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Radio-Diagnosis

KEYWORDS: COVID-19, Computed tomography (CT), CT severity score, Reverse Transcriptase - Polymerase Chain Reaction, Neutrophil-to-Lymphocyte Ratio (NL Ratio).

NEUTROPHIL-TO-LYMPHOCYTE RATIO: A PROGNOSTIC PREDICTOR OF COVID-19 INFECTION.

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ABSTRACT

Background:

COVID-19 infection requires an easily accessible yet precise variable for diagnosis and prognosis. This study aims to describe the predictive value of the Neutrophil-to-Lymphocyte Ratio (NL Ratio) for COVID-19 diagnosis and deteriorating clinical course, which has not been extensively demonstrated.

Objective:

To determine the correlation of the NL ratio and CT severity score(CTSS) with the lung injury severity in adult patients having COVID-19 infection.

Materials and Methods:

A retrospective study at a COVID centre included 123 hospitalized patients those who are COVID-19 positive by RT-PCR or Rapid Antigen Test. The study lasted six months (July 2020 - November 2020). In addition, the patient's demographics, chest CT findings, CRP, lymphocyte and neutrophil counts were documented.

Results:

The differences in NL Ratio were significant across the all grades of CT severity score groups, as well as within each group ($p<0.001$). There was an excellent correlation between the NL Ratio and the CTSS ($r = 0.863$, $p<0.001$). According to a ROC curve analysis, NL Ratio had diagnostic and prognostic relevance in COVID-19 subjects with negative or positive CT results. The AUC (area under curve) was 0.858 (95% CI: 0.728-0.903, $p<0.001$), the sensitivity was 69.9%, the specificity was 93.1%, and the optimum NL Ratio cut-off value was 3.734.

Conclusion:

NL ratio is a low-cost prognostic tool and a convenient, on-site alternative to a chest CT scan for determining the degree of lung injury in COVID-19 subjects, particularly in developing countries.

INTRODUCTION:

COVID-19 has spread fast around the globe. The illness has spread to practically every country on Earth, posing a potential danger to public health globally. The cause of COVID-19 is the SARS-CoV-2 virus (coronavirus) (1) .Coronaviruses (or CoVs) are RNA viruses with an enclosed, single-chain genome. They are capable of encoding the RNA polymerase enzyme in their genome but do not possess it. Because these viruses have crown-like protrusions on their outer surfaces, they are called COVs. Corona refers to the crown in Latin (1). These protrusions are glycoprotein spikes that coat the virus's outer surface.

Coronaviruses are classified as alpha, beta, gamma, or delta CoVs. Additionally, they are classified into several subspecies. They are classified as Orthocorona-virinae. The coronavirus of 2019 is characterized as a beta-coronavirus strain 2b. The beta-coronaviridae genomes were genetically linked to the bat SARS-like coronavirus (2). Numerous mammals, including bats, dogs, cats, pigs, and a few flying species, are infected with this kind of virus. The virus has been recognized as being transmitted to humans through intermediate zoonotic sources (3).

In December 2019, the first instance of COVID-19 infection was found in Wuhan which is located in Hubei Province, in China. The transmission was conceivable, with bats serving as the intermediary hosts (4). The virus's primary target organ was the lungs, as shown by autopsy.

Rapid antigen test kits and real-time RT-PCR assist in identifying the virus. Invitro diagnostic testing is widely used to determine illness severity, prognosis, treatment methods, and therapy monitoring (5). Thoracic computed tomography (CT) is beneficial for diagnosing, screening, quantitative grading, monitoring, and assessing the curative impact of COVID-19 pneumonia. The disadvantages of CT are that it exposes individuals to radiation and is also significantly more expensive (6).During the early phases of the illness, when lung involvement is modest, chest radiographs may appear normal. CT abnormalities may be seen in such individuals. CT findings were critical in patients who had previously received false-negative RT-PCR results (7).

CT severity ratings were used to identify the lung damage extent. This study aims to established the relationship between the NL ratio and lung injury severity in COVID-19 patients.

Recent imaging findings indicate that the parenchyma of lung has sustained significant damage, including interstitial inflammation and extensive consolidation, consistent with previously observed coronavirus infections (7,8,9).

The NL ratio is a prognosis indicator for cancer and pneumonia. It's frequently used to characterise the immune response to stressful events, assess the severity of bacterial infections, and predict prognosis in cancer and pneumonia (10) . Recent studies have indicated that changes in the NLR signify damage to T-lymphocytes produced by SARS-CoV2, which may contribute to the disease's worsening (11). The NL Ratio may be measured simply using a complete blood profile and is associated with patient's overall inflammatory condition.

Inflammation is crucial for the COVID-19 development and probably certainly has a role in its prognosis. The immunological

response to respiratory illness is marked by an influx of neutrophils into the lungs, particularly the alveoli (12,13). On the contrary, a high neutrophil infiltration may result in collateral tissue injury, cytotoxicity and vascular stasis (14). Continuous production of anti-inflammatory cytokines that trigger lymphocyte apoptosis has been demonstrated, resulting in lymphopenia (15). All COVID-19 patients had elevated neutrophil counts, and a meta-analysis of total 660 patients published recently discovered lymphopenia in more than 40% of COVID-19 case (16). A neutrophil-lymphocyte ratio imbalance may indicate a severe infection that may escalate to serious complications such as MODS, sepsis, or ARDS .

Laboratory medicine is critical in the early identification, diagnosis as well as management of diseases, all of which affect the patient's outcome (17).

MATERIALS & METHODS:-

Data collection:-

A retrospective study was aimed in a designated COVID centre after getting permission from the Institutional Ethics Committee (No. NKPSIMS & RC&LMH/IEC/26/2020). The study included 123 hospitalized patients who were confirmed to have a COVID-19 positive status with an RT-PCR or Rapid Antigen test. The study duration was for a period of 6 months (July 2020 - November 2020). Clinical and laboratory data such as neutrophil count and lymphocyte count were collected

Inclusion criteria:-

1. Symptomatic and asymptomatic patients who are tested RT-PCR or RAT positive for SARS-CoV-2.
2. Adult patients (18 years age or older) were included.

Exclusion criteria:-

1. Patients with severe hepatic or renal failure.
2. Patients with HIV infection.
3. Patients with any known haematological diseases or conditions that cause variations in blood counts,
4. Patients are on immunosuppressive medications before admission and have a low lymphocytic count.

Imaging Technique & Protocol:-

While undergoing CT scan, arrangements were made for all COVID-19 positive cases to limit its spread. All precautionary measures were taken. Toshiba Activion16; 16 slice helical MDCT scan machine was used for all examinations. CT scan was obtained by keeping the patient in the supine position on the CT table.

The recommended pre-setting by the manufacturer's standard were kept the same for scanning the parameters. Scanning parameters included the following: scan direction (craniocaudally), tube voltage (120KV), tube current (100-600 mA)-smart mA dose regulation, slice collimation (16 0.625 mm), width (0.625 0.625 mm), pitch (1), rotation time (0.5 s), and scan duration (60.00 – I300.00 s). 2-mm slice thickness images were reconstructed. Multiplanar images in the coronal and sagittal sections were reconstructed.

Imaging Analysis:-

Concerning Fleischer society, ground-glass opacity (GGO), crazy-paving pattern, and consolidation were defined.

In keeping with various publications, a diagnosis of suspect COVID-19 pneumonia was given based on the following CT patterns: GGO, crazy-paving, and consolidation.

The score was calculated considering the lung involvement extent in each of 5 lobes in all cases. We evaluated the total individual lobar scores, which was out of 25, and was graded subsequently into the severe with CT severity score of <7, moderate with CT severity score of 8-15, and mild with CT severity score of >15 categories .

Statistical analysis:-

The statistical analysis was done using Microsoft Excel and Epi Info software. Quantitative data were described as arithmetic mean +/- standard deviation, whereas qualitative (categorical) data were described as frequencies (%). Medians were used to characterize data that didn't follow normal distribution (upper quartile, lower quartile). $P < 0.05$ were considered significant. Pearson's correlation coefficient test (2 tailed test) was employed for categorical variables, with $p < 0.01$ considered statistically significant. ROC (curves) were used in order to determine the effective NL Ratio cut-off value for differentiating between negative and positive CT results in COVID-19 patients.

RESULTS:

Our study comprised 128 individuals with a nasopharyngeal swab confirmed positive by an RT-PCR or RAT test. Five patients were eliminated from the analysis. 2 because the gap between the laboratory examination and CT scan of chest was more than one day, and 3 of them had medical records missing. RT-PCR or RAT test positive patients for COVID-19 underwent HRCT of the chest on the day of hospitalization. Eventually, 123 cases had been included with the following data gathered: age, gender, laboratory tests, including neutrophil count, CRP, lymphocyte count, and neutrophil-lymphocyte ratio.

A) Demographic characteristics

The average age was 49.3 years [24–76 years]. Of the study subjects, 86 (30.1%) were males, and 37 (69.9%) were females. Patients were further divided into six age groups: 21 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, and 71 to 80 years.

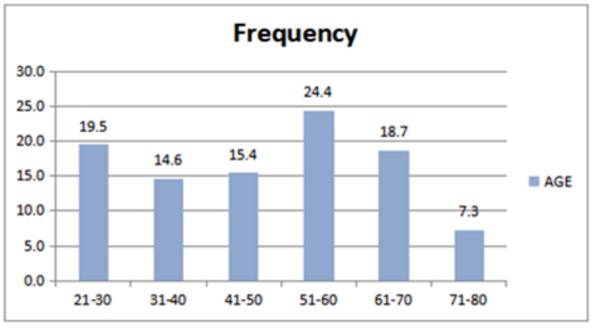

Figure 1 : Age wise distribution of study subjects

Table 1 shows maximum, i.e. 30 (24.4%) belonged to the age group of 51-60, followed by 24 (19.5 %) in the age group 21-30 years, 23(18.7%) belonged to 61-70 years, 19(15.4%) study subjects belonged to 41-50 years age group, 18(14.6%) belonged to 31-40 years and minimum 9 (7.3%) in 71-80 years.

Table 2 : Categorial distribution of study subjects in different age groups

Grades				
Age (years)	**Negative**	**Mild**	**Moderate**	**Severe**
21-30	16	7	0	1
31-40	2	8	5	3
41-50	1	2	11	5
51-60	2	5	17	6
61-70	0	4	6	13
71-80	0	4	5	0

Table 2 shows patients with younger age group had predominantly mild disease whereas severe disease was mainly seen in older age group.

Table 3 :Distribution of study subjects according to gender.

Sex	Frequency	Percent
Male	86	69.9
Female	37	30.1
Total	123	100.0

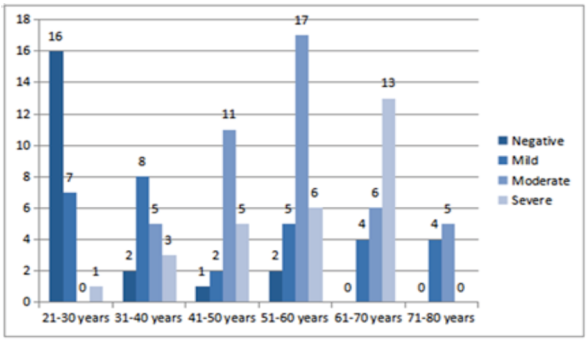

Figure 2 : Categorial distribution of different age groups for each CT severity score

Table 3 shows 86 (30.1%) study subjects were males and 37 (69.9%) were females.

There is no significant relationship between gender and CT severity score P value is greater than 0.05

Table 4 :Association between gender and CT severity score:

Gender	Mean and SD of CT severity score	P value 0.5042 df-1
Male	10.23 ± 7.15	
Female	9.29± 7.11	

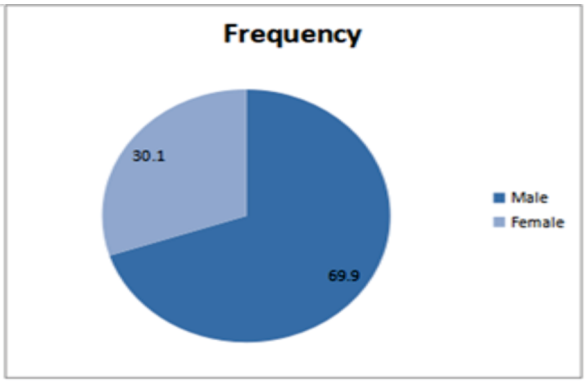

Figure 3 : distribution of study subject according to gender

Twenty-three (18.8%) had coexisting conditions, thirteen (10.5%) had COPD, five (3.70%) had bronchiectasis, three (2.8%) had type 2 diabetes, and two (1.23%) had hypertension as shown in figure 4.

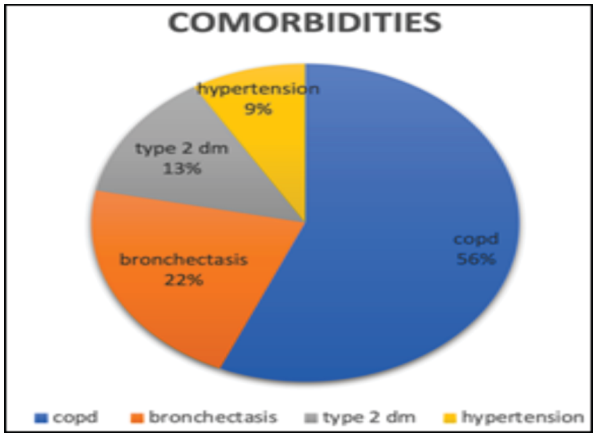

Figure 4 : Distribution of study subject according to comorbidities.

Patients with previous respiratory diseases were more prone to infection than those with other comorbidities. Sixty-one (61.5%) patients were hospitalised with an elevated body temperature (> 37.3 °C), and the axilla temperature was measured. Forty patients (32.3%) had body temperatures between 37.3°C and 38°C, 25 patients (20.3%) had body temperatures between 37.3°C and 38.2°C, 15 patients (12.2%) had body temperatures between 37.3°C and 38.2°C, and seven patients had body temperatures of more than 39°C (5.7%).

B) Laboratory values:-

Laboratory results showed reduced lymphocyte count (normal: 1500 to 4000 /microlitre) in 87(70.1%) cases , raised CRP (50 mg/L) in 50 cases(40.3%) and reduced 105 (85.3%) peripheral blood white cell count in patients as shown in figure 5.

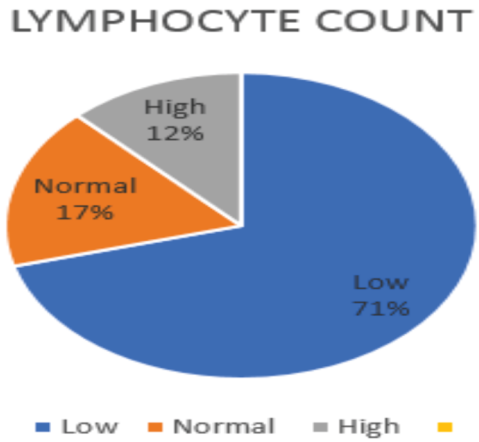

Figure 5 : Distribution of study subject according to lymphocyte count

Table 5 : Distribution of lymphocyte count among study subject

	Frequency	Percent
Low	87	70.7
Normal	21	17.2
High	15	12.1
Total	123	100

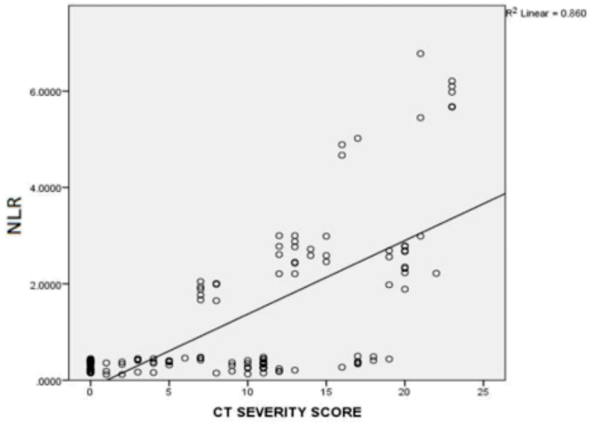

Figure 6 : Correlation of CT severity score with NLR

Table 6 : NL Ratio and CT severity score are positively co-related with p<0.005

	CT SEVERITY SCORE	NLR	
CT SEVERITY SCORE	Pearson correlation	1	.678
	Sig.(2-tailed)		.000
	N	123	123
NL Ratio	Pearson correlation	.678	1
	Sig.(2-tailed)	.000	
	N	123	123
Significant correlation at the 0.01 level (2-tailed)			

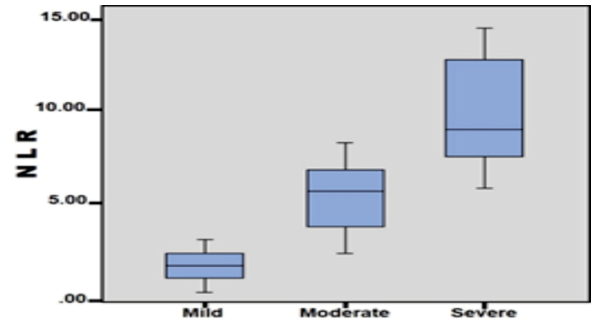

Figure 7 : Box and whisker plots of NL Ratio in the three groups

C) CT Imaging Findings

The maximum of patients (77.2%) had abnormalities on CT imaging that involved bilateral lung, with the lower lobe of the left lung being included in the majority (56.7%). Lesions with consolidation and ground-glass opacities (GGOs, 47.7%) or pure GGOs (22.1%) were found (36.5%). The vast number of lesions (64.1%) were subpleural. CT findings included lung cavitation (1 percent), interlobular septal thickening (44.9 percent), air bronchograms (37.7%), organisation or fibrosis (30.0 percent), crazy-paving patterns (40.6 percent), bronchial wall thickening (21.6 percent), and halo signals (7.4percent). Total CT severity scores varied from 0 (all in subjects with mild involvement) to 24 (in subjects with severe lung involvement).The median score was 10, with a moderate CT result of 8.50–2.25.

Table 7 : Findings on HRCT chest scans

FINDINGS ON HRCT CHEST SCANS		
FINDINGS	**NO. OF PATIENTS**	**%**
GGOs and consolidation	22	17
Absence of GGOs and consolidation	88	72
Either GGOs and consolidation present	45	36
GGOs without consolidation present	58	47
GGOs with consolidation present	5	4
Consolidation without GGOs present		
NO. OF LOBES AFFECTED	28	22
0	19	15
1	15	12
2	09	7
3	22	17
4	39	31
5	59	47
>2		
Bilateral lung disease	95	77.2
Frequency of lobe involvement	47	38
Upper lobe (Right lung)	44	35
Middle lobe (Right lung)	61	49
Lower lobe (Right lung)	50	40
Upper lobe (Left lung)	69	56
Lower lobe (Left lung)		
Total lung severity score		
Median	10	
Range	0-25	
Opacity characteristics		
Linear opacities	16	13
Rounded morphology of opacities	62	50
Wedge shaped	28	22
Lung cavitation	4	1
Crazy-paving pattern	49	40
Reverse halo sign	9	7

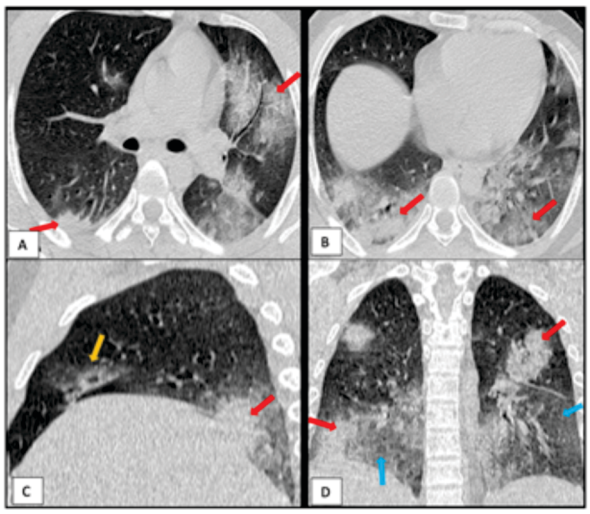

Figure 8 : High Resolution Computed Tomography (HRCT) chest in a 30 year old male, 5 days after the symptoms appeared; in axial plane (A and B), sagittal (C) and coronal (D) planes- show bilateral patchy areas of consolidation (red arrows), ground-glass opacification with interlobular septal thickening- *crazy paving pattern* (blue arrows) and an area of faint ground-glass opacification in the right middle lobe with a ring of denser consolidation- *reverse halo sign* (yellow arrow).

D) ROC curve analysis

In subjects with negative (i.e., mild) CT findings, the mean NL Ratio was 2.58±1.30, 3.5 ±1.59 in individuals with moderate CT findings, and 10.26 ± 2.76 in patients with high grade (severe) CT abnormalities. The NL Ratio levels varied significantly ($p < 0.001$) across the three groups and within each group. The NL Ratio was significantly greater in severe group than in the moderate group and significantly higher in moderate group than in the mild group. The NL Ratio and the CT severity score had a strong positive connection ($r = 0.863$, $p<0.001$). The NL Ratio value is directly proportional to the lung damage severity. The ROC curve study revealed that NL Ratio was useful for distinguishing between negative and positive CT results in COVID-19 patients. The AUC was 0.858 (95% confidence interval: 0.728-0.903, $p < 0.001$), with sensitivity of 69.9%, a specificity of 93.11% and an significant cut-off value of 3.734

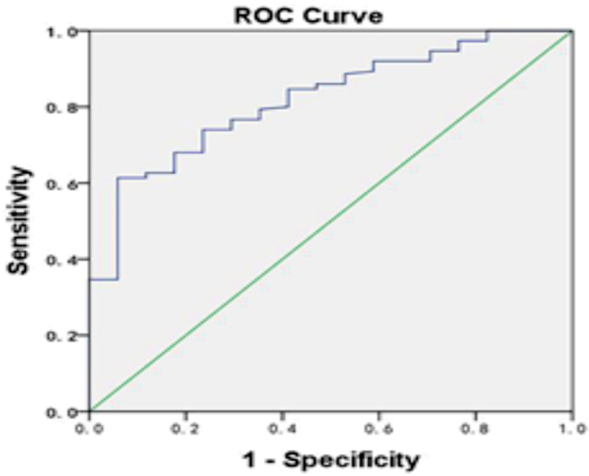

Figure 9: NL ratio ROC for discriminating between negative and positive CT findings in 123 COVID-19 patients. The AUC was 0.808, indicating sensitivity of 69.9% and specificity of 93.1%.

DISCUSSION:-

WHO recommends chest imaging when RT-PCR testing is

unavailable, or symptoms of COVID-19 are present. Clinical and radiologic collaboration should increase diagnostic and therapeutic effectiveness .

Most of our study's severely diseased participants were males. Research shows that disparity is caused by numerous variables, such as behaviour and hormonal protective effects. The COVID-19 infection was severe in the elderly (61-70 years). COVID-19 symptoms include high grade temperature, cough, dyspnoea, headache, muscular discomfort, and tiredness. According to new diagnostic and therapeutic criteria, COVID-19 may present with a mild or low temperature, or even without an elevated body temperature at all (17). Only seven of the cohort had a body temperature above 39°C. When patient has a mild to moderate illness, they may present with minimal or no fever. Around 20% of recorded cases are severe, with a 5% overall mortality rate (18). Our findings show that most patients were controllable and recovered, despite a 19.6% infection rate.

CT imaging characteristics of COVID-19 pneumonia were subpleural and bilateral GGOs and consolidative pulmonary opacities, which all indicated lung destruction. The COVID-19 lesions were predominantly seen in the lungs, with no evidence of organ damage. By summing afflicted lung lobes scores, the overall CT severity scores may be utilized to estimate the severity of lung damage in COVID-19 patients (19).

Severe lung injury had a increased NLR than moderate lung injury, and moderate lung injury had a higher NLR than mild lung injury. The NL ratio increased in correlation with lung damage severity as evaluated by CT. This conclusion is consistent as per findings of a study research by (14, 18).

COVID -19 patients who had increasing neutrophil and declining lymphocyte levels before death. Lymphocytopenia was observed as an association with COVID-19 disease severity and mortality. The NL ratio is linked with greater risk of severe COVID-19 infection (Yao et al., 2020). Compared to other more complicated models, its simplicity of screening and use may help identify individuals whose prognosis might be improved by early intervention. The viral load detected early in the illness is unlikely to produce visual pneumonia. Some instances may be unable to advance due to self-limiting infections. Others may develop infections with apparent lesions on future CT scans, causing illness (13,17).

The optimal NLR cut-off range of 3.634 for distinguishing between negative and positive CT findings in identified COVID-19 subjects was determined using ROC analysis. If the NL Ratio is more than 3.634, lung infections should be evaluated in individuals with negative CT scans. Results conclude that NL Ratio can also be used to predict the lung damage severity and can be used in conjunction with chest CT images in COVID-19 subjects.

Our research also found a strong link between serum CRP levels and CT scan severity. CRP levels can be utilized to initiate treatment early. Thus, CRP can be utilised to anticipate onset of disease. CRP levels can be utilised to initiate treatment early. Thus, the onset of disease can be predicted by CRP levels.

CONCLUSION:-

NL Ratio effectively indicated the lung injury extent and anticipated COVID-19 progression. We advocate for emphasizing the affordability and accessibility of this monitoring approach. Additionally, we can use it as an alternative technique for avoiding excessive radiation protection during prognostic CT scans. Clinical use of the NL Ratio may assist in reducing medical resource constraints in relatively undeveloped regions during the epidemic and may act as unique infection marker in other nations afflicted by COVID-19 pandemic.

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Contributions of Authors

All authors made significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; contributed to the writing of the article or critically revising it for important intellectual content; gave final approval of the published version; and agree to be accountable for all aspects of the work.

Ethical Approval

The study was approved by Medical Ethics Committee of NKP Salve Institute of Medical Sciences and Research Centre with the letter number: (NKPSIMS &RC & LMH/IEC/26/2020).

Funding:

This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All the data associated with this study are presented in the paper

Abbreviations:

ARDS(Acute respiratory distress syndrome), CI(Confidence interval): COPD(chronic congestive pulmonary disease), COVID-19(corona virus disease), CT(computed tomography), CTSS(CT severity score), SARS-CoV-2(severe acute respiratory syndrome coronavirus-2), GGO(ground glass opacity), HIV(Human Immunodeficiency Virus), HRCT(high-resolution computed tomography), Multisystem organ dysfunction syndrome(MODS), NL Ratio (Neutrophil-to-Lymphocyte Ratio), RT-PCR(reverse transcription polymerase chain reaction), RAT(Rapid Antigen Test), Receiver Operating Characteristic curve(ROC), WHO(World Health Organization),

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