infection by portraying receiver operating characteristic (ROC) curves, respectively. Optimal cut-points for CRP and PCT were defined as the point on the ROC curve that has the maximum Youden index. Furthermore, according to the optimal cut-points, the performance of PCT $\leq$ 0.18 ng/L, CRP $\leq$ 22 mg/L, PCT $\leq$ 0.18 ng/L and CRP $\leq$ 22 mg/L combined with significant clinical features to discriminate viral and bacterial infection were evaluated. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and their 95% confidence intervals (CIs) were calculated. The areas under the curve (AUCs) and 95% CIs were estimated and compared to determine the different discriminations of models. A two-sided α less than 0.05 was considered statistically significant for all statistical tests. Statistical analyses were performed by the SAS software, version 9.4 (SAS Institute Inc.), unless otherwise indicated.

Results

Between Oct 16, 2017 and Jul 13, 2018, we recruited 800 patients in the previous RCT study. After excluding 129 patients without PCT or CRP, 39 patients with mycobacterial/fungal detected, and 423 patients with no pathogens detected, 209 patients were included in the current analysis. Of these patients, the viral group accounted for 69% and the bacteria group accounted for 31%.

Baseline characteristics of study participants in viral and bacteria groups were shown in Table 1. The proportions of patients with headache or rhinorrhea were higher in patients infected with virus than that in patients infected with bacteria (36.6%, 53/145 versus 18.8%, 12/64; p = 0.0104 and 55.2%, 80/145 versus 20.3%, 13/64; p < 0.0001). The proportions of CAP patients among virus and bacteria group were 60.0% (87/145) and 35.9% (23/64), respectively. The corresponding proportions of AECOPD patients were 26.2% (38/145) and 32.8% (21/64), and 13.7% (20/145) and 31.3% (20/64) for acute exacerbation of bronchiectasis patients,

respectively. Both median PCT and CRP were significantly lower in the virus group than those in the bacteria group (0.1ng/mL (0.1,0.2) versus 0.3ng/mL (0.2, 0.7); $p < 0.0001$ and 10.4mg/L (4.0, 28.0) versus 53.0 mg/L (23.0, 96.7); $p = 0.0001$). And median neutrophil count in the virus group was lower than that in the bacteria group ($4.4 \cdot 10^9$/L (2.7, 6.7) versus $4.9 \cdot 10^9$/L (4.0, 7.3); $p = 0.0087$).

Table 1
Demographic and clinical characteristics

Variable	Virus (N = 145)	Bacteria (N = 64)	P value
Age (yrs)	64.0 (48.0, 78.0)	64.5 (54.5, 76.0)	0.8319
Gender	78 (53.8)	42 (65.6)	0.1820
Observation			
BMI (kg/cm^2)	23.4 (20.4, 25.9)	22.2 (18.6, 26.0)	0.3168
Respiratory frequency (bpm)	20.0 (20.0, 22.0)	20.0 (20.0, 21.0)	0.6199
Heart rate (bpm)	90.0 (80.0, 100.0)	95.0 (80.5, 102.5)	0.2724
Fever	105 (72.4)	39 (60.9)	0.0985
Cough	142 (97.9)	63 (98.4)	0.8018
Chest pain	36 (24.8)	15 (23.4)	0.8293
Headache	53 (36.6)	12 (18.8)	0.0104
Rhinorrhea	80 (55.2)	13 (20.3)	< .0001
Final diagnosis			< .0001
CAP	87/145 (60.0)	23/64 (35.9)	
AECOPD	38/145 (26.2)	21/64 (32.8)	
AE of bronchiectasis	20/145 (13.7)	20/64 (31.3)	
Dyspnea	110 (75.9)	53 (82.8)	0.2636
Diarrhea	25 (17.2)	6 (9.4)	0.1403
Comorbidity (%)			
Cardiovascular disease	66 (45.5)	32 (50.0)	0.5495
Diabetes	32 (22.1)	19 (29.7)	0.2372
Renal disease	9 (6.2)	3 (4.7)	0.6577
Liver disease	2 (1.4)	1 (1.6)	0.9189
Cancer	9 (6.2)	4 (6.3)	0.2493

AE, acute exacerbation; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CAP, community-acquired pneumonia;

Data are presented as median (interquartile range) for continuous variables and as percent for categorical variables.

Categorical variables were compared using χ^2 tests, and continuous variables were compared using Wilcoxon rank-sum test or Student's t-test.

Variable	Virus (N = 145)	Bacteria (N = 64)	P value
Current smoker	24 (16.6)	10 (15.6)	0.8671
Influenza vaccine(≥1 year)	14 (9.7)	11 (17.2)	0.1219
Laboratory test			
White blood cell count(*10^9/L)	6.8 (4.8, 9.5)	7.2 (5.8, 9.7)	0.0885
Lymphocyte count(*10^9/L)	1.2 (0.8, 1.7)	1.3 (0.9, 1.8)	0.1523
Neutrophil count(*10^9/L)	4.4 (2.7, 6.7)	4.9 (4.0, 7.3)	0.0087
Procalcitonin(ng/mL)	0.1 (0.1,0.2)	0.3 (0.2,0.7)	< .0001
C-reactive protein(mg/L)	10.4 (4.0,28.0)	53.0 (23.0,96.7)	0.0001

AE, acute exacerbation; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CAP, community-acquired pneumonia;

Data are presented as median (interquartile range) for continuous variables and as percent for categorical variables.

Categorical variables were compared using χ^2 tests, and continuous variables were compared using Wilcoxon rank-sum test or Student's t-test.

When using CRP to discriminate viral from bacteria LRTI, the area under the ROC curve was 0.77 (95% CI, 0.70–0.84), and the optimal CRP cut-off point was 22 mg/L (Fig. 2A). Regarding PCT, the area under the ROC curve was 0.74 (95% CI, 0.66–0.82), and the optimal PCT cut-off point was 0.18ng/mL (Fig. 2B). When CRP (≤ 22mg/L) was combined with PCT(≤ 0.18ng/mL) to discriminate viral from bacteria LRTI, the area under the ROC curve was 0.77 (95% CI, 0.70–0.84) (Fig. 2C).

We used the optimal cut-off for CRP or PCT combined with headache or rhinorrhea to discriminate viral from bacterial LRTI (Table 2). The areas under the ROC curve were 0.81 (95% CI, 0.75–0.87) and 0.80 (95% CI, 0.74–0.86) respectively when CRP (≤ 22mg/L) or PCT (≤ 0.18ng/mL) was combined with rhinorrhea, which were better than those alone or combined with headache. When CRP (≤ 22mg/L), PCT (≤ 0.18ng/mL) and rhinorrhea were combined together, the area under the ROC curve was 0.86 (95% CI, 0.80–0.91), which were statistically significant higher than that when CRP(≤ 22mg/L) or PCT (≤ 0.18ng/mL) was combined with rhinorrhea when distinguish viral or bacterial LRTI (p = 0.0107 and p = 0.0205).

Table 2
Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for optimal cut-off values of CRP and PCT level to differentiate viral from bacterial LRTI

	CRP cut-off level			PCT cut-off level			CRP and PCT cut-off level
	≤ 22mg/L alone	≤ 22mg/L and Headache	≤ 22mg/L and Rhinorrhea	≤ 0.18ng/mL alone	≤ 0.18ng/mL and Headache	≤ 0.18ng/mL and Rhinorrhea	CRP ≤ 22mg/L combined PCT ≤ 0.18ng/mL and Rhinorrhea
Sensitivity	0.71 (0.64–0.78)	0.71 (0.64–0.78)	0.90 (0.85–0.95)	0.68 (0.60–0.76)	0.68 (0.60–0.76)	0.86 (0.80–0.92)	0.73 (0.66–0.80)
Specificity	0.77 (0.67–0.87)	0.77 (0.67–0.87)	0.63 (0.51–0.75)	0.78 (0.68–0.88)	0.78 (0.68–0.88)	0.61 (0.49–0.73)	0.88 (0.80–0.96)
PPV	0.87 (0.81–0.93)	0.87 (0.81–0.93)	0.84 (0.78–0.90)	0.88 (0.81–0.94)	0.88 (0.81–0.94)	0.83 (0.77–0.89)	0.93 (0.88–0.98)
NPV	0.54 (0.44–0.65)	0.54 (0.44–0.65)	0.73 (0.61–0.84)	0.52 (0.42–0.61)	0.52 (0.42–0.61)	0.65 (0.53–0.77)	0.59 (0.49–0.69)
AUC	0.74 (0.68–0.80)	0.78 (0.71–0.84)	0.81 (0.75–0.87)*	0.73 (0.67–0.79)	0.75 (0.69–0.82)	0.80 (0.74–0.86)#	0.86 (0.80–0.91)&

* vs. & p = 0.0107 # vs. & p = 0.0205

Discussion

With etiologic detection approach covering relatively wide spectrum of pathogens in our study, we found that either CRP ≤ 22mg/L or PCT ≤ 0.18ng/mL combined with rhinorrhea could discriminate viral from bacterial infection in hospitalized non-ICU adults with LRTI, which has rarely been explored in adults. When CRP ≤ 22mg/L, PCT ≤ 0.18ng/mL and rhinorrhea were combined together, discrimination of viral from bacterial infection can be further improved.

For many years, physicians hoped to find a marker that could help discriminating bacterial infection. CRP is an inflammatory marker, which was considered to be able to distinguish between viral and bacterial infections in 1990s.[13],[14] But with the relative progress of detection technology, more studies thought CRP could not distinguish viral from bacterial infection.[11],[15],[16] Review these studies, most of them were conducted among paediatric patients, and the pathogen detection test have low sensitivity and covered limited pathogen. In this study of adults hospitalized with LRTI, we used RT-PCR and multiple nested PCR (FilmArray Respiratory Panel) testing, which were highly sensitive and accurate for the diagnosis of microbial etiology to detect viruses

and atypical bacteria. Furthermore, the types of pathogens we detected were very comprehensive. Based on this, we suggested that our grouping was more accurate and the results were more credible than those of previous studies. We found the optimal CRP cut-off point was 22 mg/L, but which alone can not identify viral or bacteria infection in adult hospitalized LRTI patients.

PCT is a widely used and recognized biomarker of bacterial infection. Though PCT can guide antibiotic use in respiratory tract infections that had been widely adopted throughout the world,[17] some recently published studies found PCT could not distinguish viral and bacterial infections.[8],[18] Self`s study used sensitive and widely available etiological detection methods found no procalcitonin threshold perfectly discriminated between viral and bacterial pathogens.[8] A meta-analysis found the sensitivity and specificity of PCT were 0.55 and 0.76 to distinguish viral from bacteria for CAP patients, which could be not reliable evidence either to mandate administration of antibiotics or to enable withholding such treatment in patients with CAP.[18] Our result showed the optimal PCT cut-off point was 0.18 ng/mL and it may not be an ideal marker to distinguish viral or bacterial infections. And this viewpoint was consistent with Self`s study. Therefore, we thought using PCT alone to identify bacterial or viral infections and to guide the use of antibiotics should be cautious.

With increased interest in PCT research, many studies have shown that CRP is inferior to PCT in identifying bacterial or viral infections.[6],[19],[16] In our study, we found that CRP is non-inferior to PCT in differentiating viral from bacterial infection in LRTI patients. Recently, one RCT found that CRP-guided prescribing of antibiotics for AECOPD resulted in a lower percentage of patients, with no evidence of harm.[4] Another study showed that the provision of PCT assay results in addition to usual care did not result in lower use of antibiotics than usual care among patients with suspected LRTI.[20] Combined with our result, we need to further examine the importance of CRP in identifying viral infections and guiding antibiotic use for it is more available and cheaper than PCT.

The most important finding of this study was that CRP ≤ 22mg/L or PCT ≤ 0.18ng/mL combined with rhinorrhea could help to discriminate bacterial or viral infection, which was firstly reported among adults with LRTI in our consciousness. A study among children found that compared to CRP ≥ 72mg/L alone, CRP ≥ 72mg/L combined with symptoms (including rhinorrhea) could improve the specificity and PPV in discriminating bacterial from viral pneumonia.[11] Some reasons could explain that the CRP optimal cut-off point of our study is lower than Bhuiyan`s[11]. First, the types of patients and diseases were different between two studies. Second, the proportion of patients who received antibiotic therapy was high before hospitalization and onset of illness to admission was long (7days) in our study, which may influence CRP value.[12] Though antiviral drugs and virus detection methods are limited clinically, clinicians should raise awareness if LRTI patient had low CRP or PCT combined with rhinorrhea and have more confidence in stopping or degradation of an antimicrobial drugs.

Our study has a number of limitations. Firstly, it is a reanalysis of a previous RCT, and not all enrolled patients received the FilmArray Respiratory Panel test. Secondly, quite a large proportion of patients who had no pathogen detected were excluded from current analysis although we did an etiology-based study. Thirdly, the study was conducted in general wards, without including patients from ICUs. Because of above limitations, extrapolation of our results should be carefully interpreted. We need further deep research to verify its accuracy in the future.

Conclusion

Either CRP ≤ 22mg/L or PCT ≤ 0.18ng/mL combined with rhinorrhea could help distinguish viral from bacterial infection in hospitalized non-ICU adults with LRTI. When CRP ≤ 22mg/L, PCT ≤ 0.18ng/mL and rhinorrhea were combined together, discrimination of viral from bacterial infection in non-ICU of hospitalized adults with LRTI can be further improved.

Abbreviations

CRP	C-reactive protein
PCT	Procalcitonin
LRTI	Lower respiratory tract infection
ICU	Intensive care unit
ROC	Receiver operating characteristic
RCT	Randomized controlled trial
CJFH	China-Japan Friendship Hospital
CAP	Community acquired pneumonia
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
MP	Mycoplasma pneumoniae
CP	Chlamydophila pneumoniae
RT-PCR	Reverse transcriptase polymerase chain reaction
PPV	Positive predictive value
NPV	Negative predictive value
CIs	Confidence intervals
AUCs	Areas under the curve

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of CJFH (2017-29).

Consent for publication

Not applicable.

Availability of data and materials

As another investigations involving this data are in progress, so the data will not be available to others. When all investigations are finished, data might be made available.

Competing interests

The authors of the manuscript declare no conficts of interest and take sole responsibility for the writing and content of the manuscript. None of the authors have been involved in legal or regulatory matters related to the contents of this paper.

Funding

This work was supported by the National Science Grant for Distinguished Young Scholars (grant number 81425001/H0104) and Chinese Academy of Medical Science Innovation Fund for Medical Sciences (2018-I2M-1-003).

Authors` contributors

Shengchen DUAN designed the trial , reviewed the medical literature, participated in the data analysis and interpretation, and drafted and wrote the manuscript.

Xiaoying GU and Guohui FAN maked the statistical analysis of data.

Fei Zhou participated in the data analysis and interpretation.

Guangfa Zhu participated in the interpretation.

Bin CAO conceived and designed the trial, supervised the trial and allocated staff, participated in the data analysis and interpretation.

All authors reviewed and contributed to the report during its development.

Acknowledgments

We thank all the patients and clinical staff at the general wards of Respiratory Critical Medical Department, Traditional Chinese Medicine (TCM) lung disease department, Infectious Disease Department and laboratory of Clinical Microbiology and Infectious Diseases in China-Japan Friendship Hospital, including clinicians, nurses, and laboratory technicians.

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Figures

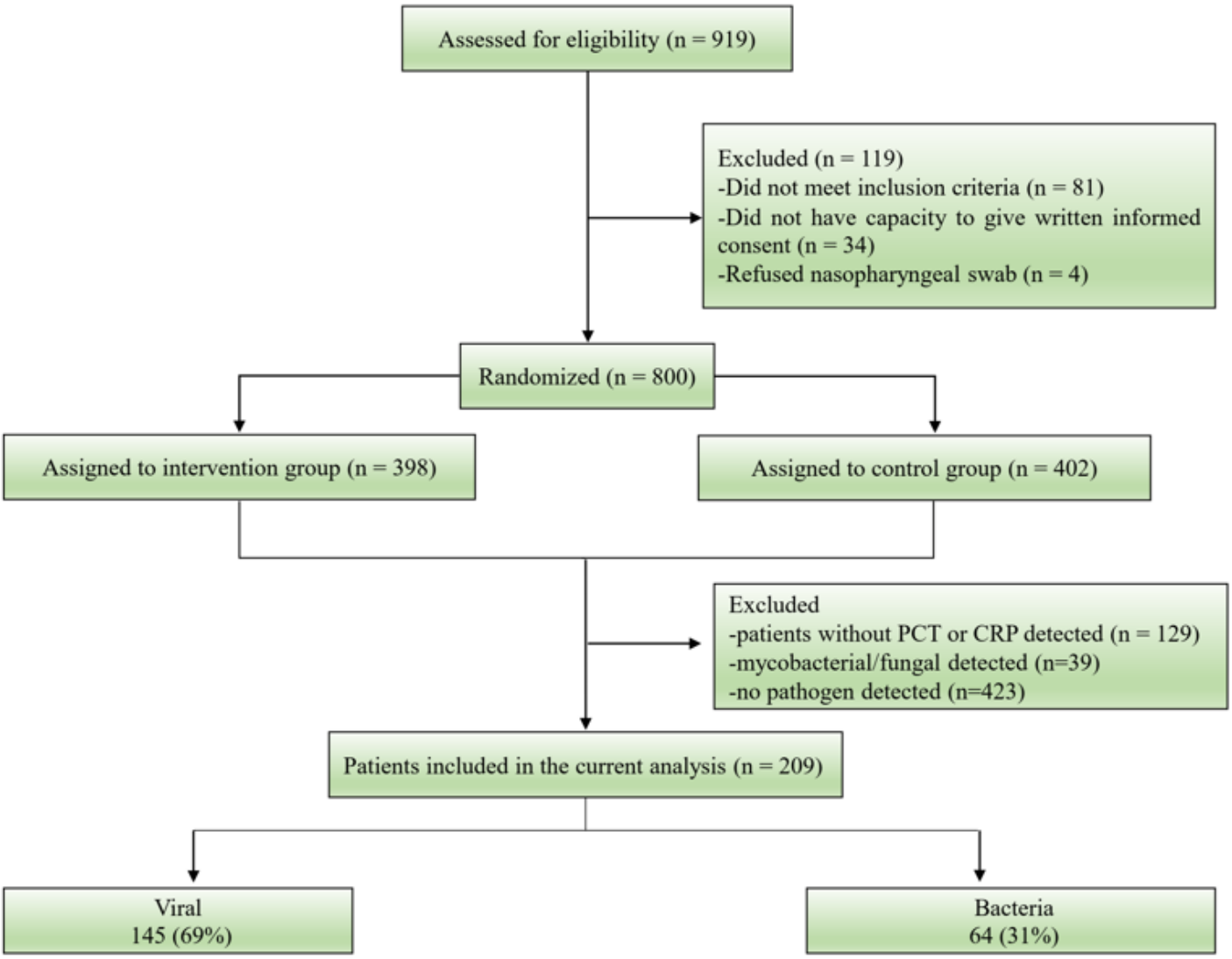

Figure 1

Flow diagram of patients included in the study.

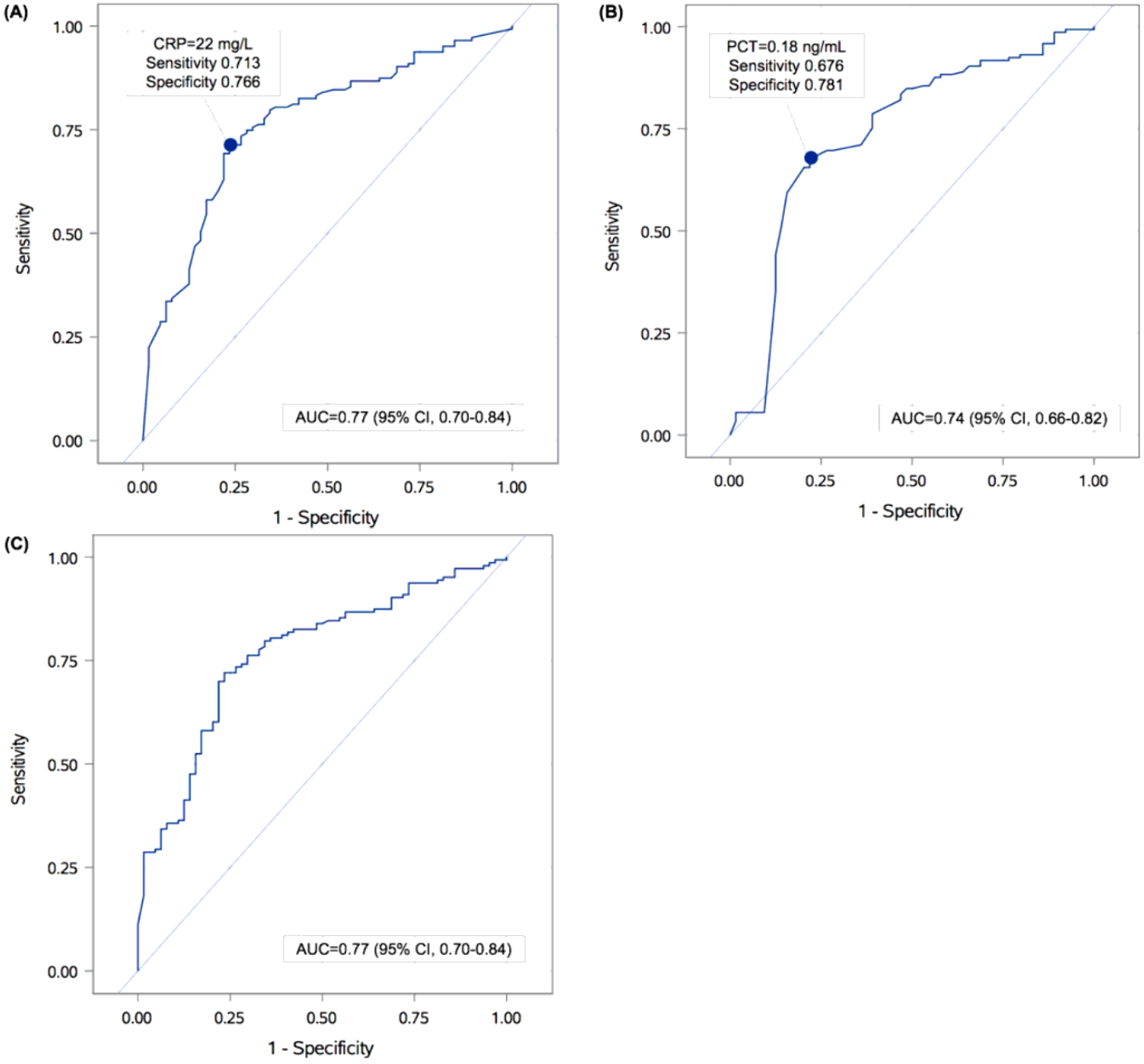

Figure 2

When using CRP to discriminate viral from bacteria LRTI, the area under the ROC curve was 0.77 (95% CI, 0.70-0.84), and the optimal CRP cut-off point was 22 mg/L (Figure 2A). Regarding PCT, the area under the ROC curve was 0.74 (95% CI, 0.66-0.82), and the optimal PCT cut-off point was 0.18ng/mL (Figure 2B). When CRP (≤22mg/L) was combined with PCT(≤0.18ng/mL) to discriminate viral from bacteria LRTI, the area under the ROC curve was 0.77 (95% CI, 0.70-0.84) (Figure 2C).