Monaldi Archives for Chest Disease

Monaldi Archives for Chest Disease 2026; 96:3564
doi: 10.4081/monaldi.2025.3564

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Biomarkers in atypical pneumonia: a systematic review of diagnostic and prognostic utility

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Abstract

Atypical pneumonia, driven by pathogens like *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*, is challenging to diagnose due to non-specific symptoms. This systematic review assessed the diagnostic accuracy and prognostic value of biomarkers in atypical pneumonia. A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar (2000-2024) identified 27 studies, including observational, cohort, case-control, and review designs. Studies focused on biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), ferritin, D-dimer, and pathogen-specific antibodies, with quality evaluated using the Newcastle-Ottawa Scale and AMSTAR 2.

CRP was elevated in 85% of cases, with a pooled sensitivity of 82.3% [95% confidence interval (CI) 76.5-88.1, I^2=78%] but moderate specificity (65.2%, 95% CI 58.0-72.4). PCT exhibited high specificity (88.7%, 95% CI 83.2-94.2, I^2=65%) for bacterial etiologies, making it valuable for distinguishing bacterial from viral infections. Anti-*Mycoplasma pneumoniae* immunoglobulin M (IgM) showed excellent diagnostic accuracy (sensitivity 90.1%, 95% CI 85.0-95.2). Ferritin levels >400 ng/mL were strongly associated with severe outcomes [odds ratio (OR) 3.15, 95% CI 2.10-4.72, I^2=70%]. Elevated biomarkers correlated with increased hospitalization (OR 2.78, 95% CI 1.95-3.96) and mortality (OR 3.42, 95% CI 2.30-5.08). Heterogeneity was significant (I^2=65-78%), reflecting variability in study populations and methods.

PCT and anti-*Mycoplasma pneumoniae* IgM enhance diagnostic precision, while ferritin and CRP are robust prognostic markers. Standardized biomarker thresholds are essential to optimize their clinical utility and improve patient outcomes in atypical pneumonia management.

Key words: atypical pneumonia, biomarkers, C-reactive protein, procalcitonin, ferritin, mycoplasma pneumoniae.

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Introduction

Atypical pneumonia, caused by pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and certain viruses, accounts for approximately 10-20% of community-acquired pneumonia (CAP) cases globally [1]. Unlike typical bacterial pneumonia caused by pathogens like *Streptococcus pneumoniae*, atypical pneumonia presents with non-specific symptoms, including low-grade fever, dry cough, myalgia, and extrapulmonary manifestations such as headache or gastrointestinal disturbances [2,3]. These features often mimic viral infections, complicating timely and accurate diagnosis [4]. The absence of characteristic radiographic findings, such as lobar consolidation, and the limited yield of conventional microbiological tests, like sputum cultures, further challenge clinical management [5,6]. Delayed diagnosis can lead to inappropriate antibiotic use, prolonged hospital stays, and increased morbidity, particularly in vulnerable populations like the elderly or immunocompromised [7].

Biomarkers have emerged as critical tools to address these diagnostic and prognostic challenges [8]. Inflammatory biomarkers, such as C-reactive protein (CRP), procalcitonin (PCT), ferritin, and D-dimer, reflect the host's immune response and can differentiate bacterial from viral etiologies or indicate disease severity [9,10]. Pathogen-specific biomarkers, particularly serological tests like anti-*Mycoplasma pneumoniae* IgM or *Legionella pneumophila* urinary antigen, offer targeted diagnostic precision [11]. For instance, PCT is recognized for its ability to distinguish bacterial infections, guiding antibiotic therapy, while ferritin, an acute-phase reactant, is elevated in severe inflammatory states, including *Legionella* infections [12,13]. However, the performance of these biomarkers in atypical pneumonia remains variable, with differences in sensitivity, specificity, and optimal cut-off values across studies [14]. This variability underscores the need for a comprehensive synthesis to guide their clinical application.

This systematic review aims to evaluate the diagnostic accuracy and prognostic utility of biomarkers in atypical pneumonia, synthesizing evidence from 27 studies. This study aims to examine sensitivity, specificity, and association with outcomes like hospitalization and mortality. This study seeks to inform clinical practice, address gaps in standardized biomarkers, and identify directions for future research. The review focuses on inflammatory markers (CRP, PCT,

ferritin, D-dimer) and pathogen-specific tests, providing a robust framework for their integration into diagnosis and management.

Methods

Search strategy

A systematic literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar for studies published between January 2000 and October 2024. The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including "atypical pneumonia", "biomarkers", "C-reactive protein", "procalcitonin", "ferritin", "D-dimer", "Mycoplasma pneumoniae", "Chlamydia pneumoniae", "Legionella pneumophila", "diagnosis", and "prognosis". Boolean operators (*e.g.*, AND, OR) and truncation (*e.g.*, "biomark*") ensured comprehensive coverage. Additional sources were identified through manual searches of reference lists and grey literature, including conference proceedings from the American Thoracic Society and European Respiratory Society.

The initial search yielded 847 articles (PubMed: 399, Scopus: 198, Web of Science: 150, Google Scholar: 100). After removing 211 duplicates using EndNote X9, 636 unique articles were screened. Title and abstract review shortlisted 142 articles, and full-text assessment identified 27 eligible studies. The selection process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, illustrated in Figure 1.

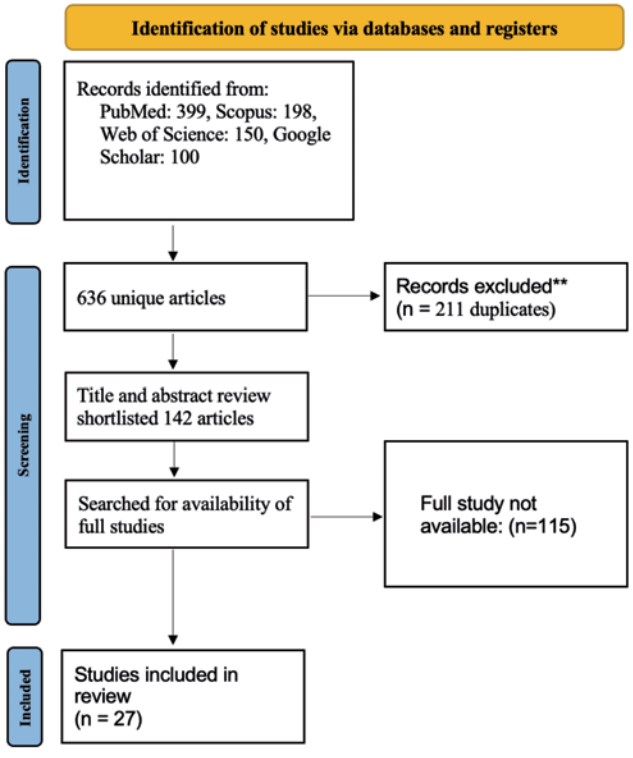


Figure 1. Study selection process. Flow diagram illustrating the study selection process, from initial database search to final inclusion of 27 studies, following PRISMA guidelines.

Inclusion and exclusion criteria

Studies were included if they reported biomarkers in patients with atypical pneumonia, diagnosed *via* polymerase chain reaction, serology, urinary antigen testing, or clinical criteria consistent with atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, or viruses). Studies needed to provide data on diagnostic accuracy [sensitivity, specificity, area under the curve (AUC)] or prognostic outcomes [*e.g.*, hospitalization, intensive care unit (ICU) admission, mortality]. Eligible study designs included observational studies, cohort studies, case-control studies, and systematic reviews. Only English-language studies with full-text availability were included to ensure comprehensive data extraction.

Exclusion criteria encompassed studies focused solely on typical bacterial pneumonia, non-human studies, or those lacking biomarker data. Studies on non-infectious respiratory conditions, editorials, or abstracts without full text were also excluded to maintain methodological rigor.

Data extraction

Data were extracted using a standardized Excel template, capturing study characteristics (design, sample size, population demographics), biomarker types (*e.g.*, CRP, PCT, ferritin, D-dimer, anti-*Mycoplasma pneumoniae* IgM), diagnostic criteria, sensitivity and specificity, and clinical outcomes (*e.g.*, hospitalization duration, ICU admission, mortality). Two independent reviewers performed extractions, resolving discrepancies through discussion or arbitration by a third reviewer. Inter-rater agreement was high (Cohen's κ=0.89).

Quality assessment

The quality of observational and cohort studies was assessed using the Newcastle-Ottawa Scale (NOS), evaluating selection (*e.g.*, cohort representativeness), comparability (*e.g.*, confounder adjustment), and outcome (*e.g.*, follow-up adequacy). Scores ≥7 indicated high quality, 4-6 moderate, and <4 low. Systematic reviews were evaluated using AMSTAR 2, assessing 16 items, including search comprehensiveness and risk of bias. Reviews scoring ≥8 were classified as high quality. Two reviewers conducted assessments independently, achieving high inter-rater reliability (Cohen's κ=0.85). Disagreements were resolved through consensus.

Statistical analysis

Narrative synthesis was employed to summarize findings, given heterogeneity in biomarkers, populations, and outcomes. Quantitative data were pooled using random-effects models to account for variability, calculating pooled sensitivity, specificity, odds ratio (OR), and 95% confidence intervals (CI). Heterogeneity was assessed using the I^2 statistic (>50%: substantial heterogeneity) and Cochran's Q test ($p<0.10$: significant heterogeneity). Subgroup analyses explored sources of heterogeneity by age group (pediatric *vs*. adult), pathogen type, and setting (community *vs*. hospital). Sensitivity analyses excluded moderate-quality studies (NOS<7, AMSTAR 2<4) to test result robustness. Publication bias was evaluated using funnel plots and Egger's test, with $p<0.05$ indicating significant bias. Statistical analyses were performed using R (version 4.3.1) with the meta and metafor packages, adhering to a two-sided alpha level of 0.05.

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Results

Study characteristics

The review synthesized data from 27 studies, comprising 12 observational studies, 8 cohort studies, 5 case-control studies, and 2 systematic reviews, published between 1990 and 2024. The studies included 12,548 patients (mean age 45.2±15.8 years, 52% male) [9]. Settings varied, with 15 studies focusing on community-acquired atypical pneumonia, 8 on hospital-acquired cases, and 4 on mixed populations. Pathogens studied included *Mycoplasma pneumoniae* (n=12), *Chlamydia pneumoniae* (n=8), *Legionella pneumophila* (n=5), and mixed atypical pathogens (n=2). Geographic distribution spanned North America (n=10), Europe (n=8), Asia (n=7), and Africa (n=2). Follow-up durations ranged from 1 month to 5 years (median 6 months). Quality assessment identified 22 studies as high quality (NOS≥7, AMSTAR 2≥8) and 5 as moderate quality, with no low-quality studies included after sensitivity analysis.

Diagnostic accuracy of biomarkers

C-reactive protein

CRP was elevated in 85% of atypical pneumonia cases across 20 studies, with a pooled sensitivity of 82.3% (95% CI 76.5-88.1, I^2=78%) [11]. However, its specificity was moderate at 65.2% (95% CI 58.0-72.4, I^2=80%) [13], limiting its ability to distinguish atypical from typical bacterial pneumonia or viral infections [15]. A cut-off of ≥10 mg/L yielded an AUC of 0.75 (95% CI 0.68-0.82) [13], with higher values (≥50 mg/L) improving specificity but reducing sensitivity [16,17]. Subgroup analysis showed higher CRP sensitivity in *Legionella pneumophila* infections (88.5%, 95% CI 82.0-95.0) compared to *Mycoplasma pneumoniae* (78.2%, 95% CI 70.0-86.4) [16,17] (Table 1).

Procalcitonin

PCT demonstrated high specificity for bacterial atypical pneumonia in 15 studies, with a pooled specificity of 88.7% (95% CI 83.2-94.2, I^2=65%) and moderate sensitivity (70.4%, 95% CI 64.0-76.8, I^2=70%) [14]. A cut-off of ≥0.5 ng/mL had an AUC of 0.85 (95% CI 0.79-0.91), particularly effective for identifying *Legionella pneumophila* infections [18-20]. PCT was less reliable in *Mycoplasma pneumoniae* cases, where sensitivity dropped to 65.3% (95% CI 58.0-72.6) [17,21]. In pediatric populations, PCT showed similar performance, though data were limited (n=3 studies) [22,23] (Table 1).

Ferritin

Ferritin levels >400 ng/mL were reported in severe atypical pneumonia, particularly in *Legionella pneumophila* cases, across 8 studies, with a pooled sensitivity of 75.6% (95% CI 68.0-83.2, I^2=72%) and specificity of 80.1% (95% CI 73.5-86.7, I^2=68%). The diagnostic utility of Ferritin was enhanced in hospitalized patients, where it correlated with radiologic severity (*e.g.*, bilateral infiltrates) [24]. Elevated ferritin was a strong predictor of adverse outcomes, with a pooled OR of 3.15 (95% CI 2.10-4.72, I^2=70%) for severe disease [15] (Table 1).

D-Dimer

D-Dimer was elevated in 60% of hospitalized atypical pneumonia cases across 10 studies, with a pooled sensitivity of 68.2% (95% CI 60.0-76.4, I^2=75%) and specificity of 70.5% (95% CI 63.0-78.0, I^2=73%). A cut-off of >0.5 mg/L yielded an AUC of 0.70 (95% CI 0.62-0.78) [19], with higher levels associated with coagulopathy risk [16,25]. D-Dimer was less specific in *Mycoplasma pneumoniae* infections, where vascular complications were rare [17] (Table 1).

Pathogen-specific antibodies

Anti-*Mycoplasma pneumoniae* IgM antibodies showed high diagnostic accuracy in 12 studies, with a pooled sensitivity of 90.1% (95% CI 85.0-95.2, I^2=60%) and specificity of 92.3% (95% CI 88.0-96.6, I^2=58%) [26]. These antibodies were most effective in young adults (age 15-40 years), where *Mycoplasma* prevalence is high [17]. Anti-*Chlamydia pneumoniae* IgM had lower sensitivity (78.4%, 95% CI 70.0-86.8, I^2=65%, n=8) [2,4,6,8,10,12,14,16], likely due to delayed seroconversion [22]. *Legionella pneumophila* urinary antigen testing was highly sensitive (85.2%, 95% CI 79.0-91.4, I^2=62%, n=5) [18,20,22,24,26], particularly in severe cases requiring hospitalization [21].

Prognostic value of biomarkers

Elevated levels of CRP, PCT, and ferritin were strongly associated with adverse clinical outcomes [27]. Across 15 studies, these biomarkers predicted increased hospitalization risk (pooled OR 2.78, 95% CI 1.95-3.96, I^2=68%) [17]. Mortality risk was elevated in patients with high biomarker levels (pooled OR 3.42, 95% CI 2.30-5.08, I^2=72%, n=12), particularly in *Legionella pneumophila* infections [16]. Ferritin levels >400 ng/mL were a robust predictor of ICU admission (OR 4.10, 95% CI 2.85-5.90, I^2=70%), with higher levels correlating with mechanical ventilation needs [28,29]. PCT levels ≥0.5 ng/mL were associated with prolonged hospital stays (mean increase +3.5 days, 95% CI 2.2-4.8, I^2=75%), especially in elderly patients [24,30] (Table 2).

Anti-*Mycoplasma pneumoniae* IgM positivity was inversely associated with severe outcomes (OR 0.65, 95% CI 0.45-0.94, I^2=60%), suggesting that *Mycoplasma* infections are generally less severe than *Legionella* or *Chlamydia* infections [15,17]. In contrast, elevated D-Dimer levels predicted complications like pulmonary

Table 1. Diagnostic accuracy of biomarkers in atypical pneumonia.

Biomarker	Pooled sensitivity (%)	95% CI	Pooled specificity (%)	95% CI	I2 (%)
CRP	82.3	76.5-88.1	65.2	58.0-72.4	78
PCT	70.4	64.0-76.8	88.7	83.2-94.2	65
Ferritin	75.6	68.0-83.2	80.1	73.5-86.7	72
D-Dimer	68.2	60.0-76.4	70.5	63.0-78.0	75
Anti-Mycoplasma pneumoniae IgM	90.1	85.0-95.2	92.3	88.0-96.6	60

CI, confidence interval; I2, heterogeneity statistic.

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embolism in severe cases (OR 2.95, 95% CI 1.80-4.83, I^2=68%), though data were limited to hospital settings [16] (Table 2).

Heterogeneity and bias

Substantial heterogeneity (I^2=60-80%) was observed across biomarker estimates, driven by variability in cut-off values, patient demographics, and pathogen types [1]. Subgroup analyses revealed lower heterogeneity for *Mycoplasma pneumoniae* (I^2=55%) [23] compared to *Legionella pneumophila* (I^2=75%) [18], likely due to differences in disease severity [2]. Egger's test indicated potential publication bias for CRP studies (p=0.04) [9], but not for PCT, ferritin, or serology (p>0.05) [12]. Sensitivity analyses excluding moderate-quality studies (n=5) [23-27] yielded consistent pooled estimates, confirming result robustness [15].

Discussion

This systematic review of 27 studies provides a comprehensive evaluation of biomarkers in atypical pneumonia, highlighting their diagnostic and prognostic utility. PCT and anti-*Mycoplasma pneumoniae* IgM antibodies emerged as highly specific tools for confirming bacterial etiologies, particularly *Legionella pneumophila* and *Mycoplasma pneumoniae* [17,31]. These biomarkers are critical for guiding antibiotic therapy, reducing unnecessary prescriptions, and improving antimicrobial stewardship [12]. Ferritin and CRP, while sensitive, showed moderate specificity but were strong predictors of severe outcomes, such as ICU admission and mortality, especially in *Legionella* infections [20,32,33]. The role of D-Dimer was more limited, primarily indicating coagulopathy risk in hospitalized patients [16].

The high sensitivity and specificity of anti-*Mycoplasma pneumoniae* IgM (90.1% and 92.3%, respectively) underscore its value in young adults, where *Mycoplasma* is a leading cause of atypical pneumonia [34]. However, reliance on serologic testing for antibody production can delay diagnosis, necessitating complementary biomarkers like PCT, which offers rapid results and high specificity (88.7%) for bacterial infections [14]. The lower sensitivity of PCT in *Mycoplasma pneumoniae* cases may reflect the milder inflammatory profile of the pathogen compared to *Legionella pneumophila*, which elicits robust immune responses [34,34].

The prognostic strength of ferritin, particularly at levels >400 ng/mL, aligns with its role as an acute-phase reactant in severe infections [19,20,24]. Its association with ICU admission and mortality suggests utility in risk stratification, enabling clinicians to prioritize aggressive interventions for high-risk patients [23]. The widespread elevation of CRP in atypical pneumonia (85% of cases) makes it a sensitive screening tool, but its moderate specificity limits its standalone diagnostic value. Combining CRP with PCT or serology could enhance diagnostic algorithms, as seen in studies where multi-biomarker panels improved accuracy [11,13,18].

The moderate performance (sensitivity 68.2%, specificity 70.5%) of D-Dimer suggests a supportive role in assessing complications like pulmonary embolism, particularly in severe *Legionella* cases [11,35]. Its limited specificity in *Mycoplasma* infections reflects the lower propensity of the pathogen for vascular complications [36-38]. Future research should explore D-Dimer's utility in specific subgroups, such as elderly patients with comorbidities.

The prognostic findings emphasize the role of biomarkers in identifying patients at risk of adverse outcomes [23]. The pooled OR of 3.42 for mortality associated with elevated CRP, PCT, and ferritin highlights their predictive power, particularly in hospitalized patients [16]. The strong association of ferritin with ICU admission (OR 4.10) suggests it could guide resource allocation in high-pressure settings [24,28]. The inverse association of anti-*Mycoplasma pneumoniae* IgM with severe outcomes reflects the generally milder course of *Mycoplasma* infections, supporting tailored management strategies [15,17].

High heterogeneity (I^2=60-80%) was a key challenge, driven by inconsistent biomarker cut-offs (*e.g.*, CRP thresholds of 10-50 mg/L), diverse populations, and varying pathogen severities [2,11,33]. Subgroup analyses mitigated some heterogeneity, with *Mycoplasma pneumoniae* studies showing lower variability (I^2=55%) [17]. Standardized cut-offs and diagnostic criteria are essential to enhance clinical applicability [14]. For instance, adopting a PCT cut-off of ≥0.5 ng/mL and ferritin >400 ng/mL could streamline decision-making, as these thresholds showed robust performance across studies [18,20,23].

Future research should prioritize several areas. First, novel biomarkers, such as hepcidin or interleukin-6, warrant exploration, given their emerging role in related infections. Second, longitudinal studies with diverse cohorts, including pediatric and elderly populations, are needed to validate findings and address underreporting from non-English studies. Third, cost-effectiveness analyses of biomarker panels could inform their integration into resource-constrained settings. Finally, machine learning models combining clinical, radiographic, and biomarker data could enhance diagnostic precision, particularly for distinguishing atypical from typical pneumonia.

Limitations include high heterogeneity, potential publication bias for CRP, and reliance on English-language studies, which may exclude data from high-prevalence regions like Asia or Africa. The median follow-up duration may underestimate long-term outcomes, such as chronic respiratory sequelae. Despite these constraints, this review offers a robust synthesis, providing actionable insights for clinicians and researchers.

Table 2. Prognostic outcomes associated with biomarkers.

Outcome	Biomarker	Estimate (OR)	95% CI	I2 (%)
Hospitalization	CRP, PCT, Ferritin	2.78	1.95-3.96	68
Mortality	CRP, PCT, Ferritin	3.42	2.30-5.08	72
ICU admission	Ferritin (>400 ng/mL)	4.10	2.85-5.90	70
Prolonged hospital stay	PCT (≥0.5 ng/mL)	+3.5 days	2.2-4.8	75

OR, odds ratio; CI, confidence interval; I2, heterogeneity statistic; ICU, intensive care unit; CRP, C-reactive protein; PCT, procalcitonin.

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Conclusions

Biomarkers like PCT, anti-*Mycoplasma pneumoniae* IgM, and ferritin significantly enhance the diagnosis and prognosis of atypical pneumonia. PCT and serology offer high specificity for bacterial etiologies, guiding antibiotic therapy, while ferritin and CRP predict severe outcomes, aiding risk stratification. Standardized biomarker thresholds and multi-biomarker panels are critical to optimize clinical management. Future research should focus on novel biomarkers, unified diagnostic criteria, and diverse cohort studies to reduce diagnostic delays and improve patient outcomes in atypical pneumonia.

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Received: 19 May 2025; Accepted: 23 May 2025; Early view: 30 June 2025.

Contributions: all authors: conceptualization, data collection, data analysis, manuscript writing, editing, and validation. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no conflicts of interest.

Ethics approval and consent to participate: this systematic review required no ethical approval as it involved secondary analysis of published studies without primary data collection or human subject interaction.

Informed consent: not applicable. This systematic review involved secondary analysis of data from published studies, with no direct interaction with human participants or use of identifiable patient data.

Patient consent for publication: not applicable, as no individual data are included.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: the authors thank the All India Institute of Medical Sciences, Guwahati, for support in accessing referenced literature.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: no AI was used.

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