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Original Contribution

C-reactive protein as predictor of bacterial infection among patients with an influenza-like illness☆,☆☆,★

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Abstract

Objective: During the influenza season patients are labeled as having an influenza-like illness (ILI) which may be either a viral or bacterial infection. We hypothesize that C-reactive protein (CRP) levels among patients with ILI diagnosed with a bacterial infection will be higher than patients diagnosed with an influenza or another viral infection.

Methods: We enrolled a convenience sample of adults with ILI presenting to an urban academic emergency department from October to March during the 2008 to 2011 influenza seasons. Subjects had nasal aspirates for viral testing, and serum CRP. Bacterial infection was determined by positive blood cultures, radiographic evidence of pneumonia, or a discharge diagnosis of bacterial infection. Receiver operating characteristic curve, analysis of variance, and Student *t* test were used to analyze results.

Results: Over 3 influenza seasons there were 131 total patients analyzed (48 influenza infection, 42 other viral infection and 41 bacterial infection). CRP values were 25.65 mg/L (95% CI, 18.88-32.41) for influenza, 18.73 mg/L (95% CI, 12.97-24.49) for viral and 135.96 mg/L (95% CI, 99.38-172.54) for bacterial. There was a significant difference between the bacterial group, and both the influenza and other viral infection groups ($P < .001$). The receiver operating characteristic curve for CRP as a determinant of bacterial infection had an area under the curve of 0.978, whereby a CRP value of <20 had a sensitivity of 100% and >80 had a specificity of 100%.

Conclusion: C-reactive protein is both a sensitive and specific marker for bacterial infection in patients presenting with ILI during the influenza season.

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1. Introduction

During the influenza season, there is a sharp increase in the number of patients presenting to the emergency department (ED) with respiratory complaints. However, the percentage of these patients with influenza infection varies anywhere from 5% to 35% [1]. The remainder of these patients are infected with another respiratory virus in circulation at that time or by a bacterial process such as pneumonia. Given that pneumonia is the leading infectious cause of death in the United States with mortality rates exceeding 5% and age adjusted rates as high as 22%, it is crucial to identify such patients so that they can receive timely antibiotic therapy [2,3].

Most symptoms traditionally associated with bacterial infection (such as fever, cough, and rigors) are not predictive of a bacterial process and are indistinguishable from influenza [4,5]. During the influenza season, patients presenting with such symptoms are grouped as to having an influenza-like illness (ILI) [6]. Physicians therefore rely heavily on the presence of an infiltrate on chest x-ray (CXR) to help make the diagnosis of bacterial pneumonia. However, the absence of an infiltrate does not preclude the diagnosis of bacterial pneumonia, as roughly 21% to 33% of patients admitted for community acquired pneumonia will have a normal chest x-ray [7,8]. White blood cell (WBC) count has widely been used to distinguish severe bacterial infection from viral infections; however, it lacks both sensitivity and specificity to do so [9,10]. Ultimately, the diagnosis of bacterial infection rests on the clinician using information pooled from history, physical, laboratory, and radiological data. Differentiating a bacterial infection, from influenza or other viral infection, is therefore challenging in the acute setting.

Biomarkers have been gaining recognition as an important tool in the diagnosis of bacterial infection. An ideal biomarker would aid the emergency physician in rapidly and reliably making the diagnosis of bacterial infection in patients with ILI. C-reactive protein (CRP), an acute phase protein produced by the liver in response to infection, is potentially such a biomarker. CRP in healthy individuals are considered less than 0.5 mg/L, and when these levels are elevated it can be helpful in establishing the etiology of some infections [11]. Elevated CRP (>20 mg/L) has been shown to be present in the majority (>97%) of patients admitted to the hospital with community acquired pneumonia [12]. However, there is limited evidence evaluating the use of CRP in the ED evaluation [4].

The primary aim of our study was to compare CRP levels among patients with ILI, diagnosed with either a bacterial infection, influenza infection, or another viral infection. Secondarily, we aimed to determine the sensitivity and specificity of CRP at determining the presence of bacterial infection in ILI patients; and also to compare CRP to the white blood cell count and differential and patient-driven symptom scores. We hypothesized that CRP levels would be significantly higher in bacterial infection. Further, if CRP levels are established to be sensitive and specific of bacterial infection, this biomarker could aid in distinguishing bacterial infections from viral in patients with ILI, potentially helping to both reduce unnecessary antibiotic use and reduce the misdiagnosis of viral infection when a bacterial one is present.

2. Methods

2.1. Study design and setting

This is a prospective, observational study of patients presenting to the ED with symptoms of ILI, which included a cough and a fever. The study setting was an urban academic Level 1 trauma center with an annual census greater than 100000 patients. This study was conducted over 3 influenza seasons. The first season spanned the months of January through March of 2009 and included subjects with seasonal influenza infection. The second and third influenza seasons spanned the months of October through March in the years of 2009 through 2011. Over this period, there was the emergence of the pandemic H1N1 influenza virus and subjects with H1N1 influenza infection were enrolled.

2.2. Selection of participants

Patients were screened for enrollment during different time blocks chosen randomly from the hours of 7 AM through 1 AM 7 days a week by trained research assistants screening patients with respiratory complaints. This study was approved by the hospital's institutional review board, and written informed consent was obtained from the patients (institutional review board number 4074-08). Patients presenting to the adult ED, 18 years of age or older, had their ED records screened for chief complaints of fever and cough. These patients we approached for enrollment. Patients with symptoms greater than 3 days, a history of liver disease, immunosuppressant medications, a recent diagnosis of pneumonia, or current antibiotics were excluded. Patients were excluded if they had symptoms greater than 3 days before arrival in the ED or reported a bacterial infection 4 weeks prior to presentation. These exclusion criteria were based upon prior work that demonstrated that CRP peaks by day 3 after the symptom onset, and then steadily declines back to pre-infection levels by 17 days. We chose a slightly longer period of 4 weeks to further decrease any interference from any precedent infection [13].

2.3. Methods and measurements

We enrolled patients presenting to the adult ED with symptoms of ILI (fever and cough). Patients underwent a survey about their past medical history, current illness,

symptom severity, and presenting vital signs. We collected all information using a standardized case reporting form. During this initial ED visit, both nasal washing and blood samples were collected from each patient by the research team. After enrollment patients were followed by chart review (if they were admitted to the hospital) or with a 4-week telephone follow-up survey. The purpose of the follow-up was to determine duration of symptoms and any potential complications which included hospitalization, diagnosis of pneumonia or other bacterial process and any antibiotic prescriptions received. Patients were subsequently excluded if we were unable to either track their hospital admission or get in contact with them by phone following discharge from the emergency department within the 4-week time period.

Patients were classified as having either bacterial infection, influenza infection, or another viral process. This first group consisted of bacterially infected patients with or without concomitant influenza infection. Classification of bacterial infection was determined by either infiltration seen on chest x-ray at presentation or diagnosis of bacterial infection made by the treating physician at time of discharge from the ED after initial presentation. In this group, besides bacterial pneumonia, there were also included upper respiratory tract infections, including culture proven streptococcal pharangitis, pharangeal abscesses, otitis media, and bacteremic patients.

The group of patients that were determined not to have a bacterial infection at initial presentation were then further divided into influenza infection or other viral infection. To determine the etiology of the viral infectious agent among these patients, we used viral cultures to verify whether the patient is infected with the influenza A or influenza B virus. The viral culture results were used to group patients into the influenza infection group. The primary purpose of this follow-up survey was to properly identify patients that ultimately had a bacterial cause to their symptoms that were not identified as such by the providing physician upon the initial ED visit among this group. Any patients in the non-bacterial group that were subsequently diagnosed with a bacterial infection within 4 weeks after their initial ED visit were excluded from analysis. We used the medical record whenever possible but also relied on the follow-up survey being that some patients would then follow-up at a hospital or medical facility where we do not have access to patient records.

The third and final group, labeled other viral infection, included patients with a negative viral culture for influenza that also did not have a bacterial cause identified either during the initial visit or upon follow-up. These patients did not have any identifiable cause of their symptoms to be able to group them in either of the first 2 groups and thus were grouped together into what we called other viral infection. It is assumed that they must have been infected with one of the many other respiratory viruses in circulation at that time.

2.4. Sample collection and storage

Following enrollment, both nasal washing and blood samples were collected from each patient by the research team. Nasal washings were collected with the patient in placed in a seated position with the head tilted backwards gently. While occluding the opposite nostril, 5 mL of sterile saline was inserted into the nasopharynx, held there for 5 to 10 seconds and then gently expelled by the patient into a sterile Petri dish. This process was repeated for the opposite nostril. Samples collected were then be frozen at −80°C for storage.

Blood samples were collected by venipuncture performed by the nurse caring for the patient. Two K2E EDTA K2 vacuette tubes were collected, for a total of 8 mL of peripheral blood. The collected blood was centrifuged at 2000 to 3000 RCF for 15 minutes at 4°C. The plasma was then immediately transferred into 1-mL aliquots and stored at −80°C.

2.5. Laboratory assays

During the months of January through March of 2009, patients (18-65 years of age) presenting to the ED who were suspected to have an acute infection with influenza were screened by the rapid point of care enzyme-linked immunosorbent assay. Only subjects who had a positive test confirming influenza antigen presence were enrolled. We subsequently had to change our methodology the following 2 influenza seasons, October through March in the years of 2009 through 2011.

During these 2 influenza seasons the rapid enzyme-linked immunosorbent assay assay had been discontinued due to the lack of sensitivity of the test in detection of the novel H1N1 influenza strain which had emerged over this time period [14]. Without a reliable rapid test to identify influenza-positive individuals we altered the study design to enroll all patients (18-65 years of age) if they presented with symptoms of ILI, specifically the complaint of a fever and a cough without identification of influenza antigen. We then tested for the presence of influenza virus by using viral culture. Nasal washes were sent to the Rhode Island Hospital Virology Laboratory where viral cultures were performed. In brief, after centrifugation of these specimens, they were processed for culture in rhesus monkey kidney cells for 2 days. Afterward, they were assessed for the detection of viral particles using monoclonal antibodies.

The CRP assay was also performed at Rhode Island Hospital using plasma samples collected from subjects and stored at −80°C. The CRP assay was run using the Beckman Coulter IMMAGE Immunochemistry Systems, reference number 447280. The serum samples were batched and run after each pneumonia season. This was performed after the phone follow-up had been completed and each patient had been assigned a group. Thus, the initial treating physician did not have access to CRP data from any patient during this study nor did the reviewers doing then phone call follow-up survey.

2.6. Symptom severity scoring and disease presentation

In order to compare the baseline characteristics of the group, a severity of symptom score was calculated for each patient as the presented to the ED. This previously validated severity of symptom (SOS) score was calculated by asking participants to record the severity of 7 symptoms: cough, nasal obstruction, sore throat, fatigue, headache, myalgia, and feverishness [15,16]. The patients rated the severity of each symptom on a scale from 0 being none to 3 being severe. This scoring system produced scores that range from 0 to 21 possible total points. We also collected information on medical history, medications, previous immunizations to influenza, and duration of both symptoms and fever.

2.7. Outcomes

The primary outcome measured was the presence of a bacterial compared to non-bacterial cause of the patients ILI and the CRP level measured at that initial visit. The secondary outcome was total number of white blood cells and percentages of band and segmented neutrophils in patients with bacterial compared to non-bacterial causes of their ILI visit.

2.8. Analysis

Subject demographics are presented as means with 95% confidence intervals. Receiver operating characteristic (ROC) curves were calculated for CRP, total WBC and percentage segmented neutrophils and band neutrophils in determining bacterial causation of symptoms. We used both analysis of variance between groups and Student *t* test to analyze differences in study groups for presenting symptoms, severity of symptom score, and laboratory data.

3. Results

3.1. Characteristics of study subjects

A total of 250 patients were screened over 3 influenza seasons, October through March in the years of 2008 through 2011. A total of 172 patients were enrolled. Of those patients, 41 (23.8%) were excluded from final analysis leaving a final total of 131 patients. Reasons for subsequent exclusion included patients being lost to follow-up (75.6%), taking immunosuppressant medication (9.8%), active liver disease (4.9%), inability to get a nasal wash sample (7.3%), and finally inability to draw blood (2.4%). These 131 patients were then divided into 3 groups based off of the viral culture results and diagnosis of bacterial infection. There were 41 patients in the bacterial infection group, 48 patients in the influenza infection group and 42 patients in the other infection group.

The bacterial infection group was composed of 68.3% (n=28) being bacterial pneumonia as determined by discharge diagnosis, all but 3 had an infiltrate on CXR at presentation as diagnosed by the radiologist reading the CXR at that time. The 3 with normal CXR read by the radiologist were determined to have bacterial cause of symptoms and treated with antibiotics by the ED physician. Only 2 (7.1%) of the bacterial pneumonia patients had blood cultures return positive. The remainder of the bacterial infection group was composed of 7 streptococcal culture–positive pharangitis (17.1%), 3 positive bacterial cultures/bacteremic (7.3%), 2 drainable oropharyngeal abscesses (4.9%), and one perforated otitis media which was diagnosed not at the initial visit but upon return to the ED 2 days later (2.4%). Of the bacterial infection group, 4 (9.8%) had a positive nasal aspirate for influenza infection.

There were 90 patients which were categorized as having a nonbacterial infection. Of the patients enrolled in the influenza group, 45 patients were infection with influenza A and 3 patients with influenza B. Amongst the influenza A infection patients 55.6% were seasonal influenza A and 44.4% were the novel H1N1 influenza strain–positive.

Subject characteristics between the 3 groups are displayed in Table 1. There was no statistical significant difference between these groups in sex, race, or duration of symptoms prior to presentation to the ED. The bacterial infection group was significantly older then the 2 other groups with an average age of 48.4 compared to 30.0 and 30.5. The SOS score was on average higher in the influenza group 14.8 (95% CI 13.4,16.1) than in the other infection 12.6 (95%CI 10.7,14.5) and the bacterial infection 12.7 (95% CI 10.8,14.6) groups (P = .017). Also influenza infected individuals presented with higher heart rates than patients in the other 2 groups (P = .030). There was a non–statistically significant trend for the percentage of influenza infected individuals to be febrile (temperature >100.4) at presentation compared to individuals with either a bacterial infection or another cause of their illness (P = .058). The bacterial infection group was admitted to the hospital more frequently (63.4%) than the influenza (20.8%) or viral infection (7.9%) groups. Of all the patients included in this study, only one of the bacterial infection patients spent any time in the intensive care unit.

3.2. Main results

Figure 1 displays CRP levels in each of the 3 groups. Patients within the bacterial infection group had a significantly higher CRP level at presentation than both the influenza or other viral infection groups (P < .001). Both the influenza and other groups had similar averages and ranges of CRP levels. We combined the CRP values for these 2 groups and compared their CRP levels to that of the bacterial infection group through the use of a ROC Curve (Fig. 2). The fitted ROC curve was 0.978. From these data, a CRP of less

Table 1 Clinical characteristics amongst patient groups

Characteristic	Bacterial (n = 41)	Influenza (n = 48)	Other (n = 42)	*P*
Age	48.4(39.0-57.8)	30.0(26.2-33.8)	30.5(24.3-36.6)	< .001
Percentage female	67.6(49.3-85.8)	52.1(35.2-69.0)	72.2(54.5-90.0)	.245
Race (%)				
White	62.2(43.3-81.1)	45.7(25.7-65.7)	55.6(35.9-75.2)	.301
Hispanic	13.5(0.2-26.8)	28.6(10.4-46.7)	25.0(7.9-42.1)	.339
Black	18.9(3.7-34.2)	20.0(3.9-36.1)	11.1(0.0-23.6)	.805
Duration PTA				
Days symptoms	2.9(2.2-3.6)	2.3(1.8-2.8)	2.4(1.4-3.3)	.486
Days fever	1.9(1.5-2.2)	1.6(1.3-2.0)	1.4(1.0-1.7)	.263
Presenting symptoms				
SOS score	12.7(10.8-14.6)	14.8(13.4-16.1)	12.6(10.7-14.5)	.018
Percentage febrile	23.1(7.1-39.0)	33.3(17.4-49.3)	12.5(0.2-24.8)	.073
Percentage tachypnic	48.7(29.8-67.6)	43.8(27.0-60.5)	19.2(8.8-41.2)	.072
Heart rate	103(96-111)	110(102-119)	98(91-106)	.030

Table showing the demographics, duration of symptoms and presenting symptoms of patients in each of the 3 groups. Data are presented as average with 95% confidence intervals in parentheses. Under presenting symptoms, a SOS score, and triage vital signs are depicted with percentage of patients febrile and tachypnic and the average heart rate. Febrile is defined as an oral temperature greater than 100.2°C and tachypnea as a respiratory rate greater than 18 breaths per minute. PTA, prior to arrival.

than 20 mg/L equated to a sensitivity of 100% and a CRP greater than 80 mg/L equated to a specificity of 100% for bacterial infection in a patient presenting to the ED with a fever and a cough. There was a range of sensitivities seen from 20 mg/L up to 80 mg/L with increasing sensitivity as the CRP level was dropped. This data is displayed graphically in Fig. 3 along with the respective 95% confidence intervals. We did a secondary analysis of the data removing the 13 non-bacterial pneumonia patients and calculated a ROC curve with only the bacterial pneumonia patients and found there was not a statistical difference in the ROC curve (fitted ROC curve bacterial pneumonia versus viral infection of 0.966).

Table 2 displays that laboratory data from this study. There was a statistically significant difference seen in the WBC ($P < .001$), segmented neutrophils ($P < .001$), and band neutrophils ($P = .008$) for the bacterial infection group when compared to the influenza and other infection groups, with the bacterial infection group having a higher WBC count and greater percentage of segmented and band neutrophils. We once again combined the influenza and other groups together to compare them against the bacterial infection group using the ROC curve (Fig. 4). The fitted ROC area was 0.788 for WBC count, 0.806 for the percentage of segmented neutrophils, and 0.730 for the percentage of band neutrophils. There was no improvement in ROC curves by using the total number of segmented and band neutrophils compared to the percentage of the total WBC used above. The ROC curve for CRP levels was superior to those of total WBC, and percentage of segmented and band neutrophils to predicting bacterial infection in patients with ILI.

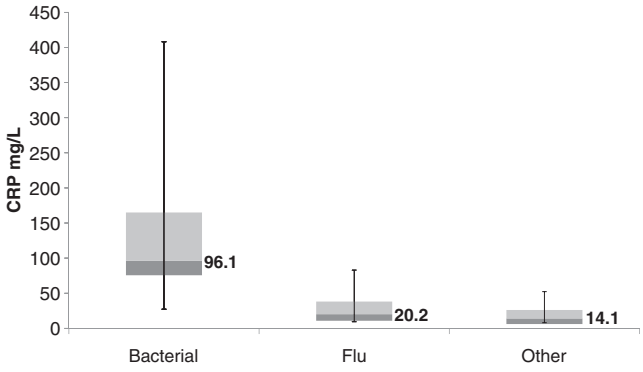

Fig. 1 Box-and-whisker diagram of the 3 groups for CRP values in mg/L. The top and bottom of the gray boxes depicts the 75th and 25th percentile of the data with band near the middle being the 50th (median) percentile with the numerical value of the median depicted next to the plot. The upper bar line represents the 98th and the lower bar line represents the 2nd percentile.

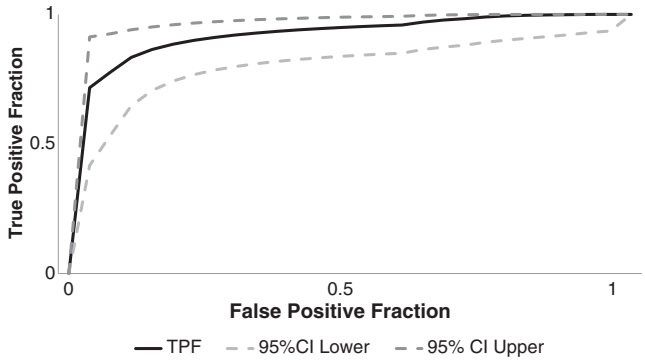

Fig. 2 The ROC curve plot of the sensitivity of C-reactive protein as a test identifying for bacterial infection. The hashed lines represent the 95% upper and lower confidence intervals (CI) and the solid line is the true-positive fraction (TPF).

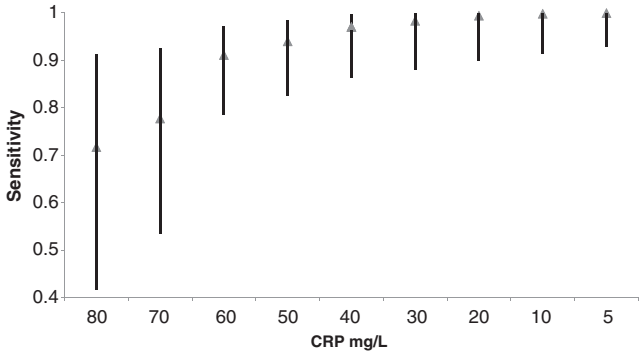

Fig. 3 The sensitivity of CRP at decreasing 10 mg/L intervals starting from 80 mg/L. The arrows are the average with the black line running from the 95% upper and lower confidence intervals. The average approaches 100% sensitivity at 20 mg/L.

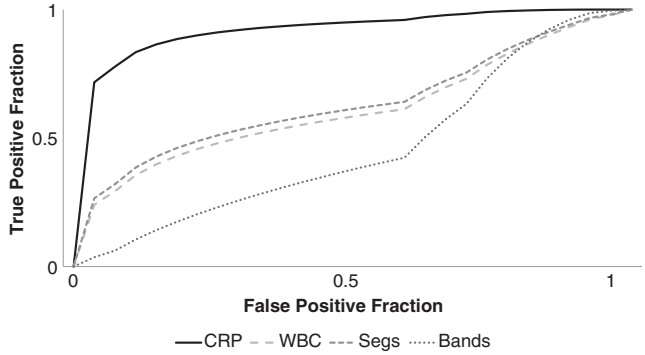

Fig. 4 The ROC curve plot of the sensitivity of CRP, WBC count, percentage segmented neutrophils (Segs) and percentage banded neutrophils (Bands) as tests to identify bacterial infection.

4. Limitations

Our study has several limitations. First, there was a difference in enrollment procedures from the first year of this study and the subsequent 2 years. During the 2008-2009 influenza season, there was a rapid point of care influenza antigen test which was used to screen patients to enroll only influenza-positive patients. The original design of this study was to look at differences in influenza-positive-only patients compared to bacterial infection group. With the emergency of the H1N1 strain and thus the loss of the rapid influenza test for our utilization, owing to sensitivity issues, we switched protocols to enroll all ILI patients and determine influenza status later using viral cultures [13]. We decided to include all 3 influenza seasons even though this variation in enrollment procedures existed for several reasons. First, all patients that were included had to have symptoms of ILI, fever, and a cough, and all subjects had their influenza status determined by viral culture, which is still gold standard. Secondly, this allowed us to enroll many more influenza-positive subjects by using the rapid test as a screen which in the end resulted in almost equal enrollment of all 3 comparison groups, influenza, other viral, and bacterial.

Another limitation is the fact that this study uses the discharge diagnosis as the definition of bacterial infection regardless of radiological of laboratory data. The potential limitation in this lies in the fact that we are relying on physician discretion and not solely on a test to make the diagnosis. There were 3 bacterial pneumonia patients in this study whose chest x-ray was interpreted as normal. These 3 patients all had focal lung findings on exam upon chart review. Since the diagnosis of bacterial pneumonia is a clinical one, we included these patients in the bacterial infection group. This was done in order to replicate what is now currently done in practice. This study however does not only use physician discretion but has the benefit of a 4-week follow-up conversation with the patient and review of the medical record. This helped to ensure that patients initially diagnosed as viral or influenza did recover without antibiotics or subsequent diagnosis of bacterial infection and captured 2 patients (perforated otitis and positive blood culture) which were initially diagnosed as having a viral infection.

A potential further limitation lies in the fact that we included other forms of bacterial infections besides bacterial pneumonia. Although bacterial pneumonia was the predominant bacterial infection we also included pharangeal abscesses, streptococcal pharangitis, bacteremia, and one case of perforated otitis media. Our reasons were to include all possible bacterial infection diagnosis encountered in patients with ILI and to show the utility of CRP in the undifferentiated patient with respiratory complaints. This study is limited in the sample size. We have very few occult

Table 2 Laboratory data for patients presenting with ILI

Characteristic	Bacterial (n = 41)	Influenza (n = 48)	Other (n = 42)	*P*
CRP	135.96 (99.38-172.54)	25.65 (18.88-32.41)	18.73 (12.97-24.49)	< .001
WBC	13.83 (11.18-16.48)	7.41 (6.38-8.44)	9.40 (7.50-11.31)	< .001
Segs (%)	81.22 (77.30-85.14)	72.29 (64.26-80.32)	78.42 (72.30-84.54)	.04
Bands (%)	4.52 (1.95-7.09)	1.31 (0.0-2.87)	0.90 (0.0-2.00)	.003
Lymphs (%)	8.12 (5.52-10.72)	14.50 (7.11-21.90)	9.87 (6.04-13.69)	.122

Table comparing the laboratory data between the 3 study groups. Data presented is average followed by 95% confidence intervals in parentheses. CRP, C-reactive protein (mg/L); WBC, white blood cell count (1×10^6 cells/ml); Segs, segmented neutrophils; Bands, banded neutrophils; Lymphs, lymphocytes. Segs/Bands/Lymphs expressed as a percentage of the total WBC.

pneumonias in this report and a larger study might better be able to address CRP's utility in diagnosing this type of bacterial infection. Another limitation was that the bacterial infection group was significantly older (by nearly 20 years) than the other 2 groups. This fact could reflect one of 2 possibilities. One is that older adults are frailer and thus more likely to get bacterial infections. The second is the possibility of bias by the treating ED clinician who might be more apt to write a "bacterial diagnosis" on the chart in this age group.

5. Discussion

This investigation is the first to demonstrate that CRP is a capable adjunct to help distinguish bacterial infection in a subset of patients with ILI. CRP was significantly elevated in bacterial infection and was both sensitive and specific for bacterial infection. Our data demonstrated that with a CRP value less that 20 mg/L, the sensitivity of the test approached 100%, whereas a CRP value of greater than 80 mg/L had a specificity approaching 100% for bacterial infection. This provides useful supplemental information in making clinical decisions in patients with undifferentiated ILI symptoms. In other words, a CRP level of less than 20 makes the diagnosis of bacterial infection extremely unlikely, whereas a CRP level greater than 80 should signal an active bacterial process. This could potentially guide patient disposition and treatment in the right clinical setting.

This is important because differentiating bacterial from viral infections can be challenging, especially during the influenza season. Interestingly, influenza patients in our study presented with higher severity of symptom scores; these patients reported worse symptoms, had higher heart rates and were more likely to have a fever than did patients in the bacterial infection group. This demonstrates how clinical presentation can be deceiving in determining bacterial infection during the influenza season. CRP levels were similar among the influenza and other viral groups but elevated among the bacterial infections.

Emergency physicians rely on data pooled from history and physical exam, radiologic, and laboratory data to make treatment decisions in patients with ILI. However, chest x-ray and peripheral blood leukocytosis have a poor sensitivity in detecting bacterial infections [7–10]. In a retrospective review by Hagman et al, 21% of admitted patients with community acquired pneumonia had a normal chest x-ray and upon 48 hour follow-up x-ray, only 56% of those patients went on to develop an infiltrate [17]. In addition, only 48% of these patients had a leukocytosis. Our study results substantiate this finding, as we demonstrated a poor sensitivity of WBC in the diagnosis of bacterial infection [18]. This same retrospective study by Hagman et al also showed that 76% of pneumonia patients had a positive sputum culture and 12.9% had a positive blood culture. Although this information would aid in diagnosis, these results are not available in the ED at the time of treatment. Chest computed tomography may provide a viable alternative in some scenarios, but this is not a realistic diagnostic test in most settings [19]. Without reliable help from imaging or other laboratory tests, the diagnosis of bacterial pneumonia has ultimately remained a clinical one. Thus identifying a biomarker, such as CRP, with improved sensitivities over conventional tests such as WBC, could become an indispensible tool in the diagnosis of bacterial pneumonia. CRP is also a test that is rapidly available in most EDs and is therefore superior to cultures results in this regard.

We report higher sensitivity and specificity of CRP than has been previously established. Previous studies looking at the predictive value of CRP for bacterial pneumonia have had sensitivities that have ranged from 10% to 98% and Specificities from 44 to 99% [11]. The reason for such variability in these previous investigations lies in the underlying methodology and criteria for diagnosing bacterial infection. Some studies used the results of a chest radiograph (infiltrate or no infiltrate) and others of microbiological work-up (blood or sputum cultures). The relationship between radiographic consolidation or microbial cultures, and pathogenesis of bacterial infection cannot always be established and is therefore limited. We therefore relied on the treating clinician's decision making, accompanied by patient follow-up, for the diagnosis of bacterial causes (in addition to radiographic or culture data). We believe that this most closely mirrors the realities of clinical practice and the patients seen in the ED setting. We followed our patients 4 weeks out from their initial ED visit to ensure proper clinical diagnosis and to look for complications of viral infection, namely undiagnosed bacterial infection.

Another advantage of our study is that we included patients with undifferentiated respiratory tract infections. Previous investigations have drawn their subjects and controls from intensive care units or hospitalized patients. We compared influenza infection not only to bacterial but to other viral infections, a group largely ignored in other studies. The patient population of our study attempts to reflect the setting of a busy emergency department during the influenza season. The results of our study are more widely applicable for use in the ED, during the influenza season when respiratory complaints are elevated.

In summary, we found that CRP was useful in predicting bacterial infection in patients presenting to the ED with acute respiratory complaints. In this setting, a CRP of less than 20 mg/L has a sensitivity of 100% and greater than 80 mg/L has a specificity of 100% for bacterial infection. Future studies should examine whether the use of CRP as a clinical aid changes clinical management or patient outcomes.

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