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Laboratory Diagnosis of COVID 19 – Perspectives

Gita Nataraj¹, Nayana Ingole¹

December 2019 saw the arrival of another novel corona virus, SARS-CoV-2 in Wuhan, China. In a very short span of time, it’s pan continental dark presence, the recognition of it’s highly contagious nature, infections in healthcare workers, the absence of effective antivirals, a differing pathogenesis in the ill, a higher mortality compared to influenza especially in the older and those with existing co-morbidities and the absence of a vaccine yet, make it a sinister opponent. As of 20th June 2020, India of a vaccine yet, make it a sinister presence, the recognition of it’s dark nature.

As of 20th June 2020, India had recorded 3,95,048 confirmed cases and 12,948 deaths.

If 2012 XDRTB report from India ignited the TB Diagnostic pathway with a strategic shift to molecular detection of TB and DRTB, Covid-19 2020 has done just the same but in a larger and faster mode with support from national, state and local administration. New molecular diagnostic laboratories have been set up, existing laboratories in the national framework have been strengthened, private laboratories have been authorised and the process is still ongoing.

As of 20th June 2020, 722 government laboratories and 259 private laboratories are operational in India for COVID-19 testing. The scaling up of laboratories and the testing capacity is expected to strengthen the diagnostic arm which is the first step in disease control.

The diagnostic pathway has to be prudently decided to benefit the patient, community and healthcare workers. Viral outbreaks require that the laboratory techniques used are rapid and accurate. Molecular diagnostic platforms are better suited for this. Fortunately being a new / novel virus with a unique genetic sequence and with its genetic sequence being made public, a plethora of RTPCR based qualitative commercial assays are now available which have received US FDA emergency use approval and / or ICMR approval. These tests primarily detect one or more of SARS-CoV-2 specific genes while some of the assays are developed as sequential assays with a screening component first and a confirmatory component later.

The questions that need to be answered in terms of testing include who, when, what, how (method) and the value of repeat testing. The answers to all these questions are yet evolving as new information is being made available. All the laboratories in India are expected to follow the ICMR testing strategy. Between 17th March and 18th May 2020, this testing strategy has undergone five revisions based on the evolving scenario of suspected cases, existing capacity and need. The primary objectives of testing are two-fold. The first is to rapidly confirm suspected cases so that they can be treated more effectively and isolated preferentially to prevent further transmission of the disease during their infective period. The period of infectivity is reported to be one to two days prior to the onset of symptoms, peaking by 5-7 days. Loss of infectivity has been reported by 8-10 days. The second objective is to test close contacts to whom the disease could have been transmitted and who are likely to be asymptomatic and may continue to spread disease if not detected early.

During the acute phase of illness (for upto 7 days), upper respiratory tract specimens provide a better yield. Reports indicate that a combined nasopharyngeal (NP) and oropharyngeal swab (OP) has the highest yield in comparison to NP or OP alone. CDC (USA) has also revised the samples to be tested from NP alone to NP / OP / nasal swab/ mid-turbinate specimen. A suggestion for self-collection of nasal swabs has also been put forth. It will not be out of context here to mention that enough material needs to be collected to improve the yield and this might mean that the swabs are placed and rotated or brushed against for atleast 10 seconds before removal which can be discomforting to patients. The swabs need to transported immediately to the testing laboratory in cold chain in order to maintain the integrity of the virus / nucleic acid. Later in the course of the disease, if hospitalized, lower respiratory tract specimens such as sputum / broncho-alveolar lavage specimens are indicated. Though the viruses are present at other sites such as urine and blood, these specimens are not recommended for testing. The utility of stool in detecting the virus is still under investigation.

rRTPCR (Real Time Reverse Transcriptase Polymerase Chain Reaction) is the recommended gold standard test / method. Most commercial assays detect SARS-CoV-2 specific genes such as N (N1, N2), S, ORF 1ab and RdRp. Some assays detect E gene which is common to all Sarbecoviruses. It is recommended to use those assays that detect atleast two genes and which also have an extraction and amplification control. The results are indicated as SARS-CoV-2 detected (when both genes are detected) or not detected or inconclusive (when only one of the two genes is detected). Invalid results indicate that the specimen quality was poor and a fresh specimen needs to be repeated.

RTPCR based tests have excellent specificity but their sensitivity ranges from 60-90 %, false negativity being mainly attributed to specimen quality and site of collection. A negative test therefore does not rule out disease. If the initial test is negative, and there is a strong clinical suspicion, it is advisable to repeat a fresh sample in 24-48 hrs when the result is likely to be more positive whilst ensuring better collection. The limit of detection of most tests is 100-250 RNA copies / ml and an infected person usually carries 10⁵ – 10⁶ copies / ml in the nasopharynx. An appropriately collected specimen is therefore unlikely to yield a false negative result. For an initial positive

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case, conversion to negative is unlikely to occur before 15-20 days after initial testing. One question that is often asked and does not escape the attention of the clinical microbiologists is whether the results can be converted in terms of numbers i.e. viral load. The commercial assays currently in use are qualitative only and therefore the results are indicated as detected or not detected when there is no amplification occurring beyond the recommended cycle numbers. However, when amplifications do occur (detected), real time based platforms provide CT values (cycle threshold), the cycle at which amplification occurs. This number is dependent on the initial viral load and the relationship is inversely proportional. It is reported that the viral load is not dependent on age, gender, severity of illness or clinical response but on the site and quality of collection and the time of collection since onset of symptoms. The viral load is inclusive of nucleic acids recovered from both live and dead viruses. Also, unlike blood specimens, in specimens such as those from the upper respiratory tract collected using a swab, neither is the distribution of the virus uniform nor is the step of release of the virus from the swabs. This question may remain unresolved at present. Conversion to negative is unlikely to occur before 15-20 days after initial testing.

One recent rapid antigen based assay has received ICMR approval and an advisory for its use has been released. It is a point of care test recommended for use in containment zones and healthcare settings. Since the test has excellent specificity, confirmation with an RTPCR assay is not warranted. A negative test result however will need to be confirmed. The results are available by 30 minutes. This may also replace a portion of the tests currently being performed in RTPCR laboratories, considering the likely burnout of manpower at the current and expected increased pace of testing.

The value of COVID 19 antibody based assays is yet to be ascertained. It’s potential utility is more expansive when compared to RTPCR based assays by identifying individuals who have been previously infected, by identifying cases who present late in the disease course, for determining disease prevalence, to identify convalescent plasma donors and to evaluate immune response to candidate vaccines. While it is known that their use in early stage of disease will give false negative results, false positivity due to cross reactivity with other common cold viruses has also been reported. It is not yet known if presence of IgG indicates protective immunity in COVID-19. Many antibody based assays have received approval from ICMR / USFDA / EU using different formats such as lateral flow / ICT / ELISA / CLIA. Until more evidence is available, antibody based assays should be used and interpreted judiciously.

At present, many questions remain unanswered or need better perspectives. This will hopefully be available as more information is gathered. A test that can measure viral loads is also needed. Until then, the judicial use and interpretation of available tests and providing universal access to testing are the options available to support the government’s policy of test, trace and treat.

References

1. Ministry of Health and Family Welfare, Govt. of India, COVID-19, Latest Updates available @ https://www.mohfw.gov.in/.
2. Indian Council of Medical research, Department of Health Research, Ministry of Health and Family Welfare, Govt. of India. Total Operational (initiated independent testing) Laboratories reporting to ICMR available @ https://www.icmr.gov.in/pdf/covid/labs/COVID_Testing_Labs_25062020.pdf.
5. Indian Council of Medical research, Department of Health Research, Ministry of Health and Family Welfare, Govt. of India. Advisory on Use of Rapid Antigen Detection Test for COVID-19 released on 14th June 2020.
COVID 19- Clinical Profile, Radiological Presentation, Prognostic Predictors, Complications and Outcome: A Perspective from the Indian Subcontinent

Manoj Saluja¹, Drishya Pillai²*, Shivcharan Jeliya³, Nitesh Bauddh³, Rahul Chandel³

Abstract

Background: Since December 2019, we have been facing one of the worst pandemics of human history. It originated from the Hubei province in China as a case of pneumonia, later named COVID-19.¹ The causative pathogen, a new enveloped betacoronavirus² is now known as Severe acute respiratory syndrome corona virus-2 (SARS-CoV 2). India reported its first case of COVID19, on 30th January 2020. We aim to identify the defining clinical and radiological characteristics, severity and prognosis, along with impact of age on outcome.

Methods: Cross sectional, observational study of patients diagnosed with COVID-19 [RT-PCR].

Results: We observed male predominance, mean age of 36 years, with less or no symptoms, majority brought in after screening and contact tracing by the screening teams. Thrombocytopenia, lymphocytosis, raised LDH was common (>35%, p<0.05). Patients over the age of 60 were the ones having severe illness and more complications (p<0.05). Radiographic abnormality was frequently associated irrespective of clinical presentation and its severity. Poor prognosis was noted in elderly, especially those with co-morbidities.

Discussion: Though the disease has a relatively mild course in this part of the subcontinent, patients aged ≥60 are at significant risk for morbidity and mortality. Clinical and laboratory findings are similar to those found in viral diseases. Increased risk of cardiac involvement needs to be looked into. Chest X-ray proves sufficient for imaging, reducing the requirement of CT scans. Studies involving larger sample size and interventional trials are need of the hour.

Introduction

In December 2019, a case of pneumonia of unknown origin was reported in Hubei Province, China.¹ The causative pathogen, isolated from human airway epithelial cells, was found to be a novel enveloped betacoronavirus,² now known as Severe acute respiratory syndrome corona virus-2 (SARS-CoV2). The disease was named COVID-19. Though it shares phylogenetic similarity with SARS-CoV, it is the seventh member of the family of coronaviridae to infect humans.³ Given the rapid spread of COVID-19 and the steep rise in morbidity and mortality it caused, the World Health Organization (WHO) declared it as a pandemic on 11th March, 2020.¹⁴⁻⁶

In the first week of April, we saw the first case of COVID-19 in Hadoti-the south eastern part of Rajasthan. By the end of one week, there was a significant surge in number of patients, the count crossing 100 within 14 days. By the end of two months the number increased to more than fourfold. We did an analysis of cases presented in this region to assess if they may help identify prognostic and diagnostic predictors along with the defining clinical characteristics and severity of the disease.

Data Sources

All hospitalized patients, with laboratory confirmed COVID-19 were included in the study. We obtained the medical records and compiled data of patients admitted in the isolation wards of New Medical College Hospital, Kota and associated hospitals from 5th April 2020 to 2nd June 2020. The data cutoff for the study was June 5th, 2020. Patients still admitted in the isolation wards were omitted from the study to remove any possible bias in outcome.

COVID-19 was diagnosed on the basis of the WHO interim guidance.⁷,⁸ A confirmed case of COVID-19 was defined as a positive result by real-time reverse transcriptase– polymerase-chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.¹

Only laboratory-confirmed cases were included in the analysis.

Study Definitions

We assessed complete blood count, blood chemical analysis, coagulation testing, liver and renal function tests, serum electrolytes, lactate dehydrogenase, and creatine kinase. Fever was defined as an axillary temperature of 37.5°C or higher. Lymphocytopenia and lymphocytosis were defined as a lymphocyte count of less than 1500 cells and more than 4000 cells per cubic millimeter, respectively. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter.

Studies involving larger sample size and interventional trials are need of the hour.
Table 1: General characteristics of COVID-19 and comparison based on symptoms:

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>All (406)</th>
<th>Asymptomatic (244)</th>
<th>Symptomatic (162)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>262 (64.5%)</td>
<td>150</td>
<td>112</td>
<td>0.114</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36 ± 15</td>
<td>35 ± 16</td>
<td>38 ± 14.5</td>
<td>0.0405</td>
</tr>
<tr>
<td>RRT/screening teams</td>
<td>266 (65%)</td>
<td>219 (89%)</td>
<td>47 (29%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time duration till first negative (days)</td>
<td>6 ± 2.92</td>
<td>6 ± 3</td>
<td>6 ± 2.83</td>
<td>0.06</td>
</tr>
<tr>
<td>Travel history</td>
<td>16 (3.9%)</td>
<td>11</td>
<td>5</td>
<td>0.47</td>
</tr>
<tr>
<td>Contact history</td>
<td>210 (51.7%)</td>
<td>135</td>
<td>75</td>
<td>0.074</td>
</tr>
<tr>
<td>Patients with comorbidity</td>
<td>79 (19.4%)</td>
<td>41</td>
<td>38</td>
<td>0.13</td>
</tr>
<tr>
<td>Cases missed by RT-PCR on 1st test</td>
<td>18 (4.4%)</td>
<td>10</td>
<td>8</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Patients with abnormal lab investigations

| K+ imbalance | 51 (12.6%) | 34 | 17 | 0.3 |
| Na+ imbalance | 27 (6.4%) | 10 | 17 | 0.011 |
| Leukopenia | 72 (17.7%) | 38 | 34 | 0.16 |
| Lymphopenia | 155 (38.1%) | 81 | 74 | 0.011 |
| Leukocytosis | 22 (5.41%) | 14 | 8 | 0.72 |
| Lymphocytosis | 7 (1.7%) | 1 | 6 | 0.012 |
| Raised HCT | 82 (20.2%) | 43 | 39 | 0.11 |
| Thrombocytopenia | 157 (38.6%) | 88 | 69 | 0.18 |
| Deranged LFT | 62 (15.3%) | 35 | 27 | 0.524 |
| Deranged RFT | 9 (2.2%) | 2 | 7 | 0.018 |
| LDH- raised | 168 (41.3%) | 91 | 77 | 0.0403 |
| CKMB- raised | 249 (61.3%) | 142 | 107 | 0.11 |
| CK-NAC- raised | 40 (9.8%) | 23 | 17 | 0.727 |
| Abnormal ECG | 131 (32.3%) | 82 | 49 | 0.47 |
| Abnormal chest x-ray | 336 (82.7%) | 195 | 141 | 0.44 |

Lab investigation: a comparison (absolute values)

| Blood sugar (mg/dl) | 104.97 ± 52.30 | 104.86 ± 57.59 | 105.04 ± 48.60 | 0.974 |
| HCT (%) | 39.41 ± 5.94 | 39.01 ± 6.11 | 40.01 ± 5.63 | 0.05 |
| TLC (cells/cumm) | 6016.41 ± 2677.62 | 6068.24 ± 2534.20 | 5938.50 ± 3119.39 | 0.63 |
| Lymphocyte (cells/cumm) | 1774.58 ± 739.38 | 1861.95 ± 682.92 | 1676.37 ± 775.17 | 0.011 |
| PLT count (lakh/cumm) | 1.72 ± 0.64 | 1.75 ± 0.64 | 1.67 L ± 0.64 | 0.22 |
| LDH (IU/L) | 497.72 ± 225.80 | 478.55 ± 378.65 | 525.34 ± 242.80 | 0.04 |
| CK-MB (IU/L) | 49.7 ± 44.3 | 45.3 ± 30.5 | 56.1 ± 58.3 | 0.023 |

Outcome

| Complications | 18 (4.4%) | 5 | 13 | 0.005 |
| ICU | 18 (4.4%) | 5 | 13 | 0.005 |
| Death | 8 (1.9%) | 0 | 8 | 0.12 |

Statistical Analysis

Continuous variables were expressed as medians and interquartile ranges or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages. For missing data, no imputation was made. We used GraphPad Prism, version 8.4.2, for statistical analysis as well as to plot the map. Two sub analyses were done, first included two subgroups, where unpaired student t-test with unequal variances and chi-square tests were used. Second analysis had three subgroups where one way ANOVA and Mc-Nemar Chi-Square test were used.

Inclusion and Exclusion Criteria

All COVID-19 confirmed patients who gave their consent were included in the study. Patients excluded: children <10 years of age, patients still admitted in isolation wards, and/or those who refused to give consent.

Results

Epidemiology

We collected and analyzed the data of 406 patients admitted in COVID-19 isolation wards. We observed an average age of 36 ± 15 years and a male predominance (2:1). 266 patients (65%) were brought in by the rapid response team, majority of whom were asymptomatic. The rapid response teams were a novel initiative started in Hadoti region for fast and effective screening of the hotspot areas and for contact tracing. 79 patients had associated comorbidity, most commonly hypertension closely followed by diabetes mellitus-2. Other underlying illnesses included ischemic heart disease, hypothyroidism, COPD and bronchial asthma. 11 patients were pregnant at the time of admission with 4 of them having delivered healthy babies soon after. 3 patients were admitted during postpartum. 210 patients gave a history of contact with positive patients while only 16 had a history of travel to disease hotspots and/or attending mass gatherings.

Demography

A longitudinal analysis of case clustering was done ad hoc. At the end of two weeks, >90% cases were from four major clusters that were present in and around Kota. By the end of one month, the disease was spotted in 21 regions including 7 major clusters. As of May 2020, patients were being brought in from almost all localities of the city.

Symptomatology and Laboratory Analysis

162 (39.9%) were symptomatic at the time of presentation, most commonly fever, dry cough and body ache. Some patients also had complaints suggestive of rhinitis, headache, nausea, vomiting and occasionally diarrhea. Shortness of breath and chest pain was not common but was usually associated with ICU admission and/or requirement for oxygen inhalation.

On analyzing the lab investigations, we found lymphopenia, thrombocytopenia and raised LDH >35% patients. Average age of patients having lymphopenia was 34.49±15.5 years while that of patients with normal lymphocyte count was 31.46±16.48 years. The age gap was not statistically significant (p-0.17). 249(61.3%) patients had raised CK-MB and 131(32.26%) had abnormalities in their ECG. Commonly found aberration included reduced QRS amplitude, inverted T waves (especially precordial leads) and ischemic changes in inferior leads. 336 patients (82.7%) had abnormal Chest X-ray at the time of admission (Table 1).

Two ad hoc analyses were done while conducting the study. One compared these baseline characteristics between symptomatic (162) and asymptomatic (244) patients. Though electrolyte imbalance was not frequently encountered in our study, statistically significant abnormality was found in serum sodium levels of symptomatic patients. Abnormal lymphocyte counts, both lymphocytosis and lymphocytopenia was proportionately higher in symptomatic patients, as
was the frequency of deranged kidney function tests and raised LDH. (P<0.05)
Comparison of absolute values of the laboratory parameters shows a higher LDH, CK-MB, hematocrit value and a lower lymphocyte count in the symptomatic group. (p<0.05)
Here, it has to be noted that rather than definite lymphocytopenia or thrombocytopenia, the values are only towards the lower limit of normal range. Similarly, hematocrit, though tends to be on the higher side, does not cross the upper limit.

Although complications such as ARDS/respiratory failure or need for ICU admission were present in <5% of the study sample, they were often seen in symptomatic patients.

Age Based Comparison

Another sub-analysis was to compare the same data based on age differentiation. Here, we divided the entire study sample into three age sets, i.e, 10-29 years (group A), 30-59 years (group B) and ≥ 60 years (group C).
Number of patients with electrolyte imbalance, deranged kidney and liver function tests, abnormal ECG and chest X-Rays were proportionately higher in number in group C. Serum blood sugar and LDH levels showed significant difference, when group A and group B were compared to group C separately. No difference was found when group A and B were compared to each other.
Outcome was poor in group C, as evidenced by increased complications and higher mortality (Table 2).

Average blood sugar and LDH was significantly higher in the third group as compared to the first two (Figures 1, 2).

**Imaging**

Chest X-ray was the preferred imaging modality. Portable X-Ray machines were used to reduce the risk of contamination and infection to health care professionals and technicians. We analyzed the first X-Ray of each patient and found that 336 out of 406 had abnormality present at presentation. Out of the remaining 70, 21 later developed opacities while 49 were

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**Table 2: Age based comparison**

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>All (n=406)</th>
<th>Group-A 10-29 years (n=151)</th>
<th>Group-B 30-59 years (n=215)</th>
<th>Group-C ≥60 years (n=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>262</td>
<td>90</td>
<td>148</td>
<td>24</td>
<td>0.15</td>
</tr>
<tr>
<td>Via RRT/screening teams</td>
<td>266</td>
<td>105</td>
<td>135</td>
<td>26</td>
<td>0.0028</td>
</tr>
<tr>
<td>Time duration till first negative</td>
<td>6 ± 2.92</td>
<td>6 ± 3.01</td>
<td>6 ± 2.84</td>
<td>7 ± 2.90</td>
<td>0.182</td>
</tr>
<tr>
<td>Travel history</td>
<td>16</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>0.54</td>
</tr>
<tr>
<td>Contact history</td>
<td>210</td>
<td>86</td>
<td>103</td>
<td>21</td>
<td>0.23</td>
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<tr>
<td>Laboratory investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K+ imbalance</td>
<td>51</td>
<td>17</td>
<td>24</td>
<td>10</td>
<td>0.043</td>
</tr>
<tr>
<td>Na+ imbalance</td>
<td>27</td>
<td>7</td>
<td>13</td>
<td>7</td>
<td>0.012</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>72</td>
<td>24</td>
<td>43</td>
<td>5</td>
<td>0.39</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>155</td>
<td>50</td>
<td>90</td>
<td>15</td>
<td>0.236</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>22</td>
<td>8</td>
<td>11</td>
<td>3</td>
<td>0.82</td>
</tr>
<tr>
<td>Raised HCT</td>
<td>82</td>
<td>34</td>
<td>42</td>
<td>6</td>
<td>0.53</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>157</td>
<td>48</td>
<td>93</td>
<td>16</td>
<td>0.084</td>
</tr>
<tr>
<td>Deranged LFT</td>
<td>62</td>
<td>11</td>
<td>40</td>
<td>11</td>
<td>0.0009</td>
</tr>
<tr>
<td>Deranged RFT</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>0.05</td>
</tr>
<tr>
<td>LDH-raised</td>
<td>168</td>
<td>56</td>
<td>89</td>
<td>23</td>
<td>0.066</td>
</tr>
<tr>
<td>CK-MB-raised</td>
<td>249</td>
<td>87</td>
<td>133</td>
<td>29</td>
<td>0.22</td>
</tr>
<tr>
<td>CKNA-C-raised</td>
<td>40</td>
<td>10</td>
<td>23</td>
<td>7</td>
<td>0.101</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>131</td>
<td>44</td>
<td>66</td>
<td>21</td>
<td>0.014</td>
</tr>
<tr>
<td>Abnormal chest X-ray</td>
<td>59</td>
<td>33</td>
<td>25</td>
<td>1</td>
<td>0.0017</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations (absolute value)</th>
<th>All (n=406)</th>
<th>Group-A 10-29 years (n=151)</th>
<th>Group-B 30-59 years (n=215)</th>
<th>Group-C ≥60 years (n=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sugar (mg/dl)</td>
<td>104.97 ± 52.30</td>
<td>89.64 ± 31.35</td>
<td>109.37 ± 54.73</td>
<td>138.9 ± 77.17</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>39.41 ± 5.94</td>
<td>39.38 ± 5.96</td>
<td>39.65 ± 5.95</td>
<td>38.26 ± 5.82</td>
<td>0.39</td>
</tr>
<tr>
<td>PLT count (lakhs/cumm)</td>
<td>1.72 ± 0.64</td>
<td>1.79 ± 0.57</td>
<td>1.68 ± 0.66</td>
<td>1.69 ± 0.75</td>
<td>0.305</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>497.72 ± 225.80</td>
<td>462.13 ± 150.14</td>
<td>491.97 ± 238.25</td>
<td>654.89 ± 310.96</td>
<td>0.000013</td>
</tr>
<tr>
<td>CK-MB (IU/L)</td>
<td>49.7 ± 44.3</td>
<td>47.96 ± 44.93</td>
<td>47.97 ± 33.94</td>
<td>64.89 ± 76.84</td>
<td>0.083</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ARDS and/or mechanical ventilation</th>
<th>18</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>0.0018</th>
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</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 1:** Graphical representation of RBS with multiple comparison of CI (TUKEY’S)
on the lung involved (left, right or both); predominant zone involved (upper, middle, lower, both middle and lower or pan-lobar); distribution of opacity (peripheral, basal, hilar or a combination of two), other findings like pleural effusion or pulmonary nodule and lastly, we calculated RALE score for every patient (Figures 3-10 and Table 3). Peripheral and perihilar demarcation was defined as halfway between lateral edge of the lung and hilum (Table 3).

To quantify the extent of infection, a severity score was calculated by adapting and simplifying the Radiographic Assessment of Lung Edema (RALE) score proposed by Warren et al. A score of 0-4 was assigned to each lung depending on the extent of involvement by consolidation or GGO (0 = no involvement; 1 = <25%; 2 = 25-50%; 3 = 50-75%; 4 = >75% involvement). The scores for each lung were summed to produce the final severity score. Baseline RALE score ranged from 0-7 with a median of 2 (IQR: 3-1). The scores were again calculated for their second X-Ray, done 2-3 days later. 43 patients saw a reduction in their RALE score while 40 saw an increase. Average RALE score changed from 2.04 to 2.01.

141 of 336 patients having abnormal X-Rays, were symptomatic implying that less than 50% of patients with imaging abnormality had any clinical presentation. No association was seen between X-Ray findings and disease course or prognosis. Patients who developed complications and/ or expired due to the disease had RALE score ranging from 1-7 and patients who had a milder disease and were discharged without complications had a score ranging from 0-6, with a median score of 2 in both the settings.

As done with basic characteristics, ad hoc sub analyses were done based on age and symptomatology. No statistically significant result was found and hence is not being elaborated in this study.

10 CT scans were done. 3 of them had normal Chest X-rays but abnormal CT scans, 1 had aberration in X-ray but a normal CT, rest 6 of the patients showed similar findings in both modalities. Ground glass opacities, consolidation, crazy paving sign (due to septal thickening), reverse halo

normal throughout the disease course.

At the time of presentation, cases missed by RT-PCR were 18/ 406 as compared to 70 by X-Ray images; suggesting lower sensitivity of the latter.

We assessed each skiagram based
was considered. It had an added disadvantage of increased exposure to healthcare workers for a marginal benefit.

**Clinical Outcome**

Patients were initially divided into wards depending on presence or absence of symptoms. Every COVID19 positive patient was treated with HCQS and azithromycin, barring those who had any contraindications or side effects. Both the drugs were tolerated well by maximum patients. Symptomatic support like antihistamines, cough syrup, oxygen support and intravenous antibiotics was also instituted. Nebulization was discouraged and use of MDI/high flow nasal oxygen was preferred. During this study, no interventional trial was done in management of patients.

Average duration for seroconversion (from positive to negative) was 6 ± 2.92 days. The disease was milder as compared to other regional reports especially from foreign countries. Post two consecutive negative reports, 388 patients have been discharged with symptomatic treatment and advised 14 days’ strict home quarantine. Only 162 patients were symptomatic. The clinical characteristics of COVID-19 were found to be similar to those of SARS-CoV and in accord with recent studies. Fever, cough and myalgia were the dominant symptoms, gastrointestinal symptoms were less common. This may indicate a different viral tropism as compared with SARS-CoV, MERS-CoV, and seasonal influenza. 49 out of 406 patients (12%) were diagnosed without clinical or X-Ray manifestations of pneumonia, pointing towards the wide array of disease presentation or lack of it thereof and needs to be studied further. Lymphocytopenia and thrombocytopenia were common, as were raised CKMB and LDH levels, a finding that was consistent with the results of two recent reports. 1,17 Average age of patients having lymphopenia was 34.49±15.5 years while that of patients with normal lymphocyte count was 31.46±16.48 years. The results indicate that with increasing age, the immune cells are

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**Fig. 6:** X-ray involving B/L middle and lower zone (basal predominance). Rale : 2+2=4

**Fig. 7:** B/L Lower lobe consolidation with peripheral and basal predominance Rale: 4

**Fig. 10:** (HRCT chest) ground glass opacity seen in bilateral posterobasal segments, consolidation seen in left lower lobe.

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**Figs. 8, 9:** (HRCT chest) focal consolidation in peripheral aspect of bilateral lower lobes with adjacent ground glass opacities

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sign and occasionally pleural effusion were the observed findings. CT was better at detecting the type and extent of pulmonary involvement but no significant advantage was noticed as far as sensitivity and specificity

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This study was started during the initial stage of disease outbreak in the region. Most of the cases were asymptomatic or had very mild clinical presentation. Screening teams played a massive role in bringing patients to the health setup. 96.4% patients were from four cluster areas in or around Kota at the end of two weeks, but by the time of data cutoff, almost all localities had been affected by the pandemic. Only 16 had travel history while 210 of the 406 had history of contact to active COVID cases. These findings concur with similar studies supporting outbreak of a family cluster and transmission from an asymptomatic patient. Transmission of SARS-CoV, MERS-CoV, and influenza is by respiratory droplets and direct contact. The same may be seen in SARS-CoV-2 as well. As SARS-CoV-2 can be detected in the gastrointestinal tract, saliva, and urine, potential transmission via these routes need to be investigated further. Two third of the patients were males and the average age was around 36 years. Only 162 patients were symptomatic. The clinical characteristics of COVID-19 were found to be similar to those of SARS-CoV and in accord with recent studies. Fever, cough and myalgia were the dominant symptoms, gastrointestinal symptoms were less common. This may indicate a different viral tropism as compared with SARS-CoV, MERS-CoV, and seasonal influenza. 49 out of 406 patients (12%) were diagnosed without clinical or X-Ray manifestations of pneumonia, pointing towards the wide array of disease presentation or lack of it thereof and needs to be studied further. Lymphocytopenia and thrombocytopenia were common, as were raised CKMB and LDH levels, a finding that was consistent with the results of two recent reports. Average age of patients having lymphopenia was 34.49±15.5 years while that of patients with normal lymphocyte count was 31.46±16.48 years. The results indicate that with increasing age, the immune cells are
more susceptible to damage by the virus, and hence their immunity maybe weakened. But unlike previous studies, the age difference was not statistically significant (p-0.17). We had a lower case fatality rate (1.9%) than the rate recently reported.17 Stringent screening and contact tracing, early isolation, diagnosis and management might have collectively contributed to the reduced mortality. This could also be due to small sample size.

Symptomatic patients had more aberrations in laboratory analysis and a worse outcome, so did the elderly population. Despite having similar presentation, patients aged more than 60 years had to face a more severe disease course and increased mortality. Though the overall occurrence of complications and mortality was less in our study, the proportion was significantly high in the geriatric population.

Imaging analysis showed that serial X-Ray monitoring suffices to aid us in our management but the extent of abnormalities does not always correlate with the clinical presentation, as findings varied from nil to extensive involvement irrespective of symptomatology and clinical status. CT imaging should be reserved for severe cases or those unresponsive to treatment. In patients with a normal X-Ray and a negative RT-PCR assay, a high index of clinical suspicion justifies the use of CT imaging. Most common findings in X-Ray include involvement of bilateral middle and lower zones with peripheral and basal predominance occasionally accompanied by lymphadenopathy, rarely seen were pleural effusion or nodules. The proportion of patients in our study exhibiting abnormal radiographic findings (336/406, 82.7%) is higher than that in the case series of 9 patients published by Yoon et al.11 (56%) and Guan W, Ni Z, Hu Y, et al.21 (80%) CT imaging defines the extent of pulmonary involvement better X-Rays, but is not superior as a diagnostic or prognostic tool in this highly contagious setting. An objective scoring though, less relevant for predicting the disease outcome, puts forth an unbiased perspective and improves the ease of follow up. ECG and CK-MB abnormalities were frequently observed; hence cardiac imaging may be incorporated into the management protocol.

The study was marred by few limitations like, first; limited sample size, second; inadequate documentation of exposure history combined with recall bias; third, inadequate infrastructure leading to omission of certain tests such as D-Dimer and pro-calcitonin; which may have improved the monitoring of various complications such as coagulopathy.

Conclusion
In 406 patients diagnosed with COVID-19, the spectrum of clinical presentation posed a major challenge. Less patients presented to the OPD with known symptoms, majority were brought in from cluster regions via screening. This implies an additional importance to increased testing and thorough screening process. The clinical presentation was milder and complications were seen in very few. Special attention is required to the geriatric population as they are more likely to have a poor outcome. In greater portion of patients, irrespective of symptoms, investigations and imaging showed features of viral illness like lymphopenia, thrombocytopenia, raised LDH and basal predominant lower lung involvement. These markers did not prove to be of much use as prognostic indicators but may help in diagnosis. Raised cardiac markers and ECG abnormalities strongly support use of advanced investigations to rule out subtle complications that we might be missing. Compared to prior studies, we fared much better in terms of outcome as only 4.4% had ARDS with need for mechanical ventilation and 1.9% mortality was observed.21 RALE score calculation may provide objective insight into pulmonary involvement. It may be of use to assess residual lung injury in a follow up study of the same patients. CT scans, though better than chest X-Ray, but routine use is discouraged if we weigh the risk benefit ratio. Larger intervention cohort trial, with extensive monitoring for complications, is need of the hour to assess the disease better, find yet unknown features, complications and possibly improved treatment protocols.

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

Amit Aggarwal, Abhinav Shrivastava, Abhinav Kumar, Adila Ali

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...
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 17\(^{th}\) 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.\(^6\)

### 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.\(^7\) 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 10\(^{th}\) April 2020 to 30\(^{th}\) 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 10\(^{th}\) April 2020 and 30\(^{th}\) 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. 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 10\(^{th}\) April 2020 to 30\(^{th}\) April 2020.

An acute respiratory infection with:

- History of fever or measured fever of ≥ 38 °C
- Cough
- Onset within the last 10 days
- Requiring hospitalization
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 the 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. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter.

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

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total (N=32)</th>
<th>Severe (N=24)</th>
<th>Non-severe (N=8)</th>
<th>P value</th>
<th>Yes (N=12)</th>
<th>No (N=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median IQR)</td>
<td>54.5 (46.25-60)</td>
<td>55.5</td>
<td>48</td>
<td>0.12</td>
<td>56.5</td>
<td>50.5</td>
<td>0.042</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (59.4%)</td>
<td>5 (62.5%)</td>
<td>14 (58.3%)</td>
<td>0.84</td>
<td>7 (58.3%)</td>
<td>12 (60%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Female</td>
<td>13 (40.6%)</td>
<td>3 (37.5%)</td>
<td>10 (41.7%)</td>
<td>0.66</td>
<td>5 (41.7%)</td>
<td>8 (40%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Co-morbidities (at least 1)</td>
<td>22 (68.8%)</td>
<td>17 (70.8%)</td>
<td>5 (62.5%)</td>
<td>0.66</td>
<td>11 (91.7%)</td>
<td>12 (55%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Co-morbidities (at least 2)</td>
<td>13 (40.6%)</td>
<td>11 (45.8%)</td>
<td>2 (25%)</td>
<td>0.30</td>
<td>8 (66.7%)</td>
<td>5 (25%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (34.4%)</td>
<td>9 (37.5%)</td>
<td>2 (25%)</td>
<td>0.52</td>
<td>7 (58.3%)</td>
<td>4 (20%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (50%)</td>
<td>13 (54.2%)</td>
<td>3 (37.5%)</td>
<td>0.41</td>
<td>10 (83.3%)</td>
<td>6 (30%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart disease</td>
<td>4 (12.5%)</td>
<td>3 (12.5%)</td>
<td>1 (12.5%)</td>
<td>1.00</td>
<td>2 (16.7%)</td>
<td>3 (10%)</td>
<td>0.58</td>
</tr>
<tr>
<td>CVA</td>
<td>1 (3.125%)</td>
<td>1 (4.2%)</td>
<td>0 (0%)</td>
<td>0.56</td>
<td>1 (8.3%)</td>
<td>0 (0%)</td>
<td>0.19</td>
</tr>
<tr>
<td>CKD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.56</td>
<td>0</td>
<td>0</td>
<td>0.56</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Chronic chest condition</td>
<td>9 (28.1%)</td>
<td>7 (29.2%)</td>
<td>2 (25%)</td>
<td>0.82</td>
<td>4 (33.3%)</td>
<td>5 (25%)</td>
<td>0.01</td>
</tr>
<tr>
<td>H/O PTB</td>
<td>2 (6.2%)</td>
<td>1 (4.2%)</td>
<td>1 (12.5%)</td>
<td>0.40</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td>0.06</td>
</tr>
<tr>
<td>COPD</td>
<td>5 (15.6%)</td>
<td>4 (16.7%)</td>
<td>1 (12.5%)</td>
<td>0.78</td>
<td>3 (25%)</td>
<td>2 (10%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 (6.25%)</td>
<td>2 (8.3%)</td>
<td>0 (0%)</td>
<td>0.40</td>
<td>1 (8.3%)</td>
<td>1 (5%)</td>
<td>0.71</td>
</tr>
<tr>
<td>ILD</td>
<td>1 (3.125%)</td>
<td>1 (4.2%)</td>
<td>0 (0%)</td>
<td>0.56</td>
<td>1 (8.3%)</td>
<td>0 (0%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (6.25%)</td>
<td>2 (8.3%)</td>
<td>0 (0%)</td>
<td>0.40</td>
<td>01(8.3%)</td>
<td>2 (5%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>22 (68%)</td>
<td>16 (66.7%)</td>
<td>6 (75%)</td>
<td>0.66</td>
<td>9 (75%)</td>
<td>13 (65%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cough</td>
<td>27 (84.4%)</td>
<td>20 (83.3%)</td>
<td>7 (87.5%)</td>
<td>0.78</td>
<td>10 (83.3%)</td>
<td>17 (85%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Cough with expectoration</td>
<td>10 (31.3%)</td>
<td>7 (29.2%)</td>
<td>3 (37.5%)</td>
<td>0.66</td>
<td>4 (33.3%)</td>
<td>6 (30%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Cough without expectoration</td>
<td>17 (53.13%)</td>
<td>13 (54.2%)</td>
<td>4 (50.0%)</td>
<td>0.84</td>
<td>6 (50%)</td>
<td>11 (55%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>29 (90.6%)</td>
<td>22 (91.7%)</td>
<td>7 (87.5%)</td>
<td>0.73</td>
<td>11 (91.7%)</td>
<td>18 (90.0%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (43.75%)</td>
<td>9 (37.5%)</td>
<td>5 (62.5%)</td>
<td>0.22</td>
<td>5 (41.7%)</td>
<td>9 (45%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Sore throat</td>
<td>9 (28.1%)</td>
<td>7 (29.2%)</td>
<td>2 (25%)</td>
<td>0.82</td>
<td>5 (41.7%)</td>
<td>5 (20%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (18.75%)</td>
<td>4 (16.7%)</td>
<td>2 (25%)</td>
<td>0.60</td>
<td>2 (16.7%)</td>
<td>4 (20%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Loose stools</td>
<td>3 (9.4%)</td>
<td>2 (8.3%)</td>
<td>1 (12.5%)</td>
<td>0.73</td>
<td>0 (0%)</td>
<td>3 (15%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Chest pain</td>
<td>6 (18.75%)</td>
<td>5 (20.8%)</td>
<td>1 (12.5%)</td>
<td>0.60</td>
<td>3 (25%)</td>
<td>3 (15%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (9.4%)</td>
<td>1 (4.2%)</td>
<td>2 (25%)</td>
<td>0.08</td>
<td>0 (0%)</td>
<td>3 (15%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Anosmia</td>
<td>4 (12.5%)</td>
<td>3 (12.5%)</td>
<td>1 (12.5%)</td>
<td>1.0</td>
<td>2 (16.7%)</td>
<td>2 (10%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>3 (9.4%)</td>
<td>3 (12.5%)</td>
<td>0 (0%)</td>
<td>0.29</td>
<td>1 (8.3%)</td>
<td>2 (10%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1 (3.125%)</td>
<td>1 (4.2%)</td>
<td>0 (0%)</td>
<td>0.56</td>
<td>1 (8.3%)</td>
<td>0 (0%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3.125%)</td>
<td>0 (0%)</td>
<td>1 (12.5%)</td>
<td>0.78</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Bodyache / myalgia</td>
<td>14 (43.75%)</td>
<td>9 (37.5%)</td>
<td>5 (62.5%)</td>
<td>0.22</td>
<td>5 (41.7%)</td>
<td>9 (45%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>2 (6.25%)</td>
<td>1 (4.2%)</td>
<td>1 (12.5%)</td>
<td>0.40</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Symptom to adm (days)</td>
<td>3 (2-4)</td>
<td>3</td>
<td>4</td>
<td>0.63</td>
<td>3.5</td>
<td>3</td>
<td>0.30</td>
</tr>
</tbody>
</table>

The swabs were expressed on the side of the cryovials and broken off into the cryovials. Specimens were stored and transported to the 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.
Table 2: Laboratory and radiological findings of patients infected with COVID-19

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total (n=32)</th>
<th>Pneumonia severity</th>
<th>P value</th>
<th>Presence of primary composite outcome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe (n=24)</td>
<td>Non-severe (n=8)</td>
<td></td>
<td>Yes (n=12)</td>
<td>No (n=20)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>10 (31.2%)</td>
<td>7 (29.2%)</td>
<td>3 (37.5%)</td>
<td>0.66</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>24 (75%)</td>
<td>18 (75%)</td>
<td>6 (75%)</td>
<td>1.0</td>
<td>10 (83.3%)</td>
</tr>
<tr>
<td>Monocytosis</td>
<td>5 (15.6%)</td>
<td>5 (20.8%)</td>
<td>0 (0%)</td>
<td>0.16</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14 (43.8%)</td>
<td>11 (45.8%)</td>
<td>3 (37.5%)</td>
<td>0.68</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>14 (43.8%)</td>
<td>9 (37.5%)</td>
<td>5 (62.5%)</td>
<td>0.22</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>10 (31.2%)</td>
<td>6 (25%)</td>
<td>4 (50%)</td>
<td>0.19</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Deranged LFT</td>
<td>4 (12.5%)</td>
<td>2 (8.3%)</td>
<td>2 (25%)</td>
<td>0.22</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>AKI</td>
<td>13 (40.6%)</td>
<td>11 (45.8%)</td>
<td>2 (25%)</td>
<td>0.30</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>22 (68.8%)</td>
<td>17 (70.8%)</td>
<td>5 (62.5%)</td>
<td>0.66</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Raised CK MB</td>
<td>8 (25%)</td>
<td>7 (29.2%)</td>
<td>1 (12.5%)</td>
<td>0.35</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>B/L chest infiltrates</td>
<td>30 (93.8%)</td>
<td>23 (95.8%)</td>
<td>7 (87.5%)</td>
<td>0.40</td>
<td>11 (91.7%)</td>
</tr>
</tbody>
</table>

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. $\text{SpO}_2 \leq 93\%$

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 $\alpha$ 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 transferred to the non-COVID wards/ ICUs for further management.
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. Representative extensive bilateral infiltrates with findings. Notably one patient had insignificant X-ray patchy nodular infiltrates and the other one had unilateral infiltration in 4 (12.5%) patients. One (3.125%) patient had unilateral 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 10 (31.2%) of the patients, with majority of patients 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

### Table 3: Quantitative Laboratory parameters of COVID-19 patients

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total (n=32)</th>
<th>Presence of severe pneumonia</th>
<th>Presence of primary composite outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes (n=24)</td>
<td>No (n=8)</td>
</tr>
<tr>
<td>Hb (g/dl) (median)(IQR)</td>
<td>12.6 (11.2-13.7)</td>
<td>12.7</td>
<td>11.65</td>
</tr>
<tr>
<td>WBC count (cells/ µl) (median)(IQR)</td>
<td>5850 (3900-8900)</td>
<td>5750</td>
<td>7700</td>
</tr>
<tr>
<td>Neutrophil count (cells/µl) (median)(IQR)</td>
<td>3921 (2722-6691)</td>
<td>3711</td>
<td>5883</td>
</tr>
<tr>
<td>Lymphocyte count (cells/µl) (median)(IQR)</td>
<td>1106 (970-1487)</td>
<td>1129</td>
<td>1080</td>
</tr>
<tr>
<td>Monocyte count (cells/µl) (median)(IQR)</td>
<td>396 (243-669)</td>
<td>396</td>
<td>370.5</td>
</tr>
<tr>
<td>Platelets (cells/µl) (median)</td>
<td>130000 (96500-207500)</td>
<td>128000</td>
<td>161000</td>
</tr>
<tr>
<td>CK-MB (u/l) (median)(IQR)</td>
<td>29 (22-70.5)</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>Bilirubin (mmol/l) (median)(IQR)</td>
<td>0.8 (0.6-1.1)</td>
<td>0.8</td>
<td>0.93</td>
</tr>
<tr>
<td>ALT (u/l)(median)(IQR)</td>
<td>28 (23-31.5)</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>AST (u/l)(median)(IQR)</td>
<td>30 (26-38)</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Urea (mmol/l) (median)(IQR)</td>
<td>51 (34-71)</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Creatinine (µmol/l) (median)(IQR)</td>
<td>1.70 (0.78-1.75)</td>
<td>1.1</td>
<td>0.98</td>
</tr>
<tr>
<td>Albumin (g/dl) (median)(IQR)</td>
<td>3.36 (3.1-3.5)</td>
<td>3.25</td>
<td>3.43</td>
</tr>
</tbody>
</table>

Treatment and main interventions

All the SARI patients received injectable antibiotics, tab oseltamir 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 (28.5%) 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
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%. 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. 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. 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. 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 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).

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
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 ARDS18 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 non-surviving 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. Alanine aminotransferase, aspartate transaminase and bilirubin were found less commonly in our study. Alcoholics with viral hepatitis, acute liver failure, drug induced liver injury and Wilson’s disease.20 Infections can also cause 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.13

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 abnormailities 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 comorbidities 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.

References


4. Sanchez S, Lyny T, Xu C, Romero-Severson E, Hengartner N, Ke R, High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. Emerging Infectious Disease 2020;


7. WHO | Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. WHO; 2018;

8. WHO. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. 2020; (December 2019): 1–19.


Prevalence of Flu-like Symptoms and COVID-19 in Healthcare Workers from India

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Abstract

Background: The current COVID-19 pandemic is unprecedented. As the numbers expand exponentially, a paucity of data regarding health care workers (HCWs), who are at the forefront of this disaster, exists. Hence we decided to conduct a study amongst the HCWs to determine the prevalence and risk factor stratification.

Methods: This was an online questionnaire-based survey of healthcare workers conducted at Max Super Speciality Hospital, Saket, New Delhi, India from 23rd March to 30th April 2020. Data on flu-like symptoms, travel history, posting in high-risk or low risk zones, and prophylactic drugs was collected.

Results: Out of the 18000 HCWs who were approached 4403 responded and adequate data of 3667 was available for analysis. 14.7% had flu-like symptoms. 1.8% (20/1113) of the participants tested were positive for the virus. HCWs posted in the high-risk zones had more symptoms than those working in low-risk zones (169/539, 31.4% vs 679/3128, 21.7%), p<0.001; but no difference in COVID-19 positivity rates (p=0.849). Symptomatic HCWs had higher positivity (10/193, 5.2%) than the asymptomatic ones (10/920, 1.1%), p=0.001. HCQ was taken by 755/1113 (67.8%) people and 14 (1.9%) of these reported positive for the virus.

Conclusion: This is the first study on healthcare workers from India to the best of our knowledge. Our findings suggest that posting in a high-risk zone with adequate PPE does not pose higher risk to the HCWs. Moreover, HCQ as a prophylactic has no use.

ClinicalTrials.gov Identifier: NCT04339608

Introduction

WHO declared COVID-19 a pandemic on 11th March 2020. As of 19th May 2020, 4,731,458 people have been infected with and the total no. of deaths were 316,156

Deaths bringing the crude mortality rate to 6.68%. Health care workers (HCWs) are apparently at a higher risk of contracting this highly contagious virus and 3300 HCWs were infected in China by the beginning of March 2020, of which 22 HCWs died. Almost 20% of the responding health care personnel in Italy have also tested positive, which is 11% (15314) of the total infections. According to the Center for Disease Control (CDC) as of 9th April 2020, of the total 315, 531 COVID-19 cases in the US, 9,282 were HCWs (health care occupation data however was only available for 16% of the total patients). South Korea has involved universal screening of the entire population. In India, only people with travel history and symptoms or their close contacts were being tested. There is paucity of data regarding the prevalence of COVID-19 amongst HCWs especially from India.

Max Hospital and its partner hospitals became COVID-19 hospitals on 27th March 2020. In order to improve our understanding of the prevalence of SARS-CoV2 within the health care community we designed this study with an aim to assess the flu-like symptoms in suspicion of COVID-19 and the associated risk factors.

Methods

The study population included healthcare workers of Max Super Speciality Hospitals, Delhi-National Capital Region (5 hospitals), BLK Hospital, Delhi and Nanavati Hospital, Mumbai. A self-assessment questionnaire was designed to obtain the baseline data on the demographics, clinical and occupational aspects of the participants which was filled out via Google Forms. The questionnaire included questions regarding work profile in hospital, clinical symptoms of flu, or history of travel. (Annexure 1).

The data was collected from 23rd March to 30th April 2020. People with flu-like illness defined as fever (more than 100°F), cough, sore throat, cold/stuffy nose, and breathlessness were considered. The hospital was divided into high risk and low risk zones. COVID-19 ward or Intensive Care Unit (ICU), Emergency, and flu-clinic were classified as high-risk zones in the hospital and others were low-risk zones. In our hospitals it was mandatory for HCWs working in high-risk zones to wear full PPE and those working in the low-risk zone were following the World Health Organization (WHO) guidelines.

Results

Approximately 18000 HCWs were approached to participate in this study and we received responses from 4403 HCWs. Out of these, 3667 had adequate information (Figure 1), which included 1910 (52.1%) males and 1757 (47.9%) females. The median age of
This population was in the range of 18-40 years. Those participants were nurses (1290, 35.2%), doctors (792, 21.6%), and other support staff (1585, 43.2%). In our HCW cohort, 539/3667 (14.7%) had flu-like symptoms. Total 1353 of 3667 people were tested for COVID-19, however only 1113 were included in the final analysis due to unavailability of results in the rest of them. We observed a prevalence of 1.8% (20/1113) in this cohort. People with travel history (in the last 30 days) had higher incidence of flu-like symptoms (44/539, 8.2% vs 113/3128, 3.6%), $p=0.001$; however, there was no difference in COVID-19 positivity rates ($p=>0.999$). Similarly, HCWs posted in the high-risk zones had more symptoms than those working in the low-risk zones (169/539, 31.4% vs 679/3128, 21.7%), $p<0.001$; but there was no difference in COVID-19 positivity rates ($p=0.849$). Travel history, posting in high-risk zones, PPE usage did not correlate with COVID-19 positivity. People who were symptomatic had higher positivity (10/193, 5.2%) as compared to those who were asymptomatic (10/920, 1.1%), $p=0.001$. Hydroxychloroquine (HCQ) was taken by 755/1113 (67.8%) people and 14 (1.9%) of these reported positive for the virus. This positivity was 6 (1.7%) in those who did not take this drug ($p=0.834$).

**Discussion**

In addition to being a pioneer study about HCWs from India, there are three unique findings we came across during our analysis. We observed that travel history, HCQ prophylaxis, and being posted in high-risk zones with adequate PPE preventions did not increase risk of COVID-19 positivity. Single most important predictor of infection was being symptomatic.

As of 8th April 2020, 22,073 cases of COVID-19 amongst HCWs from 52 countries had been reported to WHO. There is no systematic reporting so this number probably under-represents the prevalence in HCWs. Italy reported 11% (15314) of all their infections amongst HCWs, UK recorded a death of 100 National Health Service (NHS) and health care workers. According to CDC, as of 9th April 2020, of the total 315, 531 COVID-19 cases in the US, 9,282 were HCWs (health care occupation data however was only available for 16% of the total patients).

In our country, the first case of COVID-19 was detected on 30th January 2020. The prevalence among the selected population is 4.13% (112,359/2,719,434) based on pooled data of Indian Council of Medical Research (ICMR) and WHO. According to our survey, the prevalence amongst HCWs was 1.8%. Only symptomatic people, people with travel history or contacts of positive patients are being tested as per ICMR guidelines.

Posting of HCWs in high-risk areas is on a rotation basis, followed by quarantine and COVID tests. Risk of infection in people posted in high risk zones were not higher compared to those who were working in low risk zones. This was likely as HCWs working in high risk zones were aware of their continuous exposure and taking additional precaution in terms of proper personal protective equipment (PPE). A rapid review confirms that SARS-CoV-2 like other coronavirus infections are a burden on the HCWs, nonetheless, use of PPE and infection control training are associated with decreased risk.9

India implemented a countrywide lockdown from 25th March, which restricted all international and domestic travel. In our cohort, travel history did not correlate with COVID positivity. This could in part be because of the small number of subjects who actually tested positive as well as the travel restrictions and necessary quarantine that worked well in this ongoing pandemic. Kucharski et al, demonstrated a decline in the time varying basic reproduction number ($R_0$) from 2.35 before the travel restrictions to 1.05 after the travel restrictions, in Wuhan, China.10

Many HCWs were taking HCQ/Chloroquine/Azithromycin prophylaxis on an individual basis. In our study HCQ prophylaxis played no role in prevention of this infection. Multiple systematic reviews also concluded that there is no pertinent data to support use of HCQ outside that of research, and there is lack of clinical data to actually support its efficacy, adverse effects like prolongation of QTc and tends to instill a false sense of protection.

A major limitation of our study is that a large part of it is voluntary survey based participation and looks at point prevalence of flu-like illness and COVID-19 infection. Despite these limitations, we have shown that the positivity rate is significantly higher in symptomatic people (5.2% vs 1.1%). For a country of 1.3 billion with stressed healthcare resources in terms of number of testing kits and number of labs with expertise to perform it, focusing on symptomatic people and contact tracing of positive patients will help utilize these resources more optimally. Health care workers are going to be working at more than their maximal capacity in a high stressful environment. It will
be a big assurance to HCWs in India to know that their risk of acquiring this infection is not higher than the community when proper precautions like PPE etc as advised by WHO are followed. Availability of data on prevalence of infection in HCWs will help plan policies regarding how best to use this overstrained health resource in the present difficult times.

Conclusion
This is the first study on healthcare workers from India to the best of our knowledge. To conclude, our findings suggest that posting in a high-risk zone with adequate PPE does not pose higher risk to the HCWs. Moreover, HCQ as a prophylactic has no use. Further larger-scale studies on the healthcare workforce would elaborate on the correlation of risk factors with the COVID positivity.

Author contributions
SJ- conceptualized the study, designed the questionnaire, reviewed the manuscript; SS- designed the questionnaire with SJ, wrote the manuscript; AS-analyzed the data, wrote the manuscript; NB, NG, SD-collected and compiled data; RN, SB-reviewed and edited the manuscript

References

Clinico-radiological Presentation of COVID-19 Patients at a Tertiary Care Center at Bhilwara Rajasthan, India

Arun Gaur1, Surender Kumar Meena2, Ramavtar Bairwa3, Daulat Meena4, Rajan Nanda5, Shiv Raj Sharma6, Govind Singh Rajawat7

Abstract
Background: COVID-19 has now become a pandemic. From Wuhan, China, in December 2019 to European countries, USA and now it seems to gain a strong foothold in India. The objective of this work is to report the initial experience with demographic and clinical features, and management of COVID-19 patients admitted in medical college Bhilwara, India.

Methods: This is a descriptive case series of first 26 COVID-19 patients. Demographical, clinical, laboratory, and radiological characteristics and treatment and outcomes data were obtained with data collection forms and history given by 26 COVID-19 patients.

Results and Discussion: During this study 26 COVID-19 positive patients were admitted in MG Hospital, Bhilwara. Male patients were 61.54% and majority (88.46%) were below 60 years of age. Approximately 30.76 % patients were asymptomatic. Fever was the most common symptom (61.54%) followed by sore throat (53.84 %), cough (42.30%) myalgia (38.46%) and dyspnea(23.07%). Six patients (23.07%) of total 26 had comorbidities. Leucopenia was seen in 9 (34.61%) and leukocytosis was seen in 2 patient. Ten patient (38.46%) out of 26 shown increased lymphocyte/neutrophil ratio. Chest X-ray was normal in 20 patients (76.92%). Abnormalities in chest CT were detected among 10 (38.46%) patients. Typical findings were bilateral multifocal patchy peripheral subsegmental areas of consolidation more towards middle and lower zones and bilateral ground glass opacities involving multiple segments. Oseltamivir and chloroquine were given to all 26 patients. Azithromycin was given in 24 patients. Mean duration of conversion of COVID-19 patients was 6.83 days. All discharged patients advised home quarantine for 14 days as per guidelines.

Conclusion: Patients often present without fever, and many may not have abnormal radiologic findings. Patients with older age and associated comorbid conditions (COPD and diabetes) seem to have greater risk for lung injury.
Introduction

Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, with sporadic cases reported globally. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019. As of February 25, 2020, a total of 81,109 laboratory-confirmed cases had been documented globally.2,3 The WHO declared Covid-19 a global pandemic on 11th March 2020. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV.

Coronaviruses are enveloped non-segmented positive sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales and broadly distributed in humans and other mammals.4 Although most human coronavirus infections are mild, the epidemics of the two betacoronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV)5-10 and Middle East respiratory syndrome coronavirus (MERS-CoV),11,12 have caused more than 10,000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.13-14

The 2019-nCoV has close similarity to bat coronaviruses, and it has been postulated that bats are the primary source. While the origin of the 2019-nCoV is still being investigated, current evidence suggests spread to humans occurred via transmission from wild animals illegally sold in the Wuhan Seafood Market.15

Human-to-human transmission via droplets as well as through contact with fomites seems to be the critical route of the virus spread. Since 80% of the infected population are either asymptomatic or have mild disease, people have been going to their workplaces and even traveling internationally. Nevertheless, even though the virus is causing mild disease in many, the course of illness may be severe, leading to hospitalization and even death in elderly or those with comorbid conditions.16

After the outbreak of COVID-19 in China, Indian government was on alert mode and took desperate measures to stop the entrance of this virus in the country. But cases started to appear, and the first case diagnosed at 30 January in Kerala. In Rajasthan first case was diagnosed in Jaipur, on 2 March 2020 and this was the fourth case of India. He was an Italian tourist and it was later found that this patient had infected 17 other Italians who were on a tour to India. On 18th March 2020 a first case of viral like pneumonia reported from a private hospital at Bhilwara district of Rajasthan, after this cluster of pneumonia cases were reported from staff and patient of same private hospital which was further confirmed as COVID-19 pneumonia by RTPCR. Bhilwara which is famous as textile city of India now becomes an epicenter of north India with maximum number of cases in India from a single district at that time. This study is an attempt to describe the clinico-radiological profile, demographic characteristic, treatment strategy and outcome of the patients treated at MG hospital Bhilwara.

Table 1: Demographic and clinical profile of COVID – 19 patients

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<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>0-19 years</td>
<td>0</td>
<td>1</td>
<td>3.84</td>
</tr>
<tr>
<td>20-39 years</td>
<td>8</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>40-59 years</td>
<td>6</td>
<td>3</td>
<td>34.61</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>2</td>
<td>1</td>
<td>11.53</td>
</tr>
<tr>
<td>Total</td>
<td>16 (61.54%)</td>
<td>10 (38.46%)</td>
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<tr>
<td>Health care workers</td>
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<td>5</td>
<td>57.69</td>
</tr>
<tr>
<td>Hospital exposure</td>
<td>3</td>
<td>2</td>
<td>19.23</td>
</tr>
<tr>
<td>Family Exposure of positive patients</td>
<td>2</td>
<td>3</td>
<td>19.23</td>
</tr>
<tr>
<td>Unknown exposure</td>
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<td>0</td>
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<tr>
<td>Total Asymptomatic</td>
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<td>30.76</td>
</tr>
<tr>
<td>Total symptomatic</td>
<td>18</td>
<td></td>
<td>69.23</td>
</tr>
<tr>
<td>Fever</td>
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</tr>
<tr>
<td>Cough</td>
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<td>Sore throat</td>
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<tr>
<td>Myalgia</td>
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<td>Shortness of breath</td>
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<tr>
<td>Headache</td>
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<td>30.76</td>
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<tr>
<td>Diabetes</td>
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<td>7.69</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>CKD</td>
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</tr>
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<td>COPD</td>
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<td>IHD</td>
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Methods

The current study is a retrospective observational case series of demographic features and clinico-radiological manifestations of COVID-19 positive patients who were admitted in the MG hospital and medical college Bhilwara. Total 26 COVID-19 positive patients admitted between 18 March 2020-09 April 2020 during the outbreak of COVID-19.

The study was conducted by a team of physician, chest physician and involvement of other discipline as required.

Immediate isolation of suspected patients was done. The isolation facility at our hospital was assessed for preparedness according to a checklist standardized by Indian Ministry of Health and Family Welfare (MoHFW).17 All the health-care workers caring for infected patients received comprehensive training and demonstrated competence in implementing infection control practices and procedures. The nasopharyngeal
and oropharyngeal swabs were tested at SMS Medical college, Jaipur for detection of COVID-19 using quantitative polymerase chain reaction RTPCR for confirmation.

The medical records of patients were analyzed by the research team of the MG Hospital Bhilwara. Demographical, clinical, laboratory, radiological characteristics, treatment and outcomes data were obtained with data collection forms from electronic medical records and history given by patients. All data was reviewed by research team. Information recorded included demographic data, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings; chest computed tomographic (CT) scans, 2D ECHO and treatment measures (antiviral therapy, anti-retroviral therapy, anti-malarial therapy, antibiotics and respiratory support).

**Results**

Twenty-six patients were included in the study over a period of 18.3.2020 to 9.04.2020. The sociodemographic and clinical profile is summarized in Table 1. All patients were from Bhilwara district, other country travel history was not present in our study patients’ group. The mean age of participants was 37.6 years (range 17-73 years). There was a male preponderance (61.54%).

Out of 26 patients 15 were health care workers exposed from the same hospital where they were working. Remaining 11 patients were non health care workers, in which 5 were exposed from the same hospital visit. Another 5 infected patients were the family members of COVID-19 positive patients and source of exposure of one patient was unknown.

The common presentation and symptoms experienced by our patients’ group were fever, cough, sore throat, shortness of breath, myalgia and headache.

Eight patients (30.76 %) of total 26 were asymptomatic. Of those who were symptomatic (69.23%), fever was the most common complaint present in 16 (61.54%) patients. Eleven patients (42.30%) presented with cough, 14 (53.84%) patients presented with sore throat, 10 (38.46%) patients presented with myalgia, 6 (23.07%) patients presented with shortness of breath and 8 (30.76%) patient had headache.

Six patients (23.07%) of total 26 had comorbidities. The most common comorbidity was hypertension present in 4 patients. Diabetes mellitus, chronic kidney disease, CVA and ischemic heart disease were present in 2, 2, 1 and 2 patients respectively. Chronic obstructive pulmonary disease (1 patient), congenital heart disease (1 patient) and rheumatoid arthritis (1 patient) were also present.

The blood counts of patients on admission showed leucoccpenia (white blood cell count less than 4 × 10⁹/L; in 9(34.61%) out of 26 patients and leukocytosis was seen in two patients.

Ten patients (38.46%) out of 26 shown increased lymphocyte/neutrophil ratio. ESR and CRP were raised in two patients. Prothrombin time and D-dimer level on admission were normal in all study patients. Serum creatinine was higher in 2 patients. CPK-MB was elevated in 2 patients in whom the diagnosis of virus-related cardiac injury was made or may be due to underlying cardiac disease. All patients had normal serum levels of procalcitonin on admission (procalcitonin <0.1 ng/mL). Two of our chronic kidney disease and diabetic patients developed secondary infections. Vit-D, vit-B12 and serum ferritin level was normal in all patients.

Chest X-ray was normal in 20 patients (76.92%). Only six patients showed abnormality in the form of infiltrates and haziness in mid and lower zones of lung parenchyma. There was no pleural effusion or lymphadenopathy.

On admission, abnormalities in chest CT images were detected among 10 (38.46%) patients. Of the 10 patients, 8 (80%) had bilateral involvement. The typical findings of chest CT images were bilateral, multilocal, patchy peripheral, subsegmental areas of consolidation. There was middle and lower zone preponderance. Bilateral ground glass opacities involving multiple segments was also noted (Figure 1).

Mean saturation on room air (SpO2) was 95.584% (SD=2.16) and the mean respiratory rate was 17.78 (SD=2.86). Four patients (15.38%) required supplemental oxygen support. Two of these 4 patients deteriorated and had to be intubated and put on mechanical ventilation. Both these had comorbidities (CKD &CVA); subsequently died.

Oseltamivir and chloroquine were given to all our 26 patients. Azithromycin was given in 24 patients out of 26, 2 patients of cardiac morbidity who were already on chloroquine were not given azithromycin due to possibility of QT prolongation. Lopinavir + Ritonavir combination was given to only three patients, in which two patient who were on ventilator and one in whom there is no conversion after 10 days of treatment. All patients who were given Lopinavir + Ritonavir developed either gastritis or diarrhea. Vomiting was the most common side effect reported among 6 patients (23.07%) out of 26. Close monitoring
of oxygen saturation with ABG / pulse oximeter was done to monitor development of ARDS.

Conversion of COVID-19 patients occurred in 24 patients out of 26 (two patients died after two days of admission). Mean duration of conversion of COVID-19 patients was 7.6 days (males 7.14 and females 8.3) (Table 2).

All discharged patients became asymptomatic and tested negative twice according to the guidelines and third sample check at discharge on 14 days. All discharged patients were advised home quarantine for 14 days as per guidelines.

Discussion

This study included 26 COVID-19 affected patients with the median age being 37.6 years, which is around two decades younger than that reported by Wang et al\textsuperscript{18} (56.0 years), Chen et al\textsuperscript{15} (55.5 years) and a decade younger then Huang et al\textsuperscript{19} (49.0 years). Most of the patients having COVID-19 were male (61.54\%) which was like that reported by Huang et al and Chen et al which shows 73.10\% male predominance but higher than that reported by Wang et al (54.3\%).Our most of the patients who were COVID-19 infected were from a single health care center in which majority of patients (57.69\%) were health care workers and most others were also exposed to same health care center. This might be the reason of lower age group of our studied patients in comparison to other studies.

One third of our patient was asymptomatic, in symptomatic patients fever was the most common symptom present in our patients (61.54\%) followed by sore throat (53.84\%) and cough (42.30\%) which was in similar to that reported in Huang et al\textsuperscript{19} and Wang et al\textsuperscript{18} where fever was the most common symptom found (91.7\%). None of our patients had rhinitis or diarrhoea at presentation, these are similar to initial data on 18 patients from Singapore, where most of them had fever and cough with infrequent rhinorrhoea.

Ten patients (38.46\%) out of 26 shown lymphocytopenia which is lesser than reported by Zhang et al\textsuperscript{20} (75.4\%). Some patients also presented with lymphocytopenia with thrombocytopenia (15.38\%).

Our four patients requiring oxygen support were above 50 years of age, thus demonstrating that elder patients were more likely to have lung injury, out of these 4 patients 2 needs high oxygen demand and was put on invasive ventilator support, they both were comorbid, one of CKD was on dialysis and another was of ischemic heart disease. Patients requiring oxygen support were have underlying co morbidities including either of diabetes, hypertension, CKD, CAD or COPD. Only 1 (3.84\%) patient in our study had COPD as compared to that in Guan et al\textsuperscript{16} (1.1\%).

HRCT chest of patients demonstrated sub segmental multiple patchy consolidation with ground glass opacities in predilection for peripheral lung fields. Two patients CT shown consolidation with air bronchogram. one patient CT shown involvement of all the lobes of lung in form of patchy consolidations increasing towards the lower and peripheral sides. These findings were similar with Guan et al\textsuperscript{16}.

Changes in CT scan were persisted after 14 days in our COVID- 19 patients at the time of discharge who were converted early in course of time.

There was no difference in mean duration of conversion in both symptomatic and asymptomatic patients. Mean duration of conversion

<table>
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<th>Chloroquine</th>
<th>Azithromycin</th>
<th>Adverse event</th>
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was also not related to the history of exposure. One patient converted later were more symptomatic in comparison to another patient. Our two patients who have history of family exposure of COVID-19 were also converted after 2 weeks, the later conversion in these patients may be either due to heavy exposure of infection in family or due to intolerance of treatment in these patients.

Common side effect seen were nausea, vomiting, diarrhea and psychosis. Our three-patient developed psychosis in isolation ward. Diarrhea, nausea and vomiting developed in 2, 4, and 6 patients respectively.

According to guidelines patient should be discharged after two negative reports of COVID-19, but in this study the average length of stay in hospital was 14 days, as a policy of local management team to prevent relapse because it is seen in South Korea and China that multiple cases relapse after discharge from hospital before 14 days. All discharged patients advised home quarantine for 14 days as per guidelines. The other important policy adopted by hospital management team to detect earliest failure or relapse is follow-up after discharge during quarantine. It is done by daily visit to patient by a trained health care worker and by telephonically by physician every 3rd day. Plan of repeat Clinical examination and Investigations, including CT Scan Thorax after 14 days of discharge is also part of policy to detect residual lung fibrosis and to detect delayed effects on various organ systems. The support of this policy comes from a Singapore study which shows prolonged viral shedding from nasopharyngeal aspirates – up to at least 24 days after symptom onset among COVID-19 patients.21

At present we have seen the initial pattern of the disease, now it is time to come up with some guidelines for isolation, triage and treatment of these patients, globally and locally. Though initial results are not exciting, we shall continue with the search for effective treatment and vaccination. Long-term sequelae like lung fibrosis can only be evaluated with serial follow up of such patients. First, preventing transmission is the key to curtail the pandemic. Our result showing a mild disease with near complete recovery has been the similar initial trend seen in countries like Singapore and South Korea.22,23

Limitations

The sample size in the current study is characterised by a small cohort. However, this case series attempts to characterize the cluster of cases of COVID-19 reported in Bhilwara and may enhance the understanding of this novel infection. The spread of the pandemic to various geographical locations, age groups and comorbid patients may behave differently and hence these results may be difficult to generalize at national or international level.

Conclusions

According to our study patients diagnosed with COVID-19 presented with an upper respiratory tract infection, which is mild, self-resolving with preserved vitals and organ functions. The infection of 2019nCoV was of clustering onset, is more likely to infect older people with comorbidities, and can result in severe and even fatal respiratory diseases such as ARDS. The containment of spread is the most crucial determinant of the final morbidity from this COVID-19 pandemic. Although the virus is contagious and spreads globally, it is too early to comment on its virulence in India. Follow-up of disease spread and clinical presentation in the larger population will give an insight into the COVID-19 outbreak in India. Close monitoring and large-scale control strategies will be needed to prevent widespread transmission within the community.

References

Clinico-Radiological Evaluation and Correlation of CT Chest Images with Progress of Disease in COVID-19 Patients

Sudhir Bhandari1, Govind Rankawat2, Meenu Bagarhatta4, Ajeet Singh3, Aparna Singh4, Vishal Gupta3, Shrikant Sharma3, Raman Sharma3

Abstract

Purpose: The present study was undertaken to investigate and quantify the severity of COVID-19 infection on high-resolution chest computed tomography (CT) and to determine its relationship with clinical parameters. This study also aimed to see CT changes with clinical recovery or progression of disease.

Materials and methods: In an attempt to provide extensive information pertaining to clinical and radiological characteristics of COVID-19, the present study was undertaken in 80 hospitalized patients. The patients were COVID-19 confirmed positive by genomic analysis through RT-PCR at tertiary care center in Jaipur. Initially all patients were evaluated for their clinical parameters and then correlated with HRCT chest after hospitalization. CT findings correlated with duration of disease to assess progress or recovery.

Results: A total of 80 patients of laboratory confirmed COVID-19 test by RT-PCR at SMS Hospitals, Jaipur were assessed. Among the confirmed cases, most of patients were young adults in the fifth and sixth decade of age group with mean age of 50.40 years. There was a male preponderance (59% male and 41% female). Out of total analyzed patients, 39 patients (48.75%) were symptomatic, among them fever (79.47%), cough (74.35%), shortness of breath (36%) and sore throat (17.94%) were the most common presenting clinical manifestations. A few patients (12.82%) also had other symptoms like headache, chest pain, pain abdomen, altered sensorium etc. 54% patients had some underlying co morbid disease in sample population. The most prevalent comorbidities were Diabetes mellitus (56%), Hypertension (48.83%), COPD/K-Chest (12%), CAD (9.32%) and others (11.62%) like hypothyroidism, anemia, CVA etc. The lung pathological changes were evaluated by HRCT imaging and by assigning CT severity score. We found Typical COVID findings in 50% patients, Indeterminate in 11%, Atypical in 11% and 28% patients had Negative CT chest for COVID. The clinical status of patients correlated with the CT severity score, with mild cases showing score <15/25 in 45.83% patients and severe cases showing CT severity score >15/25 in 87.50% patients. The CT features varied with duration and course of disease. Proportional GGO was higher (59.37%) in early phase and it was lower (12.5%) in later stage of disease.

Conclusion: The varied spectra of COVID-19 presentation included fever, cough, shortness of breath, sore throat etc. Diabetes mellitus, hypertension, COPD/K-Chest and CAD were found as major comorbid conditions. Symptomatic presentation of COVID-19 was observed to be higher in patients with co morbid disease, especially if multiple. HRCT chest in COVID-19 patients had a major diagnostic and prognostic importance as positive CT findings were more prominent in symptomatic patients and co-morbid patients. Clinical symptoms of patients directly correlated with CT severity index. CT imaging was found to be useful in predicting clinical recovery of patients or progression of disease.

Introduction

Since November 2019, the rapid outbreak of coronavirus disease 2019 (COVID-19), which arose from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a public health emergency of international concern. COVID-19 has contributed to an enormous adverse impact globally. Infection by COVID-19 can result in a range of clinical outcomes, from asymptomatic to severe life-threatening course or death. Characterization of epidemiological, clinical, co morbid features with recovery and mortality of COVID-19 is crucial for development and implementation of effective control strategies and management protocol. Current estimates are that the incubation period is generally 3 to 7 days, and up to 14 days. As per literature median age of patients is 47–59 years with around 41.9–45.7% of patient population being of female gender. The elderly and those with underlying diseases are more seriously ill after infection. Children and infants can also be infected. On admission, many patients have reported as having at least one co morbidity with diabetes, hypertension, and cardiovascular and cerebrovascular diseases being most commonly reported conditions. The SARS-CoV-2 is highly homologous to SARS-CoV and may cause severe illness similar clinically to SARS. Symptoms...
resulting from COVID-19 infection in the prodromal phase includes fever, dry cough, and malaise, which are nonspecific. 4-7 Some patients may not even have any obvious symptoms. Therefore, chest computed tomography (CT), in particular high-resolution computed tomography (HRCT), represents valuable tools in identifying patients with COVID-19 infections in an early stage when clinical symptoms may be unspecific or sparse. 8-10 For every suspected patient, chest CT is indispensable for definitive diagnosis and reexamination. According to the World Health Organization and the Centers for Disease Control and Prevention guidelines, chest radiography and CT were the major diagnostic components when SARS was prevalent. 11 The clinical and imaging manifestations in the early stage of COVID-19 are particularly important. They can be used to confirm the diagnosis, adjust the treatment plan, and infer the prognosis. The purpose of our study was to characterize the clinical and HRCT features in patients with COVID-19 infection retrospectively, and to facilitate early identification and early isolation. We also aimed to explore the change in HRCT on a spectrum of duration of disease and whether there was a correlation between clinical and imaging features in the course of the illness. As in with influenza, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) 12 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) 13 COVID-19 more readily predisposes to respiratory failure and death in susceptible patients. 14 Recovery and mortality of patients from COVID-19 is influenced by their respiratory system involvement and other systemic comorbidities.

Method

Study Design: The present descriptive, retrospective analysis was done on eighty COVID-19 positive patients admitted in S.M.S. Medical College Hospital, Jaipur, Rajasthan from 15th April to 5th May 2020. COVID-19 was declared a public health emergency of pandemic proportions and subsequently formal screening and diagnostic investigations for SARS-CoV-2 was initiated throughout India. Our institutional review board approved this retrospective study. Informed consent was waived as the study involved no potential risk to patients. The privacy and confidentiality of patients was observed as per norms. To ensure the quality and integrity of clinical, laboratory, and imaging data, here we included 80 patients with COVID-19 who had been admitted to our institution.

Data Collection

We retrospectively collected the clinical and chest imaging data. This included epidemiological data, clinical manifestation, co-morbidities of patients, CT chest characteristics, CT severity score. After collection of all required data and careful medical chart review, the clinical data of laboratory-confirmed patients was compiled and tabulated. The diagnosis of COVID-19 was made based on the World Health Organization interim guidance, wherein confirmed cases denoted were patients whose RT-PCR assay findings for nasal and pharyngeal swab specimens were positive. 3 The epidemiological data (age, sex, residence) was recorded and clinical data, inclusive of recent exposure history, clinical symptoms and signs, co-morbidities, was obtained. All 80 patients underwent initial CT scan of chest with an average 4 days of hospitalization. The admitted patients were serially followed up for their symptomatology complex, with recovery of patients being confirmed with first negative oropharyngeal or nasopharyngeal sample by RT-PCR for COVID-19. A dedicated CT scan machine was used for scanning of COVID patients and proper disinfection protocol was followed. To assess the temporal changes of CT findings date of onset of illness of each patient and date of CT acquisition for each patient was noted. Sequential imaging was done in a few patients to look for disease progression and to guide medical therapy.

Review of CT images

Thin section CT images were acquired on a 128 slice Ingenia machine. The CT images were evaluated for the presence of ground glass haziness (seen as increased attenuation with visible broncho-vascular markings), “crazy-paving” (Ground Glass Opacities with interlobular thickening), consolidation (increased attenuation of air space opacification). The distribution of lesions centrally and peripherally, and anteriorly and posteriorly was also noted. Lesions were further characterized as having vacuolations, reverse halo sign, curvilinear bands and sub-pleural sparing. Note was also made of any additional findings such as nodules, cavities, cysts, pleural effusion and mediastinal lymphadenopathy. Any other pre-existing lung diseases such as TB, bronchiectasis, and emphysema were separately noted.

CT findings were overall classified as Typical, Indeterminate, Atypical or Negative for CT features of COVID-19 pneumonia. Typical features are those that are reported in the literature to be frequently and more specifically in COVID-19 pneumonia like bilateral, peripheral GGOs with or without consolidation or crazy paving. Indeterminate features are those that are reported in COVID-19 pneumonia specifically enough to arrive at a relatively confident radiological diagnosis like multifocal, diffuse, perihilar or unilateral GGOs. Atypical features are those that are reported to be uncommon or not occurring in COVID-19 pneumonia like lobar or segmental consolidation without GGOs or small nodules or cavitation or pleural effusion. Negative for pneumonia implies that there are no parenchymal abnormalities that can be attributed to infection. 15

The 3 lung lobes on the right and 2 lobes on the left were individually assessed and percentage involvement of the lobe was noted based on visual assessment. Visual severity scoring of CT chest was classified as Score-1 (<5% area involved), Score-2 (5-25% area involved), Score-3 (25-50% area involved), Score-4 (50-75% area involved), Score-5 (>75% area involved), making the total score 25. A CT Severity Score was assigned out of 25 based on the percentage area involved in each of the 5 lobes.

To assess the temporal changes of CT findings date of onset of illness of each patient and date of CT acquisition for each patient was noted. Sequential imaging was done for a few patients to look for disease progression specially recovery and to guide medical therapy. In early phases, areas of pure ground glass haziness were seen with visible underlying broncho-vascular markings. The density of lesions in the intermediate and late phases of disease was higher and was seen as areas of consolidation along with few
areas of pure GGOs. Both rounded and linear patterns of opacification were noted with peripheral and/or central distribution of opacities. Vacuolar sign (sign of absorption of lesion and early resolution) was also described in CT images. Curvilinear bands and sub-pleural sparing, also thought to be signs of resorption and retraction also noted. Atoll sign or reverse halo sign seen as an area of GGO surrounded by consolidation, represents a stage of organizing pneumonia. Based on time of onset of illness (time of onset of symptoms in symptomatic patients or time of positive RT-PCR in asymptomatic patients) to time of scan duration, our sample population were classified as early, intermediate and late phases. Patients were considered to be in the (I) early phase of illness if this duration was <5 days, (II) intermediate phase of illness for 5-10 days duration and late if the scan was done 11 days after the date of onset of illness.

Variables: The patient characteristics were collected at baseline and confirmed cases were diagnosed based on positive viral nucleic acid test result on throat swab samples. The variables evaluated included age and gender distribution, clinical manifestations, co morbid status, CT characteristic, CT severity score, follow-up CT images and their correlation with each other and were categorized for analysis and necessary preventive and curative protocol was

Graph 1: Age distribution of COVID patients for CT-chest

Graph 2: Sex distribution of COVID patients for CT-chest

Graph 3: Clinical presentation of COVID patients for CT-chest

Graph 4: Clinical manifestation of COVID patients

Graph 5: Comorbidity in COVID patients

Graph 6: Comorbidity in COVID patients
initiated. Age distribution graphs were constructed and sex ratio (i.e., male: female [M:F] ratio) was calculated. The clinical profile of COVID-19 positive patients was evaluated in terms of percentage prevalence. Co morbid status of patients was documented as percentage prevalence of COVID-19 in such patients and its correlation with symptomatic presentation. CT images were evaluated and assigned CT severity score, CT characteristics, pattern of opacity distribution, type of opacities characteristic, characteristics of lesion and these findings correlated with symptomatology and co-morbidity of patients. Prevalence of GGO and consolidation was correlated with total radiologically positive patients in early, intermediate and late phase of disease. Proportion of symptomatic patients with their characteristic CT findings correlated with time duration of CT imaging from date of onset of illness.

**Statistical analysis**

The present hospital based, observational descriptive study conducted on 80 COVID-19 patients at SMS Medical College Hospital, Jaipur to investigate epidemiological distribution, clinical manifestation, co morbid status, HRCT chest characteristics and clinic-radiological progression of disease for emerging COVID-19 infection at SMS Medical College Hospital, Jaipur, Rajasthan. The descriptive statistics for quantitative data was expressed as mean and standard deviation and qualitative data was expressed as proportions.

**Results**

Serial data from COVID-19 positive patients were collected, evaluated, interpreted and correlated with each other to know severity of disease by their clinical and radiological imaging in order to determine prognostic and diagnostic importance of HRCT chest. A total of 80 laboratory confirmed COVID-19 patients by RT-PCR admitted at SMS Medical College Hospital, Jaipur, Rajasthan till 5th May 2020, were assessed. In our study group most of patients in fifth and sixth decades with mean age 50.40 year. Percentage distribution of patients according to age group was found as <20 year 5%, 20-40 year 23.75%, 40-60 year 40%, >60 year 31.25% (graph 1). Females patients (41%) were lesser than males (59%) with an average sex ratio of female: male being 0.69 in our study (graph 2). Out of total analyzed patients, 39 patients (48.75%) were symptomatic while 41 patients (51.25%) were asymptomatic in our study population (graph 3). In symptomatic patient fever (79.47%), cough (74.35%), shortness of breath (36%) and sore throat (17.94%) were the most common presenting clinical manifestations while a few patients (12.82%) also had other symptoms like headache, chest pain, pain abdomen, altered sensorium etc. Prevalence of various clinical presentation in our study sample population distributed as fever in 39%, cough in 36.25%, SOB in 18%, sore throat in 8.75% and other manifestation in 6.25% (graph 4). 54% patients had some or other underlying co morbid disease in sample population (graph 5). The most prevalent co morbidity among sample population was noted as follow: Diabetes mellitus in 30%, Hypertension in 26.25%, Chronic obstructive pulmonary disease (COPD)/Old K-chest in 6%, Coronary artery disease (CAD) in 5% and other diseases like hypothyroidism, anemia, CVA in 6.25%. The percentage prevalence of comorbid disease among total comorbid patients were found as Diabetes mellitus in 56%, Hypertension in 48.83%, COPD/K-chest in 12%, CAD in 9.32% and other diseases in 11.62% (graph 6). Out of eighty patients 51 patients were found to be radiologically positive on HRCT chest imaging while 29 patients (36.25%) had normal or

**Graph 7: CT characteristics v/s clinical presentation in COVID patients**

- Symptomatic patients
- Asymptomatic patients

**Graph 8: CT severity index v/s clinical presentation in COVID patients**

- Symptomatic patients
- Asymptomatic patients

**Fig. 1:** Coronal sections of a 56 year old male patient show (A) Presence of mixed pattern with both GGO and consolidation (B) Predominance of lesions can be noted in the lower lobes in. The CT severity score in this case was 21/25
non-COVID CT findings. In this study, we assessed the involvement of lungs with CT chest images, in which nearly two third patients (63.75% patients) had positive CT findings while less than half of patients (48.75%) were symptomatic. CT severity score of asymptomatic radiologically positive patients was found to be <5/25. The lung pathological changes were evaluated according to HRCT imaging severity score, and we found Typical COVID findings in 50% patients, Indeterminate in 11%, Atypical in 2.5% and 36.25% patients had normal CT chest findings. Among radiologically positive patients 78.43% patients had typical COVID-19 findings on HRCT chest. Symptomatic clinical presentation higher (69.23%) in patients who had Typical COVID-19 findings in CT images while it was lower in indeterminate and atypical CT findings. Percentage symptomatic presentation in COVID-19 patients with respect to CT Characteristics were found as 67.50% in Typical, 44.44% in Indeterminate, 50% in atypical and 24.13% in normal CT findings (Graph 7). Average CT severity index had been found 8.44. Symptomatic presentation had found higher (in 87.50% patients) who had CT severity index >15/25 while symptomatic presentation lesser (only in 45.83% patients) who had CT severity index <15/25. Percentage symptomatic presentation in COVID-19 patients with respect to CT severity index were 87.50% in patients who had CT severity index 16-20, 36.36% in CT severity index of 11-15, 28.57% in CT severity index of 5-10 and 60.86% in CT severity index of 1-5 (figure 1B). Coincidently 38.70% symptomatic patients had zero CT severity index (Graph 8).

HRCT chest of our study population showed variety of opacity characteristics. Out of radiologically positive patients 25 patients (49.01%) had isolated Ground glass opacities (GGO) while another 25 patients (49.01%) had both GGO and consolidation (figure 1A, 2) and only one patient (1.25%) had isolated consolidation. HRCT chest had different lobe distribution of opacities in which 8 patients (10%) had only one lobe affection, 10 patients (12.50%) had two lobes affection, 4 patients (5%) had three lobes affection, 5 patients (6.25%) had four lobes affection and 24 patients (30%) had all five lobes affection while none of lobe of lungs affected in 29 patients (36.25%). In total radiologically affected 51 patients, 33 patients (64.70%) had more than two lobe affection, 39 patients (76.47%) had bilateral lung involvement. Out of study population (80 patients), 30 patients had right upper lobe involvement, 29 patients had right middle lobe involvement, 43 patients had right lower lobe involvement, 30 patients had left lower lobe involvement, 43 patients had left lower lobe involvement. Out of total radiological affected 51 patients, average 83.33% patients had predominant lower lobe involvement in COVID-19. Among study population 31 patients had predilection towards involvement of posterior surface of lung, 2 patient had anterior surface involvement while 18 patients had both anterior and posterior surface involvement (figure 3). Among radiologically positive patients 96.07% patients had complete or partial posterior surface affection.

HRCT chest of study population had variable axial distribution of opacities, among them 5 patients had
central distribution, 27 patients had peripheral distribution, 18 patients had both central and peripheral distribution (figure 4) while 1 patient had no axial distribution. Out of total radiologically affected patients, 45 patients (88.23%) had predilection towards involvement of periphery of lungs. CT chest imaging also showed some specific findings which includes pleural effusion in 6 patients (7.5%), pulmonary nodules in 6 patients (7.5%), thoracic lymphadenopathy in 19 patients (23.75%) and other nonspecific findings like granuloma, cyst, hemangioma etc. in 7 patients (8.75%) (table 1). In our study population CT chest done at various phase of disease with an average time duration from onset of illness to date of CT imaging was found to be 6.7 days. In this scenario 46 patients (57.5%) radiologically examined in early phase, 19 patients (23.75%) in intermediate phase, 15 patients (18.75%) in late phase of disease progression (graph 9). In early phase of disease (<5 days), among radiologically positive patients (32 out of 46) 59.37% patients had GGO while remaining 40.63% had both GGO and consolidation in imaging of HRCT chest. In intermediate phase of disease (6-10 days), among radiologically positive patients (11 out of 19) 45.45% patients had GGO while remaining 54.54% had both GGO and consolidation in imaging of HRCT chest. In late phase of disease (>10 days), among radiologically positive patients (8 out of 15) 12.50% patients had GGO, 75.00% patients had both GGO and consolidation (figure 5) while remaining 12.50% patients had only consolidation in imaging of HRCT chest (graph 10).

### Table 1: Imaging characteristics on HRCT-chest

<table>
<thead>
<tr>
<th>CT Features</th>
<th>Number of patients</th>
<th>% Among total patients (N=80)</th>
<th>% Among radiologically positive patients (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opacity distribution (Axial)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Axial</td>
<td>1</td>
<td>1.25%</td>
<td>1.96%</td>
</tr>
<tr>
<td>Central</td>
<td>5</td>
<td>6.25%</td>
<td>9.80%</td>
</tr>
<tr>
<td>Peripheral</td>
<td>27</td>
<td>33.75%</td>
<td>52.94%</td>
</tr>
<tr>
<td>Both</td>
<td>18</td>
<td>22.50%</td>
<td>35.29%</td>
</tr>
<tr>
<td>Underlying Lung Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Emphysema</td>
<td>4</td>
<td>5%</td>
<td>7.84%</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>4</td>
<td>5%</td>
<td>7.84%</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>6</td>
<td>7.5%</td>
<td>11.76%</td>
</tr>
<tr>
<td>K-cyst</td>
<td>4</td>
<td>5%</td>
<td>7.84%</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
<td>7.5%</td>
<td>11.76%</td>
</tr>
<tr>
<td>Ground Glass Opacity &amp; Consolidation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both Absent</td>
<td>29</td>
<td>36.85%</td>
<td>56.86%</td>
</tr>
<tr>
<td>GGO present</td>
<td>25</td>
<td>31.25%</td>
<td>49.01%</td>
</tr>
<tr>
<td>GGO &amp; Consolidation both present</td>
<td>25</td>
<td>31.25%</td>
<td>49.01%</td>
</tr>
<tr>
<td>Consolidation present</td>
<td>1</td>
<td>1.25%</td>
<td>1.96%</td>
</tr>
<tr>
<td>Frequency of Lobe Involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Upper Lobe</td>
<td>30</td>
<td>37.50%</td>
<td>58.82%</td>
</tr>
<tr>
<td>Right Middle Lobe</td>
<td>29</td>
<td>36.25%</td>
<td>56.86%</td>
</tr>
<tr>
<td>Right Lower Lobe</td>
<td>42</td>
<td>52.50%</td>
<td>82.35%</td>
</tr>
<tr>
<td>Left Upper Lobe</td>
<td>36</td>
<td>45%</td>
<td>70.58%</td>
</tr>
<tr>
<td>Left Lower Lobe</td>
<td>43</td>
<td>53.75%</td>
<td>84.31%</td>
</tr>
<tr>
<td>Involved surface of lungs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>2</td>
<td>2.50%</td>
<td>3.92%</td>
</tr>
<tr>
<td>Posterior</td>
<td>31</td>
<td>38.75%</td>
<td>60.78%</td>
</tr>
<tr>
<td>Both</td>
<td>18</td>
<td>22.50%</td>
<td>35.29%</td>
</tr>
<tr>
<td>CT Chest Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>40</td>
<td>50%</td>
<td>78.4%</td>
</tr>
<tr>
<td>Indeterminant</td>
<td>9</td>
<td>11%</td>
<td>17.64%</td>
</tr>
<tr>
<td>Atypical</td>
<td>2</td>
<td>2.5%</td>
<td>3.92%</td>
</tr>
<tr>
<td>Absent</td>
<td>29</td>
<td>36.25%</td>
<td>56.86%</td>
</tr>
<tr>
<td>CT Severity Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31</td>
<td>38.75%</td>
<td></td>
</tr>
<tr>
<td>Up to 5</td>
<td>23</td>
<td>28.75%</td>
<td>46.93%</td>
</tr>
<tr>
<td>6 to 10</td>
<td>7</td>
<td>8.75%</td>
<td>17.94%</td>
</tr>
<tr>
<td>11 to 15</td>
<td>11</td>
<td>13.75%</td>
<td>28.20%</td>
</tr>
<tr>
<td>16 to 20</td>
<td>8</td>
<td>10%</td>
<td>20.51%</td>
</tr>
<tr>
<td>21 to 25</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

(7.5%), thoracic lymphadenopathy in 19 patients (23.75%) and other nonspecific findings like granuloma, cyst, hemangioma etc. in 7 patients (8.75%). In our study population CT chest done at various phase of disease with an average time duration from onset of illness to date of CT imaging was found to be 6.7 days. In this scenario 46 patients (57.5%) radiologically examined in early phase, 19 patients (23.75%) in intermediate phase, 15 patients (18.75%) in late phase of disease progression (graph 9). In early phase of disease (<5 days), among radiologically positive patients (32 out of 46) 59.37% patients had GGO while remaining 40.63% had both GGO and consolidation in imaging of HRCT chest. In intermediate phase of disease (6-10 days), among radiologically positive patients (11 out of 19) 45.45% patients had GGO while remaining 54.54% had both GGO and consolidation in imaging of HRCT chest. In late phase of disease (>10 days), among radiologically positive patients (8 out of 15) 12.50% patients had GGO, 75.00% patients had both GGO and consolidation (figure 5) while remaining 12.50% patients had only consolidation in imaging of HRCT chest (graph 10).
Discussion

The dread and specter of COVID-19 made its first appearance in Wuhan, China and it has spread like wildfire out and across precincts of China and across the globe with a pace that has taken everyone by surprise. Confirmed cases of COVID-19 is being reported from all corners of the world and subsequently World Health Organization (WHO) officially declared COVID-19 a pandemic on March 11, 2020 (16). Research is underway to understand more about transmissibility, severity, and other features associated with COVID-19.17 The virus, SARS-CoV-2, of COVID-19 has been found to have higher levels of transmissibility with higher potential of pandeminci, as the effective reproductive number (R) of COVID-19 (2.9) is estimated to be higher than the reported effective reproduction number (R) of SARS (1.77) at this early stage.18 The SARS-related coronaviruses are covered by spike proteins that contain a variable receptor-binding domain (RBD). This RBD binds to angiotensin-converting enzyme-2 (ACE-2) receptor found in the heart, lungs, kidneys, and gastrointestinal tract19 thus facilitating viral entry into target cells. Based on genomic sequencing, the RBD of SARS-CoV-2 appears to be a mutated version of its most closely related virus, RaTG13, sampled from bats (Rhinolophus affinis).20 The mutation increased the RBD affinity to ACE-2 in humans. Binding of the SARS-CoV to the angiotensin-converting enzyme 2 (ACE-2) receptors in the type II pneumocytes in the lungs triggers a cascade of inflammation in the lower respiratory tract.21 It has been demonstrated that when the SARS spike protein binds to the ACE-2 receptor Pathogens, the complex is proteolytically processed by type 2 transmembrane protease TMPRSS2 leading to cleavage of ACE-2 and activation of the spike protein,22 similar to the mechanism employed by influenza and human metapneumovirus, thus facilitating viral entry into the target cell. It has been suggested that cells in which ACE-2 and TMPRSS2 are simultaneously present are most susceptible to entry by SARS-CoV.23 Early indications are that SARS-CoV-2 virus also requires ACE-2 and TMPRSS2 to enter cells.24 Viral entry and cell infection trigger the host’s immune response, and the inflammatory cascade is initiated by antigen-presenting cells (APC). The process starts with the APC performing two functions: (1) presenting the foreign antigen to CD4 + T-helper (Th1) cells, and (2) releasing interleukin-12 to further stimulate the Th1 cell. The Th1 cells stimulate CD8 + T-killer (Tk) cells that will target any cells containing the foreign antigen. In addition, activated Th1 cells stimulate B-cells to produce antigen-specific antibodies. It is apparent that COVID-19 infection occurs through exposure to the virus, and both immune suppressed and normal population appear to be susceptible. Some studies have reported an age distribution of adult patients between 25 and 89 years old. Most adult patients to be afflicted have been observed to be in age range of 35 and 55 years.25 A study on early transmission dynamics of the virus has reported the median age of patients to be 59 years, ranging from 15 to 89 years, with majority (59%) patients affected being male.26 It has been suggested that population most at risk may be people with poor immune function such as older people and those with renal and hepatic dysfunction.26

In the present study an attempt was made to outline distribution of age, gender, clinical features at presentation, co morbidity of patients, HRCT chest findings in COVID-19 patients, severity of patients on the basis of CT imaging and their correlation with symptomatology and comorbidity of patients to put diagnostic, therapeutic and prognostic tools for COVID-19 disease. A total of 80 patients were analyzed along the course of the study. Most of COVID-19 patients of our study group in SMS Medical College Hospital, Jaipur, Rajasthan were in their fourth to sixth decades of life with mean age of 50.40 year and male gender was affected more as compared to females, with an average sex ratio being 0.69 in our study group. In symptomatic patients, fever and cough were the most common presenting features, followed by shortness of breath, sore throat and headache while few patients also presented with chest pain and non-respiratory symptoms like pain abdomen, fatigue, joint pain, altered sensorium, etc. In our study group nearly one third of asymptomatic patients were found to be radiologically positive. This small percentage of asymptomatic COVID-19 patients, act as major carrier for transmission of virus in society, poses a real diagnostic and containment challenge for health care professionals. It was observed in the present study co morbidities have a tangible impact on clinical characteristics and course in COVID-19 positive patients. It has been observed that COVID-19 patients have circulatory and endocrine co morbidities. Patients with at least one or more co morbidity have been reported with poor clinical outcomes. In the present study population 54% patients had underlying co morbid disease with multiple co morbid diseases being was more prevalent. The most prevalent co morbidity observed in present study was Diabetes mellitus in followed by Hypertension, Chronic obstructive pulmonary disease (COPD)/Old K-chest, Coronary artery disease (CAD) and other diseases like hypothyroidism, anemia, CVA etc.

Currently the diagnosis of COVID-19 in clinic is dependent on the detection of SARS-CoV-2 nucleic acid by RT-PCR. However, it was reported that the accuracy rate is lower because it can be influenced by the viral load, the stage of the disease and the quality of specimens obtained from the upper respiratory tract.27 The prominent radiological feature of COVID-19 is bilateral ground glass opacity in the chest CT scans.28 In this study, we assessed the involvement of lungs with CT chest images, in which nearly two third patients (63.75% patients) had positive CT findings while less than half of patients (48.755) were symptomatic. CT severity score of asymptomatic radiologically positive patients was found to be <5/25. In present study more than three fourth of patients among radiologically positive patients had Typical CT chest images findings which includes GGO in bilateral, peripheral and lower lobe predominance distribution of opacities. Symptomatic clinical presentation higher (69.23%) in patients who had Typical COVID-19 findings in CT images while it was lower in indeterminate and atypical CT findings. Patients who had typical CT findings mostly presented symptomatically. Severity of clinical status of COVID-19 patients correlated with CT severity index, average CT severity index of our study population had been found 8.44. The clinical status of patients
correlated with the CT severity score, with mild cases showing score <15/25 in 45.83% patients and severe cases showing CT severity score >15/25 in 87.50% patients. As CT severity index raised clinical status of patients deteriorated hence this show poor prognostic indicator for COVID-19 patients. At present, the judgment of the patient’s condition mainly depends on symptoms and signs, blood oxygen saturation, etc., while CT images are not used as a main reference index. When the disease develops rapidly, the probability of death is greatly increased. However, we found that CT imaging changes in some patients, especially young patients, appears before the onset of signs and symptoms due to the differences in tolerability. We scored the chest CT imaging and found that clinically severe patients showed higher CT imaging score compared to that in non-severe patients. These data suggested that CT imaging score may be an informative indicator to predict the severity of the disease. In the early stages, single or multiple small ground glass infiltration, consolidation, and interstitial thickening could be seen. As the disease progressed, severe cases had more consolidation and air bronchograms in the involved lobes.

The diffuse lesions, shown as “white lungs,” were seen in the most severely affected patients. Fibrous bands could be seen during the remission stage. The distribution manners, together with the GGOs, are very characteristic and impressive. Cautious attention to symptoms and CT examination, are helpful for early detection of COVID-19 infection. Especially for those who were unaware of the concealed discomfort, HRCT can assist clinicians and epidemic workers with finding potentially infectious patients. However, the Fleischner Society guidelines suggested that imaging is not routinely indicated in asymptomatic or mildly symptomatic patients of COVID-19. This was corroborated by our study where 29/80 patients who were asymptomatic or who underwent CT in early phase of the disease showed no CT features of COVID-19 pneumonia.

HRCT chest of our study population showed variety of opacity characteristics, among radiologically positive patients nearly half of patients showed typical GGO while another half showed mixed pattern of GGO and consolidation. Mostly early CT on admission characterized by GGO and in late stage consolidation tends to be more dominating than GGO. The distribution of these lesions in our study was mostly peripheral and posterior involving the lower lobes more frequently. The predilection for these areas has also been reported previously. In patients who were imaged in the later stage of disease, findings such as vacuolations within opacification, linear consolidation and reverse halo sign were seen suggesting organization of the underlying disease process. Subsequently, subpleural sparing and curvilinear bands appeared likely due to retraction process suggesting resolution stage. In our experience, even if the total percentage area of lung involved remained the same, appearance of features such as vacuolation, subpleural sparing and curvilinear band formation indicated resorption stage and even corroborated with clinical features of improvement. A long-term follow-up of these patients should be done to assess if these findings completely resolve or some evidence of fibrotic changes persists.

The data collected at our hospital indicates that CT findings vary according to the time of scan from the onset of illness. This concurs with the results observed by Bernheim et al and Pan et al who suggested progression of disease in the form of GGOs in early stage to “crazy-paving” and consolidation in later stages. In addition, the CT findings also correlate with clinical status, showing a higher CT severity score in clinically worse patients. Thus, the percentage involvement of lung and CT severity score can help prognosticate and tailor the clinical management of patients. In radiologically positive patient multiple lobe affection by COVID-19 has been more popular compare to other bacterial or lobar pneumonia, among them nearly two third patients had more than two lobe involvement with bilateral lung affection in 76% patients. Most of radiologically positive COVID-19 patients (96%) had complete or some posterior surface involvement while nearly one third patients had mixed involvement of anterior and posterior surface of lung. As per view of axial distribution most of patients (nearly 88%) had peripheral distribution of opacities in COVID-19 positive patients. CT chest imaging also showed some specific findings which includes pleural effusion, pulmonary nodules, thoracic lymphadenopathy and other nonspecific findings like granuloma, cyst, hemangioma etc. In present study duration of disease correlated with CT chest characteristics and CT severity index. In these patients average CT severity index remained same in each phases of disease while opacities characteristics especially GGO and consolidation varied in different phases of disease. GGO, a characteristic feature of initial stage of disease found maximum in early phase of disease while in intermediate and late phase of disease proportional pure GGO reduced. In intermediate phase nearly half of patients had both GGO and consolidation on CT images while rest half had pure GGO pattern. In late stage nearly three fourth patients had both GGO and consolidation while remaining patients had pure GGO or consolidation in equal proportion. These characteristic changes were in favor of resolving pneumonia. No significant difference was observed in distribution of opacities and involvement of particular lobe or surface with progression of disease.

Conclusion

The varied spectra of COVID-19 presented with fever, cough, shortness of breath, sore throat etc. Diabetes mellitus, hypertension, COPD/K-Chest and CAD were found as major comorbid condition. Clinical severity of disease was higher in patients that had underlying co morbid disease, especially in patients with multiple co morbid conditions. HRCT chest in COVID-19 patients had major diagnostic and prognostic importance as positive CT findings more prominent in symptomatic patients and co-morbid patients. CT severity index also directly correlated with clinical symptoms of patients. CT imaging useful to see clinical recovery of patients. The results of this study confirmed that chest CT is important in the diagnosis and management of the COVID-19 infection. Despite meticulous treatments, most patients demonstrated progressions in the early stage from illness onset, according to the follow-up CT examinations. Our clinical findings show that radiological features positively correlate with the severity of lung abnormalities quantified on
initial CT. Being familiarized with the clinical and CT features and the early changes of the COVID-19 infection is of paramount importance.

Limitations: This study has some limitations. First, this is a modest-sized case series of patients admitted to the hospital. At the time of data collection, RT-PCR tests for the diagnosis of COVID-19 had been available only for suspected patients. Besides, we only included hospitalized patients for their clinical and CT correlation with follow-up CT examinations to ensure more information on clinical and CT characteristics. Possible selection bias should be noted, and further study of a larger cohort is required to obtain a definitive answer. Second, the quantitative and semiquantitative methods for measuring the pulmonary lesions may have certain subjectivity. Third, the susceptibility of COVID-19 was considered (initially and incorrectly) to be very low among infants, children, and adolescents, so we did not retrospectively study these groups. Fourth CT imaging not be possible in severely or critically ill patients. More effort should be made to identify the clinical and imaging features in these groups in future studies.

Ethical approval: Approval was not required.

Author contributions: S. Bhandari, A. Singh and G. Rankawat formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; M. Bagarhatta and Aparna Singh do HRT chest and radiological examination of patients. S. Bhandari, G. Rankawat, M. Bagarhatta refined the search strategy by conducting interactive database queries and incorporating new search terms; G. Rankawat, Aparna Singh, V. Gupta collected and analysed data; S. Bhandari and A. Singh, conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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Availability of data and materials: The data that support the findings of this study are available from the corresponding author [Dr. Govind Rankawat, Email ID goivindrankawat@gmail.com], upon reasonable request.

Declaration of competing interest: All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

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References

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Impact of COVID–19 Pandemic on Oncology Practices During Nationwide Lockdown Period: A Single Centre Experience and the Way Forward

Deepak Sundriyal1*, Amit Sehrawat1, Parmod Kumar2, Rekha Bhandari3

Abstract

**Background:** The COVID-19 pandemic has posed a grave challenge to mankind as it doesn’t appear to get controlled in the near future. Worldwide, healthcare centers are working more than their capacity with the scarcity of medical resources. Cancer patients are considered to be at higher risk of developing life-threatening complications from COVID-19 and at the same time treatment delays can lead to poorer oncological outcomes. Appropriate planning is therefore important to continue with cancer treatment services and simultaneously avoiding the risk of infection to the patients and healthcare staff and not allowing community transmission of viral infection.

**Methods and Results:** We modified our practice measures in cancer patients receiving systemic therapy. Tele-consultations and use of electronic means, providing the best supportive care at or near home, and involvement of local/family physicians were widely practiced. We minimised in-patient admissions, however, day-care chemotherapies were continued to provide optimum oncology services.

**Conclusions:** Modified oncological practice measures need to be implemented as the pandemic seems to stay for a longer time.

Introduction

A viral illness was reported in late December 2019 from Wuhan city of China which was identified and designated as novel coronavirus 2019-nCoV or COVID – 19. World Health Organisation (WHO) declared COVID – 19 outbreaks as pandemic on March 11, 2020. India reported its first positive case of COVID-19 infection on January 30, 2020. As a preventive measure, a nationwide lockdown was announced by honourable Prime Minister on March 24th, 2020. As a result of this, routine medical services were modified as per the advisory issued by competent authorities from time to time.

COVID–19 pandemic has created a cosmopolitan risk of morbidity and mortality, and it has become a double-edge sword for cancer patients as well as clinicians. On one end, cancer patients are more vulnerable to severe illness and death. Early reports from China stated that patients with malignancy affected by COVID–19 had a fivefold risk of severe events (a composite endpoint defined as the percentage of patients being admitted to the intensive care unit requiring invasive ventilation, or death) as compared to patients without malignancy. They also demonstrated poorer outcomes from COVID-19 in malignancy patients.1 A possible role of increased susceptibility to COVID–19 infection played by immunosuppression frequently seen in malignancy patients cannot be negated.2 On the other end, delaying malignancy treatment could lead to poorer oncological outcomes. Delaying cancer surgeries can lead to upstaging and some tumors could lead to obstruction, perforation, risk of bleeding, organ failure or metastasize.

Similarly, delaying neo-adjuvant and adjuvant chemotherapy could lead to upstaging or relapse of the tumor. Delaying palliative chemotherapy could lead to worsening of quality of life.

So continuing with routine cancer care could lead to increased risk of transmission of COVID-19 to cancer patients as well as community spread while at the same time suspension of cancer care could lead to poorer oncological outcomes which would have been ricocheted as increased burden after some time.

A timely and sagacious decision depending upon the various parameters can lead to the delivery of oncology services so that oncological outcomes are preserved as anticipated and simultaneously not subjecting patients to increased risk of infection and poorer outcomes as well as community transmission.

All India Institute of Medical Sciences (AIIMS), Rishikesh is a tertiary care center in Uttarakhand. AIIMS Rishikesh provides cancer treatment in a radius of almost 300 kilometers. We present out data of medical oncological practices in cancer patients during the nationwide lockdown.

**Methods**

We anticipated this situation well advance in time and an urgent meeting of medical oncologists and haematologists was held. Since a section of faculty, residents, and other healthcare staff was already segregated for COVID–19 pool care, we had to use our manpower judiciously. We discussed various clinical presentation
Table 1: Patient’s characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients seen during lockdown period</td>
<td>107</td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
</tr>
<tr>
<td>Female</td>
<td>60</td>
</tr>
<tr>
<td>Patients from Uttarakhand</td>
<td>61</td>
</tr>
<tr>
<td>Patients outside Uttarakhand</td>
<td>46</td>
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<tr>
<td>Stage</td>
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</tr>
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<td>5</td>
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<td>II</td>
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<td>III</td>
<td>41</td>
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<tr>
<td>IV</td>
<td>50</td>
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<tr>
<td>Treatment Setting prior Lockdown</td>
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<td>Neo-adjuvant Chemotherapy</td>
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<tr>
<td>Adjuvant Chemotherapy</td>
<td>27</td>
</tr>
<tr>
<td>Palliative therapy including best supportive care</td>
<td>46</td>
</tr>
<tr>
<td>Follow up</td>
<td>4</td>
</tr>
<tr>
<td>Evaluation</td>
<td>10</td>
</tr>
<tr>
<td>Patients reporting difficulties during Lockdown</td>
<td></td>
</tr>
<tr>
<td>Outside Uttarakhand</td>
<td>44</td>
</tr>
<tr>
<td>From Uttarakhand</td>
<td>37</td>
</tr>
</tbody>
</table>

of the cancer patients including the stage of the disease, stage of the treatment, performance status, comorbidities, biology of the disease, anticipated survival in cases of advanced-stage disease, availability of cancer treatment and other healthcare facilities near patient’s home, distance traveled by patient to reach tertiary care center and availability of vehicle during lockdown period.

We divided practice measures into 3 categories, namely patient-centric measures, hospital and health care professional centric measures and treatment centric measures. Patient-centric measures included (1) telephonic conversation with the patient and to counsel them to call their respective clinician prior visiting the hospital, (2) strictly following social distancing after leaving home and on arriving at hospital, (3) patient and attendant wearing face mask, (4) screening of patient for any COVID–19 related symptoms. Hospital and health care professional centric measures included (1) social distancing and application of personal protective equipment (PPE), wherever required (2) merging of day-care facility to common ward area, (3) reducing manpower (doctors, nurses, ward staff) to bare minimum and allowing only one set of workers to be involved in direct patient care; in case one set gets infected and quarantined, another set can replenish the workforce capacity. Treatment centric measures included, (1) discontinuation and/or change to oral therapies in cases wherever expected survival was limited or less than 6 months based on factors like advanced stage, patients on 2nd or subsequent line therapies, poor performance status, (2) discontinuation of maintenance chemotherapy in metastatic cancers, (3) Continuation of neo-adjuvant and adjuvant therapies, (4) continuation of emergency services, (5) to receive end of the life care and best supportive care (BSC) at home or a nearby facility wherever feasible, (6) shifting prolong infusional protocol to day-care therapies by allowing comparable efficacy protocol wherever feasible (E.g. Change of FOLFOX to CAPEOX), (7) shifting to longer interval protocols thereby minimising hospital visits wherever possible (E.g. changing dose dense paclitaxel/carboplatin to 3 weekly protocol in carcinoma ovary), (8) admitting patients on alternate beds thus maintaining adequate distance between them and limiting number of attendants per patient to 1, (9) counselling patients to receive last cycles of chemo therapy to a nearby facility wherever feasible, (10) and delaying routine follow up/visits and providing telemedicine consultations for follow up.

Data of all the patients attended in the hospital or through telemedicine was compiled as a cross-sectional study. This included demographic profile, treatment received prior lockdown, treatment modified during lockdown, and subsequently, challenges faced by patients. The study was approved by the institutional research committee.

Results

One hundred and seven patients were attended during the lockdown period (Table 1). These included 98 previously registered and 9 newly registered patients. There were 60 females and 46 male patients Forty-six patients were from states outside Uttarakhand. Most of the out stationed patients reported difficulties like commuting to the hospital due to the non-availability of conveyance and laboratory services. These difficulties were reported only by 37 out of 61 patients from the Indian state of Uttarakhand.

Thirty-one patients who were on palliative chemotherapies with limited expected survival and 1 new patient planned for neo-adjuvant chemotherapy were deferred for the initial period of lockdown. Seven patients were advised to continue chemotherapy at a nearby medical facility. Chemotherapy with curative intent was continued for 14 patients in our day-care and ward. BSC was advised to 8 patients nearby their home after consulting telephonically with their local physician. Three patients were provided supportive care in the ward. Last cycle of adjuvant chemotherapy in a patient of carcinoma ovary was discontinued permanently in the view of the patient’s inability
to travel up to the hospital and non-availability of oncology facility near her home.

Patients already on oral chemotherapy and hormonal therapy prior to lockdown were advised to continue the same telephonically after reviewing their reports on WhatsApp and email. Twenty-one patients were shifted to oral chemotherapy from intravenous therapy on subsequent consultation and advised to follow up telephonically.

Patients who were on follow up and those completing their treatment were advised to follow up telephonically or via email. Long infusional protocol was changed to day-care protocol in 2 patients, while weekly protocol was changed to 3 weekly protocol in 6 patients of carcinoma ovary (Figure 1).

Discussion

Currently, there is no evidence regarding the effectiveness of any drug against COVID-19 infection, and the availability of vaccine in the near future is a remote possibility. At present, it is predicted that the pandemic will continue for several months and we have to find a way forward as far as parallel medical care for cancer patients is concerned. To provide optimum systemic treatment to cancer patients is an uphill task for physicians because of the following reasons. Dedicated centers providing cancer treatment are in very limited numbers in India and many patients travel from one state to another for the same. Evaluation and planning of treatment for a cancer patient is a lengthy process and requires multi-modality inputs and multiple visits. Treatment itself is delivered in multiple steps and cycles. Regular follow up is an essential component of cancer care. It has to be kept in mind that curative intent treatment should not get compromised simultaneously maximizing the safety of health care staff and judicious utilization of resources. Moreover, every possible effort has to be done to provide palliative care treatment keeping in balance the quality of life of patients and the safety interests of the community.3

We suggest following adaptation of practices for a balanced approach amidst the ongoing pandemic. The intention is to decrease the length of stay so that unnecessary exposure with patients and attendants is avoided.

- Evaluation should complete as early as possible.
- Multi-disciplinary tumor board meetings should be held on virtual platforms.
- Cut down referrals to other specialties wherever possible. However, this should not compromise an essential component of routine care.
- All curative intent treatments should continue. Weekly protocols should be replaced with longer interval protocols wherever feasible without compromising the efficacy. Similarly, day-care protocols should be preferred in place of long duration infusional protocols.
- All palliative chemotherapies should continue where expected survival is more than 6 months. Every attempt should be made to consider oral therapy wherever feasible. Oral therapy may be advised for 2 or 3 cycles in a single visit with interval evaluation done via teleconsultations or electronic means.
- Every attempt should be made to provide BSC at a patient’s home or a nearby facility. This may require frequent teleconsultations with the patient’s caregiver and family or local physician. A comprehensive discussion should be done with the patient’s caregiver in this regard.
- Follow up visits in person should be limited and at longer intervals. Telemedicine or electronic communication should be emphasized if patients general condition is fair and investigations do not suggest a change in advice.
- Restrict the manpower of healthcare staff directly involved in patient care to bare minimum.
- Training of healthcare staff to meet the needs of the time and continuous update/dispense of newly generated information.
- Needless to say, basic hygiene, the use of protective equipment, and social distancing should be a norm.

Conclusions

Corona virus is anticipated to stay for a longer period. Modified oncological practice measures need to be implemented so as to continue with optimum patient care.

List of abbreviations

AIIMS: All India Institute of Medical Sciences; BSC: Best Supportive Care

References

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Clinical Utility of Ambulatory Blood Pressure Monitoring (ABPM) in Newly Diagnosed Hypertensive Patients

Santosh B Salagre1*, Anup P Khobragade2

Abstract

Background: Ambulatory Blood Pressure Monitoring (ABPM) has an upper hand in diagnosing hypertension accurately. Parameters obtained by ABPM helps us in diagnosing white coat hypertension, BP variability, dipping status and blood pressure load on organs (Hyperbaric Index) reflecting possible end organ damage.

Objectives: To evaluate clinical utility of ABPM in stage 1 newly diagnosed hypertensive subjects, to compare ABPM readings with clinic blood pressure (Clinic BP), to study dipping pattern and White Coat Hypertension (WCH) in newly labeled hypertensives.

Methodology: After institutional ethics committee approval and written informed consent from participants, an observational cross sectional prospective study was conducted in hypertension clinic of tertiary care hospital over a period of one and half years on 138 newly diagnosed stage I hypertensive patients. ABPM results were analyzed and compared with clinic BP.

Results: 86/138 (62.32%) patients were diagnosed to have true HT by ABPM. WCH was detected in 52/138 (37.68%) which is higher than that reported in international studies (21%). The mean pulse, mean systolic/diastolic BP, mean pulse pressure and MAP were significantly higher (p<0.0001) by clinic BP than ABPM. True hypertensive patients were having higher weight (p <0.001), had higher fasting blood sugar values (p=0.008) and BUN levels (p=0.034) than WCH patients. Hyperbaric Index was significantly higher for systolic and diastolic BP in true hypertensive patients as compared to WCH patients. Patients with WCH were predominantly males (71.15%), were younger (41.82 ± 12.77 years) than true hypertensives (46.45 ± 12.20years), (p =0.037). Dipping was detected in 33 (38.37%), non-dipping in 44 (51.16%) and reverse dipping in 9 (10.47%) patients.

Conclusion: Our study reflects the clinical utility of ambulatory blood pressure monitoring not only for accurate diagnosis of hypertension but also for assessing the various parameters of blood pressure.

Introduction

Blood pressure (BP) is a quantitative trait with a normal, continuous, bell shaped (Gaussian) distribution pattern, skewed to the upper end in general population. Hypertension represents a clinical definition of the upper part of the distribution curve. The JNC VII defines hypertension as office blood pressure of 140/90 mm Hg. Hemodynamic subtypes of hypertension should be taken into consideration, namely, systolic hypertension in young adult, diastolic hypertension in middle aged and isolated systolic hypertension in elderly. General approach to a patient includes accurate measurement of BP with standard procedure. In office setting the chances of misdiagnosing patients with white coat hypertension, masked hypertension and white coat effect are high. This can lead to under or over treatment of patients.

The European guidelines8 in their recent work, propose an alternative definition of white-coat hypertension, which encompasses subjects with office systolic/diastolic blood pressure readings of ≥140/90 mmHg and a 24-hour blood pressure <130/80 mmHg. Indeed, patients with white-coat hypertension may share characteristics with bona fide high-normal blood pressure like progression over a short interval of time to sustained hypertension2,3 and increased cardiovascular risk compared with a normotensive comparator group. Sung et al4 reported that white-coat hypertension might be riskier than prehypertension. A subsequent 2009 PAMELA5 report demonstrated that untreated subjects with white-coat hypertension more frequently developed sustained hypertension, suggesting the potential for increased long-term risk. Similar results were shown by the Ohasama6 study but it used home blood pressure to monitor the blood pressure.

It would seem that nocturnal BP is more related to risk than to its diurnal counterpart, and that circadian variability can refine the evaluation of hypertension risk.7,8 If the physiological fall in BP is <10% during night time, it is defined as non-dipping and is associated with increased risk of stroke, end-organ damage, and cardiovascular events including death. The MAPEC study (Prognostic Value of Ambulatory Blood Pressure Monitoring in the Prediction of Cardiovascular Events and Effects of Chronotherapy in Relation to Risk) was one of the first prospective studies to assess the prognostic value of ABPM parameters over a sufficient follow up duration.

Several papers have suggested that 24-hour mean blood pressure (BP) is superior to office BP in relation to hypertension target organ damage. A large number of studies9,10 have almost invariably shown, on a cross-sectional basis, the organ damage accompanying
hypertension is more closely related to 24-hour mean than to office BP regardless of whether the damage is quantified in the heart (left ventricular hypertrophy or dysfunction), in the kidney (proteinuria), in the brain (cerebral lacunar or white matter lesions), in the small and large arteries, or by a comprehensive organ damage score.\textsuperscript{10,11}

Hyperbaric index i.e. the blood pressure load consistently taken by the organs, is considered to be a predictor for end organ damage. This should, therefore, be determined in order to predict and prevent the end organ damage by controlling the blood pressure.

**Material and Methods**

**Study design**

After obtaining institutional ethics committee permission and written informed consent from patients this observational, prospective study was conducted over the period of 18 months i.e. May 2015 through November 2016. Patients included in the study were aged between 18 to 80 years willing to give consent and were newly labeled to have hypertension (JNC VII Stage1) as per clinic blood pressure measurement. Newly diagnosed Stage 2 hypertensives, patients clinically suspected to have secondary hypertension and pregnant females were excluded from the study.

The blood pressure of the study participants was measured by mercury sphygmomanometer in supine and sitting position on right and left upper extremity, two readings taken at 10-15 minutes interval and the mean reading of systolic and diastolic blood pressure was taken as clinic blood pressure. The participants enrolled were having their hypertensives, patients clinically hypertensive and pregnant females suspected to have secondary hypertension were excluded from the study.

Meditech ABPM 05 machine along with the software Easy-ABPM for Ambulatory Blood Pressure Monitoring was available with hypertension services of our institution. One-time ABPM was performed free of cost on study participants fulfilling inclusion-exclusion criteria. The study participants were explained about the ABPM technique in the language they understood. The ABPM cuff was applied on the left upper arm and the ABPM machine was tied at the level of waist with the help of available belts. Two to three manual pilot readings were taken through ABPM machine and patients were instructed to go home and come back the next day (after 24 hours) to the hypertension clinic. ABPM recordings of these patients were downloaded on a computer with Easy-ABPM software. The validation of Meditech Ambulatory Blood Pressure Monitors was done by AAMI/ANSI/ISO 11137-2:2013 (American National Standards Institute, International Standards Organization) and BHS (British Heart Society).

Hypertension was defined as per following criteria:

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office BP (JNC VII)</td>
<td>≥140 and/or ≥90</td>
<td></td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Daytime or awake</td>
<td>≥135 and/or ≥85</td>
<td></td>
</tr>
<tr>
<td>- Night time</td>
<td>≥120 and/or ≥70</td>
<td></td>
</tr>
<tr>
<td>- 24 hrs mean</td>
<td>≥130 and/or ≥80</td>
<td></td>
</tr>
<tr>
<td>Home BP</td>
<td>≥135 and/or ≥85</td>
<td></td>
</tr>
</tbody>
</table>

ABPM readings were considered satisfactory if, >14 daytime readings and >7 night time readings (>70 % to 85 %) were valid.

We analyzed the dipping phenomenon in our study. Normal dipping is defined as nocturnal fall of >10% and <20% of daytime values, corresponding to night/day BP ratio of >0.9, while non-dipping is absence of this nocturnal fall of BP. Extreme dipping is a fall in BP of >20% of daytime values and reverse dipping is increase in BP level during sleep to levels higher than in daytime. Hyperbaric impact of hypertension load calculated in ABPM report (termed as hyperbaric index) provides information on how long blood pressure is higher than normal and how much it is higher than upper limit of normal ambulatory blood pressure during ABPM.

Eligible patients were enquired about their symptoms, present and past medical history as well as personal habits, any significant family history, occupation and lifestyle. They were subjected to thorough clinical examination, including ophthalmic examination and routine laboratory investigations. The history, findings of the clinical examination and the available laboratory investigations were noted in the case record form.

**Statistical analysis**

The prevalence of white coat hypertensives and true hypertensives was expressed as percentage of total study population. Patient characteristics were expressed as Mean ± Standard Deviation (SD) for continuous variables and were compared using paired t-test. Frequencies were expressed as percentages for categorical variables. They have been compared using the chi-square test. Association between dipping phenomenon and end organ damage was assessed using the chi-square test. All reported p-values are two-sided and a p-value of <0.05 was considered to indicate statistical significance. All analyses were performed with software SAS, Version 9.3.

**Results**

This study was conducted as per protocol approved by Institutional Ethics Committee. The study was conducted over a period of 18 months in the hypertension clinic of tertiary care centre, 138 patients fulfilling Inclusion/Exclusion criteria were recruited in the study after written informed consent. Decade wise distribution in total 138 patients showed maximum patients in age group of 41-50 years and 51-60 years (41 in each group i.e. 29.71%). Out of total 138 patients, 72.46% were males and 27.53% were females. The mean age for males was 43.31 years and for females it was 48.65 years. In our study we found that patients <40 years had more weight (72.94 ± 13.22 Kg) as compared to patients in age group of 40-60 years (67.12 ± 12.91 Kg) and >60 years (63.9 ± 7.89 Kg). This difference was significant with p value of 0.022. The BMI in younger hypertensive patients was higher as compared to their elder counterparts; however the difference was not statistically significant. Young (<40 years) hypertensive subjects had higher waist circumference as compared to patients >40 years of age.

We compared various BP parameters related to Clinic Blood Pressure Measurements (CBPM) and ABPM in study population (N=138) and found that there was statistically significant difference between the various BP parameters i.e. pulse rate, systolic and
diastolic BP, mean arterial pressure and pulse pressure. The detailed results are depicted in Table 1.

ABPM reports of 138 patients were analyzed. It was found that 37.68% (52) patients were having White Coat Hypertension (WCH) and 62.32% (86) patients had True Hypertension (TH). Figure 1 shows typical WCH in one of our patients. Age wise, WCH patients were younger with mean age of 41.82 (± 12.77) years as compared to true hypertensives (TH) with mean age being 46.45 (± 12.20) years. This difference was statistically significant (p=0.037). Mean weight of WCH patients and TH patients was 63.98 (± 13.01) kg and 71.74 (± 12.21) kg respectively and this difference was statistically significant (p<0.001). Out of 52 WCH patients, majority i.e. 39 patients (75%) were <50 years of age with males being 71.15% (37) and females being 28.85% (15).

On comparing the systolic and diastolic BP by ABPM and CBPM we found that Mean Clinic Systolic BP in WCH patients was 144.39 (± 4.59) mm Hg and in TH patients was 149.12 (± 5.94) mm Hg. 24 hours mean SBP (ABPM) in WCH patients was 122.08 (± 5.46) mm Hg and in TH patients was 139.38 (± 9.20) mm Hg, the difference being statistically significant (p<0.0001). On comparing Mean Clinic Diastolic BP in WCH patients, 90.16 (± 4.35) mm Hg and that of TH patients, 92.54 (± 3.49) mm Hg, (p=0.001). Similar statistically significant difference (p<0.0001) was found on comparing 24 hrs mean DBP (ABPM) in WCH patients 75.56 (± 5.80) mm Hg and TH patients 87.19 (± 6.50) mm Hg.

The daytime systolic blood pressure in white coat hypertensives and true hypertensives was 125.8 (± 5.57) mm Hg and 143.0 (± 9.47) mm Hg respectively (p<0.0001). Day time diastolic blood pressure in white coat hypertensives and true hypertensives was 78.77 (± 6.23) mm Hg and 90.30 (± 6.92) mm Hg (p<0.0001). On comparing the night time systolic blood pressure in white coat hypertensives [114.7 (± 7.29) mm Hg] and true hypertensives [132.1 (± 11.01)] the p value was found to be <0.0001, suggesting lower night time BP values in white coat hypertensive patients. The night time diastolic BP was 69.04 (± 6.18) mm Hg in white coat hypertensives and 80.88 (± 7.99) mmHg in true hypertensives which was statistically significant (p<0.0001).

Considering systolic blood pressure, dipping was detected in 33 (38.37%), non-dipping in 44 (51.16%) and reverse dipping in 9 (10.47%) patients among TH patients (N=86). The mean daytime SBP in dippers [145.1 (± 8.43) mm Hg] was slightly higher than non-dippers [142.56 (± 9.91) mm Hg], (p=0.091). The mean daytime diastolic BP in dippers [92.67 (± 7.83) mm Hg] was significantly higher than non-dippers [89.43 (± 5.89) mm Hg], p=0.012. Mean night time SBP in non-dippers [136.0 (± 10.55) mmHg] was higher than dippers [125.9 (± 8.74) mmHg] with p<0.0001. The mean night time DBP in non-dippers [82.91 (± 7.05) mmHg] was higher than dippers [77.64 (± 8.46) mmHg], p=0.004. Figure 2 shows non-dipping phenomenon in one of our patients.

On comparing the laboratory parameters for dippers and systolic non-dippers we found that Serum Triglyceride levels were significantly higher in non-dippers (158.8 ± 64.40 mg/dl) as compared to dippers (130.2 ± 54.22 mg/dl) with p value of 0.031. Total Cholesterol levels in non-dippers were higher [180.6 (± 49.66) mg/dl] than dippers [167.4 (± 42.85) mg/dl], but not statistically significant (p=0.195). Serum LDL and HDL levels were comparable in both the groups (p= 0.099 and 0.404 respectively). On comparing laboratory parameters for dippers and diastolic non-dippers it was observed that Serum Cholesterol, Serum Triglyceride and Serum LDL levels were higher in non-dippers (179.2 ± 52.82, 155.3 ± 65.44 and 135.2 ± 40.98 mg/dl respectively) but not statistically significant (p= 0.491, 0.289 and 0.286 respectively). HDL levels were found to be low in non-dippers (34.78 ± 7.57 mg/dl) as compared to dippers (35.31 ± 5.43 mg/dl) but not statistically significant (p=0.708). Other parameters like haemoglobin, ESR, FBS, PLBS, BUN and Sr. Creatinine were comparable in both the groups with respect to both systolic as well as diastolic BP.

True hypertensive patients had significantly high systolic [286.02 (± 175.87)] and diastolic [223.36 (± 100.75)] Hyperbaric Index compared to white coat hypertension [Systolic and Diastolic, 53.15 (± 36.54)] and [61.75 (± 43.23) respectively]. In true hypertensive patients it was detected that younger patients had significantly higher diastolic HBI as compared to elderly hypertensive. The results of hyperbaric index in our study
population are shown in tables 2.1, 2.2, 2.3.

We observed that end organ damage was more in systolic non-dippers (N=53) as compared to dippers. In systolic non dippers, retinopathy was seen in (54.72%), followed by albuminuria (32.08%), increased echogenicity of kidneys on ultra sound (20.75%) and LVH on ECG (18.87%).

**Discussion**

The hypertension clinic of a tertiary care institute where this study was conducted had an annual patient load of approximately 2500 to 3000. Of these, newly diagnosed patients range from 250 to 300. Few of the patients attending hypertension OPD for the first time or referred to hypertension OPD by other specialties have moderately high levels of blood pressure (stage 1-JNC 7). As per clinic blood pressure measurements, such patients are labelled as hypertensive and are started on treatment as per standard guidelines. However, when these patients were subjected to ABPM, the results showed important diagnostic points which helped us in planning their further management.

In our study, we analysed various ABPM parameters and compared them with factors such as Clinic Blood Pressure Measurement, differentiating White Coat Hypertension –True Hypertension, dippers – non-dippers, and Hyperbaric Index. After thorough literature search we could not find a single study which analyzed all these parameters together. We have compared our results with available national/international studies related to few of the above parameters.

Our study population was divided according to the gender, age group (<40 years, 40-60 years and >60 years) and compared with respect to weight, BMI, waist circumference and waist/height (W/H) ratio. With maximum patients in the age group of 41-60 years, our study showed male preponderance. Also males presented at an early age as compared to females. Similar results were found in Korean Ambulatory Blood Pressure Monitoring Registry reported by Sook Kang et al. We found that younger patients (<40 years) had higher weight, BMI and waist circumference as compared to their elder counterparts. Similar results were obtained in Study of Association of Anthropometric Parameters of Obesity and Blood Pressure in Hypertensive Subjects in A Tertiary Care Hospital by Rubeena Bano et al from Lucknow.

The results of comparison between CBPM and ABPM reflect the utility of ABPM in measuring the different parameters of blood pressure. By comparing the various blood pressure parameters (pulse, systolic and diastolic blood pressure, pulse pressure and mean arterial pressure) in different age groups of the study population by ABPM and CBPM, we found that the difference was statistically significant in age group <40 years and those between 40-60 years. These findings may suggest us that the utility of ABPM is more in younger individuals as compared to elderly people. This is important particularly in our country, where the availability of ABPM machines is limited due to costs and other reasons. ‘Age’ can be one of the important factors in patient selection for ABPM in our country.

On analyzing the ABPM reports of total 138 study participants we found that 37.68% (52) patients had White Coat Hypertension (WCH) and 86 (62.32%) patients had True Hypertension (TH). Also, patients having WCH were younger and predominantly males. In a study by Pierdomenico SD et al conducted in 1995, out of 255 patients 21% (54) were found to have white coat hypertension. It is clear from above results that young male patients presenting with hypertension have more chances of having white coat hypertension. Anxiety, patient related factors, impact of clinic environment on temporary blood pressure surge in such individuals is responsible for WCH, and this important clinical aspect is detected by ABPM. 52 patients who were detected to have WCH were started on lifestyle modification, relaxation therapy, yoga sessions and were advised counseling for anxiety and other factors. By clinic blood pressure measurement method these 52 patients might have received antihypertensive medications since they were in stage 1 hypertension. The correct diagnosis of true hypertension by ABPM thus has significant impact on pharmacotherapy and cost of healthcare.

Night time blood pressure dipping can be well captured by the non-invasive technique of ABPM. In our study population, we studied the dipping phenomenon and divided the non-dippers according to systolic and diastolic blood pressure as literature does not mention if systolic or diastolic BP should be taken as the criteria for categorization. We included reverse dippers (9) in non-dippers as they are known to be associated with end organ damage. So, the total number of non-dippers was 53 [Non-dipper (44) + Reverse dippers (9)]. Considering systolic blood pressure, maximum patients had non-dipping (51.16%), while, for diastolic blood pressure, non-dipping was observed in 43.02% and reverse dipping in 4 (4.60%) patients. In a study reported by Verdecchia et al the prevalence of non-dippers in essential hypertension was 35%. These results signify the importance of ABPM in capturing night time systolic and diastolic BP, which would get missed by clinic blood pressure measurements. These findings are of clinical relevance. The cardiovascular adverse events occurring in hypertensive subjects can be explained by this sustained rise in blood pressure during night time in true hypertensive subjects who are non-dippers. Secondly, it also reflects the increased pressure in the vessels supplying vital organs for a sustained period of time, thus causing more target organ damage. Patients with

| Table 2.1: Hyperbaric Index (by ABPM) in study population (N= 138) |
|-----------------------------|-----------------------------|-----------------------------|
| Type of hypertension        | True hypertension (N=86)    | White coat hypertension (N=52) | p value |
| HBI for systolic BP (± SD) mm Hg | 286.02 (± 175.87) | 335.15 (± 164.54) | <0.0001 |
| HBI for diastolic BP (± SD) mm Hg | 223.36 (± 100.75) | 61.75 (± 43.23) | <0.0001 |

| Table 2.2: Hyperbaric Index for systolic BP related to age groups |
|-----------------------------|-----------------------------|
| True hypertensives age group wise | HBI for Systolic BP (mm Hg) |
| <40 years | 297.88 |
| 40-60 years | 276.03 |
| >60 years | 152.28 |

| Table 2.3: Hyperbaric index for diastolic BP related to age groups |
|-----------------------------|-----------------------------|
| True hypertensives age group wise | HBI for Diastolic BP (mm Hg) |
| <40 years | 208.80 |
| 40-60 years | 227.75 |
| >60 years | 89.71 |
WCH and TH were compared with respect to laboratory parameters like haemoglobin (Hb), fasting blood sugars (FBS), blood urea nitrogen (BUN) and serum Creatinine, with statistically significant difference for FBS and BUN. Also systolic non-dippers had significant hypertriglyceridemia and higher total cholesterol levels as compared to dippers. On the other hand diastolic non-dippers had higher serum total cholesterol, triglycerides and LDL levels as compared with dippers. These results reflect the higher risk for development of end organ damage in non-dippers. Thus it is important to investigate non-dippers for predicting the risk for end organ damage and intervene accordingly.

Hyperbaric impact of hypertension load calculated in ABPM report provides information on how long blood pressure is higher than normal and how much it is higher than the upper limit of normal ambulatory blood pressure during ABPM. On analyzing the HBI in our study population we found that true hypertensive patients had significantly high systolic and diastolic HBI compared to white coat hypertension. This reflects the much higher blood pressure load on organs in TH patients, which predisposes them for developing end organ damage. In true hypertensive patients it was detected that younger patients had significantly higher diastolic HBI as compared to elderly hypertensive.

Conclusion

Our study is one of the few studies in India which has extensively studied the clinical utility of ambulatory blood pressure monitoring in newly detected hypertensive patients. The study results reflected that, young males are likely to have white coat hypertension. These demographic aspects can help in selection of patients for ABPM. In our study, non-dipping of blood pressure in sleep was closely associated with end organ damage, suggesting the need for proper timing of antihypertensive medications and adherence to treatment. Similar association is seen with increased hyperbaric index in younger true hypertensive patients and end organ damage which stresses the need for strict control of BP over 24 hours. Thus, while it is not possible by the conventional methods of BP measurement to observe these various parameters of BP, ABPM on the other hand helps the physician to evaluate these factors which may further act as a guide in management of these patients. ABPM prevents over diagnosis of hypertension and thus guides the physician about judicious use of investigations and anti-hypertensive medications.

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References

Clinical Utilization Pattern of Multiple Strengths of Glimepiride and Metformin Fixed Dose Combinations in Indian Type 2 Diabetes Patients

Unnikrishnan AG, Pandit K, George J, Venkataraman S, Abhyankar MV

Abstract

Background: In Indian clinical set-up, modern sulfonylurea, particularly glimepiride is still preferred as an add-on to metformin due to its efficacy, safety and cost effectiveness. In view of this, a case-based questionnaire survey was conducted to analyze the clinical utility of multiple strengths of glimepiride and metformin fixed dose combination in type 2 diabetes mellitus (T2DM).

Methods: The case-based questionnaire survey was conducted with 174 health care professionals across India to assess the use of glimepiride and metformin fixed dose combination according to age, duration of diabetes, body mass index (BMI), diabetes complications, concomitant medications like insulin, and statin.

Results: Overall, data from 2248 patients taking multiple strengths of glimepiride and metformin fixed dose combination were analyzed. All the doses were prescribed across all the age groups and irrespective of duration of diabetes. Overall, 1429 diabetes patients had body mass index (BMI) ≥25 kg/m², among which 1176 (81.6%) patients were receiving combination of glimepiride 1 or 2 mg and metformin 500 or 850 or 1000 mg. Glimepiride and metformin fixed dose combinations were among the preferred choices in various complications like neuropathy, retinopathy, nephropathy, peripheral vascular disease, diabetic foot and cardiovascular disease. Insulin and statins were co-prescribed in 17.3% and 28.8% patients, respectively. Hypoglycemic episodes were reported in only a minority of patients, even with higher doses of glimepiride and metformin fixed dose combinations.

Conclusion: Multiple strengths of glimepiride and metformin fixed dose combinations are beneficial in T2DM, irrespective of age, duration of diabetes, BMI, diabetes complications, use of concomitant medications such as insulin and statin. Glimepiride and metformin fixed dose combinations were not associated with a significant risk of hypoglycemia.

Introduction

India is considered a major center for the global diabetes epidemic, home to 77 million adults with diabetes and the largest contributor to mortality (>3 million) attributable to diabetes and related complications. Metformin and Sulfonylurea (SU) like Glimepiride are one of the key pharmacotherapeutic agents in T2DM management. Several studies have reported the superiority of combination therapy consisting of SU and metformin for effective diabetes management. Glimepiride and metformin may be an ideal combination therapy, which promotes insulin secretion, improves insulin resistance, minimizes medication burden, improves treatment adherence and being cost effective. A real-world study showed that diabetes patients on glimepiride were associated with good clinical efficacy, lower mortality with reduced cardiovascular event risk. Similarly, glimepiride and metformin fixed-dose combination therapy is more effective in glycemic control than metformin up-titration, and is well tolerated in T2DM patients inadequately controlled on low-dose metformin monotherapy. Also, the Indian consensus recommends that SUs, as add-on to metformin, is a reasonable option for countries with high disease prevalence and resource constraints. In India, glimepiride and metformin fixed-dose combinations are widely used due to its availability in multiple strengths. This provides an ease of up-titration and down-titration for practicing physicians. To the best of our knowledge, no study has assessed the clinical usage pattern of multiple strengths of glimepiride and metformin fixed-dose combination in India. Therefore, a case-based questionnaire survey was conducted to analyze the clinical utility of multiple strengths of glimepiride and metformin fixed-dose combination in Indian T2DM patients.

Material and Methods

The case-based questionnaire survey was designed to assess the clinical utilization pattern of multiple strengths of glimepiride and metformin fixed-dose combination in T2DM. The survey questionnaire was administered to 174 health care professionals (endocrinologists, diabetologists, and physicians) across various geographical locations of India. Each doctor completed approximately 10 to 15 case profiles. A total of 2248 completed forms were collected and further descriptive analysis was performed. The results were expressed in percentages based on the responses for each question.

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Multiple strengths of glimepiride and metformin fixed-dose combination

Based on the strength of glimepiride in the combination, five groups were formed for analysis:

- Group 1 (Glimepiride 0.5 mg + Metformin 500 or 1000 mg)
- Group 2 (Glimepiride 1 mg + Metformin 500 or 850 or 1000 mg)
- Group 3 (Glimepiride 2 mg + Metformin 500 or 850 or 1000 mg)
- Group 4 (Glimepiride 3 mg + Metformin 850/1000 mg)
- Group 5 (Glimepiride 4 mg + Metformin 1000 mg)

Analysis parameters

The therapeutic utilization of multiple strengths of glimepiride and metformin fixed-dose combination was analyzed based on the age of the patient, duration of diabetes, Body Mass Index (BMI), diabetes complications, hypoglycemic episodes, and concomitant medications (insulin and statin).

Results and Discussion

Strength usage

Overall data from 2248 subjects was evaluated and the usage pattern is as shown in Figure 1. A strength of glimepiride 2 mg + metformin 500/850/1000 mg combination was most widely used in 44% diabetes patients, followed by strength of glimepiride 1 mg + metformin 500/850/1000 mg combination in 38%, a strength of glimepiride 0.5 mg + metformin 500/1000 mg combination in 9%, and glimepiride 3 mg + metformin 850/1000 mg combination in 7% patients; the least used strength was glimepiride 4 mg + metformin 1000 mg combination, in only 2% of diabetes patients.

Clinical usage pattern of multiple strengths of glimepiride and metformin fixed-dose combinations

Age of type 2 diabetes patients

Diabetes is a progressive disease and there exists a difference in the pathophysiology of T2DM in older and younger individuals. In India, unlike the western countries, diabetes is characterized by an early onset at a relatively young age, which might be due to insufficient β-cell mass, functional defects of β-cells, or both. Therefore, the American Diabetes Association (ADA) advises the use of early combination therapy including drugs with a complementary mechanism.

In our survey, 18.2% patients belonged to the age group of 18–44 years, 60.8% to the 45–64 years and 21% belonged to ≥65 years. The analysis showed that all the available strengths of glimepiride and metformin fixed dose combinations were safely prescribed for diabetes management in the young as well as the elderly population. In the elderly population (≥65 years), Glimepiride (1–2 mg) + Metformin (500–850–100 mg) combinations were the most commonly prescribed strengths by physicians (Table 1).

Duration of diabetes

The duration of diabetes has significant clinical and public health-related implications. Published evidence suggests that SUs may lose durability over the years due to β-cell exhaustion. However, SUs and metformin combination has been studied for glycemic control durability for 5 years and >10 years. A study by Srivanichakorn W et al., suggested that there is no rationale for withdrawing the SU component even after 17 years of combination therapy. In the most recent cardiovascular outcome trial (CVOT) CAROLINA, the median duration of diabetes at baseline was 6.3 years in the linagliptin group (n = 3001) and 6.2 years in Glimepiride group and later, medication exposure was 5.9 years in both the groups.

In the current survey, 5.71% of patients were newly diagnosed, 26.97% patients had diabetes for <5 years, 40.7% patients had diabetes for 5–10 years, and 19.88% patients had diabetes for >10 years. Results showed that all the strengths of glimepiride and metformin combination were used across diabetic patients irrespective of duration of diabetes. However, newly diagnosed patients and patients with <5 years of diabetes duration received relatively lower doses of glimepiride and metformin fixed dose combination, as compared to diabetes patients with >10 years diabetes duration. In group

Table 1: Usage of glimepiride and metformin fixed dose combinations based on age

<table>
<thead>
<tr>
<th>Groups (n)</th>
<th>18–44, n (%)</th>
<th>45–64, n (%)</th>
<th>≥65, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>120 (54.6)</td>
<td>70 (30.5)</td>
<td>34 (17.5)</td>
</tr>
<tr>
<td>Group 2</td>
<td>154 (21.1)</td>
<td>616 (82.5)</td>
<td>219 (29.4)</td>
</tr>
<tr>
<td>Group 3</td>
<td>19 (12.6)</td>
<td>96 (65)</td>
<td>35 (23.3)</td>
</tr>
<tr>
<td>Group 4</td>
<td>7 (3.0)</td>
<td>32 (59.3)</td>
<td>15 (27.8)</td>
</tr>
<tr>
<td>Group 5</td>
<td>196 (19.9)</td>
<td>517 (53.6)</td>
<td>219 (22.4)</td>
</tr>
</tbody>
</table>
1, 64.1% patients were newly diagnosed or had diabetes for <5 years, while 79% and 82% diabetes patients had diabetes duration of >5 years in group 4 and 5, respectively (Figure 2).

BMI of diabetes patients

Obesity is one of the major risk factors for T2DM. Being overweight and especially obese, particularly at younger ages, substantially increases the lifetime risk of diabetes. Data from clinical trials showed that long-term use of metformin stabilizes the BMI and improves body composition in the adolescent obese patients while the modern SUs are weight neutral.

In this survey, 16.9%, 19.5% and 63.6% of the diabetes patient population had BMI ≤23, 23–25 and ≥25 kg/m², respectively. Overall, 1429 diabetes patients had BMI of ≥25 kg/m², among whom 119 (8.3%) patients were on glimepiride 0.5 mg + metformin 500–1000 mg combination, 509 (35%) patients were on glimepiride 1 mg + metformin 500–850–1000 mg combination, 667 (46.6%) patients were on glimepiride 2 mg + metformin 500–850–1000 mg combination, 99 (6.9%) patients were on glimepiride 3 mg + metformin 850–1000 mg combination and 35 (2.4%) patients were on glimepiride 4 mg + metformin 1000 mg combination (Table 2). Our result was also in accordance with a SU’s consensus statement of South Asia (SAFES), which recommends the use of modern SUs (glimepiride) over conventional SUs even in overweight/obese T2DM patients.

Diabetes Patients with Complications

Diabetes patients are at risk of developing micro- and macro-vascular complications due to inadequate glycemic control as well as multiple cardiovascular (CV) risk factors. In the present survey among 2248 diabetes patients, 27% had neuropathy, 14.5% had retinopathy, 9.3% nephropathy, 6.3% had peripheral vascular disease, 6% had diabetic foot, while 15.7% had cardiovascular disease (CVD). In this population with diabetes related complications, multiple strengths of glimepiride and metformin fixed dose combinations were among the preferred choice of drugs for blood glucose control and to reduce diabetic complications (Table 3).

Concomitant Statin Therapy

Insulin monotherapy or combination therapy with an oral hypoglycemic agent may be considered for patients who are not adequately controlled, as manifested by a decrease in β-cell function in tandem with the duration of the disease. A study by Hea Yu et al., showed that administering glimepiride and metformin fixed dose combinations with insulin is relatively safe and effectively decreases glycated hemoglobin (HbA1c) and blood glucose levels in diabetes patients. In the current survey, only 648 patients (28.8%) were on statins. Statin treatment was used along with glimepiride and metformin fixed dose combinations in 24%, 25.6%, 32.8%, 26.7% and 31.5% patients in Group 1, Group 2, Group 3, Group 4 and Group 5, respectively. There is an urgent need to improve statin usage in diabetes patients, especially as primary prevention to ensure more cardio-protection.

Hypoglycemia in Diabetes Patients

Hypoglycemia is a major limiting factor in tight glycemic management.

### Table 2: Usage of glimepiride and metformin fixed dose combinations according to the body mass index (BMI)

<table>
<thead>
<tr>
<th>Groups (n)</th>
<th>BMI in kg/m² (Number of patients)</th>
<th>&lt;23</th>
<th>23–25</th>
<th>≥25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (196)</td>
<td></td>
<td>28</td>
<td>49</td>
<td>119</td>
</tr>
<tr>
<td>Group 2 (859)</td>
<td></td>
<td>164</td>
<td>186</td>
<td>509</td>
</tr>
<tr>
<td>Group 3 (989)</td>
<td></td>
<td>160</td>
<td>162</td>
<td>667</td>
</tr>
<tr>
<td>Group 4 (150)</td>
<td></td>
<td>20</td>
<td>31</td>
<td>99</td>
</tr>
<tr>
<td>Group 5 (54)</td>
<td></td>
<td>8</td>
<td>11</td>
<td>35</td>
</tr>
</tbody>
</table>

### Table 3: Use of different doses of glimepiride and metformin fixed dose combinations in diabetes patients with complication

<table>
<thead>
<tr>
<th>Groups</th>
<th>Diabetes Complications (Number of patients)</th>
<th>Neuropathy</th>
<th>Retinopathy</th>
<th>Nephropathy</th>
<th>Diabetic foot</th>
<th>CVD</th>
<th>PVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td>32</td>
<td>21</td>
<td>18</td>
<td>10</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td>177</td>
<td>94</td>
<td>57</td>
<td>35</td>
<td>87</td>
<td>40</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td>326</td>
<td>172</td>
<td>115</td>
<td>73</td>
<td>200</td>
<td>67</td>
</tr>
<tr>
<td>Group 4</td>
<td></td>
<td>62</td>
<td>32</td>
<td>15</td>
<td>16</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>Group 5</td>
<td></td>
<td>22</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

CVD: Cardiovascular disease; PVD: Peripheral vascular disease.

### Fig. 3: Insulin usage in patients on glimepiride and metformin fixed dose combinations

Statin treatment was used along with glimepiride and metformin fixed dose combinations in 24%, 25.6%, 32.8%, 26.7% and 31.5% patients in Group 1, Group 2, Group 3, Group 4 and Group 5, respectively. There is an urgent need to improve statin usage in diabetes patients, especially as primary prevention to ensure more cardio-protection.

Hypoglycemia in Diabetes Patients

Hypoglycemia is a major limiting factor in tight glycemic management.
of diabetes and may increase vascular events in addition to other possible detrimental effects. The risk of severe hypoglycemia is higher in the elderly patients. However, a consensus statement of South Asia recommends modern SUs (glimepiride) over conventional SUs in T2DM patients due to less risk of hypoglycemia.

In this case-based questionnaire survey, out of 2248 patients, only 142 patients (5.8%) experienced a hypoglycemic event (in the last 12 months); no hypoglycemia was observed in low-dose glimepiride 0.5 mg + metformin 500 mg combination group (Figure 4).

Conclusion
Glimepiride and metformin fixed dose combinations are widely used in clinical practice due to good glycemic control, minimal risk of hypoglycemia and weight gain, neutral nature with respect to cardiovascular risk, and cost effectiveness. The current case-based questionnaire analyzing data from 2248 patients showed that multiple strengths of glimepiride and metformin fixed dose combinations are prescribed in T2DM patients irrespective of age, duration of diabetes, BMI, diabetes complications, use of concomitant medications such as insulin and statins, and is devoid of risk of hypoglycemia.

Limitation
In our study, we could not correlate the glycemic control achieved by different glimepiride and metformin fixed dose combinations, as glimepiride and metformin fixed dose combinations have been prescribed with other oral antidiabetic drugs. Also, the daily frequency of dose administration was different for different patients and lastly, the duration of treatment period was not defined.

What’s New
• In clinical practice, high doses of glimepiride (2/3/4 mg) and metformin (500/850/1000 mg) fixed dose combinations are widely used even in patients with BMI ≥ 25 kg/m², highlighting its weight neutral benefit.
• In elderly population (>60 years), glimepiride and metformin fixed dose combinations are widely prescribed, highlighting the safety.
• High doses of glimepiride (2/3/4 mg) and metformin (500/850/1000 mg) fixed dose combinations are also used in combination with insulin, highlighting its weight neutrality and less hypoglycemic risk.

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Conflict of interest
There are no conflicts of interest.

Dr Abhyankar MV is an employee of USV Pvt Ltd.

Compliance with ethics guidelines
This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

References
Prognostic Factors for Adverse Outcomes in COVID-19 Infection

Zarir F Udwadia¹, Awatansh R Tripathi², Viral J Nanda², Shashank R Joshi³

Abstract
Whilst COVID-19 infection generally run a mild course in up to 80% of those affected, a number of pre-existing co-morbidities determine the severity of infection and the outcome in an individual patient. The most important of these co-morbidities that have consistently emerged in studies from across the globe, are the patients age and sex. Other important co-morbidities that adversely affect outcomes include pre-existing diabetes, obesity, hypertension, chronic lung disease and malignancy. This comprehensive review discusses the impact of these co-morbidities and the role of laboratory predictors of poor patient outcomes.

Introduction

When a new disease emerges it is crucial to know who is most at risk. Whilst COVID-19 infection generally runs a mild course in younger patients who have no other co-morbidities, it is now increasingly clear, 5 months into the pandemic, that patients with certain risk factors are disproportionately affected. This review attempts to analyse and study these factors.

1. Age: Age is widely observed to be the most important prognostic factor. Advanced age is associated with poor outcome in terms of: death, hospitalization, and Intensive Care Unit (ICU) admission. These findings have been consistent from the earliest studies conducted from the epicentre of this pandemic in Wuhan and continue to be observed in more recent studies.¹ ⁵

a. Death rates are directly co-related with advanced age: One of the earliest retrospective observations from 113 deaths due to SARS-CoV2 in a cohort of 799 patients admitted in Tongji Hospital in Wuhan, showed that the median age of deceased patients was 68 years, which was significantly older than the median age of 51 years in those who recovered. i.e. patients who died were 17 years older than those who recovered. Death rates were 83% in the age group of ≥ 60 years, 17% in 40-60 years, and 0 in patients < 40 years.¹ Another retrospective analysis of 201 patients in Wuhan revealed a statistically significant difference in mean age of the non-survivor and survivor group (i.e. 68 years vs. 50 years respectively with a p value > 0.001).²

A recent study of 5700 patients in New York also showed that with increasing age there was an increase in the duration of hospital stay, complications, ICU requirement, death and readmission, while there was a decrease in the chance of being discharged alive. Mortality was 0% in those < 19 years, in contrast to 48% in 80-89 years age group, 95% of patients were discharged alive in the 30-39 years age group, while only 36% of those > 90 years of age were discharged alive.³

b. Exponential rise in case fatality ratio over the age of 50: A model-based analysis was done to estimate severity of COVID-19. Individual-case data was collected for patients who died from COVID-19 in Hubei, mainland China, and for cases outside of mainland China.⁴ This study highlighted that the crude case fatality ratios obtained by dividing the number of deaths by the total number of cases can be misleading. Hence an infection fatality ratio was calculated which accounted for asymptomatic and mildly symptomatic patients who form the major bulk of COVID-19 disease. Here again there was a strong age gradient in the risk of death. Higher age was directly linked to death, with exponential rise over the age of 50 years. On binary division of age groups, death rates were 0.32% in the < 60 years age group and 6.38% in > 60 years age group. Highest death rate (14.8%) was seen in the age group > 80 years.⁴

c. Rate of hospitalization and ICU admission directly co-related with advanced age: In a retrospective, single-centre case series of the 138 consecutive hospitalized patients with confirmed COVID 19 at Zhongnan Hospital, Wuhan, a total of 36 (26%) patients required ICU admission. Median age of patients in the ICU was 66 years compared to 51 years in the non ICU group (p value <0.001).³

Rate of hospitalization was also higher in the older age group. The proportion of infected individuals hospitalized was higher as age advanced (50-59 years: 16%; 60-69 years: 11.8%, 70-79 years: 16.6%, and ≥ 80 years: 18.4%) in a model based analysis done on 799 patients.₅ Similar findings were replicated in a study from the United States.³

In conclusion age has consistently emerged as an independent risk factor of poor outcome, and patients above 50 years should be regarded as high risk patients.

2. Sex: Male sex has also been consistently observed as a risk factor for poor outcome. Male preponderance has been observed in the total number of cases, complications, and deaths amongst 799 COVID-19 pneumonia patients admitted at Tongji Hospital, Wuhan. Amongst patients who died, M:F ratio was around 7:3 from the 113 deceased.¹ In another retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China it was observed that 65.9%

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of all the deceased were male, while 34.1% were female (p value <0.24). Similarly of all the ARDS cases 71.4% were male and 28.6% were female (p value >0.05). Another study including 138 hospitalized patients showed the incidence of ICU admissions was 61% in males and 39% in female (p value 0.34). In Italy higher rates of complications were observed in males: 59.8%, compared to 40.2% in female. These findings could be only partially confounded by the higher incidence of comorbidities and smoking habits in males.

Possible mechanisms for this sex predilection was explained by the postulate that the biological step required for viral infectivity of the SARS-CoV-2 virus is priming of the spike proteins by transmembrane protease serine 2 (TMPRSS2) which cleaves the Angiotensin converting enzyme-2 (ACE2) receptor. Action of TMPRSS2 is enhanced by androgen, hence viral replication rate can be expected to be higher in males. Male susceptibility to the development of severe COVID-19 symptoms may be further enhanced by X-linked inheritance, since both the androgen receptor gene and the ACE2 genes are located on chromosome X. To study this hypothesis two clinical trials have been initiated, one in New York which has commenced treating COVID-19 patients with estrogen, and the other in Los Angeles which will treat male patients with progesterone, which has anti-inflammatory properties, and can potentially prevent harmful overreactions of the immune system. Protection in females has been postulated to be either due to XX linkage or estrogens with its role in negative regulation of the serene proteases including TMPRSS2. Another postulate attributes the increased male vulnerability to high ACE2 receptor concentrations in the testis.

3. Comorbidities: Up to 63% of death occurred in those who had at least one comorbidity amongst the 113 COVID-19 deaths that occurred at Tongji Hospital in Wuhan. Up to 72% (p value <0.001) of 138 patient hospitalized in Zhongnan Hospital, Wuhan requiring intensive care also had some underlying co-morbidities. Similar results were obtained in a nationwide retrospective study done at 575 hospitals throughout China compiling data of 1590 patients. 25.1% of the total deaths had at least one comorbidity. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). COPD also emerged as an important co-morbidity, even after adjusting for age and smoking status (hazard ratio, HR 2.681) as did diabetes (HR 1.59), hypertension (HR 1.58) and malignancy (HR 3.50). The HR for death was 1.79 among patients with at least one comorbidity and rose to 2.59 among patients with two or more comorbidities (p value<0.05).

A meta-analysis of seven studies including 1576 COVID-19 patients also showed the most prevalent comorbidities to be hypertension (21.1%), diabetes (9.7%), cardiovascular disease (8.4%) and chronic respiratory disease (1.5%).

i. Diabetes Mellitus (DM): Diabetes is a common comorbidity along with hypertension, adversely impacting outcomes in COVID-19 subjects. A recently published meta-analysis of 6452 patients from 30 different studies showed that diabetes was associated with composite poor outcomes in COVID-19 patients with a risk ratio (RR) of 2.38, (p < 0.001). In DM the RR for death was 2.12, for severe COVID-19 was 2.45, and for ARDS was 4.64 (p<0.001). Strikingly, meta-regression analysis showed that the magnitude of risk linked to DM as a single factor was greater in studies with younger and non-hypertensive patients, suggesting that in this population, younger and non-hypertensive diabetics were at higher risk of poor outcomes in contrast to the expected trend of older patients being at higher risk. A French nationwide study (CORONADO) revealed the phenotypes in DM which were more vulnerable to adverse outcomes. In hospitalised COVID-19 patients increased BMI and male sex emerged as important risk factors for adverse outcomes apart from age (odds ratio; OR 2.48), microvascular (OR 2.14) or macrovascular (OR2.54) complications and treated obstructive sleep apnoea (OR 2.8). The biochemical markers such as increased aspartate aminotransferase (AST), C-reactive protein (CRP), low platelet count and estimated glomerular filtration rate (eGFR) appears to be associated with risk of early death in hospitalised COVID-19 patients with DM. The mortality risk was significantly higher in patients with advanced complicated DM and long duration of disease. Oral antidiabetic agents such as thiazolidinedione, sodium glucose transporter2 (SGLT2) inhibitors, glucagon like peptide (GLP1) analogues may have some possible adverse outcomes in management and should be avoided. Often severe hyperglycaemia is observed in hospitalised patients and in patients requiring ICU. This warrants tight glycaemic control with intravenous infusion of insulin. Thus it is recommended that oral antidiabetic therapy in hospitalized patients be withheld and Insulin based therapy initiated.

ii. Obesity: Increased BMI is emerging as a clear cut independent risk factor in COVID-19 patients and underlying insulin resistance may be contributing to higher mortality. In a retrospective analysis of age stratified body mass index (BMI) in 3615 COVID-19 patients it was observed that patients with age < 60 years and BMI ≥ 35 kg/m² were 3.6 times more likely to require ICU than patients with BMI < 25. In a retrospective study amongst 124 patients the odds ratio for requirements of invasive mechanical ventilation in patients with BMI >35 vs patients with BMI <25 kg/m² was 7.36 (p=0.02). Currently it is unclear if this is the underlying reason for the higher mortality consistently observed in the ethnic minorities in Black, Asian populations (BAME) in UK and USA, which has been discussed in another section.

iii. Respiratory co-morbidities:

a. Interstitial lung disease (ILD): Most patients with ILD due to their poor lung physiology and underlying comorbidities are considered a high risk group. However no data is available on the proportional mortality rate and rate of infection amongst this group of patients.

b. Asthma: In a study conducted during the earlier phase of the pandemic, asthma was not found to increase mortality or complications in COVID-19 patients. However a recent cohort study was done using electronic health data to quantify risk factors for COVID-19 death. This study included over 17 million (17,425,445) general population enrolled in national health records who were followed.
up for around 3 months to assess the impact of comorbidities in the 5683 COVID-19 deaths in this cohort. This study uniquely highlighted that asthma was an independent risk factor for COVID-19 deaths (HR 1.23). This risk increased if the patient had a history of recent use of oral corticosteroid (HR 1.70). Deleterious effect of oral corticosteroids was also observed in another study among 600 COVID-19 patient with underlying rheumatological disease. It was found that the use of prednisolone ≥10 mg/day was associated with higher odds of hospitalisation (OR 2.05). It was also observed that around half of these patients (55%) required hospitalization and 9% died.

c. Tuberculosis (TB): COVID appears to have both direct and indirect effect on patients of tuberculosis. In a multicentre observational case control study done in 36 COVID-19 patients in Shenyang, China, TB (active or latent) was found to be amongst the most common underlying comorbidities. Of 36 enrolled patients 13 had interferon gamma release assay (IGRA) positive, of which 3 had active TB, 5 were TB calcifications on chest scans, and 2 patients had latent TB (LTBI). A modelling analysis was done to predict the cumulative incidence and mortality of TB in India, Kenya and Ukraine. This study concluded that in India every month of lockdown would lead to 144,795 excess TB cases and 40,685 excess TB deaths in the next 5 years.

iv. Smoking: Smoking has been a public health problem since decades however there is some controversy regarding its role in COVID-19 after it emerged that a recent study published from Paris’s Pitie-Salpetriere hospital found smokers had a lower chance of developing SARS-CoV2 compared with the general population. A trial has been initiated in France to study the effects of nicotine patches in COVID-19 patients. Currently one postulate claims smokers have increased numbers of ACE2 receptors but this needs validation.

v. Cancer: Patient with cancer appears to be at higher risk of COVID-19. A study involving 105 cancer patients admitted in 14 hospitals of Wuhan shown that compared to patients without cancer, the cancer patients had a higher risk of death (OR 2.34; p=0.03), of ICU admission (OR 2.84; p<0.01), and of developing severe/critical symptoms (OR 2.79; p<0.01). With regard to different types of cancer, the study found that patients with hematological malignancy had the highest risk of poor outcomes, followed by those with lung cancers. Patients with metastatic disease had an even higher risk of death (OR 5.58; p=0.01).

4. Laboratory parameters: Several routine laboratory indicators have been shown to predict a higher risk of patient mortality.

a. Routine blood investigation:
Leukocytosis, lymphopenia, neutropenia, and high BUN were all more frequently observed amongst deceased patients than survivors during the second and third week of illness (p value<0.05). C-indices of lymphocyte (0.872), prothrombin time (0.858), and CRP (0.844) were observed as strong predictors for death in these patients. Neutrophil-lymphocyte ratio (NLR) was also observed as an independent risk factor for poor outcome (HR 2.52) with a sensitivity of 88% and specificity of 63.6%.

b. D-dimer: A recently published study showed the D-dimer had the highest C-index (0.883) to predict in-hospital mortality in COVID-19 patients. Cut off values established using ROC curve, showed that a D-dimer value on admission greater than 2.0 μg/mL, could effectively predict in-hospital mortality of COVID-19 patients with a sensitivity of 92.3% and specificity of 83.3%. Another case series on 18 deaths due to myocardial infarction in COVID-19 patient reported elevated levels of D-dimer as a consistent finding in all 18. This was in contrast to a previous study where D-dimer levels were normal amongst 64% of myocardial infarction patients without COVID-19. In an analysis of 274 COVID-19 cases in Tongji Hospital in Wuhan, D-dimer concentrations were markedly greater in 113 deceased patients (4.6 μg/mL) as compared to patients who recovered (0.6 μg/mL), emphasizing the role of D-dimer as a predictor of death in COVID-19.

c. Other laboratory markers:
Concentrations of procalcitonin [deceased v/s recovered (0.33 v/s 0.5)], high sensitivity CRP (113.0 v/s 26.2) ferritin (1418.3 v/s 481.2), and erythrocyte sedimentation rate (38.5 v/s 28), were significantly higher in deceased patients than in recovered patients (p<0.05). Concentrations of Interleukin (IL) IL2 receptor, IL 6, IL8, IL10, and Tumour necrosis factor (TNFa) were also significantly higher in deceased patients than in recovered patients. Most (91%) deceased patients had undetectable concentrations of IL1β. It was observed in various studies that levels of cardiac troponin were raised in patients with severe COVID-19 disease. Similarly N-terminal pro brain natriuretic peptide (NT-Pro BNP) was recognised as an independent predictor of mortality with sensitivity and specificity of 100% and 66.67% respectively a cut off value of 88.64 pg/mL. These nonspecific elevations of cardiac troponin and NT-Pro BNP could be due to the injury caused by SARS-CoV2 to the ACE-2 receptor rich cardiac tissue. This suggests that cardiac troponin and NT-Pro BNP elevations cannot be relied on to diagnose acute myocardial infarction or heart failure in COVID-19 patients.

5. Pregnancy: Pregnant women do not appear more likely to contract the infection than the general population. However pregnancy is a state of partial immune suppression and it alters the normal physiological and immunological responses of the body uniquely. This may increase the risk of complication and severity of disease.

Studies have reported a mortality rate of 1.4% in pregnant women. There have been case reports of women with severe COVID-19 at the time of birth who have required ventilation and extracorporeal membrane oxygenation. In two retrospective studies from China, analyzing 16 females at term, all deliveries performed by Caesarian section had good outcomes. No data suggest there is an increased risk of preterm or miscarriages in COVID-19 pregnant female. There is no teratogenicity reported to date with COVID-19.

6. Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers: Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB) are amongst the most important antihypertensive drugs. However, since the Angiotensin Converting Enzyme (ACE)-2 is primarily involved in the
entry of the SARS-CoV2 virus into the host cells, and ACEI and ARB drugs could lead to over expression of this cellular receptor, promoting viral replication, the safety of these drugs was initially questioned.

Recent studies have attempted to settle this controversy. A multicenter retrospective study done by the American Heart Association in 1128 hospitalized COVID-19 patients with hypertension concluded that the inpatient use of ACEI/ARB was in fact associated with lower risk of all-cause mortality compared with ACEI/ARB non-users. Unadjusted mortality rate was lower in the ACEI/ARB group versus the non ACEI/ARB group (3.7% vs 9.8% p = 0.01). With data accumulated to date, the recommendation is that these drugs should not be discontinued or changed to other antihypertensive drug classes. There are now ongoing trials, (REPLACECOVID and CORONACION), evaluating the possible protective role of ACE/ARB in COVID-19.

7. Ethnicity: The impact of Corona virus has been disproportionate throughout the globe. This could be attributed to multiple factors, amongst which ethnicity is worth exploring. Ethnicity is a complex mix of genetic constituency, social and cultural practices, and behavioural patterns. Individuals from different ethnic backgrounds vary in behaviours, comorbidities, immune profiles, and risk of infection, as exemplified by the increased morbidity and mortality in black and minority ethnic (BAME) communities in previous pandemics.

The current pandemic appears to be following the same trend. According to most studies, people of BAME communities are most severely and disproportionately affected. In an observational study carried out by the Intensive Care National Audit and Research Centre, it was concluded that as many as one third (nearly 35%) of all ICU admission were from the minority ethnic group. In the United Kingdom of 2249 patients admitted to 201 critical care units in England, 64.8% were white, 13.8% were Asian, 13.6% were black, and 7.8% were from other or mixed ethnic groups. These were unadjusted descriptive data which took no account of factors other than ethnicity that could influence the risk of critical care admission. Similar trends were observed in Chicago where 70% of COVID-19 deaths involve black individuals, although blacks make up only 30% of Chicago’s population. These results were consistent across Louisiana, Michigan and New York City. Possible reasons for this disproportionate predilection include socioeconomic, cultural, or lifestyle factors, genetic predisposition, or pathophysiological differences in susceptibility or response to infection. Other factors such as Vitamin D deficiency, vaccination policies in their country, possible but unproven role of BCG vaccination, and higher prevalence of cardiovascular risk factors such as insulin resistance and obesity in the BAME group may also be contributory.

8. Genetic constituency: As described above, COVID-19 causes complications and deaths mainly in elderly patients with underlying health conditions. But on occasion, it may severely affect young and apparently healthy individuals, with no underlying co-morbidities. Many theories have been proposed to explain this paradox. Some suggest the role of the high viral load to which the patient (often a health care worker) is exposed, which may contribute to mortality even in a younger individual. However many believe that genetic constituency may be the cause of this unexpected vulnerability in a young and seemingly fit individual. Researchers have begun to study patients genomes for DNA variations that could help explain this mystery. This genetic hunt is expected to unmask many determinants of this pandemic, with gene encoding of ACE2 receptors an area of special interest. Apart from the role of ACE2 receptors, genetic studies have also unmasked the possible role of ABO blood groups in determining the outcome of disease. A recent genome association analyses done on 1980 patients with COVID-19 respiratory failure suggested that “A+ve” blood group was associated with higher odds of developing respiratory failure (OR 1.45) whereas blood group “O” had a protective role.(OR 0.65). In this study from Italy and Spain, those with “A+ve” blood group had a 45% higher risk of respiratory failure whilst O blood group had a 35% lower risk.

Concluding remarks

As the SARS-CoV-2 pandemic gathers speed across the globe our understanding of which groups of patients are most vulnerable has crystallised. Knowing that elderly patients, males more than females, hypertensives, diabetics, cardiac patients, those from the BAME group, those with chronic underlying lung disease, and those with cancer are more vulnerable provides extremely important insights. Shielding such high risk groups as best as possible from the ravages of the virus, and working on strategies to improve outcomes in these high-risk patients, will continue to evolve as the pandemic unfolds. As outlined, several laboratory markers such as NLR, D-dimer, procalcitonin, cardiac troponin, CRP and pro-inflammatory interleukins can also help to predict the progression of the disease and predict poor outcomes.

References


Coconut Oil and Immunity: What do we really know about it so far?

Shashank Joshi¹, Vaibhav Kaushik², Vaishali Gode³, Sudhakar Mhaskar²

Abstract
Coconut oil as health oil was recognized in Ayurvedic medicine almost 4000 years ago. The same health effects were also attributed to the mother's milk in ancient literature. Modern research has now found a common link between these two natural health products – their lipid content. The medium chain fatty acids and monoglycerides found primarily in coconut oil have miraculous healing power which act as natural antibiotic and also help modulate immunity.

The information discussed in this review explains that coconut oil, either topically applied or ingested, gets broken down to release Lauric Acid and Monolaurin – known anti-microbial agents. The studies reported in literature are discussed to evaluate the antiviral, antibacterial and antifungal benefits of coconut oil. Not only does coconut oil metabolites have antimicrobial activity but also these remarkable derivatives have been shown not to cause resistance organisms to appear. The anti-microbial mechanistic action also helps activate the anti-inflammatory nature of the immune response in human body. In vitro, animal, and human studies support the potential of coconut oil as effective and safe immune-nutritive active. New and exciting health and industrial uses of coconut oil and its derivative are possible.

Never before in recent times has the recognition of the positive health effects of coconut oil been stronger. And never before in the history of man is it so important to emphasize both need and efficacy of natural products known for their safety proposition. Immunity has been a buzzword in the current scenario and the demand for modulating immunity with natural means has been so unprecedented and so ubiquitous. Coconut oil and its value added forms can contribute to a more vigorous and healthy future.

Introduction

Coconut as ‘Super Seed’ and Coconut Tree as ‘Super Tree’ – Kalpa Vriksha – has been a part of daily use in tropical regions of the world. Coconut and its various products (milk, meat, oil, butter etc.) are a part of daily habits with usages in the form of cooking aid, food ingredient, hair and skin treatment, medicinal preparations etc.

In last decade, coconut oil has gained traction amongst media and population alike, across the globe (Figure 1). Interest in coconut oil has soared with the endorsements from celebrities, bloggers as well as doctors and dermatologists. In numerous news articles, blogs, videos etc. the Influencers have recommend the use of Coconut oil as dietary supplement and cooking media alternative to other vegetable oils. Several health benefits have been accorded to the use of coconut oil; some of them include cholesterol lowering, reduction of cardiovascular disease risk, weight loss, appetite curb, improvement of cognitive functions and strengthening of immune system.¹⁻⁵

During the same time, interest in scientific community over health benefits of coconut oil have soared. The same is reflected in the exponential growth of scientific articles and patents published over the last decade (Figure 2). There has been debate over the health promoting aspects of coconut oil and the lack of consensus is attributed to the predominant saturated nature of its composition. The immunity modulation effects of coconut oil – both during ingestion and topical application – has been an emerging area for scientific research and debate.

It is imperative that relevant scientific evidences on the antimicrobial and immunomodulation benefits of coconut oil should be examined carefully and objective information should reach the scientific minds. In this review paper, the research on 360° protection benefits of coconut oil – ingestion (inside) as well as topical application (outside) - are collated and discussed.

Coconut Oil and its Metabolic Derivatives

According to the Ayurveda – teaching inscribed in the oldest scripture of Hinduism (circa 1500 BC) – coconut oil nourishes the body and increases strength. The oil was also valued for its antimicrobial properties. Different preparations of coconut oil promote luxurious hair growth and protect the skin from bacterial, protozoal, and viral infections.

Broadly, there are two types of Coconut Oil refined, bleached, and deodorized copra oil (RCO) and virgin coconut oil (VCO). In essence, VCO is produced by wet extraction process of the fresh endosperm of the coconut while RCO is obtained by dry extraction process of the dried endosperm of the coconut fruit. Both RCO and VCO have similar fatty acids and triglycerides profile (Figure 3).⁶ However, VCO retains a higher content of bioactive compounds such as vitamin E, sterols, and polyphenols as refining removes a portion of these compounds.⁶

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Coconut oil is a unique vegetable oil because it is the only oil where ~48% of the fatty acid composition is Lauric Acid. Most of the advantages of Coconut Oil are attributed to the existence of Lauric Acid and secondary metabolite – monolaurin.

Lipids in human milk do not initially have antimicrobial activity but become antiviral, antibacterial, and antiprotozoal in-vivo after digestion in the gastrointestinal tract. Microbial killing by milk lipids is due primarily to FFAs and monoglycerides released from milk triglycerides by the lipolytic activity in the infant’s gut.

Similarly, in case of ingested coconut oil human body converts the triglycerides into Lauric Acid which gets further metabolized into monolaurin, a monoglyceride composed of a glycerol unit. However, there do not appear to be any clear data on the quantification of monolaurin formation from coconut oil in the human body. Based on a hypothesis postulated, 6% of the coconut oil gets metabolized into monoglycerides inside the human body.

**Antimicrobial Benefits of Coconut Oil and its metabolites**

Ample studies in literature are available to establish the Antibacterial, Antiviral and Antifungal benefits of coconut oil and its metabolites – Lauric Acid, Capric Acid and Monolaurin.
Antimicrobial efficacy of Lauric Acid was found to be better amongst all the fatty acids and that of monolaurin was better than Lauric Acid. Table 1 below lists few such studies with categorization into different benefit class.

**Mechanism of Action of Coconut Oil against Pathogenic Microbes**

Three modes of action have been proposed to explain the antimicrobial efficacy of Coconut Oil and its metabolites – Lauric Acid and Monolaurin (Figure 4).

- **Disintegration of the Lipid Membrane:** Study by Hierholzer and Kabara\(^{23}\) showed that monolaurin was able to reduce infectivity of 14 human RNA and DNA enveloped viruses in cell culture by >99.9%, and that monolaurin acted by disintegrating the virus envelope. Studies\(^{14,15}\) have shown Lauric Acid and Monolaurin inhibiting the growth of S. aureus with destructive mechanisms of bacterial cell walls.

- **Inhibits Pathogen Maturation:**

  - **Antibacterial**
    - Monolaurin, Lauric acid and linoleic acid
    - Monolaurin and monocaprin
    - Coconut oil
    - Lauric acid and monolaurin
    - Monolaurin

  - **Antifungal**
    - Lauric acid
    - Virgin coconut oil
    - MCFAs
    - Lauric acid and capric acid
    - Coconut oil
    - Virgin coconut oil

  - **Antiviral**
    - Monolaurin
    - Lauric acid
    - Lauric acid and monolaurin
    - Monolaurin

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**Fig. 4: Mechanistic mode of action for coconut oil against microbial growth**

VCO metabolites are known to produce highly ordered membranes, which is thought to disrupt pathogens’ cellular function by affecting signal transduction due to blockage of promoters, uncoupling of energy systems, altered respiration state, and altered amino acid uptake. In a comparison among the saturated fatty acids from C10 to C18 against Junin virus (JUNV) infection, Bartolotta and co-workers\(^{28}\) showed that Lauric acid alters the cellular distribution of the viral proteins and leads to a blockade in the assembly and/or budding of the viral progeny.

- **Prevents pathogen binding to host cell:** Lauric acid did not influence pathogens’ membrane protein synthesis, but prevented the binding of membrane proteins to the host cell membrane. It is documented\(^{24}\) that the presence of lauric acid inhibits production of infectious vesicular stomatitis virus in a dose-dependent and also reversible manner - after removal of Lauric acid, the antiviral effect disappeared.

The above mechanistic modes explain the anti-microbial action of Coconut Oil and its metabolites – lauric acid and monolaurin.

**Immunomodulation Benefits of Coconut Oil and its metabolites**

- **Immune System** is responsible for providing a response within an organism for the purpose of defending against foreign invaders. These invaders include a wide variety of different microorganisms including viruses, bacteria, and fungi which could cause serious problems to the health of the host organism if not cleared from the body. There are two distinct aspects of the immune response:

  - **The innate branch** – the body’s first reaction to an invader which is known to be a non-specific and quick response to any sort of pathogen. It includes physical barriers like the skin and mucous membranes, ROS Production, immune cells such as neutrophils, macrophages, and monocytes, and soluble mediators including cytokines like IL-8, IL-1 and TNF-a.\(^{29}\) This aspect of immune response is often referred as the inflammatory response.

    - **The adaptive branch** – the body’s immune response which is catered against specific antigens and thus, it takes longer to activate the components involved. It include cells such as dendritic cells, lymphocytes (T cells and B cells) as well as antibodies – also known as immunoglobulins – which directly interact with antigen.\(^{30}\)

The immune response mentioned above depends upon Macro-factors (age, genetics, sex, hormonal status, susceptibility to infections etc.) and Lifestyle (diet composition, mobility status, environmental pollution, chronic stress etc.).\(^{29}\) There are ways in which the immune response can be modulated to allow for optimum results. These immunomodulatory regimes have been found promising predominantly due to two reasons (1) fewer side effects and (2) less potential to create resistance in case of antimicrobial action. Immune modulating supplements provide micro-nutrients to enable improvement in the inflammatory biomarkers and/or increasing antigens availability.
Mother’s milk is considered to be one of the most potent and effective immune potion that helps a new born baby with under-developed immune system to fight off fatal bacterial invasion. When analyzed, 50% of breast milk is saturated fat, out of which 20% in the intestine were fed MCFAs or LCFA's. It is also known that 60% of Coconut Oil MCFAs are present in the human breast milk and majority of them in both the natural liquids are classified as saturated fatty acids. 6,32

Clinical Studies demonstrating Immunomodulation

Literature studies reported suggests that MCFAs and CNO metabolites influence many different aspects of the immune system, starting with their role on the epithelial lining of the intestinal lumen to cytokine secretion to fighting pathogens. Coconut oil and its derivatives have been shown to be safe and effective immunomodulatory agent in both humans and animals; however the reported human trials are few. Table 2 captures the in-vivo studies reported connecting the immune response with the administration of coconut oil or its metabolites.

Table 2: Clinical studies with immunomodulation benefits

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Effects</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naccache et al 10</td>
<td>Neutrophil suspension + different fatty acids.</td>
<td>MCFAs might stimulate aggregation and degranulation of neutrophils.</td>
<td>MCFAs are capable of modulating immune function</td>
</tr>
<tr>
<td>Wang et al 36</td>
<td>Humans + Mice</td>
<td>MCFAs reduced IL-8 production levels.</td>
<td>MCFAs reduce intestinal damage in ileitis rats due to a reduction in IL-8 secretion.</td>
</tr>
<tr>
<td>Ohta et al 37</td>
<td>Rats with ileitis in the intestine were fed MCFAs or LCFA's.</td>
<td>MCFAs bind GPR84 causing increased production of IL-12.</td>
<td>MCFAs may affect TH1/TH2 balance in a GPR84-dependent manner.</td>
</tr>
<tr>
<td>Dayrit et al 38</td>
<td>Chicken suffering from avian influenza were fed VCO (at 5, 10, 15 ml/kg of feed) in the diet for 4 weeks</td>
<td>VCO could increase the level of lymphocyte counts versus control</td>
<td>VCO is a potential immunomodulator</td>
</tr>
<tr>
<td>Dayrit et al 38</td>
<td>Human</td>
<td>11 of the patients showed higher CD4 and CD8 counts after 6 months</td>
<td>Immune Response increases with CNO and its metabolites</td>
</tr>
<tr>
<td>Widiarta et al 39</td>
<td>40 HIV subjects with VCO supplement group (45 mL daily) and control group (no VCO)</td>
<td>After 6 weeks, the VCO group showed significantly higher average CD4+ T lymphocyte counts versus control</td>
<td>Immune Response in HIV Patients improves with VCO regular use</td>
</tr>
<tr>
<td>Strunk et al 40</td>
<td>Human</td>
<td>Topical coconut oil application in very preterm infants</td>
<td>Topical coconut oil use leads to a lower incidence of late-onset sepsis</td>
</tr>
<tr>
<td>Thyagarajan et al 41</td>
<td>HaCaT Cells</td>
<td>Study demonstrated inhibition of various cytokine levels including TNF-α, IFNγ, IL-6, IL-5 and IL-8</td>
<td>Topical application of VCO promotes anti-inflammatory activity</td>
</tr>
<tr>
<td>Silalahi et al 42</td>
<td>Rats</td>
<td>Treatment of VCO 5 mL/kg BW succeeded in reducing a side effect of DOX based on increasing the TCD4+ and TCD8+ blood level</td>
<td>VCO could increase the level of TCD4+ and TCD8+</td>
</tr>
<tr>
<td>Thyagarajan et al 43</td>
<td>Rats’ diet supplemented with 4%, 8%, and 16% of VCO</td>
<td>VCO diet upregulated neuroprotective factors, and suppressed inflammatory mediators and oxidative stress</td>
<td>VCO might modulate immune responses through intracellular signaling pathways</td>
</tr>
</tbody>
</table>

Discussion

Coconut Oil – with major MCFA contribution in its composition – is known to have many beneficial effects ranging from reducing belly fat to enhancing satiety to preventing heart disease, and staying off dementia. The focus of this review is to describe the current knowledge on the effect of Coconut Oil on the holistic ‘inside-out’ protection – antimicrobial benefits as well as immune modulation.

Literature indicates that coconut oil as is does not possess the antimicrobial power but its conversion to Lauric acid and further to Monolaurin – whether on skin or inside body – provides in-situ antimicrobial efficacy. 34 In an in-house study (Mhaskar et al, Unpublished Data, 2012), the hydrolysis of Coconut Oil was studied both in-vitro and ex-vivo. Sabouraud Broth with 3% coconut oil and 1% Tween-80 was incubated with two different microbial samples - M. furfur and swab samples from scalp of healthy volunteers. At the end of 72h incubation, in both the cases TLC analysis confirmed the degradation of Coconut Oil into Lauric Acid, Di-Glycerides and Mono-Glycerides.

In a clinical study on humans, Strandberg et al, 46 reported an inhibitory effect of monolaurin on Staphylococcus aureus. In 2018 double-blind controlled study by Verallo-Rowell et al 17 on 52 subjects suffering from Atopic Dermatitis, topical application of VCO Application was prescribed. Atopic dermatitis skin is dry and readily colonized by Staphylococcus aureus (SA). Of the 20 patients whose cultures were positive and who were randomized to VCO, only 1 subject (5%) remained positive at the end of 4 week treatment.

Van der Sluis et al studied in Taiwan poultry farms, where outbreak of high pathogenic avian influenza (AI) is common, the effect of including alpha-monolaurin dry at a low level (1-2 kg/ton of feed) in the chicken diet for 70 days. At the end of the trial, there was no sign of AI left in the flock. 26

In one of the studies by Verallo-Rowell et al, 46 the antiseptic effectiveness of 70% isopropyl alcohol and 1.5% lauricidin against the mechanical effect of Ivory soap was compared. It was concluded that with a single wash both agents had anti-microbial activity that was ~40% greater than that of the control non-antimicrobial hand wash and both the agents showed progressive decrease with increased wash cycles (10 cycles in total). In 2010 study by Oyi et al, 47 creams containing 5 to 40% coconut oil were prepared and applied on skin inoculated with Bacterial and Fungal species. Skin activity test confirmed that the cream performed antibacterial
and antifungal function on the skin. Summary of the antimicrobial benefits is shown in Figure 5.

Studies pointed out in this review suggests that Coconut oil influences various aspects of immune system, starting with their role on the cytokine secretion by epithelial cells. In 1984 Naccache et al. reported MCFAs stimulating neutrophil aggregation – stimulating an immune response. Both Nanjil et al and Ohta et al found a decrease in IL-8 production in rat intestinal cells fed with MCTs and MCFAs respectively.

Wang et al. confirmed the role of GPR84 – a receptor for MCFAs (9-14 carbon atoms) – on immune function. Since, GPR84 is mostly expressed in immune cells, it is likely that MCFAs would modulate the function of these cells. Yuniwarti et al documented that the chickens fed with VCO have higher number of lymphocyte and Th-CD4 at the end of 4 weeks.

The first clinical trial using coconut oil (45 mL daily) and monolaurin (95% purity, 800 mg daily) against HIV-AIDS was conducted in the Philippines. This study involved 15 HIV patients, aged 22 to 38 years, 5 males and 10 females, for 6 months. There was only one fatality in very pre-term infants who are most susceptible to immune response and blood infections. They concluded the use of topical VCO for 14 days increases the monolaurin level in blood plasma. They also concluded that monolaurin at ~280 µg mL/L is highly active against prototypical gram-positive late-onset sepsis pathogens such as S. epidermidis and S. aureus as well as C. albicans. Studies on pre-term neonates suggest that Coconut oil massage has beneficial effects on the weight gain. Theo have shown that topical application of VCNO suppresses the inflammatory activity (cytokines level) and improves skin barrier function.

Although many consumers are raving about health benefits they have experienced from coconut oil, research into the oil is still in its infancy. The exact mechanism with which coconut oil exhibit anti-microbial and immunomodulatory benefits is still being discovered. However, the various clinical studies reported on Coconut Oil and/or its metabolites (Lauric Acid and Monolaurin) establish beyond doubt the end benefits of the holistic protection – topical as well as ingestible route.

**Conclusion**

Coconut Oil action as an immune-nutritive agent is deliberated in this review. Science behind Coconut Oil usage as nutraceutical – ingestion related immunity response – and cosmeceutical – topical immunity benefits – was discussed. Scientific studies on coconut oil and its benefits as anti-microbial and further as an immunomodulation agent are still emerging.

Multiple in-vitro and in-vivo studies have confirmed the safety of coconut oil usage as immune-nutritive agent. Metabolites of coconut oil have been established for their anti-

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**Fig. 5: Antimicrobial benefits summary of coconut oil and its derivatives**

- **Antibacterial**
  - Significant activity against gram +ve bacteria and not any against gram -ve
  - Lauric Acid - effective inhibitor against S. aureus & P aeruginos - common in immuno-compromised individuals

- **Antiviral**
  - Viruses inactivated to varying extent by monolaurin include HIV, measles, Herpes simplex-1, vesicular stomatitis, visna virus, and cytomegalovirus

- **Antifungal**
  - Lauric Acid has strong ability to inhibit growth of C. albicans at low concentration but higher incubation period
  - VCNO on vaginal candidiasis patient improved T-Cells and Cytokine (IL-2) Levels

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Never before in recent times has the recognition of the positive health effects of coconut oil been stronger. And never before in the history of man is it so important to emphasize the value provided by these natural agents with 360° protection – nutraceutical as well as cosmeceutical benefits. Coconut oil and its various forms can contribute to a more vigorous and healthy future.
Fahr Syndrome Due to Idiopathic Hypoparathyroidism

Vidyapati1, Prajit Mazumdar2, Divakar Kumar3, Malyaban Das2

Fig. 1: Calcification in cerebellum

Case History

A middle aged female was admitted to our hospital with complaints of intermittent episodes of tingling and numbness, generalized weakness and headache for last 2-3 months.

The family members also gave history that of late the patient had become irritable and at times got aggressive for no reason for last 2-3 weeks. There was also history of two episodes of seizure 1 day prior to admission.

On examination, the patient had stable vitals and systemic examination was within normal limits. Blood glucose at time of admission was normal. However, Trousseau sign was positive.

Since the patient had seizure and had Trousseau sign positive, metabolic profile of the patient was checked which showed low serum ionized calcium, high serum phosphate along with low parathyroid. However, serum alkaline phosphate was normal.

Hence, a diagnosis of primary hypoparathyroidism was made.

There was also no history of thyroidectomy and radiation exposure and autoimmune profile of the patient was negative. Hence the cause of hypoparathyroidism seemed to be idiopathic.

Computed Tomography (CT Scan) of the brain revealed symmetric bilateral areas of calcification in basal ganglia and thalamus, periventricular and supraventricular white matter and cerebellum.

Discussion

Diffuse calcification in the brain can be divided into two main forms: primary and secondary.

The primary form is Fahr disease which is an inherited autosomal dominant disease or sporadic disorder clearly defined as bilateral basal ganglia calcification in presence of neuropsychiatric and extrapyramidal features with normal calcium and parathyroid.1

In contrast to the primary form, Fahr syndrome is characterized by bilateral and symmetric calcification of the brain secondary to endocrine cause like hypoparathyroidism and pseudohypoparathyroidism, infectious, mitochondrial myopathy.2 Clinical features of Fahr syndrome includes neurological features such as seizures, headache, vertigo, spasticity, and psychiatric features such as depression, manic symptoms, irritability, aggression and deterioration of intelligence.

Our patient presented with many of the above clinical features and had positive Trousseau sign, low serum calcium and decreased PTH levels, raised serum phosphate and normal alkaline phosphate and prolonged QT interval on electrocardiographic examination.

Furthermore, features of basal ganglia, cerebellar and thalamic calcification on CT Scan of brain completed the diagnosis of Fahr syndrome due to idiopathic hypoparathyroidism.

References


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Cardiorenal Amyloidosis

Meenakshi N1, P Soni2, R Anand3, S Bali2, Hari1

Abstract
Amyloidosis is a conglomeration of diseases due to production and deposition of amyloid, a proteinaceous substance, into organs, tissues, nerves and other places in the body affecting their normal function. This case report is of a 65 year old gentleman, resident of Bihar admitted with a short history of two months. He came with chief complaints of swelling in both lower limbs associated with heaviness in legs, shortness of breath, dizziness, fatigue and passage of frothy urine for two months. He was investigated and found to have proteinuria, low voltage ECG, Echocardiography showed left ventricular hypertrophy, diastolic dysfunction, mitral regurgitation. Cardiac MRI showed dilated cardiomyopathy due to amyloidosis.

Introduction
Amyloidosis (“osis” means increased or an abnormal supply) or “Orphan disease” is a conglomeration of diseases due to production and deposition of amyloid, an abnormal insoluble low molecular weight protein. Amyloid deposition into organs, tissues, nerves and other places in the body affects the normal function of the area. Correct diagnosis is extremely important as each of the affected system is diseased and each has a different management. Characteristic cross-β-sheet amyloid fibrils accumulate systemically or are localized to specific organs in amyloidosis. There are several different types of amyloid proteins and the three most common systemic Amyloidosis diseases are AL – A for amyloid and L for Light Chain, AA – A for amyloid, A is for Serum A Protein (also known as SAA) and ATTR – A for amyloid, TTR is for Transthyretin (also known as TTR) protein. In this case report we want to highlight a patient with combined cardiac and renal amyloidosis, a rare entity.

Case
A 65 year old gentleman, resident of Madhubani district, Bihar was admitted with chief complaints of swelling in both lower limbs gradually increasing for 2 months associated with heaviness in legs. He also had shortness of breath, dizziness, fatigue and passage of frothy urine for the same duration. No history of fever, reduced urine output, hematuria, dysuria, nausea, diarrohoea, constipation, loss of weight and appetite, numbness, tingling, hypertension, diabetes, tuberculosis, asthma, previous hospitalizations.

On examination the patient was alert, conscious, oriented with no pallor, cyanosis, clubbing, icterus, lymphadenopathy. He was afibrile, pulse 68/min, BP 100/60mmHg, RR 16/ min. He had bilateral pitting edema. On auscultation of the chest there were bilateral crepitations; cardiovascular examination soft S1 and S2 with pansystolic murmur radiating to the axilla and no thrill. Per abdomen examination showed parietal edema and no neurological findings on examination.

The patient was investigated Table 1. Hemogram showed normal leucocyte count (10,000), raised ESR (38). RBS normal (76), LFT showed hypoalbuminemia (OT/PT 52/60,TP 6, Alb 2.2, Glob 3.8, A/G,5/1), KFT was normal (B. urea 22, s. creatinine.9). Coagulation and Thyroid profile was normal. Nephrotic range proteinuria (albuminuria-8.514) His Chest X-ray was normal and Ultrasound showed hepatomegaly with Benign prostatic hypertrophy and left kidney cyst. CT abdomen showed mild hepatomegaly with bilateral pleural effusion and diffuse abdominal wall edema.

The patient was further investigated Table 2 which showed hyponatremia and proteinuria. To rule out Multiple myeloma, serum and urine protein electrophoresis were done which showed no M spike. Kappa and lambda light chains in serum and urine were sent and were normal. In view of the systolic murmur, ECG and Echocardiography was done. ECG showed low voltage complexes. Echocardiography showed no regional wall motion abnormality of left ventricle. Global LVEF 60%, moderate concentric

Table 1: Hemogram

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>12.3</td>
</tr>
<tr>
<td>TLC</td>
<td>10,000</td>
</tr>
<tr>
<td>MCH</td>
<td>95.3</td>
</tr>
<tr>
<td>MCHC</td>
<td>30.9</td>
</tr>
<tr>
<td>RDW</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Table 2: Hemogram

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>12.4</td>
</tr>
<tr>
<td>PCV</td>
<td>37.1</td>
</tr>
<tr>
<td>TLC</td>
<td>6.0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>54.8</td>
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<tr>
<td>Lymphocytes</td>
<td>38.4</td>
</tr>
<tr>
<td>Monocytes</td>
<td>6.3</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1.0</td>
</tr>
<tr>
<td>Basophils</td>
<td>4.0</td>
</tr>
<tr>
<td>Platelet count</td>
<td>197</td>
</tr>
<tr>
<td>RBC</td>
<td>3.97</td>
</tr>
<tr>
<td>MCV</td>
<td>93.4</td>
</tr>
<tr>
<td>MCH</td>
<td>31.3</td>
</tr>
<tr>
<td>MCHC</td>
<td>33.5</td>
</tr>
<tr>
<td>RDW</td>
<td>13.1</td>
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</table>

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left ventricular hypertrophy, increased myocardial echogenicity ?infiltrative cardiomyopathy ?amyloidosis, LA high normal, mild MR and trace TR, Grade 1 diastolic dysfunction (E/E' > 15) and minimal pericardial effusion and no intracardiac clot/vegetation (Figures 1, 2, 3).

He was advised a cardiac MRI which revealed left ventricular concentric hypertrophy showing diffuse delayed enhancement consistent with amyloidosis, normal LV systolic function, bilateral minimal pleural effusion, mild MR and trace TR (Figures 4, 5, 6). In view of continuing proteinuria, he was advised a kidney biopsy. The biopsy showed nephrotic syndrome with AL amyloidosis (Figure 7). Bone marrow aspiration was also done to rule out Multiple myeloma showed focal marrow lymphoplasmacytosis (foocally increased lymphocytes upt0 60% and focially increased plasma cells upt0 6-8%) (Figure 8). Bone marrow biopsy was advised. Bone marrow immunofixation showed hypercellular marrow for age with scattered plasma cells. Congo red staining showed typical apple green birefringence (Figure 9). Patient was given symptomatic treatment in form of diuretics and planned for traditional chemotherapy.

Discussion

Amyloidosis is a systemic disease described by Rudolph Virchow in 1854. AL Amyloidosis (earlier called Primary Amyloidosis) is a light chain disease of the bone marrow affecting men more than women and age group 50-80 years of age. It is rare with an incidence of 8.9 per million population. The plasma cells, a subgroup of white blood cells makes antibodies which are proteins or immunoglobulins. The immunoglobulin has a basic structure of heavy and two light chains. The light chains (kappa and lambda) get free from an antibody and misfold.
Neuro-Behcet’s Disease, a Diagnostic Challenge

Nishit Biniwale¹, Rutuja Kibe², Avanti Biniwale³

Abstract

Neuro-Behcet’s disease (NBD) is a rare neurological manifestation of the systemic small vessel vasculitis called Behcet’s disease. It can present in various ways with predilection for the brain stem, thalamo-hypothalamic regions, cerebellum and basal ganglia. In this case, we describe a case of young stroke that was later attributed to NBD.

Introduction

Behcet’s disease (BD) is a multi-systemic vasculitic disorder of unknown etiology. It is characterized by oral and genital ulcers, though the inflammatory perivasculitis can arise in almost any tissue. Neurological complications occur in about 5 to 25% of all patients with BD which accounts for long term morbidity and mortality. Here we present a case of BD with a solely neurological presentation.

Case Report

A nine-year-old girl presented for the first time with double vision and right ptosis. She had no preceding symptoms of vertigo, ataxia, dysphagia, fever or history of trauma. Neurological examination revealed a right third nerve palsy. MRI was inconclusive and her symptoms resolved with steroids. Four days later she had recurrence of symptoms with additional ataxia and drowsiness. MRI now showed a hyper-intense lesion in the right midbrain. Investigations for young stroke were performed which were normal. On enquiry, she mentioned that she suffered from infrequent oral ulcers. Ten years later she developed slurred speech and gait ataxia. MRI revealed a new lesion in the left half of the midbrain (Figure 2). Yet again her symptoms responded to corticosteroids.

References

2. Ankarcrona M, Winblad B, Monteiro C, Fearn C, Powers ET, Johansson J, Witsenmark GT, Presto J, Ericsson BG, Kelly JW (Department of Neurobiology Care Sciences and Society, Division of Neurogenetics, Center for Alzheimer Research, Karolinska Institutet, Huddinge, Sweden; Department of Chemistry The Skaggs Institute for Chemical Biology, La Jolla, CA, USA; Department of Molecular and Experimental Medicine, The Scripps Research Institute; Department of Medical Cell Biology, Uppsala University Uppsala Sweden and Division of Transplantation Surgery, Karolinska University Hospital, Stockholm, Sweden). Current and Future Treatment of Amyloid Diseases (Review Symposium). J Intern Med 2016; doi: 10.1111/joim.12506
The nervous system involvement is one of the most serious manifestations of BD, leading to headache, confusion, paresis, cranial nerve palsy, cerebellar ataxia, or meningeal irritation signs. Headache is the most common neurological symptom accounting for about 70% of patients. In this case, the patient presented for the first time as a child old but diagnosis was difficult because all specific diagnostic clinical manifestations were not present at the same time. Two categories of neurological involvement in BD that have been accepted: parenchymal involvement and non-parenchymal involvement, also called cerebral Angio-Behcet's syndrome. Also, since there is no specific laboratory diagnostic test, the diagnosis of NBD depends essentially on clinical findings, radiological findings and after careful exclusion of other possible diseases. The differentials to be considered are mainly autoimmune and demyelinating illnesses. MS being one such condition can be readily differentiated from NBD on MRI. The MRI image of our patient was compatible with the characteristics of NBD. Brainstem-thalamic-basal ganglia lesions in the proper clinical context can strongly support the diagnosis of acute/subacute parenchymal NBD, and on occasions can raise this possibility even when the systemic features of BD are scarce.

Of the systemic vasculitides the common culprits affecting the brain include granulomatosis with polyangitis (Wegners), Polyarteritis Nodosa and Behcets disease. Vasculitis secondary to SLE and RA must also be considered. Both pANCA and cANCA along with an autoimmune screen are helpful in ruling out these other causes when suspecting NBD. ESR has not been proven to be helpful in diagnosing or monitoring NBD disease activity. This was validated in our patient who had normal ESR and CRP.

The treatment of parenchymal NBD primarily consists of glucocorticoids (high-dose pulse intravenous and/or oral) and azathioprine. Because of its relatively predictable and low side effect profile, azathioprine is commonly used as a first-line disease modifying treatment in many centers for the serious manifestations of BD, particularly NBD.

**References**

Medical Balloonists

Jayant Pai-Dhungat

Montgolfier Brothers made the first hot air balloon flights in France in 1783. Two medically related aeronauts soon attempted the adventures. Jean Francois Pilatre de Rozier (1754-1785), a pharmacist, drug chemist, surgical assistant, turned to experimental physics. Rozier became the first human being to ascend in a balloon. He used combination of hydrogen and hot-air to lift his balloon and made flight with Laurent in 1783. They flew over Paris for approximately 25 minutes. Rozier then attempted to become the first balloonist to cross the English Channel with d’ Arlandes. However, he and his co-pilot were killed when hydrogen exploded at an altitude of about 2,950 feet during the attempt.

John Jeffries (1745-1819) was born in Boston (1745), graduated at Harvard in 1763 and studied in England, where he received an M.D. at Aberdeen in 1769. He was educated under Hunter and Smellie and in 1771 Admiral Montague, appointed Jeffries as assistant surgeon of a ship on line, with a hospital on shore, a position he held until 1774. His British sympathies held true during the Revolution. After the evacuation he accompanied the British to Halifax and eventually was appointed surgeon-major to the forces in America. He settled in England at the close of civil war.

Jeffries made his first balloon voyage over London in 1784. Frenchman Blanchard was in London at the time, trying to raise money for a flight across the Channel. Blanchard invited Jeffries to make an ascent from Grosvenor Square. This raised a great deal of interest and the spectators included the Prince of Wales, the future King George IV (1820-1830). This ascent was made for scientific study of the air at high levels, and not solely for spectacular purposes. Jeffries carried with him a reliable barometer, thermometer, hygrometer, electrometer, folding telescope, mariner’s compass, and seven small bottles for obtaining samples of air at different heights. He certainly reached an elevation exceeding 6560 feet. The flight lasted two hours and came down near Dartford, Kent. His observations were turned over to the Royal Society to be discussed; they were analyzed by no less a chemist than Cavendish. Readings matched the accepted values. By this time Jeffries said he would pay all the expenses for the proposed cross-Channel flight.

On January 7, 1785, about five weeks after the London ascent, Jeffries and Blanchard attempted to cross the English Channel, from Dover. During the journey the balloon came down several times, almost to sea level. The two men countered this by first throwing the cargo and then the clothes they were wearing. Finally they even had to discharge 5-6 lbs. of “secretions from kidneys”. At last the two landed in the forest of Guineas (Forêt de Guines) about six miles south of Calais. Flight had taken two and a half-hours; by this time, both men were almost naked and extremely cold but crowds gathering, including the local magistrate greeted them; the flight had been successful; Blanchard and Jeffry’s main concern was their lack of attire, but the magistrate provided them with appropriate dress.

The year 1790 marked the return of Jeffries to Boston, where he practiced surgery, medicine and midwifery until near the time of his death, in September 1819, from strangulated hernia.
Can Mild Anemias be Associated with Low Serum Lipid Concentration?

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Gautam Kumar Saharia²,
Manaswini Mangaraj³
¹ 18th Semester MBBS student, ² Associate Professor, ³ Professor and Head, Department of Biochemistry, AIIMS, Bhubaneswar, Odisha

Sir,

The burden of coronary artery disease (CAD) in India is increasing and addressing the risk factors for the same is the need of the hour to reduce its prevalence.¹ Another equally important public health concern is the prevalence of anaemia. Dyslipidaemia may be more prevalent in an affluent society, whereas anaemia obviously more common in people with low socioeconomic status ² and most CAD risks are attributable to smoking, uncontrolled diabetes mellitus and sedentary lifestyle habits. Keeping these aspects in mind, we hypothesized that the serum lipid profile consisting of total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL) shall be lower in the anaemic group. Hence the objectives of our study were to evaluate the serum TC, TG, LDL and VLDL concentrations in anaemic patients and to find out any relation of lipid profile between anaemic and non-anaemic group. It was a hospital based clinical observational study done in Department of Biochemistry, AIIMS Bhubaneswar, which is a premiere tertiary care center in Eastern India. After getting approval from Institutional Ethics Committee (IEC), thirty-eight numbers of patients of 18 years and above diagnosed with anemia were analyzed with equal number of age sex matched controls over a period of two months from 1st August 2018 to 30th September 2018.

Patients visiting Medicine OPD having hemoglobin <13 g% in men and <12 g% in women were taken in the anemia group and equal number of age sex matched control were taken.³ Smokers, diabetics, patients taking lipid lowering drugs, chronic disease conditions, pregnant lady and lactating mothers were excluded from the study. Blood Hb% and MCV were obtained from Sysmax XT4K analyzer. The assays were done for serum TC, TG, LDL and HDL using Beckman Coulter AU5800 automated analyzer in the laboratory of Department of Biochemistry and the concentration of VLDL was calculated. Serum ferritin was estimated using ELISA kit from Bio-Detect, USA and statistical analysis was done.

Mean age of study population in our study: 50.5±10.6 years with 22 male and 16 female subjects in each group. Table 1 presents the mean blood Hb%, MCV, Serum TC, TG, LDL, HDL and Ferritin concentrations in two groups of anaemic and non-anaemic subjects.

It is evident from the from above table that there is alteration of lipid profile in anaemic patients with decrease in all components with decreasing haemoglobin concentration except TG and VLDL. The present study found raised levels of both TG and VLDL cholesterol levels in the anaemic subjects, as compared to healthy controls. Similar results were observed by Antappanavar VB et al. in Karnataka.⁴ The present study observed significantly reduced levels for LDL cholesterol only in the anaemic group as compared to controls, no statistical significance was there for increase or reduction of other lipoproteins and TG between both the groups. This finding is contrary to the findings of Shirvari M et al. where they have got significant decrease in all lipoproteins except HDL.⁵ Another study by Chowta NK et al. described significant decrease in lipid profile amongst anaemic patients.¹ A study by Ohira et al. found that the serum level of cholesterol increases following the increased haemoglobin through blood transfusion. They argued that the amount of red blood cells probably affects cholesterol synthesis or its displacement from tissue to plasma. Various other studies have been performed to define the related mechanisms underlying dyslipidaemias in anaemia, especially iron deficiency anaemia (IDA). High TG levels have been explained on the basis of impaired carnitine biosynthesis together with increased TG synthesis and decreased TG degradation in IDA while lower serum cholesterol has been related to be due to decreased hepatic synthesis or dilutional effects of serum.⁴ The exact mechanism by which iron regulates or functions in lipid metabolism has not yet been established.

Iron deficiency anaemia (IDA) is the world’s most widespread nutritional disorder, regardless of age, gender and socioeconomic status, affecting both industrialized and developing countries. The significance of the results obtained by this study is, at present, unclear, perhaps due to small data. The authors feel that in future a larger randomized controlled trial with iron supplementation can be planned for long duration, by adopting more vigilant screening for anaemia and CAD and motivating those suspected of the condition who may be symptomatic or asymptomatic, for follow up in the hospital, where relevant cardiovascular and biochemical investigations could be performed on them.

Table 1: Status of anaemia indices and lipid profile in all the subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anaemic (Mean±SD)</th>
<th>Non-anaemic (Mean±SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g%)</td>
<td>10.96±2.05</td>
<td>13.78±1.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>82.01±13.71</td>
<td>87.08±16.73</td>
<td>0.0051</td>
</tr>
<tr>
<td>Ferritin (µg/dl)</td>
<td>74.56±3.74</td>
<td>110.67±92.64</td>
<td>0.1183</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>171.79±31.81</td>
<td>190.5±41.84</td>
<td>0.6435</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>181.09±45.25</td>
<td>157.15±51.61</td>
<td>0.3045</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>92.41±24.18</td>
<td>107.19±10.18</td>
<td>0.0386</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>45.18±1.41</td>
<td>49.05±5.65</td>
<td>0.1354</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>36.21±9.05</td>
<td>33.99±10.32</td>
<td>0.6320</td>
</tr>
</tbody>
</table>

Fig. 1: Age distribution of study population
Safety Practices in Haemodialysis Unit

Dilip Rangarajan,
Ramprasad Ramalingam,
Ramakrishnan S, Kiran Chandra Patro
Department of Nephrology, NU Hospitals, Bangalore, Karnataka

Introduction

Haemodialysis (Haemodialysis) is a life saving procedure for patients with severe renal failure. There are multiple areas in the delivery of this treatment where things could go wrong if proper attention is not given. Having a check list and corrective actions in place plays an important part in ensuring safety for patients. Adverse events contributing to death in dialysis patients mainly relate to the everyday management of common medical problems and not the technical aspects of RRT. It is important to acknowledge medical errors, encourage the reporting of errors, root cause analysis and improve systems to reduce the likelihood of future errors.

Problems that occur are medication errors, needle disconnections, failure to follow haemodialysis protocols, needle infiltration, falls, equipment / facility failures, and cloting.

Quality of water, reuse of dialyzer, and infection control are key areas of safety risk, and adverse events have been reported in each area. Infection-related causes are second only to cardiovascular events as a cause for mortality among ESRD (End Stage Renal Disease) patients. Inadequate hand hygiene and inadequate disinfection of machine can lead to problems.

We have evolved some safety practices in dialysis and have been implementing the same for few years now. We have looked at the efficacy of the safety practices in this study.

Methods

Retrospective analysis was done of the impact of the various safety practices on the clinical and biochemical parameters of patients on maintenance haemodialysis over a three year period. Statistical analysis was done using vassarstats.

Findings

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12463</td>
<td>11809</td>
<td>13120</td>
<td></td>
</tr>
<tr>
<td>Central line associated infection (CLABSI)/1000 catheter days</td>
<td>7.2</td>
<td>5.68</td>
<td>2.25</td>
<td>0.04</td>
</tr>
<tr>
<td>Missed identity of dialyser(nos)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C Conversion(nos)</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>Bp Misses (%)</td>
<td>2.1</td>
<td>1.4</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>Extravasation (%)</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypotension Recognition(%)</td>
<td>4.4</td>
<td>6.5</td>
<td>14.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Haemoglobin(gm/dl)</td>
<td>8.5</td>
<td>11</td>
<td>9.60</td>
<td>0.19</td>
</tr>
<tr>
<td>S.Albumin (gm/dl)</td>
<td>3.2</td>
<td>2.8</td>
<td>3.1</td>
<td>0.58</td>
</tr>
<tr>
<td>S.Potassium(mEq/L)</td>
<td>5.4</td>
<td>5.7</td>
<td>5.6</td>
<td>0.44</td>
</tr>
<tr>
<td>K+</td>
<td>1.1</td>
<td>1.3</td>
<td>1.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Central Line Rates (%)</td>
<td>24.5</td>
<td>30.9</td>
<td>32.5</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Discussion

With education of the staff, monitoring of hand hygiene through infection control nurses, patients themselves and through CCTV cameras, we have been able to significantly bring down the central line associated blood stream infection rates over a period of time. With regular surface cleaning of the haemodialysis machine surface in between dialysis schedules and with surface cleaning of the patient cots hepatitis C transmission has been curtailed to a great extent. This is also aided by grouping together of positive serology patients to a certain area of the dialysis unit.

Analysis of reasons for blood pressure misses during every shift and strict monitoring both direct and through CCTV has enabled us to reduce it considerably which lead to considerable decrease in morbidity and hospital stays.

Quality of dialysis as measured by biochemical parameters have also been maintained with the various measures of monitoring and actions taken.

One area which has not improved is reduction of central line usage despite various measures taken to motivate patients to go in for permanent vascular access.

Conclusion

Following Safety practices in dialysis units, reducing adverse events significantly is proven in our experience. There is an enormous need for dialysis units in the sub-continent due to the rising incidence of chronic kidney disease. Government and private sectors have started extending this life saving support to the suburban and district head quarters. Nephrologists and Dialysis trained physicians should ensure this expansion occurs without the compromise in safety issues.

References

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