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RESEARCH ARTICLE

C-reactive protein as an independent predictor of multidrug-resistant bacterial infections in hospitalized patients with community-acquired pneumonia: A retrospective study

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ABSTRACT

C-reactive protein as an independent predictor of multidrug-resistant bacterial infections in hospitalized patients with community-acquired pneumonia: A retrospective study

Introduction: The increasing prevalence of antibiotic-resistant bacteria in communities makes empirical antibiotic therapy in community-acquired pneumonia (CAP) treatment more difficult than ever. C-reactive protein (CRP) is an acute-phase protein, primarily synthesized by the liver in response to the stimulation of pro-inflammatory cytokines, including interleukin 6 (IL-6), interleukin 1 (IL-1), and tumor necrosis factor-alpha (TNF-α). Recent studies have shown that CRP levels may be higher in patients with antibiotic-resistant infections than in those with susceptible infections. This study aimed to demonstrate that CRP is a reliable biomarker for identifying CAP patients with MDR infections at admission.

Materials and Methods: The retrospective observational cohort study analyzed data on hospitalized patients diagnosed with CAP, obtained from electronic medical records. Univariate and multivariate logistic regression were used to assess the association between surveyed factors and MDR infection. The diagnostic accuracy of CRP was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC).

Results: CRP was an independent predictor of a higher likelihood of MDR infection in hospitalized patients with CAP [odds ratio = 1.52, 95% confidence interval (CI): 1.12 – 2.05, p = 0.007]. CRP levels provided modest discrimination between CAP patients with MDROs and non-MDROs infections (AUC =

0.67, 95% CI: 0.57 – 0.76). The cut-off value of 42.59 mg/L produced a sensitivity of 76.06% and a specificity of 53.23%. The multivariate model significantly improved diagnostic accuracy in distinguishing these two patient groups (AUC= 0.81, 95% CI: 0.73–0.88).

Conclusion: CRP can be a practical adjunct to the initial assessment of CAP patients for early stratification of MDR infections. Notably, given its limited diagnostic accuracy, it should be considered alongside other clinical parameters when making antibiotic decisions.

Key words: C-reactive protein; community-acquired pneumonia; MDR infections

ÖZ

Toplum kökenli pnömoni nedeniyle hastaneye yatırılan hastalarda çoklu ilaç dirençli bakteriyel enfeksiyonların bağımsız bir öngördürücüsü olarak C-reaktif protein: Retrospektif bir çalışma

Giriş: Toplumlarda antibiyotiğe dirençli bakterilerin prevalansının artması, toplum kökenli pnömoni (TKP) tedavisinde ampirik antibiyotik tedavisini her zamankinden daha zor hale getirmektedir. C-reaktif protein (CRP), başta interlekin 6 (IL-6), interlekin 1 (IL-1) ve tümör nekroz faktörü-alfa (TNF-α) olmak üzere proenflamatuvar sitokinlerin uyarısına yanıt olarak karaciğer tarafından sentezlenen bir akut faz proteindir. Son çalışmalar, antibiyotiğe dirençli enfeksiyonu olan hastalarda CRP düzeylerinin duyarlı etkenlerle gelişen enfeksiyonu olan hastalara kıyasla daha yüksek olabileceğini göstermiştir. Bu çalışmanın amacı, başvuru sırasında çok ilaca dirençli (MDR) enfeksiyonu olan TKP hastalarının belirlenmesinde CRP'nin güvenilir bir biyobelirteç olduğunu göstermektir.

Materyal ve Metod: Retrospektif gözlemsel kohort çalışmasında, TKP tanısıyla hastaneye yatırılan hastalara ait elektronik tıbbi kayıtlardan elde edilen veriler analiz edildi. İncelenen faktörler ile MDR enfeksiyon arasındaki ilişkiyi değerlendirmek için tek değişkenli ve çok değişkenli lojistik regresyon analizleri kullanıldı. CRP'nin tanılabilirliği, ROC eğrisi altında kalan alan (AUC) kullanılarak değerlendirildi.

Bulgular: CRP, TKP nedeniyle hastaneye yatırılan hastalarda MDR enfeksiyon olasılığının daha yüksek olmasının bağımsız bir öngördürücüsüdür (odds oranı= 1,52, %95 güven aralığı: 1,12–2,05, $p=0,007$). CRP düzeyleri, MDRO enfeksiyonu olan ve MDRO enfeksiyonu olmayan TKP hastalarını ayırt etmede orta düzeyde bir ayırt edicilik sağlamıştır (AUC= 0,67, %95 GA: 0,57–0,76). 42,59 mg/L eşik değeri, %76,06 duyarlılık ve %53,23 özgüllük sağlamıştır. Çok değişkenli model, bu iki hasta grubunu ayırt etmede tanılabilirliği anlamlı ölçüde artırmıştır (AUC= 0,81, %95 GA: 0,73–0,88).

Sonuç: CRP, MDR enfeksiyonların erken sınıflandırılması amacıyla TKP hastalarının ilk değerlendirmesinde pratik bir yardımcı belirteç olabilir. Bununla birlikte, tanılabilirliğinin sınırlı olması nedeniyle antibiyotik tedavisine ilişkin kararlar verilirken diğer klinik parametrelerle birlikte değerlendirilmelidir.

Anahtar kelimeler: C-reaktif protein; toplum kökenli pnömoni; MDR enfeksiyonlar

INTRODUCTION

Antimicrobial resistance (AMR) poses a significant global health challenge in the 21st century. In 2021, it is estimated that 4.71 million deaths were associated with AMR bacteria (1). The burden of AMR is exceptionally severe in low and middle-income countries, with the highest prevalence in South Asia (31.1%) (2). In recent decades, antibiotic-resistant bacteria that were once limited to the hospital environment have increasingly emerged in the community. The rising presence of multidrug-resistant organisms (MDROs) in the community has changed empirical antibiotic treatment strategies for community-acquired pneumonia (CAP). In clinical practice, physicians tend to choose alternative regimens, which are often broad-spectrum antibiotics, instead of first-line agents recommended for CAP, to optimize patient outcomes (2). However, this practice accelerates the development of antibiotic resistance, worsening the AMR situation. The vicious cycle is ended only if there is a tool that guides an appropriate antibiotic therapy initially, minimizing unnecessary antibiotic use while effectively treating infected patients.

Microbiological testing remains the gold standard for detecting bacterial pathogens. However, traditional cultures and drug susceptibility testing (DST) often take a long time to yield results and have low sensitivity (3-5). Real-time polymerase chain reaction is a significant invention, but it is costly and requires modern laboratories, making it difficult to use routinely, particularly in developing countries. Existing MDR prediction scores are not commonly implemented in clinical practice due to their limited diagnostic performance and reliance on clinical information that may not always be readily available (6,7). As a result, an affordable, simple, rapid, and easily accessible biomarker will be a practical solution for early risk stratification of MDRO infection in patients with CAP at the time of admission.

C-reactive protein (CRP) is an acute-phase protein, primarily synthesized by the liver in response to the stimulation of pro-inflammatory cytokines, including interleukin 6 (IL-6), interleukin 1 (IL-1), and tumor necrosis factor-alpha (TNF-α). IL-6 is reported to be the primary inducer of CRP gene expression in hepatocytes. CRP is an inflammatory biomarker widely used

to diagnose and monitor infections. Following initial inflammatory stimulation, CRP concentrations tend to increase significantly within 6-8 hours, reaching the peak at 24-48 hours (8). The normal range of plasma CRP is generally lower than 5 mg/L (9). However, in severe bacterial infections, CRP concentrations can increase by up to 1000-fold. After the stimulus is eliminated, CRP levels decrease rapidly over 18-20 hours, consistent with a half-life of approximately 19 hours (8,9). Furthermore, CRP elevation is associated with several other conditions, including malignancy, tissue necrosis, injury, autoimmune disorders, and surgical procedures. CRP levels may rise from 10 mg/L to 5000 mg/L within 24 to 72 hours in cases such as trauma or progressive cancer (2). In CAP, CRP measurement is a critical marker for supporting diagnosis, assessing disease severity, and monitoring response to antibiotics. According to research by España et al., hospitalized patients have higher CRP levels than outpatients, and CRP levels correlate with the CURB-65 pneumonia severity score (10). Studies have shown that CRP above 100 mg/L is predictive of complications and mortality in CAP cases (11,12). Beyond its demonstrated clinical significance, recent studies have shown that CRP levels may be higher in patients with antibiotic-resistant infections than in those with susceptible infections. Pathological hypotheses have proposed that drug-resistant bacterial infections may induce a more intense and prolonged cytokine cascade, possibly due to delayed pathogen clearance or persistent tissue damage (13,14).

In Southeast Asian countries, particularly Vietnam, implementing diagnostic tools to detect causative pathogens remains a persistent challenge, especially in resource-limited regions. Consequently, clinicians are more likely to opt for broad-spectrum antibiotics empirically to ensure bacterial coverage without relying on any objective evidence, thereby further exacerbating antibiotic resistance. Therefore, there is an urgent need to develop a test that can assist appropriate antibiotic selection at the early stage of treatment in these areas. C-reactive protein is a promising tool for distinguishing CAP caused by MDROs from non-MDROs at admission. As a low-cost and accessible biomarker, CRP could be highly valuable for predicting MDR bacterial pneumonia if its performance is validated.

The aim of the study was to evaluate whether CRP levels are a reliable indicator for distinguishing CAP patients with MDR infections at hospitalization.

MATERIALS and METHODS

Study Design and Population

The retrospective observational cohort study was conducted at Pham Ngoc Thach Hospital, a 960-bed hospital in Ho Chi Minh City, Vietnam. As a Tuberculosis and Lung Diseases Center, the hospital serves around 300,000 patients with respiratory problems each year. In the study, electronic medical records of patients diagnosed with CAP admitted to the hospital from January 2023 to May 2025 were retrospectively collected. Adults (≥ 18 years) with CAP and a positive lower respiratory tract culture collected within 48 hours of admission were eligible for inclusion. The diagnosis of CAP was based on the presence of 1) a new pulmonary infiltrate on chest radiography or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales); 2) at least one acute symptom, including fever or hypothermia, dyspnea, sputum production, cough, pleuritic chest pain; 3) onset of symptoms before admission. All patients with pneumonia occurring more than 48 hours after admission were considered hospital-acquired pneumonia. Exclusion criteria were as follows: patients with active malignancy, autoimmune diseases, any inflammatory diseases unrelated to respiratory infection; liver dysfunction classified as Child-Pugh Grade C; immunocompromised patients; sepsis shock (hypotension requiring vasopressors); history of surgery one month before admission; patient transferred from a referring facility. Cases with missing critical laboratory data, such as plasma CRP and complete blood count (CBC) measured at the same time point of admission, were also excluded. Patients were considered immunosuppressed if they had HIV infection, administration of immunosuppressive agents, or corticosteroid treatment (20 mg/day for ≥ 2 weeks or 1 mg/kg/day for ≥ 3 days prednisolone or equivalent). All adult inpatients diagnosed with pneumonia during the study period were identified, and then their respiratory specimen culture results were extracted. Subsequently, only patients with positive cultures underwent a comprehensive medical record review to verify the diagnosis of community-acquired pneumonia and to ensure fulfillment of all inclusion and exclusion criteria.

Sample Calculation

The sample size was calculated using Buderer's formula for diagnostic test evaluation based on expected sensitivity and specificity. The three components of the diagnostic evaluation are: the baseline serum

CRP level at hospital admission (Index test), culture results from lower respiratory tract specimens (Reference standard), and detection of MDR bacteria by drug susceptibility testing (Diagnostic endpoint). We assumed a sensitivity and specificity of 80% and pre-specified an MDR bacterial CAP prevalence of 53%, consistent with the findings reported by Le Tien Dung at University Medical Center, Ho Chi Minh City (15). A margin of error (precision) of 0.10 and a 95% confidence level ($Z = 1.96$) were used for the calculation. The required sample size to estimate sensitivity and specificity was 116 and 131 participants, respectively. The larger estimate was used as the minimum required sample size. After incorporating a 10% allowance for incomplete data, the final sample size was 144 participants. Although the study included all eligible patients, the sample size calculation was performed to ensure that our final cumulative cohort possessed adequate statistical power.

Ethics Approval

The study was approved by the Ho Chi Minh City University of Medicine and Pharmacy Ethics Committee of (Decision no: 939/QD-DHYD, Date: 20.05.2021).

Data Collection

Patient information was obtained from the institutional electronic medical record system. Collected variables included demographic data (age and sex), clinical characteristics (medical history, comorbidities, and final diagnosis, respiratory support, and admission ward), and laboratory findings. Biochemical parameters included CRP, glucose, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, and lactate. From the CBC panel, only leukocyte-related variables (white blood cell count, neutrophil count and percentage, and immature granulocyte count and percentage) were collected for analysis. Microbiological data included lower respiratory tract (LRT) cultures and drug-susceptibility testing. CRP measurement, CBC, and microbiological testing were mandatory for study inclusion.

Laboratory Testing

All laboratory results were extracted from the hospital's electronic medical record system. The testing procedures adhered to the institution's Standard Operating Procedures.

Blood samples for biochemical and hematological testing were drawn at hospital admission, prior to LRT sample collection, and first antibiotic dose. Plasma

biochemical parameters, including CRP, glucose, urea, creatinine, AST, ALT, total bilirubin, direct bilirubin, and lactate, were measured using the AU680 automated chemistry analyzer (Beckman Coulter, Japan). CRP was measured by the immuno-turbidimetric method. CBC was analyzed by the Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Japan).

Culture testing was conducted on one of three LRT samples - sputum, tracheal fluid, bronchoalveolar lavage (BAL) - collected within 48 hours of hospitalization. Conventional cultures were processed using a semi-quantitative four-quadrant streaking method, and DST was performed on the BD Phoenix M50 automated system (Becton, Dickinson and Company, USA). The quality of sputum samples was evaluated using the Bartlett scoring system, based on the number of neutrophils and squamous epithelial cells per low-power field, and the presence of mucous strands, with samples scoring >0 considered acceptable for culture (16). A bacterial isolate was considered a presumptive causative pathogen if its concentration reached $>10^7$ CFU/ml in sputum or $>10^6$ CFU/ml in tracheal aspirates and BAL specimens. DST was carried out following the Clinical and Laboratory Standards Institute 2025 guidelines. Isolates were classified as MDR or non-MDR according to the Centers for Disease Control and Prevention 2008 criteria. MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories (17).

Statistical Analysis

Quantitative variables were reported as mean $\pm$ SD for normal distributions or as median [interquartile range (IQR): 25th–75th percentile] for non-normal distributions, while categorical variables were presented as counts and percentages. Baseline characteristics were compared between MDR and non-MDR infection groups. Group differences were assessed using the Chi-squared test or Fisher's exact test for categorical variables, depending on expected cell counts, and using the independent sample t-test or the Mann–Whitney U for quantitative variables according to data distribution. Correlation analyses were performed using Pearson's or Spearman's coefficients based on distribution normality.

Univariate and multivariate logistic regression analysis were used to examine the association between factors (sex, age, comorbidity, laboratory parameters) and MDR infection. Multivariable linear regression

was used to demonstrate the independent association between MDR infection and CRP levels, regardless of clinical severity. All skewed continuous variables underwent natural logarithmic transformation (ln) before being entered into the logistic regression models. Linearity between each ln-transformed variable and the log-odds of the outcome was checked using restricted cubic splines. A non-significant test for non-linearity ($p > 0.05$) indicated that the ln transformation provided an adequate linear fit. Variables with a p -value < 0.20 in the univariate analysis were entered into the multivariable model using backward stepwise selection. The diagnostic accuracy of CRP for distinguishing CAP caused by MDR bacteria was assessed using the area under the ROC AUC. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the optimal

CRP cut-off was identified by using Youden's index. The improvement in discrimination of the multivariable model (including CRP and other variables) was evaluated using DeLong's test. The calibration of the model was evaluated by the goodness-of-fit Hosmer-Lemeshow χ^2 statistic. All tests were two-sided, and a p -value < 0.05 was considered statistically significant. Data analysis was performed using Stata statistical software, version 17.0 (StataCorp LLC, College Station, TX, USA).

RESULTS

A total of 133 patients with CAP were included in our study, comprising 96 males (72.18%) and 37 females (27.82%). Two-thirds of the participants were aged 65 years or older. A consort diagram describing the study flow is presented in Figure 1.

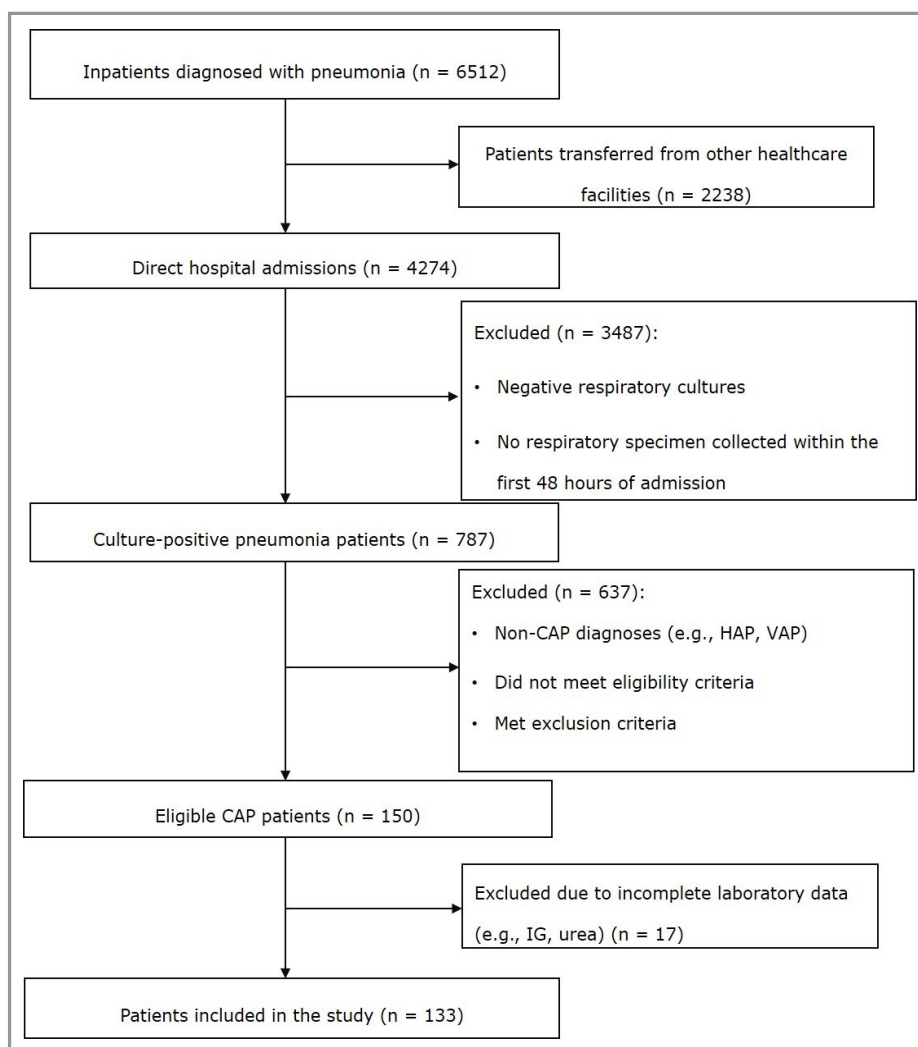


Figure 1. Study flow diagram.

Microbiological Etiology

Most pathogens isolated were gram-negative bacteria (96.2%). The four most frequently identified bacteria, in order, were *Klebsiella pneumoniae* (28.6%), *Acinetobacter baumannii* (20.3%), *Pseudomonas aeruginosa* (17.3%), and *Escherichia coli* (11.3%). Gram-positive bacteria were isolated from only five participants (5.0%), including *Staphylococcus aureus* (four cases) and *Streptococcus pneumoniae* (one case). In addition to core pathogens, the study also detected a variety of other gram-negative bacteria, including *Haemophilus* spp., *Enterobacter cloacae*, *Citrobacter* spp., *Proteus mirabilis*, *Achromobacter* spp. and *Klebsiella aerogenes* demonstrating the microbiological diversity among causative pathogens in CAP. Notably, *H. influenzae*, a common causative agent of community-acquired pneumonia, was isolated in only one case in this study (Table 1).

As presented in Table 1, the proportion of MDROs varied considerably among the pathogens: all *E. coli* isolates (100%) were multidrug-resistant, representing the highest rate, whereas only 13.04% of *P. aeruginosa* isolates were multidrug-resistant. The rates of multidrug resistance in the *K. pneumoniae* and *A. baumannii* bacterial groups were also very high, at 66.67% and 50.0%, respectively. Additionally, 75% of *S. aureus* isolates were methicillin-resistant (MRSA). Remarkably, *E. coli* isolates exhibited complete resistance (100%) to fluoroquinolones and third- and fourth-generation cephalosporins; *K. pneumoniae* maintained a high rate of susceptibility to Carbapenems, while high prevalences of resistance to this antibiotic class were observed among *A. baumannii*, *P. aeruginosa*, and *E. coli*.

As shown in Figure 2, MDR pathogens were isolated from 53.38% of the respiratory specimens in hospitalized CAP patients, representing a higher propor-

Table 1. Distribution of bacterial pathogens in hospitalized community-acquired pneumonia based on conventional cultures

Bacterial pathogens	Total n (%)	MDR n (%)	Key resistance patterns (%)
<i>K. pneumoniae</i>	38 (28.6%)	19 (50.0%)	Fluoroquinolone: 55% Cephalosporin III-IV: 41% Carbapenem: 16% Aminoglycoside: 26%
<i>A. baumannii</i>	27 (20.3%)	18 (66.67%)	Fluoroquinolone: 67% Carbapenem: 67% Cephalosporin III-IV: 78% Aminoglycoside: 74%
<i>P. aeruginosa</i>	23 (17.3%)	5 (13.04%)	Fluoroquinolone: 48% Carbapenem: 48% Cephalosporin III-IV: 17% Aminoglycoside: 14%
<i>E. coli</i>	15 (11.3%)	15 (100%)	Fluoroquinolone: 100% Carbapenem: 47% Cephalosporin III-IV: 100% Aminoglycoside: 60%
Gram-negative bacilli (others)	25 (18.8%)	12 (48%)	
Gram-positive bacteria	5 (3.8%)	3 (60%)	
<i>S. aureus</i>	4 (3.0%)	3 (75%)	Penicillin, Cephalosporin I-II: 100% Cephalosporin III-IV: 75% Macrolide: 75% 100% susceptible to Vancomycin and Linezolid
<i>S. pneumoniae</i>	1 (0.8%)	0 (0%)	Resistant to Macrolide; Susceptible to Fluoroquinolone

Data are presented as counts (percentage).

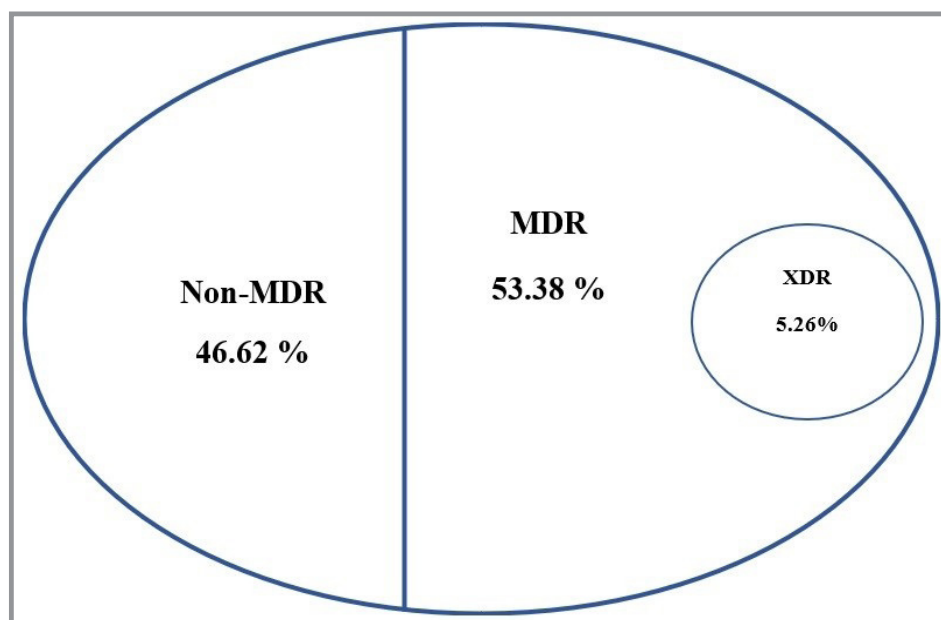


Figure 2. Distribution of non-MDR, MDR, and XDR pathogens isolated from respiratory samples.

tion compared to non-MDR isolates (46.62%). In addition, extensively drug-resistant bacteria were also observed in the study, at a low rate of 5.26%.

Baseline Characteristics

Baseline demographic and clinical characteristics of the study population are summarized in Table 2.

Sex distribution in the study population was skewed towards males, with males approximately 2.5 times as numerous as females. The proportions of patients with MDR and non-MDR bacterial pneumonia were relatively similar across the gender groups. Median age of the study population was 69 years (IQR: 60–77), with no significant differences between MDR and non-MDR groups. The most common comorbidities were obstructive respiratory diseases (asthma, chronic obstructive pulmonary disease), with 51.88%. This was followed by hypertension (39.85%), diabetes mellitus (27.07%), history of pulmonary tuberculosis (23.31%), and pulmonary tuberculosis (18.05%). Heart failure and chronic kidney disease were infrequent, accounting for 5.26% and 3.01% of the study population, respectively. Notably, among these comorbidities, only hypertension demonstrated a statistically significant difference between the MDR and non-MDR groups ($p = 0.017$).

In terms of laboratory findings, the significant differences between MDR and non-MDR groups were observed in CRP, Urea, WBC, neutrophil count, neutro-

phil percentage, immature granulocytes (IG) count, and IG percentage ($p < 0.05$).

In our study, clinical severity was assessed based on intensive care unit (ICU) admission and the requirement for respiratory support. Overall, 19.55% of the patients were admitted to the ICU. Regarding respiratory interventions, 43.61% breathed room air, 45.11% required oxygen therapy, and 11.28% necessitated mechanical ventilation. However, there were no statistically significant differences in these severity indicators between the MDR and non-MDR groups ($p > 0.05$).

Independent association between MDR infection and elevated CRP levels regardless of clinical severity

To assess the effect of disease severity on CRP concentration, a multivariable linear regression was analyzed, using the need for respiratory intervention as an indicator of clinical severity. The model showed that neither oxygen therapy nor mechanical ventilation was significantly associated with CRP elevation. In contrast, the model revealed that MDR infection was significantly and independently associated with higher CRP levels, even after adjusting for the requirement of respiratory interventions ($\beta = 46.6$, 95% CI: 15.85 – 77.36, $p = 0.003$) (Table 3). Consistent with the initial comparative analysis, univariable logistic regression demonstrated that ICU admission was not significantly associated with MDR infection (OR = 0.84, 95% CI: 0.35 – 1.99, $p = 0.7$) (Table 4).

Table 2. Study population characteristics and the comparison between the non-MDR and MDR groups

Characteristics	Total	Non-MDR (n= 62)	MDR (n= 71)	P value
Demographics				
Male, n (%)	96 (72.18%)	41 (66.13%)	55 (77.46%)	0.146*
Female, n (%)	37 (27.82%)	21 (33.87%)	16 (22.54%)	
Age (years), median (IQR)	69 (60 – 77)	68 (55 – 74)	71 (63 – 78)	0.281†
Clinical severity				
ICU admission, n (%)	26 (19.55%)	13 (21.0%)	13 (18.3%)	0.149*
General Respiratory Ward, n (%)	107 (80.45%)	49 (79.0%)	58 (81.7%)	0.829*
Respiratory support				
Room air, n (%)	58 (43.61%)	26 (41.9%)	32 (45.1%)	
Oxygen therapy, n (%)	60 (45.11%)	28 (45.2%)	32 (45.1%)	
Mechanical ventilation, n (%)	15 (11.28%)	8 (12.9%)	7 (9.8%)	
Comorbidities				
Obstructive airway diseases, n (%)	69 (51.88%)	35 (50.72%)	34 (49.28%)	0.324*
Pulmonary tuberculosis, n (%)	24 (18.05%)	11 (45.83%)	13 (54.17%)	0.932*
History of Pulmonary TB, n (%)	31 (23.31%)	18 (58.06%)	13 (41.94%)	0.145*
Diabetes mellitus, n (%)	36 (27.07%)	13 (36.11%)	23 (63.89%)	0.139*
Hypertension, n (%)	53 (39.85%)	18 (33.96%)	35 (66.04%)	0.017*
Heart failure, n (%)	7 (5.26%)	1 (14.29%)	6 (85.71%)	0.121‡
Chronic kidney diseases, n (%)	4 (3.01%)	0 (0%)	4 (100%)	0.123‡
Laboratory Findings				
CRP (mg/L) (n= 133)	73.92 (17.32 -150.35)	40.91 (5.27 – 103.45)	94.25 (42.59 – 162.36)	0.001†
Glucose (mmol/L) (n= 110)	7.28 (5.8 – 10.51)	6.72 (5.52 – 10.09)	8.14 (6.3 – 11.65)	0.051†
Urea (mmol/L) (n= 133)	5.78 (4.03 – 7.65)	5.01 (3.91 – 6.75)	6.09 (4.1 – 9.14)	0.047†
Creatinine (µmol/L) (n= 133)	76.8 (60 – 93.6)	77.25 (59.3 – 85.6)	76.8 (61 – 103.5)	0.248†
AST (U/L) (n= 132)	27.25 (18.55 – 36.5)	26.65 (18.8 – 36.0)	27.7 (18.4 – 37.5)	0.753†
ALT (U/L) (n= 132)	23.95 (16.7 – 34.1)	22.9 (15.8 – 30.9)	24.95 (17 – 40.9)	0.314†
Bilirubin Total (µmol/L) (n= 130)	10.1 (8 – 14.6)	9.65 (7.5 – 13.1)	10.85 (8.2 – 15.95)	0.172†
Bilirubin Direct (µmol/L) (n= 130)	2.2 (1.5 – 3.4)	2.00 (1.4 – 3.0)	2.3 (1.6 – 3.8)	0.119†
Lactate (mmol/L) (n= 12)	3.6 (1.71 – 5.18)	4.85 (3.35 – 5.37)	2.94 (1.5 – 4.8)	0.234†
WBC (K/µl) (n= 133)	12.95 (9.72 – 16.87)	11.37 (8.75 – 16.28)	13.78 (11.53 – 18.14)	0.017†
Neutrophil (K/µL) (n= 133)	10.75 (7.18 – 14.44)	9.40 (6.15 – 13.39)	11.12 (8.35 – 14.81)	0.031†

Table 2. Study population characteristics and the comparison between the non-MDR and MDR groups (continue)

Characteristics	Total	Non-MDR (n= 62)	MDR (n= 71)	P value
Neutrophil (%) (n= 133)	80.9 (71.5 – 87.8)	78.55 (70.4 – 86.2)	82.9 (74.2 – 88.9)	0.146 [†]
IG (K/ μ l) (n= 133)	0.15 (0.06 – 0.31)	0.085 (0.05 – 0.21)	0.23 (0.08 – 0.38)	0.002[†]
IG (%) (n= 133)	0.9 (0.6 – 2.0)	0.7 (0.5 – 1.3)	1.3 (0.6 – 2.4)	0.016[†]

Data are presented as median (interquartile range) or counts (percentage).
* P-values were obtained by Chi-square test.
[†] P-values were obtained by Mann-Whitney U test.
[‡] P-values were obtained by Fisher's exact test.

Table 3. Association between MDR infections and CRP levels, adjusted for respiratory support

Characteristics	Coefficient (β)	95% CI	p value
MDR infection (Yes/No)	46.60	15.85 – 77.36	0.003
Respiratory support			
- Oxygen therapy	2.05	-30.49 – 34.59	0.901
- Mechanical ventilation	9.81	-41.44 – 61.06	0.705

Data were analyzed by multivariable linear regression
CI: Confidence Interval; CRP: C-reactive protein; MDR: Multi-drug resistant.

Table 4. Univariate and multivariate logistic regression analysis of factors and MDR infection

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
CRP (mg/L) *	1.51 (1.17 – 1.93)	0.001	1.51 (1.12 – 2.04)	0.007
Urea (mmol/L) *	2.06 (1.07 – 3.95)	0.031		
WBC K/μL) *	2.33 (1.03 – 5.27)	0.043		
Neutrophil (K/ μ L) *	1.88 (0.97 – 3.65)	0.060		
IG (K/μL) *	1.68 (1.19 – 2.36)	0.003	1.44 (0.99 – 2.12)	0.058
ICU admission	0.84 (0.35 – 1.99)	0.700		
Hypertension	2.38 (1.16 – 4.88)	0.018	3.10 (1.33 – 7.18)	0.008
Heart failure	5.63 (0.66 – 48.13)	0.114	7.07 (0.73 – 67.96)	0.090
Diabetes mellitus	1.81 (0.82 – 3.97)	0.141		
History of Pulmonary tuberculosis	0.55 (0.24 – 1.24)	0.147	0.46 (0.17 – 1.26)	0.133
Pulmonary tuberculosis	1.04 (0.43 – 2.52)	0.932	0.31 (0.10 – 1.03)	0.056
Obstructive airway diseases	0.71 (0.36 – 1.41)	0.325	0.45 (0.18– 1.12)	0.086
Male	1.76 (0.82 – 3.79)	0.148	2.79 (1.04 – 7.46)	0.041
Age $\geq$ 65	0.99 (0.48 – 2.06)	0.987		

* Skewed continuous variables were transformed using the natural logarithm (ln) prior to inclusion in the logistic regression analysis.
CRP: C- reactive protein; WBC: White blood cell; IG: Immature granulocyte, ICU: Intensive care unit.

Diagnostic Performance of CRP for MDR Identification

Several clinical and laboratory parameters are significantly associated with MDRO-infected CAP, as presented in Table 4. Regarding laboratory parameters, univariate logistic analysis using log-transformed continuous variables showed that higher $\ln(\text{CRP})$ (OR= 1.51, 95% 1.17 – 1.93, $p= 0.001$), $\ln(\text{WBC})$ (OR= 2.33, 95% 1.03 – 5.27, $p= 0.043$), $\ln(\text{IG})$ (OR= 1.68, 95% 1.19 – 2.36, $p= 0.003$), and $\ln(\text{Urea})$ (OR= 2.06, 95% 1.07 – 3.95, $p= 0.031$) were significantly associated with MDR infections. These demographics and comorbidities, which include age, sex, heart failure, diabetes mellitus, history of pulmonary tuberculosis, and obstructive airway diseases, were not significantly associated with MDR infections ($p > 0.05$) in either univariate or multivariate analysis. In the multivariable logistic analysis, only $\ln(\text{CRP})$ (OR= 1.52, 95% CI: 1.12 – 2.05, $p= 0.007$) and hypertension (OR= 3.140, 95% CI: 1.35 – 7.29, $p= 0.008$) remained immediately associated with MDR infection.

The admission level of CRP provided modest discrimination between CAP patients with MDROs and non-MDROs infections (AUC= 0.67, 95% CI: 0.57 – 0.76). The optimal cut-off value of 42.59 mg/L (Youden index= 0.29) produced a sensitivity of 76.06% and a

specificity of 53.23%, a NPV of 66.0%, and a PPV of 65.06%. In the multivariable logistic regression model incorporating CRP ≥ 42.59 mg/L, IG count ≥ 0.06 K/ μL , male, obstructive airway diseases, hypertension, heart failure, pulmonary tuberculosis, history of pulmonary tuberculosis, CRP ≥ 42.59 mg/L (OR= 5.02, 95% CI: 2.01 – 12.52, $p= 0.001$), IG ≥ 0.06 K/ μL (OR= 2.97, 95% CI: 1.24 – 7.15, $p= 0.015$), male (OR= 3.13, 95% CI: 1.14 – 8.61, $p= 0.026$), obstructive airway diseases (OR= 0.33, 95% CI: 0.13 – 0.85, $p= 0.022$), hypertension (OR= 3.57, 95% CI: 1.48 – 8.63, $p= 0.005$), pulmonary tuberculosis (OR= 0.23, 95% CI: 0.07 – 0.82, $p= 0.023$) demonstrated as the independent factor of predicting MDR infection (Table 5). In addition, ICU admission showed no statistical significance in the univariate screening; the backward stepwise selection algorithm automatically excluded this variable from the final multivariate model as it failed to significantly improve the model fit. This model remarkably improved diagnostic accuracy for distinguishing two patient groups (AUC= 0.81, 95% CI: 0.73 – 0.88, p -value for AUC comparison= 0.001). The multivariate model yielded a sensitivity of 74.46% and a specificity of 74.19%, an NPV of 74.19%, and a PPV of 77.46%. The Hosmer-Lemeshow goodness-of-fit test indicated an adequate fit for the model ($\chi^2(8)= 6.69$, $p= 0.57$) (Figure 3).

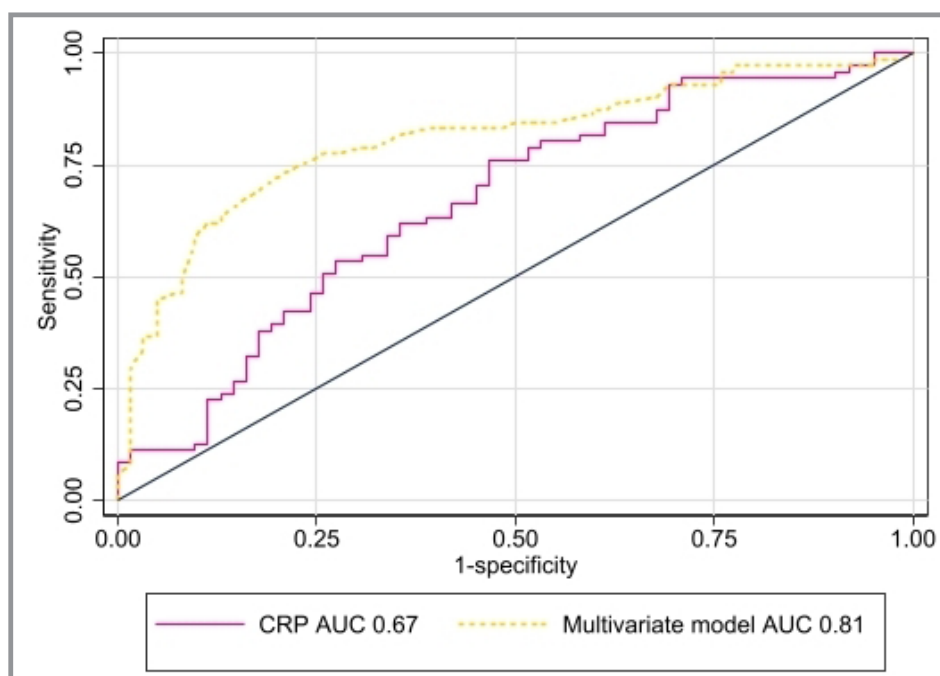


Figure 3. The ROC curves for CRP and multivariate model on differentiating CAP caused by MDROs and non-MDROs.

DISCUSSION

Laboratory parameters, including CRP, WBC, IG, neutrophil count, and urea, show significant differences between CAP inpatients with and without MDRO infection ($p < 0.05$). The increases in these parameters were also significantly associated with MDRO infection in CAP patients in univariate analysis. However, in multivariate analysis, only elevated CRP levels remained an independent predictor of a higher likelihood of MDR infection. The exclusion of urea and WBC from the final multivariable model was predictable and aligns with previous medical knowledge. Specifically, blood urea, as a component of the Pneumonia Severity Index (PSI), and the CURB-65 Score is widely used in clinical practice to assess disease severity and predict mortality in patients with CAP. Elevated blood urea is recognized as a marker of impaired kidney function, decreased renal perfusion, and increased catabolism in severe infections or sepsis (18,19). Therefore, blood urea is considered an indicator of CAP severity, mortality risk, and complications rather than a specific marker for MDR infection. Similarly, leucocyte indices were not significantly associated with MDR infections, possibly because leucocyte elevation is strictly bound by the bone marrow's production capacity. Leucocyte counts may be low or in the normal range due to bone marrow suppression in severe infections or immunosenescence in older people. Moreover, circulating leucocyte counts represent only a fraction of the total immune response, as a substantial proportion of leukocytes migrate to and settle at sites of tissue infection. Additionally, bacterial toxins—particularly those produced by virulent MDR strains—may directly induce leucocyte destruction (6,20). Some previous studies have reported that, although both leucocytes and CRP are commonly used to assess the severity of bacterial infections, only CRP demonstrated a significant difference between patients with MDR and non-MDR infections (6,20). These findings from our study and previous studies highlight the superiority of CRP over WBC in discriminating between the two groups.

The precise pathophysiological mechanisms underlying higher CRP levels in the MDR group compared to the non-MDR cohort have not yet been clearly established. CRP is traditionally considered a non-specific inflammatory marker, synthesized by hepatic cells through a pro-inflammatory cytokine cascade (IL-6, IL-1, and TNF- α) (10). Prior research has highlighted

the clinical value of CRP in predicting pneumonia severity and mortality, as well as the utility of monitoring its kinetics to guide the escalation or de-escalation of antibiotic treatment (12). However, at the molecular level, the host immune response exhibits significant heterogeneity across bacterial species (21). Specifically, cytokine upregulation in bacterial infections results from a combination of factors (such as bacterial molecular structures, host immune response, and tissue injury). The key mechanism explaining the higher CRP elevation in MDR versus susceptible infections may lie in biofilm formation, which triggers persistent immune stimulation. The formation of a biofilm protects bacteria from attack by the host immune system and from antimicrobial agents. The biofilm matrix containing polysaccharides, proteins, and DNA from resident bacteria prevents drug-resistant bacteria from being eliminated, allowing them to multiply rapidly within the host's body and continuously stimulate immune cells, leading to a massive cytokine response (22). Bacterial resistant strains activate Toll-like receptors on the surface of immune cells, initiating a pro-inflammatory signaling pathway that results in a massive release of interleukin-6, which ultimately targets hepatocytes to stimulate rapid gene transcription and synthesis of CRP (9,23).

In addition, although MDR bacteria with a fitness cost reduce acute virulence, the inflammatory response does not necessarily decrease (23,24). This may be explained by the fact that this adaptation enables them to survive and multiply, thereby sustaining a cytokine cascade. Indeed, Lisboa et al. (2008) demonstrated that CRP is positively correlated with bacterial load at the site of inflammation (25). Moreover, it is traditionally believed that MDR bacteria trade virulence for the development and maintenance of drug resistance genes (26). However, a biological fitness cost is not an absolute occurrence. Many bacterial strains, particularly those predominantly isolated in our study such as *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus*, retain their virulence even upon acquiring drug resistance (24,26). This phenomenon occurs when bacteria acquire secondary compensatory mutations allowing them to restore their original virulence and fitness while maintaining their MDR phenotype. Alternatively, this retention of virulence happens because antimicrobial resistance genes and virulence factors are collocated on the same mobile genetic elements (26).

Another notable finding in our study is that MDR infection emerged as an independent risk factor for elevated CRP, even after adjusting for respiratory distress, a representative marker of clinical pneumonia severity. This observation suggests that while respiratory distress is one consequence of overreactive inflammatory responses, the presence of MDR pathogens may primarily contribute to the strong inflammatory stimulus. Interestingly, our study showed that while CRP levels differed significantly between the MDR and non-MDR groups, clinical outcomes, such as respiratory distress severity and ICU admission rates, were similar. It is the fact that more clinical severity is often observed in MDR patients, yet the direct causal mechanisms remain poorly defined (7,27). Ilknur Kaya et al. (2026) also proposed that the frequently observed association between clinical severity and MDR pathogens may reflect confounding factors or reverse causation rather than a direct causal relationship (28). Similarly, ICU admission did not contribute significantly to our multivariate logistic regression model, further reinforcing the idea that, when true risk factors for MDR infection (such as comorbidities) are present, clinical severity may not be an independent risk factor for MDR infection. Furthermore, the highest proportion of *P. aeruginosa* (32.26%) in the non-MDR group, a pathogen that frequently causes severe clinical symptoms, may explain why overall clinical severity did not differ between the MDR and non-MDR cohorts.

Importantly, while *K. pneumoniae* is the leading pathogen in our study, hypervirulent *K. pneumoniae* (hvKp) was undetectable because this testing is not a routine hospital practice. Since hvKp can drive an exaggerated inflammatory response, the lack of this data could potentially confound the difference in CRP levels between the MDR and non-MDR groups. However, whether the immune response and cytokine levels are genuinely stronger in hvKp compared to classical *K. pneumoniae* (cKp) remains controversial (29,30). Although Vietnam has a recognized epidemiological prevalence of hvKp, its presence might not be a significant confounding factor in this study for two main reasons. Firstly, considering the clinical presentation of the study participants, the rate of hvKp infections is likely low. Specifically, hvKp is classically described as predominating in immunocompetent individuals and is frequently associated with multiorgan infections such as endophthalmitis, meningitis, and septic arthritis (31). Regarding isolated pulmonary infec-

tions, the rate of hvKp infection is much lower than that of cKp (32). Meanwhile, our study population predominantly consisted of elderly individuals with comorbidities and excluded cases with extrapulmonary infections, aligning with the high-risk demographic for cKp infection. Secondly, although the incidence of multidrug-resistant hvKp is increasing, it remains lower than that of cKp, especially in pneumonia cases (32,33). These combined epidemiological and clinical factors suggest that the confounding effect of hvKp on elevated CRP may be negligible. Nevertheless, the inability to identify hypervirulent strains and eliminate the confounding factor was a limitation of our study. To clearly elucidate the relationship between CRP, MDR, and clinical severity, further studies investigating the cytokine response should be designed to account for microorganism-specific inflammatory patterns and the true causal relationships.

The study cohort did not fully represent the community CAP population, as it focused on patients with moderate or severe CAP who required hospitalization. Most of the patients were aged over 65 years (67.67%) and presented with comorbidities, predominantly chronic respiratory diseases. This demographic profile aligns with global epidemiological trends, which reflect an increasing CAP burden among older adults with underlying diseases (e.g., COPD, asthma, chronic cardiovascular disease, diabetes mellitus, immunocompromised) (34,35). In clinical practice, this subpopulation is considered the most vulnerable patient group, carrying the highest risk of hospital admission. Thus, a notable consideration to avoid misunderstanding is that these findings may not be fully representative of the overall CAP population but specifically reflect the high-risk hospitalized demographic that would most benefit from early MDR stratification at admission.

In terms of pathogen distribution, most isolated pathogens were Gram-negative bacteria (96%), whereas Gram-positive bacteria were found in only 4% of cases. Remarkably, *Acinetobacter baumannii* and *Klebsiella pneumoniae* collectively constituted nearly half of the total isolates. This distribution is not relevant to the epidemiology of CAP pathogens, as shown by studies using molecular methods (36,37). However, our observation is consistent with other reports that used conventional culture to detect causative agents. Gram-positive bacteria such as *S. pneumoniae* and *H. influenzae* – primary bacterial pathogens in CAP

– were isolated at low rates, which is explained by the inherently low positive culture rate with community bacteria (4,37). Bacterial culture has low sensitivity for detecting CAP pathogens, cannot identify viral agents, and takes a long time to yield results. The prevalence of MDR strains among these isolates was alarmingly high, with 53.38% of the pathogens isolated from cultures in hospitalized CAP patients, which is equivalent to the rate from previous studies in Vietnam and other Asian countries, but higher than in Western countries (15,38). Bacterial strain distribution was generally comparable between the MDR and non-MDR groups, except for *P. aeruginosa* and *E. coli*. Only 13.04% of the *P. aeruginosa* isolates were identified as MDR strains, whereas the entire *E. coli* population was multidrug resistant. These figures reflect the local epidemiology of pathogens and are highly consistent with data reported worldwide (39). Despite the high infection rate associated with *Pseudomonas* species, most community *P. aeruginosa* strains retain antibiotic susceptibility. Conversely, the *E. coli* isolates have already established profound resistance levels even outside hospital environments. The emergence of MDR bacteria traditionally associated with the hospital environment in the community represents a concerning shift in bacterial epidemiology. More importantly, the findings showed a high rate of resistance to third-generation cephalosporins and fluoroquinolones – the first-line empirical antibiotics. The rising burden of MDR infections in the community poses a substantial challenge for health-care systems.

A CRP cut-off of 42.59 mg/L shows modest diagnostic performance in distinguishing CAP caused by MDROs from non-MDROs (AUC= 0.67, 95% CI: 0.57 – 0.76). Despite its limited specificity, CRP is a moderate screening indicator for CAP patients at high risk of MDR infections at admission, with a sensitivity of 76.06%. Moreover, the multivariable model, including CRP (≥ 42.59 mg/L), IG count (≥ 0.06 K/ μ L), and comorbidities, remarkably improved diagnostic accuracy, yielding a sensitivity of 74.46% and a specificity of 74.19% (AUC= 0.81, 95% CI: 0.73 – 0.88). According to Meifang Jiang et al. (2020), CRP shows good discrimination between MDR and non-MDR infections in COPD patients with pulmonary infections with a specificity of 75.6%, a sensitivity of 81.8% (AUC= 0.811, 95% CI: 0.79 – 0.83) (20). Li Wang et al. (2020) reported that CRP, in combination with other clinical factors (male sex and higher Pitt bacte-

remia scores), had moderate discrimination for MDR infections in ICU patients (AUC= 0.77, 95% CI 0.70–0.84) (40). Another study conducted in India (2023) also indicated that CRP may serve as a useful adjunctive biomarker for early risk stratification of bloodstream MDR infections, particularly in settings where blood culture results are pending or delayed (13). The valuation of CRP in our study and others suggests that although CRP alone is not an optimal marker for a definitive diagnosis of MDR infections, it is a potential biomarker for early identification of MDR infection in CAP patients, enabling more timely and appropriate antibiotic selection. In low- and middle-income countries with high antimicrobial resistance, CRP could help clinicians make more informed decisions about empirical antibiotic therapy before culture results are available. However, an important limitation of our model is the absence of data on hospitalization in the preceding 90 days and prior oral antibiotic use. We were unable to collect this information due to the retrospective extraction of medical records, which lacks the specific historical details. Although we mitigated potential bias from prior intravenous antibiotic therapy by excluding all patients transferred from other healthcare facilities, the absence of comprehensive outpatient data inherently diminishes the robustness of our model. Therefore, future studies with more comprehensive data and rigorous control of confounding factors are warranted to re-evaluate the validity and reliability of this predictive model, ultimately leading to a more optimized version.

The findings of our study offer a different perspective on the empirical management of hospitalized patients with CAP. In the settings where resistance to common antibiotics and even broad-spectrum agents such as carbapenems is increasingly prevalent, identifying the risk of MDRO infection as early as possible is clinically relevant. While conventional practice often associates the need for broad-spectrum therapy primarily with clinical severity, our data suggest that clinical markers—such as oxygen requirements or ICU admission—may not always align directly with the presence of MDR pathogens. However, our study demonstrated that CRP was an independent predictor for MDR infections in CAP-admitted patients, even after adjusting for these clinical indicators. Consequently, relying solely on clinical severity to guide empirical antibiotics may be insufficient. Integrating CRP as a moderate screening indicator could provide clinicians with additional evidence to select appropri-

ate initial antibiotics. It is important to acknowledge that due to its limited discrimination ability, CRP cannot be considered a diagnostic standard for MDR infections. Specifically, using CRP levels alone to make definitive decisions regarding antibiotic selection is not recommended. Instead, CRP should be utilized as a supplementary screening tool. In clinical practice, an elevated CRP should serve as a 'flag' that alerts to a more thorough review of the patient's risk factors and closer monitoring, rather than serving as a single indicator for prescribing broad-spectrum antibiotics. Our study suggests that CRP can be a practical adjunct for initial assessment of CAP patients upon hospital admission, particularly in resource-limited settings, due to its cost-effectiveness, rapid turnaround, and widespread availability.

Our study has several limitations, limiting its immediate applicability to clinical practice. Reliance on conventional culture methods may have distorted the true distribution of pathogens, while the exclusive inclusion of hospitalized CAP patients with microbiologically confirmed positive cultures may introduce selection and ascertainment bias. Furthermore, conducting this study at a single tertiary respiratory hospital likely enriched the cohort with severe cases, despite our exclusion of patients referred from other hospitals. Consequently, our final cohort likely represents a selected subgroup with more severe pneumonia, which may limit the external validity and generalizability of our findings to the broader CAP population. Moreover, because diagnostic verification was restricted to the culture-positive group, our study is also susceptible to verification bias. Another limitation is that, as is inherent in a retrospective study, we cannot be certain that all data on patients' medical history and symptoms were fully recorded. As a result, our study lacked comprehensive data, such as history of hospitalizations and prior antibiotic use, to investigate the multivariate model. Finally, while excluding patients with septic shock helped mitigate the impact of systemic inflammatory response, our results may still be limited by the lack of concurrent blood culture data to definitively rule out underlying bloodstream infections that could contribute to CRP elevation. Given the potential of CRP, additional studies should be conducted to more accurately determine CRP's value in classifying MDR infections and to develop a robust CRP-based risk-stratification scoring system for clinical application.

CONCLUSION

The development of rapid, cost-effective diagnostic tools is essential for the early stratification of drug-resistant infections among CAP patients, particularly in resource-limited settings. Early identification of MDR can help guide initial antibiotic selections and minimize the unnecessary use of broad-spectrum agents. While CRP may be a promising screening test to identify MDR infections at admission, it is a nonspecific inflammatory biomarker influenced by multiple clinical conditions and comorbidities. Therefore, in clinical practice, it should be considered alongside other clinical parameters in the antibiotic decision-making process. Further studies are required to establish the predictive value of CRP definitively and to evaluate the direct causal relationship between this marker and antimicrobial resistance.

Ethical Committee Approval: The study was approved by the Ho Chi Minh City University of Medicine and Pharmacy Ethics Committee of (Decision no: 939/QD-DHYD, Date: 20.05.2021).

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CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: DTTB, TBSN, THP

Analysis/Interpretation: DTTB, TMN

Data Acquisition: DTTB

Writing: DTTB

Clinical Revision: TBSN, THP

Final Approval: TBSN

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