ORIGINAL ARTICLE

# Peripheral Blood Smear Atypical Lymphocytes Association With Covid-19 Mortality

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## ABSTRACT

**Introduction:** COVID-19 disease is currently pandemic, and its prevalence in Saudi Arabia is concerning. The SARS-CoV-2 virus primarily affects the lungs, but it also affects the haematopoietic system. The atypical lymphocytes on peripheral blood film that have a distinct morphological appearance were of particular interest in this study. Our goal was to see a link between atypical lymphocytes and COVID-19 patient mortality. **Methods:** This four-month single-centered prospective descriptive study was conducted in Makkah, Saudi Arabia. COVID-19 patients of both genders were randomly selected based on inclusion criteria. The data from the patient's electronic medical record was extracted. All patients' peripheral blood film parameters were recorded on days 3, 7, and 14 after admission. The statistical data was analysed using SPSS version 23. The Fisher's exact test was used to determine the relationship with mortality. A p value of 0.05 was considered significant. **Results:** The total number of cases enrolled in the study was 226. The patients' average age was 58 years (SD 0.5289). On the third day of admission, 88.2 % of patients with COVID-19 had atypical lymphocytes, with a mean of 2.35 ± 0.927. A significant correlation ($p < 0.001$) exists between atypical lymphocytes decreasing percentage number on the 3rd, 7th, and 14th days of admission and death. **Conclusion:** The decrease in the number of atypical lymphocytes on peripheral blood film has a significant association with the patients' mortality. This fact can be used to develop a tailored management strategy based on the observation of peripheral blood film.
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## INTRODUCTION

The COVID-19 pandemic began in December 2019. The first case of this disease was found in Wuhan, China (1). Later, it spread throughout the world, including Saudi Arabia. The number of COVID-19 patients in Saudi Arabia is increasing at an alarming rate. COVID-19 disease is caused by the Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) virus, which is a systemic disorder affecting the lungs being the main target organ. The clinical presentation of patients ranges from asymptomatic to critical, culminating in acute respiratory failure, sepsis, multi-organ failure, and, eventually, death (2). Even though patients with milder symptoms and a good prognosis are more common. COVID-19 patients have experienced some unusual haematological changes. An increase in neutrophil count (neutrophilia), a decrease in lymphocyte count (lymphocytopenia), a decrease in monocyte count (monocytopenia), a decrease in eosinophil count (eosinopenia), and a decrease in platelets (thrombocytopenia) are among the haematological changes. Generally, infectious diseases cause morbidity and mortality through two mechanisms: either the pathogen directly damages the host or indirectly by the excessive immune response (3,4). This last phenomenon is most likely seen in COVID-19 disease. Lymphocytes (CD8+ T and Natural Killer cells) have a protective role in clearing the virus from the body. In severe disease, the absolute number of these lymphocytes decreases significantly. Eventually, the immune status of the body

and eventually the lymphocyte count improve as the patient's condition improves (5). These compensatory activated lymphocytes (atypical lymphocytes) with increased cytotoxic potential have special characteristics (6). These lymphocytes appear highly pleomorphic, showing deeply basophilic cytoplasm and loose chromatin (6). A plasmacytoid appearance with eccentric nuclei and one or more nucleoli is observed in some lymphocytes (7). Daniela Hermelin, a pathologist, gives the name "covicytes" to the atypical lymphocytes seen in COVID-19 (8). Literature documented that there are two types of atypical lymphocyte (AL) morphology seen in this disease: The first category includes plasmacytoid features, which are small mature lymphocytes with an eccentric nucleus and deep blue cytoplasm; included in this category are cells with plasmablastic features, in which the cell is slightly larger with open chromatin and a prominent nucleolus (9). The second category is Downey II-like cells; large lymphocytes with open chromatin and a prominent nucleolus with abundant cytoplasm and occasional cytoplasmic granules similar in morphology to the original Downey II cells (10).

The COVID-19 recent literature documents that the progressive decrease in the peripheral smear lymphocytes is one of the clinical predictors of severity in COVID-19 patients. There are several different predictors of disease severity documented in the literature (11-15). Literature documents almost the same factors, along with the older age group and people with co-morbidities, might be at higher risk for severe micro thrombosis (16). So, SARS-CoV-2 also affects the haematological cellular elements (with characteristic changes) that can be readily identified on peripheral blood film (PBF) and serially monitored. Thus, routine monitoring of the peripheral blood parameters has importance for its diagnostic and prognostic purpose in Covid-19 disease. This study's aim and objective were to observe the association of peripheral blood atypical lymphocytes (ALs) with the mortality of COVID-19 patients.

## MATERIALS AND METHODS

This was a single-center prospective descriptive study done in Makkah, Saudi Arabia from March 10, 2020, to July 10, 2020 (4-month period) on admitted COVID-19 total 266 patients. Patients classified as having moderate, severe, and very severe diseases of COVID-19 (11) of either gender with an age > 14 years were considered in the study (N=226). Mild cases of COVID-19 admitted for other indications, as well as pediatric group (age 14 years) patients, were excluded from the study (n=40). A simple random sampling technique was adopted to document the patients. COVID-19 positive confirmation was done through real-time polymerase chain reaction testing via nasal and throat swabs. 2.5 milliliters of whole blood were collected under sterile conditions in an EDTA tube and mixed for five minutes in a mixer. A drop of EDTA blood was placed in the central line. Following that, the drop was quickly spread with a spreader at a 30-degree angle, and the slide was allowed to air-dry at room temperature. The air-dried films were flooded with Leishman stain for two minutes, and distilled water was added with the doubled volume of the stain for five to seven minutes. After washing in a stream of water, the back of the slide was wiped clean and placed upright to dry. All the above procedure was done by an expert laboratory technician. A peripheral blood smear was viewed by two haematologists within four to six hours after sampling the blood. Both observers' mean numbers of atypical lymphocytes (ALs) of both types (9,10)/100 leukocytes were documented in percentage. All enrolled patients' peripheral blood smear parameters were recorded on the 3rd, 7th, and 14th days of admission. Patients' other data was collected from their electronic medical records, and patients were divided into two groups (survivor group v/s non-survivor group), and data was analysed using a Microsoft Excel sheet and SPSS (Statistical Package for Social Sciences) version 23. Categorical variables were documented as counts and percentages while continuous variables were processed for their means and standard deviations. The association between independent variables and patient mortality was assessed by Fisher's exact test. A p value of $< 0.05$ was deemed significant.

Ethical approved was taken from Institutional review board, Security Forces Hospital under no.0381-12092.

## RESULTS

There was a total of 226 admitted cases enrolled in the study. Males constituted 53.9% of the patients, and females accounted for 46.1% of the patients. The mean age was 58 years, with a standard deviation of 0.5289. Patients older than 40 years of age were 76.6%, and only 23.5% were in the 21–40-year-old age group. The two most prevalent comorbidities were hypertension (14.2%) and diabetes (15.9%). The most prevalent symptoms were fever (77.4%), cough (77%), and shortness of breath (53.5%). Haematological abnormalities, including anaemia 15.5% (n=35), leukopenia 16.4% (n=37), neutrophilia 85.4% (n=193), lymphocytopenia 54.4% (n=123), monocytosis 4.4% (n=10), eosinopenia 59.7% (n=135), and thrombocytopenia 9.3% (n=21), were observed in this study and had significant association with mortality ($p < 0.001$). Table I shows demographic information and blood count parameters for two groups of COVID-19 patients, (survivors and non-survivors) and their correlation with mortality. In Table II, there is documentation of atypical lymphocytes on subsequent days of admission and their link to mortality. ALs were identified in 88.2 % of cases on the 3rd day of admission. There was a significant association ($p < 0.001$) of atypical lymphocytes with mortality in COVID-19 patients. The mortality rate was observed to be 8.4% (n=19) during the four-month period. The median time from admission to death was 6 days (IQR, 22-16 days).

**Table I: Demographics & Blood count parameters among COVID-19 patients**

| Variables | Total cases | Outcome (survivor/non-survivor) | | P-value |
|---|---|---|---|---|
| | Total (n=226) | Survivor (n= 207) | Non-survivor (n=19) | |
| **Age** | | | | |
| 21-40 years | 23.5% | 23.5% | 0.0% | <.001 |
| 41-65 years | 69.5% | 67.7% | 1.8% | |
| > 65 years | 7.1% | 0.4% | 6.6% | |
| **Gender** | | | | |
| male | 53.9 % | 50% | 3.9% | .633 |
| female | 46.1% | 41.6% | 4.4% | |
| **Smoking History:** | 25.7 % | 21.2% | 4.4% | .011 |
| **Diabetes History** | 15.9% | 7.5% | 8.4% | <.001 |
| **Hypertension History** | 14.2% | 14.2% | 0.0 | .083 |
| **ICU admision** | 13.3% | 4.8% | 8.4% | .001 |
| **SPO2 %** | | | | |
| > 96 % | 0.0 | 0.0 | 0.0 | <.001 |
| 93-96 % | 92.9% | 88.9% | 3.9% | |
| < 93 % | 7.1% | 2.6% | 4.4% | |
| **Hemoglobin gm/l** | | | | |
| <100 | 7.1% | 7.1% | 0.0% | <.001 |
| 100-120.5 | 8.4% | 5.3% | 3.1% | |
| 120.6 -160 | 83.6% | 78.3% | 5.3 % | |
| >160 | 0.9% | 0.9% | 0.0% | |
| **Total Leukocytes with differentials** | | | | |
| **WBCsx$10^9$/l** | | | | |
| <4000 | 16.4% | 10.2% | 6.2% | <.001 |
| 4000-11000 | 74.8% | 72.6% | 2.2% | |
| 11000-20000 | 8.8% | 8.8% | 0.0% | |
| **Neutrophil count** | | | | |
| % <50 | 5.3% | 5.3% | 0.0% | .028 |
| 50-70 | 9.3% | 6.2% | 3.1% | |
| 71-80 | 77.0% | 71.7% | 5.3% | |
| 81-90 | 8.4% | 8.4% | 0.0% | |
| **Monocytes %** | | | | |
| 0-5 | 45.1% | 44.7% | 0.4% | .001 |
| 6-8 | 50.4% | 43.4% | 7.4% | |
| 9-20 | 4.4% | 3.5% | 0.9% | |
| **Lymphocytes %** | | | | |
| <5 | 6.6% | 1.8% | 4.9% | <.001 |
| 5-10 | 32.7% | 29.2% | 3.5% | |
| 11-20 | 15.0% | 15.0% | 0.0% | |
| 21-40 | 45.6% | 45.6% | 0.0% | |
| **Eosinophil Count %** | | | | |
| 0.0-0.4% | 30.1% | 24.3% | 5.8% | <.001 |
| 0.5-0.7% | 29.6% | 27.0% | 2.6% | |
| 0.8-1% | 37.6% | 37.6% | 0.0% | |
| >1.1% | 2.7% | 2.7% | 0.0% | |
| **Platelets count** 150-400x$10^9$/l | | | | |
| <100 | 7.1% | 1.8% | 5.3% | |
| 100-150 | 2.2% | 2.2% | 0.0% | <.001 |
| 151-400 | 73.0% | 69.9% | 3.1% | |
| >400 | 17.7% | 17.7% | 0.0% | |

Normal Hemoglobin is 120.5-160 gm/l. Normal total leukocytes are 4000-11000x$10^9$/l. Normal neutrophils is 50-70%. Normal Monocytes is 2-8%. Normal platelets count is 150-400x$10^9$/l. Normal Eosinophils is 0.6-4%. Fisher's exact test was applied to analyze this data.

In this study we observed two types of atypical lymphocytes. The first category were small mature lymphocytes with an eccentric nucleus and deep blue cytoplasm (plasmacytoid features) (Figure 1a). The second category lymphocytes were large with open chromatin and a prominent nucleolus with abundant cytoplasm and occasional cytoplasmic granules (Downey II-like cells) (Figure 1. b & c). Figure 2 show the percentage of atypical lymphocytes (ALs) in the following days of admission in both groups of patients. These lymphocyte percentage along the course of disease (on the 3rd, 7th, and 14th days of admission) show a downward trend in the non-survivor group (brown line) versus an upward steady trend in the survivor group (blue line).

**Table II: Atypical lymphocytes count association with mortality among COVID-19 patients (n=226)**

| Atypical lymphocytes (Covicytes) | Mean (SD.) | P -Value |
|---|---|---|
| **Covicytes percentage** (On 3rd day of admission) | 2.29 (.850) | < .001 |
| **Covicytes percentage** (On 7th day of admission) | 2.26 (.681) | < .001 |
| **Covicytes percentage** (On 14th day of admission) | 3.42 (.960) | < .001 |

## DISCUSSION

Patients with COVID-19 infection have several haematological abnormalities that are detected during blood parameter measurements and blood film examinations. Clinical, laboratory data, and treatments in which certain haematological and biochemical parameters have been associated with the severity of the disease (2,17,18). Even though the possible role of ALs in the prognosis of COVID-19 infection has not been well reported previously. This study observed the presence of ALs in the peripheral blood films of COVID-19 patients and evaluated their association with patient mortality. Lymphocytes are "the major pillars of humoral and cellular immunity" against viral infections like COVID-19 (19). Recent literature has discussed T cell responses to SARS-CoV-2 infection. CD4+ T lymphocytes have evidence of functional impairment and increased expression of activation and/or exhaustion (20). The same phenomenon was observed in CD8+ T lymphocytes in COVID-19 disease. The ALs are observed more in number in patients with COVID-19 as compared to other infections caused by different viruses (21). So, the possibilities of decreased lymphocyte count in the peripheral blood include the mobilization of the cells into infection sites and the virus-induced destruction of T cells (19).

Lymphocytopenia was defined when lymphocyte count decreased less than 20%, neutrophilia >70%, monocytosis >8%, and eosinopenia <1.0% of total leukocytes, respectively. Thrombocytopenia was labelled when platelet count less than 150x$10^9$/l (22). COVID-19 has significant mortality, especially in older age groups and those with chronic medical conditions. Important distinguishing factors include advanced age, dyspnea, hypoxia, lymphocytopenia, monocytosis, eosinopenia, thrombocytopenia, C-reactive protein, ferritin, Lactate dehydrogenase, and D. dimer, which

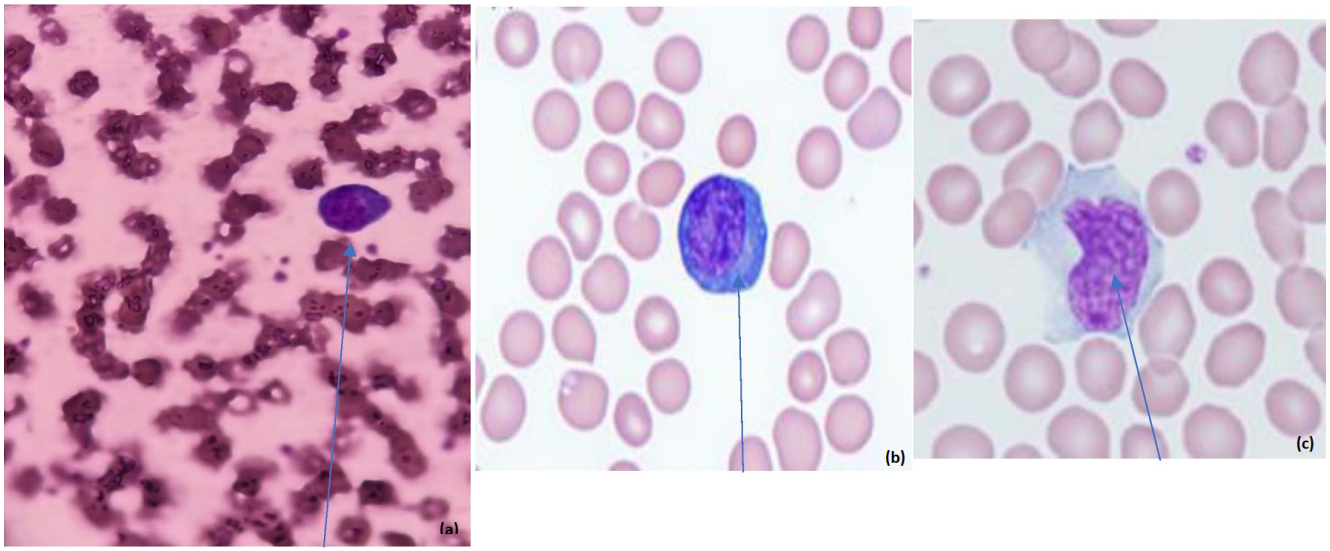


**Figure 1: (a) atypical lymphocyte with plasmacytoid features (small cell with eccentric nucleus with dark blue cytoplasm). (b & c) atypical lymphocytes has Downey II - like cell features (large cells with more cytoplasm and indented nucleus and few cytoplasmic granules.** All peripheral blood films were prepared with Lesihaman stain and observed under light microscope magnification x 100.

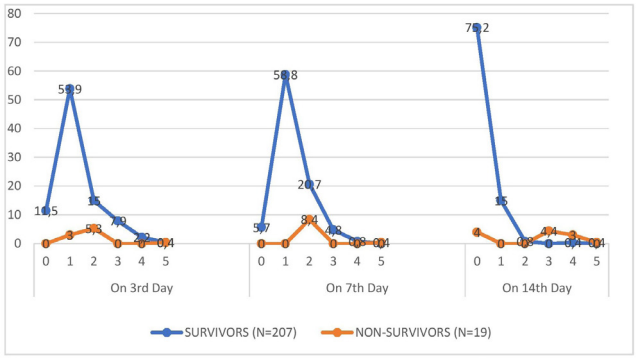


**Figure 2: Atypical lymphocytes percentage along the course of disease in two groups survivor and non-survivor group. X-axis denotes the days of disease from day of admission (0). Y-axis denotes the percentage of atypical lumphocytes**

lead to severe disease and mortality (23).

This study showed a decreasing trend of hemoglobin, total leukocytes, neutrophils, lymphocytes, and platelets was observed in non-survival group patients. These results were consistent with three Chinese studies (15,24,25). These Chines studies observed that severe cases of COVID-19 had a lower level of total lymphocytes than mild cases (24,25). In our study, ALs were identified in 88.2 % of cases on the 3rd day of admission. The non-survivor group had a persistently low ALs count, whereas the survivor group had an increasing trend in lymphocyte count until the 14th day, with a significant ($p < 0.001$) association with mortality. Weiber SE et al observed the presence of ALs (93.3%) in most of the blood films in 15 COVID-19 patients (26). Ahmed S S et al studied 175 patients with a mean age of 53.73 and found that 28% of them had lymphocytopenia 28% (27). ALs was documented 21.14%. El Jamal SM et al analysed 33 COVID-19 patients with 79% lymphocytopenia, and 75% ALs (9).

So, these studies have highlighted that ALs' increasing numbers trend during the disease course correlates with a better outcome of the disease (15,25). This different AL percentage can be justified by the small sample size, and severity of disease variability. Liu YP et al observed 23 patients with ALs 0.83% (average), with the highest percentage seen in PBF (28) being 4%. This study's lower AL percentage is due to more (18) mild COVID-19 cases out of 23 total cases. Merivo et al found that COVID-19 ALs in PBF are related to better evolution and prognosis (29). Therefore, our observation, supported by this study, that the increasing number of ALs during the disease course in COVID-19 patients showed a better outcome. Wu C et al observed 201 admitted severe COVID-19 cases (30). This study demonstrates that patients with ARDS were older, more patients with dyspnea, and had a higher proportion of comorbidities, including hypertension and diabetes. Lymphopenia was observed in 64% of patients more in ARDS patients, but it was not correlated with death. The death rate was 21.9%. The higher death rate and lymphopenia non-significant association with mortality in this study compared to our study may be due to severe disease, more ICU cases (26.4%), and treatment used. Nazarullah A et al observed PBF in 12 cases, almost all had atypical lymphocytes, and lymphocytopenia was documented in 16.6% of patients (31). The death rate was 16%. ALs were not correlated with mortality. Berber I et al. observed that ALs increased compared to the control group but found no association between ALs and disease prognosis (32). The small sample size (N=50), young population (median age 44), low ALs (37.5%), and low mortality rate (4%) may preclude establishing a link between ALs findings and disease prognosis. The above studies (Wu C, Nazarullah A, & Berber I) showed varying percentages of lymphocytopenia, varied percentages of ALs in PBF, and their non-significant association with mortality. The

subjective method of detecting these cells, sampling size, sampling to observation time difference, comorbidities, immune status of patients, severity of disease variability, demographics, and population effects can all be explained as the influencing reasons for these different results from our study.

So, generally, literature has highlighted that ALs' increasing numbers trend during the disease course correlates with a better outcome of the disease. The same trend of ALs is observed in our study. Some variations in count and their trend from other studies can be justified by the influencing factors mentioned above. Further research is needed to overcome these limitations.

## CONCLUSION

Atypical lymphocytes' appearance in peripheral blood film (PBF) can be considered as an important basic laboratory finding with prognostic prospective. During the disease course, it is vital to observe the peculiar morphological findings of affected lymphocytes along with their percentage numbers, which would help to assess the disease severity. Changes in PBF ALs number along the course of disease can help clinicians with disease management promptly, especially in the absence of sophisticated laboratory tests.

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