Original Article

Chest X Ray and C-reactive Protein as Diagnostic Modalities for Monitoring Complications of Mild to Moderate COVID-19 Infections: Experience from a Dedicated COVID Hospital, Kolkata

Soumyasarathi Mondal[1], Arup Chakraborty[2], Ria Mukherjee[3], Adwitiya Das[4]

[1]Associate Professor, Department of General Medicine, Medical College Hospital, Kolkata, [2]Associate Professor, Department of Community Medicine, Medical College Hospital, Kolkata,[3]Senior Resident, Department of Community Medicine, Medical College Hospital, Kolkata, [4]Assistant Professor, Department of Community Medicine, Medical College Hospital, Kolkata.

How to cite this article: Soumyasarathi Mondal, Arup Chakraborty, Ria Mukherjee et. al. Chest X Ray and C-reactive Protein as Diagnostic Modalities for Monitoring Complications of Mild to Moderate COVID-19 Infections: Experience from a Dedicated COVID Hospital, Kolkata. Indian Journal of Public Health Research and Development/Volume 15 No. 2, April - June 2024.

Abstract

Introduction: SARS-COV-2 has created havoc during 2019-2021. Diagnosis and managing complications needed both laboratory investigations and imaging modalities.

Aims and objectives: To find out the association between socio-demographic and clinical profiles of the study subjects with their different laboratory investigations and imaging modalities and to compare normal investigations with their gold-standard variants.

Materials and Methods: During the first wave of COVID-19, a descriptive, observational, and cross-sectional study was carried out on 120 consecutive samples of mild to moderate COVID patients using a convenience sampling technique in a COVID indoor ward of Medical College, Kolkata. The semi-structured data collection form used in the study was predesigned, pretested, face and content validated. SPSS version 25 and Microsoft Excel version 19 was used for data analysis after coding. Ethical approval was taken. (Ref No. MC/KOL/IEC/Non-Spon/842/11/2020).

Results: Old age, uncontrolled diabetes and hypertension, presence of symptoms especially shortness of breath is significantly associated with low levels of SpO2, elevated C reactive protein (CRP) and D-dimer, abnormal Chest X-ray (CXR) and CT Thorax. A Kappa analysis suggested CRP and CXR can also be done instead of D-dimer and CT Thorax respectively, in a COVID patient for monitoring complications.

Conclusion: CRP and CXR are cost-effective alternatives and can be used as diagnostic modalities for monitoring of complications of mild to moderate COVID-19 infections.

Keywords: COVID-19, Kolkata, CRP, Chest X-ray, cost-effective

Corresponding Author: Adwitiya Das, Assistant Professor, Department of Community Medicine, Medical College Hospital, Kolkata.

E-mail: doc.adi.007.second@gmail.com

Contact: +91 6289108614

Submission date: Jul 25, 2023, **Revision date:** Aug 18, 2023, **Published date: Apr 4 2024**

Introduction

The seventh human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan, Hubei province, China, in January 2020.[1] Similar to SARS (2002 and 2003) and Middle East respiratory syndrome (MERS) (2012 to the present), two other coronavirus outbreaks that occurred in the past 18 years, the Covid-19 outbreak has presented significant difficulties for the fields of public health, research, and medicine.[2]Infection occurs through human-to-human transmission as well as interaction with infected environmental surfaces. In order to avoid contamination, good hand hygiene is essential. In some circumstances, wearing personal protection equipment is advised. Fever, cough, lethargy, mild dyspnoea, sore throat, headache, conjunctivitis, and gastrointestinal problems are the predominant signs and symptoms of COVID-19. Using samples from a nose swab, tracheal aspirate, or bronchoalveolar lavage, real-time PCR (RT PCR) is employed as a diagnostic technique. Findings from computed tomography are crucial for both diagnosis and follow-up.[3]

During hospitalisation, CRP values over 100 mg/dL and D-dimer levels over 500 ng/ml may indicate an increased risk of in-hospital mortality. Higher levels at presentation could be a sign of impending clinical decline.[4] According to a study, non-survivors' D-dimer and CRP levels were higher than those of survivors, as well as increasing more quickly. This implies that D-dimer and CRP dynamics may be used to track the progression of diseases.[5]

A study suggests using CXRs to identify patients for further RT-PCR testing first. This could be helpful in a hospital situation where the current systems are having trouble deciding whether to retain the patient in the ward with other patients or isolate them in COVID-19 sections. Additionally, it would assist in identifying patients who had a high risk of having COVID and who had a false-negative RT-PCR and required further testing.[6]Thorax CT has a high sensitivity in COVID-19 individuals with false-negative RT-PCR results, and it is crucial for diagnosis and follow-up. In the early stages, thorax CT abnormalities may be present even before the beginning of symptoms.[7]

It is evident that CXR and CRP are equally useful in monitoring complications of mild to moderate COVID-19 as well as in its diagnosis. This study aims to determine the relationship between the sociodemographic and clinical characteristics of the study subjects and their various laboratory investigations and imaging modalities in order to compare standard investigations with their gold-standard variants.

Methodology

A descriptive, observational and cross-sectional study has been conducted in COVID indoor ward of a dedicated COVID tertiary care hospital of Kolkata, West Bengal; during the first wave of COVID-19. 120 consecutive samples of mild to moderate COVID patients had been chosen by convenient sampling technique. According to ICMR guidelines, mild case was defined as cases with upper respiratory tract symptoms without shortness of breath and moderate case was defined as respiratory rate > 24/min and SpO2 < 94% on room air. Addiction among the subjects was defined as a chronic, relapsing disorder characterized by compulsive drug seeking and use despite adverse consequences.[8] The confirmed COVID positive patients who were admitted in indoor wards were included in this study excluding the subjects who were admitted in CCU (critical care unit) and HDU (high dependency unit). As the study involved inflammatory markers like CRP, other causes of raised CRP like arthritis or inflammatory bowel disease were excluded from the study. The study tool used was a predesigned, pretested, semi-structured data collection form, which was face and content validated by experts of Medicine and Public health. It consisted of four sections. The initial section consisted of socio-demographic profile which included Age in completed years, Gender, Addiction, if any, in their lifetime and presence of contact history. The next section consisted of the comorbidity profiles of the patient which stated presence of comorbidity, if any. The details of separate comorbidity included Diabetes, whether on control, Hypertension, whether on control, cardiovascular disease, Respiratory diseases, Cancer, Liver Diseases, Thyroid disorders. (Record based). In the subsequent section, the symptomatology of COVID were captured (history of symptoms experienced, if any, history

of fever, cough, sore-throat, shortness of breath (SOB), diarrhea, vomiting, myalgia in last 7 days or on admission). The final section was about the investigations data of the study subjects, consisting of SpO2 of patients, blood levels of CRP, D- dimer, interpretation of CXR and CT Thorax. At the end the collected data was coded and entered in Microsoft Excel software version 10 and analyzed in SPSS version 25 software. Written consent was taken from each of the respondents before interview and ethical approval taken from Institution Ethics Committee of Medical College and Hospital. (**Ref No. MC/KOL/IEC/Non-Spon/842/11/2020), Date-5/11/2020**.

Results and discussion

Table 1: Distribution of study subjects according to their sociodemographic profile (n=120)

S. No	Attribute	Sub-group	Frequency	Percentage
1	Age (in years)	<18	3	2.50
		18-59	63	52.50
		>=60	54	45.00
2	Gender	Male	75	62.50
		Female	45	37.50
3	Addiction	Yes	51	42.50
		No	69	57.50
4	Contact history	Yes	50	41.67
		No	70	58.33
5	Any comorbidity	Yes	89	74.17
		No	31	25.83

Comments: Majority of the study subjects belong to the adult age group (52.5%), followed by geriatric population (45%). 62.5% of them were males, majority (57.5%) did not have any history of addiction in their lifetime, 58.33% did not have contact history, whereas 74.17% has history of comorbidity.

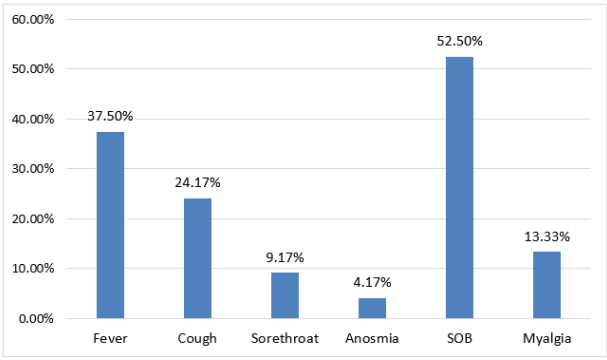

Fig 1: Distribution of study subjects according to the symptoms experienced during COVID (n=120)

Comments: The above bar diagram shows that majority of study subjects experienced SOB (52.5%), followed by fever (37.5%) and cough (24.17%)

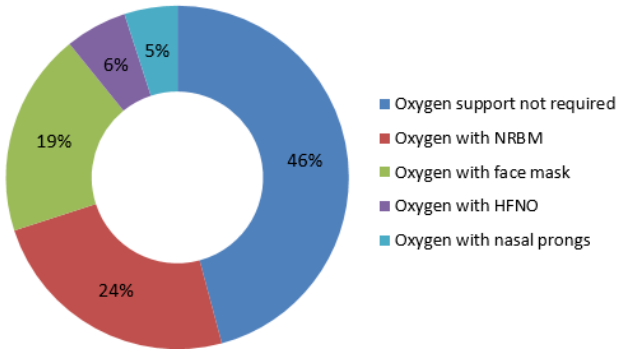

Fig 2: Distribution of sudy subjects according to their need of oxygen for survival with modality of oxygen delivery (n=120)

Comments: The above Doughnut shows that majority of the study participants survived with room air (46%). Out of the people who required oxygen, majority needed non-rebreathing mask(NRBM)(24%), followed by face mask (19%),high flow nasal oxygen (HFNO) (6%) and lastly nasal prongs (5%)

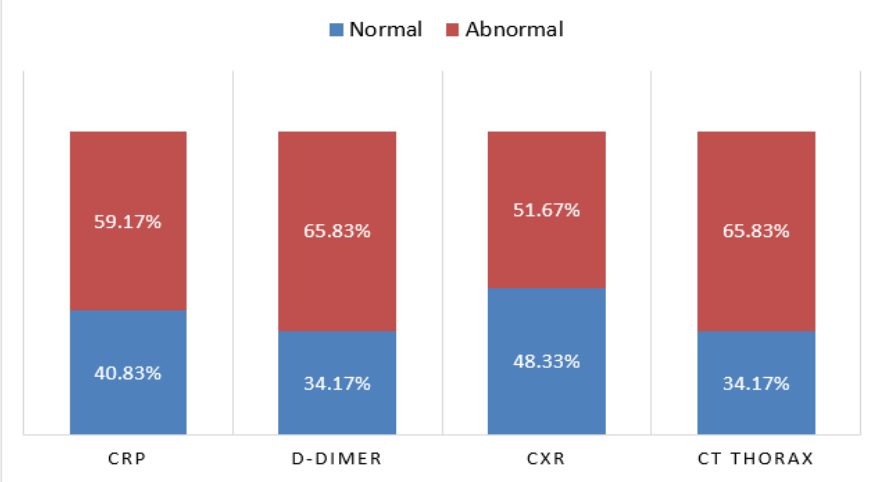

Fig 3: Distribution of study subjects according to laboratory investigations and findings of imaging modality (n=120)

Comments: The above diagrams show that D-dimer has increased more (65.83%) than CRP (59.17%) in COVID patients. Also, CT thorax depicts clearly about the abnormalities better (65.83%), than those with CXR (51.67%).

Table 2: Association of sociodemographic and clinical profiles with outcome variables.

Variable (n)	P-value				
	Low Spo2	High CRP[d]	High D-dimer[e]	Abnormal CXR[f]	Abnormal CT Thorax[g]
Old age[a] (120)	0.080	0.131	0.013	0.132	0.004
Presence of addiction (120)	0.379	0.659	0.54	0.014	0.035
Presence of comorbidity (120)	0.243	0.32	0.001	0.208	290
Uncontrolled Diabetes[b] (43)	0.049	0.001	0.082	0.137	0.238
Uncontrolled Hypertension[c] (58)	0.195	0.476	0.488	0.039	0.196
Presence of cardiac disease (120)	0.049*	0.346	0.181	0.526	0.035
Presence of symptoms (120)	0.001	0.011	0.564	0.000	0.000
Presence of fever (120)	0.603	0.039	0.345	0.509	0.881
Presence of cough (120)	0.144	0.000	0.001	0.994	0.624
Presence of SOB (120)	0.000	0.000	0.004	0.000	0.000

*Fischer's exact test, [a] Age ≥ 60 years, [b] Capillary blood glucose > 200 on admission or on OHA/ insulin from records, [c] Blood pressure ≥ 140/90 on admission or on antihypertensives from records, [d]CRP < 10mg/L, [e]D-dimer <0.5 mg/L FEU, [f]Abnormal CXR includes prominent broncho-vascular markings, opacification, pleural effusion, interstitial abnormalities, cardiomegaly, [g] Abnormal CT Thorax includes ground glass opacity.

Comments: The above table shows that old age is significantly associated with elevated D-dimer and abnormal findings in CT Thorax, which is around 2 and 3 times respectively, than that of lower age. Addiction is significantly associated with abnormal findings of CXR and CT Thorax. Presence of comorbidity in COVID patients causes significant increase in Ddimer. Uncontrolled diabetes lowers SpO2 4 times than diabetic COVID patient on control, whereas uncontrolled hypertension causes significant abnormality in CXR. Cardiac disorders are responsible for significantly lowering the SpO2 and causing abnormality in CT Thorax. Symptomatic COVID patients has 16 times significantly lower SpO2, 5 times elevated CRP, 2 times abnormal CXR and 28 times abnormal CT Thorax than asymptomatic COVID patients. CRP in a COVID patient increases more if the patient has fever. Presence of cough elevates CRP 5 times and D-dimer 4 times in a COVID patient than the patient without cough. Presence of shortness of breath is significantly associated with SpO2, CRP, D-dimer, CXR and CT Thorax.

Table 3: Kappa analysis for laboratory investigations and imaging modality. (n=120)

Variables	D-dimer		% Agreement	p-value
CRP	Normal	High		
Normal	32	17	78.33	0.000
High	9	62		
	CT Thorax			
CXR	Normal	Abnormal		
Normal	40	18	84.17	0.000
Abnormal	1	61		

Comments: The above table shows Kappa analysis between laboratory tests and various imaging modality. Assuming D-dimer a gold standard test for COVID patients, the percentage agreement found between CRP and D-dimer is 78.33%, which is a good one (p=0.000). Also, assuming CT Thorax, a gold standard imaging modality for COVID patients, a good percentage agreement is found between CRP and D-dimer (84.17%, p=0.000). Thus, CRP and CXR can also be done instead of D-dimer and CT Thorax in a COVID patient for monitoring complications.

Discussion

The present study showed that abnormal CXR and high CRP both can act as important tools for monitoring complications in mild to moderate COVID 19. While abnormal CXR was significantly associated with presence of addiction, uncontrolled hypertension, presence of symptoms and presence of SOB, high CRP was associated with uncontrolled diabetes, presence of symptoms, presence of fever, presence of cough, and presence of SOB. Assuming D dimer and CT thorax as gold standard investigations in COVID 19, there was good agreement between high CRP and high D dimer. Similarly, good agreement was observed between abnormal CXR and CT thorax.

As there was a surge of COVID 19 cases worldwide, it became evident that some patients might experience rapid clinical deterioration without premonitory symptoms.[9]Hence, research focused on different biomarkers as predictors of progression to severe disease. Severe or fatal cases of COVID-19 are associated with an elevated white cell count, blood urea nitrogen, creatinine, liver enzymes, CRP, IL-6, lower lymphocyte (<1000/µl) and platelet counts ($<100\times10^9$ /L) as well as lower albumin levels compared with milder cases.[10,11,12] Commonly used laboratory biomarkers like D-dimer or PT/ aPTT can be used as markers of disease severity in a controlled setting.

CRP is a widely available and cost-effective test to assess disease severity in a multitude of inflammatory and infectious conditions. As inflammation and cytokine release are the basis of development of complications in COVID 19, CRP assay finds use in COVID 19 cases as well. Studies have shown that higher levels of CRP in the initial phase of infection occurs in critically ill patients.[13] CRP values were very high in selected patients who succumbed to the disease.[14] Increasing or decreasing trend in the serial

values of CRP can predict disease progression or resolution, as also response to tocilizumab therapy. [10] An elevated CRP in a mildly symptomatic individual warrants close monitoring for early identification of complications.[15]

In order to minimize morbidity and mortality, early detection of COVID 19 is required.[16] Though HRCT chest is the imaging modality of choice in COVID 19, it is not available in most centres, and is also costly. It may be pertinent to go for a CXR in all patients with confirmed or suspected COVID 19, given the wide availability and significantly lower cost. Though CXR is frequently non-contributory in the early phase of disease, it is abnormal in severe disease.[17] It is sometimes the only imaging feasible, as in ventilated patients or very severely ill patients. A portable antero-posterior CXR provides adequate information on the severity and extent of lung involvement, as well as presence of complications like pleural effusions, pneumothorax or lung collapse. It also provides information on any pre-existing cardiac condition, and helps to identify pulmonary edema.[18] Baseline CXR findings consist of consolidation and hazy opacification.[19] Different CXR-based scoring systems were used in risk stratification of COVID-19 patients to plan early interventions and management.[20,21] In countries with resource constraints, CXR may remain the most frequently used tool to identify and monitor patients with moderate to severe COVID 19.

Limitation

The scope of obtaining history from patients was often limited to available documents only. All CXR and HRCT reports could not be availed at the time of data collection, hence sample size needed to be reduced as matching was not possible.

Conclusion

The study concluded that a symptomatic patient especially with presence of SOB lowers SpO2, elevates serum levels of CRP and D-dimer, portrays abnormalities in CXR and CT Thorax. On the other hand, it also becomes evident thatCRP and CXR can also be done instead of D-dimer and CT Thorax in a COVID patient for monitoring complications of mild to moderate COVID-19 infection.

Recommendation: As the above study suggests checking serum levels of CRP and performing CXR can also monitor complications of mild to moderate COVID-19 and these tests are cost-effective, we recommend to use the above tests before checking D-dimer or a CT Thorax.

Conflict of interest: Nil

Source of Funding: Self

Ethical Clearance: Ethical approval was taken from Institution Ethics Committee of Medical College and Hospital. (**Ref No. MC/KOL/IEC/Non-Spon/842/11/2020), Date-5/11/2020.**

References

1. Ciotti M, Ciccozzi M, Terrinoni A, Jiang WC, Wang CB, Bernardini S. The COVID-19 pandemic. Critical reviews in clinical laboratory sciences. 2020 Aug 17;57(6):365-88.
2. Fauci AS, Lane HC, Redfield RR. Covid-19—navigating the uncharted. New England Journal of Medicine. 2020 Mar 26;382(13):1268-9.
3. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE. COVID-19 diagnosis and management: a comprehensive review. Journal of internal medicine. 2020 Aug;288(2):192-206.
4. Ullah W, Thalambedu N, Haq S, Saeed R, Khanal S, Tariq S, Roomi S, Madara J, Boigon M, Haas DC, Fischman DL. Predictability of CRP and D-Dimer levels for in-hospital outcomes and mortality of COVID-19. Journal of community hospital internal medicine perspectives. 2020 Sep 2;10(5):402-8.
5. Valerio L, Ferrazzi P, Sacco C, Ruf W, Kucher N, Konstantinides SV, Barco S, Lodigiani C. Course of D-dimer and C-reactive protein levels in survivors and nonsurvivors with COVID-19 pneumonia: a retrospective analysis of 577 patients. Thrombosis and Haemostasis. 2021 Jan;121(01):098-101.
6. Mangal A, Kalia S, Rajgopal H, Rangarajan K, Namboodiri V, Banerjee S, Arora C. CovidAID: COVID-19 detection using CXR. arXiv preprint arXiv:2004.09803. 2020 Apr 21.
7. Gündüz Y, Öztürk MH, Tomak Y. The usual course of thorax CT findings of COVID-19 infection andwhen to perform control thorax CT scan. Turkish Journal of Medical Sciences. 2020;50(4):684-6.
8. Drug Misuse and Addiction | National Institute on Drug Abuse (NIDA) (nih.gov) (last accessed on 30th August, 2022)

9. Su Y, Ju MJ, Xie RC, Yu SJ, Zheng JL, Ma GG, et al. Prognostic Accuracy of Early Warning Scores for Clinical Deterioration in Patients With COVID-19. Front Med (Lausanne). 2021;7: 624255.
10. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46: 846-848.
11. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al; China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020; 55: 2000547.
12. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med Overseas Ed 2020; 382: 2372–4.
13. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020; 92: 856–62.
14. Fan H, Zhang L, Huang B, Zhu M, Zhou Y, Zhang H, et al. Cardiac injuries in patients with coronavirus disease 2019: Not to be ignored. Int J Infect Dis. 2020; 96: 294–7.
15. Cassone G, Dolci G, Besutti G, Muratore F, Bajocchi G, Mancuso P, et al. Acute-phase reactants during tocilizumab therapy for severe COVID-19 pneumonia. Clin Exp Rheumatol. 2020; 38: 1215-1222.
16. Isakadze N, Engels MC, Beer D, McClellan R, Yanek LR, Mondaloo B, et al. C-reactive Protein Elevation Is Associated With QTc Interval Prolongation in Patients Hospitalized With COVID-19. Front Cardiovasc Med. 2022; 9: 866146.
17. Prasetya IB, Cucunawangsih, Lorens JO, Sungono V, El-Khobar KE, Wijaya RS. Prognostic value of inflammatory markers in patients with COVID-19 in Indonesia. Clin Epidemiol Glob Health. 2021; 11: 100803.
18. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 2020; 323: 1612-1614.
19. Hanif N, Rubi G, Irshad N, Ameer S, Habib U, Zaidi SRH. Comparison of HRCT Chest and RT-PCR in Diagnosis of COVID-19. J Coll Physicians Surg Pak. 2021; 31: S1-S6.
20. Kim HW, Capaccione KM, Li G, Luk L, Widemon RS, Rahman O, et al. The role of initial CXR in triaging patients with suspected COVID-19 during the pandemic. Emerg Radiol. 2020; 27: 617-621.
21. Wong HYF, Lam HYS, Fong AHT, Leung ST, Chin TWY, Lo CSY, et al. Frequency and distribution of chest radiographic findings in COVID-19 positive patients. Radiology 2019; 27: 201160.