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Original Article

Clinical presentation & laboratory diagnosis of SARS-CoV-2: An observational study from a tertiary care centre in New Delhi, India

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1. Introduction

The pandemic of corona virus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) has aggravated human suffering with the number of suspected cases and deaths increasing daily. Since March 2020, when the first case was detected in Delhi, 340,436 confirmed cases and 6,128 deaths have been reported by 22 October 2020 [1]. Data regarding the clinical characteristics and associated markers in laboratory confirmed patients of COVID-19 is sparse from India.

According to recent studies from China, where the disease was reported first, clinical spectrum of SARS-CoV2 varies from asymptomatic infection, mild upper respiratory infection to severe pneumonia resulting in respiratory failure [2–4]. But one challenging feature of COVID-19 in India has lately been identified as being asymptomatic in a large number of cases [5]. Given the rapid spread of COVID-19, an updated analysis of cases in New Delhi might help identifying the defining clinical characteristics and severity of this disease.

The aim of the current study is to analyze the patient demographics, clinical presentations, laboratory findings and risk factors associated with mortality in SARS- CoV-2 infected patients in North India which is important in planning and execution of control strategies.

2. Materials and methods

2.1. Study design and participants

This is a retrospective observational study conducted at a tertiary care hospital in New Delhi. Covid-19 screening by reverse transcriptase polymerase chain reaction (RT-PCR) was started from 28 March 2020 after obtaining approval from Indian Council of Medical Research (ICMR). The patients tested from 28 March - 3 June 2020 were enrolled in the study. All suspected cases of SARS CoV-2 infection presented to our hospital in different outpatient departments, emergency department as well as suspected admitted patients who were subjected to COVID -19 testing were included in the study. The decision to test was based on clinical and epidemiological factors assessing the likelihood of infection as per the national guidelines [6]. RT-PCR was done for symptomatic cases and for asymptomatic close contacts of laboratory confirmed cases. This criteria for testing kept on evolving with time [7,8]. Patients were categorized as per the categories suggested by ICMR (Table 1) which were 5 to begin with, followed by 6, 7, 8 & 9 categories [7,8].

Nasopharyngeal swabs or throat swabs collected were transported to the laboratory in viral transport medium. All other specimens including sputum, endotracheal aspirate and broncho alveolar lavage, stool samples etc. were collected in sterile container and transported to the laboratory within 30 min. Specimens were stored at 2–8 °C & the tested within 48 h of receiving.

The study was approved by the Institutional Ethics committee (Letter dated 27 August 2020) and the requirement of informed consent was waived off.

2.2. Laboratory procedures

RNA extraction was performed in a bio safety level-2 facility using DSP DNA Midi extraction kit in automated Qiasymphony (Qiagen, USA) extractor. Various RT-PCR platforms targeting viral genes nucleocapsid (N), envelope (E), spike (S), RNA dependent RNA polymerase (RdRp) and open reading frames (ORF) were performed depending on the availability of test kits. Each nucleic acid amplification test (NAAT) run included both external & internal controls and results were interpreted as per the manufacturer's guidelines. A positive result by NAAT was reported when at least 2 targets were positive of which at least 1 was specific for SARS CoV-2. An inconclusive result was tested by another NAAT assay with a different platform. The Cartridge based nucleic acid amplification (CBNAAT) platforms (GeneXpert & BioFire) were used mainly in situations where severely sick patients requiring emergency surgery or intensive care unit (ICU) care were received in the casualty.

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Table 1
Patient categories of SARS-Cov-2 positive cases (n = 1456).

ICMR Category	Number of patients
1: Symptomatic international traveler in last 14 days	0
2: Symptomatic contact of lab confirmed case	272
3: Symptomatic healthcare worker	200
4: Hospitalized SARI (Severe acute respiratory illness) patient	70
5a: Asymptomatic direct and high risk contact of lab confirmed case	172
5b: Asymptomatic healthcare worker in contact with confirmed case without adequate protection	42
6: Symptomatic influenza like illness (ILI) patient in hospital	452
7: Pregnant women in/near labor	5
8: Symptomatic (ILI) among returnees and migrants (within 7 days of illness)	5
9: Symptomatic influenza like illness (ILI) patient in Hotspot/ Containment zones	63
Others	175

ICMR, Indian Council of Medical Research; SARS-CoV-2, severe acute respiratory syndrome corona virus 2.

2.3. Data collection

Patient demographics were collected from the specimen referral forms (SRF). All repeat RT-PCR tests of a patient once labeled COVID-19 positive were excluded from the data. In case of admitted patients, additional investigation results were collected from hospital information system (HIS) and electronic medical records (EMR) which included clinical and laboratory data, associated co-morbidities and treatment outcomes. Other investigations such as complete blood count, coagulation profile, serum biochemical tests, plasma/serum based biomarkers including interleukin-6 (IL-6), serum ferritin, D-dimer, procalcitonin, C-reactive protein (CRP) and lactate dehydrogenase (LDH) wherever available were included in the study. The readings of first instance of investigations after admission were taken for analysis in all the above cases. Imaging results like Chest X-ray & computed tomography (CT) scan thorax were also analyzed in admitted patients wherever available. Other bacterial or fungal cultures were done wherever required for pneumonia, blood stream infections (BSI) or urinary tract infection (UTI). The outcome analysis was the rate of in-hospital death during a follow-up period of 45 days from the date of admission.

2.4. Statistical analysis

Descriptive data is expressed as mean (SD) or median (IQR) for continuous variables and number (%) for categorical variables. We used the Mann Whitney *U* test, X^2 test, or Fisher's exact test to compare differences between survivors and non-survivors.

3. Results

Of the total 6378 suspected cases subjected to RT-PCR for SARS CoV-2, 1456 (22.8%) were positive. The maximum number of positive cases (31%) belonged to the category 6. Since category 8 & 9 also were ILI, the total number of cases presented with ILI was 35.7% of the positive patients (Table 1).

The various platforms used for RT-PCR are shown in Table 2. Patient demographics of all the samples tested including positive cases are shown in Table 3. Most of the positive cases were from Delhi (96.8%) and the rest belonged to UP (2.5%) and Haryana (0.6%). The commonest sample collected was a nasopharyngeal swab (99.3%). Other samples included endotracheal aspirate (38 cases), throat swab (3 cases) and one stool sample.

Majority of the cases (61.1%) were between 21 and 50 yrs of age (Table 3). The median duration from onset of symptoms to testing was 3 days (IQR 2–5 days) which varied between 1 and 21 days. A total of 242 (16.6%) cases were health care workers (HCWs). The percentage positivity was observed to be marginally higher in case of CBNAAT platforms, 27.5% compared to regular PCR platforms, 22.7% (p value 0.085) (Table 2).

Fever (59.8%) followed by cough (42.7%) were the most common presenting symptoms. Other predominant symptoms were sore throat (26%) and body ache (23.6%). Nausea (2.1%) or vomiting (2.7%) and diarrhea (1.7%) were uncommon (Table 4). 20.5% of positive cases were

Table 2
The various PCR platforms used for testing (n = 6378).

Name of the kit (Manufacturer)	Number of tests performed	Number of positive tests
Real Star SARS-CoV-2 RT PCR kit 1.0 (Altona Diagnostics GmbH, Germany)	344	34
Tru PCR SARS-CoV-2 RT qPCR kit (3B BlackBio Biotech india Ltd, India)	550	47
Patho Detect Coronavirus-qualitative PCR kit in humans (Mylab Discovery solutions, India)	768	19
Argene SARS-CoV-2 R-Gene (Biomerieux, France) (Rapid platform)	4483	1292
GeneXpert Xpress SARS-CoV-2 (Cepheid, USA) (CBNAAT)	31	12
Biofire COVID-19 test (Biomerieux, France) (CBNAAT)	202	52

SARS-CoV-2, severe acute respiratory syndrome corona virus 2; RT-PCR, Reverse transcriptase polymerase chain reaction; CBNAAT, Catridge based nucleic acid amplification test.

Table 3
Demographics of patients subjected to SARS-CoV-2 RT-PCR (n = 6378).

Parameters	Number of patients investigated	Positives (%Positivity)
Gender		
Male	3644	931 (25.6%)
Female	2734	525 (19.2%)
Age in Years		
<10	308	42 (13.6%)
11–20	283	60 (21.2%)
21–30	1319	285 (21.6%)
31–40	1517	342 (22.6%)
41–50	1001	262 (26.2%)
51–60	958	255 (26.6%)
61–70	642	143 (22.3%)
>70	350	67 (19.1%)

SARS-CoV-2, severe acute respiratory syndrome corona virus 2; RT-PCR, Reverse transcriptase polymerase chain reaction.

Table 4
Symptoms reported at the time of specimen collection in case of SARS-Cov-2 positive patients (n = 1456).

Symptom	Number (%)
Fever	870 (59.8%)
Cough	621 (42.7%)
Sore throat	379 (26%)
Body ache	344 (23.6%)
Breathlessness	217 (14.9%)
Vomiting	39 (2.7%)
Diarrhea	25 (1.7%)
Abdominal pain	24 (1.7%)
Nausea	30 (2.1%)
Nasal discharge	52 (3.6%)
Sputum	38 (2.6%)
Chest pain	28 (1.9%)
Headache	19 (1.3%)
Haemoptysis	13 (0.9%)
Loss of taste	2 (0.1%)
Blurring of vision & red eyes	1 (0.1%)
Asymptomatic	298 (20.5%)

SARS-CoV-2, severe acute respiratory syndrome corona virus 2.

asymptomatic, who were either contacts of laboratory confirmed cases or those who got admitted in hospital for major surgeries or other procedures. Among the overall positive cases 12.7% had at least one coexisting illness (e.g. hypertension, diabetes, chronic renal, liver or heart disease, malignancy or other immunosuppressive conditions). Only 47% of positive patients gave history of contact with a known case of COVID-19 infection.

Out of the 1456 COVID-19 positive cases, 517 patients were admitted in hospital. Patient demographics, laboratory findings and outcomes were analyzed in those who were hospitalized (Table 5). Median age of 62, leucocytosis, raised levels of aspartate aminotransferase (AST), lactate dehydrogenase, serum creatinine, D-dimer, serum ferritin, IL-6, prothrombin time, C-reactive protein and procalcitonin were observed to be associated with increased mortality (Table 5).

The typical findings of chest X-ray were bilateral patchy or diffuse pulmonary infiltrates with a tendency towards the lung periphery & lower lobe (Fig. 1) CT thorax images of admitted patients showed typical findings of bilateral ground glass opacity & sub segmental areas of consolidation (Fig. 2).

There were 31 episodes of secondary infections involving 24 patients, which included 13 episodes of blood stream infection (BSI), 13 episodes of pneumonia, and 5 episodes of UTI. The commonest organism involved was *Klebsiella pnuemoniae* causing 76.9% of BSI & 46.2% of pneumonia cases. Other major organisms causing pneumonia included *P. aeruginosa* followed by *A. baumanii*. Out of the secondary infections, 5 were fungal isolates including one case of *Aspergillus flavus* from endotracheal secretions, two Candida species causing BSI (one *C. albicans* and one *C. auris*) and two Candida species causing UTI (one *C. glabrata* and one *C. tropicalis*). Among those who had secondary infections, 15 out of 24 (62.5%) patients died in hospital.

On subsequent follow up of admitted patients, 53 (10.3%) patients expired in hospital. The median age of nonsurvivors was 62 years (IQR 52 to 68). 73.6% of these patients were associated with one or more comorbidities like diabetes, hypertension, heart disease, kidney disease, malignancy or transplant recipients. Hypertension (37.7%) was the commonest comorbidity in our study followed by diabetes (33.9%). However, 26.4% of non survivors didn't have any known comorbid conditions.

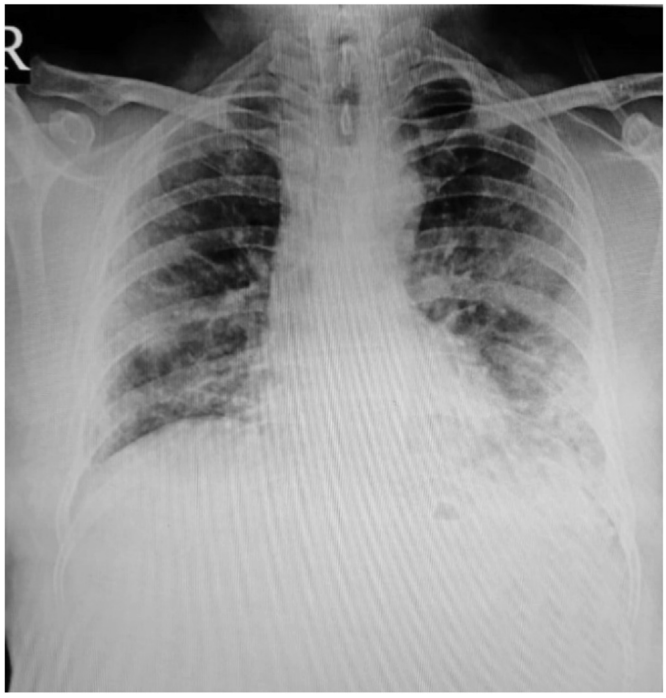

Fig. 1. Chest X ray: Bilateral peripheral, lower zone patchy consolidation classical of SARS-CoV-2 infection. SARS-CoV-2, severe acute respiratory syndrome corona virus 2.

4. Discussion

In the current study, 20.5% of positive cases didn't have any symptoms at the time of reporting to hospital. Majority of these cases were asymptomatic family contacts of laboratory-confirmed cases or health care workers exposed without adequate PPE. This category also included few patients who had reported to hospital for some surgical procedure, dialysis or chemotherapy & antenatal women in third trimester. Asymptomatic carriers have been reported in many previous studies as well, including a recent study from Delhi (44.4%) and they remained so during the hospital stay [5,9,10]. Because of these asymptomatic spreaders, it is imperative that testing programs include those without

Table 5
Demographics and laboratory findings of admitted & their outcome.

Demographics & Laboratory findings	No report	Survivor (n = 464)	No report	Non-survivor (n = 53)	P value
Age, years (Median & IQR)		45 (33–57)		62 (52–68)	<0.001
Sex					
Male		266 (57.3%)		40 (75.5%)	0.011
Female		198 (42.7%)		13 (24.5%)	0.011
White blood cell countx10^3 per L	65		6		
<4		34/399 (8.5%)		1/47 (2.1%)	1.123
4-10		318/399 (79.7%)		19/47 (40.4%)	<0.001
>10		48/399 (12%)		27/47 (57.5)	<0.001
Median Hemoglobin	72	12.8 (11.4–14.0)	7	10.9 (8.7–12.5)	<0.001
Platelet count x 10^3per L	70		6		
Median Platelet count		200 (150–252.3)		211 (126–284)	0.993
<150		96/394 (24.4%)		16/47 (34%)	0.150
Prothrombin time, s Median	250	12.4 (11.6–14.0)	10	14.5 (13.2–16.2)	<0.001
Creatinine ≥1.25 mg/dL	86	45/378 (11.9%)	2	24/51 (47.1%)	<0.001
Lactate dehydrogenase ≥250 IU/L	224	129/240 (53.8%)	26	24/27 (88.9%)	0.0005
Aspartate aminotransferase >40U/L	123	119/341 (34.9%)	11	21/42 (50%)	0.055
Procalcitonin ≥0.5 ng/ml	347	19/117 (16.2%)	8	34/45 (75.6%)	<0.001
C-reactive protein ≥10 mg/L	225	131/239 (54.8%)	22	31/31 (100%)	<0.001
D-dimer, ≥0.5 mg/L	307	44/157 (28%)	30	18/23 (78.3%)	<0.001
Serum ferritin, >300ug/L	208	100/256 (39.1)%	23	26/30 (86.7%)	<0.001
IL-6,pg/mL median	271	39.7 (9.3–119.5)	20	132 (78.9–230.3)	<0.001

Data are median (IQR), n(%) or n/N, where N is the total number of patients with available data. P values comparing survivors and non survivors are from x^2 test, Fisher's exact test or Mann-Whitney *U* test. IQR, interquartile range; IL-6, interleukin-6.

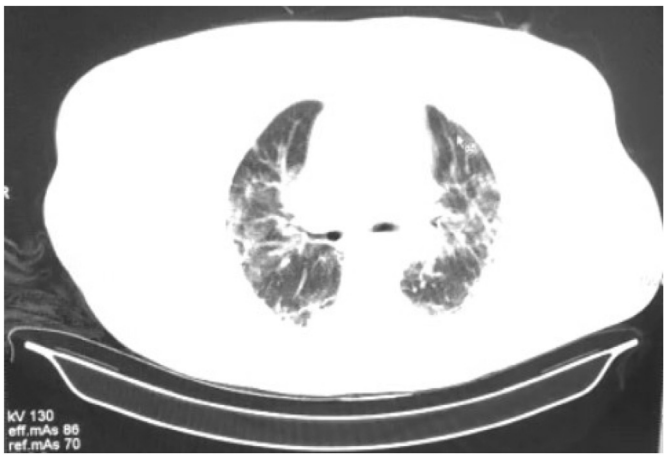

Fig. 2. Non-enhanced High-Resolution Computed Tomography Thorax: Peripheral and peri-bronchial patchy consolidation suggestive of COVID-19 infection. COVID-19, corona virus disease 2019.

symptoms as well in order to halt transmission. Studies have shown that such cases may be associated with subclinical lung abnormalities as detected by computed tomography [11].

Only 59.8% (870) of patients in our study, had fever as presenting complaint, so afebrile cases may be missed if the surveillance case definition focuses on fever alone. A study from China had similar observation which quotes fever in 43.8% of cases at admission and 88.7% of cases during hospitalization [4]. A meta-analysis from China showed fever (83.3%), cough (60.3%) and fatigue (38.0%) were the commonest symptoms [12]. Studies from CDC, USA as well South East Asian countries also report similar 3 prominent symptoms [13,14]. Uncommon gastro intestinal (GI) symptoms as per our study was also observed by other studies [4,13]. This makes it different from SARS-CoV or MERS-CoV where more than 30% of patients presented with GI symptoms [15,16]. Fu L et al. observed that the prevalence of diarrhea was significantly higher in studies in which proportion of patients with any coexisting medical condition was larger [12]. A recent study published from Delhi on patients admitted in ICU reported 12.3% of patients with some degree of GI symptoms [17].

CBNAAT helped us in providing report within 2 h after receipt of sample compared to the RT PCR platforms which was reported within 24–48 h. The higher percentage positivity observed in case of rapid platforms (27.5% vs. 22.7%) may be due to the patient selection bias and was not statistically significant. Whether there was an improved sensitivity in case of rapid PCR assays needs more studies with comparative analysis of both the platforms. A multicenter evaluation study had concluded 100% concordance between GeneXpert and in house RT-PCR assays [18].

The mortality of 10.3% in our study was higher than the estimated case fatality rate of 1–4% in other studies [14,19]. This may be because, the mortality was calculated only among those who were admitted in hospital with severe COVID-19 disease or were associated with co morbidities or both. 73.6% of non survivors were also observed to have associated co morbidities. Hypertension followed by diabetes was the commonest comorbidities in our non survivor group. A study by Zhou et al. also share similar findings, with hypertension (48%) and diabetes (31%) as the commonest comorbidities associated with mortality [3]. Hypertension as the commonest comorbidity associated with mortality was consistent with data from China, Italy and USA [20,21].

Patients' age differed significantly between survivors and non survivors (Table 5). Previously, older age has been reported as an important independent predictor of severe illness and increased mortality in SARS-COV-2 infection [3,20]. It may be due to defects in T-cell and B-cell function associated with advanced age which might lead to deficiency in control of viral replication leading to prolonged proinflammatory response and poor outcome [22]. Another study from China also confirms elderly and patients with co-morbidities were likely to develop critical illness [23].

There was an overall male preponderance among all COVID-19 positives in the current study (63.9%), as well as those who were admitted in hospital (59.2%). Mortality was also observed to be higher in males (13.1%) compared to females (6.2%) similar to other studies [24]. However, there are studies which have reported no such significant difference between male and females patients in terms of case fatality rate or severity of infection [12].

There was a significant increase in inflammatory markers CRP, procalcitonin, serum ferritin and IL-6 in the non survivor group compared to survivor group in the current study. It is already documented that viral infection triggered Inflammatory responses play a significant role in the severity of pulmonary pathology [25]. The median in IL-6 was much higher in the non survivor group compared to survivors (132 vs. 39.7), similarly the proportion of CRP $\geq$10 mg/L (100% vs. 54.8%) and procalcitonin $\geq$0.5 ng/ml (75.6% vs. 16.2%). It has been reported that, during SARS-CoV-2 infection, a small subgroup of patients experience a cytokine storm caused by excessive release of proinflammatory cytokines like IL-2, TNF-α, IL-7 & interferon-γ [26]. The proportion of patients with D-dimer, $\geq$0.5 mg/L was also higher in the non survivor group (78.3% vs. 28%; p value $<$ 0.001).

CT scan is useful in picking up pulmonary involvement early and also tell the extent of the disease and is helpful in the patients who have a negative RT-PCR test but strong clinical suspicion of COVID-19. General hallmarks of SARS-CoV-2 infection as per literature are similar to our observation which include chest X-ray findings of bilateral pulmonary infiltrates and chest CT findings of bilateral & peripheral ground glass and consolidated opacities, with an absence of concomitant pulmonary nodules, cavitation, adenopathy & plural effusion [2,27].

Among hospitalized patients in our study, 4.6% developed secondary infections during their hospital stay, *Klebsiella pnuemoniae* was the commonest causative agent causing BSI & pneumonia. Data on secondary infections during COVID-19 is limited. 13.5% of patients were reported to have secondary infection in a single centered retrospective study from China which included mostly hospital acquired pneumoia caused by organisms like *Klebsiella pneumoniae* or Aspergillus species [28]. A review of 9 studies mainly from China reported 8% of secondary bacterial or fungal infections which included mostly respiratory infections & bacteremia [29]. There are also reports of presumptive invasive aspergillosis among immunocompetent patients who developed acute respiratory distress syndrome (ARDS) during COVID-19 episode [30].

In this study 16.6% of total positive cases in our hospital were HCWs. A study from New York also reports 5% of their patients as HCWs [20]. This reinforces the usage of fit-tested N95 masks and other personal protective equipments for HCWs. It is recommended to closely monitor HCWs for any symptoms of infection and should immediately be subjected to RT-PCR and quarantined till the results are available.

The limitation of our study is that majority of our patients were diagnosed in outpatient settings, who were not subjected to other laboratory testing or were not followed up for subsequent development of symptoms or outcome analysis. Also due to the retrospective nature of study, all tests were not done in all patients especially LDH, serum ferritin, D-dimer and procalcitonin.

5. Conclusions

This study offers an overview of the epidemiology of COVID-19 patients in the Northern region of Indian sub continent and compares with the findings in other areas of the world. Our center being one of the earliest private setup approved for COVID-19 testing in Delhi, the data is a valuable contribution in understanding the pattern of infection in the capital city. We observed that some patients with COVID-19 did not present with fever and more than 20% of infections were asymptomatic. Older age, associated co morbidities along with secondary infections had

higher mortality rate. Higher levels of CRP, IL-6 and D-dimer were also associated with severe disease and fatality.

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Declaration of competing interest

The author declares no conflicts of interest.

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