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Morphological changes in WBC and Its Prognostic Importance in COVID-19 patients: A study conducted over 1000 patients at a tertiary care centre

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ABSTRACT

Background*: Pandemic COVID-19 massively affected the globe health wise and in every other possible aspects of life and many studies have been already published, representing only tip of the iceberg and a lot is still in discovery mode. It is a highly communicable disease which primarily enters human through respiratory system but it can affect any system. As this virus is continuously multiplying and new strains are rapidly emerging, a combat against the elimination of this virus in body is visible in morphology of WBC and is of prognostic implication.*

Aim*: To evaluate different morphological patterns in white blood cell (WBC) and its prognostic nature in covid-19 patients at Tertiary Care Centre, HBT medical college and Dr. RN cooper hospital.*

Material and method: *This is a 1 year retrospective cross sectional study which is conducted a over sample size of 1000 COVID-19 affected patients, from April 2020 to March 2021. In this study 1000 peripheral smear of affected patient are studied and morphology of WBC is being noted.*

Result & Conclusion: *In our study, in the initial stages of infection there is a neutrophil predominance with left shift, immature forms and dysmorphism and abnormal nuclear shapes. After several days of treatment, a shift towards lymphocyte activation and reactive plasmacytoid forms of lymphocytes are seen. The most common cytomorphological variants found were neutrophil with distorted nucleus, reactive lymphocytes and activated monocytes. Majority patients with reactive lymphocytes and activated monocytes had good prognosis whereas prognosis in patients with distorted nucleus of neutrophil were variable.*

Key word-COVID-19, WBC morphology, reactive lymphocytes, activated monocyte, neutrophil with distorted nucleus and survival outcome.

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I. INTRODUCTION

First case of Covid-19 was reported in Wuhan, a city of China in 2019, after that number of cases explosively increased over the globe and turned out to be the greatest pandemic of history[(1)] and is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leading to serious mental, social, economic and health consequences.[2]the clinical presentation varies widely. Some patients presents with acute respiratory distress syndrome (ARDS)[(3)], requiring intubation and mechanical ventilation, coagulopathy, multiorgan failure and death. This complicated course is due to the cytokine storm characterized by overproduction of TNF, IL6, IL1ß, and G-CSF and generalized vascular hyperpermeability. [(4)] There is an imbalance between proinflammatory and anti-inflammatory mechanism and it is easily complicated in patients with additive risk factors and comorbidities such as diabetes, hypertension, those already on immunosuppressive drugs and cancer chemotherapeutics, whereas a non-negligible proportion of healthy young individuals without comorbidities, also develops the severe form of the disease. On the other hand, a subset of patients copes well with the virus and display only mild symptoms of viral illness.

This virus enters the body by its surface glycoprotein spikes S with ACE-2 present in the body. ACE-2 is distributed in various tissues like nasopharyngeal and oropharyngeal epithelium, lung, kidney and GIT. This

distribution explains the involvement of various organ in COVID-19 patients. The clinical picture varies from mild to hospitalized to critical care, unleashing a series of immune responses, characterized by a reduction of T & B lymphocytes and an increment of monocytes and neutrophils. [5,6,7,8,9] A detailed understanding of this altered immunological state is crucial for the design and development of effective therapeutic strategies. In the present work, we studied various changes in white blood cells in peripheral smears of the Covid-19 patients. All these patients were tested positive for RTPCR for Covid-19. EDTA blood samples were collected and peripheral smears were examined for changes in the myeloid precursors, monocytes and lymphocytes in all the cases.The most common hematological findings include lymphocytopenia, neutrophilia, shift to left in myeloid series, eosinopenia, mild thrombocytopenia. [7] The morphological abnormalities are seen in neutrophils, lymphocytes, monocytes and platelets. These abnormalities includes both nuclear and cytoplasm abnormalities. The various cytomorphological changes in neutrophil were bilobed and unsegmented neutrophils, pseudo pelger like nuclei, doughnut shaped nuclei, unsegmented nuclei with coarsely clumped chromatin, cytoplasm is hypergraular or neutrophils with marked cytoplasmic hypo granularity. The cytomorphological changes in lymphocytes and monocytes include large polypoid reactive lymphocytes, lymphocytes with hyperbasophilic cytoplasm, plasmacytoid lymphocytes, activated monocytes, large granular lymphocytes and giant vacuolated platelets. [7]

Aims and objective

To know diagnostic and prognostic value of morphological changes in WBC in Covid -19 patients.

II. Material And Method

Study design: This is 1 year retrospective cross sectional study.

Study location: This was a tertiary care hospital-based study done in Hinduhrudaysamrat Balasaheb Thackarey Medical College (HBTMC) and Dr. Rustom Narsi Cooper Municipal General Hospital (R.N. Cooper hospital), Mumbai, Maharashtra.

Study duration: April 2020 to March 2021

Sample size: 1000 patients

Inclusion criteria: All the cases who presented to our hospital with Covid-19 infection and are tested positive with RTPCR test.

Exclusion criteria: Patients who are tested negative in RTPCR for Covid- 19 infection. People who are infected with viral and bacterial diseases other than Covid-19.

Procedure methodology: Blood was collected in EDTA tubes according to the standard covid 19 protocols. All the mandatory precautions were taken and safety guidelines were followed. EDTA tubes were then run on 5 part hematology analyzer. Tongue shaped blood smears were then made on glass slide, were air dried and fixed in methanol for 1 minute followed by staining using Field's stain.

Field stain consists of two components, Field A & B. Field stain is a dark violet colour commercially available powder (5grams) mixed in 600 ml distilled water (heated at 80^{o}C, until the powder dissolves. Solution is then filtered and labelled with the date. Fields stain B is also a commercially available powder which is orange coloured (4.5grams) mixed in 600 ml distilled water (heated at 80^{o}C, until the powder dissolves. Solution is then filtered and labelled with the date. The major component of Field A is Methylene Blue (basic dye) which stains the nuclei of cell (acidic components) to violet/blue (depending on the cell type) whereas the major component of Field B is eosin (acidic dye) which stains the basic component of cells such as cytoplasm. [10]

Staining Procedure for Field Stain A And B:

1. Fill up two Coplin jars or wide-mouth bottles:
1. Field Stain A (Blue stain).
2. Field Stain B (Red stain).
2. Make a blood smear on a clean glass slide, and it is dried in the air.
3. Fix in methanol for one minute or get Spray 'Easyfix'.
4. Dry in the air.
5. Dip fixed smear to Field Stain B (Red Stain) for 5 to 6 seconds.
6. Wash in running tap water.
7. Dip smear into Field Stain A (Blue Stain) for 10 to 30 seconds (adjust it).
8. Wash in running tap water.
9. Dry at air and see under oil immersion objective.
10. 10-The staining time may be adjusted

After staining, the slides were examined for morphological evaluation of cells, along with that findings were also correlated with other hematological parameters in the 5-part analyzer.

Statistical analysis: Binomial logistic regression analysis: A logistic regression analysis was conducted to predict the chances of death and survival among the individuals with COVID-19.
Based on the statistically significant variables found in the above bivariate tests, variables were selected and included in the binomial logistic regression analysis after checking for multicollinearity using scatter plots and calculation of Pearson's correlation coefficient. Also, initially an exploratory forward binomial logistic regression was run on the shortlisted variables to find the variables which were most contributory in the regression equation.
The following predictor variables were included:

Categorical variables
1. Reactive Plasmacytoid Lymphocyte in Peripheral Smear
2. Activated Monocyte in Peripheral Smear

Continuous variables
1. Age (in years)
2. Absolute lymphocyte count
3. Interleukin-6 level

The results of the analysis are as follows:
A test of the full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between participants who survive and those who do not (chi square = 616.7, $p < 0.0005$ with df = 5). Nagelkerke's R^2 of 0.701 indicates a good relationship between prediction and grouping. Prediction success overall was 90.8% (94.4% for survival and 78.5% for death). The Wald criterion demonstrated that all the predictors in the equation made a significant contribution to prediction.

Data were collected for over 1000 smears and were analyzed using Microsoft excel 2007 and Microsoft word. Chi-square test used. #Fisher's Exact test used. *Significant as p value <0.05.

III. RESULTS AND DISCUSSION

In present study, various cytomorphological patterns (Figure 1) observed in neutrophils and myeloid series is shifted to left, bilobed neutrophils (Pesudopelger appearance) with hypogranularity, irregular segmentation and cytoplasmic vacuolations, fetoid shaped nucleus, doughnut shaped nucleus, irregular segmentation with hypergranularity, irregular chromatin distribution and blastoid forms. [10,11,12]

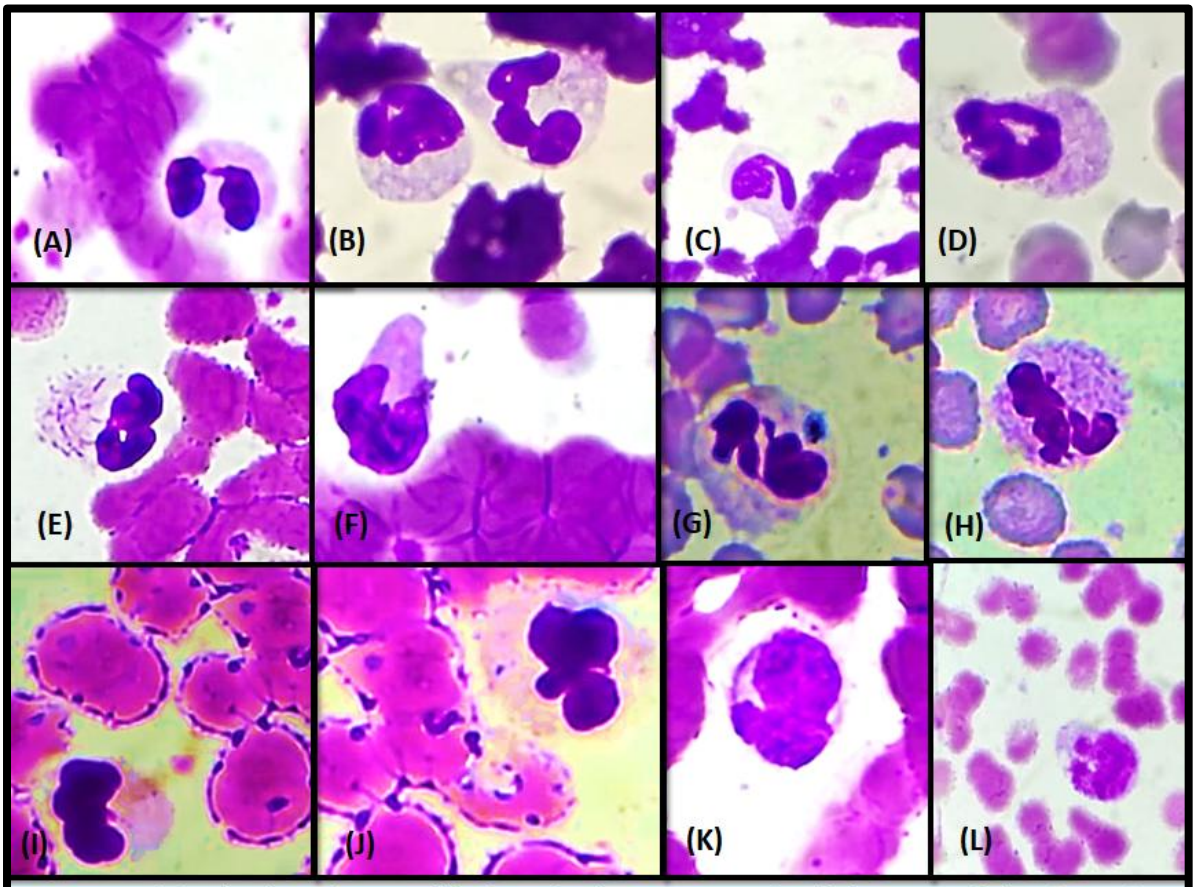

FIGURE 1:(A) Binucleated neutrophils (Pseudopelger appearance) with hypo granularity; (B,G,H) Neutrophil with irregular segmentation and cytoplasmic vacuolations; (C,E,F,I,J) Neutrophil with fetoid nucleus (D) Neutrophil with doughnut shaped nucleus; (H) Neutrophil with irregular segmentation and cytoplasmic hypergranularity; (K,L) Neutrophil with irregular chromatin distribution

Lymphocytes (Figure 2) in these patients are usually larger in size. Atypical lymphocytes have loose chromatin network, lobulated appearance of chromatin, broad cytoplasm. At places cytoplasm show cytoplasmic pods formation and seems adherent to erythrocytes. Reactive plasmacytoid lymphocytes having morphology similar to plasma cells with eccentric nucleus, with dark basophilic cytoplasm, presence of vacuole in cytoplasm, and at places nucleoli can be seen, resembling Downey's cell of infectious mononucleosis. The morphological changes were quite similar to the findings in study done by Berber et al. [13,14] Monocytes (Figure 2) are large cells with eccentric kidney shaped nucleus and a light blue gray cytoplasm. Activated monocytes showed increased and prominent vacuolations and few granules in cytoplasm in these Covid -19 patients, which signifies that the cell is trying to combat against the infection. There is anisocytosis in cell as well as nuclear shape and nuclear overlapping was also observed. Similar changes were reported by Singh A et al. [14]

It is also observed that that in the initial stages of infection there is a neutrophil predominance with left shift, immature forms and dysmorphism and abnormal nuclear shapes. After several days of treatment, a shift towards lymphocyte activation and reactive plasmacytoid forms of lymphocytes seen which is similar to the observations seen in the studies of Zini G et al. [7]

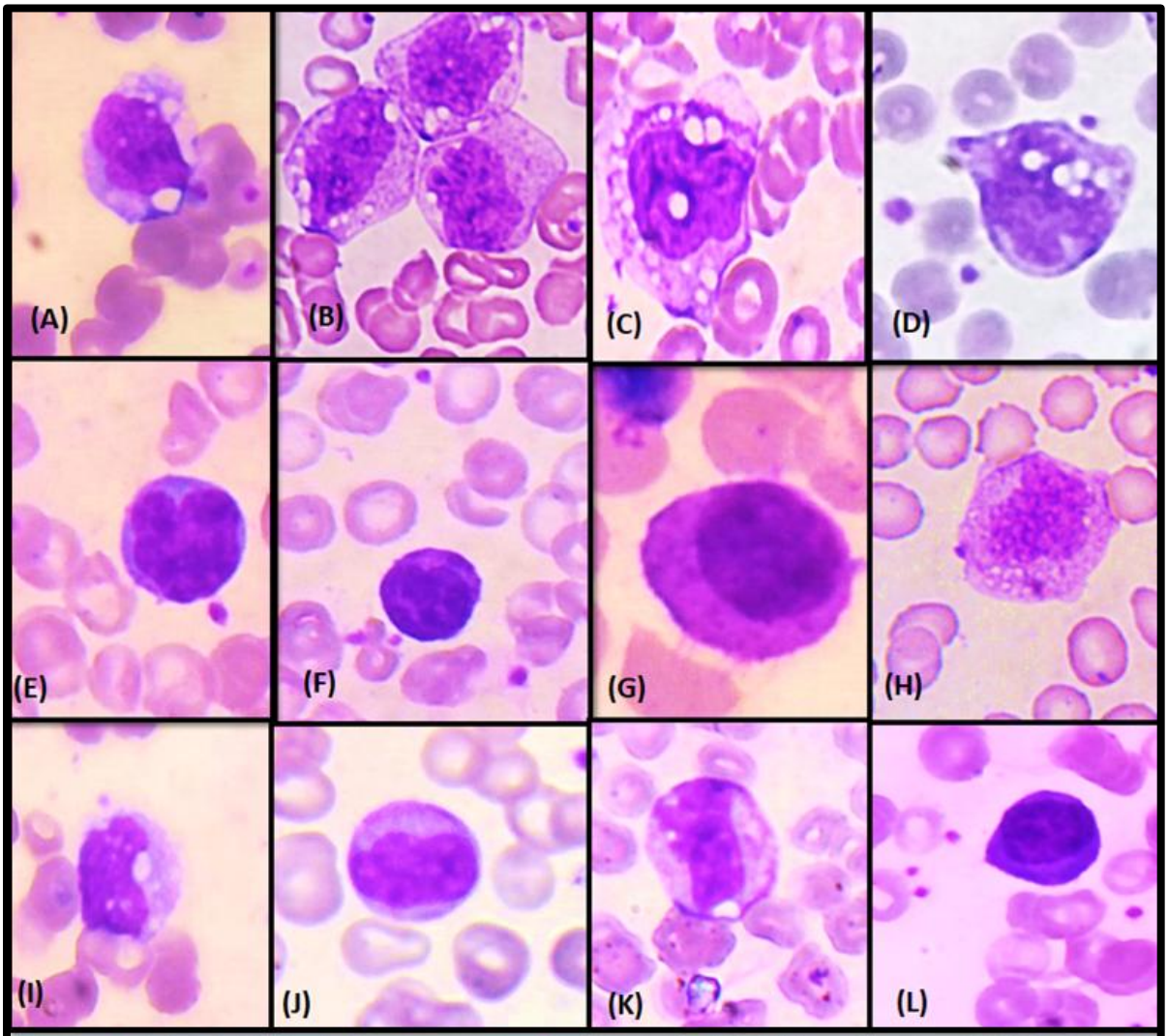

Figure 2: Morphological changes seen in Monocytes (A-D) & Lymphocytes (E-L) in Covid-19 patients: Field's and Leishman stain(100x): Activated monocytes with increased and prominent vacuolations and few granules in cytoplasm; signifies that the cell is trying to combat against the infection. There is anisocytosis as well as nuclear overlapping. Atypical lymphocytes have loose chromatin network, lobulated appearance of chromatin, broad cytoplasm, cytoplasmic pods formation at places. Reactive plasmacytoid lymphocytes having morphology similar to plasma cells with eccentric nucleus, dark basophilic cytoplasm, presence of vacuole in cytoplasm, and at places nucleoli can be seen, resembling Downey's cell of infectious mononucleosis.

Microscopic examination of all the peripheral smears done and patients were categorized based on WHO criteria of severity of disease in Covid patients (mild, moderate, severe and critically ill). In our study it is observed that cases of myeloid series with left shift is maximum in critical patients (71.9%) followed by severe (48.8%)> moderate (26.7%)> mild (13.7%). Immature myeloid population such as promyelocytes-myelocytes, metamyelocytes, band forms, neutrophils, monocytic precursors, and activated monocytes predominated which is due to myeloid cell activation in immune response, DNA and RNA processing, defense response to the virus, and response to type 1 interferon.[8]

Table 1:Comparison of microscopic features of WBC in different severities of COVID-19 [frequency (percentage)].

	Microscopic features of WBC		Mild	Moderate	Severe	Critical	Total	p value
1	**Left Shift in Peripheral Smear**	Yes	70 (13.7)	62 (26.7)	98 (48.8)	41 (71.9)	271 (27.1)	**<0.0005***
		No	440 (86.3)	170 (73.3)	103 (51.2)	16 (28.1)	729 (72.9)	
2	**Neutrophils with distorted nucleus in Peripheral smear**	Yes	502 (98.4)	232 (100)	201 (100)	57 (100)	992 (99.2)	0.085#
		No	8 (1.6)	0 (0)	0 (0)	0 (0)	8 (0.8)	
3	**Reactive Plasmacytoid Lymphocyte in Peripheral Smear**	Yes	510 (100)	78 (33.6)	4 (2)	1 (1.8)	593 (59.3)	**<0.0005***
		No	0 (0)	154 (66.4)	197 (98)	56 (98.2)	407 (40.7)	
4	**Activated Monocyte in Peripheral Smear**	Yes	57 (11.2)	10 (4.3)	5 (2.5)	2 (3.5)	74 (7.4)	**<0.0005***
		No	453 (88.8)	222 (95.7)	196 (97.5)	55 (96.5)	926 (92.6)	
	Total		510 (100)	232 (100)	201 (100)	57 (100)	1000 (100)	-

Chi-square test used. #Fisher's Exact test used. *Significant as p value <0.05.

Neutrophils in the peripheral smear showed neutrophils with distorted nucleus , seen in 100% cases of critical, severe and moderately severe cases each and 98.4% cases in mild category. Hence statistically, neutrophil with distorted nucleus proves to be diagnostically important but prognostically insignificant (p value >0.05%) in present study. It is comparable to the study done by Kaur G. et.al. [15,16] In their study, the most common morphological change was neutrophil with clumped chromatin, multiple abnormal nuclear shapes, peusopelger-huet deformity and smudged neutrophil. Lymphocytes showed abundant blue cytoplasm, lymphoplasmacytoid morphology and monocytes were activated with abnormal shape and multiple vacuolations.

Reactive plasmacytoid changes seen in the peripheral smear and it is observed that with reactive plasmacytoid lymphocytes were maximum in mild cases (100%) followed by moderate (33.6%)> severe (2%)> critical (1.8%), and is statistically significant (p value=0.0005%), in mild, moderate, severe and critical cases. Reactive plasmacytoid changes in lymphocytes are least observed in critically ill patients.

Activated monocytes in peripheral smear of Covid 19 patients are seen and it is found to be maximum (11.2%) in mild category followed by moderate (4.3%)> critical (3.5%) > severe (2.5%), which is statistically significant (p value=0.0005%). From this result we can infer that presence of activated monocytes is associated with good prognosis, which corresponds to a case study of Singh A et al [14] and very few of other studies.

In a study of Coradi et al [16] they have observed that patients with SARS-CoV-2 virus had numerical and morphological alterations in the leukocyte lineage, with lymphopenia and neutrophilia being more significant which corresponds with our study. As for morphology, several anomalies were observed. Among these hypolobulated neutrophils, classified as acquired Pseudo Pelger-Huet anomaly, were also present. These were correlated with a greater chance of admission to the ICU and progression to death whereas Plasmacytoid and Downey cell-like reactive lymphocytes were frequently seen in patients with better prognosis.

Unlike ours, most of studies including Van de berg DF et al [17] & Shaath H et al[18] showed presence of activated monocyte is positively associated with severity of COVID-19 which can be explained by the fact that percentage of patients with existing comorbidity are more in our study as compare to other studies, also patient in our study presented late to hospital with bacterial superinfection. In studies where patient presented early with activated macrophages and raised IL-6 had landed into inflammatory storm followed by inflammatory shock, irreversible vascular damage which resulted in poor clinical outcome.

Table 2:Comparison of microscopic features of WBC in different outcomes of COVID-19.

	Microscopic features of WBC		Outcome		p value
			Survival	Death	
1	**Left Shift in Peripheral Smear**	Yes	155 (57.2)	116 (42.8)	**<0.0005***
		No	616 (84.5)	113 (15.5)	
2	**Neutrophils with distorted nucleolus in Peripheral smear**	Yes	763 (76.9)	229 (23.1)	0.210[#]
		No	8 (100)	0 (0)	
3	**Reactive Plasmacytoid Lymphocyte in Peripheral Smear**	Yes	580 (97.8)	13 (2.2)	**<0.0005***
		No	191 (46.9)	216 (53.1)	
4	**Activated Monocyte in Peripheral Smear**	Yes	72 (97.3)	2 (2.7)	**<0.0005***
		No	699 (75.5)	227 (24.5)	
	Total		**771 (77.1)**	**229 (22.9)**	-

Chi-square test used. [#]Fisher's Exact test used. *Significant as p value <0.05

Hence, from present study, in Covid 19 mild category patients, presence of reactive plasmacytoid lymphocytes and neutrophil with distorted nucleus is seen much more frequently followed by shift to left and activated monocytes.

In moderate cases neutrophil with distorted nucleus add to the bulk of cases, followed by reactive plasmacytoid lymphocytes, shift to left and lastly activated monocytes. In severe cases, shift to left and distorted nucleus is an important finding followed by activated monocytes and reactive plasmacytoid cells. In critical cases, most common finding apart from neutrophils with distorted nucleus is left shift followed by activated monocytes and reactive plasmacytoid lymphocytes.

The above findings in PBS of Covid-19 patients are also related with the survival death outcomes and it is observed that left shift in neutrophil series is present in 57.2% cases among the survivors where as 42.8% cases were deceased (poor outcome), which is statistically significant (p value <0.0005). Neutrophils with distorted nucleus seen in 76.9% were survivor and 23.1% were deceased, is statistically insignificant (p value = 0.210). Reactive plasmacytoid lymphocytes in 98.7% patients were survivors and 2.2% were deceased, which is statistically significant (p value <0.0005). In peripheral smear with activated monocytes, 97.3% were survivors whereas 2.7% were deceased, which is statistically significant (p value <0.0005). Hence, we can also conclude that activated monocytes are associated with good survival outcome in Covid-19 patients.

IV. CONCLUSION

All the COVID 19 hospitalized patients should undergo a comprehensive daily CBC analysis with peripheral smear examination with manual WBC differential to monitor numerical and cytomorphological changes predictive of poor outcome and signs of disease progression. [(19)] In the initial stages of infection there is a neutrophil predominance with left shift, immature forms and dysmorphism and abnormal nuclear shapes. After several days of treatment, a shift towards lymphocyte activation and reactive plasmacytoid forms of lymphocytes are seen. The most common cytomorphological variants found were neutrophil with distorted nucleus, reactive lymphocytes and activated monocytes. Majority patients with reactive lymphocytes and activated monocytes had good prognosis whereas prognosis in patients with distorted nucleus of neutrophil were variable.

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