# RESEARCH

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# Acute phase reactants in non-COVID-19 community-acquired pneumonia



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# Abstract

**Background** Acute phase reactants (APR) are markers of inflammation that could be applied for the assessment of community-acquired pneumonia (CAP) severity in association with various pneumonia severity scores. So, the aim of the study was to assess levels of APR such as total leucocytic count (TLC), platelets, neutrophils, neutrophils-tolymphocyte ratio (NLR), CRP, D-dimer, ferritin, and ESR in patients with CAP and to correlate between their values and disease severity.

Methodology The study included 51 patients diagnosed as non-COVID-19 (CAP). Patients were classified into two groups group A (pneumonia only) and group B (pneumonia complicated with empyema/complicated para-pneumonic effusion). All patients underwent clinical evaluation, CURB65, radiological assessment, and blood sampling to measure APR.

Results The mean age of patients was 47 ± 17 years. The main symptoms were productive cough (90.2%) and Fever (92.2%).TLC, platelets, neutrophils, CRP, D-dimer, ferritin, and ESR were elevated than normal values. Significant positive correlations were found between the duration of fever and CRP, D-dimer, and ferritin with p values = 0.024, 0.012, and 0.034 respectively. Significant positive correlations were found between CURB65 and both CRP and ferritin with p values = 0.007 and 0.020. A significant increase in platelet count and ESR values was found in group B than in group A.

Conclusion APR are important markers that can be used in the assessment of CAP in collaboration with clinical evaluation and severity scores. CRP, D-dimer, and ferritin were positively correlated with CURB65, while ESR and platelets could be considered predictors of the development of complications.

Trial registration Retrospectively registered, registration number NCT05926089, date of registration is 06/29/2023. Keywords Acute phase reactants, Community-acquired pneumonia, CURB65

# Background

Community-acquired pneumonia (CAP) is the most prevalent respiratory infectious disease. It is defined as an acute infection of the lung parenchyma that is acquired outside the hospital [1, 2].

CAP is associated with increased morbidity and mortality, Especially in the elderly population, patients with

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chronic debilitating diseases, smoking, and alcohol consumption [3]

Acute phase reactants (APR) are inflammatory mediators that show significant alternations in serum levels in response to inflammation, these markers are responsible for some adverse effects such as anorexia, fever, fatigue, and anemia of chronic illness [4]. APR can be applied for the assessment of disease severity in CAP in collaboration with clinical evaluation and pneumonia severity scores [5].

The most common APR are leucocytic count, CRP, and ESR, changes in the level of these indices can be used in



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the diagnosis and prognosis of inflammatory and infectious diseases [6].

NLR is a rapid, simple, and cheap maker of the systemic inflammatory process, it is calculated as the ratio between neutrophil count to lymphocyte count from peripheral blood sample. Numerous researches have assessed the role of NLR in many infectious diseases such as sepsis, bacteremia, and septic shock, in addition, it can predict the severity and outcome of CAP [7].

So, the aim of the current study was to assess levels of APR such as total leucocytic count (TLC), platelets, neutrophils, neutrophils-to-lymphocyte ratio (NLR), CRP, D-dimer, Ferritin, and ESR in patients with CAP (as a primary outcome) and to correlate between their measured values and disease severity (as a secondary outcome).

# Methodology

A cross-section prospective study was carried out in the Chest Department, Faculty of Medicine, Cairo University, during the period between October 2020 to April 2021. The research ethical committee at the Faculty of Medicine, Cairo University had approved the study (code: MS-358–2020) before patient enrollment.

The study included 51 patients diagnosed with non-COVID-19 community-acquired pneumonia (CAP). Diagnosis of CAP was considered if there were new radiological infiltrates in the presence of symptoms compatible with pneumonia (e.g., cough, sputum production, fever, dyspnea, and chest pain) [8].

#### Inclusion criteria

All patients above 18 years old, both sexes, fulfilling diagnosis of CAP with 2 PCR negative swabs for COVID-19 at least 1 day apart (based on Egyptian Ministry of Health recommendations).

#### **Exclusion criteria**

COVID-19 infection, non-pulmonary infections, HIV infection, recent pulmonary embolism, liver, renal, and cardiac diseases.

Data were collected from all patients with special emphasis on symptoms of pneumonia, risk factors (smoking, COPD, diabetes mellitus, and malignancy), clinical evaluation with assessment of disease severity using CURB-65 which is a score for triage decisions, length of stay, and risk stratification in cases of pneumonia. It gives one point for each of the following (confusion, urea > 7 mmol/L, respiratory rate  $\geq$  30 breaths/min, blood pressure < 90 mmHg (systolic) or  $\leq$  60 mmHg (diastolic), age  $\geq$  65 years). Score 0–1; suitable for home treatment, low mortality (1.5%), score 2; consider hospital treatment, intermediate mortality (9.2%) and score  $\geq$  3; assess the need for ICU admission, high mortality (22%)

[9]. Chest X-ray and/or computed tomography (CT) of the chest was performed to confirm pneumonia diagnosis and to assess the site, number of the affected lobes, associated signs like cavitations, bronchiolar dilatation, site, and amount of pleural effusion if present. Multilobar pneumonia was defined as chest-radiograph infiltrates involving  $\geq 2$  lobes; bilateral when the involved lobes were in both the right and left lungs, and localized when only one pulmonary lobe was involved [10].

Aspiration of pleural fluid was performed in some cases, diagnosis of empyema was confirmed by the presence of frank pus or bacteria by gram stain or culture in the pleural fluid [11]. Complicated parapneumonic effusion was defined if there is a low glucose level, pleural fluid PH is below 7.20, and cultures from fluid are negative [12]. Patients were classified into two groups group A (pneumonia only) and group B (pneumonia complicated with empyema /complicated para-pneumonic effusion).

Sputum Gram stain and/or culture was not performed routinely in CAP cases managed at home, reserved for cases admitted to the hospital especially if classified as severe pneumonia or when MRSA or pseudomonas aeruginosa were suspected [8].

Venous blood samples for complete blood picture, differential leucocytic count, and platelets count which was done by the newly developed automated hematology analyzer XN (Sysmex, Kobe, Japan) enumerates and classifies blood cells by a combination of direct current detection and flow cytometry [13]. Normal value of total leucocytic count (TLC) is  $(4-7)10^3/\mu$ l. Normal neutrophils range is (2.5-7) 10<sup>3</sup>/µl normal lymphocytes range is (1-4.8) 10<sup>3</sup>/µl and normal platelets count is  $(150-450)10^3/\mu l$  [14]. The neutrophil-to-lymphocyte ratio (NLR) is easily obtained by dividing the absolute neutrophil count by the absolute lymphocyte count from peripheral complete blood counts. The normal range of NLR is in the range of 1-2 (0.8-2.2). The values above 3.0 and below 0.7 in adults are pathological [15]. C-reactive protein (CRP) is determined by photometric measurement of the latex agglutination reaction, the normal value of CRP is less than 6 mg/L [16]. D-dimer was done using Sysmex CS-5100 System is a fully automated, computer-interfaced coagulation analyzer intended for in vitro diagnostic use, and the normal value of D-dimer is less than 0.5 ng/ml [17]. Ferritin was performed using a standard auto-analyzer. Cobas c501 biochemistry human-driven ferritin shows agglutination with latex particles covered with anti-ferritin antibodies [18]. The normal value of ferritin is 10-291 ng/ml. Examination of erythrocyte sedimentation rate (ESR) was performed manually using the Westergren reference method. The normal value of ESR is the first-hour mm/h up to 10 and the second hour up to 20 [19]. All samples were taken within 24–48 h of the onset of the symptoms.

## Statistical methods

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the nonparametric Mann–Whitney test [20]. For comparing categorical data, a chi-square ( $\chi$ 2) test was performed. An exact test was used instead when the expected frequency was less than 5 [21]. Correlations between quantitative variables were done using the Spearman correlation coefficient [22]. *P* values less than 0.05 were considered statistically significant.

# Results

The current study was a cross-section prospective study that included 51 patients diagnosed with non-COVID-19 community-acquired pneumonia (CAP). The mean age of studied patients was 47 ( $SD \pm 17$ )

years, more than half of them were males (56.9%) and smokers (54.9%). About (45.1%) suffered from DM and (39.2%) were known COPD. The main presenting symptoms were productive cough (90.2%) and fever (92.2%)with a mean duration of fever of 4.67 (SD  $\pm$  4.38) days. Other symptoms included Dyspnea (39.2%) and Chest pain (43.1%). Forty-four (86.3%) of patients were admitted and managed at a hospital and 7 (13.7%) were treated in as outpatients setting. The mean values of TLC, platelets, neutrophils, CRP, D-dimer, Ferritin, and ESR were elevated than normal values in the studied patients. The range of NLR was (1.3-4.7) with a mean value  $2.3 \pm 0.72$ . Risk stratification of patients was done using CURB65 score  $(2.58 \pm 0.9)$ . The study group was classified into 2 groups; pneumonia only (Group A) included 33 patients (64.7%) and pneumonia+empyema or complicated para-penumonic effusion (group B) consisted of 18 patients (35.3%) (Tables 1 and 2).

The most common radiological findings were lobar consolidation (i.e., one lobe affected) in 42 patients

Table 1 Sex, risk factors, clinical symptoms, site of management, and classification of the study population

		Count	%
Sex	Male	29	56.9%
	Female	22	43.1%
Smoking	Yes	28	54.9%
	No	23	45.1%
DM	Yes	23	45.1%
	No	28	54.9%
Malignancy	Yes	0	0%
	No	51	100%
COPD	Yes	20	39.2%
	No	31	60.8%
Cough	Productive	46	90.2%
	dry	5	9.8%
Dyspnea	Yes	20	39.2%
	No	31	60.8%
Chest pain	Yes	22	43.1%
	No	29	56.9%
Fever	Yes	47	92.2%
	No	4	7.8%
Site of management	Hospital admission	44	86.3%
	Outpatient	7	13.7%
Classification of cases	Pneumonia only	33	64.7%
	Pneumonia + empyema and/or complicated parapneumonic effusion	18	35.3%
Radiological findings	Lobar consolidation (one lobe involved)	42	82.3%
	Bilateral and/or multi-lobar consolidation	9	17.7%
	Pleural effusion	18	35.3%
	Cavitation	4	7.8%
	Bronchiolar dilation	2	3.9%

 Table 2
 Age, fever duration, CURB65, and levels APR of the study population

	Mean	Standard deviation	Median	Minimum	Maximum
Age (years)	46.84	17.35	48.00	18.00	75.00
fever duration (days)	4.67	4.38	3.00	0.00	15.00
TLC (10 <sup>3</sup> /µl)	13.73	6.35	13.20	3.50	28.00
Platelets (10 <sup>3</sup> /µl)	320.63	171.74	300.00	16.00	812.00
CRP (mg/L)	142.72	108.62	106.00	4.00	427.00
D.dimer (ng/ml)	1.26	1.05	0.90	0.19	3.30
ESR 1 h	57.31	37.44	50.00	3.00	150.00
ESR 2 h	82.10	33.32	85.00	8.00	150.00
Ferritin (ng/ml)	547.55	498.90	410.00	21.80	2443.00
CURB 65 score	2.58	0.90	2.00	1.00	4.00
Neutrophils (10³/µl)	8.7	4.2	8.1	1.98	17.4
lympho- cytes(10 <sup>3</sup> /µl)	3.96	1.9	3.8	0.83	10.2
NLR	2.30	0.72	2.10	1.30	4.70

*TLC* Total leucocytic count, *CRP* c-reactive protein, *ESR* Erythrocyte sedimentation rate, *NLR* Neutrophil-to-lymphocyte ratio

(82.3%), bilateral consolidation and/or multi-lobar affection in 9 patients (17.7%), pleural effusion 18 patients (35.3%), cavitations and bronchiolar dilations in 4 (7.8%) and 2 (3.9%) patients respectively.

Significant positive correlations were found between the duration of fever and the following markers; CRP, D-dimer, and ferritin with p values = 0.024, 0.012, and 0.034 respectively (Table 3). Statistically significant positive correlations were found between CURB65 and both CRP and ferritin with p values = 0.007 and 0.020 as described in (Table 4).

Considering the age of patients, group B was significantly older than group A, P=0.03 (Table 5). Moreover, DM was predominant in Group B, but with an insignificant p value=0.06. However, other risk factors and sex had a non-significant impact between both groups.

ESR levels in the 1st, 2nd h, and platelets count were significantly higher in group B than in group A, P=0.001, < 0.001, and 0.023 respectively. However, other markers did not show a significant difference between both groups (Table 5).

# Discussion

Community-acquired pneumonia (CAP) is one of the most common disorders faced in clinical practice [1], and the most common cause of mortality among infectious diseases [3].

The present study included 51 patients diagnosed with non-COVID-19 community-acquired pneumonia,

**Table 3** Correlation between TLC, PLT, CRP, D-dimer, ferritin,ESR1st, ESR2nd, neutrophils, lymphocytes, and NLR and durationof fever in the study population

-0.086- 0.546 51
0.546 51
51
-0.024-
0.865
51
0.315
0.024
51
0.349
0.012
51
0.298
0.034
51
-0.003-
0.984
51
0.038
0.791
51
-0.088-
0.539
51
-0.151-
0.289
51
0.120
0.401
0.401

TLC Total leucocytic count, CRP c-reactive protein, ESR Erythrocyte sedimentation rate, NLR Neutrophil-to-lymphocyte ratio

and the mean age of patients was 47 (SD  $\pm$  17) years, males represented (56.9%) of the study group, risk factors for pneumonia were smoking (54.9%), DM (45.1%), and COPD (39.2%).

It is well known that the incidence of pneumonia increases with age and the risk of CAP seems to be higher in males than females and in patients with chronic respiratory diseases, DM, smoking, alcohol consumption, and immune-compromising conditions [23–25].

In the current study, the chief complaints were productive cough (90.2%) and fever (92.2%) with a mean duration of fever of 4.67 (SD  $\pm$  4.38) days. This was matched with previous studies in which the mean fever duration was  $5.5 \pm 1.1$  days and productive cough among pneumonia cases ranged from 86 to 100% [26, 27]. **Table 4** Correlation between TLC, PLT, CRP, D-dimer, ferritin,ESR1st, ESR2nd, neutrophils, lymphocytes, and NLR and CURB-65in the study population

		CURB 65 score
Tlc	Correlation coefficient	0.019
	<i>P</i> value	0.917
	Ν	33
Platelets	Correlation coefficient	-0.123-
	<i>P</i> value	0.497
	Ν	33
CRP	Correlation coefficient	0.457
	<i>P</i> value	0.007
	Ν	33
D.dimer	Correlation coefficient	0.161
	<i>P</i> value	0.371
	Ν	33
Ferritin	Correlation coefficient	0.402
	<i>P</i> value	0.020
	Ν	33
ESR 1h	Correlation coefficient	0.268
	<i>P</i> value	0.131
	Ν	33
ESR 2h	Correlation coefficient	0.241
	<i>P</i> value	0.177
	Ν	33
neutrophils	Correlation coefficient	-0.013-
	<i>P</i> value	0.941
	Ν	33
lymphocytes	Correlation coefficient	-0.054-
	<i>P</i> value	0.764
	Ν	33
NLR	Correlation coefficient	0.107
	<i>P</i> value	0.554
	Ν	33

TLC total leucocytic count, CRP c-reactive protein, ESR erythrocyte sedimentation rate, NLR neutrophil-to-lymphocyte ratio

Acute inflammatory response triggered by infection of the lower respiratory tract as in pneumonia is considered a complex interaction between the immune system and inflammatory cytokines in order to regulate the inflammatory process [28].

APR are biomarkers of inflammation, their levels show significant changes during active inflammation. They are categorized as positive or negative based on their serum level during the inflammatory process [29].

The present study reported an increase in the mean values of TLC, platelets, and neutrophils than normal values, with an NLR range was 1.3-4.7 and a mean value of  $2.3 \pm 0.72$ .

This was matched with previous studies that reported elevated TLC and neutrophils in CAP and emphasized

their role in diagnosis and follow-up of treatment response [30, 31].

NLR is a useful and simple marker, one study demonstrated that NLR can perform better than conventional biomarkers in the assessment of severity and predicting mortality in elderly patients with CAP [32], these findings were not matched with our results this may be related to differences in the age, co-morbid diseases and number of enrolled patients in their study.

On the other hand, another study confirmed that NLR is not analogous to traditional biomarkers such as CRP and procalcitonin in the diagnosis and evaluation of the severity of pneumonia [33] which is matched with our findings.

Recent meta-analysis concluded that NLR is a promising marker in predicting the prognosis of pneumonia either alone or in a combination of other biomarkers or scoring systems; however, further studies are needed to confirm these findings [34].

Platelets are crucial inflammatory cells that release a lot of inflammatory mediators in response to infection hence considered as acute phase reactant. It has been reported that changes in platelet count might be used as diagnostic and prognostic markers of various inflammatory disorders [35].

Although little is known about the role of platelets in CAP, a previous study reported that changes in platelets may be considered a better marker than leucocytic abnormalities in children with pneumonia [6].

In our study, platelet count was significantly higher in pneumonia cases complicated with empyema/para-pneumonic effusion (group B) than in group A, p value = 0.023 (Table 5). This was consistence with another study that described the role of platelet count as a predictor of CAP complications [36].

We found that mean values of CRP, D-dimer, and ferritin were elevated in the study population than normal values. Positive significant correlations were found between the duration of fever and the following markers; CRP, D-dimer, and ferritin with p values=0.024, 0.012, and 0.034 respectively, when correlating pneumonia severity using CURB65 with APR, positive significant correlation was noticed between CURB65 and both CRP and ferritin only with p values=0.007 and 0.020.

CRP is one of the positive acute-phase proteins produced by hepatocytes in response to infection or inflammation [37].

Previous studies described elevated CRP in pneumonia and found a proportional relation between its level and pneumonia severity as assessed by the APACHE II scores [33, 38].

D-dimer is a product of fibrin degradation by plasmin, high levels of D-dimer were observed in

	Group A (pneumonia only) (N=33)					Group B (pneumonia + empyema or complicated para-pneumonic effusion) ( <i>N</i> =18)				P value	
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age (years)	40.06	15.20	40.00	18.00	71.00	50.55	17.54	55.00	18.00	75.00	0.038
Fever duration (days)	3.94	3.01	3.00	0.00	11.00	6.00	6.05	3.50	1.00	25.00	0.315
Tlc (10 <sup>3</sup> /µl)	13.04	6.58	12.80	3.50	27.00	14.99	5.87	13.60	7.20	28.00	0.237
Platelets (10 <sup>3</sup> /µl)	286.76	180.77	276.00	16.00	812.00	382.72	137.58	361.00	170.00	653.00	0.023
CRP (mg/L)	135.74	110.75	97.00	4.00	384.00	155.51	106.52	121.00	30.97	427.00	0.324
D.dimer (ng/ml)	1.32	1.09	1.10	0.19	3.30	1.16	1.00	0.72	0.19	3.10	0.820
ESR 1h	45.91	35.85	37.00	3.00	150.00	78.22	31.43	73.00	25.00	125.00	0.001
ESR 2h	71.18	34.27	75.00	8.00	150.00	102.11	19.97	105.00	55.00	130.00	< 0.001
Ferritin (ng/ml)	518.18	470.81	412.00	21.80	1820.00	601.39	556.84	377.10	113.00	2443.00	0.672
NLR	2.21	0.70	2.10	1.30	3.90	2.46	0.75	2.40	1.50	4.70	0.176

 Table 5
 Comparison of both groups regarding age, fever duration, and APR

TLC Total leucocytic count, CRP c-reactive protein, ESR Erythrocyte sedimentation rate, NLR Neutrophil-to-lymphocyte ratio

conditions associated with fibrin synthesis and catabolism such as deep venous thrombosis (DVT), pulmonary embolism (PE), post-operative state, trauma, severe infections and disseminated intravascular coagulopathy (DIC) [39]. Previous studies have suggested that elevated levels of D-dimer in CAP are directly related to intra- and extra-vascular coagulation triggered by acute damage of lung parenchyma during the infectious process [40].

Some studies reported a positive correlation between D-dimer level and pneumonia severity using the pneumonia severity index (PSI) and the extent of radiological involvement [41, 42]. In the current study, we assessed pneumonia severity using the CURB65 score but it was not significantly correlated to D-dimer.

Ferritin is a protein produced by liver cells, kupffer cells, and macrophages, it is considered one of the acute phase reactant as its level increases in response to infectious and various inflammatory conditions [43].

One study reported a marked elevation of ferritin concentration in 10% of CAP patients admitted to the ICU [43]. Another one found higher levels of ferritin in patients with CAP who developed sepsis [44] suggesting that higher ferritin levels may be associated with pneumonia severity which is matched with our results.

ESR is a non-specific inflammatory marker, any condition that affects red blood cells or fibrinogen levels can affect ESR values.

It was found that ESR was elevated than normal values in the study population and levels in the 1st and 2nd h were significantly higher in group B than group A, P=0.001 and <0.001 respectively. So, we can assume that elevated ESR may be used as a predictor of complications in CAP but further studies on larger populations are needed.

Our results were matched with previous research which reported high ESR values in CAP [27, 32].

Another study found significantly high values of ESR in young children with lobar pneumonia, but it confirmed that procalcitonin can perform better than ESR in the prediction of CAP in children [45].

# Limitations

This study has several limitations:

- (1) Single-center study with small numbers of patients.2) We did not exclude patients on prior use of antibi-
- otics, this may affect the level of APR.
- 3) Follow-up levels of APR and assessment of the response to treatment were not included in the study.4) We did not correlate between APR and mortality.

### Conclusions

In patients with non-COVID-19 community-acquired pneumonia markers such as TLC, neutrophils, platelets, CRP, D-dimer, ferritin, and ESR were elevated than normal reference values. Significant positive correlations were found between the duration of fever and CRP, D-dimer, and ferritin. Assessment of pneumonia severity was done using CURB65 score which was positively correlated with CRP and ferritin. It was found that Platelets and ESR values were significantly elevated in the CAP group complicated with empyema or complicated para-pneumonic effusion assuming that both markers could be used as predictors of complications in CAP; however, further researches are needed to emphasize or decline this assumption.

## Abbreviations

APR	Acute phase reactant
CAP	Community-acquired pneumonia
COVID-19	Coronavirus infection of 2019
CURB65	Confusion, urea, respiratory rate, blood pressure, and age above 65
NLR	Neutrophils-to-lymphocyte ratio

CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
PCR	Polymerase chain reaction
HIV	Human immune deficiency virus
ICU	Intensive care unit
CT	Computed tomography
DM	Diabetes mellitus
COPD	Chronic obstructive pulmonary disease
APACHE	Acute physiology and chronic health evaluation
DVT	Deep venous thrombosis
PE	Pulmonary embolism
DIC	Disseminated intravascular coagulation
PSI	Pneumonia severity index

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#### Authors' contributions

Yosri Akl was responsible for the acquisition of data, analysis, drafting of the article, and final approval. Ahmed Elkomy was responsible for the acquisition of data, analysis, drafting of the article, and final approval. Eman Kamal Ibrahim was responsible for the conception and design, revising, writing, and final approval of the article.

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No.

#### Availability of data and materials

Data from the current study are available from the corresponding author upon re upon reasonable request.

### Declarations

#### Ethics approval and consent to participate

All methods were carried in accordance with relevant regulations and guidelines, informed consent was obtained from all participants and/or their legal guardians, and the study was approved by the research ethical committee, Cairo University with code (MS-358–2020).

#### **Consent for publication**

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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