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Insights into the diagnostic and prognostic value of paraoxonase 1-related variables and inflammatory markers in community-acquired pneumonia

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ABSTRACT

Community-acquired pneumonia (CAP) remains a major health concern, with oxidative stress and inflammation playing key roles in its pathophysiology. This study examines the potential of paraoxonase-1 (PON1)-related variables as biomarkers for diagnosing and managing CAP. A prospective case-control study included 78 patients with community-acquired pneumonia (CAP) who were hospitalized and 80 healthy controls. Serum PON1 concentration (PON1c), PON1 arylesterase (ARE) and paraoxonase (PARX) activities, and inflammatory markers (C-reactive protein, procalcitonin, and C–C motif chemokine ligand 2 were measured and compared with lipid profiles and clinical severity scores. Receiver operating characteristic curve analysis was used to assess their diagnostic and prognostic value. CAP patients exhibited significantly lower ARE and PARX activities but higher PON1c levels than controls, with these changes correlating with increased inflammatory markers and decreased total and high-density lipoprotein cholesterol concentrations. PON1-related variables demonstrated strong diagnostic accuracies (areas under the curve >0.90), outperforming traditional inflammatory markers. However, although these variables provided insights into disease severity and pathophysiology, their prognostic value and ability to differentiate microbial etiologies were limited. These findings suggest that PON1-related variables may serve as promising diagnostic biomarkers for CAP, but their role in prognosis and guiding antimicrobial therapy requires further investigation. Future studies should validate these results in larger and more diverse populations while exploring the mechanistic involvement of PON1 in CAP progression.

1. Introduction

Pneumonia is a severe respiratory infection that primarily affects the lungs and can be caused by various pathogens, including bacteria, viruses, and fungi [1]. It is classified as either community-acquired (CAP) or hospital-acquired. CAP is a paramount public health concern, with global annual incidence rates ranging from 1.6 to 13.4 cases per 1,000 people [2,3]. This disease is the most common infection leading to hospitalization, with around 40 % of affected individuals requiring inpatient care and about 10 % of those being admitted to Intensive Care Units (ICUs). Mortality rates vary, from approximately 2 % among outpatients to as high as 14 % in those hospitalized [4]. In 2014, the World Health Organization reported that lower respiratory tract infections, including pneumonia, ranked the third leading cause of death globally and the second leading cause of lost life expectancy [5].

Despite advancements in medical treatments, CAP continues to pose a major challenge, particularly for high-risk groups such as children, older people, and individuals with weakened immune systems [3]. Timely and accurate diagnosis, prognosis, and monitoring are essential for effectively managing pneumonia. However, traditional diagnostic

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tools such as sputum cultures and chest radiographs have notable limitations, including low accuracy, invasiveness, and delayed results. Clinical scoring systems, such as CURB-65 (which includes Confusion, Urea >7 mmol/L, Respiratory rate ≥30/min, low Blood pressure, and age ≥65 years) and the Pneumonia Severity Index (PSI), are widely used to assess pneumonia severity and guide management; however, both have significant drawbacks. CURB-65 may oversimplify complex clinical scenarios by excluding comorbidities and microbiological factors. Conversely, the PSI provides a more comprehensive assessment but is time-consuming and may overestimate risk in older patients due to its age-weighted scoring, potentially leading to unnecessary hospitalizations [6–8]. These challenges underscore the increasing demand for non-invasive biomarkers that provide faster, more accurate, and patient-friendly solutions for diagnosing and managing pneumonia [9]. A promising avenue of research focuses on identifying biomarkers in peripheral circulation, particularly molecules associated with infection-induced effects, such as oxidative stress, inflammatory responses, and components of the innate and adaptive immune systems [10,11]. C-reactive protein (CRP) and procalcitonin (PCT) are the most commonly utilized biomarkers in clinical settings. CRP, a hepatic acute-phase reactant, is synthesized in response to pro-inflammatory cytokines, primarily interleukin-6, which promotes the transcription of its mRNA. Consequently, circulating CRP concentrations serve as an indirect measure of hepatic output and, by extension, the magnitude of the inflammatory response. In contrast, PCT, a precursor of calcitonin, is synthesized systemically during bacterial infections due to the upregulation of the calcitonin gene. This process leads to PCT secretion primarily by monocytes and macrophages within the liver, lungs, and gastrointestinal tract [12–14]. However, despite their widespread clinical use, the diagnostic and prognostic value of these biomarkers in lung diseases remains modest, highlighting the ongoing need for more reliable markers [15].

Infections often result in oxidative stress, which impairs mitochondrial function and further increases free radical production [16]. The body's innate immune defenses include mechanisms to mitigate oxidative stress, with paraoxonase-1 (PON1) crucial in this process. This enzyme, primarily produced in the liver, circulates in the bloodstream bound to high-density lipoproteins (HDL) and degrades harmful lipoperoxides in both lipoproteins and cells. This function of PON1 makes it a potential biomarker for assessing oxidative stress and inflammation levels in the organism [17,18]. PON1 is a promiscuous enzyme with multiple catalytic activities, including the hydrolysis of aryl esters (arylesterase activity, ARE) and organophosphates such as paraoxon (paraoxonase activity, PARX). Both genetic and environmental factors influence their activity and concentration. Notably, common single nucleotide polymorphisms, such as Q192R and L55 M, have a substantial impact on PARX activity, whereas ARE activity is less affected. These polymorphisms result in distinct phenotypes with varying enzymatic efficiencies, which may influence individual susceptibility to oxidative stress and inflammation [19]. Previous studies have demonstrated that serum PON1 activity is lower in patients with bacterial or viral infections compared to healthy individuals, with these reductions closely associated with immune responses and inflammation [20–24]. Furthermore, we previously proposed that HDL cholesterol levels could be a valuable biomarker for evaluating the acute-phase response in CAP patients, predicting clinical outcomes, and identifying complications [25]. A reduction in PON1 activity is frequently linked to increased synthesis of C–C motif chemokine ligand 2 (CCL2). This chemokine drives the migration and infiltration of monocytes into target tissues, where they differentiate into macrophages and amplify inflammatory responses [18].

Our study examines the changes in PON1-related variables, CRP, PCT, CCL2, and clinical outcomes in CAP patients, presenting preliminary data on their potential as indicators of diagnosis and treatment response.

2. Materials and methods

2.1. Participants and study design

We conducted a prospective case-control study involving 78 patients hospitalized for the treatment of CAP in the Department of Internal Medicine of Hospital Universitari de Sant Joan between January 1, 2017, and December 30, 2019. CAP was defined as an acute illness characterized by two or more clinical signs, including fever, chills, cough, sputum production, pleuritic chest pain, and lung consolidation, along with a chest X-ray showing an infiltrate consistent with pneumonia [26]. A binary sex categorization (male/female) was designated at birth. The inclusion criteria required patients to be 18 years or older with a confirmed diagnosis of CAP at discharge. Patients who did not meet these criteria or had nosocomial pneumonia were excluded from the study.

Blood samples were collected from all included patients at admission, and medical data were systematically recorded. These data comprised demographic information, comorbidities, clinical findings, vital signs, microbiology results, clinical course during hospitalization, and follow-up at 30 and 90 days post-discharge. Lung injury was evaluated by an expert radiologist and was classified into three categories: mild (1), moderate (2), and severe (3). The PSI considers 20 different clinical and laboratory factors, such as vital signs, blood test results, and underlying health conditions. Based on these factors, PSI classifies patients into five categories, ranging from low to high risk of complications and mortality [27]. The CURB-65 score predicts the risk of death from pneumonia using the five key indicators described above. Patients were classified into three risk categories: low, moderate, or high [28]. In addition to these scores, we measured the Charlson Comorbidity Index, which estimates a patient's 10-year survival based on the presence of eight medical conditions [29].

Table 1 summarizes commonly prescribed medications for CAP and its frequent comorbidities, highlighting their reported effects on PON1 activity based on available experimental and clinical evidence [30–36].

For the control group, we used serum samples from 80 healthy individuals who had no clinical or biochemical signs of infectious diseases, diabetes mellitus, renal insufficiency, liver conditions, cancer, or neurological disorders and were as matched as possible with the patients with respect to age, sex, and smoking status. Their samples were collected before the COVID-19 pandemic as part of a study conducted by our University's Epidemiology Department, which targeted a healthy population. Participants were recruited through telephone interviews based on data from municipal censuses in the region. Each individual completed a clinical interview, underwent basic laboratory testing, and was confirmed to be free from any health conditions that could potentially affect the study's results [37].

Sera and EDTA plasma aliquots from both CAP patients and the control group were stored under optimal conditions at −80 °C in the Biobank of the Institut d'Investigació Sanitària Pere Virgili until batched

Table 1
Medications used in the present study and their reported effects on paraoxonase-1 (PON1) activity.

Drug Class	Influence on PON1	Reference
Cephalosporins	Inhibitory effect *in vitro*	[30]
Amoxicillin	No reported data.	
Clavulanic acid	No reported data.	
Macrolides	Inhibitory effect *in vitro*.	[31]
Quinolones	Inhibitory effect *in vitro*.	[30]
Corticoids	Contradictory data.	[32,33]
ACE inhibitors	No evident effect.	[34]
Beta-blockers	Limited data suggest an increase.	[35,36]
Statins	Increased activity in humans.	[34]
Aspirin	Increased activity in humans.	[34]

ACE: Angiotensin-converting enzyme.

analyses were performed. Our hospital's Clinical Research Ethics Committee approved the study with reference CEIm: 081/2020 for the infected patients and CEIm: 222/2020 for the control group. The investigation was conducted in accordance with our institution's guidelines and the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all the study participants.

2.2. Microbiological diagnosis of pneumonia

We followed the recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology [38]. Two sets of aerobic and anaerobic blood culture bottles were obtained. For sputum, tracheal aspirates, and bronchoalveolar lavage samples, only those having leukocytes and scant or no squamous epithelial cells on Gram stain were accepted for culture. Bacterial counts were considered significant when they reached or exceeded 10^9 cfu/L in tracheal aspirates or 10^7 cfu/L in bronchoalveolar lavage samples. Additionally, urinary antigen fluorescence tests were used to detect *Streptococcus pneumoniae* and *Legionella pneumoniae*.

Fungal identification was carried out using selective Sabouraud-chloramphenicol agar. The diagnosis of pneumonia caused by mycobacteria involved smear microscopy with Ziehl-Neelsen and auramine-rhodamine stains, culture on solid Löwenstein-Jensen medium and liquid medium using an automated BacT/Alert® system, and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* in selected cases. Serum immunoglobulin G and M tests for atypical bacteria, including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Coxiella burnetii*, and *Chlamydia psittaci*, were performed using enzyme immunoassay. Detection of influenza virus was conducted using PCR on nasopharyngeal samples, while Pneumocystis jirovecii was identified using PCR on bronchoalveolar lavage samples.

2.3. Analytical measurements

Serum ARE activity was measured by tracking the enzymatic hydrolysis of phenylacetate (Sigma-Aldrich, St. Louis, MO, USA) at 270 nm ($\varepsilon = 1310\ M^{-1}\ cm^{-1}$) and a temperature of 25 °C. The assay was performed in 96-well microplates using a buffered solution containing 9 mM Tris–HCl (pH = 8.0) and 0.9 mM $CaCl_2$ [39]. The serum was diluted 1:80, and 20 μL of the diluted serum was added to each well, resulting in a final volume of 200 μL. Absorbance was recorded every 40 s for 4 min. Activity was expressed in U/L. Serum PARX activity was determined by monitoring the hydrolysis of paraoxon (Sigma-Aldrich) at 410 nm ($\varepsilon = 17{,}100\ M^{-1}\ cm^{-1}$) and 37 °C in a buffered solution composed of 0.05 M glycine (pH = 10.5) with 1 mM $CaCl_2$ [40–42]. The reaction was carried out in 96-well microplates with serum diluted 1:50. A volume of 50 μL of diluted serum was added to each well, resulting in a total reaction volume of 200 μL. Activity was expressed in U/L. Due to the toxicity and volatility of paraoxon, all assays were conducted in a fume hood with the operator wearing appropriate personal protective equipment. Serum PON1 concentrations (PON1c) were determined using a previously established in-house ELISA developed with antibodies raised in rabbits against the CRNHQSSYQTRLNALREVQ peptide from mature human PON1 [43,44]. Serum samples were diluted 1:500 in 0.05 M sodium carbonate buffer and incubated overnight at room temperature in 96-well microplates alongside a standard curve prepared from serial dilutions (1:80 to 1:10,240) of a freshly thawed PON1 standard. After blocking with PBS containing 1 % BSA, plates were incubated with a primary rabbit anti-PON1 antibody (1:5000), followed by a horseradish peroxidase-conjugated anti-rabbit secondary antibody (1:2500). Color development was achieved using 3,3′,5,5′-tetramethylbenzidine (Sigma-Aldrich) as the substrate, and the reaction was stopped with 2 M sulfuric acid. Absorbance was measured at 450 nm, and PON1 concentrations were calculated based on the standard curve. Results were expressed in mg/L. Specific activities of ARE and PARX were then calculated by dividing each enzymatic activity by the respective PON1 concentration. Plasma CCL2 levels were measured by enzyme-linked immunosorbent assay (Peprotech, London, UK). All PON1-related variables and CCL2 were analyzed in a Biotek Synergy HT Multi-Mode Microplate Reader (Thermo Fisher Scientific, Waltham, MS, USA), and the intra- and inter-assay coefficients of variation for all these measurements were below 10 %. Samples were randomly distributed among plates. Serum CRP concentrations were quantified using a latex-enhanced immunoturbidimetric assay on a COBAS® c702 automated analyzer (Roche Diagnostics, Basel, Switzerland). Serum PCT concentrations were analyzed by electrochemiluminescence immunoassay in a COBAS® e411 automated analyzer (Roche Diagnostics). Standard biochemical and hematological analyses were conducted on COBAS® 8000 (Roche Diagnostics), and Sysmex XN-1000TM (Sysmex GmbH, Norderstedt, Germany) automated analyzers. Automated analyzers ensured standardization and minimized technical variability. All measurements were performed using the same batch of reagents and under identical conditions to minimize batch effects. This overall approach was designed to control for potential variability related to the storage or handling of frozen biobank samples.

2.4. Statistical analyses

Quantitative data are presented as medians and 95 % confidence intervals, and differences were assessed with the Mann–Whitney *U* test. Qualitative data are shown as numbers and percentages, and differences were evaluated with the $\chi 2$ test. Correlations were calculated by using the Spearman rho test. The influence of selected parameters on PON1-related variables was analyzed by multiple regression analysis. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curves, from which the optimal cut-offs were determined to achieve the best balance between sensitivity and specificity. Moreover, the positive predictive value (PPV) and negative predictive value (NPV) were calculated based on these thresholds [45].

Statistical analyses and data visualization were conducted using RStudio (version 4.4.3). All packages were updated to the latest versions available on CRAN [46]. Boxplots were generated to evaluate variations in PON1, ARE, PARX, CCL2, PCT, and CRP levels across different groups. The *ggplot2* package was used for plot creation, *ggsignif* was employed to annotate statistical significance and *ggsave* facilitated plot export. Network correlation and correlation matrices were employed to explore relationships among variables. The *igraph* package was used for these analyses to construct and visualise network graphs. *Hmisc* was used to compute correlation matrices, *qgraph* for creating clear and interpretable network visualisations, and *dplyr* for data manipulation and preprocessing. ROC curves were generated using MetaboAnalyst, version 6.0 [47]. A p-value <0.05 was considered statistically significant.

2.5. Sample size calculation

After completing the study, we performed a post hoc analysis to assess whether the sample size was sufficient to draw statistically valid conclusions. We selected ARE activity as the reference variable, as changes in its levels were less pronounced than those observed for other PON1-related variables. Based on the observed values (254 [SD: 93] in the control group and 120 [SD: 40] in CAP patients) and assuming a statistical power of 80 % and a significance level of 5 %, the minimum required sample size was estimated to be 6 participants per group. Since our actual sample size was considerably larger, the statistical power is deemed adequate not only for ARE activity but also for the other PON1-related variables, given that their between-group differences were of similar or greater magnitude [48].

3. Results

3.1. Patient characteristics

There were no significant differences in sex distribution or smoking status among the participant groups. However, CAP patients were slightly older than the control group. They had higher serum glucose concentrations, γ-glutamyl transferase activities, leukocyte counts, and lower albumin, hematocrit, and hemoglobin levels. Most patients had mild radiological lesion extension, with hospital stays typically lasting 1–2 weeks, and 20.5 % required admission to the ICU. Systemic inflammatory response syndrome (SIRS) and fever were common. Patients generally presented with high PSI scores, moderate CURB-65 scores, and moderate Charlson index values. The most frequent comorbidities were arterial hypertension and chronic obstructive pulmonary disease (Table 2).

3.2. Microbiological results

Microorganisms responsible for pneumonia were identified in 38 out of 78 patients with CAP (48.7 %). The distribution of these microorganisms is detailed in Table 3. Two sputum samples were polymicrobial, each yielding two distinct isolates.

Table 2
Clinical characteristics of patients with pneumonia and the control group.

Variable	Control group (n = 80)		Patients (n = 78)	
	Men (n = 54)	Women (n = 26)	Men (n = 52)	Women (n = 26)
Age	63 (39–83)	53 (34–80)[a]	68 (26–88)	74 (29–95)[c]
Smoking	18 (33.3)	9 (34.6)	28 (53.8)	5 (19.2)[b,d]
Glucose (mmol/L)	4.6 (3.7–6.1)	4.9 (3.5–7.2)	7.7 (4.5–19.4)[d]	7.6 (4.9–20.5)[d]
Creatinine (μmol/L)	71.0 (51.2–92.5)	69.5 (51.3–93.8)	80.0 (42.3–234.7)	57.9 (29.4–578.1)
Albumin (g/L)	42.0 (30.1–48.4)	42.8 (30.5–48.5)	33.0 (20.8–43.6)[d]	34.0 (22.3–42.3)[d]
AST (μkat/L)	0.35 (0.26–0.56)	0.33 (0.25–0.56)	0.37 (0.19–1.68)	0.38 (0.19–3.36)
ALT (μkat/L)	0.32 (0.20–0.77)	0.29 (0.15–0.73)	0.42 (0.15–1.91)	0.35 (0.17–3.30)
GGT (μkat/L)	0.24 (0.08–0.81)	0.17 (0.06–1.21)	0.90 (0.15–2.76)[d]	0.76 (0.15–7.39)[d]
Hematocrit (%)	42.2 (37.2–47.4)	42.2 (33.3–48.4)	39.0 (30.3–45.7)[d]	34.0 (25.3–42.4)[b,d]
Hemoglobin (g/L)	14.4 (12.6–16.0)	14.4 (11.4–16.6)	13.0 (9.8–15.0)[d]	11.0 (8.5–13.5)[b,d]
Leukocytes (x 10^9/L)	7.1 (4.9–9.9)	6.9 (4.6–11.2)	11.9 (2.7–29.7)	13.3 (3.5–27.9)[d]
Platelets (x 10^9/L)	239.5 (153.2–338.5)	214.0 (157.1–301.0)	221.0 (105.4–500.0)	260.0 (251.7–416.1)
Microorganism*				
Lesion radiological extensión				
1			26	13
2	NA	NA	11	5
3			15	8
Days of hospitalization	NA	NA	8 (2–34)	9 (1–46)
ICU admittance	NA	NA	11	5
Invasive mechanical ventilation	NA	NA	6	2
Fever	NA	NA	3	5
Pleural effusion	NA	NA	9	3
SIRS	NA	NA	41	22
PSI				
1			4	6
2	NA	NA	7	5
3			11	2
4			27	10
5			3	3
CURB-65				
0			10	2
1	NA	NA	17	12
2			15	6
3			10	5
4			0	1
Charlson index				
0			14	12
1	NA	NA	8	4
2			14	4
3			8	5
4			7	1
7			1	0
Shock	NA	NA	4	2
Mortality at 90 days	NA	NA		
COPD	NA	NA	22	5[a]
Type 2 diabetes mellitus	NA	NA	12	2
Dyslipidemia	NA	NA	12	3
Arterial hypertension	NA	NA	25	14
Cancer	NA	NA	8	2
Chronic liver disease	NA	NA	0	0
Congestive heart failure	NA	NA	8	4
Stroke	NA	NA	4	2

Categorical variables are presented as numbers and percentages (in parentheses), with statistical differences assessed using the X^2 test. Quantitative variables are reported as medians and 95 % Confidence Intervals (in parentheses), with differences analyzed using the Mann-Whitney *U* test. [a] $p < 0.05$, [b] $p < 0.001$, with respect to men; [c] $p < 0.05$, [d] $p < 0.001$, with respect to the control group. * Microorganism isolated in culture. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COPD: Chronic obstructive pulmonary disease; CURB-65: Score for pneumonia severity based on confusion, urea, respiratory frequency, blood pressure and age >65; GGT: γ-glutamyl transferase; ICU: Intensive Care Unit; PSI: Pneumonia severity index; SIRS: Systemic inflammatory response syndrome.

Table 3
Distribution of pathogens in patients with community-acquired pneumonia (n = 78).

Microorganism	Number of isolates	%
Streptococcus pneumoniae	22	28.2
Mycoplasma pneumoniae	8	10.2
Legionella pneumophila	3	3.8
Influenza virus (H1N1)	2	2.6
Chlamydophila pneumoniae	2	2.6
Mycobacterium tuberculosis	1	1.3
Pneumocystis jirovecii	1	1.3
Moraxella catarrhalis	1	1.3

Microbiologically confirmed CAP: 38 patients (48.7 %). Percentages exceed 100 % due to mixed infections.

3.3. Serum PON1-related variables and inflammatory markers in CAP patients and the control group

We observed significantly higher PON1c and lower ARE and PARX activities in CAP patients than in the control group. As a result, the specific activities of ARE and PARX were significantly lower in these patients. These changes were accompanied by significant increases in the inflammatory markers CCL2, PCT, and CRP and decreases in total cholesterol and HDL cholesterol levels (Fig. 1).

The bivariate analysis revealed significant positive and negative correlations among several parameters across all study participants, with robust associations observed among the PON1-related variables and between these variables and cholesterol levels. Notably, these parameters also showed relevant correlations with CCL2 and CRP. Still, there was no significant association with PCT (Fig. 2A). This pattern was further supported by the correlation network analysis, which demonstrated that most nodes formed a tightly interconnected cluster. In contrast, the PCT node was distinctly isolated from the other parameters (Fig. 2B).

Given the high degree of mutual dependence among most variables, we conducted multiple linear regression analyses to identify independent factors associated with PON1-related variables. Results showed that CAP status was the only independent factor significantly associated with all PON1-related variables, while CRP was also linked to PON1c, smoking was associated with PARX, and age was associated with PARX specific activity. Comorbidities showed no significant influence overall, although cancer had a minor but statistically significant association with PON1 concentration, suggesting that pneumonia itself remains the primary determinant of the observed alterations. (Supplementary Table 1–5).

3.4. Serum PON1-related variables and inflammatory markers in the diagnosis of CAP

Next, we compared the diagnostic accuracy of PON1-related variables and inflammation markers in diagnosing CAP. The results, derived from the ROC curves, are presented in Fig. 3 and Supplementary Table 6. The highest areas under the curve, exceeding 0.99, were observed for PON1c and the specific activities of ARE and PARX. Optimal sensitivity and specificity were achieved at the following cut-off values: PON1c = 237.98 mg/L, ARE specific activity = 0.869 U/mg, and PARX specific activity = 1.281 U/mg. These thresholds corresponded to PPV ranging from 0.949 to 0.977 and NPV from 0.962 to 0.976. These diagnostic accuracies were markedly superior to those of cholesterol or inflammatory markers, allowing for clear differentiation between patients and controls with minimal ambiguity.

3.5. Associations between PON1-related variables, inflammatory markers and clinical outcomes in patients with CAP

We evaluated the potential utility of PON1-related variables and inflammatory markers in predicting prognosis, assessing clinical characteristics, and determining disease severity in patients with CAP. While some associations were observed, the overall results were modest.

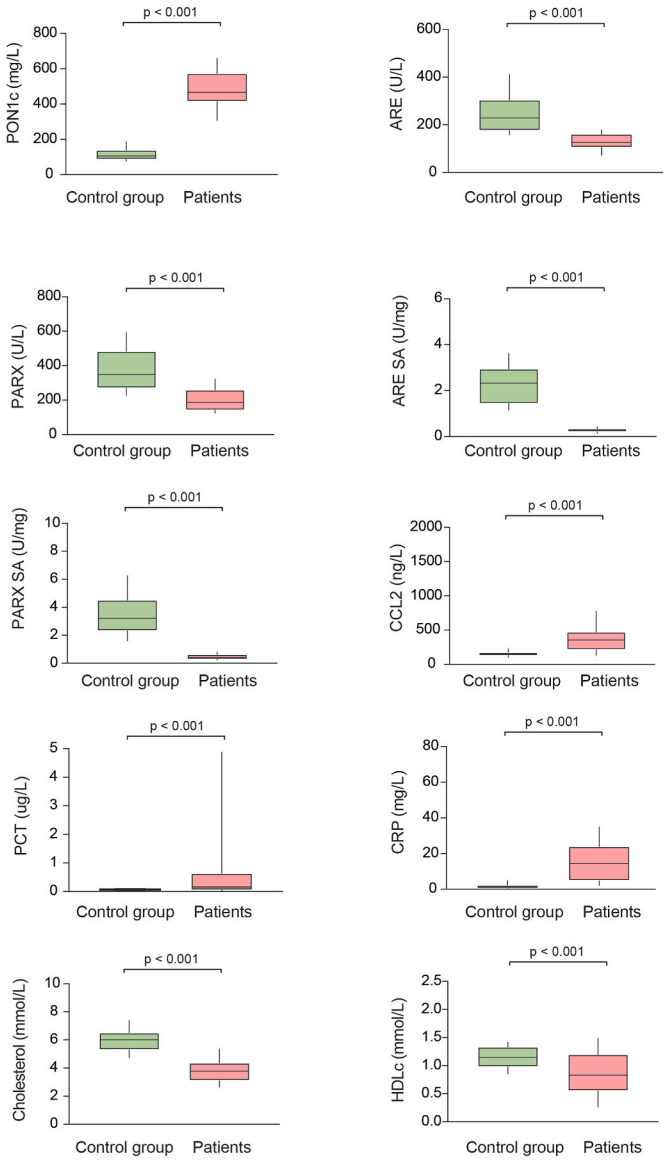

Fig. 1. Box plots depicting selected analytical variables in the control group and patients with community-acquired pneumonia. Statistical significances were assessed by the Mann-Whitney *U* test. ARE: arylesterase activity; ARE SA: arylesterase-specific activity; CCL2: CC-motif chemokine ligand 2; CRP: C-reactive protein; HDLc: high-density lipoprotein cholesterol; PARX: paraoxonase activity; PARX SA: paraoxonase specific activity; PON1c: paraoxonase 1 concentration; PCT: procalcitonin.

Patients requiring ICU admission had significantly lower serum ARE activities, cholesterol, HDL cholesterol levels, and higher CRP concentrations. Additionally, lower ARE activities were noted in patients who either required invasive mechanical ventilation or died (Fig. 4). Diagnostic accuracy, assessed via ROC curve analysis, revealed high NPVs but low PPVs, presumably due to the low number of positive cases (Fig. 5 and Supplementary Table 7).

Patients with a PSI score ≥3 showed lower ARE activities than those with PSI <3. Similarly, patients with hospital stays exceeding 10 days had reduced PON1c and ARE levels alongside elevated CRP concentrations (Supplementary Fig. 1). However, these differences were slight and lacked clinical relevance. The combined assessment of PSI and ARE did not outperform ARE alone in discriminating between patients requiring

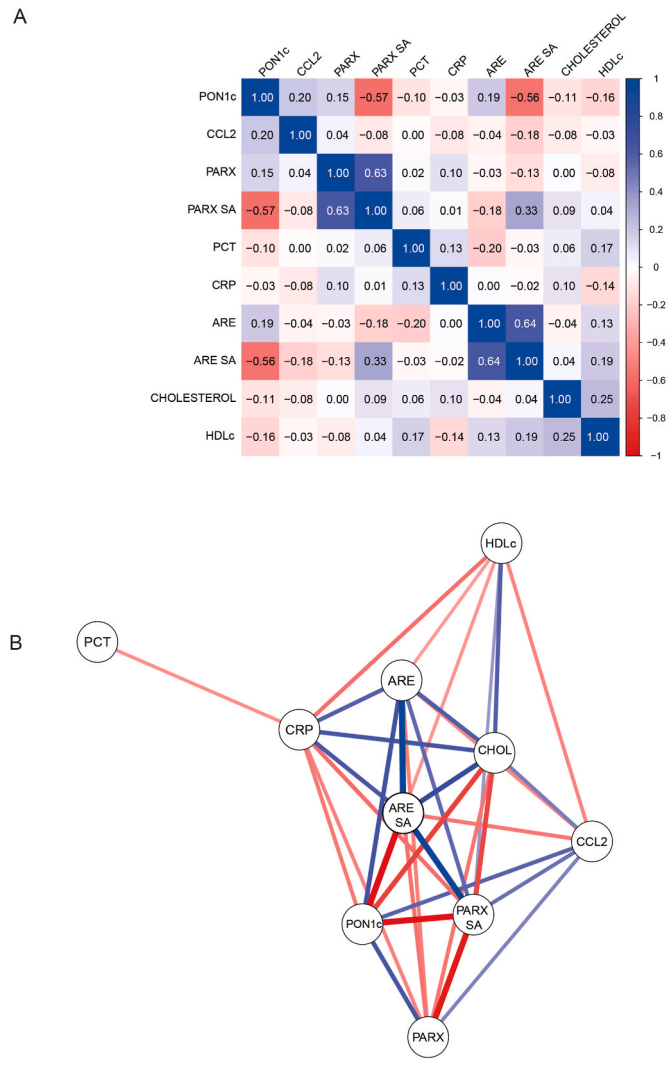

Fig. 2. (A) Correlation matrix showing pairwise Spearman correlation coefficients among selected clinical and biochemical variables in healthy controls and patients with community-acquired pneumonia (CAP). Each cell represents the correlation between a pair of variables, with blue tones indicating positive correlations and red tones indicating negative correlations. The intensity of the color reflects the strength of the correlation (from −1 to +1), and white text has been added in high-saturation areas to improve visibility of the rho values. (B) Correlation network analysis derived from the same dataset, visualizing the structure and strength of statistically significant correlations among the variables.

Nodes represent individual variables, while edges represent significant correlations: blue lines for positive and red lines for negative associations. The thickness and proximity of the lines reflect the strength of the correlations, with shorter and thicker lines indicating stronger interactions. This network highlights clusters of variables with closely interrelated patterns, allowing visualization of the systemic relationships in CAP-related metabolic and inflammatory profiles. ARE: arylesterase activity; ARE SA: arylesterase-specific activity; CCL2: CC-motif chemokine ligand 2; CRP: C-reactive protein; HDLc: high-density lipoprotein cholesterol; PARX: paraoxonase activity; PARX SA: paraoxonase specific activity; PON1c: paraoxonase 1 concentration; PCT: procalcitonin. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

ICU admission and those who did not (Supplementary Fig. 2).

Patients with *Streptococcus pneumoniae* isolated in their cultures had lower PON1 concentrations than those infected with other microorganisms or those with unknown etiology. However, differences were slight and without discriminatory power (Supplementary Fig. 3).

No other significant associations were found between analytical, clinical, or microbiological variables.

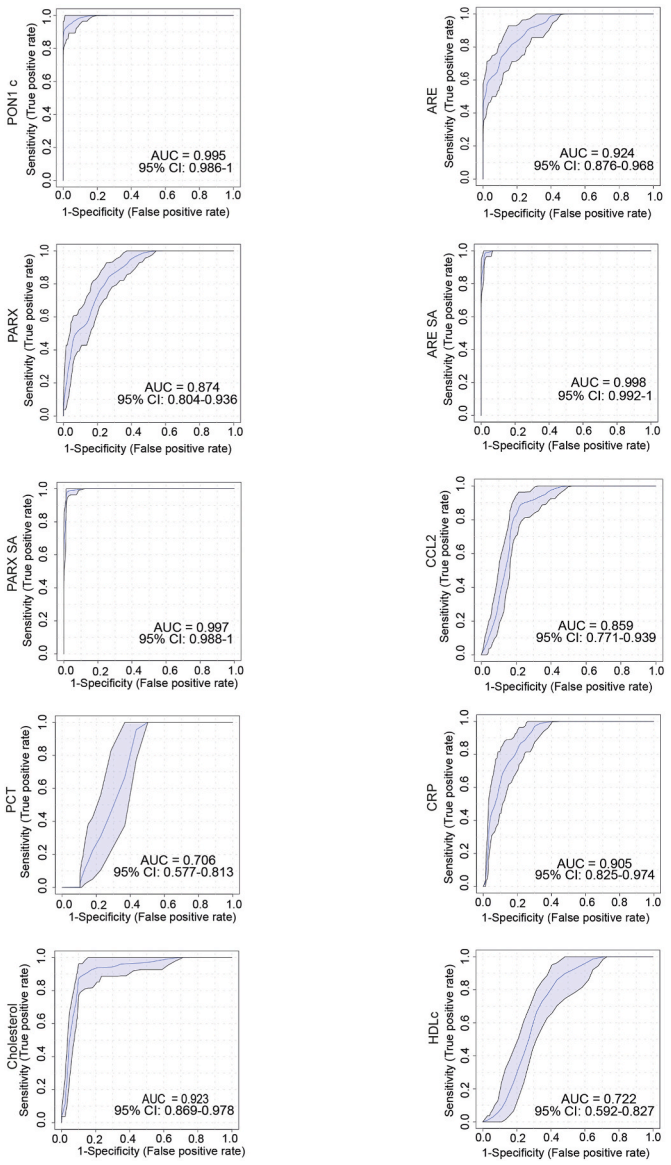

Fig. 3. Receiver Operating Characteristic (ROC) curves evaluating the diagnostic performance of selected PON1-related and inflammatory variables in distinguishing patients with community-acquired pneumonia (CAP) from healthy controls.

The Area Under the Curve (AUC) quantifies the overall diagnostic accuracy of each variable, with values closer to 1.0 indicating better discrimination. Shaded regions around each curve represent the 95 % Confidence Intervals (CIs), illustrating the precision of the AUC estimates. ARE: arylesterase activity; ARE SA: arylesterase-specific activity; AUC: area under the curve; CCL2: CC-motif chemokine ligand 2; CRP: C-reactive protein; HDLc: high-density lipoprotein cholesterol; PARX: paraoxonase activity; PARX SA: paraoxonase specific activity; PON1c: paraoxonase 1 concentration; PCT: procalcitonin.

4. Discussion

Our study provides novel insights into the role of PON1-related variables in patients with CAP. We found significantly lower serum ARE and PARX activities but higher serum PON1c in CAP patients compared to the healthy population. These alterations were accompanied by increased inflammatory markers and reduced levels of total and HDL cholesterol. Importantly, all serum samples were obtained before 2020, ensuring these alterations cannot be confounded with those

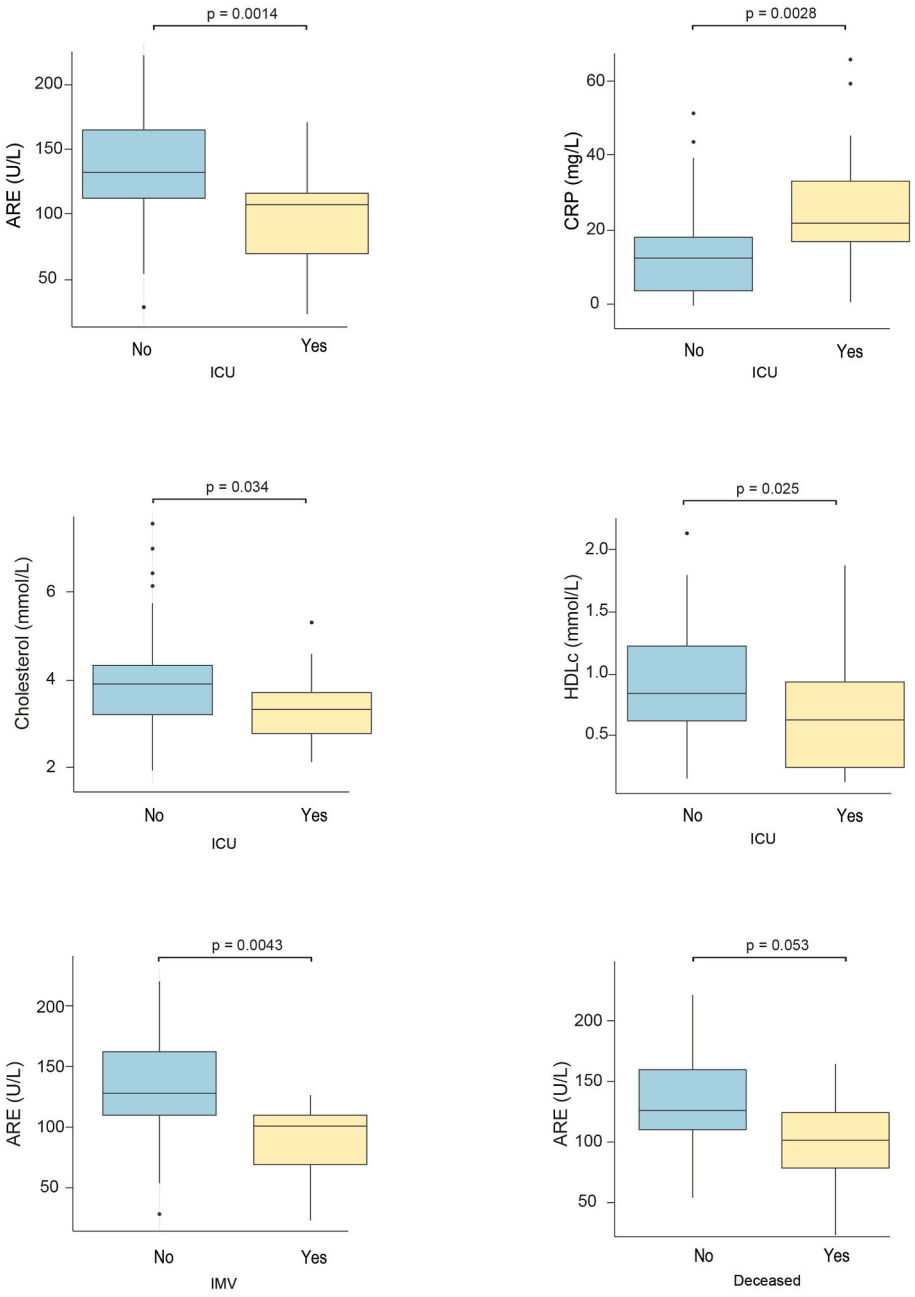

Fig. 4. Box plots of selected biochemical variables stratified by clinical outcomes in patients with community-acquired pneumonia.
Statistical significances were assessed by the Mann-Whitney *U* test. ARE: arylesterase activity; CRP: C-reactive protein; ICU: Intensive Care Unit; IMV: Invasive mechanical ventilation.

observed in COVID-19 pneumonia. This distinction is crucial, as previous studies by our group and others have reported significant quantitative and qualitative differences in the metabolic profiles of patients with COVID-19 pneumonia and those with severe CAP [49,50].

Our findings are consistent with previous reports suggesting that serum PON1 activities may be reduced in conditions involving oxidative stress and inflammation, such as bacterial and viral infections [20–24, 51,52]. Similar reductions have been observed in chronic diseases, such as liver disorders, cardiovascular conditions, and cancer, which could indicate a broader role of PON1 in disease pathophysiology [16–18].

Several mechanisms could underlie this decrease. The catalytic inactivation of PON1 might occur when its active site forms covalent bonds with lipoperoxide substrates, potentially rendering the enzyme inactive and lowering its overall activity [19]. Additionally, inflammation-induced alterations in HDL composition, such as decreased cholesterol content and increased serum amyloid A, could disrupt PON1's local environment, thereby diminishing its function [23, 49,50,53]. Elevated CRP levels, reflecting immune activation, might also correlate with impaired HDL function and reduced PON1 activity, suggesting a complex interaction between lipid metabolism, immunity, and inflammation [54–58].

Interestingly, despite reduced enzymatic activity, serum PON1 concentrations appeared elevated in CAP patients, which is in line with previous observations in chronic liver disease, HIV, and COVID-19 [19, 20,24,51]. This dissociation could reflect a complex interplay of factors. While compensatory hepatic synthesis may increase circulating PON1 levels, it may not fully account for the decline in enzymatic activity. Post-translational modifications, such as oxidation, glycation, or nitrosylation, could impair PON1 function by altering its structure or HDL binding without reducing its concentration.

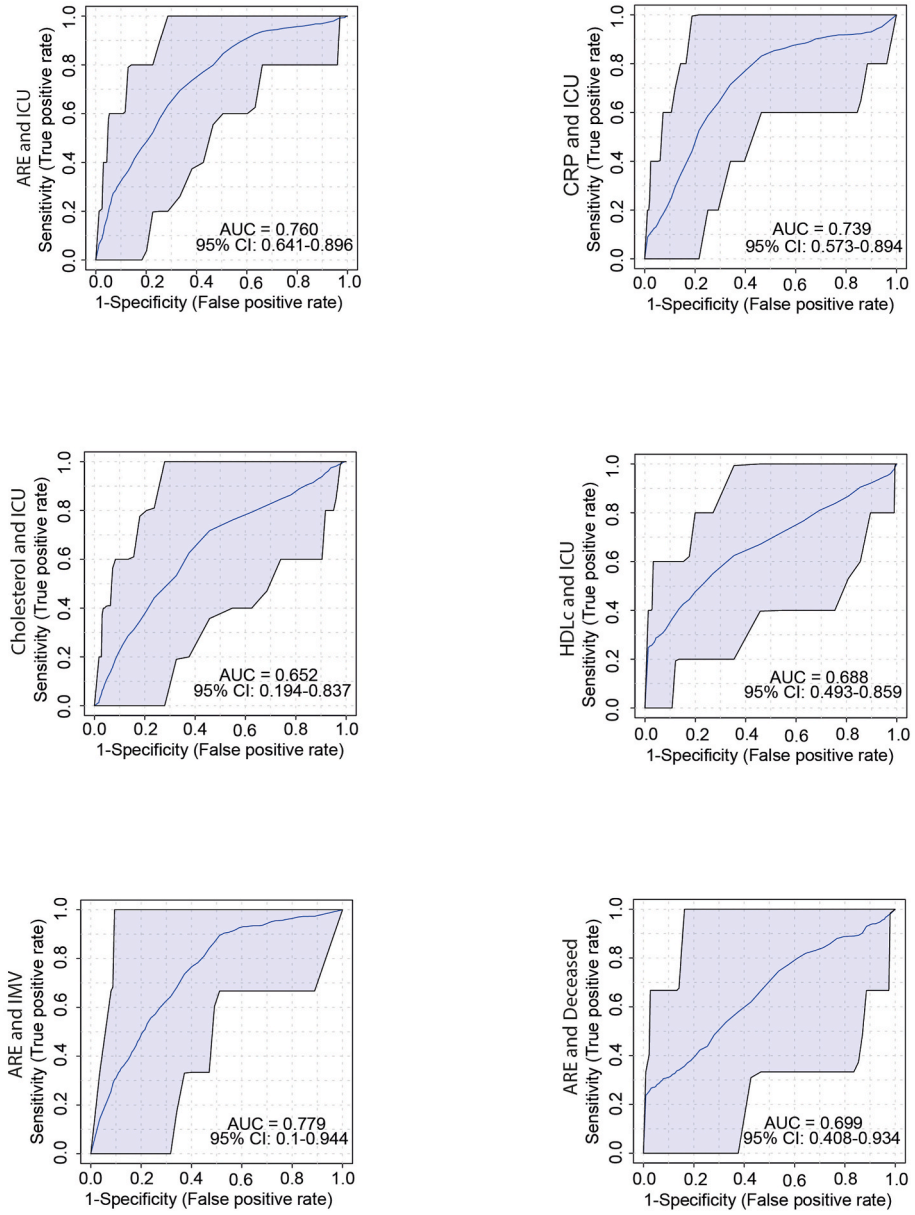

Fig. 5. Receiver Operating Characteristic (ROC) curves for selected biochemical variables in predicting clinical outcomes in patients with community-acquired pneumonia (CAP). The Area Under the Curve (AUC) quantifies the overall diagnostic accuracy of each variable, with values closer to 1.0 indicating better discrimination.

Shaded regions around each curve represent the 95 % Confidence Intervals (CIs), illustrating the precision of the AUC estimates. ARE: arylesterase activity; AUC: area under the curve; CRP: C-reactive protein; ICU: Intensive Care Unit; HDLc: high-density lipoprotein cholesterol; IMV: Invasive mechanical ventilation.

It is important to note that these proposed mechanisms remain hypothetical and were not directly assessed in this study. Further investigations, including proteomic and structural analyses, would be needed to clarify the mechanisms underlying impaired PON1 activity in CAP.

Our results do not support a significant effect of the medications administered for CAP or its comorbidities on PON1-related variables. These drugs cannot be included as independent variables in the multiple regression models because their use is inherently dependent on the presence of CAP or comorbid conditions. Consequently, their influence is more appropriately addressed qualitatively rather than through formal statistical modeling. Among the drugs used, statins and aspirin are the most consistently associated with increased PON1 activity according to previous studies quoted above [34]. However, despite their frequent use in our cohort, we observed markedly decreased PON1-related activities in patients with CAP. This suggests that the inflammatory and metabolic disturbances associated with the infection itself may override any potential pharmacological increase in PON1 activities.

The changes in PON1-related variables and inflammatory markers may also reflect alterations in innate immunity during severe infections. Innate immunity is the body's first line of defense against pathogens, triggering a rapid and nonspecific response to infections and injuries. HDL plays a crucial role in this response due to its anti-inflammatory and antioxidative properties, partly mediated by PON1, which hydrolyzes lipid peroxides and mitigates oxidative stress [17,18]. However, as discussed, the acute phase response alters HDL composition, impairing its protective functions and contributing to reduced PON1 activity.

Additionally, reduced PON1 activity has been linked to enhanced synthesis and secretion of CCL2 [59–61]. Overexpression of this

chemokine is implicated in chronic inflammatory diseases and severe infections [18,62,63]. The association between reduced PON1 activity and elevated CCL2 levels suggests that PON1 may play a role in modulating monocyte infiltration and immune cell recruitment. This role likely involves PON1's ability to reduce oxidative stress, thereby downregulating CCL2 expression. Conversely, elevated CCL2 levels may contribute to endothelial dysfunction and exacerbate inflammation, creating a negative feedback loop that further suppresses PON1 activity [18].

Given these data, it is unsurprising that our network analysis revealed strong correlations among these parameters. However, we were unable to establish a clear relationship with PCT levels. This may be because PCT increases in severe bacterial infections but not viral ones. Indeed, PCT is primarily used as a biomarker to differentiate bacterial from viral infections and to assess the severity of bacterial sepsis [64]. While some studies, particularly those involving patients with bacterial sepsis in intensive care, have suggested an inverse correlation between PON1 activity and PCT [65,66], this pattern was not evident in our population.

The diagnostic accuracy of PON1c and ARE measurements, along with the specific activities of ARE and PARX, as reflected by AUC values exceeding 0.99, underscores their potential as robust biomarkers for the detection of CAP. These results are particularly relevant given the limitations of conventional inflammatory markers, including CRP and PCT, in the context of pulmonary infections. While highly sensitive, CRP lacks specificity, as its values between 3 mg/L and 10 mg/L may be influenced by various non-infectious conditions such as obesity, smoking, and diabetes mellitus, among others [67]. PCT is a more specific biomarker for bacterial infections, as its levels rise in response to systemic bacterial invasion while remaining low in viral infections. Importantly, PCT levels correlate with the severity of bacterial pneumonia and can guide antimicrobial stewardship by assessing the need for antibiotics and monitoring treatment response [68]. However, its effectiveness is diminished in specific contexts, such as tropical infectious diseases, where it may not reliably distinguish bacterial from non-bacterial causes. [12,15,69]. Furthermore, CRP and PCT exhibit only modest diagnostic performance when measured as a single determination [15]. Overall, the findings highlight the need for alternative or complementary biomarkers with enhanced diagnostic accuracy in CAP and other pulmonary infections. Our results suggest that PON1-related variables may represent promising diagnostic biomarkers with high performance in this context.

However, PON1-related variables demonstrate limited value in predicting the course of CAP prognosis, as they do not effectively predict disease evolution. While some associations with disease severity indicators were identified, their clinical relevance appears limited. Lower ARE activity and reduced cholesterol and HDL cholesterol levels were observed in patients requiring ICU admission, as well as in those needing invasive mechanical ventilation or those who died. Similarly, patients with PSI scores of$\geq$3 and prolonged hospital stays (more than 10 days) had decreased PON1c and ARE levels, accompanied by elevated CRP concentrations. However, the absolute differences were modest, and ROC curve analysis indicated high NPVs but low PPVs, suggesting limited predictive utility. The low prevalence of severe cases in our cohort may partly explain these findings. Moreover, the combination of ARE and PSI does not improve performance compared to ARE alone.

Determinations of PON1-related variables did not provide insight into the etiology of CAP. Although patients with *S. pneumoniae* infection exhibited lower PON1c levels than those with other microbial etiologies, the differences were small and unlikely to serve as a reliable marker for microbial differentiation.

5. Strengths and limitations

A key strength of this study is the comprehensive evaluation of PON1-related variables in the diagnosis and prognosis of community-acquired pneumonia (CAP), supported by robust ROC curve analyses and clinically meaningful endpoints. The clear biochemical distinction between cases and controls strengthens the internal validity of our findings.

However, several limitations must be acknowledged. First, the study compared CAP patients exclusively with healthy controls, without including patients with other acute respiratory or infectious conditions, which may limit the ability to distinguish CAP from similar clinical entities using PON1-related markers. Second, the exceptionally high AUC values (>0.99) reported for several PON1-related variables may reflect a risk of overfitting, particularly because the ROC analyses were performed on the original dataset without cross-validation or bootstrapping, which could potentially introduce optimism bias. Third, the relatively small and homogeneous sample size (limited to a single center) reduces the generalizability of the findings to more diverse CAP populations, especially those with multiple or more severe comorbidities. It also restricts the statistical power for subgroup and prognostic analyses, hinders the exploration of interaction effects between variables, and limits etiological comparisons (e.g., bacterial vs. viral). Fourth, the low number of severe CAP cases may have reduced the predictive accuracy for adverse outcomes; longitudinal assessment through serial measurements during hospitalization might enhance prognostic utility. Finally, PON1 concentration was measured using an ELISA-based method, which, although consistently applied in our previous studies with validated antibodies [19,70–73], may lack the precision of mass spectrometry-based approaches.

6. Conclusion and perspectives

Our findings suggest that PON1-related variables, particularly PON1c and the specific activities of ARE and PARX, may serve as valuable diagnostic biomarkers for CAP, offering superior accuracy compared to conventional inflammatory markers. However, their prognostic utility remains uncertain, and their inability to distinguish microbial etiologies limits their application in guiding antimicrobial therapy. Future clinical studies should validate these findings in larger and more heterogeneous populations to confirm their generalizability. In parallel, mechanistic research is warranted to elucidate the role of PON1 in the pathophysiology of CAP. In this context, the application of advanced proteomic and lipidomic approaches could provide valuable insights into the structural and functional alterations of HDL particles during CAP, as well as the interactions between PON1 and its lipid-protein microenvironment.

CRediT authorship contribution statement

Frederic Ballester: Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xavier Gabaldó-Barrios:** Writing – review & editing, Software, Investigation, Formal analysis, Data curation. **Andrea Jiménez-Franco:** Software, Investigation, Formal analysis. **Isabel Pujol:** Investigation. **Simona Iftimie:** Investigation. **Jordi Camps:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Sandra Parra:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Funding acquisition. **Antoni Castro:** Resources, Funding acquisition. **Jorge Joven:** Resources, Funding acquisition.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized CHAT GPT 4.0 (developed by OpenAI) to assist in improving the grammar, syntax, and clarity of the text and Grammarly (from Grammarly Inc.) for orthographic corrections. After using these tools, the authors reviewed

and edited the content as needed and took full responsibility for the content of the published article. The content, ideas, and scientific conclusions presented in this manuscript are solely the authors' work and have not been generated by AI. The AI tools were utilized exclusively to enhance the readability and presentation of the text.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jordi Camps reports financial support was provided by FUNDACIÓ LA MARATÓ DE TV3 (201807–10), Barcelona, Spain. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cbi.2025.111606.

Data availability

Data will be made available on request.

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Corrigendum to "Insights into the diagnostic and prognostic value of paraoxonase 1-related variables and inflammatory markers in community-acquired pneumonia" [Chem. Biol. Interact. 418 (2025) 111606]

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The authors regret that an incomplete version of Table 2 was inadvertently submitted and subsequently published. This version did not incorporate all the intended data and calculations. As a result, information on microorganisms and 90-day mortality was missing, the frequency of fever in patients was incorrectly reported, and percentages for categorical variables were not displayed despite being mentioned in the footnote. These errors originated from the use of a preliminary draft of the table in error and unfortunately went unnoticed during the review and editorial process.

The corrected Table 2 is now provided, ensuring that all data are accurately presented. These corrections do not affect the overall conclusions or the scientific content of the article.

The authors would like to apologise for any inconvenience caused.

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Table 2
Clinical characteristics of patients with pneumonia and the control group.

Variable	Control group (n = 80)		Patients (n = 78)	
	Men (n = 54)	Women (n = 26)	Men (n = 52)	Women (n = 26)
Age	63 (39–83)	53 (34–80)[a]	68 (26–88)	74 (29–95)[c]
Smoking	18 (33.3)	9 (34.6)	28 (53.8)	5 (19.2)[b,d]
Glucose (mmol/L)	4.6 (3.7–6.1)	4.9 (3.5–7.2)	7.7 (4.5–19.4)[d]	7.6 (4.9–20.5)[d]
Creatinine (μmol/L)	71.0 (51.2–92.5)	69.5 (51.3–93.8)	80.0 (42.3–234.7)	57.9 (29.4–578.1)
Albumin (g/L)	42.0 (30.1–48.4)	42.8 (30.5–48.5)	33.0 (20.8–43.6)[d]	34.0 (22.3–42.3)[d]
AST (μkat/L)	0.35 (0.26–0.56)	0.33 (0.25–0.56)	0.37 (0.19–1.68)	0.38 (0.19–3.36)
ALT (μkat/L)	0.32 (0.20–0.77)	0.29 (0.15–0.73)	0.42 (0.15–1.91)	0.35 (0.17–3.30)
GGT (μkat/L)	0.24 (0.08–0.81)	0.17 (0.06–1.21)	0.90 (0.15–2.76)[d]	0.76 (0.15–7.39)[d]
Hematocrit (%)	42.2 (37.2–47.4)	42.2 (33.3–48.4)	39.0 (30.3–45.7)[d]	34.0 (25.3–42.4)[b,d]
Hemoglobin (g/L)	14.4 (12.6–16.0)	14.4 (11.4–16.6)	13.0 (9.8–15.0)[d]	11.0 (8.5–13.5)[b,d]
Leukocytes (x 10^9/L)	7.1 (4.9–9.9)	6.9 (4.6–11.2)	11.9 (2.7–29.7)	13.3 (3.5–27.9)[d]
Platelets (x 10^9/L)	239.5 (153.2–338.5)	214.0 (157.1–301.0)	221.0 (105.4–500.0)	260.0 (251.7–416.1)
Microorganisms*	NA	NA	20 (38.5)	18 (69.2)[a]
Lesion radiological extensión				
1	NA	NA	26 (50.0)	13 (50.0)
2			11 (21.2)	5 (19.2)
3			15 (28.8)	8 (30.8)
Days of hospitalization	NA	NA	8 (2–34)	9 (1–46)
ICU admittance	NA	NA	11 (21.2)	5 (19.2)
Invasive mechanical ventilation	NA	NA	6 (11.5)	2 (7.7)
Fever	NA	NA	30 (57.7)	15 (57.7)
Pleural effusion	NA	NA	9 (17.3)	3 (11.5)
SIRS	NA	NA	41 (78.8)	22 (84.6)
PSI				
1	NA	NA	4 (7.7)	6 (23.1)
2			7 (13.5)	5 (19.2)
3			11 (21.1)	2 (7.7)
4			27 (51.9)	10 (38.5)
5			3 (5.8)	3 (11.5)
CURB-65				
0	NA	NA	10 (19.2)	2 (7.7)
1			17 (32.7)	12 (46.2)
2			15 (28.8)	6 (23.1)
3			10 (19.2)	5 (19.2)
4			0 (0)	1 (3.8)
Charlson index				
0	NA	NA	14 (26.9)	12 (46.2)
1			8 (15.4)	4 (15.4)
2			14 (26.9)	4 (15.4)
3			8 (15.4)	5 (19.2)
4			7 (13.5)	1 (3.8)
7			1 (1.9)	0 (0)
Shock	NA	NA	4 (7.7)	2 (7.7)
Mortality at 90 days	NA	NA	3 (5.8)	5 (19.2)
COPD	NA	NA	22 (42.3)	5 (19.2)[a]
Type 2 diabetes mellitus	NA	NA	12 (23.1)	2 (7.7)
Dyslipidemia	NA	NA	12 (23.1)	3 (11.5)
Arterial hypertension	NA	NA	25 (48.1)	14 (53.8)
Cancer	NA	NA	8 (15.4)	2 (7.7)
Chronic liver disease	NA	NA	0 (0)	0 (0)
Congestive heart failure	NA	NA	8 (15.4)	4 (15.4)
Stroke	NA	NA	4 (7.7)	2 (7.7)

Categorical variables are presented as numbers and percentages (in parentheses), with statistical differences assessed using the X^2 test. Quantitative variables are reported as medians and 95 % Confidence Intervals (in parentheses), with differences analyzed using the Mann-Whitney *U* test. [a] $p < 0.05$, [b] $p < 0.001$, with respect to men; [c] $p < 0.05$, [d] $p < 0.001$, with respect to the control group. * Microorganisms isolated in culture. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COPD: Chronic obstructive pulmonary disease; CURB-65: Score for pneumonia severity based on confusion, urea, respiratory frequency, blood pressure and age >65; GGT: γ-glutamyl transferase; ICU: Intensive Care Unit; PSI: Pneumonia severity index; SIRS: Systemic inflammatory response syndrome.