ORIGINAL ARTICLE

Clinical and Epidemiological Features of SARS-CoV-2 Patients in SARI Ward of a Tertiary Care Centre in New Delhi

Amit Aggarwal[1*], Abhinav Shrivastava[2], Abhinav Kumar[3], Adila Ali[4]

Abstract

Importance: Rapid spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Wuhan, China, prompted heightened surveillance in India. Since the first laboratory confirmed case of SARS-CoV-2 was reported from Kerala on January 30, 2020 novel coronavirus infected pneumonia (NCIP) has been presenting to the hospital emergencies as severe acute respiratory illness (SARI). We aim to find out the rate of SARS-CoV-2 positivity in SARI cases and further clarify the epidemiological and clinical characteristics of NCIP in New Delhi, India.

Aims and Objectives: To find out the rate of SARS-CoV-2 positivity in SARI cases presenting to the hospital emergency and describe the epidemiological and clinical characteristics of NCIP.

Design, Setting and Participants: Retrospective, single-center case series of the 82 consecutive hospitalized patients with SARI and subsequent confirmed NCIP cases at Dr Ram Manohar Lohia Hospital, New Delhi between 10th April 2020 and 30th April 2020.

Main Outcomes and Measures: Epidemiological, demographic, clinical, laboratory, radiological, and treatment data were collected and analyzed. The primary composite end-point was admission to an intensive care unit (ICU), the use of mechanical ventilation or death. Patients were categorized as severe pneumonia and non-severe pneumonia at time of admission and outcome data was compared.

Results: Of the 82 SARI cases, 32(39%) patients were confirmed to be SARS-CoV-2 positive. The median age of NCIP cases was 54.5 years (IQR, 46.25 - 60) and 19(59.3%) of them were males. 24(75%) cases were categorized as severe pneumonia on admission. 22(68.8%) patients had 1 or more co-morbidities. Diabetes mellitus 16(50%), hypertension 11(34.4%) and chronic obstructive airway disease 5(15.6%) were the most common co-existing illnesses. Compared with the patients who did not meet the primary outcome, patients who met the primary outcome were more likely to be having at least 1 underlying comorbidity (p-0.03), diabetes (p-0.003) and hypertension (p-0.03). Common symptoms included dyspnea 29(90.6%) followed by cough 27(84.4%), fever 22(68%), bodyache and myalgias 14(43.75%). Median time from symptom onset to hospital admission was 3 days. The most common pattern on chest X-ray was bilateral patchy nodular or interstitial infiltration seen in 30(93.8%) patients. Leucopenia was present in 10(31.2%) of the patients, with majority of patients presenting with lymphocytopenia, 24(75%) [lymphocyte count (1106 cells/ dL), interquartile range {IQR}, (970-1487)]. Thrombocytopenia was seen in 14(43.8%) patients, pancytopenia in 10(31.2%) patients and anemia was seen in 14(43.8%) patients. Hypoalbuminemia was present in 22(68.8%) cases. Raised CK-MB was seen in 7(21.9%) patients. The primary composite end-point occurred in 12(37.5%) patients, including 9(28.13%) patients who required mechanical ventilation and subsequently expired. 3(9.3%) of these patients who recovered, were subsequently shifted to COVID-19 ward from the ICU. The patients who met the primary outcome were older in age (56.5 years vs 50 years), had significantly higher SOFA scores (6 vs 3.5), were in shock (41.7% vs 5%), in higher respiratory distress (66.7% vs 10%), had lower mean arterial oxygen saturation (85% vs 89.5%), had higher CK-MB values (66 vs 26)U/L [6(54.5%) vs 2(9.5%)], had hypoalbuminemia (100% vs 50%) and acute kidney injury 8(72.7%) vs 5(23.8%) on admission. Of the 50 non-COVID-19 SARI patients in our study cohort, 13 (26%) patients met the primary composite outcome. Of them 9 (18%) patients expired and remaining 4 patients have subsequently recovered. As on 17th May 2020, 23 patients were still hospitalized, recovering in COVID-19 ward.

Conclusion and Relevance: In this single-center case series from New Delhi, out of 82 patients of SARI, 32 patients were confirmed NCIP, with a COVID-19 positivity of 39%. 75% of NCIP presented in severe pneumonia and 37.5% required ICU care. The case fatality rate was 28%.

Introduction

In December 2019, a cluster of cases of acute respiratory illness with unknown etiology was detected in Wuhan city in the Hubei province of China which was related to Huanan seafood market. A previously unknown betacoronavirus was isolated through the use of genomic sequencing in samples from these patients with pneumonia. This SARS-CoV-2 virus

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Received: 03.06.2020; Accepted: 23.06.2020

as per the International Committee on Taxonomy of Viruses or COVID-19 as we now know, has been rapidly spreading worldwide thereafter. It is the third in the line of coronaviruses that have emerged among the human population in the last two decades. The other two being the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak in 2002-03 and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012-13.[1] As on 17th May 2020, around 4.5 million confirmed cases and 306,000 confirmed deaths have been reported worldwide. India has reported over 90,000 confirmed cases and around 2900 deaths from the disease.[2]

Although likely to have been started as a zoonotic transmission in the large sea food market of Wuhan, human-to-human transmission via droplets and contact with fomites has since been established to be the modus operandi of the virus spread.[3] Recent data suggests a reproductive number (R_0) of 5.7, higher than earlier studies.[4]

COVID-19 infection encompasses asymptomatic infection, mild upper respiratory tract illness, fever, cough, fatigue, shortness of breath, pneumonia, and other respiratory tract symptoms and in many cases progresses to severe respiratory failure and death.[5,6]

There are four major structural proteins encoded by the coronaviral genome on the envelope, one of which is the spike (S) protein that binds to angiotensin-converting enzyme-2 (ACE-2) receptor and mediates subsequent fusion between the envelope and host cell membranes to aid viral entry into the host cell. The nasal epithelial cells have the highest expression of ACE-2 receptors in the respiratory tree hence it has been utilized for the detection of viral RNA from the nasopharyngeal swabs. It also results in the symptomatology of anosmia and nasal congestion in these patients.

In India, the initial COVID-19 testing strategy included people who had international travel history with symptoms, symptomatic contacts of laboratory-confirmed COVID-19 patients and symptomatic healthcare workers managing Influenza like illness (ILI)/severe acute respiratory illness (SARI) patients.[16]

ILI case definition[7]

An acute respiratory infection with:

- Measured fever of ≥ 38 C°
- Cough
- Onset within the last 10 days

SARI case definition[7]

An acute respiratory infection with:

- History of fever or measured fever of ≥ 38 C°
- Cough
- Onset within the last 10 days
- Requiring hospitalization

While most people with COVID-19 infection develop only mild or uncomplicated illness, approximately 14% develop severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit.[8] At present, there are no effective therapies or vaccines for COVID-19.

Severe acute respiratory illness (SARI) are among the leading cause of hospitalization and deaths worldwide. SARI is associated with a large number of different viral and bacterial agents, notably influenza A and B viruses, parainfluenza viruses, coronaviruses, respiratory syncytial viruses (RSV), adenoviruses (AV), and rhinoviruses.[9]

The initial sentinel survey done by the ICMR for determining the incidence of COVID-19 among the SARI patients done in March 2020 showed an incidence rate of 1.8%. About a third of COVID-19 positive SARI cases did not have any history of contact with a laboratory-confirmed case or international travel history.[10]

The testing strategy adopted by our hospital has been to include all SARI patients in line with the ICMR guidelines. As SARI constitutes an important cause of mortality and morbidity, continued surveillance of COVID-19 among SARI patients would help us to prioritize, plan and mobilize our resources for optimum utilization.

The objective of this case series from a tertiary care healthcare facility in New Delhi, India is to analyze and describe the epidemiological and clinical characteristics of COVID-19 positive SARI cases during a three week period from 10th April 2020 to 30th April 2020.

Methods

Study design and participants

This retrospective observational study included adult SARI patients (>18 years of age) admitted in Dr Ram Manohar Lohia hospital, a tertiary care center in New Delhi designated for the management of COVID-19 patients. The study included all the adult patients who were diagnosed with SARI as per WHO case definition[7] and screened for SARS-CoV-2/COVID-19 between 10th April 2020 and 30th April 2020.

Preventive measures and management protocol for all the suspected patients suggested by the Indian Ministry of Health and Family Welfare (MoHFW) was followed by our center. All patients presenting to our hospital were triaged for SARI in a separate isolation area in the emergency services building and all the infection prevention and control practices were followed including personal protective equipments by the doctors and nursing staff. Individuals with severe acute respiratory illness were admitted to our SARI isolation ward. The isolation facility at our hospital was assessed for preparedness according to a checklist standardized by MoHFW and National Centre for Disease Control (NCDC), New Delhi.

Data collection

Epidemiological, demographic, laboratory, clinical management and outcome data were extracted from all the SARI patients admitted in our hospital. The data was checked by two physicians and a third researcher adjudicated any difference in interpretation between the two primary reviewers.

Study outcomes

The primary composite end-point was admission to an intensive care unit (ICU), the use of mechanical ventilation or death.

Laboratory procedures

The nasal and oropharyngeal swabs were taken from all SARI patients in our study and tested at our center for detection of COVID-19 using rRT-PCR for confirmation. Specimens were obtained for SARS-CoV-2 rRT-PCR examination on day of admission and again on day 5 of admission in case first sample was negative. After collection, the nasal and pharyngeal swabs were inserted into the same 2 ml cryovial

Table 1: Baseline demographic and clinical profile of the COVID patients

Baseline characteristics	Total (N=32)	Pneumonia severity			Presence of primary composite outcome		
		Severe (N=24)	Non-severe (N=8)	P value	Yes (N= 12)	No (N= 20)	P value
Age (median IQR)	54.5 (46.25-60)	55.5	48	0.12	56.5	50.5	0.042
Sex							
Male	19 (59.4%)	5 (62.5%)	14 (58.3%)	0.84	7 (58.3%)	12 (60%)	0.93
Female	13 (40.6%)	3 (37.5%)	10 (41.7%)		5 (41.7%)	8 (40%)	
Co-morbidities (at least 1)	22 (68.8%)	17 (70.8%)	5 (62.5%)	0.66	11 (91.7%)	12 (55%)	0.03
Co-morbidities (at least 2)	13 (40.6%)	11 (45.8%)	2 (25%)	0.30	8 (66.7%)	5 (25%)	0.02
Hypertension	11 (34.4%)	9 (37.5%)	2 (25%)	0.52	7 (58.3%)	4 (20%)	0.03
Diabetes mellitus	16 (50%)	13 (54.2%)	3 (37.5%)	0.41	10 (83.3%)	6 (30%)	0.003
Heart disease	4 (12.5%)	3 (12.5%)	1 (12.5%)	1.00	2 (16.7%)	3 (10%)	0.58
CVA	1 (3.125%)	1 (4.2%)	0 (0%)	0.56	1 (8.3%)	0 (0%)	0.19
CKD	0	0	0	-	0	0	-
Malignancy	0	0	0	-	0	0	-
Chronic chest condition	9 (28.1%)	7 (29.2%)	2 (25%)	0.82	4 (33.3%)	5 (25%)	0.61
H/O PTB	2 (6.2%)	1 (4.2%)	1 (12.5%)	0.40	0 (0%)	2 (10%)	0.26
COPD	5 (15.6%)	4 (16.7%)	1 (12.5%)	0.78	3 (25%)	2 (10%)	0.26
Asthma	2 (6.25%)	2 (8.3%)	0 (0%)	0.40	1 (8.3%)	1 (5%)	0.71
ILD	1 (3.125%)	1 (4.2%)	0 (0%)	0.56	1 (8.3%)	0 (0%)	0.19
Hypothyroidism	2 (6.25%)	2 (8.3%)	0 (0%)	0.40	01(8.3%)	2 (5%)	0.71
Symptoms							
Fever	22 (68%)	16 (66.7%)	6 (75%)	0.66	9 (75%)	13(65%%)	0.55
Cough	27 (84.4%)	20 (83.3%)	7 (87.5%)	0.78	10 (83.3%)	17 (85.%)	0.90
Cough with expectoration	10 (31.3%)	7 (29.2%)	3 (37.5%)	0.66	4 (33.3%)	6 (30%)	0.84
Cough without expectoration	17 (53.13%)	13 (54.2%)	4 (50.0%)	0.84	6 (50%)	11 (55%)	0.78
Dyspnoea	29 (90.6%)	22 (91.7%)	7 (87.5%)	0.73	11 (91.7%)	18 (90.0%)	0.87
Fatigue	14 (43.75%)	9 (37.5%)	5 (62.5%)	0.22	5 (41.7%)	9 (45%)	0.85
Sorethroat	9 (28.1%)	7 (29.2%)	2 (25%)	0.82	5 (41.7%)	5 (20%)	0.19
Headache	6 (18.75%)	4 (16.7%)	2 (25%)	0.60	2 (16.7%)	4 (20%)	0.82
Loose stools	3 (9.4%)	2 (8.3%)	1 (12.5%)	0.73	0 (0%)	3 (15%)	0.16
Chest pain	6 (18.75%)	5 (20.8%)	1 (12.5%)	0.60	3 (25%)	3 (15%)	0.48
Abdominal pain	3 (9.4%)	1 (4.2%)	2 (25%)	0.08	0 (0%)	3 (15%)	0.16
Anosmia	4 (12.5%)	3 (12.5%)	1 (12.5%)	1.0	2 (16.7%)	2 (10%)	0.58
Nasal discharge	3 (9.4%)	3 (12.5%)	0 (0%)	0.29	1 (8.3%)	2 (10%)	0.88
Haemoptysis	1 (3.125%)	1 (4.2%)	0 (0%)	0.56	1 (8.3%)	0 (0%)	0.16
Vomiting	1 (3.125%)	0 (0%)	1 (12.5%)	0.78	0 (0%)	1 (5%)	0.43
Bodyache / myalgia	14 (43.75%)	9 (37.5%)	5 (62.5%)	0.22	5 (41.7%)	9 (45%)	0.85
Altered sensorium	2 (6.25%)	1 (4.2%)	1 (12.5%)	0.40	0 (0%)	2 (10%)	0.26
Symptom to adm (days) (IQR)	3 (2-4)	3	4	0.63	3.5	3	0.30

containing viral transport medium. The swabs were expressed on the side of the cryovials and broken off into the cryovials. Specimens were stored and transported to laboratory at 4°C. Single positive test was sufficient to declare positive results. For patients of SARI having highly suspicious radiological appearance on chest x-ray, two consecutive negative tests were done before being discharged or shifted to non-COVID ward.

Routine blood examinations were complete blood count, arterial blood gases, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), cardiac enzymes and procalcitonin. Chest radiographs were also done for all inpatients. Frequency of examinations was determined by the treating physician. All epidemiological, clinical and laboratory data were prospectively recorded.

Definitions

Fever was defined as axillary temperature of at least 37·5°C. Sepsis and septic shock were defined according to the 2016, Third International Consensus Definition for Sepsis and Septic Shock. Secondary infection was diagnosed when patients showed clinical symptoms or signs of pneumonia or bacteremia and a positive culture of a new pathogen was obtained from lower respiratory tract specimens (qualified sputum, endotracheal aspirate, or bronchoalveolar lavage fluid) or blood samples after admission. Acute kidney injury was diagnosed according to the KDIGO clinical practice guidelines and acute respiratory distress syndrome (ARDS) was diagnosed as per the Berlin Definition. Acute cardiac injury was diagnosed if serum levels of cardiac biomarker, CK-MB was above the 99th percentile upper reference limit, or if new abnormalities were detected on electrocardiography and echocardiography. Hypoalbuminemia was diagnosed when serum albumin was < 3.5 g/dL. Leucopenia was defined by a total leucocyte count of less than 4000 cells per cubic millimeter. Lymphocytopenia was defined as absolute lymphocyte count of less than 1500 cells per cubic millimeter. Monocytosis was defined as absolute monocyte count of more than 950 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter.

Table 2: Laboratory and radiological findings of patients infected with COVID-19

Baseline characteristics	Total (n=32)	Pneumonia severity		P value	Presence of primary composite outcome		P value
		Severe (n=24)	Non-severe (n=8)		Yes (n=12)	No (n=20)	
Leucopenia	10 (31.2%)	7 (29.2%)	3 (37.5%)	0.66	4 (33.3%)	6 (30%)	0.84
Lymphocytopenia	24 (75%)	18 (75%)	6 (75%)	1.0	10 (83.3%)	14 (70%)	0.40
Monocytosis	5 (15.6%)	5 (20.8%)	0 (0%)	0.16	4 (33.3%)	1 (5%)	0.03
Thrombocytopenia	14 (43.8%)	11 (45.8%)	3 (37.5%)	0.68	5 (41.7%)	9 (45%)	0.85
Anaemia	14 (43.8%)	9 (37.5%)	5 (62.5%)	0.22	6 (50%)	8 (40%)	0.58
Pancytopenia	10 (31.2%)	6 (25%)	4 (50%)	0.19	3 (25%)	7 (35%)	0.56
Deranged LFT	4 (12.5%)	2 (8.3%)	2 (25%)	0.22	1 (8.3%)	3 (15%)	0.58
AKI	13 (40.6%)	11 (45.8%)	2 (25%)	0.30	9 (75%)	4 (20%)	0.002
Hypoalbuminemia	22 (68.8%)	17 (70.8%)	5 (62.5%)	0.66	12 (100%)	10 (50%)	0.003
Raised CK MB	8 (25%)	7 (29.2%)	1 (12.5%)	0.35	6 (50%)	2 (10%)	0.01
B/L chest infiltrates	30 (93.8%)	23 (95.8%)	7 (87.5%)	0.40	11 (91.7%)	19 (95.%)	0.71

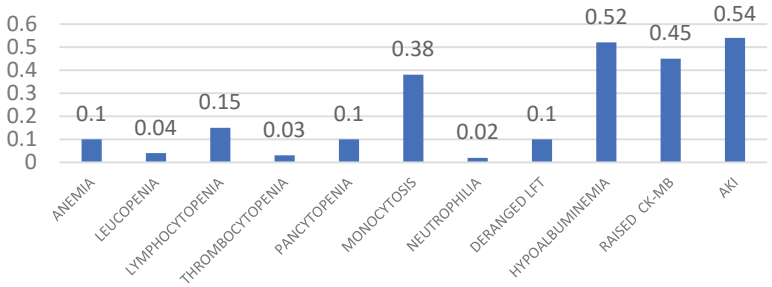

Fig. 1: Co-relation of laboratory parameters with primary outcome

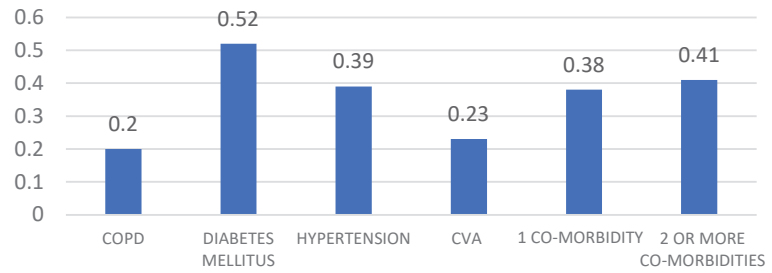

Fig. 2: Co-relation of presence of co-morbidities with primary outcome

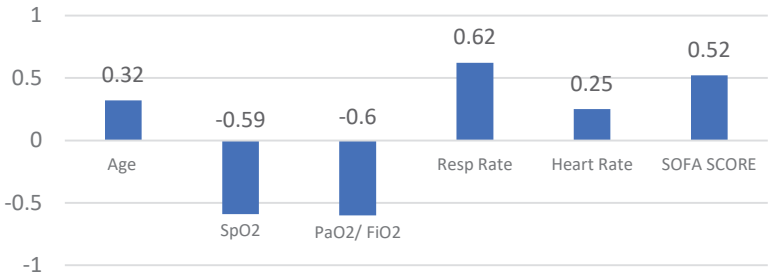

Fig. 3: Co-relation of clinical profile with primary outcome

As per WHO, NCIP was taken as severe if the patient presented with fever or suspected respiratory infection plus one of following –

1 respiratory rate more than 30 breaths per minute

2 severe respiratory distress

3 $SpO_2 \leq 93\%$

The patients of NCIP not fulfilling the above conditions were labeled as non-severe pneumonia.

Statistical Analysis

Categorical variables were described as frequency rates and percentages, and continuous variables were described using mean, median, and interquartile range (IQR) values. Means for continuous variables were compared using independent group t tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Proportions for categorical variables were compared using the chi-square test. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 20.0 software (SPSS Inc). For unadjusted comparisons, a 2-sided α of less than 0.05 was considered statistically significant. The analyses have not been adjusted for multiple comparisons and given the potential for type I error, the findings should be interpreted as exploratory and descriptive.

Results

Patient characteristics

The demographic characteristics of the patients are as shown in Table 1. All the patients were residents of Delhi, India. The study population included 82 patients of SARI. The patients were admitted in isolation SARI ward and managed as COVID-19 suspects. 32(39.5%) of them subsequently were confirmed to be SARS-CoV-2 positive and labeled NCIP (novel coronavirus infected pneumonia). The patients who tested twice negative five days apart, were subsequently transferred to the non-COVID wards/ ICUs for further management.

The median age was 54.5 years (IQR, 46.25 – 60) and 19(59.3%) were males. Of these patients, 24(75%) were categorized as severe pneumonia of which 12(37.5%) patients were shifted to ICU care and among these, 9(28.13%) patients required mechanical ventilation and subsequently expired. Rest 3(9.3%) patients recovered and were subsequently shifted to COVID-19 ward from the ICU. Patients with severe disease were older than non-severe disease by a median of 7.5 years. The patients who had met the primary outcome were older by a median of 5 years.

The median duration from onset of first symptom to hospital admission

Table 3: Quantitative Laboratory parameters of COVID-19 patients

Baseline characteristics	Total (n=32)	Presence of severe pneumonia		P value	Presence of primary composite outcome		P value
		Yes (n=24)	No (n=8)		Yes (n=12)	No (n=20)	
Hb (g/dl) (median)(IQR)	12.6 (11.2-13.7)	12.7	11.65	0.41	12.4	12.8	0.75
WBC counts (cells/ µl) (median)(IQR)	5850 (3900-8900	5750	7700	0.68	5500	6300	0.69
Neutrophil count (cells/µl) (median)(IQR)	3921 (2722-6691)	3711	5883	0.85	3711	4276	0.73
Lymphocyte count (cells/ µl) (median)(IQR)	1106 (970-1487)	1129	1080	0.44	1129	1106	0.61
Monocyte count (cells/ µl) (median)(IQR)	396 (243-669)	396	370.5	0.33	407	301	0.10
Platelets (cells/ µl) (median)(IQR)	130000 (96500-207500)	128000	161000	0.75	135000	128000	0.88
CK-MB (u/l) (median)(IQR)	29 (22-70.5)	26	39	0.93	66	26	0.03
Bilirubin (mmol/ l) (median)(IQR)	0.8 (0.6-1.1)	0.8	0.93	0.55	0.9	0.8	0.39
AST (u/l)(median)(IQR)	28 (23-31.5)	28	29	0.64	22	18	0.67
ALT (u/l)(median)(IQR)	30 (26-38)	30	32	0.43	33	28	0.45
Urea (mmol/l) (median)(IQR)	51 (34-71)	55	45	0.98	70	41	0.02
Creatinine (µmol/l) (median)(IQR)	1.07 (0.78-1.75)	1.1	0.98	0.72	1.7	0.9	0.03
Albumin (g/dl) (median)(IQR)	3.36 (3.1-3.5)	3.25	3.43	0.53	3.10	3.48	0.001

was 3 days, IQR (2-4). The most common symptom was dyspnea (90.6%) followed by cough (84.4%), fever (68%) and myalgias (43.75%). Less common symptoms were abdominal pain, chest pain, headache, sore throat, nasal discharge, anosmia, loose stools, altered sensorium and vomiting. One patient presented with hemoptysis and pneumomediastinum. Of the 32 admitted NCIP patients, 22 (68.8%) had 1 or more co-morbidities. Diabetes mellitus (50%), hypertension (34.4%) and COPD (15.6%) were the most common co-existing illness.

Compared with patients who did not meet the primary outcome (n = 20), patients who met the primary outcome (n = 12) were older, more likely to be having at least one underlying comorbidity [10 (90.9%) vs 13 (61.9%)], diabetic [9 (81.8%) vs 7 (33.3%)] and hypertensive [7 (58.3%) vs 4 (20%)].

Radiological and Laboratory findings

The laboratory parameters and clinical characteristics of the patients on admission are as shown in Tables 1, 2, 3 and 4. All the patients admitted with us had abnormal chest X-rays. The most common pattern on chest X-ray was bilateral patchy nodular or interstitial shadows in 30 of 32 patients (93.8%). Patterns on chest X-Ray were bilateral peripheral and basal nodular-interstitial infiltration in 18 (56.25%) patients, bilateral peripheral interstitial infiltration in 6 (18.75%) patients and bilateral basal nodular-interstitial infiltration in 4 (12.5%) patients. One (3.125%) patient had unilateral patchy nodular infiltrates and the other one had insignificant X-ray findings. Notably one patient had extensive bilateral infiltrates with pneumomediastinum. Representative X-ray findings are provided in Figure 4.

On admission, hypoalbuminemia was present in 22 (68.8%) patients and was the most common finding. Leucopenia was present in 10 (31.2%) of the patients, with majority of patients having lymphocytopenia 24 (75%) and 5 (15.6%) patients having monocytosis. Thrombocytopenia was seen in 14 (43.8%), anaemia in 14 (43.8%) and pancytopenia in 10 (31.2%) of the patients. Monocytosis was found to be more in patients who met the primary outcome. Raised CK-MB was seen in 8 (25%) patients and 13 (40%) patients developed AKI and both were significantly more in patients who met the primary outcome. Alanine aminotransferase, aspartate aminotransferase and serum bilirubin were elevated less commonly. Patients who met the primary outcome had more pronounced hypoalbuminemia.

Vital signs and organ dysfunction

The vital signs and clinical characteristics of the patients are shown in Table 4. These measures were recorded on the day of hospital admission for all patients, then divided into those who later met the primary composite outcome or not and on the severity of pneumonia. As expected the patients with a severe pneumonia had more tachycardia, tachypnea and reduced levels of SpO_2 and PaO_2. The patients who met the primary outcome had significantly more tachypnea 7(58.3%), respiratory distress 8(66.7%), and reduced levels of SpO_2 (< 93%) 12(100%). These patients also had more organ injury in form of acute kidney injury 9(75%), raised CKMB and had increased SOFA scores. The median SpO_2 was 85%, PaO_2 was 62 mmHg, PaO_2/FiO_2 was 103 and SOFA score was 6 in the patients who met the primary composite outcome (Table 4).

Treatment and main interventions

All the SARI patients received injectable antibiotics, tab oseltamivir and supplemental oxygen therapy initially. Patients who tested positive for SARS-CoV-2 were given hydroxychloroquine (400 mg twice daily on day 1 followed by 200 mg twice daily for 4 days) and azithromycin (500 mg once daily for 5 days). Those with low bleeding risk score were also given LMWH. A total of 6 (18.75%) patients received vasopressors. 12 (37.5%) patients required ICU care and 9 (28.25%) required mechanical ventilation. Of the 12 patients requiring ICU care, 9 patients who were on mechanical ventilation expired and rest 3 recovered and subsequently shifted to COVID ward after hemodynamic improvement. Of the 24 patients of severe pneumonia, 12 recovered and 9 patients required mechanical ventilation and subsequently expired. 3 patients required ICU admission due to multi-organ dysfunction. All the 8 patients of non-severe pneumonia recovered. As on 17th May 2020, 23 patients were still hospitalized, recovering in COVID-19 ward.

Discussion

This report, to our knowledge, is the largest case series to date of hospitalized patients with COVID-19 from India. Patients coming to the emergency services of our hospital were triaged into non-SARI and SARI. All SARI patients were treated as COVID-19 suspects and were transferred to SARI isolation ward. 82 patients of SARI were recruited in this study and 32 (39%) patients were diagnosed as

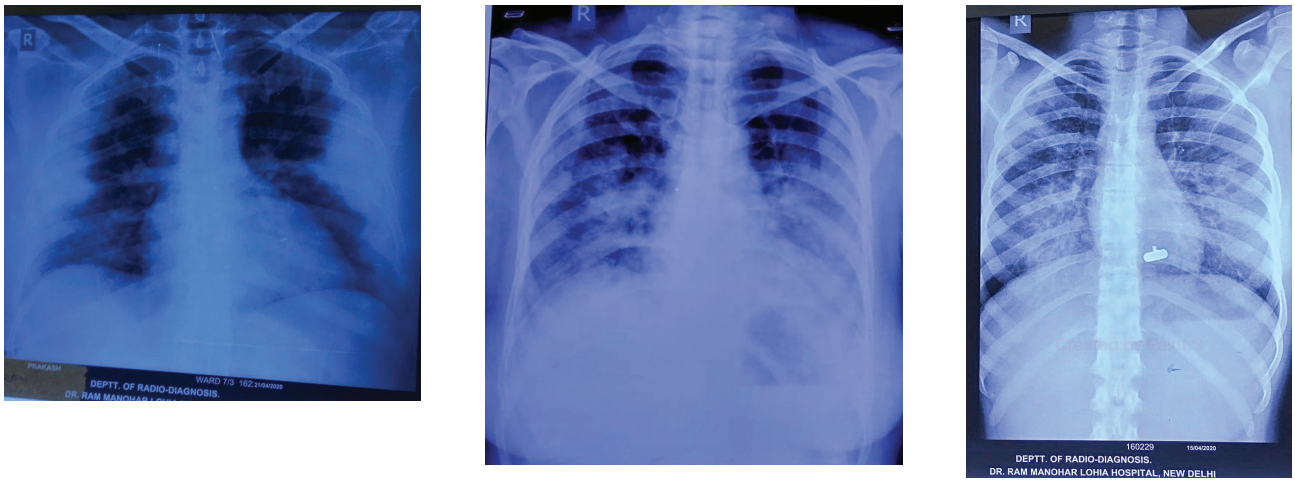

Fig. 4: Typical radiological findings in some of the confirmed NCIP patients in our SARI ward, showing peripheral based interstitial and scattered alveolar infiltrates

SARS-COV-2 positive by rRT-PCR. The earlier and only COVID-19 sentinel survey in India of SARI patients was conducted by ICMR in March 2020 and had revealed a COVID-19 positivity of 1.8%.[2] Our study has found a substantial increase from that number. None of our patients gave a history of contact with a COVID-19 positive patient or a foreign travel or contact with any healthcare professional or frontline COVID-19 worker except one police constable who was posted in frontline to control crowds. The possible explanation may be due to community transmission of the disease.

The median age of NCIP patients was 54.5 years (IQR, 46.25 – 60) and 19 (59.3%) were males which was similar to an earlier study by Wang et al.[6] The higher incidence in male patients found in previous studies can possibly be explained by more exposure by the male counterparts of the family for foray outside homes and partly by the higher concentration of angiotensin-converting enzyme-2 in males than in women.[11] ACE-2 is expressed ubiquitously in multiple organ systems, enabling SARS-CoV-2 binding into the cell membranes and its subsequent entry. Since ACE-2 is an X-linked gene, further exploration is required for in depth analysis of the sex related differences.

Of the 32 NCIP patients, 24 (75%) were categorized as severe pneumonia. This number is significantly high as our patient cohort was of SARI with majority of them presenting with dyspnoea and cough in emergency as opposed to the previous studies which have taken patients of COVID-19 positivity from general population.

Out of the 12(37.5%) NCIP patients who met the primary composite outcome, 9 (28.13%) required mechanical ventilation and subsequently expired, 3 (9.3%) recovered and were shifted to general COVID wards. Overall 23 NCIP patients are still hospitalized but are doing well.

Median time from symptom onset to hospital admission was 3 days. The most common symptom was dyspnoea (90.6%) followed by cough (84.4%), fever (68%), bodyache and myalgias (43.75%). Less common symptoms were abdominal pain, chest pain, headache, sore throat, nasal discharge, anosmia and vomiting. Chemosensory dysfunction have been found to be strongly associated with COVID-19 infection.[12] Three patients presented with atypical symptoms like loose stools, altered sensorium and pain abdomen. A recent study showed that SARS-CoV-2 was detected in stool samples of patients with abdominal symptoms[13] explaining some of the atypical symptoms. Notably one patient presented with hemoptysis and pneumomediastinum. The high percentage of dyspnea and cough in our study is also explained by our patient cohort (Table 1).

Of the 32 admitted NCIP patients, 22 (68.8%) had 1 or more co-morbidities. Diabetes mellitus (50%), hypertension (34.4%) and COPD (15.6%) were the most common co-existing illness. These figures are substantially more than the earlier study[6] where the percentages of co-morbidities were much lower. This can be partly explained by our patient cohort of severe disease and partly by the fact that patient with co-morbidites were shown to be more prone to develop symptomatic NCIP as shown in earlier studies.[6,1] Compared with patients who did not meet the primary outcome, patients who met the primary outcome were more likely to be having at least 1 underlying comorbidity (p – 0.03), diabetes (p- 0.003) and hypertension (p - 0.03) in line with previously published data.[1,6] These comorbidities frequently co-exist. A greater number of comorbidities also correlated with poorer clinical outcomes in a previous study.[14] Our study too shows the results on a similar trend. Patients with 2 or more co-existing comorbidities are more likely to have poorer baseline well-being which contribute to their relatively poor outcome (Figures 1, 2 and 3).

Leucopenia was present in 10 (31.2%) of the patients, with majority of patients having lymphocytopenia 24 (75%). Lymphocytes have been shown to express the ACE-2 receptor on their surface and, being an ACE-2 receptor tropic virus, directly infects them leading to their ultimate lysis. Furthermore, severe SARS-CoV-2 infection is characterized by a cytokine storm and markedly increased levels of interleukins (IL-6, IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, MCP-1, MIP1-a) and tumor necrosis factor (TNF)-alpha, which may promote lymphocyte apoptosis leading to lymphocytopenia.

Growing evidence have implicated an excessive monocyte-macrophage activation and associated cytokine

Table 4: Clinical characteristics of patients infected with COVID-19

Baseline clinical characteristics	Total (n=32)	Pneumonia severity			Presence of primary composite outcome		
		Severe (n=24)	Non-severe (n= 8)	P value	Yes (n= 12)	No (n= 20)	P value
GCS (median)	15	15	15	0.41	15	15	0.27
GCS < 15	2 (6.2%)	1 (4.2%)	1 (12.5%)	0.40	0 (0%)	2 (10%)	0.26
HR (median)(IQR)	107 (102-113)	108	96	0.01	108	107	0.16
HR > 100/ min	25 (78.1%)	22 (91.7%)	3 (37.5%)	0.001	12 (100%)	13 (65%)	0.02
RR (median)(IQR)	26 (22.3-29.5)	27	20.5	0.001	29	24	0.001
RR > 30/ min	9 (28.1%)	9 (37.5%)	0 (0%)	0.04	7 (58.3%)	2 (10%)	0.003
Severe respiratory distress	10 (31.2%)	10 (41.7%)	0 (0%)	0.03	8 (66.7%)	2 (10%)	0.001
Systolic BP <90 mmhg	6 (18.75%)	6 (25%)	0 (0%)	0.117	5 (41.7%)	1 (5%)	0.01
SpO2 (%)(median)(IQR)	88 (84-91.5)	86	94	0.001	85	89.5	0.001
SpO2 < 93% @ RA	24 (75%)	24 (100%)	0 (0%)	0.001	12 (100%)	12 (60%)	0.01
PaO2 (mm Hg) (median)(IQR)	97 (64-119)	-	-	-	62	114	0.001
PaO2/ FiO2(mm hg) (median)(IQR)	161.5 (106-199)	-	-	-	103	190	0.001
SOFA score(median)(IQR)	4 (3-5)	-	-	-	6	3.5	0.02
Severe pneumonia	24	-	-	-	12 (100%)	12 (60%)	0.01

storm with the pathophysiology of severe SARS-CoV-2 disease related complications. Despite this, there are no studies showing abnormalities in number of monocytes in patients with COVID-19 although functional abnormalities have been shown.[15] In our study, 5 (15.6%) patients had monocytosis with it being more common in patients having met the primary outcome. Thrombocytopenia was seen in 14 (43.8%), and pancytopenia in 10 (31.2%) of the patients mostly due to similar pathophysiology. Our findings were similar to previous study by Guan et al where the vast majority of patients had presented with lymphocytopenia (83.2%), whereas 36.2% had thrombocytopenia, and 33.7% showed leukopenia. Anemia was seen in 14 (43.8%) patients and this can partly be attributed to the high prevalence of anemia in India.

Hypoalbuminemia was present in 22 (68.8%) patients. Hypoalbuminemic patients admitted for community-acquired pneumonia have been shown to have increased mortality and morbidity in earlier studies.[16] Although there are no reports yet to prove an association between COVID-19 and hypoalbuminemia, those with low albumin levels have a poorer prognosis. Low albumin levels were seen in 80% of the non-surviving patients.[17] In our study, hypoalbuminemia was found to be more common in patients who met the primary outcome (100% vs 50%). Hypoalbuminemia is frequently observed in chronic conditions like hypertension, diabetes and chronic heart failure. It is this subgroup which has been hardest hit with COVID-19 infection in our study. Hypoproteinemia has been shown to co-relate with the development of ARDS[18] and was established as an independent predictor of poor outcome. This can be utilized as a valuable prognostic indicator in NCIP especially in a country like India where nutritional deficiency is prevalent.

Raised CK-MB was seen in 7 (21.9%) patients and was found to be significantly increased in the patients of the primary outcome group [6 (54.5%) vs 2 (9.5%)]. This finding is in line with the earlier study by Shaobo et al. where cardiac injury with raised CK-MB levels was a common condition among hospitalized patients with COVID-19 and was associated with higher risk of in-hospital mortality.[19] These patients did not have any significant findings on the ECG.

Elevated levels of alanine aminotransferase, aspartate aminotransferase and bilirubin were found less commonly in our study. Viral infections are often associated with "bystander hepatitis", meaning mild elevations of transaminases without compromising liver function. This may also be seen with COVID-19 infection where liver failure has not been specifically reported, even in the most severe and fatal cases.[1,3]

The patients who met the primary outcome had significantly more acute kidney injury 8 (72.7%) vs 5 (23.8%). This finding as has been previously described, highlights the importance of AKI recognition as well as the association of AKI with mortality in hospitalized COVID-19 patients.[20] Acute kidney injury has been related to three probable pathologic mechanisms. Firstly, the direct effect of the virus on the nephrons, secondly sustained hypoxia due to type I respiratory failure and finally circulatory shock.

The abnormalities found in our study suggest that COVID-19 infection may be associated with cellular immune deficiency, myocardial injury, kidney injury and hepatic injury.

SOFA score is a good diagnostic marker for sepsis and septic shock and reflects the degree of multi-organ dysfunction. Although bacterial infections are usually regarded as a leading cause of sepsis, viral infection can also cause sepsis syndrome. Previously, it has been shown that sepsis occurred in nearly 40% of adults with community-acquired pneumonia due to viral infections.[21] No bacterial pathogens were detected in these patients. Sepsis and raised SOFA score was a common complication, which might be directly caused by SARS-CoV-2 infection, but further research is needed to investigate the pathogenesis of sepsis in COVID-19 illness. In this study the patients who met the primary outcome had SOFA scores more than the patients who did well (6 vs 3.5) (Table 4). Septic shock was a harbinger of poor outcome and was significantly more common in patients who met the primary outcome (41.7% vs 5%). Also these patients had more severe tachycardia, tachypnoea, respiratory distress, lower mean arterial oxygen saturation and higher mean SOFA scores at admission as shown in Table 4. These manifestations should signal a prognostic red flag in their management and early intensive care should be provided to them to reduce mortality.

Of the 50 non COVID-19 SARI patients in our study cohort, 13 (26%) patients met the primary composite

outcome. Of them 9 (18%) patients expired and remaining 4 patients have subsequently recovered.

Critical to tracking the spread of COVID-19, is active contact tracing and placing high risk individuals in monitored isolation for early detection of symptoms of severe disease. It is of prime importance to identify the high risk strata of the society which includes older age group and people with co-morbidities and early identification of high risk symptoms and placing them in appropriate care. The patients presenting to us in our emergency were in respiratory distress and the delay in presentation to our health services was of a median of 3 days. Early detection and contact tracing of positive individuals and awareness of these symptoms in the society should help reduce this delay and possibly have a dramatic favorable effect on the outcome of the disease. In our study majority of the patients presented to us in a state of severe pneumonia resulting in a very high case fatality of 28% which was higher than that of non-COVID-19 SARI (18%). Close monitoring and large-scale control strategies will be needed to prevent widespread transmission within the community and avoid delayed presentation of a COVID-19 positive individual in a state of severe pneumonia to the health setup.

The patients admitted to the ICU or who expired, were older and had a greater number of comorbid conditions than those not admitted to the ICU. This suggests that age and comorbidity may be risk factors for poor outcome. However, there was no difference in the proportion of men and women between them. The most common laboratory abnormalities observed in this study were depressed total lymphocytes, thrombocytopenia, anemia, hypoalbuminemia, raised CK-MB and raised urea and creatinine. Poor outcome occurred in patients who developed severe pneumonia, severe respiratory distress, cardiac injury in form of raised CK-MB, hypoalbuminemia, acute kidney injury and shock. Until now, other than meticulous supportive care no specific approved treatment has been recommended for novel coronavirus infection. The treatment is symptomatic with appropriate intravenous antibiotics and oxygen therapy represents the major treatment intervention for patients with severe disease. Mechanical ventilation is necessary in cases of respiratory failure refractory to oxygen therapy although it has a poor outcome. Anticoagulation with LMWH should be used in low bleeding risk individuals as there is high risk of thrombotic vascular events. Hemodynamic support is essential to tide over the event of a septic or cardiogenic shock. Trials are ongoing for the elusive remedy for the SARS-COV-2 infection including convalescent plasma therapy, monoclonal antibodies and antiviral drugs. Meanwhile scientific research is growing to develop a vaccine.

This study has several limitations. Firstly, due to the retrospective study design and resource-limited settings, not all laboratory tests were done in all patients, including lactate dehydrogenase, d-dimer, PT/aPTT. Therefore, their role could not be estimated in predicting in-hospital death. Secondly, no antiviral drugs except hydroxychloroquine were used in any patient as specific antiviral therapy; hence, the role of protease inhibitors cannot be elucidated. Last but not least, interpretation of our findings might be limited by the sample size. However, by including all adult patients in the designated time frame of 3 weeks, we believe our study population is representative of cases diagnosed in New Delhi.

Conclusion

In this single-center case series in New Delhi, India, of 82 hospitalized patients of SARI, 32 patients were confirmed NCIP, with a COVID 19 positivity of 39%. 75% of NCIP presented in severe pneumonia and 37.5% required ICU care and case fatality rate was 28%.

Keywords: SARS-CoV-2, COVID-19, Novel Coronavirus Infected Pneumonia (NCIP), SARI.

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