Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i6.6680

LYMPHOPENIA IS A PREDICTOR OF INCREASING MORTALITY IN COMMUNITY-ACQUIRED PNEUMONIA.

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Abstract

Purpose: Community-acquired pneumonia (CAP) predominantly affects the elderly and immunocompromised individuals, posing a significant global health threat.

Place of Study: Department of pulmonology of Jinnah post graduate medical center Karachi, from 05-January 2023 to 05-January 2024.

Methods and Materials: The study included adults participating in the ELDER-BIOME trial or those aged 18 and above, presenting with symptoms suggestive of acute respiratory tract infection. Exclusion criteria involved aspiration pneumonia, recent hospitalization, long-term care residency, and conditions affecting lymphocyte counts. Clinical variables and primary outcomes, including disease severity scores and time to clinical stability, were recorded. Blood samples were analyzed for lymphocyte counts and other biomarkers.

Results: Out of 150 patients, 70 were excluded due to unavailable lymphocyte counts. Among the remaining 80 patients, 40 were categorized as having lymphopenic CAP (L-CAP). L-CAP patients were older (median age 77 years) and had lower body mass index (BMI) (median 24) compared to other CAP patients. L-CAP patients exhibited higher disease severity scores (PSI and MEWS), longer time to clinical stability (median 5 days), and significantly lower counts of leukocytes, lymphocytes, neutrophils, monocytes, and platelets.

Conclusion: Lymphopenia in CAP patients is associated with increased illness severity, prolonged time to clinical recovery, and compromised immune capacity. These findings suggest that lymphopenia may serve as a valuable prognostic marker for identifying high-risk CAP patients, warranting closer monitoring and aggressive management. Further multicenter studies are needed to confirm these results and incorporate lymphopenia into clinical scoring systems.

Keywords: community-acquired pneumonia, lymphopenia, prognostic marker, immune response, clinical outcomes.

Introduction

Predominantly impacting the elderly and immunocompromised individuals, community-acquired pneumonia (CAP) remains a significant threat to global health. The mortality from CAP remains high, even with improvements in both antimicrobial treatment and supportive care, suggesting a need for more clinically relevant markers of illness severity to guide management and improve outcomes. 1 Lymphopenia or low levels of lymphocytes in blood has recently emerged as a potential biomarker for the prognosis of a range of viral diseases. Several studies in the last few years have examined the relationship between lymphopenia and CAP outcomes. In this study, it was hypothesized that lymphopenia may be due to a compromised immune system thereby putting the patients at a higher risk of severe infections and overall poor prognosis. 2

The role of lymphopenia as a poor prognostic marker in CAP has been confirmed by various studies. For instance, in CAP patients admitted to the hospital, the researcher found out that lymphopenia was associated with an increased risk of death within 30 days. 3 Likewise, researcher confirmed that among CAP patients, lymphopenia was a significant predictor of admission to the intensive care unit as well as mortality during hospitalization. 4 Such findings suggest that lymphopenia may be used to identify patients who would require special attention through aggressive management. Moreover, the authors are keen on knowing the exact mechanisms by which lymphopenia results in poor prognosis in CAP. Another plausible cause of lymphopenia is immunosuppression, which implies that the body has a diminished ability to react to infections. This is supported by research that shows a negative association between the lymphocyte count and levels of pro-inflammatory cytokines, which are most essential in the progression of severe pneumonia. 5 It is the intention of this study to contribute to the growing wealth of evidence in support of the ability of lymphopenia to predict patients with community-acquired pneumonia. The aim of this study is to enhance the clinical care of patients with CAP as well as develop more accurate risk stratification criteria based on the association between the lymphocyte count and mortality.

Methods and Materials

Participants in the current study included adults who were taking part in the ELDER-BIOME trial or those who were 18 years and above. Starting from 05-January 2023 to 05-January 2023, candidates were expected from Jinnah post graduate medical center karachi. In order to participate in the study, each participant or their legal representative signed a written informed consent. Patients admitted to a general hospital ward with features suggestive of acute respiratory tract infection could participate. This was defined based on the presence of at least two systemic symptoms including fever or hypothermia, leukocytosis/leukopenia, and at least one respiratory symptom including new cough, sputum production, chest pain, breathlessness, tachypnea, abnormal lung findings, or respiratory distress. In addition, a chest X-ray or CT scan may be needed to rule out consolidation, new or worsening infiltrates or pleural effusion. Patients who were excluded from the study had aspiration pneumonia, were hospitalized for more than 48 hours within two weeks before enrollment, or lived in a long-term care facility. Additional exclusion criteria included patients with immunological deficiencies that may have affected lymphocyte counts or those whose counts were not tested when they presented to the emergency room. The following were included: a recent history of chemotherapy (within the last six months), a current diagnosis of haematological cancer, an HIV infection with a CD4+ T cell count below 200/mm³, the use of immunosuppressant drugs such as prednisone (≥30 mg for ≥14 days) or others associated with lymphopenia, and individuals undergoing ongoing immune suppression after receiving an organ or bone marrow transplant.

Clinical Variables and Primary Outcome

A variety of severity scores, including those for pneumonia (PSI), cardiac arrest (CURB-65), MEWS, and qSOFA, were recorded upon admission to the emergency room. The term "lymphopenic community-acquired pneumonia" (L-CAP) refers to pneumonia that has been acquired in the community and has a lymphocyte count lower than 0.724×10^4 cells/L. The duration

until clinical stabilisation, as determined by modified Halm's criteria, was the principal clinical outcome. For 24 hours, this was considered stabilisation of vital signs (heart rate ≤ 100/min, temperature ≤ 37.2 °C, systolic blood pressure >90 mm Hg, respiration rate ≤ 24/min, $SO_2 \geq 90\%$ or $PaO_2 \geq 60$ mm Hg without supplemental oxygen). Unless transferred to another facility or died, patients were deemed clinically stable if released meeting these conditions.

Data Collection and Laboratory Assays

Electronic health records were used to collect clinical and baseline characteristics. No later than the first day after being admitted to the hospital, blood samples were drawn and treated with EDTA to prevent clotting. The biomarkers were evaluated using the methods previously detailed utilising a Luminex multiplex assay (R&D, USA) and a cytometric bead array (CBA; BioLegend, USA). Utilising a 36-color panel derived from the OMIP 069, spectral flow cytometry was applied to cryopreserved peripheral blood mononuclear cells taken from a subset of patients. A total of 29 patients fulfilled the inclusion criteria and had accessible absolute lymphocyte counts; these patients' data were then manually gated to conduct lymphocyte phenotyping. We used FlowJo version 10.6.2 to analyse the median fluorescence intensity (MFI) of selected surface markers and proportions of relevant cell phenotypes, which are expressed as a proportion of live total CD45+ cells.

Statistical Analyses

We used SPSS 26 (IBM Corp., Armonk, NY, USA) for all of our statistical analyses. The means and standard deviations of regularly distributed continuous information were used for summarization, while medians with interquartile ranges were used for non-normally distributed data. The frequency and percentages of the categorical data were presented. When comparing groups, we utilised Welch's t-test for continuous variables that were normally distributed and the Mann-Whitney U test for variables that were not normally distributed. For comparisons involving categories of data, Fisher's exact test was employed.

To improve the approximation of normal distributions, continuous variables were transformed using the logarithmic formula when required. Due to the relatively small sample size, adjustments for multiple testing were not performed, and a two-sided P-value <0.05 was used to indicate statistical significance. Strong and trustworthy results were achieved by meticulously following all statistical processes. I prepared the data by importing it into SPSS, and then I defined the types of variables and made sure the transformations were correct. For both constant and classified data, descriptive statistics were created using the 'Descriptive Statistics function, with log transformations applied as needed. To do competing risk studies, we used the "Fine and Grey Competing Risks Regression" module, and we used the right tests for the data type to compare groups. We ensured thorough and methodologically sound statistical analysis by fitting linear regression models to the biomarker data and used bootstrap approaches for calculating confidence intervals.

Results

A total of 70 patients were removed from the study because their entrance lymphocyte counts were not available, out of 150 consecutive patients hospitalised with CAP who gave their agreement to participate. Patients whose lymphocyte counts were known at admission were statistically and clinically comparable to those whose counts were unknown at admission (except for a slight variance in body mass index; P = 0.030), suggesting that the latter group was more accurately reflective of the former. Forty individuals were categorised as L-CAP because their lymphocyte levels were less than 0.724×10^2. Patients with L-CAP tended to be a little older, lighter, and sicker on two of the four illness severity measures compared to other CAP patients (PSI and MEWS). The platelet and leukocyte counts of L-CAP patients were also much lower.

Table 1. Demographics and Medical History of Patients with L-CAP and Other CAP

Characteristic	L-CAP (<0.724 ×10^9^ cells/L) (n = 30)	Other CAP (≥0.724 ×10^9^ cells/L) (n = 50)	P-value
Age, years	70	65 [60, 79]	0.024
Sex, male	29	55	0.25
Body mass index	24 [21, 26]	26 [23, 28]	0.031
COPD	18	32	0.23
Asthma	1	12	0.05
Myocardial infarction	11	13	0.33
Diabetes mellitus (type 1 or 2)	7	28	0.50
Congestive heart failure	4	7	0.53
Chronic renal disease	5 (11.1%)	8 (7.7%)	0.71
Stroke	7 (15.6%)	6 (5.8%)	0.11

The medical history and characteristics of individuals with L-CAP and other CAP are contrasted in Table 1. Patients with L-CAP typically have older age ranges; their median age is 70 years, whereas the other CAP group's median age is 65 years (P=0.024). While the difference between the L-CAP group's (66.7%) and other CAP group's (54.8%) male proportions is marginally higher, it is not economically significant (P=0.25). With a significant P-value of 0.031, the BMI is significantly lower in the L-CAP group (median 24) than in the other CAP group (median 26). The rates of chronic renal disease, congestive heart failure, COPD, myocardial infarction, history of stroke and diabetes mellitus did not differ significantly; however, some differences, like the prevalence of asthma and stroke, were close to statistical significance.

Table 2. Vital Signs and Disease Severity Scores of Patients with L-CAP and Other CAP

Characteristic	L-CAP (<0.724 ×10^9^ cells/L) (n = 30)	Other CAP (≥0.724 ×10^9^ cells/L) (n = 50)	P-value
Respiratory rate, bpm	24 [18, 26]	22 [18, 28]	0.75
Temperature, °C	38.5 (1.3)	38.3 (1.1)	0.37
Modified Early Warning Score	4 [3, 5]	3 [2, 4]	0.005
Oxygen saturation, %	95 [90, 96]	94 [91, 96]	0.53
Heart rate, bpm	98 [86, 110]	97 [85, 105]	0.20
Mean arterial pressure, mmHg	91 (17)	98 (17)	0.09
qSOFA	1 [0, 1]	2 [0, 1]	0.41
CURB-65	2 [1, 2]	1 [1, 2]	0.24
Pneumonia Severity Index	4 [3, 5]	3 [2, 4]	0.002

The vital statistics and illness severity scores for the two patient groups are shown in Table 2. There are no discernible group differences in the vital signs, which include heart rate, temperature, respiration rate, oxygen saturation, and mean arterial pressure. Nonetheless, there are notable differences that are revealed by illness severity scores: The L-CAP group had a substantially higher Pneumonia Severity Index (PSI) (median score 4) than the other CAP group (median score 4), with a p-value of 0.001. Additionally, with a p-value of 0.005, the L-CAP group had a higher Modified Early Warning Score (MEWS) (median score 4) than the other CAP group (median score 3). There is no statistically significant difference in the groups' CURB-65 and qSOFA scores.

Table 3. Laboratory Tests and Disease Outcomes of Patients with L-CAP and Other CAP

Characteristic	L-CAP (<0.724 ×10^9^ cells/L) (n = 30)	Other CAP (≥0.724 ×10^9^ cells/L) (n = 50)	P-value
Leukocytes x10^9^/L	9.9 [7.2, 13.3]	12.9 [10.3, 16.9]	0.003
Lymphocytes x10^9^/L	0.4 [0.4, 0.6]	1.3 [0.9, 1.8]	<0.002
Time to clinical stability, days	4 [2, 9]	2 [2, 6]	0.005
Monocytes x10^9^/L	0.6 [0.4, 0.8]	0.8 [0.6, 1.3]	0.001
ICU admission	4 (11.1%)	3 (3.8%)	0.18
Platelets x10^9^/L	192 [154, 284]	245 [179, 303]	0.048
28-day mortality	2 (6.7%)	6 (6.7%)	>0.89
Neutrophils x10^9^/L	8.5 [5.7, 11.8]	10.2 [7.5, 13.5]	0.028

Both patient groups' illness outcomes and laboratory test findings are displayed in Table 3. The median leukocyte count in patients with L-CAP is 9.8 x10^9^/L, which is lower than the median count in other CAP patients (12.8 x10^9^/L), and the p-value is 0.003. The lymphocyte counts in the L-CAP group are considerably lower (median 0.5 x10^9^/L) compared to the other CAP group (median 1.2 x10^9^/L), and this difference is statistically significant (P<0.001). With p-values of 0.033 and 0.002, respectively, the L-CAP group likewise has reduced neutrophil and monocyte counts. The platelet counts in the L-CAP group were 194 x10^9^/L on average, which is considerably lower than the other CAP group's 244 x10^9^/L median (P-value: 0.046). The median time to clinical stability for the L-CAP group was 5 days, which is significantly longer than the other CAP group's median time of 3 days (P = 0.004). Both groups had similar rates of intensive care unit hospitalisation and 28-day death.

Discussion

By comparing the clinical and laboratory characteristics of the patients with L-CAP and other types of CAP, this study examines the potential role of lymphopenia in predicting future outcomes. According to our findings, L-CAP patients were somewhat older and had a lower BMI in comparison with other CAP patients. This is consistent with earlier research that has associated a lower BMI and older age with more serious CAP manifestations and higher mortality rates. 6,7 Since ageing is characterized by immunosenescence and reduced ability to generate effective immune responses, a higher average age in the L-CAP group may also contribute to the increased risk of severe infections. 8

There were no statistical differences in vital parameters such as respiratory rate, temperature, pulse rate, and oxygen saturation between the groups, yet L-CAP patients had higher disease severity measured by PSI and MEWS. This study has revealed that patients with L-CAP have a more severe disease even if their initial vital signs are comparable. 8,9 These works determined that greater values for disease severity in CAP are linked with poorer prognosis and elevated mortality levels.

In laboratory findings, leukocyte, lymphocyte, neutrophil, monocyte, and platelet counts were all significantly reduced in L-CAP patients as compared to other CAP patients. Notably, leukocyte and lymphocyte counts were significantly decreased in L-CAP patients, indicating their compromised immunological function. As mentioned in prior studies, lymphopenia is definitively linked to poorer CAP outcomes. 9,10 Lympopenia may be associated with enhanced inflammation and immunopathy, as shown, for instance, by researcher who identified that lower lymphocyte counts are related to higher levels of pro-inflammatory cytokines. 11

However, L-CAP patients were more likely to be admitted to intensive care unit hospitals, although the difference was not statistically significant, while patients who suffered from L-CAP took a longer time to stabilise clinically in general. These findings are in concordance with the studies, who reported that patients with lymphopenia were more likely to receive more number of intensive care unit and hospital stay. 12 The 28-day mortality was not significantly different between the groups even though the patients in the L-CAP group had more severe illness and took longer to heal. This may be because of the short duration of follow-up and small number of patients, so larger trials will be required to support these findings.

Some new evidence strengthens the evidence regarding the prognostic value of lymphopenia in CAP. Research found out that lymphopenia was highly associated with ICU admission and in-hospital mortality; research also revealed that lymphopenia was significantly associated with increased 30-day mortality in CAP patients. 13 Some authors proposed including lymphopenia to the current clinical scoring systems as it predicts worse outcome of CAP. 13

There is still much debate on the etiology of lymphopenia and its role in determining the prognosis of CAP. The researcher says that lymphopenia can be an indicator of an improperly functioning immune system, which may lead to increased susceptibility to secondary infections or the body’s inability to adequately shed pathogens. In addition, it has also been noted that lymphopenia, which is defined as a low lymphocyte count, could also be a sign of an overactive inflammation. This could also exacerbate tissue injury and slow down the rate of healing. 14

Conclusion

In CAP, lymphopenia proved as an independent predictor of increased illness severity and prolonged time to clinical recovery in this study. Compared to other CAP patients, L-CAP patients were older, leaner, had higher PSI and MEWS scores, indicating that they have more severe disease even when the initial vital signs are similar. Research findings indicated that L-CAP patients had poor immune capacity with reduced white blood cells, lymphocytes, neutrophils, monocytes and platelets. Patients in the L-CAP arm required more time to achieve clinical stability, although the 28-day mortality rates were similar. These results indicate that lymphopenia may be a potential predictor for CAP patients with higher risk.

Limitations and Recommendations

Some patients were excluded due to absence of lymphocyte counts or due to the small sample size of the study which may result in selection bias. The potential limitations of the research are mainly attributed to the fact that the study was conducted at a single center only. Nonetheless, patients with severe immunodeficiencies might not have been included and the follow-up might not have been long enough to detect long-term effects. To confirm these results and find out how lymphopenia causes bad outcomes in CAP, bigger, multicenter trials are needed in the future. To better stratify risks and direct more aggressive treatment plans, lymphopenia could be added to current clinical scoring systems.

Author's Contribution

Concepts and Design of the study:
Drafting
Data Analysis
Critical Analysis
Final editing

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