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Original Research Article

Correlation analysis between CT-THORAX findings with Biochemical characteristics of RT-PCR negative COVID-19 Symptomatic patients

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ABSTRACT

Background – Undoubtedly, the end of 2019 will be recorded as one of the most sinister times in the history of medicine, when an outbreak of fatal pneumonia caused by a novel coronavirus. RT-PCR test may show false negativity due to various reasons. Studies have shown that chest CT has a high sensitivity for the diagnosis of COVID-19.

Objectives: The main objective of this study was to determine the computed tomography findings in the patients presenting with COVID-19 like symptoms, to study the biochemical and inflammatory marker profile of patients presenting with COVID-19 like symptoms and to establish correlation of all the above parameters and CT severity score.

Methods: 100 cases who presented with COVID-19 like symptoms and were COVID-19 RT-PCR negative in a tertiary care center were included in the study. Patients have undergone various lab investigations like CRP; D-dimer; IL-6 and Serum Ferritin. HRCT were done for all the 100 patients.

Results: In our study, highest number of patients belong to 51 to 60 years and 71 to 80 years age group i.e., 22 each. Majority of patients in our study are male i.e.,74% and females are 26%. The most common finding was ground glass opacities followed by consolidation on HRCT. There is statistically significant difference in mean value of various biochemical markers like CRP, S. ferritin, IL-6 and D-Dimer and CT severity score. We found that D-dimer is the best predictor for outcome of the patients followed by S. ferritin, CRP and HRCT thorax.

Conclusion: Chest CT can serve as a superior screening tool to RT-PCR. Increase in severity of disease as evident by higher CT score leads to increase in value of various inflammatory and bio chemical markers.

1. INTRODUCTION

Undoubtedly, the end of 2019 will be recorded as one of the most sinister times in the history of medicine, when an outbreak of fatal pneumonia caused by a novel coronavirus (later designated as SARS-CoV-2) [1,2] hits the headlines. In fact, the original heartfelt belief of the world that the disease—reported from Wuhan [3,4]—is nothing more than a common cold was disappeared in the blink of an eye when the World Health Organization (WHO) issued a public health emergency on 30 January 2020 [3], followed by the declaration of a viral pandemic on 11 March [5]. Even though the general belief— by matching the number of deaths to the total number of infected cases—is that most patients with coronavirus disease

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2019 (abbreviated to COVID-19) have recovered, stealing a glance at the outrageous statistics of deaths increased day after day recaps that SARS-CoV-2 still is taking toll [6].

Timely identification of COVID-19 carriers is critical not only to mitigate viral spread but also to alleviate disease progression in a well-controlled manner. Notwithstanding the fact that the nucleic acid test serves as the gold standard method for the etiological detection of SARS-CoV-2 infection, the existence of the false-negative results is the main challenge [7, 8]. Also, variable distribution of virus across the respiratory tract between patients, missing patients who have recovered from the disease, and the pre requisite of certified laboratories, expensive equipment and skilled personnel denote other limitations to PCR-based diagnostic methods [9]. Recitation of this concern from the fact that such limitations are even more highlighted in countries with restricted assets further uncovers the urgent necessity for alternative tests to timely detect COVID-19 patients.

Real-time polymerase chain reaction (RT-PCR) remains the standard test of COVID-19 pneumonia but various factors can delay the diagnosis like standby time for viral detection with RT-PCR tests, incomplete sampling techniques, variations in viral load, and false-negative rates of a test depending on the kit sensitivity. Although the first test is negative in a number of cases, it has been reported that positivity develops in the second, third, or even subsequent tests [10-14]. There are also cases in the literature with multiple negative RT-PCR test results from nasopharyngeal samples that are positive in tests using bronchoalveolar lavage (BAL) samples. The target receptor of the virus is angiotensin-converting enzyme 2 (ACE2). This receptor is not expressed at the nasal and oral levels but substantially in type 1 and type 2 alveolar epithelial cells, making the BAL method more effective [15]. Although the symptoms of the disease may be similar to those of other viral infections, differences in imaging findings can facilitate the differential diagnosis [16]. Imaging techniques such as radiography and computed tomography (CT) have gained importance for disease detection [17]. Studies have been performed by radiologists to determine typical and atypical CT findings of COVID-19 infection, and radiologists have attempted to reach consensus regarding these findings. Common CT findings of COVID-19 pneumonia are mostly ground-glass opacity (GGO), consolidation and crazy paving pattern, and less commonly subpleural curvilinear line, air bubble sign, halo and reversed halo sign, air bronchogram, airway changes, and fibrous stripe formations [18–21].

Biochemical parameters can be useful in predicting negative outcomes in COVID-19 patients [22]. Several prognostic biomarkers of this disease predicting the severity have been validated till date [23,24]. However, in-hospital patient's clinical findings especially hematological, inflammatory markers, and biochemical parameters as well as viral load of SARS-CoV-2 are needed for the assessment of severity of COVID-19 infection. Biomarkers may be classified as a susceptibility or risk, diagnostic, tracking, prognostic and predictive for any disease including the classify patients that are more likely to have a certain outcome [25]. C-reactive protein (CRP) is a liver-produced protein; indicate the early indicator of infection and inflammation [26]. It has been identified as a key marker that changes dramatically in extreme COVID-19 patients [27]. D dimer (coagulation factor) acts as a biomarker among severe COVID- 19 patients [28,29]. It was elevated among most deaths, may be caused by systemic microvascular thrombosis or coagulopathy, according to a recent autopsy [30]. Serum ferritin, lactate hydrogenase (LDH), serum urea and creatinine were also used as biomarkers of COVID-19 especially unexplained weakness or shortness of breath, inflammatory cell damage and signs of kidney or liver damage, respectively [23,31-32]. However, little is known about these biochemical markers in relation to COVID-19 progression and rate of mortality.

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In this study, we aimed to emphasize the importance of non-contrast CT in the diagnosis of COVID-19 disease by comparing the thoracic CT findings of COVID-19 patients with clinical suspicion of COVID-19 but with negative RT-PCR results and the correlating the CT severity score with biochemical lab markers.

2. MATERIALS AND METHODS

A prospective observational study has been carried out between April 1,2021 to March 31,2022 and was approved by the ethical committee. 100 Cases who fulfilled the selection criteria during the study period were included. Selection of the cases was based on convenience sampling.

Patient selection:

- All the patients of age more than 18 years, who presented with COVID-19 like symptoms and came as COVID-19 RT-PCR negative at GMC Kota & Attached Group of Hospitals during the period of study satisfying our inclusion and exclusion criteria have been included in the study. RT-PCR positive patients and pregnant females were excluded from the study,
- Clinical data of study subjects have been collected.
- Complete medical history including present clinical symptoms and details of comorbidities obtained.
- Vital parameters-pulse, blood pressure, respiratory rate, saturation, temperature have been monitored regularly and systemic examination noted as per case need.
- Patients have undergone following lab investigations: -
  - Quantitative C-Reactive Protein
  - D-dimer
  - Interleukin-6
  - Serum Ferritin
- Inflammatory markers done irrespective of testing methodology from standard laboratory with valid results be included in the study. Any deviation from normal values as per laboratory standards will be considered abnormal.

Radiological Evaluation:

- After approval by the ethical committee of the Institute, the detailed information about the study was explained to the patients found eligible for inclusion in the study. Informed consent was taken from all of them.
- Demographic profiles of the patients were noted and complete details about the clinical diagnosis and laboratory diagnosis was noted in the study proforma.
- CT of thorax was done on GE CT BRIGHTSPEED 16 SLICE CT SCANNER (GE HEALTHCARE, USA).
- Patient questionnaires were completed during each screening visit.

HRCT Technique:

- CT scan was performed according to a standard single breath hold protocol in supine position with full inspiration. Sections of 1 mm slice thickness were obtained using high spatial frequency volumetric reconstruction algorithm.
- Standard CT protocol was used with topogram length of 512 cm, 120 kV and 35 mA.

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- Images were attained in axial mediastinal and lung windows and reconstructed in thin 0.625-1.25 mm lung window.
- All CT images were reconstructed to 0.625-1.25‑mm thin slices.
- At work station, multiplanar images were acquired using the multiplanar reformatting (MPR) technique.
- The CT chest images thus obtained were studied by a radiologist for presence of ground glass opacities, consolidation, septal thickening, fibrosis and other findings as described.

STATISTICAL ANALYSIS:

- The data was collected and entered into Microsoft Excel spreadsheet. Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program.
- Descriptive statistics included computation of percentages, means and standard deviation.
- Chi square, independent t test, Kruskal Wallis test and Mann Whitney U tests were applied and p value <0.05 was considered significant

3. RESULTS

The Present study was conducted on patients who were RT-PCR COVID-19 negative patients but came for HRCT scan with covid like symptoms to the Department of Radiology in Government Medical College Kota, Rajasthan. The study was conducted between April 1, 2021 to March 31, 2022 with aims to determine the computed tomography findings in the patients presenting with COVID-19 like symptoms, to study the biochemical and inflammatory marker profile of patients presenting with COVID-19 like symptoms and to establish a correlation of all the above parameters and HRCT score. A Total of 100 patients were enrolled for this study.

74% of the patients were males and 26% were females. Most of the patients were between 51-60 & 71-80 years of age (22%) followed by 31-40 (18%), 41-50 years of age (13%), 61-70 years of age (12%), 21-30 years of age (10%), 81-90 years of age (2%) and 91-100years of age (1%). 38% patients had hypertension followed by 25% patients had diabetes as co-morbidities. Majority of patient were on ventilator (50%) followed by 18% patients were on NRM and 14% on NIV and Room air each. GGO was the most common finding in HRCT scan followed by consolidation **(TABLE-1). Chart 1** shows that there is positive co-relation between HRCT thorax score and duration of hospital stay ($p<0.05$). It shows that duration of hospital stay increases with increase in CT severity score. **Table 2** shows that there is statistically significant difference in mean value of various biochemical markers like CRP, S. ferritin, IL-6 and D-Dimer across various CT score categories as evident by Kruskal Wallis test. ($p<0.05$). Mean value of all these markers increase with increase in HRCT severity and score. There are higher percentage of deaths (51.3%) among those patients who had CT severity score more than 15 with severe category followed by 30.8% deaths in moderate and 23.1% in mild categories. This difference is statistically significant ($p<0.05$). **ROC curve in chart 2** shows that D-dimer is the best predictor for outcome of COVID-19 patients followed by S. ferritin, CRP and HRCT thorax. Area under curve for all these investigations are 0.59 and more as shown in **table 3.**

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TABLE 1– Spectrum of CT Chest findings

	Frequency	Percent
GGO	100	100
Consolidation	69	69
Septal thickening	63	63
Sub pleural atelectasis	54	54
Revers halo sign	3	3
Fibrotic changes	12	12
Emphysema	13	13
Mediastinal lymph adenopathy	25	25
Pleural effusion	14	14
Pneumothorax	2	2

Chart 1: Co-relation between CT severity score and duration of stay in hospital (N=100)

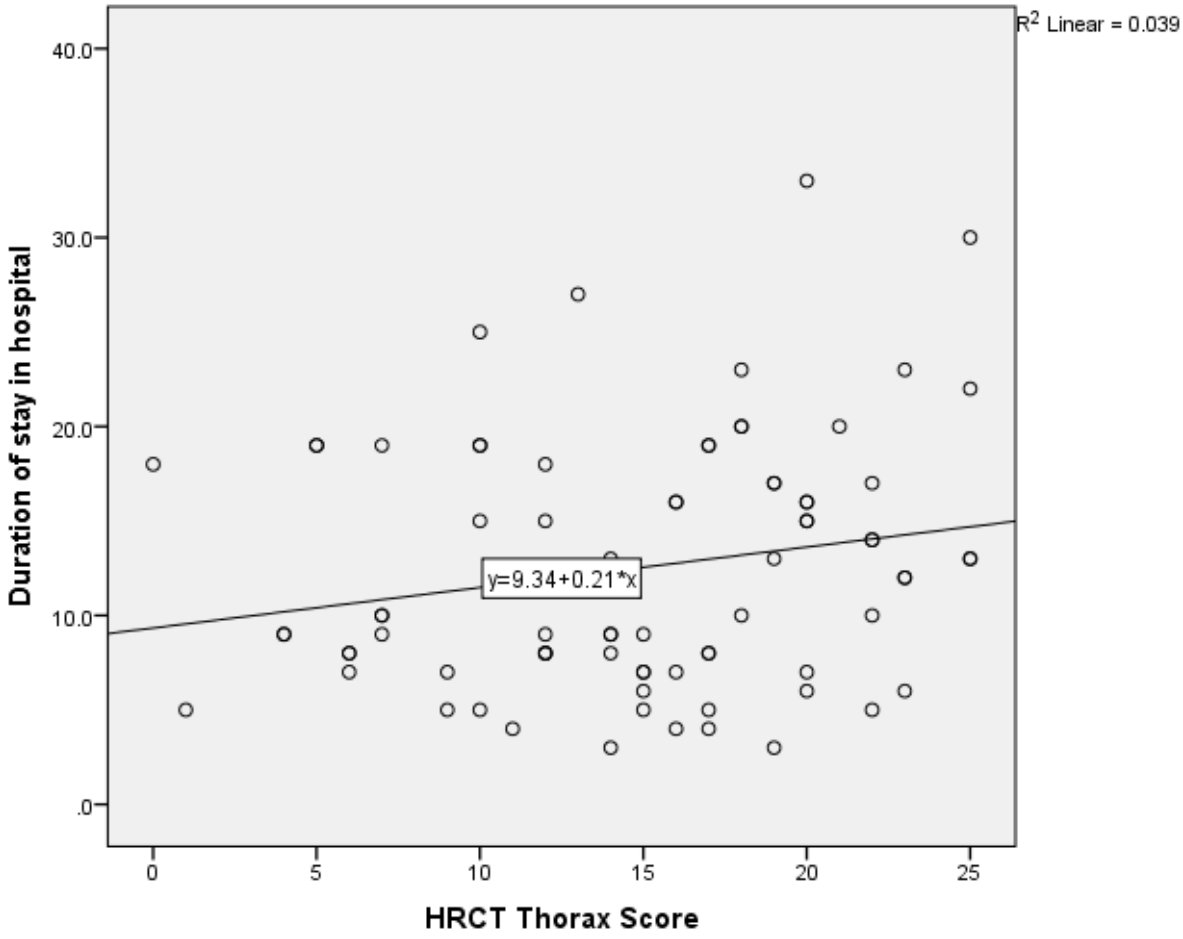

Table 2: Co-relation of biochemical markers with CT severity score of the patients (N=100)

Biochemical Markers	CT severity score categories						Test statistics Kruskal Wallis Test
	Mild ≤ 8		Moderate 9–15		Severe > 15		
	Mean	SD	Mean	SD	Mean	SD	P value
CRP	40.48	21.8	65.45	23.9	73.87	45.8	<0.05
S. Ferritin	571	730	581.1	956	764	196	<0.05

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IL-6	341	106.7	360	633.1	477.3	751.9	<0.05
D-Dimer	1805	371.1	2943.5	2147.7	6964	3982.5	<0.05

Chart 2: ROC curve for important investigation for prediction of outcome among the patients

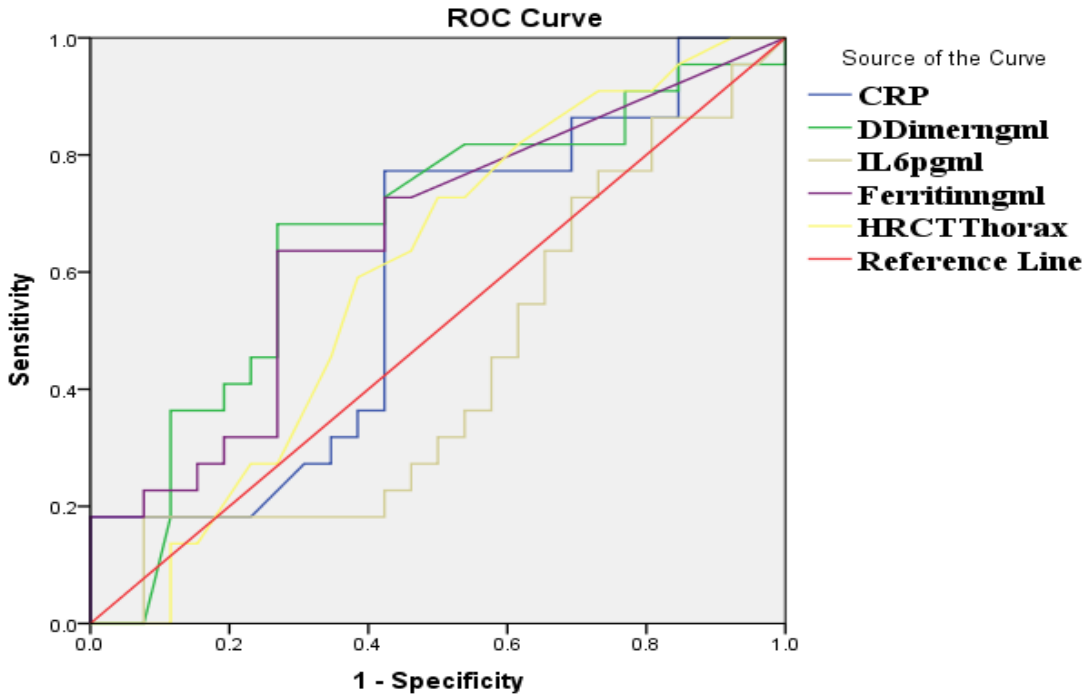

Table 3: Area under ROC curve for important investigations for prediction of outcome among the patients

Investigation	Area under curve	95% CI of Area under curve
IL-6	0.43	0.26-0.59
CRP	0.59	0.42-0.75
D-Dimer	0.66	0.5-0.82
S. Ferritin	0.65	0.5-0.81
HRCT Thorax score	0.59	0.43-0.76

CASE 1-

a) Axial scan shows large areas of ground glass opacities in bilateral upper and right middle lobe with interlobular septal thickening in subpleural area.

b) Coronal scan of same patient shows multifocal areas of consolidations and ground glass opacifications predominantly involving lower lobes.

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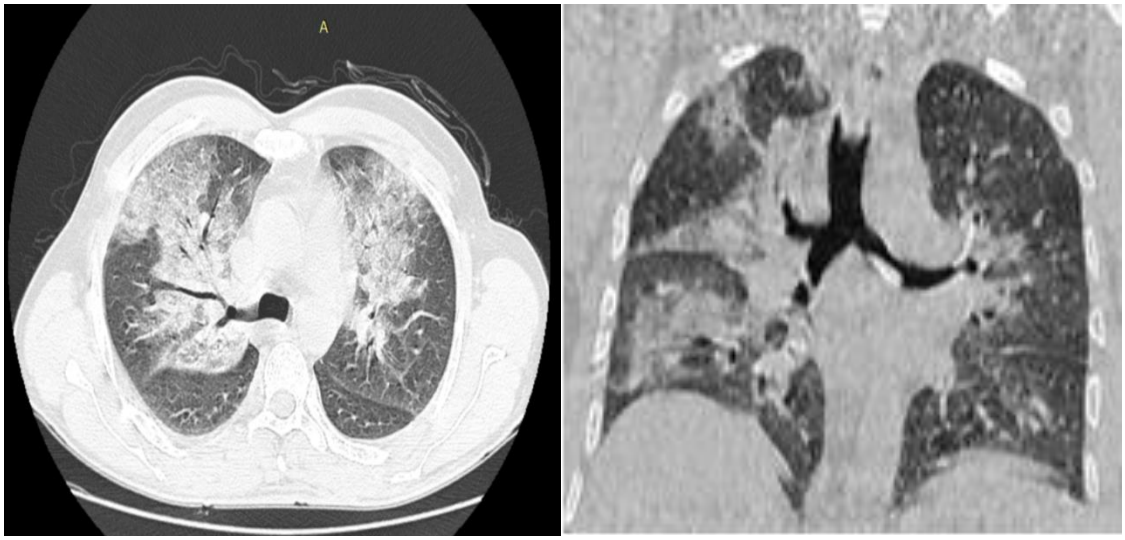
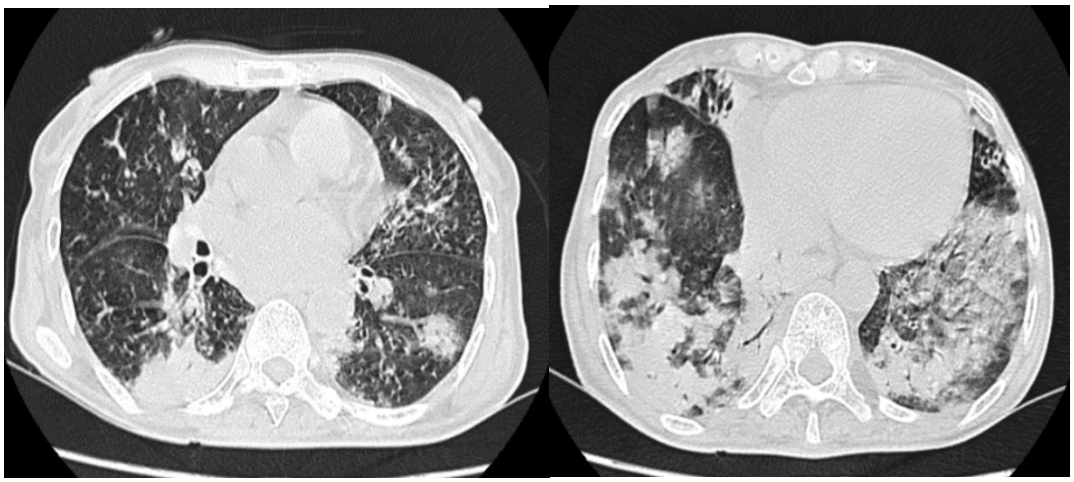


CASE 2 –
2a) and 2b)- HRCT Axial scan shows multiple patches of consolidation, ground glass opacification with interlobular septal thickening bilaterally involving all lobes which are peripheral in location more extensive on right side. No pleural or pericardial effusion.



SUMMARY

This Hospital based observational prospective study was carried out among RT-PCR negative COVID 19 patients admitted in hospitals with complaints of COVID like symptoms with the objective to determine the computed tomography findings in the patients presenting with COVID-19 like symptoms and to evaluate co-relation between HRCT score and various inflammatory markers. RT-PCR test may not be positive in these patients due to reasons such as incomplete sampling techniques, variations in viral load, sampling time after contact, late transfer to the laboratory, and kit sensitivity. Studies comparing the diagnostic accuracy of RT-PCR tests and CT findings in COVID-19 disease reported that the RT-PCR test may show false-negative results; the sensitivity of the test varies between 50 and 83%. Moreover, some studies suggest that the sensitivity of CT findings is higher than that of RT-PCRs [33-35]. In a study by **Ai et al**., 1014 patients were examined and CT findings were detected in 308 patients with negative RT-PCR results. Bilateral lung lesions consisting of ground glass

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opacities and consolidations were detected in lung CT of these 308 patients. For patients with a follow-up RT-PCR test, the mean interval between the initial negative to positive RT-PCR results is reported as 4–8 days. In this study, when RT-PCR results were taken as the reference standard, the sensitivity, specificity, and accuracy of chest CT in demonstrating COVID-19 infection were found to be 97%, 25%, and 68%, respectively [36]. Highest number of patients in our study belong to 51 to 60 years and 71 to 80 years age group i.e., 22 each followed by 31 to 40 years having 18 patients. Mean age of patients is 54.35 years with SD being 17.12. Patients with minimum age in our study is 21 years and 96 years is the highest age of patient. Majority of patients in our study are male i.e.,74% and females are 26%. The study shows that 71% patients had shortness of breath followed by 59% patients of COVID 19 had fever while cough was present among 49% patients. Other symptoms (9%) included diarrhea, loss of smell and loss of taste. 38% patients of COVID-19 disease had hypertension followed by 25% patients had diabetes as co-morbidities. Majority of patient of COVID-19 disease were on ventilator (50%) followed by 18% patients were on NRM and 14% on NIV and Room air each. The most common finding was ground glass opacities followed by consolidation on HRCT. GGO's were found in all the patients. There is positive co-relation between CT severity score and duration of hospital stay ($p<0.05$). It shows that duration of hospital stay increases with increase in CT severity score. There is statistically significant difference in mean value of various biochemical markers like CRP, S. ferritin, IL-6 and D-Dimer across various HRCT categories as evident by Kruskal Wallis test. ($p<0.05$). Mean value of all these markers increase with increase in HRCT severity and score. There is increase in median CRP value (as represented by middle thick line of box) with increase in severity of HRCT according to its score. Simultaneously there is also increase in upper range of CRP (as represented by upper most point of each plot) with increase in HRCT thorax score. There is positive co-relation between HRCT thorax score and CRP ($p<0.05$). There is increase in CRP level with increase in HRCT thorax score. There is increase in median D-Dimer value (as represented by middle thick line of box) with increase in severity of HRCT according to its score. Simultaneously there is also increase in upper range of D-Dimer (as represented by upper most point of each plot) with increase in HRCT thorax score. There is positive co-relation between CT severity score and D-Dimer ($p<0.05$). There is increase in D-Dimer level with increase in CT severity score. There is increase in median IL-6 value (as represented by middle thick line of box) with increase in severity of HRCT according to its score. Simultaneously there is also increase in upper range of IL-6 (as represented by upper most point of each plot) with increase in CT severity score. There is positive co-relation between CT severity score and IL-6 ($p<0.05$). There is increase in IL-6 level with increase in CT severity score. There is increase in median S. ferritin value (as represented by middle thick line of box) with increase in severity of CT score. Simultaneously there is also increase in upper range of S. ferritin (as represented by upper most point of each plot) with increase in CT severity score. There is positive co-relation between CT severity score and S. ferritin ($p<0.05$). There is increase in S. ferritin level with increase in HRCT thorax score. There are higher percentage of deaths (51.3%) among those patients of COVID-19 disease who had CT severity score more than 15 with severe category followed by 30.8% deaths in moderate and 23.1% in mild categories. This difference is statistically significant ($p<0.05$). There is statistically significant difference in median value of CRP, D-Dimer, IL-6, S. Ferritin and CT severity score as evident by Mann Whitney U test between discharged and death patients. Median value of all these investigations is higher among those who expired than discharged. **ROC curve in chart 2** shows that D-dimer is the best predictor for outcome of COVID-19

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patients followed by S. ferritin, CRP and HRCT thorax. Area under curve for all these investigations are 0.59 and more as shown in **table 3.**

4. CONCLUSION

Studies have shown that chest CT has a high sensitivity for the diagnosis of COVID-19 and it can serve as a superior screening tool to RT-PCR in case of resource shortages in tests. Increase in severity of disease as evident by higher CT score leads to increase in value of various inflammatory and bio chemical markers. Outcome in severe category of HRCT score is worse than mild and moderate categories. According to our study, D-Dimer is better predictor of outcome of COVID-19 disease; however, CRP, S. ferritin and IL-6 are also useful in prediction of outcome among COVID-19 disease. RT-PCR test may show false negativity due to various reasons. A patient with high clinical suspicion of COVID-19 infection and with a history of contact should not be removed from isolation without a CT scan, even if RT-PCR tests are negative. If patients with negative RT-PCR tests but positive CT findings are discharged without isolation or other precautionary measures, the rates of human-to human transmission may increase, and the patients may deteriorate.

5. REFERENCES

1) World Health Organization (2020) Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. https:// www. who. int/ director- general/ speeches/ detail/ who- director- general s remarks- at- the- media- briefing- on- 2019-ncov- on- 11- February- 2020
2) O'Shea PM, Lee GR, Griffin TP, Tormey V, Hayat A, Costelloe SJ et al (2020) COVID-19 in adults: test menu for hospital blood science laboratories. Ir J Med Sci (1971-) 189:1147–1152
3) Lu H, Stratton CW, Tang YW (2020) The Wuhan SARS-CoV-2— what's next for China. J Med Virol 92(6):546–547
4) Bashash D, Abolghasemi H, Naseri P, Cheraghali AM, Soltanpoor MJ, Fooladi AAI (2021) The association of age sex and RT-PCR results with the lymphocyte and neutrophil counts in SARS-CoV-2 infection: a cross-sectional analysis of 1450 Iranian patients with COVID-19. Iran J Allergy Asthma Immunol 1–11
5) Cucinotta D, Vanelli M (2020) WHO declares COVID-19 a pandemic. Acta Biomed Atenei Parmensis 91(1):157–160
6) Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G (2020) Real estimates of mortality following COVID-19 infection. Lancet Infect Dis 20(7):773
7) Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J (2020) Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. Radiology 296(2):E41–E45
8) Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W et al (2020) Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 296(2):E32–E40
9) Tahamtan A, Ardebili A (2020) Real-time RT-PCR in COVID- 19 detection: issues affecting the results. Expert Rev Mol Diagn 20(5):453–454
10) Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, Schluger NW, Volpi A, Yim JJ, Martin IBK, Anderson DJ, Kong C, Altes T, Bush A, Desai SR, Goldin, Goo JM, Humbert M, Inoue Y, Kauczor HU, Luo F, Mazzone PJ, Prokop

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

M, Remy-Jardin M, Richeldi L, Schaefer-Prokop CM, Tomiyama N, Wells AU, Leung AN (2020) The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Radiology 296(1):172–https://doi.org/10.1148/radiol.2020201365

11) Fan L, Liu SY (2020) CT and COVID-19: Chinese experience and recommendations concerning detection, staging and follow-up. Eur Radiol 30(9):5214–5216. https://doi.org/10.1007/s00330-020-06898-3
12) Xu B, Xing Y, Peng J, Zheng Z, Tang W, Sun Y, Xu C, Peng F (2020) Chest CT for detecting COVID-19: a systematic review and meta-analysis of diagnostic accuracy. Eur Radiol 30(10):5720–5727. https://doi.org/10.1007/s00330-020- 06934-2
13) Li Y, Yao L, Li J, Chen L, Song Y, Cai Z, Yang C (2020) Stability issues of RTPCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19. J Med Virol. 92(7):903–908. https://doi.org/10.1002/jmv.2 5786
14) Hao W, Li M (2020) Clinical diagnostic value of CT imaging in COVID-19 with multiple negative RT-PCR testing. Travel Med Infect Dis. 34:101627. https://doi.org/10.1016/j.tmaid.2020.101627
15) Winichakoon P, Chaiwarith R, Liwsrisakun C, Salee P, Goonna A, Limsukon A, Kaewpoowat Q (2020) Negative nasopharyngeal and oropharyngeal swabs do not rule out COVID-19. J Clin Microbiol. 58(5). https://doi.org/10.1128/JCM.00297-20
16) Hosseiny M, Kooraki S, Gholamrezanezhad A, Reddy S, Myers L (2020) Radiology perspective of coronavirus disease 2019 (COVID-19): lessons from severe acute respiratory syndrome and Middle East respiratory syndrome. AJR. 214(5):1078–1082. https://doi.org/10.2214/AJR.20.22969
17) Fu F, Lou J, Xi D, Bai Y, Ma G, Zhao B, Liu D, Bao G, Lei Z, Wang M (2020) Chest computed tomography findings of coronavirus disease 2019 (COVID-19) pneumonia. Eur Radiol. 30(10):5489–5498. https://doi.org/10.1007/s00330-020-06920-8
18) Ye Z, Zhang Y, Wang Y, Huang Z, Song B (2020) Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol.30(8):4381–4389. https://doi.org/10.1007/s00330-020-06801-0
19) Jin YH, Cai L, Cheng ZS et al (2020) A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Med Res. 7(1):4. https://doi.org/10.1186/s40779-020-0233-6
20) Sabri YY, Fawzi MMT, Nossair EZ, el-Mandooh SM, Hegazy AA, Tadros SF (2020) CT findings of 795 COVID-19 positive cases: a multicenter study in Egypt. Egypt J Radiol Nucl Med 51(1):237. https://doi.org/10.1186/s43055-02 0-00351-7
21) Ali TF, Tawab MA, Elhariri MA (2020) CT chest of COVID-19 patients: what should a radiologist know? Egypt J Radiol Nucl Med 51(1):120. https://doi.org/10.1186/s43055-020-00245-8
22) Carkci S. The Role of Urine Biochemical Parameters for Predicting Disease Severity in COVID-19 Patients. Authorea Preprints. 2020 Sep 16.
23) Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19-A systematic review. Life Sci 2020; 254:117788.
24) Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res 2020; 8:37.
25) Caruso FP, Scala G, Cerulo L, Ceccarelli M. A review of COVID-19 biomarkers and drug targets: resources and tools. Brief Bioinform 2021; 22(2):701-13.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

26) Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol 2005; 117(2):104-11.
27) Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J. C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation. Open Forum Infect Dis 2020; 7(5):ofaa153.
28) Harper PL, Theakston E, Ahmed J, Ockelford P. D-dimer concentration increases with age reducing the clinical value of the D-dimer assay in the elderly. Intern Med J 2007; 37: 607-13.
29) Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care 2020; 8:49.
30) Luo M, Guo L, Yu M, Jiang W, Wang H. The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public - A systematic review and meta-analysis. Psychiatry Res 2020; 291:113190.
31) Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah. Biomarkers and outcomes of COVID-19 hospitalizations: systematic review and meta-analysis. BMJ Evid Based Med 2020;
32) Keddie S, Ziff O, Chou MKL, Taylor RL, Heslegrave A, Garr E. Laboratory biomarkers associated with COVID-19 severity and management. Clinical Immunology 2020; 221:108614.
33) Long C, Xu H, Shen Q, Zhang X, Fan B, Wang C, Zeng B, Li Z, Li X, Li H (2020) Diagnosis of the coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol. 126:108961. https://doi.org/10.1016/j.ejrad.2020.108961
34) He JL, Luo L, Luo ZD, Lyu JX, Ng MY, Shen XP, Wen Z (2020) Diagnostic performance between CT and initial real-time RT-PCR for clinically suspected 2019 coronavirus disease (COVID-19) patients outside Wuhan, China. Resp Med 168:105980. https://doi.org/10.1016/j.rmed.2020.105980
35) Fang Y, Zhang H, Xie J et al (2020) Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology 296:115–117
36) Ai T, Yang Z, Hou H et al (2020) Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 296:32–40