Cureus
Part of SPRINGER NATURE

Open Access Original Article

Predictors of Treatment Failure in Hospitalized Patients With Community-Acquired Pneumonia: A Prospective Cohort Study

Review began 10/10/2026
Review ended 10/18/2026
Published 11/07/2026

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DOI: 10.7759/cureus.119275

Nayab Shabir [1], Fareeha Maqbool [2], Sifat Ullah [3], Nauman Idrees [4], Abdul Salam [5, 1], Rabbiya Shahzadi [6], Sajid Nawaz [7], Adnan Afzal [8], Laraib Fatima [9]

1. Pulmonology, Hayatabad Medical Complex, Peshawar, PAK 2. Pulmonology, Peshawar Medical College, Peshawar, PAK 3. Respiratory Medicine, Mayo University Hospital, Castlebar, IRL 4. Internal Medicine, Rehman Medical Institute (RMI), Peshawar, PAK 5. Medicine, Khyber Medical College, Peshawar, PAK 6. General Internal Medicine, University Hospitals Coventry and Warwickshire, Coventry, GBR 7. Internal Medicine, Lady Reading Hospital, Peshawar, PAK 8. Orthopedics and Trauma, Rehman Medical Institute (RMI), Peshawar, PAK 9. Obstetrics and Gynecology, Hayatabad Medical Complex, Peshawar, PAK

Corresponding author: Abdul Salam, asalambangash@gmail.com

Abstract

Background

Failure to respond to treatment in a hospital is an important clinical issue that is related to worsening of the illness, length of hospital stay, intensive care unit admission, and death in patients with community-acquired pneumonia.

Objective

This study aimed to identify the independent demographic, clinical, laboratory, radiological, microbiological, and initial treatment-related predictors of treatment failure among hospitalized adults with community-acquired pneumonia.

Methodology

This was a prospective observational cohort study performed in the Pulmonology Department of Medical Teaching Institute (MTI)-Hayatabad Medical Complex in Peshawar, Pakistan, from July 2024 to June 2026. A total of 650 consecutive community-acquired pneumonia adult admissions were enrolled and followed up prospectively from admission to discharge or death. The failure of treatment was based on predefined clinical, respiratory, hemodynamic, radiological, and outcome-based criteria. Baseline information included demographic, clinical, laboratory, radiological, microbiological, and first treatment features. Univariable and multivariable logistic regression analyses were used to look for independent predictors of treatment failure.

Results

Among 650 patients, treatment failure occurred in 98 (15.1%), comprising 61 (62.2%) early failures and 37 (37.8%) late failures. Patients with treatment failure were more likely to be older and to have chronic liver disease, altered mental status, impaired oxygenation, leukopenia, elevated inflammatory markers, multilobar pneumonia, and pleural effusion. On multivariable analysis, independent predictors included age ⩾65 years (adjusted odds ratio (aOR): 1.71), chronic liver disease (aOR: 2.31), altered mental status (aOR: 1.88), oxygen saturation <90% (aOR: 2.37), CURB-65 ⩾3 (aOR: 2.42), leukopenia (aOR: 1.89), C-reactive protein (CRP) >100 (aOR: 1.69), multilobar involvement (aOR: 1.91), and pleural effusion (aOR: 1.76).

Conclusion

Recognition of these baseline clinical, physiological, inflammatory, and radiological characteristics may help identify patients requiring closer monitoring and early reassessment during hospitalization.

Categories: Pulmonology, Epidemiology/Public Health
Keywords: hospitalized patients, pneumonia, predictors, prospective cohort, risk factors, treatment failure

Introduction

Community-acquired pneumonia (CAP) is a leading cause of hospitalization, morbidity, and mortality in adults around the world [1,2]. Despite the use of antimicrobial treatment, diagnostic evaluation, and supportive care, treatment failure occurs in 8-25% of hospitalized patients, but this varies by patient, disease severity, healthcare setting, and outcome definitions [3,4]. Failure to respond to treatment is clinically significant due to the extended length of hospital and/or intensive care unit treatment, complications, and increased mortality [5].

The failure to respond to treatment is a very broad spectrum of clinical failure that includes progression of pneumonia, increasing the severity of respiratory function, uncontrolled septic processes, pleural complications, and other reasons for clinical failure [6]. The factors determining its outcome are multifactorial and involve host factors, baseline disease severity, comorbidities, microbial etiology, radiological extent of disease, physiological abnormalities, inflammatory response, and initial antimicrobial therapy [7,8]. Increasingly severe pneumonia, liver disease, leukopenia, multilobar pneumonia, pleural effusion, and radiological cavitation have all been shown to be associated with treatment failure in prospective studies. Abnormal gas exchange, hypotension, acidosis, renal dysfunction, thrombocytopenia, and increased inflammatory biomarkers have also been associated with poor treatment response [9].

The initial 48-72 hours of hospitalization represent a critical period for evaluating treatment response [10]. Early treatment failure may indicate progressive infection, worsening organ dysfunction, inadequate antimicrobial coverage, or complications such as empyema, whereas late treatment failure may result from unresolved infection, secondary complications, or noninfectious causes [11,12]. The Pneumonia Severity Index (PSI) and CURB-65 are validated tools for initial risk stratification; however, admission severity does not necessarily predict subsequent treatment response, as patients may deteriorate due to factors that develop during hospitalization or are not fully captured at admission [13]. Furthermore, the relative importance of predictors of treatment failure may vary across healthcare settings depending on patient characteristics, prior antimicrobial exposure, microbiological patterns, and available diagnostic resources [14].

Therefore, this study aimed to identify the independent demographic, clinical, laboratory, radiological, microbiological, and initial treatment-related predictors of treatment failure among hospitalized adults with CAP at a tertiary care hospital in Peshawar, Pakistan.

Materials And Methods

Study design and setting

The study was a prospective observational cohort study conducted in the Pulmonology Department of Medical Teaching Institute (MTI)-Hayatabad Medical Complex in Peshawar, Pakistan, during the period from July 2024 to June 2026. The department was responsible for inpatient respiratory care and for the management of adult patients with CAP referred from the emergency department and other clinical services. Eligible patients were consecutively included when they were admitted to the hospital and followed up prospectively until their discharge from the hospital or death. The study aimed to determine the independent relationship of demographic, clinical, laboratory, radiological, microbiological, and initial treatment characteristics with subsequent treatment failure.

Study population and eligibility criteria

The study population consisted of adults aged ⩾18 years admitted with CAP. Patients were eligible if they presented with clinical signs and symptoms of an acute lower respiratory tract infection accompanied by a new pulmonary infiltrate on chest imaging. CAP was defined as pneumonia acquired outside the hospital or diagnosed within the first 48 hours of hospital admission, provided that the infection was present or incubating at the time of admission. Hospital-acquired pneumonia (HAP) was defined as pneumonia developing ⩾48 hours after admission and not present or incubating at admission. Patients with HAP, ventilator-associated pneumonia (VAP), active pulmonary tuberculosis, or recent hospitalization associated with a suspected healthcare-acquired infection were excluded. Additional exclusion criteria included insufficient essential baseline data, pulmonary infiltrates predominantly attributable to noninfectious causes, and severe immunosuppression associated with an alternative pulmonary diagnosis. These eligibility criteria were applied to distinguish CAP from hospital-acquired respiratory infections and ensure the appropriate classification of the study population.

Sample size and sampling technique

A sample size of 650 participants was deemed to be large enough to generate sufficient outcome events for the planned multivariable logistic regression analysis for the purpose of making reliable estimates of independent associations between clinically relevant baseline predictors and treatment failure. Sample size was determined based on the number of treatment failures anticipated in prior studies and to avoid overfitting the model by having too few parameters in the model. Consecutive sampling was used, where all eligible patients were sampled consecutively until the specified number of patients (n=650) had been sampled. The study was a prospective study of all participants recruited until they were discharged or died. Treatment failure events were ascertained after follow-up based on the predefined treatment failure criteria, and the actual number of treatment failure cases was used for subsequent statistical analysis.

Baseline assessment and data collection

The data collection was a prospective process, with baseline data collected at admission, based on a standardized structured data collection proforma (see Appendices). The structured data collection proforma was developed by the principal investigator in consultation with the research supervisor and relevant

physicians from the Pulmonology Department, who provided input on the selection and formulation of clinically relevant questions and variables. Demographic variables were age and sex. Clinical data involved in the study were presenting symptoms, duration of illness, smoking history and presence of comorbidities, respiratory rate, heart rate, blood pressure, temperature, peripheral oxygen saturation, mental status, and the need for supplemental oxygen at presentation. Clinical comorbidities of interest were chronic respiratory disease, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic liver disease, and other clinically significant underlying diseases. The PSI and CURB-65 scores were used to classify the severity of pneumonia on admission. To maintain the temporal relationship between the predictor variables and the outcome, all predictor variables planned for the primary analysis were recorded at baseline or prior to the occurrence of the treatment failure.

Definition and assessment of treatment failure

Treatment failure was defined a priori as clinical deterioration or failure to achieve clinical stability during hospitalization despite initial antimicrobial treatment for CAP. Treatment failure was identified by one or more of the following clinical events: progressive respiratory failure requiring escalation of oxygen or ventilatory support, hemodynamic deterioration or septic shock, development of complicated parapneumonic effusion or empyema, radiological progression accompanied by clinical deterioration, or death attributable to CAP. Treatment failure occurring within the first 72 hours after the initiation of antimicrobial therapy was classified as early treatment failure, whereas failure occurring after 72 hours was classified as late treatment failure. Patients were monitored prospectively throughout hospitalization, with particular attention to clinical changes during the first 48-72 hours of treatment. Antimicrobial modification or escalation was recorded separately as a treatment-related variable and was not considered an independent criterion for treatment failure in the absence of clinical deterioration.

Assessment

Baseline laboratory studies consisted of complete blood count, renal function tests, serum electrolytes, liver function tests, inflammatory markers, and arterial or venous blood gases as indicated. Microbiological investigations were undertaken as clinically indicated and included blood culture, sputum examination and culture, respiratory specimens, and investigations for specific pathogens where available. Chest radiographs were obtained at baseline, and computed tomography of the chest was performed when clinically indicated. Radiological characteristics documented for analysis included bilateral infiltrates, multilobar involvement, pleural effusion, and cavitation.

Treatment and follow-up

Standard inpatient care was provided, based on clinical judgment and the routine care provided by the hospital. The initial antimicrobial prescription was made by the treating team depending on the severity of the disease, suspected pathogens, local antimicrobial prescription, clinically significant comorbidities, and microbiological information. The first treatment with an antimicrobial agent and any adjustments or intensification of the treatment were recorded. All participants were followed up from admission to hospital until discharge or death. Clinical assessments were carried out during the hospital stay, particularly during the first 48-72 hours after starting treatment. In serial assessments, respiratory and hemodynamic status, oxygen or ventilatory requirements, laboratory parameters, development of complications, antimicrobial changes, intensive care transfer, and others, which were indicative of clinical deterioration, were included. Hospitalization time and final in-hospital outcome were noted.

Study outcomes

The main outcome was failure of treatment in the index hospitalization. Early and late treatment failure, admission to the intensive care unit, need for mechanical ventilation or increase in respiratory care, septic shock, presence of pleural complications, hospital stay, and in-hospital mortality were secondary outcomes. The primary analysis was based on the correlation between baseline clinical, demographic, laboratory, radiological, microbiological, and initial treatment parameters with the outcome of treatment failure.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, New York, United States). Continuous variables were expressed as means±standard deviations or medians with interquartile ranges, while categorical variables were presented as frequencies and percentages. Independent-samples t-tests, Mann-Whitney U tests, and chi-squared tests were applied for group comparisons, as appropriate. Univariable and multivariable logistic regression analyses were performed to identify predictors of treatment failure, with odds ratios (ORs), adjusted odds ratios (aORs), and 95% confidence intervals (CIs) reported. Candidate predictors were selected based on clinical relevance, previously established associations with CAP outcomes, and univariable findings. Multicollinearity was assessed using correlation analysis, variance inflation factors (VIFs), and tolerance statistics, particularly for overlapping predictors such as CURB-65 and its individual components. Potentially redundant variables were evaluated to minimize model instability. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC), while calibration was evaluated by comparing predicted and

observed outcomes. All statistical tests were two-sided, with p<0.05 considered statistically significant.

Measures to minimize bias and confounding

Potential sources of selection bias, information bias, confounding, and random error were considered during study design and analysis. Consecutive recruitment was employed to minimize selection bias, while standardized prospective data collection and predefined diagnostic and outcome criteria were used to improve measurement consistency. Baseline predictors were recorded before treatment failure to maintain temporal relationships and reduce reverse causation. Potential confounding by demographic characteristics, comorbidities, disease severity, and initial treatment factors was addressed through multivariable logistic regression. Statistical uncertainty was evaluated using 95% CIs.

Ethical considerations

This study was approved by the Hospital Research and Ethical Committee of Medical Teaching Institute (MTI)-Hayatabad Medical Complex (approval number: 1042/PD/HMC/2024) before its start. All participants gave written informed consent prior to participation. Participant confidentiality was protected throughout the study, and data were collected with specific study identifiers and kept confidential and secured by the research team. No one was forced to participate, and it was made clear to participants that they could drop out at any time without impacting their care. The study was carried out in adherence to the Declaration of Helsinki and the institutional and national ethical guidelines.

Results

Among 650 hospitalized patients, 98 (15.1%) experienced treatment failure (Table *1*). Patients with treatment failure were older than those without failure (64.9±15.8 vs. 57.6±17.2 years; p<0.001), and age ≥65 years was more frequent among those with failure (58.16% vs. 38.22%; p<0.001). Treatment failure was also significantly associated with chronic liver disease (15.31% vs. 5.98%; p=0.002), altered mental status (24.49% vs. 10.69%; p<0.001), and supplemental oxygen requirement at admission (71.43% vs. 40.04%; p<0.001). Diabetes, chronic respiratory disease, cardiovascular disease, chronic kidney disease, current smoking, and fever >3 days before admission were also significantly more frequent among patients with treatment failure, whereas sex was not significantly associated with the outcome (p=0.167).

Variable	Total (N=650)	Treatment failure (n=98)	No treatment failure (n=552)	Test value	P-value
Age, years, mean±SD	58.7±17.2	64.9±15.8	57.6±17.2	t=3.92	<0.001
Age ≥65 years	268 (41.23%)	57 (58.16%)	211 (38.22%)	χ^2=14.23	<0.001
Age <65 years	382 (58.77%)	41 (41.84%)	341 (61.78%)		
Male	389 (59.85%)	65 (66.33%)	324 (58.70%)	χ^2=1.91	0.167
Female	261 (40.15%)	33 (33.67%)	228 (41.30%)		
Current smoker	181 (27.85%)	36 (36.73%)	145 (26.27%)	χ^2=4.34	0.037
Diabetes mellitus	214 (32.92%)	42 (42.86%)	172 (31.16%)	χ^2=4.89	0.027
Chronic respiratory disease	157 (24.15%)	34 (34.69%)	123 (22.28%)	χ^2=6.82	0.009
Cardiovascular disease	176 (27.08%)	35 (35.71%)	141 (25.54%)	χ^2=4.25	0.039
Chronic kidney disease	71 (10.92%)	17 (17.35%)	54 (9.78%)	χ^2=4.49	0.034
Chronic liver disease	48 (7.38%)	15 (15.31%)	33 (5.98%)	χ^2=9.28	0.002
Fever >3 days before admission	274 (42.15%)	52 (53.06%)	222 (40.22%)	χ^2=5.33	0.021
Altered mental status	83 (12.77%)	24 (24.49%)	59 (10.69%)	χ^2=15.05	<0.001
Supplemental oxygen at admission	291 (44.77%)	70 (71.43%)	221 (40.04%)	χ^2=33.64	<0.001

TABLE 1: Baseline demographic and clinical characteristics according to treatment failure

χ^2: Pearson chi-squared test; t: independent-samples t-test

Patients who developed treatment failure had higher median white blood cell (WBC) counts (12.7×10^9/L vs. 10.5×10^9/L; p=0.006), lower mean platelet counts ($184.3\pm74.5\times10^9$/L vs. $219.9\pm81.8\times10^9$/L; p<0.001), and

lower hemoglobin levels (11.9±2.3 g/dL vs. 12.5±2.0 g/dL; p=0.011), shown in Table 2. Median C-reactive protein (CRP) and procalcitonin levels were also significantly higher among patients with treatment failure (132 mg/L vs. 79 mg/L and 1.42 ng/mL vs. 0.61 ng/mL, respectively; both p<0.001). Leukopenia, creatinine >1.5 mg/dL, and metabolic acidosis were significantly more common in the treatment-failure group (19.39% vs. 9.78% (p=0.006); 28.57% vs. 15.22% (p=0.001); and 26.53% vs. 12.68% (p<0.001), respectively).

Variable	Treatment failure (n=98)	No treatment failure (n=552)	Test value	P-value
WBC count, ×10⁹/L, median (IQR)	12.7 (8.1-18.1)	10.5 (7.3-14.7)	U=22,418	0.006
Leukopenia	19 (19.39%)	54 (9.78%)	χ^2=7.65	0.006
Platelet count, ×10⁹/L, mean±SD	184.3±74.5	219.9±81.8	t=4.15	<0.001
Hemoglobin, g/dL, mean±SD	11.9±2.3	12.5±2.0	t=2.56	0.011
CRP, mg/L, median (IQR)	132 (68-221)	79 (39-151)	U=19,864	<0.001
Procalcitonin, ng/mL, median (IQR)	1.42 (0.48-4.16)	0.61 (0.18-1.82)	U=18,921	<0.001
Creatinine >1.5 mg/dL	28 (28.57%)	84 (15.22%)	χ^2=10.34	0.001
Metabolic acidosis	26 (26.53%)	70 (12.68%)	χ^2=12.44	<0.001

TABLE 2: Baseline laboratory characteristics according to treatment failure

WBC: white blood cell; IQR: interquartile range; CRP: C-reactive protein; χ^2: Pearson chi-squared test; t: independent-samples t-test; U: Mann-Whitney U test

Baseline radiological abnormalities were more frequent among patients who subsequently developed treatment failure (Table 3). Bilateral infiltrates (52.04% vs. 33.70%; p<0.001), multilobar involvement (62.24% vs. 40.76%; p<0.001), pleural effusion (34.69% vs. 19.75%; p=0.001), and cavitation (11.22% vs. 5.07%; p=0.018) were significantly more common in the treatment-failure group. Blood cultures were obtained more frequently among patients with treatment failure (62.24% vs. 47.10%; p=0.006), and among those who underwent blood culture testing, positive results were more frequent (26.23% vs. 15.77%; p=0.045). Sputum cultures were also obtained more frequently in the treatment-failure group (54.08% vs. 40.76%; p=0.015), whereas identification of a bacterial pathogen was not significantly different between groups (19.39% vs. 13.04%; p=0.099).

Variable	Treatment failure (n=98)	No treatment failure (n=552)	Test value	P-value
Bilateral infiltrates	51 (52.04%)	186 (33.70%)	χ^2=12.04	<0.001
Multilobar involvement	61 (62.24%)	225 (40.76%)	χ^2=15.43	<0.001
Pleural effusion	34 (34.69%)	109 (19.75%)	χ^2=11.36	0.001
Cavitation	11 (11.22%)	28 (5.07%)	χ^2=5.61	0.018
Blood culture obtained	61 (62.24%)	260 (47.10%)	χ^2=7.61	0.006
Positive blood culture	16 (26.23%)	41 (15.77%)	χ^2=4.02	0.045
Sputum culture obtained	53 (54.08%)	225 (40.76%)	χ^2=5.92	0.015
Identified bacterial pathogen	19 (19.39%)	72 (13.04%)	χ^2=2.73	0.099

TABLE 3: Baseline radiological and microbiological characteristics according to treatment failure

χ^2: Pearson chi-squared test

Percentages were calculated using the total number of patients in each treatment-outcome group, except for positive blood cultures, for which the denominator was the number of patients who underwent blood culture testing (61 and 260, respectively).

During hospitalization, 61 patients (62.24% of treatment-failure cases) developed early treatment failure,

and 37 (37.76%) developed late treatment failure (Table 4). Intensive care unit transfer occurred in 48 (48.98%) patients with treatment failure compared with 25 (4.53%) without failure (p<0.001), while escalation of oxygen or ventilatory support occurred in 79.59% versus 6.88%, respectively (p<0.001). Mechanical ventilation, septic shock, pleural complications/empyema, and radiological progression with clinical deterioration were also substantially more frequent among patients with treatment failure (all p<0.001). Patients with treatment failure had a longer median hospital stay (12 vs. 6 days; p<0.001) and higher in-hospital mortality (24.49% vs. 0.91%; p<0.001).

Outcome during hospitalization	Total (N=650)	Treatment failure (n=98)	No treatment failure (n=552)	Statistical tests	P-value
Early treatment failure (≤72 h)	61 (9.38%)	61 (62.24%)	0 (0%)	-	-
Late treatment failure (>72 h)	37 (5.69%)	37 (37.76%)	0 (0%)	-	-
Intensive care unit transfer	73 (11.23%)	48 (48.98%)	25 (4.53%)	χ^2=164.94	<0.001
Escalation of oxygen/ventilatory support	116 (17.85%)	78 (79.59%)	38 (6.88%)	χ^2=300.08	<0.001
Mechanical ventilation	48 (7.38%)	38 (38.78%)	10 (1.81%)	χ^2=166.26	<0.001
Septic shock	31 (4.77%)	27 (27.55%)	4 (0.72%)	χ^2=131.87	<0.001
Pleural complication/empyema	39 (6%)	25 (25.51%)	14 (2.54%)	χ^2=77.88	<0.001
Radiological progression with clinical deterioration	67 (10.31%)	58 (59.18%)	9 (1.63%)	χ^2=298.18	<0.001
Antimicrobial modification/escalation	154 (23.69%)	73 (74.49%)	81 (14.67%)	χ^2=164.71	<0.001
Length of hospital stay, days, median (IQR)	7 (5-10)	12 (9-17)	6 (4-8)	U=8,630	<0.001
In-hospital mortality	29 (4.46%)	24 (24.49%)	5 (0.91%)	χ^2=108.60	<0.001

TABLE 4: Clinical outcomes and in-hospital course according to treatment failure

χ^2: Pearson chi-squared test; U: Mann-Whitney U test; IQR: interquartile range

P-values for categorical variables were calculated using the Pearson chi-squared test, while length of hospital stay was compared using the Mann-Whitney U test. Early treatment failure was defined as occurring within 72 hours of initiating antimicrobial therapy, whereas late treatment failure occurred after 72 hours. These categories were descriptive subdivisions of the primary outcome; therefore, separate significance tests comparing them with patients without treatment failure were not applicable (-).

In univariable analysis, several baseline characteristics were significantly associated with treatment failure, including age ⩾65 years, chronic liver disease, altered mental status, SpO_2 <90% at admission, CURB-65 ⩾3, leukopenia, CRP >100 mg/L, creatinine >1.5 mg/dL, multilobar involvement, pleural effusion, cavitation, and broad-spectrum initial therapy (Table 5). In the multivariable model, independent associations remained for age ⩾65 years (aOR: 1.71; 95% CI: 1.04-2.81; p=0.034), chronic liver disease (aOR: 2.31; 95% CI: 1.12-4.76; p=0.023), altered mental status (aOR: 1.88; 95% CI: 1.03-3.44; p=0.040), SpO_2 <90% (aOR: 2.37; 95% CI: 1.46-3.85; p<0.001), CURB-65 ⩾3 (aOR: 2.42; 95% CI: 1.45-4.05; p=0.001), leukopenia (aOR: 1.89; 95% CI: 1.02-3.49; p=0.043), CRP >100 mg/L (aOR: 1.69; 95% CI: 1.05-2.73; p=0.031), multilobar involvement (aOR: 1.91; 95% CI: 1.17-3.12; p=0.009), and pleural effusion (aOR: 1.76; 95% CI: 1.03-3.00; p=0.038). Creatinine >1.5 mg/dL, cavitation, and broad-spectrum initial therapy were not independently associated with treatment failure after adjustment.

Predictor	Univariable OR (95% CI)	P-value	aOR (95% CI)	P-value
Age ≥65 years	2.25 (1.45-3.49)	<0.001	1.71 (1.04-2.81)	0.034
Male sex	1.39 (0.88-2.20)	0.167	1.27 (0.77-2.10)	0.352
Chronic liver disease	2.84 (1.45-5.58)	0.002	2.31 (1.12-4.76)	0.023
Altered mental status	2.71 (1.58-4.64)	<0.001	1.88 (1.03-3.44)	0.040
SpO_2 <90% at admission	3.14 (2.02-4.88)	<0.001	2.37 (1.46-3.85)	<0.001
CURB-65 ≥3	3.89 (2.45-6.17)	<0.001	2.42 (1.45-4.05)	0.001
Leukopenia	2.22 (1.27-3.89)	0.005	1.89 (1.02-3.49)	0.043
CRP >100 mg/L	2.08 (1.34-3.23)	0.001	1.69 (1.05-2.73)	0.031
Creatinine >1.5 mg/dL	2.23 (1.39-3.58)	0.001	1.61 (0.95-2.73)	0.075
Multilobar involvement	2.39 (1.53-3.73)	<0.001	1.91 (1.17-3.12)	0.009
Pleural effusion	2.16 (1.34-3.48)	0.002	1.76 (1.03-3.00)	0.038
Cavitation	2.36 (1.10-5.07)	0.028	1.82 (0.78-4.23)	0.164
Broad-spectrum initial therapy	1.74 (1.12-2.70)	0.013	1.29 (0.79-2.12)	0.305

TABLE 5: Univariable and multivariable logistic regression analysis of predictors of treatment failure

OR: odds ratio; CI: confidence interval; SpO_2: peripheral oxygen saturation; aOR: adjusted odds ratio; CRP: C-reactive protein

Adjusted estimates represent associations rather than causal effects. Age ≥65 years and altered mental status overlap with components of the CURB-65 score, potentially introducing multicollinearity and affecting the stability and interpretation of regression coefficients. These estimates should be interpreted cautiously until the corresponding multicollinearity diagnostics and model specification have been verified.

The final multivariable model demonstrated good discriminatory ability for treatment failure, with an AUC of 0.82 (95% CI: 0.78-0.86), shown in Table 6. The model was described as having acceptable calibration, indicating reasonable agreement between predicted and observed outcomes. The model was developed using the cohort of 650 patients, including 98 treatment-failure events.

Model parameter	Result
AUC	0.82
95% CI	0.78-0.86
Calibration assessment	Acceptable
Treatment-failure events	98
Total participants	650

TABLE 6: Performance of the final multivariable model

AUC: area under the receiver operating characteristic curve; CI: confidence interval

Discussion

A total of 98 patients in the present prospective cohort (15.1%) experienced treatment failure: 62.24% of the patients failed within 72 hours and 37.76% after 72 hours. This is similar to the frequency in hospitalized populations with CAP, but varies with the definition and duration of follow-up. A large secondary analysis of hospitalized patients with moderately severe CAP found a higher failure rate of 26.8%, but different outcome definition and patients who had become clinically stable by day 3 [15]. The relatively high proportion of early failures is also consistent with the clinical literature of the last 72 hours being crucial for the

recognition of deterioration and the response to treatment [6].

Older age was an important finding in our study: patients with treatment failure had a mean age of 64.9±15.8 years versus 57.6±17.2 years, and 58.16% versus 38.22% were aged ⩾65 years; age ⩾65 remained independently associated with failure (aOR: 1.71; 95% CI: 1.04-2.81; p=0.034). This is in line with Dinh et al., who found age to be independently associated with treatment failure in CAP patients in hospital who were clinically stable, with an aOR of 1.02 per year [15]. In another large study, conducted in China, of over 18,000 hospitalized adults, older age was independently associated with treatment failure [16]. The vulnerability may be greater, and the multimorbidity and reserve may be decreased in older hospitalized patients.

There were multiple clinical predictors of failure, each independently associated with failure. In our cohort, altered mental status (aOR: 1.88; 95% CI: 1.03-3.44), SpO_2 <90% (aOR: 2.37; 95% CI: 1.46-3.85), and CURB-65 ⩾3 (aOR: 2.42; 95% CI: 1.45-4.05) were significant predictors. These results are consistent with evidence highlighting the importance of hypoxemia, neurological dysfunction, and increased severity scores as predictors of subsequent deterioration. Gündüz et al. showed that treatment failure was related to higher PSI and CURB-65 scores and lower PaO_2/FiO_2 ratio and that PSI and oxygenation remained as independent risk factors [9]. The present results thus confirm that widely available indicators of admission severity have clinical relevance, especially in resource-poor environments.

Important associations were also found in the laboratory and inflammatory abnormalities. Patients with failure had higher median WBC counts (12.7×10^9/L vs. 10.5×10^9/L; p=0.006), lower platelet counts (184.3×10^9/L vs. 219.9×10^9/L; p<0.001), and higher CRP (132 mg/L vs. 79 mg/L) and procalcitonin (1.42 ng/mL vs. 0.61 ng/mL), with both biomarkers showing p<0.001. Leukopenia (aOR: 1.89; p=0.043) and CRP >100 mg/L (aOR: 1.69; p=0.031) were independent factors associated with failure. These results are very similar to previous biomarker studies that showed a correlation between increased CRP and procalcitonin levels at admission and treatment failure [17]. Martin-Loeches et al. also found elevated levels of CRP and procalcitonin in failure patients and found inflammatory biomarkers to predict early or late failure [18].

Another consistent predictor was radiological disease burden. Multilobar involvement (62.24% vs. 40.76% for failure and non-failure, respectively) and pleural effusion (34.69% vs. 19.75%, respectively) were both independently associated with failure (aOR: 1.91 (p=0.009) and aOR: 1.76 (p=0.038), respectively) in our study. The cavitation was important in univariable analysis but was no longer significant after adjustment (aOR: 1.82; p=0.164). In addition, Martin-Loeches et al. reported that pleural effusion was an independent predictor of early failure and multilobar involvement an independent predictor of late failure [18]. These results emphasize the need for patients to be evaluated for the anatomical severity and complications of PNA even at admission not only on clinical severity scores.

Last, failure was significantly associated with more adverse hospital outcomes, such as transfer to the intensive care unit (48.98% versus 4.53% of patients), mechanical ventilation (38.78% versus 1.81% of patients), septic shock (27.55% versus 0.72% of patients), and in-hospital mortality (24.49% versus 0.91% of patients), in our cohort; the median hospital stay was 12 versus 6 days. These results highlight the critical need for early recognition. Another large study conducted in 2013 also found that treatment failure was linked to increased hospitalization and mortality (8.5% vs. 3.3%) [19]. The final model in our study showed an AUC of 0.82 (95% CI: 0.78-0.86), which was deemed to be useful for discrimination. In summary, our results suggest that treatment failure is associated with older age, baseline physiological severity, inflammatory abnormalities, and higher radiological disease burden, which all warrant systematic assessment on admission and close monitoring during the first 72 hours.

Strengths and limitations

This study has several strengths, including its prospective cohort design, relatively large sample size of 650 patients, consecutive enrollment, standardized data collection, and prospective follow-up throughout hospitalization. The application of predefined treatment failure criteria and systematic evaluation of demographic, clinical, laboratory, radiological, microbiological, and initial treatment-related variables strengthened the assessment of factors associated with treatment failure. Furthermore, distinguishing early treatment failure (within 72 hours) from late treatment failure (after 72 hours) provided additional clinical insight into the timing of unfavorable outcomes. The study also contributes valuable evidence from a tertiary care hospital in Pakistan, where patient characteristics, antimicrobial resistance patterns, and healthcare resources may differ from those in other settings.

Nevertheless, several limitations should be acknowledged. The single-center observational design limits generalizability and does not permit causal inference, while residual confounding and treatment-selection bias cannot be entirely excluded. Although CAP was defined according to the timing of infection onset and diagnosis within 48 hours of admission, retrospective uncertainty regarding symptom onset or prior healthcare exposure may have introduced some patient misclassification. Potential multicollinearity between composite severity measures, particularly CURB-65, and overlapping predictors such as age and altered mental status may have influenced the stability of regression estimates despite statistical assessment. Microbiological investigations were performed according to clinical indications, potentially introducing diagnostic selection bias. Moreover, variations in antibiotic selection, dosing, duration, and

subsequent treatment modifications, determined by treating physicians and institutional practices, may have influenced treatment outcomes and limited assessment of individual antimicrobial regimens. The analysis was restricted to in-hospital outcomes, excluding post-discharge treatment failure. Finally, external validation in independent patient populations is necessary before the identified predictors can be reliably applied in broader clinical settings.

Conclusions

In this prospective cohort of 650 hospitalized adults with CAP, treatment failure occurred in 15.1% of patients. Advanced age, chronic liver disease, altered mental status, admission hypoxemia, elevated CURB-65 scores, leukopenia, increased CRP levels, multilobar involvement, and pleural effusion were independently associated with treatment failure in the fitted multivariable model. The model demonstrated good apparent discrimination (AUC: 0.82); however, potential multicollinearity among overlapping predictors, residual confounding, and the single-center observational design warrant cautious interpretation. These findings highlight clinically relevant characteristics associated with unfavorable in-hospital outcomes and may inform further risk assessment research. Independent external validation and evaluation of model calibration are necessary before considering clinical application.

Appendices

Section/parameter	Response/recorded value
Study identification	
Proforma no.	_____
Hospital/medical record no.	_____
Date of admission	_____
Date of discharge/death	_____
1. Eligibility and baseline information	
Age	_____ years
Sex	□ Male □ Female
Eligibility criteria	□ Age ≥18 years □ Clinical features of acute lower respiratory tract infection □ New pulmonary infiltrate on chest imaging □ Community-acquired pneumonia
Exclusion criteria	□ Hospital-acquired pneumonia □ Ventilator-associated pneumonia □ Active pulmonary tuberculosis □ Recent hospitalization □ Non-infectious pulmonary infiltrate as primary diagnosis □ Severe immunosuppression with predominantly non-infectious pulmonary disease □ Insufficient essential baseline data
2. Presenting clinical features	
Duration of illness before admission	_____ days
Presenting symptoms	□ Fever □ Cough □ Sputum production □ Dyspnea □ Pleuritic chest pain □ Hemoptysis □ Altered mental status □ Other: _____
Fever >3 days before admission	□ Yes □ No
Smoking status	□ Current smoker □ Former smoker □ Never smoker
Altered mental status at admission	□ Yes □ No
3. Comorbidities	
Diabetes mellitus	□ Yes □ No
Chronic respiratory disease	□ Yes □ No
Cardiovascular disease	□ Yes □ No

Chronic kidney disease	□ Yes □ No
Chronic liver disease	□ Yes □ No
Other significant comorbidity	□ Yes □ No; Specify: _____
4. Baseline clinical and physiological parameters	
Respiratory rate	_____ /min
Heart rate	_____ /min
Systolic BP	_____ mmHg
Diastolic BP	_____ mmHg
Temperature	_____ °C
SpO_2	_____ %
SpO_2 <90%	□ Yes □ No
Supplemental oxygen required	□ Yes □ No
Oxygen flow/device	_____
5. Pneumonia severity assessment	
CURB-65: Confusion/altered mental status	□ Yes □ No; Score: ___
CURB-65: Urea >7 mmol/L	□ Yes □ No; Score: ___
CURB-65: Respiratory rate ≥30/min	□ Yes □ No; Score: ___
CURB-65: BP <90 systolic or ≤60 diastolic	□ Yes □ No; Score: ___
CURB-65: Age ≥65 years	□ Yes □ No; Score: ___
Total CURB-65 score	_____ /5
CURB-65 ≥3	□ Yes □ No
PSI score	_____
PSI risk class	□ I □ II □ III □ IV □ V
6. Baseline laboratory investigations	
WBC count	_____ $\times 10^9$/L
Leukopenia	□ Yes □ No
Hemoglobin	_____ g/dL
Platelet count	_____ $\times 10^9$/L
CRP	_____ mg/L
Procalcitonin	_____ ng/mL
Serum creatinine	_____ mg/dL
Creatinine >1.5 mg/dL	□ Yes □ No
Serum sodium	_____ mmol/L
Serum potassium	_____ mmol/L

ALT	_____ U/L
AST	_____ U/L
Arterial/venous pH	_____
HCO_3^-	_____ mmol/L
Metabolic acidosis	□ Yes □ No
7. Baseline radiological findings	
Chest X-ray performed	□ Yes □ No
Chest CT performed	□ Yes □ No
Unilateral infiltrates	□ Yes □ No
Bilateral infiltrates	□ Yes □ No
Multilobar involvement	□ Yes □ No
Consolidation	□ Yes □ No
Pleural effusion	□ Yes □ No
Cavitation	□ Yes □ No
Other radiological abnormality	□ Yes □ No; Specify: _____
Site/lobes involved	_____
8. Microbiological assessment	
Blood culture obtained	□ Yes □ No
Blood culture result	□ No growth □ Positive □ Contaminant □ Pending/not available
Organism identified on blood culture	_____
Sputum/respiratory specimen obtained	□ Yes □ No
Sputum/respiratory culture result	□ No bacterial pathogen identified □ Bacterial pathogen identified □ Other: _____
Organism identified	_____
Other microbiological investigation	_____
9. Initial treatment	
Initial antimicrobial drug(s)	_____
Dose	_____
Route	_____
Frequency	_____
Initial antimicrobial category	□ Standard-spectrum therapy □ Broad-spectrum therapy □ Other: _____
Date/time antimicrobial therapy started	_____
Other initial supportive treatment	□ Supplemental oxygen □ IV fluids □ Bronchodilator □ Other: _____
10. Prospective follow-up	
SpO_2 (%)	Baseline: ___; 24 h: ___; 48 h: ___; 72 h: ___; Later: ___
Oxygen requirement	Baseline: ___; 24 h: ___; 48 h: ___; 72 h: ___; Later: ___

Respiratory rate	Baseline: ___; 24 h: ___; 48 h: ___; 72 h: ___; Later: ___
Ventilatory support	Baseline: ___; 24 h: ___; 48 h: ___; 72 h: ___; Later: ___
Blood pressure	Baseline: ___; 24 h: ___; 48 h: ___; 72 h: ___; Later: ___
Heart rate	Baseline: ___; 24 h: ___; 48 h: ___; 72 h: ___; Later: ___
Septic shock	Baseline: ___; 24 h: ___; 48 h: ___; 72 h: ___; Later: ___
11. Treatment failure assessment	
Treatment failure during hospitalization	□ Yes □ No
Date/time of treatment failure	_____
Type of treatment failure	□ Progressive respiratory failure □ Escalation of oxygen/ventilatory support □ Hemodynamic deterioration □ Septic shock □ Complicated parapneumonic effusion/empyema □ Radiological progression with clinical deterioration □ Death due to CAP □ Other: _____
Timing of treatment failure	□ Early (≤72 hours) □ Late (>72 hours)
Clinical details	_____
12. In-hospital clinical outcomes	
ICU transfer	□ Yes □ No; Date: _____
Escalation of oxygen/ventilatory support	□ Yes □ No
Mechanical ventilation	□ Yes □ No
Septic shock	□ Yes □ No
Pleural complication/empyema	□ Yes □ No
Radiological progression with clinical deterioration	□ Yes □ No
Antimicrobial modification/escalation	□ Yes □ No
Reason for antimicrobial modification/escalation	_____
Repeat radiological assessment performed	□ Yes □ No
Length of hospital stay	_____ days
Final in-hospital outcome	□ Discharged alive □ Referred/transferred □ Death
If death occurred, CAP considered primary cause	□ Yes □ No □ Uncertain
13. Final outcome classification and verification	
Final treatment failure classification	□ Yes □ No
Failure category	□ Early (≤72 h) □ Late (>72 h) □ Not applicable
Baseline data complete	□ Yes

Follow-up data complete	☐ Yes
Outcome verified from medical record	☐ Yes
Name/initials of data collector	_____
Date of completion	_____
Principal investigator's verification	_____

TABLE 7: Questionnaire for predictors of treatment failure in hospitalized patients with CAP

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BP: blood pressure; CAP: community-acquired pneumonia; CRP: C-reactive protein; CT: computed tomography; HCO_3^-: bicarbonate; ICU: intensive care unit; PSI: Pneumonia Severity Index; SpO_2: peripheral oxygen saturation; WBC: white blood cell

Credits: Nayab Shabir, Fareeha Maqbool, Sifat Ullah, Nauman Idrees, Abdul Salam, Rabbiya Shahzadi, Sajid Nawaz, Adnan Afzal, Laraib Fatima

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Acquisition, analysis, or interpretation of data: Abdul Salam, Nayab Shabir, Fareeha Maqbool, Sifat Ullah, Nauman Idrees, Rabbiya Shahzadi, Sajid Nawaz, Adnan Afzal, Laraib Fatima

Drafting of the manuscript: Abdul Salam, Nayab Shabir, Fareeha Maqbool, Nauman Idrees, Rabbiya Shahzadi, Sajid Nawaz, Adnan Afzal, Laraib Fatima

Critical review of the manuscript for important intellectual content: Abdul Salam, Nayab Shabir, Fareeha Maqbool, Sifat Ullah, Nauman Idrees, Rabbiya Shahzadi, Sajid Nawaz, Adnan Afzal, Laraib Fatima

Supervision: Fareeha Maqbool, Sifat Ullah

Concept and design: Sifat Ullah

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Hospital Research and Ethical Committee of Medical Teaching Institute (MTI)-Hayatabad Medical Complex issued approval 1042/PD/HMC/2024. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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