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Anti-coagulation in COVID-19: Dare I Give, Dare I Don’t!

Trupti H Trivedi¹, Priyanshu D Shah²

The world has witnessed over 185 million cases of COVID-19 infection, out of which over 30 million cases are from India. Apart from causing four million deaths, the pandemic has affected almost every aspect of human life globally. Although COVID-19 presents primarily as a lower respiratory tract infection transmitted via air droplets, multi-organ involvement is possible in patients secondary to virus binding on angiotensin-converting enzyme 2 (ACE2) receptors located on different human cells. The severity of lung involvement in COVID-19 infection ranges from asymptomatic or mild pneumonia (81%) to severe disease-associated hypoxia (14%), critical disease associated with shock, respiratory failure and multi-organ failure (5%) or death (2.3%).¹

COVID-19 has a significant impact on the haemato poetic system and homeostasis. Lymphopenia, thrombocytopenia and high Neutrophil/lymphocyte ratio have a role in determining severity of case/prognosis. Furthermore, hypercoagulability is common in hospitalized COVID-19 patients, especially amongst those with severe disease. It is unclear whether COVID-19-associated thrombotic events are due to conventional mechanisms leading to venous thrombo-embolism (VTE), immunothrombosis or a combination of both. This has significant implications in diagnostic and management strategies. Elevated and consistently rising D-dimer levels are associated with clinical deterioration.² The mechanisms contributing to increased thrombosis in COVID-19 involve extensive cross-talk between haemostasis and the immune system.² Emerging evidence suggests that COVID-19 can infect endothelial cells with activation of inflammatory pathways resulting in dysregulation of the endothelium, leukocyte activation, Neutrophil extracellular trap (NET) generation, complement deposition, and platelet consumption. Other sources of endothelial injury include conventional factors like intravascular catheters and mediators of the acute systemic inflammatory response, including cytokines such interleukin (IL)-6 and acute phase reactants as in non COVID-19 patients.

Hypercoagulability in COVID-19 manifests as a spectrum ranging from venous thrombosis involving pulmonary vessels, central venous sinus thrombosis (CVST) and arterial microvascular thrombosis (e.g. “COVID toes”) to large arterial thrombosis with limb ischemia, myocardial infarction, large vessel occlusive(LVO) strokes and other complications like clotting of intra-vascular catheters. A meta-analysis of 42 studies involving 8271 patients showed that overall (VTE) rate was 21% (31% in ICU), with Deep Venous Thrombo-embolism (DVT) rate of 20% (28% in ICU) and Pulmonary Embolism (PE) rate of 13% (19% in ICU) while Arterial thrombo-embolism (ATE) rate was 2% (5% in ICU) in hospitalized patients. The largest study, which included 3334 individuals (829 ICU and 2505 non-ICU) reported stroke in 1.6% and myocardial infarction in 8.9%.³ Thrombotic complications correlate with disease severity (increasing the odds of mortality by 74%) and higher D-dimer(>500 ng/mL) at hospital admission. Mild thrombocytopenia with increase in fibrin, fibrin degradation products, fibrinogen, and D-dimer and prolonged prothrombin time are commonly encountered abnormalities in hospitalized patients. Monitoring of D-dimer is done as a prognostic marker but anti-coagulation therapy is guided by clinical features and monitoring of aPTT for heparin. Rarely anti-factor Xa activity needs to be monitored for patients with BMI ≥40 kg/m² who are unstable or experience unexpected thrombo-embolic/bleeding complications or require prolonged VTE treatment or when heparin resistance is suspected. As usual pathology is de-novo pulmonary thrombosis duplex ultrasound for DVT detection is not recommended routinely. In patients with unexplained hypotension, tachycardia, worsening hypoxia out of proportion to pulmonary findings, computed tomography with pulmonary angiography (CTPA) is the preferred test to confirm or exclude the diagnosis of PE.

Reduced incidence of thrombosis in second wave may be due to better use of anti-inflammatory and anti-viral therapy or early use of anti-coagulation in hospitalized patients. There are multiple national (ICMR, AIMS) and international guidelines (AHS, ACCP, NIH) for use of anticoagulants in COVID-19.⁴ Most guidelines recommend low-dose prophylaxis with un-fractionated heparin (UFH) or low molecular weight heparin (LMWH) in all hospitalized patients and therapeutic dose anti-coagulation in confirmed/strongly suspected cases of PE. Heparin has additional anti-inflammatory and possibly anti-viral properties and less drug-interaction and hence preferred over oral anti-coagulants. LMWH has more predictable action, less requirement for monitoring, and less chances of bleeding. In patients with renal failure and creatinine clearance < 30ml/min or on renal replacement therapy, UFH is preferred. Both heparin and LMWH should be avoided in patients with Heparin induced thrombocytopenia (HIT). Recommendation for intensity of anti-coagulation is variable for ICU patients on mechanical ventilation. A State task force guidelines published earlier in this journal⁵ recommends low, intermediate and high - dose regimens based on severity of COVID-19, bleeding risk and VTE risk. Observational studies comparing intermediate-dose or therapeutic-dose

¹Additional Professor, ²Assistant Professor, Medical ICU, Department of Medicine, LTM Medical College and General Hospital, Mumbai, Maharashtra
anti-coagulation versus prophylactic-dose anti-coagulation have produced mixed results. Both INSPIRATION and ACTION trials have failed to demonstrate advantage of higher prophylactic dose of LMWH/Direct Oral Anti-coagulant (DOAC) in addition to increasing risk of bleeding.\(^6\)\(^7\) In COVID-19 patients with arterial thrombosis leading to myocardial infarction, thrombolysis and/or high dose anti-coagulation is given. Therapeutic dilemma exists for large cerebral infarctions with arterial thrombosis due to COVID-19 as there is increased risk of secondary bleeding.\(^8\) Early initiation of UFH or LMWH in hospitalized (non-ICU) COVID-19 patients within 24 hours of admission has shown to reduce mortality without increasing risk of significant bleeding.\(^9\) Peri-operative and obstetric patients detected to have COVID-19 should receive anticoagulation with UFH/LMWH. If surgery or delivery is expected in 24-48 hours then UFH is preferred over LMWH so that reversal of anti-coagulation is possible when needed.

Usually prophylactic anti-coagulation is not given to COVID-19 patients receiving home treatment. But, if a patient with severe disease is treated at home due to non-availability of hospital bed or is at high risk for thrombosis due to pre-existing disease (cancer, bed-ridden), with low risk of bleeding then anti-coagulation can be given at home. DOACs like rivaroxaban or apixaban are preferred over warfarin due to difficulty in monitoring of prothrombin time for COVID-19 patients at home and increased risk of bleeding. Individuals with documented VTE require a minimum of three months of anti-coagulation therapy. The role of aspirin and other anti-platelet drugs for prophylaxis in COVID-19 is under investigation.\(^10\) Presently there are no separate recommendations for thrombo-prophylaxis in pediatric age group patients with COVID-19.

Another issue that has emerged recently is Covid vaccine related thrombotic events. While immune thrombocytopenia and bleeding without thrombosis are reported after exposure to the messenger RNA (mRNA)-based vaccines, there are reports of CVST, ATE and even splanchnic thrombosis after few days of receiving adenovirus-based vaccines.\(^11\) The latter is diagnosed by episode of thrombosis after 4 to 30 days of vaccination associated with thrombocytopenia, and elevated PF\(^4\)-polyanion antibody assay, resembling HIT type II, described as vaccine induced thrombocytopenic thrombocytopenia (VITT). Recent unpublished research has suggested incidental intravenous administration of vaccine may be responsible for this adverse effect.\(^12\) The overall incidence of such events is extremely low and benefits of vaccination far outweighs the risk, but physicians should be vigilant when occasional patient reports symptoms suggestive of CVST or other thrombotic event after vaccination.

**Summarizing, thrombosis is important in the pathogenesis of severe COVID-19 cases with potentially life-threatening complications secondary to venous or arterial thrombosis. Guidelines for anti-coagulation are dynamic but prophylactic anti-coagulation with UFH or LMWH is recommended for all hospitalized patients. While therapeutic dose of anti-coagulation is required in confirmed and highly suspected cases of PE, myocardial infarction and limb ischemia, in patients of LVO disease with massive cerebral infarctions there is increased risk of secondary hemorrhage. All patients on anti-coagulants should be monitored for bleeding complications. Decision to continue anti-coagulation prophylaxis post-hospital discharge should be taken after considering risk factors for VTE, bleeding and feasibility and not on the basis of D-dimer levels. Role of aspirin and other anti-platelet drugs and recommendations for anti-coagulation in pediatric patients with COVID-19 need to be studied in near future.

**References**

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BP: Blood pressure
Seroprevalence of SARS-CoV-2 Antibodies and Associated Factors in Health Care Workers

Chavhan Smita Santosh¹, Dhikale Prasad Tukaram²*, Kumbhar Maharudra³, Adsul Balkrishna⁴, Gokhale Chinmay⁵, Ingale Aniket⁶, Kirti Kinge⁵, Jadhav Nilam⁷

Abstract

Objectives: To estimate the seroprevalence of SARS-CoV-2 antibodies among HCWs, and to study the factors associated with this seroprevalence.

Material and methods: A cross-sectional study of HCWs from a Dedicated COVID Hospital was conducted from December 2020 to February 2021. Universal sampling for qualitative testing (by COVID-19 IgG rapid test device by Voxpress) was done and the samples which tested positive were subjected to quantitative testing (chemiluminescent immunoassay) by Serial testing.³

Results: A total of 1005 HCWs were tested out of which 124(12.3%) tested positive by qualitative test and 101(10%) tested positive by both tests. Out of the 1005 HCWs, 155(15.4%) were doctors and 496 (49.4%) were nurses. There was statistically no significant difference between the seropositivity of HCWs with regards to the designation, age, place of work, duration of work in this DCH and Comorbidities. Most HCWs received training in Infection prevention and control (IPC) 988(98.3%), used personal protective equipment (PPE) whenever indicated 997(99.2%), performed hand hygiene before and after handling patients or their material 981(97.6%). Out of 1005 HCWs, 116(11.5%) had a history of COVID-19. The seroprevalence in HCWs not having history of COVID-19 was 74(8.3%).

Conclusion: Good infection prevention practices can keep the infection rate in HCWs low. HCWs with mild symptoms should also be tested and asymptomatic HCWs should be screened periodically to decrease the spread of COVID-19.

Introduction

Healthcare workers (HCW) have greater exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and have a higher risk of Corona Virus Disease (COVID-19).¹ Many COVID-19 patients remain asymptomatic or mildly symptomatic, so prevalence estimates based on PCR-positive cases alone can underestimate the true prevalence. IgG antibodies to SARS-CoV-2 generally become detectable beginning 10 – 14 days following infection but may occur later.² Knowing the seroprevalence of SARS-CoV-2 antibodies among HCWs is important to understand COVID-19 spread among health care facilities.

Objectives

To estimate the seroprevalence of SARS-CoV-2 antibodies among HCWs, and to study the factors associated with this seroprevalence.

Material and Methods

Study design and settings: Cross-sectional study of HCWs from a Dedicated COVID Hospital (DCH).

Study period: December 2020-February 2021

Sampling: Universal sampling for qualitative testing and the samples which tested positive were subjected to quantitative analysis (Serial testing).³

Inclusion criteria: Doctors, nurses, security staff, and other staff working in this DCH were considered as HCWs and were included in the study. HCWs working for more than 14 days in this DCH and who gave voluntary informed consent were included.

Exclusion criteria: HCWs who were pregnant or lactating at the time of study were excluded.

Study procedure: Participants had undergone phlebotomy for serum collection and answered the survey questions. Initially, qualitative test of antibodies was done using COVID-19 IgG rapid test device by Voxpress approved by ICMR. The kit used the lateral flow immune-chromatography technique and has a sensitivity of 94% and specificity of 100%. The samples which tested positive were subjected to a quantitative test. For quantitative test the iFlash-SARS-CoV-2 IgG assay, a paramagnetic particle chemiluminescent immunoassay (CLIA) having a sensitivity of 97.3% and specificity of 96.3% was used. Only when both tests were positive the individual was considered as positive (series testing).³

Statistical analysis: Data entry was done by using Microsoft Excel version 2010 and statistical analysis was done using IBM SPSS Statistics for windows, version 22. Chi-square test, Fischer’s Exact test, T Test and ANOVA test were used.

Results

A total of 1005 HCWs were tested out of which 124(12.3%) tested positive by qualitative test for IgG antibodies against SARS-CoV-2. Out of these 124

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Table 1: Seroprevalence in HCWs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>Total (Column %)</th>
<th>IgG positive (Row %)</th>
<th>IgG negative (Row%)</th>
<th>Chi2 value, df, p-value</th>
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<tr>
<td>Designation</td>
<td>Doctors</td>
<td>155 (15.4)</td>
<td>13 (8.4)</td>
<td>142 (91.6)</td>
<td>6.951, 4, 0.266</td>
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<td></td>
<td>Nurses</td>
<td>496 (49.4)</td>
<td>41 (8.3)</td>
<td>455 (91.7)</td>
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<td></td>
<td>PCAs and Housekeeping</td>
<td>151 (15)</td>
<td>18 (11.9)</td>
<td>133 (88.1)</td>
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<td></td>
<td>Phlebotomists and Technicians</td>
<td>38 (3.8)</td>
<td>6 (15.8)</td>
<td>32 (84.2)</td>
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<tr>
<td></td>
<td>Others</td>
<td>165 (16.4)</td>
<td>23 (13.9)</td>
<td>142 (86.1)</td>
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<td>Age</td>
<td>18-30</td>
<td>762 (75.8)</td>
<td>69 (9.1)</td>
<td>693 (90.9)</td>
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<td>31-40</td>
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<tr>
<td></td>
<td>41-50</td>
<td>58 (5.8)</td>
<td>9 (13.8)</td>
<td>50 (86.2)</td>
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<tr>
<td></td>
<td>&gt;50</td>
<td>29 (2.9)</td>
<td>4 (13.8)</td>
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<td>Sex</td>
<td>Male</td>
<td>310 (30.8)</td>
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<td>Female</td>
<td>695 (69.2)</td>
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<td>Education</td>
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<td></td>
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<td>89 (8.9)</td>
<td>16 (18)</td>
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<td>Post-graduation</td>
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<td>10 (83.3)</td>
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<td>Workplace</td>
<td>ICU</td>
<td>321 (32.3)</td>
<td>34 (10.6)</td>
<td>287 (89.4)</td>
<td>0.943, 3, 0.815</td>
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<td>Wards</td>
<td>394 (39.6)</td>
<td>36 (9.1)</td>
<td>358 (90.9)</td>
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<tr>
<td></td>
<td>Others</td>
<td>13 (1.3)</td>
<td>2 (15.4)</td>
<td>11 (84.6)</td>
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<td></td>
<td>ICU with Wards or Casualty</td>
<td>266 (26.8)</td>
<td>28 (10.5)</td>
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<td>Duration of work</td>
<td>&lt; 3 months in DCH</td>
<td>249 (24.8)</td>
<td>21 (8.4)</td>
<td>228 (91.6)</td>
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<td>4-6 months in DCH</td>
<td>329 (32.7)</td>
<td>29 (8.8)</td>
<td>300 (91.2)</td>
<td></td>
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<tr>
<td></td>
<td>7-9 months in DCH</td>
<td>427 (42.5)</td>
<td>51 (11.9)</td>
<td>376 (88.1)</td>
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<td>History of Covid</td>
<td>Yes</td>
<td>116 (11.5)</td>
<td>27 (23.3)</td>
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<td>25.376, 1, &lt;0.001</td>
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<td>No</td>
<td>889 (88.5)</td>
<td>74 (8.3)</td>
<td>815 (91.7)</td>
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<tr>
<td>Think have antibodies against COVID-19</td>
<td>Yes</td>
<td>363 (36.1)</td>
<td>43 (11.8)</td>
<td>320 (88.2)</td>
<td>2.028, 1, 0.154</td>
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<tr>
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<td>No</td>
<td>642 (63.9)</td>
<td>58 (9)</td>
<td>584 (91)</td>
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<td>Comorbidities</td>
<td>Yes</td>
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<td>6 (10.5)</td>
<td>51 (89.5)</td>
<td>0.15, 1, 0.217</td>
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<tr>
<td></td>
<td>No</td>
<td>948 (94.3)</td>
<td>95 (10)</td>
<td>853 (90)</td>
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<td>Prophylaxis</td>
<td>Yes</td>
<td>295 (29.4)</td>
<td>35 (11.9)</td>
<td>260 (88.1)</td>
<td>1.521, 1, 0.217</td>
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<tr>
<td></td>
<td>No</td>
<td>710 (70.6)</td>
<td>66 (9.3)</td>
<td>644 (90.7)</td>
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<tr>
<td>Total</td>
<td>1005</td>
<td>101 (10.05)</td>
<td>904 (89.95)</td>
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</table>

Table 2: Seroprevalence in HCWs who were RTPCR positive

<table>
<thead>
<tr>
<th>Categories</th>
<th>Total (Column %)</th>
<th>IgG positive (Row %)</th>
<th>IgG negative (Row%)</th>
<th>Chi2 value, df, p-value</th>
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</thead>
<tbody>
<tr>
<td>Interval between COVID 19 and sample collection</td>
<td>Days (Mean ± SD)</td>
<td>185.47 ± 66.704</td>
<td>180.63 ± 67.287</td>
<td>186.93 ± 66.84</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>No (Home isolation and 1-10 days Hospitalisation)</td>
<td>57 (49.14)</td>
<td>10 (17.5)</td>
<td>47 (82.5)</td>
</tr>
<tr>
<td>Oxygen Requirement</td>
<td>Yes</td>
<td>5 (4.3)</td>
<td>1 (20)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>ICU support</td>
<td>Yes</td>
<td>111 (95.7)</td>
<td>26 (23.4)</td>
<td>85 (76.6)</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>27 (23.3)</td>
<td>89 (76.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Fishers exact test; *-test was used

samples, 101(81.45%) tested positive by quantitative ELISA test. Both the tests were positive in 101(10%) of HCWs and they were considered as positive by series testing. Out of the 1005 HCWs, 155(15.4%) were doctors, 496 (49.4%) were nurses, 151(15%) were Patient Care Attendants (PCAs) and Housekeeping staff, 38 (3.8%) were Phlebotomists and Technicians, 165 (16.4%) had other designations like security staff, clerk. Most 762(75.8%) of the HCWs were young (18 to 30 years). There was statistically no significant difference between the seropositivity of HCWs with regards to the designation, age, place of work, duration of work in this DCH, Comorbidities, think(believing that they) have antibodies against COVID-19, prophylaxis for COVID 19. Most HCWs received training in Infection prevention and control (IPC) 997(99.2%), performed hand hygiene before and after handling patients or their material 981(97.6%). None of the HCW had taken the COVID-19 vaccine in this study.

The seroprevalence in male HCWs 43(13.9%) was more than that of female HCWs 58(8.3%) and the difference was statistically significant. Out of 1005 HCWs, 116(11.5%) had a history of prior COVID-19. The seroprevalence in HCWs with a history of suffering from COVID-19 disease 27(23.3%) was more than the seroprevalence in HCWs not having this history 74(8.3%) and the difference was statistically significant. The seroprevalence in HCWs with lesser education was more than those with higher education and the difference was statistically significant.

Totally 190(19%) HCWs had taken Hydroxychloroquine, 98(9.8%) had taken Vitamin C, 69(6.9%) had taken Zinc and 72(7.2%) had taken B complex for prophylaxis. Out of the 295 HCWs who had taken prophylaxis 233(79%) had taken it for less than 1 month, 44 (14.9%) had taken it for less than 2-4 months, 12 (4.1%) had taken it for 4-6 months, 62% had taken it for 7-9 months. Totally 80(51.6%) doctors, 182(36.7%) Nurses, 33(9.3%) other employees had taken prophylaxis.

As shown in Table 2, out of the 116 HCWs who had a history of COVID-19, 10 were home quarantined and none of them were positive for IgG antibodies, while 6(50%) of those hospitalized for 21-30 days were positive for IgG antibodies and the difference was just significant.

As shown in Table 3 out of the 116 HCWs who had history of
COVID-19, 30 were positive in the qualitative antibody test. Out of these 30 HCWs, 3 had negative titer (<10) in the quantitative test. The mean titer decreased as duration after COVID positivity increased but the reduction was not significant.

**Discussion**

The seroprevalence in healthcare workers was 10% indicating the previous infection. In another seroprevalence study among HCWs in Mumbai the seroprevalence was similar i.e.11%. In the third round of the Indian Council of Medical Research’s National Serological Survey the seroprevalence was 21.4% in the general adult population and 25.7% in healthcare workers. The difference can be due to the differences in testing methods, study populations, etc.

There was no significant difference in seroprevalence between different categories of healthcare workers. The risk of infection in doctors and nurses is not raised probably due to good IPC activities like universal training of HCWs in IPC, proper use of PPEs, hand hygiene before and after handling patients or their material. A study in the USA and a review article had similar findings. Also place of work, duration of work did not affect seroprevalence, probably due to good IPC activities. Infection can also be acquired by HCWs when they are not caring for patients for example during meals, at home, during travel, markets, where adequate masks, social distancing, hygiene may not be followed. HCWs having higher education were having lesser seroprevalence as they were more likely to follow better infection prevention practices both inside and outside the workplace. In our study males had more seroprevalence and seropositivity did not differ significantly with age or comorbidities. Another study in Mumbai had similar findings.

Among healthcare workers, without a history of suffering from COVID-19, the seroprevalence was 8.3%. These HCWs might be in contact with other HCWs, patients during their infective period and spreading the disease. There were similar findings in another study in Mumbai. The asymptomatic and mildly symptomatic can contribute significantly to the spread of infection so they need to be tested and isolated. The seroprevalence in HCWs with a history of suffering from COVID-19 disease (23.3%) was significantly more than the seroprevalence in HCWs not having this history (8.3%). There were similar findings in another study.

In our study the mean interval between COVID-19 and sample collection was lesser in those with IgG positive than those with IgG negative, also the mean IgG titer was more when this interval was less but the difference was not significant. A study in HCWs in Mumbai had similar findings.

We have used the testing in series approach which improved specificity but sensitivity may be decreased.

**Conclusion**

Good infection prevention practices can keep the infection rate in HCWs low. HCWs with mild symptoms should also be tested and asymptomatic HCWs should be screened periodically to decrease the spread of COVID-19.

**Acknowledgment**

We thank the Municipal Corporation of Greater Mumbai for providing the funding for the testing of antibodies against COVID-19.

**References**

In high grade fever & pain

Nise
Nimesulide 100 mg tablets

Get well. Sooner...

STARTS ACTION WITHIN
15 MINUTES

References

Nise (Nimesulide) 100 mg tablets

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) used to relieve symptoms of inflammation and pain. It is commonly prescribed for conditions such as arthritis, dental procedures, and surgery. However, it is important to note that nimesulide is not recommended for use in children and adolescents.

Precautions:
- Nimesulide should be used with caution in patients with a history of peptic ulcer disease, cardiovascular disease, or kidney disease.
- Nimesulide should not be used in combination with other NSAIDs, aspirin, or other medications that increase the risk of bleeding.
- Nimesulide should be used with caution in patients with a history of liver disease.

For the use of a Registered Medical Practitioner, Hospital or Laboratory only.

Dr. Reddy's Laboratories Ltd., Global Generics India, 7-1-27, Ameerpet, Hyderabad - 500 016, India. www.drreddys.com
Clinical Efficacy and Safety of Remdesivir among Hospitalised Adult Patients with RT PCR Confirmed COVID 19 Requiring ICU Care in Kalyana Karnataka

Swaraj Waddankeri¹, Sharan Shravan Hesarur², Swati S Hiremath², Sangamesh A³, Shoukat AR³, Basavaraj Patil Raikod⁴, Satish Kinagi⁴, Sangram Biradar⁴, Basavaraj Belli⁴, Shivanand Melkundi⁵, Gajendra Singh⁶

Abstract

Background: Despite global efforts, COVID 19 pandemic is still posing a serious challenge with dearth of effective treatment options. Remdesivir has got FDA approval as the first COVID-19 anti-viral agent in adult and paediatric patients (aged ≥12 years and weighing at least 40 kg) requiring hospitalization.

Objective: The present prospective, observational, cross sectional study was planned to evaluate the impact of early initiation of Remdesivir on clinical outcomes in moderate to severe COVID 19 patients requiring ICU care.

Materials and Methods: In this study, 100 consecutive symptomatic RT-PCR positive COVID 19 patients requiring admission to Intensive care unit based on predefined criteria were included for evaluation. All such moderate to severely ill patients were given Remdesivir intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose for the next four days along with other standard care. The main outcome measure analysed was the impact of early initiation of Remdesivir on recovery assessed by number of days in hospital, recovery, biochemical improvements and death.

Results: Out of total 100 patients, 84 patients recovered with Remdesivir along with supportive treatment and were discharged from the hospital. Mean age of patients at presentation 53.5± 14.8 years with 5:1 male preponderance. Mean duration of hospital stay was 11.6 ± 5.9 days. D-dimer, CRP, Ferritin, IL-6 decreased significantly post treatment with P values <0.05, <0.001, <0.001, <0.01 respectively when compared to values at admission. No significant side effects were seen with remdesivir infusion.

Conclusion: This real-world experience suggests that in the subset of hospitalized patients with moderate to severe pneumonia, early use of Remdesivir can lead to better clinical outcomes and help in reduction of associated mortality and morbidity of COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease (COVID-19),¹ has led to a dramatic loss of human life worldwide with more than a million deaths as of September 29th, 2020. SARS-CoV-2 is transmitted from people with clinical disease or asymptomatic infection, primarily through the respiratory route, by both respiratory aerosols and droplets and, less commonly, by direct contact or by fomites.²,³

Despite global efforts and multitude of nations going into nationwide lockdowns, until now COVID 19 has led to nearly 120 million infections with over 2.6 million reported deaths worldwide.⁴ The fragility of healthcare system was exposed across the globe and the healthcare delivery system was challenged across various modalities - diagnosis, quarantine, and treatment of suspected or confirmed cases. Given the virulence of the virus, its contagious nature and high morbidity and mortality associated with this disease, the development of an effective and safe treatment was of public health priority. Reducing time to recovery of hospitalized patients who require supplemental oxygen can have a positive impact on mortality outcomes and is an important aspect of therapies used.

Remdesivir received FDA Emergency Use Authorization (EUA) on May 1, 2020 for treatment of moderate-to-severe COVID-19.⁵ On October 22, 2020, the FDA approved Remdesivir as the first COVID-19 anti-viral agent in adult and pediatric patients (aged ≥12 years and weighing at least 40 kg) requiring hospitalization.⁶ Remdesivir is a monophosphoramidate prodrug of an adenosine analogue that has a broad antiviral spectrum including filoviruses, paramyxoviruses, pneumoviruses and coronaviruses.

Research indicates the potential benefits of early initiation of Remdesivir in patients with COVID-19. With Remdesivir therapy in adult patients hospitalized for severe COVID-19 treated within 10 days of symptoms as compared with placebo, early clinical improvement was documented (18 vs 23 days) and significant lowering in a lower 28-day mortality (11% vs 15%) was seen.⁷,⁸ But release of the recent Solidarity trial results raised several

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Received: 12.06.2021; Accepted: 29.06.2021
In tertiary COVID dedicated centre of Basaveshwar Teaching and General Hospital, Kalaburagi, Kalyana Karnataka attached to Mahadevappa Rampure Medical College, a prospective, observational, cross sectional study based on data collected to evaluate the efficacy and safety of intravenous Remdesivir in hospitalized adult patients with RT-PCR confirmed COVID 19 was initiated.

**Study Design**

In the present study, 100 consecutive symptomatic RT-PCR positive COVID 19 patients admitted from 17th July to 10th October 2020 were evaluated. COVID 19 patients who were RT PCR positive, requiring admission to Intensive care unit, defined as hypoxia (SpO2 ≤ 94% on room air), HRCT showing lesions of COVID 19 (ground glass opacities), raised inflammatory markers (D Dimer, Ferritin, LDH, IL-6) either of these parameters in isolation or combination were included for evaluation.

Asymptomatic patients aged < 18 years and > 80 years with normal HRCT thorax, pregnant and nursing mothers, underlying chronic or newly diagnosed liver and / or renal dysfunction and pre-existing malignancy were excluded from evaluation. Written informed consent was obtained from each patient or from the patients’ legally authorized representative if the patient was unable to provide consent.

Patients who had moderate to severe disease, Remdesivir was administered intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily for the next four days, with other standard care (like enoxaparin, methylprednisolone/dexamethasone, IV antibiotics as per the hospital protocol) according to the standard of care given by Rajiv Gandhi University of Health Sciences (RGUHS), Bengaluru Karnataka in accordance with the recommendations of RGUHS and ICMR.

**Outcome Measures**

The main outcome measure analysed was the impact of early initiation of Remdesivir on recovery assessed by number of days in hospital, clinical improvement, biochemical improvements in the markers of inflammation. Data on clinical and laboratory findings, including length of hospital stay (LOHS), CT scans for assessing involvement of lungs, comorbidities, mortality, and safety outcomes (adverse events [AEs], serious adverse events [SAEs], were recorded and analysed. Demographic parameters analysed included age, sex, and comorbidities (diabetes mellitus, hypertension, CKD, chronic heart disease [CHD], and chronic respiratory diseases among others) were also assessed.

**Statistical Analysis**

The collected data was initially analysed using Python 3 for basic data exploration and visualisation using Jupiter Notebook. Statistical inferences were made using the PASW Statistics 18 (formerly SPSS Statistics). *Limitations*: ‘Those who did not survive’ (‘Expired’) sample size is low and not statistically valid for significance testing, but readily helps in knowing the treatment related outcome trend. This analysis was powered by Medeva (https://medeva.io), analytics embedded Electronic Health Record platform.

Data was analysed by using two-sided testing for all the statistical deductions and the statistical significance level was p < 0.05. Continuous variables were expressed as mean ± standard deviation. Statistical analysis was done for lab parameters and the change in the lab parameters at discharge was compared with that at admission, using “Paired t test”. The frequencies of demographic and clinical characteristics of populations are

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**Table 1: Demographic and clinical profile at admission**

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<th>Number of patients (n) = 100</th>
</tr>
</thead>
<tbody>
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<td><strong>Demographic Details</strong></td>
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<td>Men</td>
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<tr>
<td>Women</td>
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<tr>
<td>BMI</td>
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<tr>
<td><strong>Vital parameters</strong></td>
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<tr>
<td>≤ 94%</td>
</tr>
<tr>
<td><strong>Personal history</strong></td>
</tr>
<tr>
<td>H/O covid in the family</td>
</tr>
<tr>
<td>Health care worker</td>
</tr>
<tr>
<td>Associated co-morbidities</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Ischemic heart disease (IHD)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Bronchial Asthma</td>
</tr>
<tr>
<td>Evans syndrome</td>
</tr>
<tr>
<td>More than 1 co-morbidity</td>
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</tbody>
</table>

* Mean ± SD; # Number of patients
Oxygen requirement in patients (n=100)

<table>
<thead>
<tr>
<th>Percentage involvement of lung</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25% involvement</td>
<td>19</td>
</tr>
<tr>
<td>26 - 49% involvement</td>
<td>22</td>
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<tr>
<td>50 - 75% involvement</td>
<td>53</td>
</tr>
<tr>
<td>&gt; 75% involvement</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2: Lung involvement (n=100)

Expressed as the number (percentage).

Results

A total of 100 patients with moderate-to-severe COVID-19 infection confirmed by RT-PCR received remdesivir, the median (range) age was 53.5±14.8 years, with the majority being male (n = 80; 80.0%; Table 1), with an average BMI of 24.1 ± 4.6. Most common presenting symptoms were fever 89%, breathlessness 88%, cough 76%, myalgia 48%, sore throat 26%. Loss of smell / taste was seen in 5 patients (Figure 1).

Most common comorbidity was diabetes mellitus (44%) and 20% of patients had more than one comorbidity. Mean duration of symptoms before hospital admission was 4.1 ± 2.6 days. Mean duration of hospital stay was 11.6 ± 5.9 days.

Out of 100 patients, 25 patients did not require supplemental oxygen. 75 patients required supplemental oxygen therapy (Figure 2). Oxygen was delivered through nasal prongs for 4 patients, through facemask for 22 patients, through non-re-breathable facemask for 44 patients, high flow nasal oxygen for 30 patients. Non-invasive ventilation was used for 23 patients who did not respond to the lower modality of oxygen delivery, were provided with the next higher modality of oxygen delivery. The patients were shifted from one mode of oxygen delivery to other based on the clinical response.

CT chest imaging was performed on a 16-slice CT machine (Philips). It consists of contiguous axial sections of thickness 5mm of thorax in cranio-caudal direction. Reconstruction was done with a slice thickness of 1.25 mm. All images viewed in a range of lung and mediastinal window settings.

Table 2 shows percentage involvement of the lung lobes. A semi-quantitative scoring system was used to quantitatively estimate the lung involvement of all these based on the area involved. Each of the 5 lobes was visually scored from 0-5. As 0 = no involvement; 1 = < 5% involvement; 2 = 5% involvement; 3 = 5-25% involvement; 4 = 25-75% involvement; 5 = > 75% involvement. The total CT score is the sum of lung involvement (5 lobes, score 1-5 for each lobe, range 0 none, 25 maximum) was determined. Mean CT severity score was 12.7 ± 5.5.

Table 3 shows the characteristic features of lung involvement with the number of lobes involved and the distribution of the lesions. The most common pattern of disease included the number of lobes involved and the features of lung involvement with involvement of the lung lobes. A semi-quantitative scoring system was used to quantitatively estimate the lung involvement of all these based on the area involved.

### Discussion

Effective therapeutics for COVID-19 are the need of the hour to reduce the fatality of the COVID 19 infection, especially in those with underlying medical conditions and those who have immunocompromised status. The impact in terms of hospital stay and associated mortality of COVID 19 has been severe in patients with comorbidities. Also, the minimum incubation period, that is first indicator of viral infection, to the onset of the first symptom to and exposure could be anywhere between 5 days to 14 days. Faster the treatment initiation or minimum interval between symptom onset and treatment initiation better are the outcomes.

Remdesivir is the first specific drug in the management of COVID-19. Most global evidence have evaluated the effects of remdesivir in COVID-19 by comparing with placebo or different durations of treatment. The ACCT-1 study group which compared remdesivir against placebo showed that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Another study by Spinner and colleagues of 584 patients pointed that 5 days of remdesivir had a higher odd of having a better clinical status distribution compared with those receiving standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; P = .02). But very few studies have focussed on impact of early initiations of therapy and its clinical impact. It is important to focus on early initiation of Remdesivir therapy and objective of this study was to evaluate clinical benefits of early treatment.

Other than the timing of initiation of Remdesivir, some studies have also evaluated the impact of duration of Remdesivir therapy on clinical outcomes in COVID 19 patients. A study...
than half of our patients had other severe disease and comorbidity. More cross sectional study had moderate to in this prospective, observational, stay was evaluated. Most patients treatment with Remdesivir and other admitted and their response to positive COVID 19 patients were given for 5 or 10 days to patients outcomes when Remdesivir was demonstrated that adding Baricitinib by Goldman JD et al. demonstrated that there is no difference in clinical outcomes when Remdesivir was given for 5 or 10 days to patients with severe Covid-19 not requiring mechanical ventilation. Another study demonstrated that adding Baricitinib to Remdesivir could further reduce the recovery time and accelerate decrease in lung disease. It prevents the progression of lung infection to severe pneumonia, which may lead to acute respiratory distress syndrome, which is the common cause of death among COVID-19 patients. In our centre experience, the mean duration of symptom onset and hospital admission was 4.1 ± 2.6 days, and Remdesivir was initiated on admission and that resulted in mean duration of hospital stay of about 11.6 ± 5.9 days, as compared to Pan F et al. have reported the mean duration of hospital stay was 17.4 ± 4 days. This may be due to better understanding of the treatment strategies and availability of drugs like Remdesivir in July 2020 as compared to January 2020 when the study was conducted due to limited treatment options. COVID-19 patients suffer from similar symptoms such as fever, breathlessness on exertion and rest, dry cough, myalgia and sore throat. The study indicated the percentage of complaints by expired patient; 81% fever (p=0.0718), 88% breathlessness on exertion (p=0.126), 81% dry cough (p=0.0108), 63% myalgia (p=0.3472), 25% cough with expectoration (p=0.0000), 31% sore throat (p=31%) and 25% breathlessness at rest (p=0.0000) and improved patients; 90% fever (p=0.0718), 80% breathlessness on exertion (p=0.126), 65% dry cough (p=0.0108), 45% myalgia (p=0.3472), 5% cough with expectoration (p=0.0000), 25% sore throat (p=31%) and 4% breathlessness at rest (p=0.0000). The overall observation of COVID-19 patients with respect to complaints of symptoms indicates that improved patients had reduced complaints regarding the symptoms as compared to the expired patients (Figure 1).

The treatment of COVID-19 symptoms suggested higher chances of improvement and decrease in the mortality rate. In terms of mortality, a significant difference was seen in the duration of symptoms before hospitalization in patients suffering from symptoms for more than 8 days and patients hospitalized within a week (Figure 3). The study presented evidence suggesting that COVID-19 patients hospitalized earlier showed decreased mortality as compared to the patients hospitalized later.

The data analysis revealed that the mortality group had significant comorbidities like hypertension and diabetes and two third of expired patients were smokers (Figure 4). Based on the Odds ratio as compared to >60 age group patients, <=60 age group patients hospitalized later.  

### Table 3: HRCT Chest Patterns with lobar involvement

<table>
<thead>
<tr>
<th>Pattern</th>
<th>No. of pts.</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>LLL</th>
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<tr>
<td>Ground Glass Opacities</td>
<td>100</td>
<td>90</td>
<td>79</td>
<td>91</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>Consolidation</td>
<td>24</td>
<td>14</td>
<td>14</td>
<td>24</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Crazy Paving Pattern</td>
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<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Vascular Dilation</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subpleural Bands</td>
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<td>2</td>
<td>1</td>
<td>7</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Nodular Opacities</td>
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<td>1</td>
<td>1</td>
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</table>

RUL – Right upper lobe, RML Right middle lobe, RLL Right lower lobe, LUL Left upper lobe and LLL Left lower lobe.

### Table 4: Inflammatory Markers

<table>
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<tr>
<th>Marker</th>
<th>Min. (ng/mL)</th>
<th>Max. (ng/mL)</th>
<th>Mean ± SD (pg/mL)</th>
<th>p value</th>
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<tr>
<td>CRP at admission</td>
<td>1.7</td>
<td>145.0</td>
<td>49.1±32.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP at discharge</td>
<td>6.6</td>
<td>145.0</td>
<td>25.8±33.8</td>
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</tr>
<tr>
<td>D-DIMER at admission</td>
<td>108.0</td>
<td>9684.0</td>
<td>1436.9±1941.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>D-DIMER at discharge</td>
<td>116.0</td>
<td>7690.0</td>
<td>1004.7±1619.5</td>
<td></td>
</tr>
<tr>
<td>FERRITIN at admission</td>
<td>22.2</td>
<td>2862.0</td>
<td>477.7±377.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FERRITIN at discharge</td>
<td>12.4</td>
<td>921.0</td>
<td>308.5±225.3</td>
<td></td>
</tr>
<tr>
<td>IL-6 at admission</td>
<td>2.0</td>
<td>271.0</td>
<td>33.7±60.9</td>
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<tr>
<td>IL-6 at discharge</td>
<td>2.0</td>
<td>271.0</td>
<td>33.7±60.9</td>
<td></td>
</tr>
</tbody>
</table>

CRP (mg/L) at admission (n=100) 24 14 14 24 16 24 | FERRITIN (mg/L) at admission (n=100) 108.0 9684.0 1436.9±1941.3 | D-DIMER (mcg/mL) at admission (n=95) 116.0 7690.0 1004.7±1619.5 | FERRITIN (mg/L) at discharge (n=100) 22.2 2862.0 477.7±377.2 | D-DIMER (mcg/mL) at discharge (n=95) 116.0 7690.0 1004.7±1619.5 | IL-6 (pg/mL) at admission (n=95) 2.0 271.0 33.7±60.9 | IL-6 (pg/mL) at discharge (n=95) 2.0 271.0 33.7±60.9 |
respiratory rate has a chance to improve 4.53 times (p=0.055) more in normal patients than tachypnoea patients (95% CI - 0.97 to 21.23) and for NLR, showed <6 patients 4.2 times more (p=0.020) likely to have improved as compared to >=6 patients (95% CI - 1.25 to 14.11) (Figure 5).

Apart from the clinical outcomes, significant improvements in laboratory findings were also noted in the study. Mean CRP significantly reduced from 49.1±32.6 mg/L to 25.8±33.8 mg/L. Mean D-Dimer value at admission was 1436.9±1941.3 mcg/mL indicating high risk of thrombosis in many of them, which reduced to 1004.7±1619.5 mcg/mL at the time of discharge. IL-6 is a marker to estimate the risk of cytokine storm was significantly high (119.0±255.1 pg/mL) at presentation and it had reduced drastically in patients who improved at the time of discharge from hospital (33.7±60.9 pg/mL) (Figure 6).

Significant improvements were also observed in serum ferritin, ESR and LDH values. LDH values in patients that improved decreased from 657.6 U/L (CI=95%) at admission to 308.4 U/L (CI=95%) at the time of discharge. In improved patients, ferritin in the blood reduced form 501.0 ng/ml to 247.0 ng/ml (CI=95%) (Figure 6).

Francone M et al. have shown that patients with CT score of >18 were at a significantly higher risk of death.12 The mean CT score was 12.7 ± 5.5 in our study. Mean CT score among those who died was 16.1 ± 5.6. (Figure 7).

The Haematological and biochemical profile summaries of the patients enrolled in the study have been mentioned in Table 5.

Limitations of the study: Owing to the ethical restraints of the current pandemic we could not do a case control study. It is difficult to know the impact of remdesivir from other

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**Fig. 5: Odd ratio comparison of normal individuals vs individuals having tachypnoea**

**Fig. 6: Improvements in laboratory findings**

patients are 4.7 times (p=0.007) more likely to have improved (95% CI - 1.53 to 14.44) and for SPO2, >=90 group patients have a probability of 6.7 times (p=0.002) to improve18 (95% CI - 1.97 to 22.7). The Odds ratio indicated that the
COVID-19 validated medications such as steroids, LMWH, antibiotics as it is one of the few studies to report uniform use of all these agents.

**Conclusion**

In summary, in the subset of hospitalized patients with moderate to severe pneumonia, our centre experience findings incline us towards early use (within 8 days of symptom onset) of remdesivir for better clinical outcome and help in reduction of associated morbidity and mortality of COVID-19.

**Additional information**

All authors contributed to study design, data collection, and interpretation. All authors critically reviewed and approved the final manuscript for publication. All authors had full access to the complete study manuscript for publication. All authors had full access to the complete study manuscript for publication.

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Four Cases of Multisystem Inflammatory Syndrome in Adults Associated with SARS-COV-2 Infection – An Overview of Clinical Features, Diagnosis and Treatment

G Varadaraj*, B Sangeetha2, Sunmeet Sandhu3, G Santhiya4

Abstract
The varied spectrum of presentation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is intriguing. Multisystem inflammatory syndrome in children (MIS-C) is a well described and documented condition that is associated with the active or recent COVID-19 infection. A similar presentation in adults is termed as Multisystem inflammatory syndrome in Adults (MIS-A).

With only very limited cases reported from the west, MIS-A is considered a rare and serious complication of COVID-19. However, it is not as uncommon as we think. Many cases go undiagnosed for lack of COVID-19 like symptoms and unawareness among treating clinicians about this newer clinical entity. Further, antibody testing and inflammatory markers are not easily available in many of the Indian hospitals especially in rural India where the second wave had been intense, thereby making it difficult for the diagnosis of MIS-A. Also, there is no clear treatment guideline for MIS-A unlike MIS-C where the treatment protocol is well laid out.

Awareness about MIS-A among treating clinicians can thus help in further evaluation and increased identification of the syndrome at the early stages thereby helping in the early institution of treatment. Our tertiary COVID care hospital in South India which has handled about 5200 cases of COVID-19 is been able to identify 04 cases of MIS-A proving that this clinical entity is not as rare as it is thought but lacks reporting and prompt identification. Here we describe 04 cases of MIS-A and strive to bring in the various aspects of it, including the clinical presentation, laboratory markers, diagnostic criteria and treatment considerations in this post second wave of the COVID-19 pandemic in India.

Introduction
The Coronavirus disease 2019 (COVID-19) pandemic has emerged as the biggest threat to mankind after nearly about 100 years of the deadly Spanish Flu, commonly termed as the “Bombay Fever” in India. While the first wave of COVID-19 wreaked havoc in the developed countries of the west, the disease unfurled its lethality during its second wave in the Indian subcontinent during the months of April and May 2021. While intensive care units in India saw unprecedented admissions due to COVID-19 especially in the second wave, the disease is far from over and we are gearing up to face the next wave and also the sequela of the culminating second wave.

The varied spectrum of presentation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is intriguing. Multisystem inflammatory syndrome in children (MIS-C) is a well described and documented condition that is associated with the active or recent COVID-19 infection. A similar presentation in adults is termed as Multisystem inflammatory syndrome in Adults (MIS-A). The Centre for Diseases Control (CDC) has recognized this recent entity in adults and has published a case series of 27 cases from United Kingdom and United States during the period March-August 2020. Though MIS-A is claimed to be a rare post-COVID-19 syndrome with only limited cases identified in the west, our tertiary COVID care hospital in South India which has handled about 5200 cases of COVID-19 is been able to identify 04 cases of MIS-A proving that this clinical entity is not as rare as it is thought but lacks reporting and prompt identification.

Here we describe 04 cases of MIS-A and strive to bring in the various aspects of it, including the clinical presentation, laboratory markers, diagnostic criteria and treatment considerations in this post second wave of the COVID-19 pandemic in India.

Case 1
A previously healthy 26 year old male presented with complaints of five days of fever associated with generalized myalgia, three days of abdominal pain and two days of decreased urine output. There was no respiratory symptom associated with his illness. On admission, his COVID-19 RT-PCR was negative. On evaluation, he was febrile (103.8F), tachycardic (126/min) and hypotensive (84/59 mm Hg). His general examination was unremarkable except for weak peripheral pulses. On investigation, he had elevated inflammatory markers and evidence of acute kidney injury (Table 1). Transthoracic Echocardiogram (TTE) revealed normal study with 65% left ventricular ejection fraction (LVEF). Computed Tomography (CT) of his Chest and abdomen did not reveal any significant abnormality. On high index

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*Corresponding Author
Received: 24.06.2021; Accepted: 02.07.2021
Table 1: Demographic, clinical features, investigation and mainstay treatment of four cases of MIS-A

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Underlying medical condition(s)</th>
<th>Clinical Signs &amp; Symptoms</th>
<th>Previous respiratory illness/SARS CoV 2 testing</th>
<th>RT-PCR for SARS-CoV-2</th>
<th>Total SARS-CoV-2 Antibody (IgG+IgM) (Normal &lt; 1.0) AU/mL</th>
<th>CRP (mg/dL) (Normal 0-6)</th>
<th>D-dimer (ng/mL) (Normal 0-200)</th>
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<th>Troponin I (ng/L) (Normal 0-200)</th>
<th>LDH (U/L) (Normal 81-234)</th>
<th>Procalcitonin (ng/L) (Normal 0-5)</th>
<th>Hemoglobin (g/dL)</th>
<th>Platelets (cells/mm²)</th>
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</tr>
<tr>
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<td>17.2</td>
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<td>251</td>
<td>1.37</td>
<td>10.8</td>
<td>10910/N72</td>
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</tr>
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Table: Demographic, clinical features, investigation and mainstay treatment of four cases of MIS-A

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<td>1.37</td>
<td>10.8</td>
<td>10910/N72</td>
<td>2.73</td>
</tr>
</tbody>
</table>

of suspicion for SARS-CoV-2 infection, his RT-PCR was repeated and found negative again. Serial blood cultures and Urine culture were sent. While he was empirically managed as a case of sepsis with shock, his Anti-SARS-CoV-2 antibody were significantly raised to 46.35 AU/mL, confirming a recent previous COVID-19 infection. He was managed with intravenous crystalloids and Norepinephrine infusion in view low blood pressure. Also, empirical low molecular weight heparin (LMWH) and antibiotics were given till initial negative blood culture reports were available. His initial Sequential Organ Failure Assessment (SOFA) score was four (Norepinephrine requirement and raised creatinine) and thereafter assessed every 24 hours. There was no raise in SOFA score on subsequent days of admission and individual was taken off norepinephrine after four days of admission. Patient showed gradual improvement and fever subsided after 11 days of illness. He was discharged from the hospital after 16 days of admission.

Case 2

This case was reported by us to the British Journal of Dermatology and accepted for publication as a Research letter (doi:10.1111/BJD.20574). Permission obtained from the journal for reuse in own article.

A 22 year old male presented with fever, tachypnea and tachycardia. He had bilateral non-exudative conjunctival injection, fissured lips with hyperpigmentation, multiple generalized erythema and hyperpigmented macules over his face, trunk and all extremities. Though his RT-PCR for COVID-19 was negative (done twice), his Anti-SARS-CoV-2 antibody were raised to 18 AU/mL. He was managed as a case of Kawasaki-like Multisystem inflammatory Syndrome in adults with LMWH and empirical antibiotics. His initial SOFA score on admission was one (raised bilirubin). Individual showed gradual improvement and fever subsided after 14 days of illness. He was discharged from the hospital after 26 days of admission.

Case 3

A 21 year old previously healthy male presented with complaints of fever of 03 days duration associated with generalized myalgia. There were no potential diagnostic clues for his illness. Individual did not have skin rashes or respiratory symptoms. On admission, his COVID-19 RT-PCR was negative. On evaluation, he was febrile (104°F), tachycardic (116/min) and hypotensive (78/42 mm Hg) and had weak peripheral pulses. On investigation, he had elevated inflammatory markers (Table 1). TTE and CT Chest & Abdomen did not reveal any significant abnormality. His repeat RT-PCR also turned out negative. Serial blood cultures and Urine culture were sent while he was empirically managed as a case of sepsis with shock. However, his Anti-SARS-CoV-2 antibody were raised to 17.2 AU/mL, confirming a recent previous COVID-19 infection. He had persistent fever and hypotension despite fluid resuscitation requiring Norepinephrine infusion. Empirical LMWH and intravenous antibiotics were given till initial negative blood culture reports were available. However, on second day of admission, he developed multiple maculopapular rashes over both the extremities, palms and soles. His fever gradually declined in intensity and rashes started to disappear after the fifth day of admission. His fever
30 year old male presented with complaints of fever and swelling over right side of neck of 03 days duration associated with generalized myalgia. He did not have skin rashes or respiratory symptoms. His COVID-19 RT-PCR on admission and a repeat test were negative. On evaluation, he was febrile (103.6°F), tachycardic (127/min) and hypotensive (88/56 mm Hg). On investigation, his inflammatory markers were elevated (Table 1). TTE and CT Chest & Abdomen did not reveal any significant abnormality. He was empirically managed as a case of sepsis with shock awaiting blood and urine culture reports. However, his Anti-SARS-CoV-2 antibody were raised to 37.2 AU/mL, confirming a recent previous COVID-19 infection. His neck ultrasound showed enlarged cervical lymph nodes at levels II, III, IV and V. Like the patient described previously, he had persistent fever and hypotension despite fluid resuscitation requiring Norepinephrine infusion. Empirical LMWH and intra-venous antibiotics were given till initial negative blood culture reports were available. His fever gradually declined in intensity and he became afebrile after 07 days of admission. He was taken off Norepinephrine on the fourth day of admission. His initial SOFA score was four (Norepinephrine requirement, acute kidney injury) and thereafter assessed every 24 hours. There was no raise in SOFA score on subsequent days of admission. He was discharged from the hospital after 17 days of admission.

**Discussion**

During the current COVID-19 pandemic, several cases of multisystem inflammatory syndrome in children (MIS-C) have been increasing in USA and Europe. As of December 4, 2020, 1288 pediatric MIS-C cases and 23 deaths have been reported in USA. Since June 2020, several reports of a similar multisystem inflammatory syndrome in adults (MIS-A) have been reported; the list of 27 cases has been published in Oct 2020 by Centre for Disease Control (CDC) which fits the description of MIS-A. Another report of 15 cases of MIS-A was recently reported in May 21 by Giovani et al in JAMA network. There are no available case series or reports of MIS-A originating from the Indian subcontinent.

CDC report has highlighted that adult patients of all ages can develop hyper-inflammatory syndrome either with current SARS-CoV-2 infection or as a post infectious phenomenon. 30% adults had negative PCR and positive COVID-19 antibody suggesting MIS-A to be a post infectious phenomenon although persistent extrapulmonary infection might be possibility. In our series, all 4 patients were RT-PCR negative on repeated testing suggesting that a vast majority of asymptomatic COVID-19 patients who develop features of MIS-A might have been missed. There is a dilemma regarding interval between infection and MIS-A. It took 2-5 weeks to develop MIS-A from prior COVID-19 symptoms onset. While 30% patients reported by CDC never had any preceding respiratory symptoms, none of our patients had any respiratory symptoms making it difficult for actual estimation of prior infection. Hence, it becomes pertinent to do COVID-19 antibody testing along with RT-PCR to facilitate timely recognition of MIS-A and adequate treatment.

MIS-A tends to be predominantly affecting the immunologically robust young individuals. Among the 16 patients reported by CDC, 08 patients were less than 35 years of age, another 08 patients were less than 50 years of age and none were above 50 years of age. A similar feature was observed in our series with all 4 patients being less than 35 years of age. Also, while 09 out of 16 patients reported by CDC never had any previous co-morbidity, none of our 4 patients had any co-morbidity. This reiterates the fact that MIS-A tends to affect the young and immunologically better individuals.

The initial symptoms for all of our 04 patients were fever and myalgia. While three patients were hypotensive on initial presentation requiring vasopressor support, associated skin lesions and evidence of acute kidney injury were noted in two patients. Pleural effusion and cervical lymphadenopathy were documented in one patient each. The average duration of fever was 11 days since the onset of symptoms and the average duration of Norepinephrine infusion requirement was 4.3 days. The clinical findings commensurate with the cases reported earlier where the commonest findings included fever, gastrointestinal symptoms, dermatological manifestation and pleural effusion.

Liver enzyme abnormality in COVID-19 is not uncommon and the most common pattern of liver abnormality is the elevation of aminotransferases. The pathogenesis for such elevation is multi-factorial. The commonest attributed etiologies include direct liver injury, hepatic ischemia and drug induced liver injury.

We adopted the Morbidity and Mortality Weekly Report (MMWR) criteria for diagnosing multisystem MIS-A in our patients (Table 2). Laboratory testing for inflammatory markers is the key to diagnosis as many of the presenting symptoms were non-specific and did not have respiratory complaints. The commonest parameters which were elevated include serum Ferritin, C-reactive protein, D-dimer and Troponin. Majority of these tests are not easily available especially in
rural India and even if available, they have huge financial implications for the patient. Hence, these testing should be reserved for clinically suspected and indicated patients with multi-organ involvement rather than being used as screening tool for all patients with fever.

Management strategies

Based on the case reports fulfilling working case definition of MIS-A, potential therapies used were intravenous immunoglobulin, aspirin, anticoagulation, corticosteroids and tocilizumab. As understanding of MIS-A is evolving, treatment protocols are yet to be standardized. Of note will be to monitor patients receiving tocilizumab for emergence of coronary artery aneurysm.

Since there is no well laid down treatment protocol for the management of MIS-A patients, there exists a treatment dilemma on whom to be treated aggressively. While use of intravenous immunoglobulin, aspirin, anticoagulation, corticosteroids and tocilizumab were contemplated as potential therapies, overzealous use of the same can result in more risk than benefit to the patient.

Sequential Organ Failure Assessment (SOFA) Score is a mortality risk predictor for patients who are critically ill. The scoring is based on various lab parameters and clinical data of six organ systems obtained on admission and at every 24 hours thereafter. The SOFA score uses the worst lab and clinical value in the preceding 24 hours for calculation. It helps in the assessment of level of organ damage and thereby predicts the mortality risk.

Hence, we decided to use corticosteroids, immunoglobulin and tocilizumab only for moderate to severe organ dysfunction indicated by a SOFA score of more than 6 or change in SOFA score by 2 or more points. None of our patients had a SOFA score of more than 6 on admission and also did not deteriorate on subsequent days thereby avoiding the need for escalation of treatment modalities. Further, follow up cardiac evaluation did not show any sequelae to any of our patients.

We highlight this case series to reiterate the presence of multisystem inflammatory syndrome in adults associated with COVID-19 and timely diagnosis through identification of clinical symptoms and necessary investigation for inflammatory markers. Antibody testing should be undertaken in adults with signs and symptoms compatible with MIS-A case definition when COVID-19 RT PCR is negative. It is pertinent that multidisciplinary approach be considered for optimum outcome in patients.

Conclusion

MIS-A though a rare and serious complication of COVID-19, it is not as uncommon as we think. Many cases go undiagnosed for lack of COVID-19 like symptoms and unawareness among treating clinicians about this newer clinical entity. Further, antibody testing and inflammatory markers are not easily available in many of the Indian hospitals especially in rural India where the second wave had been intense, thereby making it difficult for the diagnosis of MIS-A. Awareness about MIS-A among treating clinicians can help in further evaluation and increased identification of the syndrome at the early stages thereby helping in the early institution of treatment. Also, there is no clear treatment guideline for MIS-A unlike MIS-C where the treatment protocol is well laid out. Awaiting treatment guidelines for MIS-A, clinicians can resort to sequential organ failure assessment and may up-titrate the treatment modalities with systemic corticosteroids, immunoglobulins and tocilizumab, if deemed necessary. A cautious wait and watch approach would be ideal for those patients having mild symptoms of MIS-A and no further disease progression, rather than staring corticosteroids, tocilizumab upfront.

Acknowledgements

We are thankful to the British Journal of Dermatology for granting permission to include a case published in their journal in this article as a part of larger patient data base.

References

India’s Novel Immunomodulator

For Gram –ve Sepsis,

Sepsivac®
(Heat killed Mw)

Immunomodulatory Action

- Potent TLR 2 agonist
- Poly TLR antagonist (TLR 4,5,7,9) to control cytokine storm
- Induces innate immune response by inducing Th 1
- Reverses gene expression induced in sepsis

An adjunct therapy in Gram-ve Sepsis

- Offers 11% reduction in mortality & significant improvement in SOFA score
- Significant reduction in days on ventilator, vasopressor, length of ICU & hospital stay

Intradermal Administration Dosage

0.3 ml per day for 3 consecutive days
(0.1 ml intradermal at 3 different sites)

Each kit contains:

- 1 vial
- 3 syringes
- 3 needles of 24 G (to draw medicine)
- 3 needles of 26 G (to inject medicine)

Approved by DCGI
Comparison of Predictive Ability of Epidemiological Factors, Inflammatory Biomarkers, and CT Severity Score for Mortality in COVID-19

Ashish Jain¹, Rajeev Kasliwal², Srishti Suresh Jain², Divyansh Gupta³, Rohit Jain³, Anand Jain³, Ravi Jain³*

Abstract

Introduction: COVID-19 patients are categorized as per their clinical severity and their level of care is decided based on the clinical severity. Apart from clinical severity of patients, a need for robust predictors was also felt for early categorization and accurate prediction of final fatal outcome in hospitalized patients.

Material and Method: In this retrospective observational cohort study all the adult patients admitted during November month were included. Available data for epidemiological factors, inflammatory biomarkers and CT severity score were collected and analyzed by univariate and multivariate logistic regression analysis to know predictive ability of each variable. A Receiver operating characteristic analysis was done to compare the predictive ability of each factor for final outcome of death.

Results: We analyzed records of 735 total patients. Most of them were male (72.38%), have a median (IQR) age of 60 years (50-69). Diabetes (42.85%), and hypertension (39.86%) were the most common co-morbidities.

After univariate and multivariate regression analysis we could find that CRP, D-Dimer and CT severity score levels only can predict final outcome of death. During multivariate regression and receiver operative characteristic (ROC) analysis also, age and Charlson’s co-morbidity index failed to predict in hospital mortality. CRP and D-Dimer on admission positively predicts final outcome of in hospital mortality with AUROC of 0.749 (p=0.007, Cl 0.61-0.88), and 0.864 (p=0.000, Cl 0.74-0.9) respectively. Whereas, CT severity score had AUROC 0.73 (p=0.014, CI 0.575-0.83). Cut off for CRP was 45 mg/L (Sn 0.8, Sp 0.56), D-dimer was 1000 µg/L (Sn:0.8, Sp: 0.9), and CT severity score was 15 (Sn 0.8, Sp 0.58).

Conclusion: CRP level of 45 mg/L, D-dimer level of 1000 µg/L and CT severity level of >15 at the time of admission can be added to conventional clinical severity algorithm to more accurately predicting final outcome and stratifying the level of care offered at the time of admission, and hence may improve odds off survival.

Introduction

COVID-19 pandemic has posed many new challenges. Patient management and categorization was largely based clinical severity of the disease criteria laid down by the regional health authorities guidelines.1,2 During several studies it was found that apart from clinical severity, epidemiological factors, Charlson’s co morbidity index, D-dimer and other inflammatory biomarkers can help in predicting disease severity and predict final outcome.3-7 Radiological scores obtained by High resolution Computed tomography (HRCT) was also reported to predict mortality in COVID-19.

During other corona virus epidemic (middle east respiratory syndrome) biomarkers and other laboratory investigation were found to be predicting short term fatal outcomes due to disease.8,9 However during present pandemic case categorization is still done clinically only.

Case categorization based on clinical severity alone may fail to categorize and predict fatal outcomes. Hence, there is need to expand the case severity criteria for better categorization and stratify the level of care offered to these patients to improve outcomes. In the present work we hypothesized to identify epidemiological, bio-markers or radiological factors for predictive ability and compare them for in hospital mortality.

Material and Methods

This is a single center retrospective observational cohort study to explore the performance of epidemiological factors, inflammatory biomarkers and CT severity score for predicting final outcome of death. We included all adult patients admitted to our institute during the month of November'2020, with a clinical and microbiological confirmed diagnosis of COVID-19. All the patients were categorized in three clinical categories (mild, moderate and severe) at the time of admission as per the criteria laid down by the local guidelines. We collected all the available epidemiological, laboratory and clinical data of these patients in standard research forms.
Cases included in Multivariate analysis n (%): 225 (30.61)
Missing cases: 510 (69.39)

Factors included in Multivariate analysis
- Age
- Charlson’s co morbidity index
- CRP on admission
- D-dimer on admission
- CT severity on admission

Univariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Missing Values (n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Charlson’s co morbidity index</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Primary symptoms</td>
<td>7 (0.95)</td>
</tr>
<tr>
<td>Disease severity at admission</td>
<td>103 (14.01)</td>
</tr>
<tr>
<td>CRP on admission</td>
<td>87 (11.84)</td>
</tr>
<tr>
<td>D-Dimer on admission</td>
<td>134 (18.23)</td>
</tr>
<tr>
<td>Ferritin on admission</td>
<td>178 (24.22)</td>
</tr>
<tr>
<td>CT severity on admission</td>
<td>394 (53.60)</td>
</tr>
<tr>
<td>Oxygen therapy requirement</td>
<td>97 (13.20)</td>
</tr>
<tr>
<td>Ventilator requirement</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Final outcome</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Univariable analysis

- Adult 19+ yrs
- Diagnosed case of COVID-19 (by SARS-CoV-2 RT-PCR)
- Admitted to the institute during the month of Nov’ 2020

Fig. 1: Case selection and study matrix

Table 1

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived</td>
<td>665 (90.48)</td>
</tr>
<tr>
<td>Deceased</td>
<td>70 (9.52)</td>
</tr>
<tr>
<td>Total</td>
<td>735</td>
</tr>
</tbody>
</table>

There were 735 total admissions to our COVID-19 care unit. We retrieved all the available data for these patients. Study data evolution is depicted in Figure 1. Majority of these patients were male (72.38%), have a median (IQR) age of 60 yrs (50-69). Diabetes (42.85%), and hypertension (39.86%) were the most common co-morbidities among the admitted patients, with a median (IQR) Charlson’s co-morbidity index of 2(1-3). Most of the patients were admitted with acute respiratory illness (68.16%). Among the admitted patients (27.75%) were admitted to ICU, (11.97%) ventilator support, and among them (9.52%) required invasive ventilation. A comparative statistics chart of epidemiological, laboratory, radiological features and therapies offered to these survivors and deceased group patients is presented in Table 1.

In univariate analysis of independent variables we found that Age, CCI, CRP, D-dimer, and ferritin levels at the time of admission, CT severity score at the time of admission could predict the final adverse outcome of death during the hospitalization. We did a stepwise multivariate analysis using above variables (Table-2). CRP, D-dimer and CT Severity score only could predict final outcome at the entry of binary logistic regression. Hence, these variables along with age and CCI were selected to develop receiver operative characteristic (ROC) analysis curves (Figure 2) and draw comparison among these variables (Table 3). In studied population age and Charlson’s co-morbidity index failed to predict any final outcome and had an AUROC of 0.49 (p= 0.94, CI 0.30- 0.67) and 0.584 (p= 0.36,CI 0.419-0.749) respectively on ROC. CRP and D-Dimer on admission positively predicts final outcome of death and had an AUROC of 0.749 (p=0.007, CI 0.61-0.88), and 0.864 (p= 0.000, CI 0.74-0.99) respectively. Whereas, CT severity score had AUROC 0.73 (p= 0.014, CI 0.575-0.83). As these variables were recorded at the time of admission and we were aiming to successfully predicting final outcome we selected test cut offs with Sensitivity of 0.8 and maximum specificity (Table 3). Cut off for CRP was 45 mg/L (Sn 0.8, Sp 0.56), D-dimer was 1000 µg/L (Sn:0.8, Sp 0.9), and CT severity score was 15 (Sn 0.8, Sp 0.58).

Discussion

COVID-19 is truly a multisystem disorder, which has a final common pathological mechanism behind its manifestations.11 This final common pathway has evidences of pulmonary and systemic vascular endothelialtis, microangiopathies, thrombosis and hyper inflammatory reaction at its core.11–13 These pathophysiological explanations along with other observational evidences lead a global search for suitable biomarker or other indicator that can predict final outcome early and hence can reliably aid rapid stratification of first hand care.4,6,7,10,12,14 Here at our institute also we tested a common hypothesis of testing predictive ability of epidemiological factors, biomarkers along with CT severity score.

We analyzed records of 735 total patients at our institute. Most of them were male (72.38%), have a median...
Bio marker profile [median (IQR)]

| CRP on admission (mg/Lt) | 39.2 (14.57-86.25) |
| D-dimer on admission (µg/Lt) | 294 (229-625) |
| Ferritin on admission (µg/Lt) | 262.6 (140-547.1) |

Radiological profile [median (IQR)]

| CT severity score | 14(9.0-18) |

Therapy profile

| Remdesivir | 631 |
| Anti-Coagulation | 675 |
| Steroids | 703 |
| Immune modulation therapy | 212 |
| Oxygen Therapy | 301 |
| ICU stay | 204 |
| Ventilation support | 88 |
| Mode of ventilation | No | Non-invasive | Invasive |

| No | 615 |
| Non-invasive | 18 |
| Invasive | 70 |


(IQR) age of 60 yrs (50-69). Diabetes (42.85%), and hypertension (39.86%) were the most common co-morbidities. After univariate and multivariate regression analysis we could find that level can predict final outcome of death. During multivariate regression and receiver operative characteristic (ROC) analysis also, age and Charlson’s co-morbidity index failed to predict in hospital mortality. CRP and D-Dimer on admission positively predicts final outcome of in hospital mortality with AUROC of 0.749 (p=0.007, CI 0.61-0.88), and 0.864 (p=0.000, CI 0.74-0.99) respectively. Whereas, CT severity score had AUROC 0.73 (p= 0.014, CI 0.575-0.83). Cut off for CRP was 45 mg/L (Sn 0.8, Sp 0.56), D-dimer was 1000 µg/L (Sn:0.8, Sp: 0.9), and CT severity score was 15 (Sn 0.8, Sp 0.58).

In this study we evaluated three different type of independent factors for disease outcome prediction. Epidemiological factors like age, co-morbidities or Charlson’s co-morbidity index have been studied extensively for COVID-19.4,6,7,10,16  A meta-analysis studied 3962 patients with COVID-19 demonstrated that patients with COVID-19 in the non-severe group had lower levels for CRP (WMD = -41.78 mg/l, 95% CI = [-52.43,-31.13], P < 0.001), Ferritin (WMD = -398.80 mg/l, 95% CI = [-28.34,-14.31], P < 0.001) and CT severity score had AUROC 0.73 (p= 0.014, CI 0.575-0.83). Cut off for CRP was 45 mg/L (Sn 0.8, Sp 0.56), D-dimer was 1000 µg/L (Sn:0.8, Sp: 0.9), and CT severity score was 15 (Sn 0.8, Sp 0.58).

CRP, Ferritin, D-dimer and other inflammatory biomarker were studied extensively for COVID-19.4,6,7,10,16 A meta-analysis studied 3962 patients with COVID-19 demonstrated that patients with COVID-19 in the non-severe group had lower levels for CRP (WMD = -41.78 mg/l, 95% CI = [-52.43,-31.13], P < 0.001), Ferritin (WMD = -398.80 mg/l, 95% CI = [-28.34,-14.31], P < 0.001) and CT severity score had AUROC 0.73 (p= 0.014, CI 0.575-0.83). Cut off for CRP was 45 mg/L (Sn 0.8, Sp 0.56), D-dimer was 1000 µg/L (Sn:0.8, Sp: 0.9), and CT severity score was 15 (Sn 0.8, Sp 0.58).

Similarly another large meta-analysis, studied 5350 patients from 25 studies with COVID-19 demonstrated that patients with COVID-19 in the non-severe group had lower levels for CRP (WMD = -41.78 mg/l, 95% CI = [-52.43,-31.13], P < 0.001), Ferritin (WMD = -398.80 mg/l, 95% CI = [-28.34,-14.31], P < 0.001) and serum ferritin (WMD = -398.80 mg/l, 95% CI = [-625.89, -171.71], P < 0.001).4 Similarly another large meta-analysis, studied 5350 patients from 25 studies and concluded that Elevated CRP is associated with an increased composite poor outcome [risk ratio (RR) 1.84 (1.45, 2.33), P < 0.001; I2: 96%] and A CRP >10 mg/L has a 51% sensitivity, 88% specificity, and an area under curve (AUC) of 0.84 for prediction of final positive composite poor outcome. Similarly, an elevated D-dimer level was associated with an increased composite poor outcome [RR 2.93 (2.14, 4.01), p < 0.001; I2: 77%]. A D-dimer >0.5 mg/L
Table 2: Summary of multivariate regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Selected cases</td>
<td>225</td>
<td>30.6</td>
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<td>Missing cases</td>
<td>510</td>
<td>69.4</td>
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<td>Total</td>
<td>735</td>
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<tr>
<td>Unselected cases</td>
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<td>0</td>
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<tr>
<td>Total</td>
<td>735</td>
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<tr>
<td>Variable not in the equation</td>
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</tr>
<tr>
<td>Score</td>
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<tr>
<td>Df</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Step 0
- Age: 0.462, 1, 0.496
- Charlson's comorbidity index: 7.109, 6, 0.311
- CRP on admission: 7.438, 1, 0.006
- D-dimer on admission: 9.341, 1, 0.002
- Ferritin on admission: 1.879, 1, 0.170
- CT severity score: 4.457, 1, 0.035

Model summary
- Step 1: -2 Log likelihood Cox & Snell R square Nagelkerke R square 58.360 0.074 0.258
- Hosmer and Lemeshow Test for goodness of fit: 14.309 8 0.074

Variables in the Equation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sig.</th>
<th>Exp (B)</th>
<th>95% CI for EXP(B)</th>
<th>Lower limit</th>
<th>Upper limit</th>
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<tbody>
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<td>Age</td>
<td>0.902</td>
<td>0.994</td>
<td>0.908</td>
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<td>CRP on admission</td>
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<td>1.005</td>
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<td>D-Dimer on admission</td>
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<td>Ferritin on admission</td>
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<td>CT severity score on admission</td>
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Table 3: Comparison of the ROC curves of the final five variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area</th>
<th>Std. Error</th>
<th>Sig</th>
<th>Asymptotic 95% confidence interval</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower limit</td>
</tr>
<tr>
<td>Age</td>
<td>0.493</td>
<td>0.095</td>
<td>0.942</td>
<td>0.307</td>
</tr>
<tr>
<td>Charlson's comorbidity index</td>
<td>0.584</td>
<td>0.084</td>
<td>0.366</td>
<td>0.419</td>
</tr>
<tr>
<td>CRP on admission</td>
<td>0.749</td>
<td>0.071</td>
<td>0.007</td>
<td>0.610</td>
</tr>
<tr>
<td>D-Dimer on admission</td>
<td>0.864</td>
<td>0.064</td>
<td>0.000</td>
<td>0.738</td>
</tr>
<tr>
<td>CT severity Score on admission</td>
<td>0.729</td>
<td>0.079</td>
<td>0.014</td>
<td>0.575</td>
</tr>
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</table>

Co ordinates of the curve

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cut-off value</th>
<th>Sensitivity (Sn)</th>
<th>1-Specificity</th>
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</thead>
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<tr>
<td>Age</td>
<td>51.0</td>
<td>0.80</td>
<td>0.73</td>
</tr>
<tr>
<td>Charlson’s Co-morbidity index</td>
<td>1.50</td>
<td>0.80</td>
<td>0.664</td>
</tr>
<tr>
<td>CRP on admission</td>
<td>45.95</td>
<td>0.80</td>
<td>0.442</td>
</tr>
<tr>
<td>D-Dimer on admission</td>
<td>998.0</td>
<td>0.80</td>
<td>0.109</td>
</tr>
<tr>
<td>CT Severity Score on admission</td>
<td>14.5 and above</td>
<td>0.80</td>
<td>0.427</td>
</tr>
</tbody>
</table>

*Variables included ‘at the time of admission’ and should predict final at the admission only, hence we took 80% sensitivity and maximum specificity on the plotted ROC curve for the cut-off value.
**standard unit: D-dimer (µg/Lt) and CRP (mg/Lt)

In our study also we have found CRP and D-dimer ‘at the time of admission’ have good predictive ability for final fatal outcome. And their cutoff values on ROC have been provided (Figure 2, Table 3).

In a study exploring the CT severity index and biomarkers for predictive ability of disease severity, and short term prognosis showed a significant higher risk of death with CT score of ≥18 (HR, 8.33; 95% CI, 3.19–21.73; p < 0.0001). Author also detailed correlation of risk of death with increasing age (HR, 1.07; 95% CI, 1.03–1.11; p = 0.0014), CRP (HR, 1.06; 95% CI, 1.03–1.09; p < 0.0001). Another work explored the radiological data for prediction of severe disease, they however had a different reporting manner. They found out optimal CT severity Cut off for identifying severe COVID-19 was 19.5/40 (AUROC = 0.892), with 83.3% sensitivity and 94% specificity. Present work also found CT severity as a useful tool for severity prediction and its analysis and cut off value is presented in (Figure 2, Table 3).

Strength, and Limitations

Our work is unique in many ways as it is probably first of its kind study from our region, it explored three different kind of predictors for disease has a 58% sensitivity, 69% specificity, LR+ of 1.8, LR- of 0.6, and an AUC of 0.69. These meta-analyses emphasizes the importance of the association of levels of biomarkers with the severity of COVID-19 and composite final outcome respectively. Thus one can conclude that measurement of inflammatory markers may assist in early diagnosis of severe disease than its clinical manifestations (hypoxemia) and it may help in prognostication of the individual cases. Another exploration for inflammatory biomarker showed in their proportional hazard model that IL-6 and CRP can be used as an independent predictor of the severe COVID-19. Further, level of IL-6 > 32.1 pg/mL or CRP > 41.8 mg/L were associated with severe complications. In our study also we have found CRP and D-dimer ‘at the time of admission’ have good predictive ability for final fatal outcome. And their cutoff values on ROC have been provided (Figure 2, Table 3).
Epidemiology and Antifungal Susceptibility of Candida Species causing Blood Stream Infections: An Eastern India Perspective

Mandira Chakraborty¹, Hasina Banu², Manoj Kumar Gupta³

Abstract

Introduction: Candidemia is the fourth common cause of blood stream infection worldwide leading to increased mortality and morbidity. A paradigm shift of Candida albicans to Non-albicans candida (NAC) had led to the increase in resistance to empirically used antifungals. So, an epidemiological study and antifungal susceptibility is essential for meticulous use of antifungals.

Aims and Objectives: To find out the prevalence and antifungal susceptibility of Candida species causing candidemia.

Methods: automated blood culture done in BACTEC system followed by its identification and susceptibility testing in VITEK-2 system.
Results: Non-albicans candida was isolated from 73% cases of candidemia. The commonest isolate among neonates and adults were C.krusei and C.tropicalis respectively. C.haemulonii was significantly high among adult population while C.krusei was significantly high among the neonates. 10.4% NAC isolates were resistant to amphotericin B, flucytosine resistance among 37% NAC isolates and among 44% C.albicans isolates, fluconazole resistance was found among 13% and 15% of NAC and C. albicans respectively. Echinocandins were comparatively sensitive to the candida spp.

Introduction

Worldwide candida is distributed ubiquitously in nature. They present as commensals in humans skin and gastrointestinal tract. However, recently it has emerged as one of the potential causes of invasive fungal infections especially blood stream infection. In United States, Candida species is the fourth most common pathogen causing blood stream infection in hospitalized patients.1 The Asian data is lacking due to absence of multicentric study, however prevalence of candidemia ranges from 6% to 18% based on studies done from different parts of India. The probable reason for such increasing incidence of candida infection is due to increased number of immunocompromised patients and irrational use of antimicrobials.2 The important predisposing factors for candidemia includes long term exposure to antimicrobials, presence of invasive medical devices, low birth weight neonates, critically ill medical and surgical patients, neutropenic patients and immunosuppressed patients.1,2 Shift of the species from C.albicans to non albicans candida (NAC) is now accounted for approximately half of all cases of candidemia.2 The most important cause of this shift is the empirical use of antifungals against candida infections because some of the candida species are intrinsically resistant to these commonly used antifungals. Also, the frequency of the various candida species depends on geographical region, population involved, previous antifungal used, and patient age.3 So recognition of this shift in the laboratory by species identification and susceptibility testing is clinically important to initiate timely and adequate treatment.

Methodology

The study was retrospectively done in a tertiary care hospital, Kolkata, West Bengal, India from January 2015 to October 2018. Ethical clearance was obtained from the respective institution. All the blood culture yielding pure growth of candida were included and were analysed. Blood samples were collected maintaining all the aseptic protocol, from the patient with clinical features suggestive of sepsis and were cultured in BACTEC 9120 (Becton Dickinson) automated blood culture system. Gram staining were performed directly from blood culture bottle giving positive signals and simultaneously samples were sub-cultured on Sabauraud Dextrose agar and blood agar to avoid the chance of contamination. Culture plates were incubated at 37°C for 3-4 days.4 Blood samples showing yeast in direct gram-stained smear and yielding pure growth of yeast colonies on blood agar and Sabauraud Dextrose agar were processed further. Isolated yeast colonies were then identified using Vitek-2 compact automated system using VITEK-2 cards for identification of yeast and yeast-like organisms (ID-AST card) and antifungal susceptibility (AFST) were done by VITEK-2 susceptibility card (AST-YS07 card). The breakpoints used to define susceptible, intermediate and/or Dose dependent-sensitivity and resistant were those defined by CLSI M27-A3. CLSI breakpoints were not available for some NAC species like C.guillermundi, C.haemulonii, C.inconspicua and C.utilis so we followed the FDA guidelines for this isolates. Susceptibility testing could not be done for C.famata, C.magnoliae, C.sperata and C.sake. Statistical analysis was done using Chi-square with Yates’ correction and p value <0.01 was taken to be statistically significant data.

Result

Out of the total 1280 positive blood cultures in BACTEC 9120 automated system, 192 samples yielded candida species. Our study population included those 192 candida isolates among which 52 samples (27%) were candida albicans and the remaining 140 (73%) were non-albicans candida (NAC). Thus NAC isolates were significantly high (p value 0.0001) than C.albicans among the study population. C.albicans was isolated from 27 cases (52%) and 25 cases (48%) of adults and neonates respectively. According to Table 1 which showed the species distribution of NAC among the two cohorts of neonates and adults, commonest isolate among neonates and adults were C.krusei and C.tropicalis respectively. While comparing among the adult and neonatal populations, C.haemulonii was significantly high among adult population while C.krusei was significantly high among the neonates.

As shown in Table 2, only 3 (10.4%) NAC isolates were resistant to amphotericin B (AMB) of which 2 species were C.krusei and 1 isolate was C.parapsilosis. On the contrary, none of the C.albicans isolates were resistant to AMB. There was a much higher frequency of flucytosine (FCT) resistance showing resistance among 50 (37%) NAC isolates and among 23 (44%) C.albicans isolates. Though there is no such intrinsic resistance known, all C.krusei (27), C.parapsilosis (15) isolates and C.glabrata (3) isolates were found to be resistant to FCT. 13% NAC isolates, 12 C.haemulonii, 3 C.tropicalis, 2 C.pelliculosa and 1 C.parapsilosis, were found to be resistant to fluconazole (FLU). C.kruei exhibits intrinsic resistance to fluconazole and C. glabrata can develop high-level resistance after exposure to azole antifungals.5 8 (15%) C.albicans isolates were resistant to FLU. Only 4% and 3% of NAC isolates were resistant to micafungin (MCF) and caspofungin (CAS) respectively. MCF was found to be resistant among 4 (8%) C.albicans isolates while none were resistant to CAS.

Discussion

Candidemia has become an important cause of increased mortality and morbidity especially among hospitalised patients. A retrospective study in United States found that candidemia caused 14.5% increase in mortality rate. Reports from India
stated wide variation of incidence and prevalence of candidemia, ranging from 5.7% as reported by Kumar et al. to 18% according to a study from New Delhi. Moreover, the shift towards NAC is also an alarming situation to the clinicians to think twice before initiating antifungals empirically. The emergence of NAC, especially C.tropicalis had been reported from all part of India. The epidemiological data related to candidemia in a particular geographical area is the key for prompt and timely management of it. This prompted us to do the retrospective study in our setting. As in line with other studies done from different parts of India, we found candida was the third most common cause of BSI accounting for 15% according to a study from New Delhi. Moreover, the shift towards NAC is also an alarming situation to the clinicians and mutations that affect its membrane sterol content are associated with significant fitness costs. In our study, 10.4% of Candida isolates, mostly C.haemulonii were resistant to AMB, almost similar to a study done by Ravinder Kaur et al where the percentage was 7.8. C. haemulonii has been reported to be intrinsically resistant to amphotericin B and azoles, thus posing therapeutic challenges. Fluconazole is usually the recommended treatment option for candidemia in both neutropenic and non-neutropenic patients. However, the major concern is about the increasing frequency of azole resistance among the candida species, especially among the NAC. Azoles inhibit 14-α-sterol demethylase, encoded by the ERG11 gene, which is an enzyme involved in the biosynthesis of the fungal-specific membrane sterol ergosterol. Resistance to FLU in C.albicans can occur due to accumulation of mutations in the fungal-specific membrane sterol ergosterol. Resistance to FLU in C.albicans can occur due to accumulation of mutations in the ERG11 gene. Increased azole efflux by overexpression of ABC transporters as well as mutation of the C5,6 sterol desaturase gene ERG3 can increase azole resistance in some species. 28% of our candida isolates were resistant to FLU, the data almost close to the study done by P Bhattacharjee.

**Table 1: Distribution of NAC among neonates and adults**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Total n(%)</th>
<th>Neonates n(%)</th>
<th>Adults n(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=192)</td>
<td>N=73</td>
<td>N=67</td>
<td></td>
</tr>
<tr>
<td>C.albicans</td>
<td>52 (27)</td>
<td>25</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>C.saccharolyticum</td>
<td>2 (1.5)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0.3164</td>
</tr>
<tr>
<td>C.glabrata</td>
<td>3 (1.5)</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>0.5616</td>
</tr>
<tr>
<td>C.guilliermondii</td>
<td>4 (2)</td>
<td>4 (6)</td>
<td>0</td>
<td>0.1308</td>
</tr>
<tr>
<td>C.haemulonii</td>
<td>18 (9)</td>
<td>0</td>
<td>18 (27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>C.incassita</td>
<td>1 (0.5)</td>
<td>1 (1)</td>
<td>0</td>
<td>0.3164</td>
</tr>
<tr>
<td>C.krusei</td>
<td>27 (14)</td>
<td>24 (33)</td>
<td>3 (4.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>C.lusitania</td>
<td>1 (0.5)</td>
<td>1 (1)</td>
<td>0</td>
<td>0.3164</td>
</tr>
<tr>
<td>C.magnoliae</td>
<td>1(0.5)</td>
<td>1 (1)</td>
<td>0</td>
<td>0.3164</td>
</tr>
<tr>
<td>C.parapsilosis</td>
<td>16 (8.5)</td>
<td>5 (7)</td>
<td>11 (16)</td>
<td>0.1980</td>
</tr>
<tr>
<td>C.pelliculosa</td>
<td>15 (8)</td>
<td>11 (15)</td>
<td>4 (6)</td>
<td>0.1113</td>
</tr>
<tr>
<td>C.pseudomycetica</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0.3164</td>
</tr>
<tr>
<td>C.sakazakii</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0.3164</td>
</tr>
<tr>
<td>C.tropicalis</td>
<td>47 (24.5)</td>
<td>21 (29)</td>
<td>26 (39)</td>
<td>0.5224</td>
</tr>
<tr>
<td>Cutilis</td>
<td>3 (1.5)</td>
<td>2 (3)</td>
<td>1 (1.5)</td>
<td>0.5616</td>
</tr>
</tbody>
</table>

**Table 2: Sensitivity pattern of the isolated NAC**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Drug</th>
<th>WT % (n)</th>
<th>NON-WT % (n)</th>
<th>S % (n)</th>
<th>I % (n)</th>
<th>SDD % (n)</th>
<th>R % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.glabrata</td>
<td>AMB</td>
<td>100(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC</td>
<td>100(47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCF</td>
<td>100(27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FCT</td>
<td>100(15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FLU</td>
<td>100(15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.krusei</td>
<td>AMB</td>
<td>93(14)</td>
<td>7(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC</td>
<td>100(47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCF</td>
<td>100(27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FCT</td>
<td>100(15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.parapsilosis</td>
<td>AMB</td>
<td>93(14)</td>
<td>7(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC</td>
<td>100(47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCF</td>
<td>100(27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FCT</td>
<td>100(15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.pelliculosa</td>
<td>AMB</td>
<td>93(14)</td>
<td>7(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC</td>
<td>100(47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCF</td>
<td>100(27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FCT</td>
<td>100(15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.tropicalis</td>
<td>AMB</td>
<td>100(47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC</td>
<td>100(47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCF</td>
<td>100(27)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FCT</td>
<td>100(15)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

According to some studies, infections caused by C. albicans are associated with varying levels of fluconazole resistance depending on the type of infection. C. albicans isolates from candidemic patients have the lowest incidence ofazole resistance (0–5%). However, 15% of our C. albicans was resistant to it. C. glabrata is frequently less susceptible to fluconazole in vitro. It generally exhibit bimodal susceptibility to azoles, with some isolates demonstrating frank azole resistance (MIC, >64 µg/mL), whereas others are significantly more susceptible. In our case, all C. glabrata isolates had MIC in the susceptibility-dose-dependent region, thus demonstrating the increasing trends of resistance to FLU. Similarly, some strains of C. tropicalis also exhibit azole resistance, although, generally, the MIC90 for this species indicates general susceptibility to azoles, and often in vitro resistance appears because of its strong tendency to produce trailing growth. C. krusei is intrinsically resistant to FLU. Although resistance to fluconazole among C. tropicalis isolates has increased, we had only three C. tropicalis (6.38%) isolates that were resistant to FLU. Acquired resistance to azole in C. tropicalis could be due to overexpression of CtERG1 gene associated missense mutation. Although C. parapsilosis strains are usually susceptible to azoles, recent reports indicate the emergence of invasive infections due to fluconazole (FLC)-resistant C. parapsilosis isolates. However in our study, only one patient had candidemia due to FLU resistant C. parapsilosis. In vitro testing showed a poor susceptibility of C. pelliculosa strains to azole compounds. Though there are reports on increasing resistance to Voriconazole (18%), a triazole with a structure similar to fluconazole, surprisingly all our isolates were sensitive to it. The echinocandin drugs (caspofungin, micafungin and anidulafungin) target and inhibit the membrane-associated (and fungal specific) β-1,3-d-glucan synthase and block the biosynthesis of β-1,3-glucan, a major structural component of the fungal cell wall. The enzyme complex consists of a structural/catalytic subunit encoded by FKS genes; and its activity is regulated by Rho, a GTP-binding protein. Clinical resistance involves modification of the Fks subunits, FKS 1 in C. albicans and FKS1 and FKS2 in C. glabrata. Echinocandin resistance generally always arises during therapy and is associated with repeated or chronic drug exposure, although resistance can also follow brief drug exposure. This was recently documented in a 10-year survey at the Duke University hospital where the echinocandin resistance rate increased from 4.9% to 12.3% in 2001–10. A similar trend has been observed in the nation-wide fungemia survey in Denmark, although on a smaller scale. In consistence to the above findings, we observed increased MIC of echinocandin among 7.5% of our isolates. Overall candida has become one of the important causes of BSI and there is an observed shift from C. albicans to NAC. Most importantly, C. krusei, the one known for its maximum mortality rates among candida and increased frequency of resistance rates to antifungals, was the predominant isolate among neonates in our study. We can conclude by stating that identification and susceptibility testing of Candida species causing candidemia is the one of the important tools of good clinical practice as it will reduce the mortality and morbidity rates in hospitals.

References

Ferritin and Hemoglobin as Predictors of Fatal Outcome in COVID-19: Two Sides of the Same Coin

Nishant Raman¹, Padmaprakash KV²*, Kuldeep Kumar Ashta³, Vasu Vardhan⁴, Sandeep Thareja⁴, Muthukrishnan J⁴, Abhinav Kumar⁵, Basavaraj⁵

Abstract

Introduction: Infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have multisystemic involvement with hyperinflammation being a cardinal feature and deranged iron metabolism having a possible role. In this premise, we studied the prognostic value of two markers of iron metabolism—ferritin and hemoglobin.

Methodology: A retrospective-cohort study was carried out in a tertiary hospital in northern India involving 210 hospitalized COVID-19 patients aged 15-and-above. Analysis was done for clinical profile, comorbidities and basic laboratory indices including ferritin-hemoglobin ratio (FHR) with primary end-point being in-hospital all-cause mortality.

Results: Median serum ferritin levels (640.00ng/mL vs 220.00ng/mL) were significantly higher among non-survivors as against survivors while median hemoglobin levels were significantly lower (12.12g/dL vs 13.73g/dL). Serum ferritin levels >400ng/mL (Sn 80%, Sp 70%) predicted mortality with high sensitivity and specificity. Notably, serum ferritin levels >400ng/mL (HR 11.075 [1.481-82.801]) and anemia, defined as a hemoglobin of <12g/dL for females and < 13g/dL for males and were significantly associated with the risk of mortality in a univariable Cox-proportional hazards regression. The median FHR was significantly higher among non-survivors compared to survivors (56.98 vs 17.17), FHR>31 (Sn 85% Sp 71.6%) was highly sensitive and specific for predicting mortality. The multivariable analysis indicated that FHR >31 remained an independent risk factor for mortality (HR 12.293 [3.147-48.028]).

Conclusion: Ferritin-hemoglobin ratio (FHR), which encompasses into a single index, the effects of both elevated levels of ferritin and the severity of anemia, seems to perform particularly well as a prognostic marker and emerged as an independent risk factor for mortality in COVID-19 patients. Hyperferritinemia and anemia, both, are inexorably interlinked in addition to having a role, directly or indirectly in the disease pathophysiology. Ferritin and hemoglobin, hence should be seen as two sides of the same coin rather than as two discrete entities.

Introduction

The coronavirus disease (COVID)-19 in its severe form results in an atypical form of the acute respiratory distress syndrome (ARDS) with relatively well preserved lung mechanics but a disproportionately severe hypoxia.¹ This suggests that the pulmonary inefficiency observed in COVID-19 patients may not be caused by cell damage in the lungs alone and that the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 may affect oxygenation and oxygen delivery via paths not directly correlated with pulmonary function.² Otherwise stated, its effect on the oxygen delivery system begins in the lungs, continues in the red blood cells and goes all the way to the tissues.³

Mounting evidence links accelerated pathogenesis in severe COVID-19 patients to a hyper-inflammatory state involving a ‘cytokine storm’ with massive and over-exuberant expression of interleukin (IL)-6.⁴ A multi-organ involvement has been highlighted with possible roles of hemoglobinopathy (anemia) and cell iron-overload (hyperferritinemia) in a hyperinflammatory milieu.⁵

Iron is a micronutrient essential for the host as well as for the pathogen.⁶ Hemoglobin and ferritin are two major reserves of iron in the body. Hemoglobin binds oxygen to its iron containing core and carries oxygen to organs and tissues. Ferritin is the primary site of iron storage in the cell and is regulated by both, iron availability and inflammation. It is postulated that an innate immune response exerts control over the iron metabolism limiting its availability during infection.⁶ Ferritin, an acute phase protein increases in the background of a strong inflammatory response during an acute infection.⁷ Inflammation, therefore, causes alterations of iron homeostasis hallmarkd by functional iron deficiency (ID), hyperferritinemia and anemia of inflammation (AI).⁸ Dysregulated iron homeostasis in COVID-19 hence alters the levels of both hemoglobin and ferritin.

Both these iron associated proteins are inexorably interlinked by the seemingly simple yet complex metabolism of the body’s handling of its iron reserves. Serum ferritin levels increase during an acute phase response, but its final concentration is dependent on the underlying iron status, which in turn also affects the hemoglobin levels. The present study approaches this disease beyond the traditional concepts and focuses on...
an oxygen deprived multifaceted syndrome. The research question from the above observations was whether a dysregulated iron metabolism with cellular iron overload marked by hyperferritinemia in conjunction with inefficient oxygen transport in the form of decreased hemoglobin levels affects outcomes of this disease. With this in premise, the present study reports the association of ferritin-hemoglobin ratio (FHR) as a predictor of mortality in COVID-19 patients.

**Methodology**

This retrospective study included 210 RTPCR confirmed COVID-19 patients who were 15 years or older and were hospitalized in a tertiary hospital in Northern-India over a 3-month period from May-August 2020. Cases that did not have complete data were excluded. Data collected included demographic data, signs and symptoms, comorbidities, vitals at admission and data on outcome (i.e., discharge or death). Routine laboratory tests at admission were done on the day of admission and were inclusive of complete blood count including total leukocyte-count (TLC), hemoglobin-level (Hb), platelet-count (PLT); liver and renal function tests including serum bilirubin, aspartate-transaminase (AST), alanine-transaminase (ALT) and serum creatinine and markers of inflammation such as ferritin and C-reactive protein. Additionally, absolute lymphocyte count (ALC) and neutrophil counts (ANC) and neutrophil-lymphocyte ratio (NLR) were included.

**Statistical analysis**

Continuous variables were presented as median and interquartile-ranges (IQR) and were compared by means of t-test for normally-distributed variables and Mann-Whitney U test for non-normally distributed data. Receiver-Operation Curves (ROCs) were plotted and optimal cut-off values were decided based on appropriate trade-off between sensitivity and specificity in order to recode them into dichotomized variables. Categorical variables were described as percentages and frequencies and were compared by Chi-square tests. Cox-proportional hazards regression was employed for survival analysis with the primary end-point being in-hospital all-cause mortality. Multivariable-models were constructed using backwards elimination procedure. A two sided alpha <0.05 was considered significant for 95% confidence-interval. Considering 80% power, the number of cases were deemed adequate. MS Excel 2016 and SPSS 23 were used respectively for data handling and analysis.

**Results**

**Demographic characteristics, clinical profile and laboratory investigations at admission**

The median age of patients was 47 years, interquartile-range (IQR) of 23 years with 172 (81.9%) males and 38 (19.4%) females. Among the 210 patients, 73 (34.8%) patients had a moderate-to-severe disease at presentation while 137 (65.2%) patients were admitted with a mild disease. A total of 20 patients suffered fatal outcome (case-fatality rate of 9.5%). The baseline characteristics, clinical presentation, underlying comorbidities and the laboratory investigations at admission are summarized in Table 1.

**Use of optimum cutoff values of laboratory results**

Certain laboratory parameters were dichotomized based on standard definitions. Hb was categorized into low and high by taking a cutoff of 12 g/dL for females and 13 g/dL for males. CRP of greater than 10 mg/L was considered raised. Thrombocytopenia was defined as PLT count of less than 1,50,000 cells/mcL. For Ferritin, ALC, ANC, NLR and FHR, no standardized or unified cutoffs were available. Hence for these parameters, ROC curves were used to identify the cut-offvalues that predicted mortality with considerable sensitivity and specificity. The ROC curves for Ferritin ALC, ANC, NLR and FHR as predictors of mortality are presented in Figure 1. Area under curve (AUC) >0.5 was considered significant. A ferritin >400 ng/mL (Sn 80%, Sp 70%, AUC 0.785 95%CI 0.689-0.880), an ALC ≤901cells/mcL (Sn 70% Sp 78.4%, AUC 0.181 95%CI 0.083-0.278), ANC >4966 cells/mcL (Sn 80% Sp 81.6%, AUC 0.829 95%CI 0.717-0.941), NLR >3.718 (Sn 85% Sp 76.8%, AUC 0.874 95%CI 0.792-0.955) and FHR >31 (Sn 85% Sp 71.6%, AUC 0.808 95%CI 0.713-0.902) predicted mortality with highest sensitivity and specificity.

**Association of ferritin to hemoglobin ratio with mortality**

To assess FHR as a risk factor for mortality among COVID-19 patients, Cox-proportional hazard regression analysis was performed. Univariable and multivariable models were constructed which included baseline characteristics, symptoms at admission, comorbidities and laboratory parameters at admission. The laboratory parameters were inclusive of Hb, TLC, ALC, ANC, NLR, FHR, PLT, Bilirubin, AST, ALT and serum creatinine. While ALC, ANC, NLR, FHR, Hb, PLT, ferritin and CRP were dichotomized either based on standard laboratory reference values or based on ROC curves, other confounding laboratory parameters including TLC, bilirubin, AST, ALT and serum creatinine were included as continuous variables. The unadjusted and adjusted hazards ratios are given in Table 2.

In the univariable analysis factors significantly associated with mortality included age (HR 1.065 [1.038-1.094]), dyspnea at presentation (HR 38.587 [5.154-288.903]), tachycardia at admission (HR 5.873 [2.440-14.139]), all grades of hypoxia, i.e., mild (HR 8.306 [1.858-37.138]), moderate (HR 22.644 [6.957-73.702]) and severe hypoxia (HR 41.072 [10.175-165.791]). Among comorbid conditions, diabetes mellitus (HR 8.766 [3.559-21.595]), coronary artery disease (HR 5.379 [1.952-14.825]), chronic kidney disease (HR 5.958 [1.380-25.720]), chronic liver disease (HR 0.049 [0.000-520905]), malignancy (HR 5.906 [3.112-1.207]) and presence of other comorbidities such as endocrine disorders (HR 1.105 [0.148-8.262]) were risk factors of mortality. Laboratory indices having a significant association with mortality included of anemia (HR 3.970 [1.582-9.960]), serum creatinine (HR 1.361 per unit increase [1.117-1.657]), ferritin >400ng/mL (HR 11.075 [1.481-82.801]), ALC ≤901cells/mcL (HR 5.913 [2.359-14.826]), ANC >4966cells/mcL (HR 16.285 [5.426-48.880]), NLR >3.718 (HR 16.538 [4.837-56.547]) and FHR >31 (HR 13.022 [3.809-44.516]).

The multivariable analysis indicated that FHR >31 remained an independent risk factor for mortality after adjusting for baseline data and laboratory indices (HR 12.293 [3.147-48.028]). Raised ferritin and anemia independently
### Table 1: Baseline characteristics, clinical presentation and comorbidities of 210 RTPCR confirmed hospitalised COVID-19 patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Died (n=20)</th>
<th>Survived (n=190)</th>
<th>Total (n=210)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.5 (21.00)</td>
<td>43 (22)</td>
<td>47.00 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>3 (15%)</td>
<td>35 (18.4%)</td>
<td>38 (18.1%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>20 (100%)</td>
<td>162 (85.3%)</td>
<td>182 (56.6%)</td>
<td>0.083</td>
</tr>
<tr>
<td>Fever</td>
<td>15 (75.0%)</td>
<td>122 (63.7%)</td>
<td>137 (65.2%)</td>
<td>0.586</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (6%)</td>
<td>87 (45.7%)</td>
<td>75 (47.1%)</td>
<td>0.247</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19 (95.0%)</td>
<td>59 (31.1%)</td>
<td>70 (37.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sore throat</td>
<td>3 (15%)</td>
<td>38 (20.0%)</td>
<td>41 (19.5%)</td>
<td>0.771</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (30%)</td>
<td>19 (10%)</td>
<td>25 (11.9%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (10.0%)</td>
<td>17 (9.5%)</td>
<td>19 (9.1%)</td>
<td>0.381</td>
</tr>
<tr>
<td>Vitals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>10 (50.0%)</td>
<td>24 (12.6%)</td>
<td>34 (16.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>17 (85.0%)</td>
<td>44 (23.1%)</td>
<td>61 (29.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Fever at admission</td>
<td>1 (5.0%)</td>
<td>4 (2.1%)</td>
<td>5 (2.4%)</td>
<td>0.397</td>
</tr>
<tr>
<td>Mild hypoxemia (SpO2-90-94%)</td>
<td>3 (15%)</td>
<td>15 (7.9%)</td>
<td>18 (8.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate hypoxemia (75-90%)</td>
<td>9 (45.0%)</td>
<td>12 (6.3%)</td>
<td>21 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>Severe hypoxemia (&lt;75%)</td>
<td>4 (20.0%)</td>
<td>2 (1.0%)</td>
<td>6 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one comorbidity</td>
<td>18 (90.0%)</td>
<td>67 (35.3%)</td>
<td>85 (40.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single comorbidity</td>
<td>8 (40%)</td>
<td>37 (19.5%)</td>
<td>45 (21.4%)</td>
<td></td>
</tr>
<tr>
<td>Two comorbidities</td>
<td>7 (35%)</td>
<td>18 (9.5%)</td>
<td>25 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Multiple comorbidities (3 or more)</td>
<td>3 (15%)</td>
<td>12 (6.3%)</td>
<td>15 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (60.0%)</td>
<td>26 (13.7%)</td>
<td>38 (18.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (35.0%)</td>
<td>34 (17.9%)</td>
<td>41 (19.5%)</td>
<td>0.078</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (25.0%)</td>
<td>9 (4.7%)</td>
<td>14 (6.6%)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease &amp; bronchial asthma</td>
<td>1 (5.0%)</td>
<td>3 (1.6%)</td>
<td>4 (1.9%)</td>
<td>0.332</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2 (10.0%)</td>
<td>2 (1.0%)</td>
<td>4 (1.9%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1 (5.0%)</td>
<td>8 (4.2%)</td>
<td>9 (4.3%)</td>
<td>0.601</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>4 (20.0%)</td>
<td>26 (13.7%)</td>
<td>30 (14.3%)</td>
<td>0.498</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe disease</td>
<td>20 (100.0%)</td>
<td>53 (27.9%)</td>
<td>73 (34.8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 2: Predictors of mortality- Cox proportional hazards regression

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Crude HR (95% CI)</th>
<th>P Value</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Per 1 year increase in age)</td>
<td>1.065 (1.038-1.094)</td>
<td>&lt;0.001</td>
<td>1.058 (1.019-1.098)</td>
<td>0.003</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>0.897 (0.263-3.064)</td>
<td>0.862</td>
<td>0.241 (0.062-0.940)</td>
<td>0.040</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>25.283</td>
<td>(0.97-6559.219)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>38.587</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vital parameters at admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1.870</td>
<td>0.542</td>
<td>(0.250-13.981)</td>
<td>-</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5.873</td>
<td>&lt;0.001</td>
<td>(2.440-14.139)</td>
<td>-</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>16.301</td>
<td>(4.769-55.719)</td>
<td>&lt;0.001</td>
<td>3.210</td>
</tr>
<tr>
<td>Mild hypoxemia</td>
<td>8.306</td>
<td>0.06</td>
<td>(1.858-37.138)</td>
<td>-</td>
</tr>
<tr>
<td>Moderate hypoxemia</td>
<td>22.644</td>
<td>&lt;0.001</td>
<td>(6.957-73.702)</td>
<td>-</td>
</tr>
<tr>
<td>Severe hypoxemia</td>
<td>41.072</td>
<td>&lt;0.001</td>
<td>(10.175-165.791)</td>
<td>-</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.766</td>
<td>(3.559-21.995)</td>
<td>&lt;0.001</td>
<td>5.938</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.481 (0.989-6.227)</td>
<td>&lt;0.053</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5.347</td>
<td>0.001</td>
<td>(1.952-14.825)</td>
<td>-</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease &amp; bronchial asthma</td>
<td>3.110</td>
<td>0.269</td>
<td>(0.416-23.252)</td>
<td>-</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5.958</td>
<td>0.017</td>
<td>(1.380-25.720)</td>
<td>-</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>0.049</td>
<td>0.049</td>
<td>(0.000-520005)</td>
<td>-</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5.906 (3.112-1.207)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>1.105 (0.148-8.262)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Laboratory indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC, cells/ml. (per unit increase)</td>
<td>1.000</td>
<td>(1.000)</td>
<td>0.003</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>3.970 (1.582-9.960)</td>
<td>0.003</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.941 (0.375-2.359)</td>
<td>0.897</td>
<td>4.433 (1.352-14.538)</td>
<td>0.014</td>
</tr>
<tr>
<td>Bilirubin, mg/dL (per unit increase)</td>
<td>2.597</td>
<td>0.234</td>
<td>(0.539-12.509)</td>
<td>-</td>
</tr>
<tr>
<td>AST, U/L (per unit increase)</td>
<td>1.002 (0.995-1.009)</td>
<td>0.567</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALT, U/L (per unit increase)</td>
<td>1.000 (0.991-1.010)</td>
<td>0.984</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CREAT, mg/dL (per unit increase)</td>
<td>1.361 (1.117-1.657)</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>11.075</td>
<td>(1.481-82.801)</td>
<td>0.019</td>
<td>-</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.439 (0.547-3.780)</td>
<td>0.461</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALC, cells/ml.</td>
<td>5.913</td>
<td>&lt;0.001</td>
<td>(2.359-14.826)</td>
<td>-</td>
</tr>
<tr>
<td>ANC, cells/ml.</td>
<td>16.285</td>
<td>&lt;0.001</td>
<td>16.780 (5.426-48.880)</td>
<td>0.001</td>
</tr>
<tr>
<td>NLR</td>
<td>16.538</td>
<td>&lt;0.001</td>
<td>(4.183-56.547)</td>
<td>-</td>
</tr>
<tr>
<td>FHR</td>
<td>13.022</td>
<td>&lt;0.001</td>
<td>12.293 (3.849-44.516)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Discussion

Iron, redox biology and inflammation

failed to show an association in the adjusted model.
are invariably interlinked. During infection, increased ferritin levels represent an important innate defense mechanism, depriving the pathogen of its much needed iron and by limiting the formation of free radicals. Iron overload has rather been shown to worsen prognosis in certain viral infections such as hepatitis B (HBV) and hepatitis C (HCV) by promoting fibrosis, while iron supplementation has been associated with increased risk of mortality in HIV patients. Ferritin is a key acute phase reactant, considered by some as an ‘innocent bystander’ and a biomarker of uncontrolled inflammation while a different school of thought considers it to be a part of a protective feedback loop. Recent evidence points towards more sinister effects of hyperferritinemia, suggesting that ferritin levels may not only reflect an underlying acute phase but may also have immunomodulatory effects.

Recent accord has been given to the multisystemic nature of COVID-19. Hyperinflammation remains central to this with hyperferritinemia a hallmark of severe disease. This observational study involving 210 RTPCR confirmed hospitalized COVID-19 patients focuses on serum ferritin and hemoglobin, two key indices associated with iron homeostasis. Further, this is the first study which links ferritin-hemoglobin ratio (FHR) as a prognostic indicator for mortality in COVID-19 patients.

Major differences in serum ferritin levels have been reported in patients with severe disease compared to non-severe cases, and among non-survivors as against survivors. Lin et al, in a retrospective analysis of 147 COVID-19 patients in China showed in a multivariable logistic regression analysis that ferritin was an independent risk factor for disease severity and reported serum ferritin >500 ng/mL as predictor of severe disease. In another Chinese study, Zhou, et al retrospectively analysed data of 191 patients and reported significantly higher serum ferritin levels in non-survivors (Median 1435·3, IQR 264·0–921·5) compared to survivors (Median 503·2, IQR 349·00). They also found that serum ferritin levels were significantly higher among non-survivors, and among non-survivors as against survivors. Lin et al, in a retrospective analysis of 259 patients showed that serum ferritin levels were not significantly associated with odds of severe disease. The serum ferritin cutoff level of 500 ng/mL in their study was based on the HLH-2004 diagnostic criteria. Similarly, in a retrospective analysis of 942 COVID-19 patients admitted to a large New York City New York City health system, Feld, et al established that patients who died had significantly higher median admission (915 ng/ml vs 634 ng/ml) and maximum serum ferritin levels (1648 ng/mL vs 928 ng/mL) than those who did not.

Cheng, et al, in a meta-analysis involving 10,614 COVID 19 patients showed that serum ferritin levels were significantly increased in non-survivors (WMD 677.17[95%CI- 391.01-963.33]) compared to survivors and was also associated with disease severity (WMD 397.77[95%CI 306.51-489.02]).

In the present study it was observed that levels of serum ferritin were significantly higher among non-survivors (Median 640, IQR 552.00) compared to survivors (Median 220, IQR 349.00). However, the median levels of serum ferritin among both non-survivors and survivors were comparatively lower than that reported in previous studies. This study further reports serum ferritin >400 ng/mL is an accurate predictor of mortality. Serum ferritin >400ng/mL also showed a significant association with the risk of mortality (HR 11.075 [1.481-82.801]) in the Cox univariable proportional-hazards regression. These findings are in congruence with the observations by Zhou, et al.

Ferritin can hence be considered as an independent predictor of severe disease and ARDS. However, hyperferritinemia seems to add little prognostic information when mortality is considered. Feld, et al, in their study, reported higher serum ferritin levels among non-survivors, but concluded that even so elevated admission serum ferritin levels >799 ng/mL and maximum serum ferritin levels >862 ng/mL represented optimal cutoffs for predicting mortality, but lacked the sensitivity and specificity to be discerned as accurate predictors of fatal outcomes. Weiler et al in a retrospective analysis of 259 patients reported that higher serum ferritin levels were not significantly associated with the risk of death. A prospective cohort study Masetti et al found serum ferritin >1799ng/mL to predict mortality with considerable sensitivity and specificity, but only a univariable association between ferritin levels and mortality was described. Similarly,

![ROC Curve](image-url)
Zhou, et al have at best reported a univariable association between raised ferritin levels and the odds of suffering a fatal outcome. Likewise, the present study demonstrates a univariable association of hyperferritinemia as a risk factor for mortality, however ferritin as an independent risk factor of mortality could not be established. Only in the study by Gandini et al, it was shown that ferritin was an independent risk factor and an accurate predictor of mortality.

Yet another harbinger of a faulty iron homeostasis is anemia, a state of decreased hemoglobin levels. Tao et al, through a retrospective observational study involving 222 patients established anemia to be an independent risk factor of severe disease (OR 3.47 [1.02-11.75]). Similarly, Weiler, et al in their retrospective study of 259 hospitalised patients have reported anemia to be an independent risk factor for in hospital mortality (OR 3.729 [1.739-7.995]).

Hariyanto and Kurniawan through a meta-analysis involving 9,912 COVID-19 patients showed a significant association of anemia with severe COVID-19, with moderate heterogeneity [OR 2.44 (95 % CI 1.75-3.40), p < 0.00001, I² = 47 %, random-effect modelling]. In yet another meta-analysis of 57,563 COVID-19 patients, Taneri, et al found that severe COVID-19 cases, compared to moderate cases had lower hemoglobin levels [weighted mean difference (WMD), - 4.08 g/L (95% CI - 5.12; - 3.05)] and red blood cell count [WMD, - 0.16 × 10¹²/L (95% CI - 0.31; - 0.014)], and higher ferritin [WMD, - 473.25 ng/mL (95% CI 382.52; 563.98)] and red cell distribution width [WMD, 1.82% (95% CI 0.10; 3.55)].

The present study reports significant differences in the hemoglobin levels between non-survivors (Median 13.73, IQR2.51) and survivors (Median 12.12, IQR2.87). Anemia as a risk factor for mortality was observed in univariable analysis (HR 3.970 [1.582-9.960]), but anemia as an independent risk factor of mortality could not be ascertained.

Iron metabolism biomarkers can hence contribute to risk stratification. In this premise, Weiler, et al have investigated two such biomarkers, ferritin and transferrin and have demonstrated ferritin-transferrin ratio to be a predictor of the risk of a severe disease, ICU admission or requirement of mechanical ventilation. Based on the findings that significantly higher levels of serum ferritin and lower hemoglobin levels were observed in the present study among non-survivors compared to survivors and other studies linking hyperferritinemia and anemia with disease outcomes, we studied whether ferritin-hemoglobin ratio would be an even stronger predictor of mortality. Ferritin-hemoglobin ratio is calculated by dividing the ferritin level, an acute phase reactant, a marker of hyperinflammation, and predictor of severe disease and hemoglobin, another iron associated protein which reflects the overall host condition. Ferritin hemoglobin ratio was observed to be significantly higher in non-survivors (Median 56.98, IQR 48.57) compared to survivors (Median 17.17, IQR 25.44). FHR >31 predicted mortality with good sensitivity and specificity and in a multivariable analysis, became apparent as an independent risk factor of mortality (HR 12.391 [3.110-49.367]).

In the present study, when ferritin and hemoglobin were combined into a single index in the form of ferritin-hemoglobin ratio, statistical significance was observed. In point of fact, ferritin-hemoglobin ratio, which takes into account both the levels of ferritin and severity of anemia, emerged as an independent risk factor of mortality whilst having a high sensitivity and specificity in predicting mortality. To our best knowledge, this is the first study reporting the prognostic significance of ferritin-hemoglobin ratio in COVID-19. Ferritin-hemoglobin ratio, can hence be a robust and easily available marker for risk stratification at admission. In addition, the observations from the present study add further insight into the role of iron homeostasis in COVID-19 and reiterate the fact that hyperferritinemia, a consequence of inflammation induced dysregulation of iron homeostasis and cellular iron overload, and anemia, an outcome of a faulty iron metabolism and a beacon of the underlying state of the body, both, are inexorably interlinked in addition to being related, directly or indirectly to the disease pathophysiology. Ferritin and hemoglobin, hence should be seen as two sides of the same coin rather than as two discrete entities.

This study broadens the horizon for our understanding of this relatively new and potentially fatal disease, giving insights into the multi-dynamic nature of this disease. With a focus on deranged iron homeostasis, this study reports a novel, yet readily available marker, ferritin-hemoglobin ratio as an independent risk factor for mortality and in addition describes in brief the pathophysiological background behind its predictive role.

However, the present study has certain limitations. Due to the retrospective nature of this study, analysis for other variables including transferrin, serum iron and hepcidin, other markers of iron metabolism which may have a possible role in disease pathophysiology and severity, was not possible. The number of variables that could be included in the multivariable analysis was limited by the relatively smaller sample size. Further, outcomes were evaluated at the end of the follow up period and not at fixed times during the course of the disease.

**Conclusion**

In our study, Ferritin-hemoglobin ratio (FHR), which encompasses into a single index, the effects of both elevated levels of ferritin and the severity of anemia, seems to perform particularly well as a prognostic marker for mortality in COVID-19 patients. FHR emerged as an independent risk factor for mortality in COVID-19 patients. This may open venues for newer therapies in management of COVID 19, such as the anti-hipcidin or the anti-ferroptosis therapies in order to counter oxidative stress and lipoperoxidation, which are precipitants of the cytokine-storm, an immune over-response. Targeting the iron homeostasis, may hence emerge as the focus of COVID 19 therapy in future.

**References**


Effect of Training and Checklist Based Use of Ventilator Associated Pneumonia (VAP) Prevention Bundle Protocol on Patient Outcome: A Tertiary Care Centre Study

Ragesh Radhakrishnan1, Rita Sood2, Naveet Wig3, Prayas Sethi3*, Manish Soneja4, Arvind Kumar4, Neeraj Nischal5, Ashutosh Biswas2, RM Pandey6

Abstract

Objective: VAP prevention bundle includes daily sedation free interval, DVT prophylaxis, raising head end of bed, use of orogastric rather than nasogastric tube. This study aims to study the practices regarding VAP prevention bundle and its compliance, educating about the practices and effects on patients outcome.

Design: Quasi-experimental study, conducted in 3 phases.

Setting: Hospital based

Participants: Invasive Mechanically ventilated patients in the Department of Medicine of a tertiary care hospital. 50 patients included in phase 1 and 3.

Intervention: Phase 1 and Phase 3 were pre and post intervention phases respectively when compliance to VAP prevention bundle was assessed with intermediate Phase 2, the intervention phase where the residents and nurses were educated about VAP bundle through various means. A checklist was attached to patient records.

Outcome Measures: Incidence of VAP, total hospital and ICU stay, duration of mechanical ventilation and mortality.

Results: On comparing the 2 phases, it was found that there was increase in the compliance to VAP bundle(p<0.001), use of iron supplementation in relation to mortality among HIV-infected patients receiving highly active antiretroviral therapy in Tanzania. Am J Trop Med Hyg [Internet]. 2019 Apr 22 [cited 2020 Dec 4] ;100(4):1512–20. Available from: http://www.ajtmh.org/content/journal/10.4269/ajtmh.18-0096


of orogastric tube (p<0.001) and use of daily sedation free interval (p<0.001). Statistically insignificant increase in the use of DVT prophylaxis (p=0.996) and raising the head end of the bed (p=0.513), and decline in the number of days of ICU (p=0.804) and hospital stay (p=0.907), the duration of mechanical ventilation (p=0.909), mortality (p=0.315) and incidence of VAP (p=0.715) was noted. Among those who developed VAP, there was lower compliance to bundle.

Conclusions: Practices like use of VAP prevention bundle improve on teaching efforts and use of checklist which improves patient care.

Introduction

Ventilator-associated pneumonia (VAP), a type of hospital acquired pneumonia (HAP) that develops more than 48 hours after endotracheal intubation, has an estimated incidence of 9 to 27%, and a mortality rate of 30 to 70%. Considering this high mortality rate and the high cost that is incurred to the health care system, different agencies and organizations including Infectious disease society of America (IDSA) have issued guidelines from time to time for prevention of VAP.1

Many risk factors for VAP, both modifiable and non-modifiable have been identified.2 Many of the interventions have shown to reduce the incidence of VAP.2

There have been many attempts to combine these individual components into a bundle with the objective of reducing the incidence of VAP. A set of evidence-based clinical practices that when individually implemented improve care and if combined together, magnify improvement. This is called a care “bundle”.4 Hospitals with a VAP prevention bundle have even achieved zero rates of VAP for long periods.5

The institute for healthcare improvement (IHI) ventilator bundle combines 4 components of care which are elevating the head of the bed, daily sedative interruption and assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep vein thrombosis prophylaxis.6

Despite such data demonstrating the preventability of VAP, there is a wide gap between knowledge, attitude and actual practices. The success of efforts to improve adherence to VAP prevention guidelines depends upon several factors such as the awareness and attitude of all the concerned staff, the provision of adequate organizational support like infrastructure, reminders, reinforcements and effective monitoring. Efforts to improve knowledge and influence attitudes towards prevention of VAP must address the existing level of knowledge about incidence and risk factors, the severity of consequences and thus lay the ground for motivation in behaviour change.

There is a paucity of studies on VAP prevention from India. Moreover, as per our observations in the past, there is an urgent need to improve the attitude and practices related to this important healthcare quality improvement issue. This study aims to examine the current practices related to VAP prevention bundle in patients on mechanical ventilation and the effect of education and checklist on the change in the compliance to the bundle and ultimately the patient outcome.

Methods

It was a quasi experimental prospective interventional study which included patients on mechanical ventilation admitted in medicine department from may 2012 to november 2013. Children less than 12

Table 1: Clinical profile of patients at the time of recruitment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-intervention group (n=50)</th>
<th>Post- intervention group (n= 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean)</td>
<td>43.4±19.8</td>
<td>45.2±20.7</td>
<td>0.648</td>
</tr>
<tr>
<td>History of COAD (in %)</td>
<td>16%</td>
<td>24%</td>
<td>0.317</td>
</tr>
<tr>
<td>History of CVA(in %)</td>
<td>6%</td>
<td>2%</td>
<td>0.617</td>
</tr>
<tr>
<td>History of smoking (in %)</td>
<td>22%</td>
<td>18%</td>
<td>0.617</td>
</tr>
<tr>
<td>History of alcohol intake (in %)</td>
<td>12%</td>
<td>6%</td>
<td>0.487</td>
</tr>
<tr>
<td>History of diabetes mellitus (in %)</td>
<td>10%</td>
<td>12%</td>
<td>0.749</td>
</tr>
<tr>
<td>History of hypertension (in %)</td>
<td>10%</td>
<td>10%</td>
<td>1.00</td>
</tr>
<tr>
<td>History of CAD (in %)</td>
<td>6%</td>
<td>0%</td>
<td>0.242</td>
</tr>
<tr>
<td>Patients in hypotension</td>
<td>28%</td>
<td>22%</td>
<td>0.488</td>
</tr>
<tr>
<td>Patients with thrombocytopenia</td>
<td>30%</td>
<td>22%</td>
<td>0.362</td>
</tr>
<tr>
<td>Patients with acute kidney injury</td>
<td>46%</td>
<td>56%</td>
<td>0.317</td>
</tr>
<tr>
<td>Patients with major active bleed</td>
<td>2%</td>
<td>4%</td>
<td>1.000</td>
</tr>
<tr>
<td>GCS (out of 15)</td>
<td>9.1±4.4</td>
<td>10.6±3.4</td>
<td>0.067</td>
</tr>
<tr>
<td>HR (beats per minute) (mean)</td>
<td>108±28</td>
<td>101.1±19.3</td>
<td>0.159</td>
</tr>
<tr>
<td>SBB (mm hg) (mean)</td>
<td>102.1±23.6</td>
<td>108.1±26.8</td>
<td>0.236</td>
</tr>
<tr>
<td>DBP (mm hg) (mean)</td>
<td>64.2±14.7</td>
<td>69.5±14.1</td>
<td>0.065</td>
</tr>
<tr>
<td>RR (breaths per minute) (mean)</td>
<td>21.9±6.9</td>
<td>24.7±7.9</td>
<td>0.058</td>
</tr>
<tr>
<td>Temp (fahrenheit) (mean)</td>
<td>98.8±1.1</td>
<td>99.1±1.7</td>
<td>0.087</td>
</tr>
<tr>
<td>APACHE II (mean)</td>
<td>18.3±6.9</td>
<td>17.5±5.1</td>
<td>0.635</td>
</tr>
</tbody>
</table>

(COAD- Chronic obstructive airway disease, CVA- Cerebrovascular accident, CAD- Coronary artery disease, GCS- Glasgow coma scale, HR- Heart rate, SBB- Systolic blood pressure, DBP- Diastolic Blood pressure, RR- Respiratory rate, Temp- Temperature, APACHE II- Acute physiology and chronic health evaluation II)
years, patients who had been intubated before being brought to our hospital, pregnant women and patients with history of intubation within last 2 months were excluded from the study.

Study was conducted in three phases. The first phase was the pre intervention phase in which identification of current level of practice of VAP prevention bundle was assessed applying a standardized checklist and proforma. The second phase was an interventional phase in the form of providing the residents standardized checklist and multiple educational sessions on VAP prevention. This was followed by the post intervention phase in which the change in compliance to the bundle components and outcome implications of implementing ventilator associated pneumonia prevention bundle in preventing VAP was assessed.

Both the pre and post intervention phase groups had 50 patients each. This sample size was based on the estimated number of possible intubated patients that can be conveniently studied in 6 months time. This short term of the study was based on the need to study the effect of the change in the practice by training of same residents. Also, it was intended to improve the quality of care which is an ongoing activity.

The pre-intervention (baseline) phase lasted for 6 months. In this phase, data was collected daily on compliance to the bundle components on all the recruited patients with the use of a proforma. Data obtained in proforma included patient demographics, clinical data, ventilation settings data, and the data related to the compliance to VAP bundle, development of VAP and mortality.

In the intervention phase, the concerned health care professionals were educated in the form of interactive lectures highlighting the VAP prevention bundle and its importance. This was followed by one to one communication to ensure that all care givers are aware of the protocols and are motivated to convert them into practice. The treating staff were familiarized with the bundle checklist which was prepared to serve as a reminder. The target group of interventional phase was identified to be the residents and nursing staff of department of medicine. Feedback was provided to the physicians and nursing staff on the number of patients who met indications for the bundle, data on compliance with bundle components and patient outcomes of the pre-intervention phase.

A series of nine interactive lectures on VAP prevention was designed keeping in mind the appropriate use of visual communication. Posters were displayed across the medical wards and prominent hospital areas. Social media was used for online communication. The intervention phase lasted for 3 months.

In the post intervention phase a checklist containing the four prevention components of the bundle implemented intervention group, were all the four components of the bundle implemented in none of the patients in the pre-intervention group and post-intervention group respectively. Respiratory distress and poor sensorium were the reasons for intubation in the majority of patients in both the groups. Both groups were comparable at time of recruitment.

In none of the patients in the pre-intervention group, were all the four components of the bundle implemented in none of the patients in the pre-intervention group and post-intervention group respectively. Respiratory distress and poor sensorium were the reasons for intubation in the majority of patients in both the groups. Both groups were comparable at time of recruitment.

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on all days of ventilation whereas in 28% of the patients in the post-intervention group, all the four components of the bundle were implemented on all days of ventilation. This difference was found to be statistically significant (p value < 0.001). The compliance to head-end of bed elevation was 0.64 in mean of proportion of days of ventilation, i.e., if a representative patient in the group had total 100 days of ventilation, on 64 days the patient’s head-end of the bed was elevated to 30 to 45 degrees. This was 0.68 in the post intervention phase. The compliance to sedation free interval, orogastric tube insertion in preference to the nasogastric tube and DVT prophylaxis in pre intervention phase were 0.89, 0.36 and 0.45 respectively in mean of proportion of days of ventilation whereas it was 0.98, 0.72 and 0.45 respectively in the post intervention phase. Table 3 shows the compliance to the bundle components in the pre-intervention vs post intervention phase.

Total hospital stay in the pre-intervention group was 656 days with a median of 10 days (range 2 to 60 days) and 642 days with a median of 10 days in the post intervention group. This difference was not statistically significant (p=0.907). The total duration of ventilation was 379 days with a median of 4.5 days (range 2 to 42) in the pre-intervention group and 293 days with a median of five days (range 1 to 22 days) in the post intervention group. This difference was not statistically significant (p=0.909). Total ICU stay was also lower in the post intervention group (206 days with a median of seven days) when compared to the pre-intervention group (274 days with a median of six days), though this difference was not statistically significant (p=0.804).

The mortality rate of the post intervention group was lower than the pre-intervention group (50 % versus 60% respectively), but the difference was not statistically significant (p= 0.315).

Ten percent of the patients developed VAP in the pre intervention phase which decreased to 6 percent in post intervention phase. However, it was statistically insignificant (p<0.715). These findings comparing patient outcomes are summarised in Table 4.

The observed compliance to the four bundle components was compared in patients who had developed VAP with those who did not. It was observed that in patients who had developed VAP, compliance to head-end elevation, orogastric tube and sedation free interval was lower than the patients who did not develop vap, though the differences were not significant statistically. The compliance to DVT prophylaxis was similar in both groups, with or without VAP. A comparison of the bundle compliance in patients with and without vap is shown in Table 5.

### Discussion

The whole idea of a VAP prevention bundle is that the implementation of the bundle components, would translate into better outcomes in terms of lower incidence of VAP, hospital mortality and hospital length of stay in patients on mechanical ventilation. Several studies highlight the fact that the incidence of VAP decreases with the use of bundles aimed at VAP prevention. The ventilator bundle designed by the Institute for Healthcare Improvement’s (IHI) which was developed to improve outcomes of the ventilated patients was also shown to reduce the incidence of VAP.9

Other studies on prevention of VAP by the bundle approach like that done by Lansford T et al have also shown to decrease the incidence of VAP.8 In another study conducted by al manoel to examine the effect of the IHI’s ventilator bundle plus oral decontamination with chlorhexidine (odc) on the incidence of VAP in an ICU, a daily checklist which served as reminders to observe the five components was used. This resulted in improved adhesion to the whole bundle (9% and 86%) (p < 0.001) and lower incidence of VAP.9

Compliance to all the 4 components on all days of ventilation was 28 % in post-intervention group when compared to the pre-intervention group where none of the patients had shown compliance with all the four components of the bundle, this difference was found to be statistically significant (p<0.000). This difference is lower than the magnitude of improvement achieved by the Barenholtz group (32 % in pre-intervention to 84% post-intervention). In our study, the lack of compliance to all the components might have been due to certain factors like hypotension preventing the rising of the head end of the bed, DVT prophylaxis due to already existing coagulopathy secondary to sepsis or DIC (high APACHE 2 scores) which form a major burden of our ICU, and discomfort related to orogastric tube. However, still there was a potential to improve and 28 percent increase in compliance was noted. Information regarding the APACHE 2 scores, hemodynamic status or thrombocytopenia in the study done by Barenholtz et al is not available.

Though the difference observed in decline in VAP was not statistically significant, there was a decline in incidence of VAP from 10 % in the pre-intervention group to six percent in the post-intervention group. The results of this study showed a similar trend as that of a before and after cohort study done by Barenholtz in which the bundle decreased VAP rate from a median of 5.5 cases per 1000 ventilator-days at baseline to a median of zero cases at 16 to 18 months after implementation.10 In comparison, study sample size of this study was smaller, had fewer total days of ventilation and was of shorter duration. In a prospective longitudinal study conducted on adult intensive care unit (ICU) patients by Bukhari et al implementing a VAP prevention bundle reduced the VAP incidence rate and lowered the cost of care, the reduction being statistically significant.11

The overall rates of VAP in both the pre and post-intervention phases in the present study were lower in comparison to the rates described in many other studies. In a study conducted by Dey et al in an ICU of an Indian tertiary hospital the incidence was found to be nearly 45 %.12 In another Indian study done by Charles et al, the incidence of VAP was found to be nearly 53 per 1000 ventilator days.13 Probably a further study with a larger sample size would be needed to determine the effect of the proposed VAP prevention bundle on the incidence of VAP.

This study did not measure other confounding factors like hand hygiene, fomite borne transmission, oral care. These factors per se could have also had an impact on VAP incidence. In both the groups the onset of VAP was late. This might have been influenced by the high antibiotic usage in both groups, considering that antibiotic use may decrease incidence of early VAP. Also in
both the groups’ lower limit of range of duration of stay was very less (1 day in the post-intervention group and 2 day in the pre-intervention group) mostly due to their early demise due to their critical condition. Thus many patients did not survive long enough due to their primary illness before potentially developing VAP.

In this study it was seen that except for DVT prophylaxis, compliance to the other three components were lower in the group who subsequently developed VAP when compared to those who did not. But these differences were not statistically significant, probably due to the low incidence of VAP and a low sample size. In a RCT conducted by Drakulovic MB et al published in 1999, frequency of nosocomial pneumonia was lower in the semi-recumbent group when compared to the supine group (three of 39 [8%] vs 16 of 47 [34%]; 95% CI for difference 10.0-42.0, p=0.003), showing supine recumbent group when compared to the group who subsequently developed VAP. Thus the excess mortality due to VAP and a low sample size would bring out a significant change in these parameters.

There was no significant difference in the mortality between the two groups. This study primarily focussed on VAP prevention bundle and not primarily on mortality reduction due to other causes. In the pre-intervention group, the incidence of VAP was only 10% (n-five patients) of which three patients died. Thus the excess mortality due to VAP in the pre-intervention group would at the maximum be 6% (additional three patients). Thus the study is not powered to answer the question on mortality reduction considering the low incidence of VAP in the study population. Similarly there was no significant difference in hospital stay, ICU stay and duration of mechanical ventilation between the two groups. This is following the trend of a study done by Boudama et al, in which there was no significant difference in hospital mortality and duration of mechanical ventilation, though the ICU stay was lower post intervention unlike this study.15

In a RCT done by John P. Kress on 128 patients on mechanical ventilation, comparing daily sedation interruption, median duration of mechanical ventilation was 4.9 days in the intervention group, as compared to 7.3 days in the control group (p=0.004), and the median length of stay in the intensive care unit was 6.4 days as compared with 9.9 days, the difference being statistically significant.16 The sample size in the present study was not large enough to detect a significant change in mean hospital or ICU stay. The sample size was not sufficient because the compliance with sedation free interval with was already high even prior to the intervention. Probably a similar study with a much larger sample size would bring out a significant change in these parameters.

Conclusions

VAP prevention can be achieved to a large extent with the use care bundles. However, a major road block is the lack of adherence to the set protocols by the healthcare professionals. Educating them through targeted training and issuance of checklists can have a significant impact on the improvement in adherence, and ultimately patient outcomes.

Limitations of the Study

Sample size was small. Since the investigator was not present at site for 24 hours, it was not possible to ascertain whether the bundle components were persistently adhered to. It was a non randomized study. Confounding factors like adherence to hand hygiene, glove use, oral hygiene, appropriate suction methods etc independently may lead to changes in incidence of VAP. There was only a marginal increase in the compliance to the VAP prevention bundle. This means that there are many variables involved in the process improvement. But in this study, these barriers to bundle compliance improvement including the contribution of physician and allied staff behavior was not measured. Identifying and rectifying these variables could have led to a better rate of compliance with VAP prevention bundle in this study.

References

The Pattern of Post-viral Arthritis in COVID Pandemic State: An Experience of Tertiary Care Centre

Prakruthi Jaladhar1, Chandrashekara S2*, Manasa Salanke3, Devaraj Kori4

Abstract

Background: Acute onset polyarthritis is a common presentation in rheumatology outpatient consultations, which include both post-infectious arthritis and autoimmune rheumatic diseases (AIRDs). COVID pandemic has added to the list of infectious agents that could result in arthritis.

Materials and Methods: The retrospective observational study was conducted at a tertiary care centre. The study included patients who presented with clinical suspicion of post-infectious arthritis between July-September 2019 and 2020. The study was extended for another 2 months to include patients who presented between October-November 2020. The patients were categorized into post-viral arthritis, post-COVID arthritis, chikungunya arthritis and AIRDs. The demographics, comorbidities, clinical presentation, examination findings and laboratory parameters and the response to treatment for each participant were collected and assessed.

Results: In the year 2019 and 2020 (July-Sep), the corresponding number of patients analyzed were 20 and 33. The mean duration of presentation was 1.53 (±3.10) weeks. Chikungunya arthritis was noted in 10% of patients in 2019, while it was 15.15% in 2020. Other post-viral arthritis was identified in 65% and 66.67% of patients in 2019 and 2020 respectively. In the second part of the study, 65.68% of patients were classified as post-viral arthritis, including chikungunya arthritis, post-COVID arthritis and other post-viral arthritis. Around 27% were categorized as AIRDs. Rheumatoid factor negativity and anti-nuclear antibody negativity were found to be significant (P 0.0) in categorizing the patients into post-viral arthritis group, while presence of urinary symptoms (P 0.0) classified the patients into reactive arthritis.

Conclusion: The study revealed that the presence of chikungunya arthritis across the two years was comparable. Post-COVID arthritis needs to be considered as a potential differential in post-infectious arthritis. There are no identifiable characteristics (clinical or a simple routine laboratory parameter) that could differentiate the causes of post-infectious arthritis from AIRDs.

Introduction

Acute onset polyarthritis is one of the common presentations in out-patient consultations of both rheumatology and general medicine departments. It may develop secondary to bacterial or viral infections. The most common viruses causing arthritis and/or arthralgias include (it can be either acute or chronic) parvovirus, alphaviruses, hepatitis B, hepatitis C, Epstein-Barr virus (EBV), and tropical viruses such as zika and chikungunya.

However, epidemiological studies on viral arthritis are limited, and the etiology may differ according to the geographic area. The diagnosis of post-viral arthritis is often difficult to establish and should be considered in patients presenting with acute onset polyarthritis. To the exhaustive list of infective agents, the COVID-19 pandemic has added another potential cause for post-viral arthritis.

A surge in such cases was observed between July to September, which coincided with the monsoon season. The same pattern had been described in 2017 in a private setting in Delhi. In the year 2019, the causes of acute onset polyarthritis were predominantly secondary to chikungunya arthritis, reactive arthritis and other post-viral arthritis, along with rheumatological causes like rheumatoid Arthritis (RA) and other connective tissue diseases (CTDs). However, in the year 2020, post-viral arthritis along with the aforementioned causes, following a COVID infection, was also noted. The social and behavioural changes that occurred due to COVID pandemic would have changed the pattern of presentation of viral arthritis.

The present study has compared the pattern of presentation of short duration arthritis, indicative of post infectious arthritis during the period July to September in 2019 and 2020, with reference to etiology, epidemiology, demographics, clinical presentation and laboratory parameters. The study also evaluated the laboratory or clinical parameters that would be beneficial in identifying the cause of post infective arthritis in peripheral health centres where limited investigations are available.

Materials and Methods

The retrospective observational study was conducted at a tertiary super speciality referral center for rheumatological and immunological diseases in Southern India. The study involved patients who presented with clinical suspicion of post-infectious arthritis (viral or reactive arthritis) between July to September in 2019 and 2020. The details such as
Table 1: Demographic and disease characteristics of the patients presented in 2019 and 2020 (July-September)

<table>
<thead>
<tr>
<th>Descriptive statistics</th>
<th>Number (percentage) / Mean (std. deviation)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Male; female</td>
<td></td>
</tr>
<tr>
<td>2019 (n=20)</td>
<td>3 (15);17 (85)</td>
<td></td>
</tr>
<tr>
<td>2020 (n=33)</td>
<td>15 (45.45);18(54.55)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>40.35 ± 15.08</td>
<td></td>
</tr>
<tr>
<td>2019 (n=20)</td>
<td>45.18 ±14.9</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>2019 (n=20)</td>
<td>10 (30.3)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Rashes</td>
<td></td>
</tr>
<tr>
<td>2019 (n=20)</td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td>2020 (n=33)</td>
<td>6 (18.18)</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>Laboratory parameters</strong></td>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>2019 (n=20)</td>
<td>11.84 ± 3.049</td>
<td></td>
</tr>
<tr>
<td>2020 (n=33)</td>
<td>12.96±1.61</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Chikungunya arthritis</td>
<td></td>
</tr>
<tr>
<td>2019 (n=20)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>2020 (n=33)</td>
<td>5 (15.15)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Statistical Analysis

ANOVA was carried out for continuous variables and chi-square for categorical variables.

Results

Part I

During the period July 2019 to September 2019, 1189 new cases were registered at the setting, out of these subjects, 46 patients who presented with acute onset polyarthritis were selected for the study and 26 patients were excluded either due to previous history of AIRD or lack of complete data. During the same time period for the year 2020, 861 new cases were registered and out of these, 61 patients were included and 28 were excluded. Demographic characteristics of the patients who presented between 2019 and 2020 (July-Sep) are provided in Table 1. The mean duration of symptoms at presentation was 1.53 (±3.10) weeks.

The absence of rheumatoid factor (RF) and antinuclear antibody (ANA-IF) was found to be significant in classifying the patients as post-viral arthritis (P 0.0).

Part II

Out of 1559 new cases registered, the second part of the study included 130 patients who presented between July 2020 and November 2020 with symptoms suggestive of postinfectious arthritis. Twenty-eight patients were excluded in view of presence of previous arthritis or due to the lack of follow-up data till confirmation of diagnosis. The patients were categorized into those having post-viral arthritis (including post-COVID arthritis, chikungunya arthritis, other post-viral arthritis), AIRDs and reactive arthritis. The comparison of demographic and clinical characteristics of these categories with respect to both clinical and laboratory parameters is briefed in Table 2.

RF and ANA( IF) negativity was found to be significant (P 0.0) in categorizing the patients into post-
viral arthritis group, while presence of urinary symptoms (p=0.0) classified the patients into reactive arthritis. Twenty-eight patients who presented with features suggestive of post-viral arthritis were eventually classified as AIRDs, and they satisfied the criteria for a specific AIRD.

**Discussion**

Among the study population, around 66% patients with polyarthritis of <6 weeks duration was classified into categories other than AIRDs. Out of these, 42% had a post-viral arthritis other than chikungunya and COVID, while 14% had post-COVID arthritis. The proportion of chikungunya arthritis did not significantly differ in the current cohort even amidst COVID pandemic. Presence of antibodies was the only specific indicator differentiating viral arthritis from specific AIRD. However, the presence of post-viral arthritis was comparable between 2019 and 2020 (65% and 66.67% cases respectively). The number of chikungunya arthritis was marginally higher in 2020 (15.15%), but the presence of reactive arthritis remained same in both the years. Only one case of post-COVID arthritis was identified during the time period.

Increased female preponderance was noted in the study cohort. There were no clinical or routine laboratory parameters identified that could differentiate between these categories without the analysis of serology for chikungunya (IgM), COVID (IgG) and autoantibodies like RF and anti-cyclic citrullinated peptide (anti-CCP). The study did not identify any clinical characteristics that could be useful as a screening tool at peripheral centres to differentiate chikungunya arthritis from other forms of arthritis. It is also evident from the present study that it is imperative to perform serological tests like chikungunya IgM to classify such patients.

Pathak et al. noted that the presentations of patients with chikungunya were acute (<6 weeks) to subacute (<3 months) with symmetric polyarthritis involving both small and large joints. The study highlighted the necessity of investigations like RT-PCR for chikungunya virus in 1st week of illness and serological markers like chikungunya IgM, IgG in second week in suspected patients. These findings are in concurrence with the present study, which has reported the duration of symptoms of presentation as acute (<6 weeks) and the need for serological evaluation with chikungunya IgM for diagnosis.

Though the cumulative number of patients who presented with acute polyarthritis during July to September in 2020 was higher compared to previous year, the result was not statistically significant. This could be the result of other hospitals being pre-occupied by COVID care and not due to an increased occurrence. However, the proportion of the patients diagnosed with post-viral arthritis and reactive arthritis remained same with only a marginal increase in cases of chikungunya arthritis in 2020 as compared to 2019.

In the present study, a sizeable proportion of patients were classified as having post-viral arthritis. They did not satisfy the criteria for reactive arthritis and were serologically negative for RF, ANA(IF) as well as chikungunya (IgM). They presented with fever followed by acute or subacute onset of polyarthritis with symmetric involvement of both large and small joints. These patients fared well with a short course of NSAIDs, as against patients with chikungunya who required an additional disease modifying agent like hydroxychloroquine. These findings were similar to that noted in previous studies. A small proportion of post-viral arthritis patients required hydroxychloroquine at first follow-up, if they had persistent polyarthritis.

A 2009 study, reported 21 cases of chikungunya fever from Reunion Island in Indian Ocean, and further follow-up of 27.6 months concluded the diagnosis as rheumatoid arthritis and in most cases the outcome was severe. The present study included 14 patients who were identified as having post-COVID arthritis in this 5-month period of observation. One patient tested positive for both chikungunya IgM and COVID IgG was not included in the analysis. Post-COVID arthritis, which was earlier reported in October 2020 during the first wave of COVID pandemic has been well established as a clinical entity requiring medical attention. Post-COVID arthritis patients in the study generally required an additional disease modifying agent like hydroxychloroquine along with NSAIDs, and this is in agreement with literature review performed by Gasparotto et al.10 Tapering dose of low dose steroids was added in a few cases who presented with severe symptoms.

About 28 patients who presented with fever followed by acute polyarthritis eventually turned out to be AIRD and were diagnosed as per criteria. It is very essential to rule out autoimmun causes in patients who appear to be postinfectious arthritis. Delay in diagnosis and treatment, may result in persistence of erosive arthritis, and subsequent development of joint damage and other complications. Literature findings conclude that patients visiting a rheumatologist by 6 weeks of onset of symptoms have a higher chance of achieving drug-free remission and better quality of life.11,12 Early arthritis clinics also reduce the unwarranted delay in diagnosis due to delayed referral and hence a delayed initiation of treatment.13,14 An article by Holland et al. in 2013 has reiterated the need to rule out AIRD when arthritis symptoms persist beyond 6 weeks.15

A study carried out in Birmingham (1993) included 112 patients who were followed up for 1 year to differentiate self-limiting synovitis from persistent synovitis. In an era prior to the introduction of assessment of anti-citrullinated peptide antibodies, the study identified 29 subjects with persistent synovitis and 36 with self-limiting synovitis. The study hypothesized that rheumatoid arthritis exists in two forms, a persistent form and less identified abortive form.16 There are no other studies who have focused on the aforementioned concept. There is a possibility that the self-limiting synovitis could be postinfectious.

The radiological studies of all the current patients with postinfectious arthritis (posteroanterior view of both hands) were unremarkable. A few patients who were diagnosed with AIRD showed diffuse erosive changes or juxta articular osteoporosis.

The findings of the present study are not generalizable due to the single-centre study design. In addition, due to the retrospective nature of the study, the observations are not tailor made and specific. Larger studies at community level are required to assess the incidence and prevalence of post
Infective arthritis and its types.

**Conclusion**

The presence of chikungunya arthritis across the two-year study period was comparable. Post-COVID arthritis needs to be considered as a potential differential in postinfectious arthritis. There are no identifiable characteristics (clinical or a simple routine laboratory parameter) that could differentiate the different causes of postinfectious arthritis and from AIRD and it is imperative to perform serological tests like rheumatoid factor, anti-CCP, antinuclear antibody, serological tests like rheumatoid arthritis needs to be considered as a definable AIRD.

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**Primary Prophylaxis Patterns for Hepatic Encephalopathy in Patients with Liver Cirrhosis: What are the Current Prescribing Trends in Specialty Practice?**


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**Abstract**

**Introduction:** Hepatic encephalopathy (HE) is a significant complication of severe chronic liver insufficiency characterized by altered sensorium, motor, and cognitive dysfunction. This was a cross-sectional multicenter, epidemiological study to understand the prescribing pattern for primary prophylaxis of overt HE (OHE) in patients with cirrhosis in India.

**Methods:** The study was conducted at eight centers across different geographical regions of India. A total of 200 patients (100%) were screened, of which 197 (98.50%) met all the inclusion criteria. The prescribing pattern of the physicians was studied by calculating the percentage (subject to availability of sufficient data) of OHE-naïve patients with cirrhosis who were prescribed with different classes of drugs as primary prophylaxis of HE (such as lactulose, rifaximin, neomycin, sodium benzoate, and L-ornithine L-aspartate). The risk factors responsible for initiation of primary prophylaxis of HE were also determined.

**Results:** All the 197 patients (100%) were prescribed with prophylactic treatment. The factors that were considered by treating physicians to pose a risk for precipitating OHE for which prophylaxis was initiated were constipation in 111 (56.35%), infections in 51 (25.89%) and gastrointestinal bleeding in 35 (17.77%). Of the total 197 patients, 122 (61.93%) patients were prescribed a monotherapy, and 75 (38.07%) were prescribed a combination therapy. Of the patients on combination therapy, 68 (34.52%) patients were prescribed with two primary prophylaxis agents (dual therapy), and seven (3.55%) patients were prescribed with three primary prophylaxis agents (triple therapy). Lactulose was the most commonly prescribed agent for primary prophylaxis, followed by rifaximin.

**Conclusion:** These findings may guide recommendations on primary prophylaxis for OHE in patients with liver cirrhosis that may help reduce the occurrence of first episode of overt HE, and thereby prevent subsequent cognitive impairment in these patients.

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**References**

15. Practitioners TRAC of G. RACGP - Viral arthritis [Internet]. [cited 2021 Jun 4].
Introduction

Hepatic encephalopathy (HE) is a major complication of severe chronic liver insufficiency, characterized by altered sensorium, motor, and cognitive dysfunction. HE is categorized into different grades based on the underlying cause: Type A (related with acute liver failure), type B (a result of portal-systemic shunts when liver dysfunction is not present), and type C (in patients diagnosed with liver cirrhosis and portal-systemic bypass). In most of the patients, type C HE occurs in episodic fashion in response to precipitating factors such as infection, gastrointestinal bleeding, diuretic overdose, electrolyte disorder, constipation, psychoactive medication, dehydration, and disturbed dietary pattern.

HE can be differentiated into two main categories based on severity: covert HE (CHE) and overt HE (OHE), which are both components of the spectrum of neurocognitive impairment in cirrhosis (SONIC). CHE is prevalent in 30%-85% patients with liver cirrhosis, whereas OHE occurs in up to 30%-50% of patients, with an annual risk for development of 20%. Clinical management of HE focuses on 4 axes guided by (i) the underlying disease, (ii) severity of the condition, (iii) time-course, and (iv) presence or absence (spontaneous) of precipitating risk factors.

Besides treatment, the prevention and recurrence of HE are important aspects of HE management. In some cirrhotic patients at high risk of developing OHE, the prevention of first episode of OHE (primary prophylaxis of OHE) is considered crucial since each episode of OHE is associated with irreversible impairment of cognitive functions. HE also has a high morbidity and mortality burden.

Therapy available for primary prophylaxis of HE predominantly focuses on reducing the intestinal production and systemic buildup of ammonia to alleviate its neurotoxic effects. Commonly prescribed therapeutic modalities include non-absorbable antibiotics, protein- (or nitrogen-) restricted diet, disaccharide enema, oral disaccharides such as lactulose and lactitol, intravenous/oral L-ornithine-L-aspartate (LOLA), intravenous/oral branched-chain amino acids (BCAA), levodopa and zinc supplementation. Among these primary prophylaxis agents, disaccharides, such as lactulose and lactitol, constitute the first-line management for HE in patients with liver cirrhosis.

However, there is paucity of data on primary prophylaxis modalities by patient profiles, indications/risk factors, and prescription practices in the Indian setting. The present study was undertaken to obtain insights on the management practices for primary prophylaxis of OHE in Indian patients with cirrhosis.

Methods

Patient population

This was a cross-sectional multicenter, epidemiological study conducted across 8 centers in India to evaluate management practices for primary prophylaxis of OHE in patients with cirrhosis. One hundred and ninety-seven out of 200 (98.50%) screened patients met all the inclusion criteria and were considered for analysis in the study. This being an observational study, there was no control group. Adult patients (18-70 years) diagnosed with cirrhosis who never had an episode of OHE (OHE-naïve) and who were recommended primary prophylaxis for HE were included in the study. Key exclusion criteria were patients with a history of alcohol intake during the past 6 weeks; patients with hepatocellular carcinoma, or non-hepatic metabolic encephalopathies, comorbid illness, such as heart, respiratory, renal failure, or neurologic diseases, like Alzheimer’s disease and Parkinson’s disease, and patients prescribed psychoactive drugs, such as antidepressants or sedatives. Other conditions that led to the exclusion of patients were previous transjugular intrahepatic portosystemic shunt surgery or any condition that in the opinion of the investigator did not justify the patient inclusion in the study. The study involved a single visit.

This study was conducted in compliance with the principles of the Declaration of Helsinki, International Council for Harmonization-Good Clinical Practices (ICH-GCP) guidelines, and Indian Council of Medical Research and Indian GCP guidelines. The study protocol was approved by the independent ethics committees of all participating centers, and informed consent was obtained from all patients before data collection.

Primary analysis

Sociodemographic characteristics (age, gender, lifestyle habits [smoking/alcohol consumption], occupation, and socioeconomic status) and clinical characteristics such as body mass index, onset of cirrhosis, etiology of cirrhosis, comorbidity burden, available prognostic markers (model for end-stage liver disease [MELD] score, and Child-Turcotte-Pugh [CTP] score) were assessed as primary analysis.

Secondary analysis

The number and percentage (subject to availability of sufficient data) of patients prescribed with different drug classes (lactulose, rifaximin, neomycin, sodium benzoate, and L-ornithine-L-aspartate) and the number and percentage of patients with presence of risk factors for initiation of prophylaxis of OHE such as electrolyte imbalance, constipation, infections and gastrointestinal bleeding, use of opioids and benzodiazepines, were assessed as part of secondary analysis.

Assessments

Disease severity was assessed based on the Child-Turcotte-Pugh (CTP)
score and the model for end-stage liver disease (MELD) score. The CTP scores were calculated based on prothrombin time, albumin and total bilirubin levels, and ascites and encephalopathy findings and stratified as classes A (scores 5-6), B (scores 7-9), or C (scores 10-15). These categories corresponded to minimally, moderately, and severely altered hepatic functional reserve, respectively. The MELD scores were assessed using serum total bilirubin, serum creatinine, and international normalized ratio (INR).

**Statistical analysis**

Summary statistics were provided for all primary and secondary analyses. Continuous variables were summarized descriptively. Categorical data were summarized as numbers and percentages. Statistical analysis was performed using Statistical Analysis Software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

**Results**

**Sociodemographic characteristics**

Of the 197 patients analyzed, most were male (161 [81.73%]), while 36 (18.27%) were female. The mean ± standard deviation (SD) age of the study population was 50.5 ± 11.26 years.

Clinical characteristics related to cirrhosis are depicted in Table 1. Different etiologies of cirrhosis were alcoholic liver disease (78/197; 39.59%), non-alcoholic fatty liver disease (72/197; 36.55%), idiopathic (20/197; 10.15%), hepatitis B virus (HBV) infection (15/197; 7.61%) and hepatitis C virus (HCV) infection (8/197; 4.06%). Furthermore, approximately 51% of the enrolled patients were classified under CTP class B indicating moderately severe altered hepatic function reserve. The mean (SD) MELD score of the enrolled patients was 19.2 (6.95).

Constipation was reported in 111 (56.35%) patients as the most common factor responsible for the initiation of the prophylaxis for OHE, followed by infections in 51 (25.89%) patients, and gastrointestinal bleeding in 35 (17.77%) patients.

**Prescription patterns**

Of the total 197 patients, 122 (61.93%) patients were prescribed a monotherapy, and 75 (38.07%) patients were prescribed a combination therapy. Of the patients on combination therapy, 68 (34.52%) patients were prescribed with two primary prophylaxis agents (dual therapy), and seven (3.55%) patients were prescribed with three primary prophylaxis agents (triple therapy).

As depicted in Figure 1, most of the study patients (176 [89.34%]) were prescribed lactulose as primary prophylaxis agents. Of these 176 patients, 102 (58.0%) were prescribed lactulose as monotherapy, while lactulose was given as combination therapy in 74 (42.0%) patients. A total of 87 (49.43%) patients were prescribed with rifaximin, of which 71 (40.34%) were prescribed rifaximin as an add-on medication with some other primary prophylaxis agent.

Of the 68 patients prescribed with dual therapy, 63 (92.65%) were prescribed rifaximin and lactulose, 4 (5.88%) were prescribed lactulose and L-ornithine-L-aspartate, and 1 (1.47%) patient was prescribed L-ornithine-L-aspartate and rifaximin as combination therapy. Of the 7 (3.55%) patients who were prescribed with triple therapy, 5 (71.43%) patients were prescribed lactulose, L-ornithine-L-aspartate (LOLA), and rifaximin, whereas the remaining 2 (28.57%) patients were prescribed lactulose, sodium benzoate, and rifaximin.

**Safety**

There was no investigational product in the study. No intervention procedures were to be undertaken for the purpose of this study. As in every doctor-patient-setting, there was some possibility for patients spontaneously reporting their experiences with any of their treatments to investigators or their designee, who were trained to report any adverse drug reactions (ADRs) or other pharmacovigilance relevant information (OPRI) to sponsor or respective other marketing authorization holders as applicable. However, there were no safety concerns (neither ADRs nor OPRI) associated with the use of a pharmaceutical product reported during this epidemiological study.

**Discussion**

HE is a major neuropsychiatric complication in patients with liver disease. Clinically manifest or OHE begins with lethargy and disorientation that results in asterixis, which is eventually followed by stupor and coma. The development of OHE negatively impacts quality of life and reduces the chances of patient survival. Additionally, OHE has a profound negative effect on neurocognitive function before and after liver transplantation.25,26 Also, each occurrence of OHE is linked with a greater risk of further OHE episodes.27 In view of the above considerations, approaches aimed at the effective prevention of OHE in cirrhotic patients are urgently required.
derivative of rifampin i.e., rifaximin, was prescribed in ~45% of cirrhotic patients as a primary prophylactic agent. Published data also suggest that a combination of lactulose and rifaximin may be more effective than lactulose alone in the treatment of OHE. With regard to the prescribing patterns of clinicians for primary prophylaxis of HE, results of the present study confirmed those from previous studies demonstrating that lactulose is the choice of therapeutic agent for primary prophylaxis of HE in cirrhotic patients. The study results revealed that majority of the patients were prescribed lactulose both as monotherapy and as combination prophylaxis therapy. In our study, rifaximin was the second most prescribed prophylactic agent, prescribed mostly as combination therapy along with lactulose. Also, a lesser proportion of patients in our cohort were prescribed L-ornithine-L-aspartate and sodium benzoate as prophylaxis treatment for HE.

An important strength of our study is that this is the first of its kind pan-India study that evaluated reasons for initiating primary prophylaxis of OHE and prescribing patterns of clinicians in Indian patients with cirrhosis. This study highlighted the need to have clear recommendations on the primary prophylaxis of overt HE in patients with liver cirrhosis. Moreover, this study was conducted in a broader clinical context vis a vis existing studies conducted in specific groups of patients. However, this being a single-visit study, the study findings could not provide insights on the impact of various agents on long-term outcomes with respect to preventing the first episode of OHE and any possible effect on mortality, considering CTP class and MELD score.

Another shortcoming of this study is that being an observational study, no comparator analysis was performed.

Conclusion

Findings from this cross-sectional multicenter, epidemiological study conducted across 8 centers in India suggest that physicians frequently consider primary prophylaxis for OHE in patients with liver cirrhosis, constipation, infection, and GI bleeding as the most common risk factors for initiation of primary prophylaxis, and lactulose followed by rifaximin, is the most commonly prescribed primary prophylactic agent. These findings will help guide recommendations on the primary prophylaxis of overt HE in patients with liver cirrhosis that may reduce the occurrence of first episode of overt HE and subsequent cognitive impairment in these patients.

Acknowledgment

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Disclosure

This study was funded by Abbott India Ltd. All authors were the investigators in the study.

References

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- **Glycomet GP 2:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 2 mg.
- **Glycomet GP 1/850:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 850 mg and glimepiride USP 1 mg.
- **Glycomet GP 3/850:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 850 mg and glimepiride USP 3 mg.
- **Glycomet GP 0.5 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 1 mg.
- **Glycomet GP 1 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 2 mg.
- **Glycomet GP 2 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 4 mg.

**INDICATIONS:**

Glycomet GP is indicated for the management of patients with type 2 diabetes mellitus (T2DM) when diet, exercise and single agent (metformin hydrochloride or glimepiride alone) do not result in adequate glycemic control.

**DOSAGE AND ADMINISTRATION:**

Dosage of Glycomet GP should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of glimepiride 8 mg and metformin 2000 mg.

- **Initial dose:** 1 tablet of Glycomet GP should be administered once daily during breakfast or the first main meal. Do not crush before administration.

**CONTRAINDICATIONS:**

- Patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, metformin or any of the excipients of Glycomet GP.
- History of a known hepatic disease or severe liver impairment.
- Severe renal dysfunction.
- Pregnancy or lactation.
- Early pregnancy.

**WARNINGS:**

- Hypoglycemia: The risk of hypoglycemia is increased when metformin is used in combination with other insulin secretagogues, sulfonylureas or insulin.
- Hyponatremia: Hyponatremia may occur due to inappropriate secretion of antidiuretic hormone, which may develop during or after treatment, and may be associated with the therapeutic use of thiazide diuretics.

**PRECAUTIONS:**

- In the initial weeks of treatment, the risk of hypoglycemia may be increased and necessitates especially careful monitoring.
- Serum creatinine levels should be determined before initiating treatment and regularly thereafter:
- At least annually in patients with normal renal function.
- More frequently in patients with impaired renal function.

**ADVERSE REACTIONS:**

- For glimepiride: Hypoglycaemia; temporary visual impairment; gastrointestinal symptoms like nausea, vomiting, abdominal pain, diarrhoea may occur; increased liver enzymes, cholestasis and jaundice may occur; allergic reactions may occur occasionally.
- For metformin: Gastrointestinal symptoms like nausea, vomiting, abdominal pain or discomfort may occur.

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Glycomet®-GP 0.5
Metformin Hydrochloride 500 mg SR + Glimepiride 0.5 mg

Glycomet®-GP 0.5 FORTE
Metformin Hydrochloride 1000 mg SR + Glimepiride 0.5 mg

In Newly Diagnosed & Early Stage of T2DM

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Metformin Hydrochloride 500 mg SR + Glimepiride 0.5 mg

Glycomet®-GP 1/850
Metformin Hydrochloride 1000 mg SR + Glimepiride 0.5 mg

Glycomet®-GP 2/850
Metformin Hydrochloride 1000 mg SR + Glimepiride 1 mg

Glycomet®-GP 3/850
Metformin Hydrochloride 1000 mg SR + Glimepiride 3 mg

In Uncontrolled Obese T2DM

Glycomet®-GP 1 FORTE
Metformin Hydrochloride 1000 mg SR + Glimepiride 1 mg

Glycomet®-GP 2 FORTE
Metformin Hydrochloride 1000 mg SR + Glimepiride 2 mg

Glycomet®-GP 4 FORTE
Metformin Hydrochloride 1000 mg SR + Glimepiride 4 mg

In Overweight T2DM

Glycomet®-GP 1/850
Metformin Hydrochloride 850 mg SR + Glimepiride 0.5 mg

Glycomet®-GP 2/850
Metformin Hydrochloride 850 mg SR + Glimepiride 1 mg

Glycomet®-GP 3/850
Metformin Hydrochloride 850 mg SR + Glimepiride 3 mg

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1000XR

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Glycomet® Trio Forte 2
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Sibling Risk Factor Study in Premature Coronary Artery Disease

Shruthi Subramanyan¹, Rema Pai¹, Jaideep C Menon²*

Abstract

Background: Family history of premature coronary artery disease as a risk factor in first degree relatives has been well established by various studies. This study aims at identification and assessment of the presence of risk factors in asymptomatic siblings of patients with documented premature coronary artery disease. Prevalence of Systemic Hypertension in siblings (both male and female) of patients with premature coronary artery disease (males <45yrs, females <55yrs, confirmed by coronary angiography) was analysed. Other risk factor prevalence estimation was also done which included, dyslipidaemia, diabetes mellitus, tobacco use, alcohol intake, obesity, passive smoke exposure, diet and exercise. The study also estimated the percentage of sibling awareness regarding the risk factors for cardiovascular disease.

Materials and Methods: This was a cross sectional study where all patients (both In and Out patient), visiting Amrita Institute of Medical Sciences, Kochi and diagnosed as having angiographically proven Premature Coronary Artery Disease from December 2014 to June 2016 were identified and risk factor screening was done for both male and female siblings of any age of these patients. Laboratory tests included fasting blood sugar and fasting lipid profile were analysed after sample collection.

Results: 47.6% of male siblings and 35.7% of female siblings were found to be hypertensive, 17.3% of the male siblings and 18.7% of the female siblings were found to have abnormal levels of LDL cholesterol, 22.7% of male siblings and female siblings were found to have abnormal fasting plasma sugar levels, 30.5% of male siblings and 20% of male siblings were found to be overweight. 19.1% of male siblings and 21.4% of female siblings were found to be obese. Only 18.1% of male siblings and 5.7% of female siblings performed any kind of exercise on a regular basis. Among male siblings, 21.9% of male siblings were currently using tobacco in some form. Among non-smokers in both sexes, as many as 36% were exposed to some form of passive smoke. Almost half of the male siblings (49.5%) consumed alcohol containing beverages on a regular basis.

Conclusions: Previously undetected risk factors were found to be highly prevalent among the studied siblings. Significant number of siblings were found to be hypertensive and in addition some had elevated fasting blood sugar levels. Other modifiable risk factors like obesity, alcohol consumption, tobacco use, passive smoking and lack of exercise were also found to be widely prevalent. An important aspect that the study highlighted is the widespread lack of awareness in the study population about risk factors for disease.

Background

With advance in the field of medicine and advent of vaccines, the global threat that was posed by communicable diseases has by and large been tackled effectively in most nations. However, rapid development, industrialization and modern amenities have brought with them a new set of challenges in the field of medicine posed by an alarming increase in the incidence and prevalence of non-communicable diseases with far reaching consequences.¹ WHO data suggests that non communicable diseases kill 38 million people each year. Almost three quarters of NCD deaths i.e. 28 million occur in low and middle income countries. Sixteen million NCD deaths occur before the age of 70 with 82% of these occurring in low and middle income countries. An increase in life expectancy has brought a large section of population to an age where CVD starts manifesting itself.

Coronary artery disease (CAD), as we know it is a leading cause of morbidity and mortality in the world today with an alarming rise in prevalence in Lower Middle Income countries (LMIC) like India. It poses a unique public health challenge as it is a progressive, lifelong disease with sudden death often a sentinel event. Hence numerous studies have been focused on preventing and treating CAD since the early 1950s and even before. However, an emerging Public Health challenge is the increasing incidence of CAD in younger and working populations, more so in the developing nations. Disability in younger age groups as a result of disease poses tragic consequences for family, friends, society and the economy as a whole and from this stems the need to target strategies aimed at early identification of risks groups and intervention prior to the onset of disease as treatment options for disease are often expensive and prolonged with no uniformity in outcome. Through modern clinical epidemiological methods, the landmark Framingham study helped define the field of preventive cardiology and identification of modifiable risk factors for Cardiovascular Disease.

Most of the knowledge on CAD risk factors in different age groups is from studies carried out in the migrant Indian population overseas, which has

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an inherent limitation in it not being truly representative of the Indian diaspora with certain communities being over represented and some not at all. Furthermore, Indians who have migrated to affluent countries are at a higher demographic transition state than those residing in India. For these reasons, it has been widely speculated that the observations in the emigrant population may not hold true for the Indian population.2-5

A family history of premature coronary heart disease (CHD) is a known risk factor for CHD events. Large epidemiological studies have shown that a family history of coronary heart disease (CHD) is an independent risk factor for cardiovascular disease.6-10 First-degree relatives of persons with premature CHD have been shown to have a 2 to 12-fold increased risk of CHD. Among primary relatives, siblings of persons with clinically documented CHD bear the highest risk for future CHD events,11 they have also been shown to have a high prevalence of multiple CHD risk factors.12 Light has however been shed in the form of newer studies on sibling risk factor as another important component of focus in the field of preventive cardiology for the early identification and prevention of premature CAD.

The Inter Heart Study, a major Canadian led Global study has identified nine potentially modifiable yet important risk factors that account for over 90% of the risk of acute myocardial infarction. This study also found that these risk factors are the same in almost every geographic region and every racial/ethnic group worldwide and are consistent in men and women.

This study hence focuses on the early identification of prevalent risk factors in siblings of patients with premature coronary artery disease. The study also focuses on creation of awareness in the general population of these important risk factors in otherwise asymptomatic individuals in order to encourage health consciousness, thereby aiding in early diagnosis and prompt treatment of an otherwise debilitating disease process in its late stages.

Objective

The primary objective was to study the prevalence of risk factors – mainly systemic hypertension in asymptomatic siblings (both male and female) of patients with premature coronary artery disease (males <45 years and females <55 years, confirmed by coronary angiography). Secondary objectives included estimation of the prevalence of other risk factors including elevated fasting blood sugars, abnormal fasting lipid profile, obesity, tobacco use, alcohol consumption, exposure to passive smoke, diet and exercise and pre-existing co-morbid conditions. The study also aimed at assessment of the number of siblings already aware of the risk factors and their disease status.

Ethics

The study was presented to the Institutional Ethics committee, Amrita Institute of Medical Sciences and approval taken prior to recruitment. There were no ethical or social dilemmas associated with the study. A written informed consent was obtained from all the study subjects after detailed explanation of procedures involved.

Methods

All patients (both in and out-patients), visiting Amrita Institute of Medical Sciences, Kochi and diagnosed as having Premature Coronary Artery Disease (fulfilling the criteria) from December 2014 to June 2016 were identified.

Inclusion criteria

All consenting siblings of individuals admitted and treated for an acute coronary syndrome or with documented coronary artery disease were included in the study.

Exclusion criteria

Siblings already diagnosed with coronary artery disease or history of acute coronary syndrome, symptomatic siblings and those unavailable due to geographical reasons were excluded from the study.

Siblings of all ages of these patients (fulfilling the inclusion and exclusion criteria) were then identified and contacted. Eligible siblings were recruited in the study after obtaining informed consent. Initial screening assessment of the study population was carried out using a pre-designed Performa. This was a cross-sectional study and did not require a control population.

The cut points of 140 mm Hg for systolic blood pressure and 90 mm Hg for diastolic blood pressure were selected to define Hypertension as these correspond with the Joint National Committee 8 on High Blood Pressure classification.

American Diabetes Association (ADA) guidelines were used for the diagnosis of diabetes mellitus.

The Quetelet classification was used to calculate body mass index in the study subjects. Cut off for waist circumference was obtained in accordance with International Diabetes Federation (IDF) criteria for the diagnosis of Metabolic Syndrome while the World Health Organisation (WHO) criteria was used to define abnormal waist to hip ratio, both of these being important components for the diagnosis of central obesity.

Venous blood samples were collected after 10-12 hours of overnight fasting plasma glucose, HbA1c and lipid profile. FBS and FLR were done using GOD-POD and CHOD-PAP methods respectively. The tests were done using a Beckman-Coulter automated analyser based on spectrophotometry method in the central biochemistry lab of Amrita Institute.

Sample Size estimation

Based on the prevalence rate of the main risk factor – Hypertension in asymptomatic siblings (male and female), of patients with premature CAD observed in an earlier publication and with 20% allowable error and 95% confidence, minimum sample size was 105 cases with respect to male siblings and 140 with respect to female siblings.

For selection of study subjects, all asymptomatic, siblings (both male and female of any age) of patients (field, OP and IP) with documented premature coronary artery disease (by coronary angiography or h/o acute coronary syndrome) at Amrita Institute of Medical Sciences from December 2014 to June 2016 were selected for the study.

Performa. This was a cross sectional study, the assessment of the study population were recruited in the study after obtaining informed consent. Initial screening assessment of the study population was carried out using a pre-designed Performa. This was a cross-sectional study and did not require a control population.
Table 1: Blood Pressure Profile of the Study Population

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>145</td>
<td>59.2</td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>40.8</td>
</tr>
<tr>
<td>Total</td>
<td>245</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Out of 245 subjects (105 males and 140 females respectively), 100 (40.8%) were found to have abnormal blood pressure.

Fig. 1: Blood pressure profile

Premature CAD was diagnosed if patients (males less than 45 years and females less than 55 years) undergoing coronary angiogram (CAG) for any standard indication had at least 50% diameter stenosis, in at least 1 major epicardial coronary artery.

For data analysis plan and statistical tests, numerical variables were expressed as Mean and Standard Deviations and Categorical variables were expressed as Frequency and Percentages. To obtain the association between Categorical variables, Chi Square test was applied. To compare the mean differences of clinical parameters and Lab parameters between Hypertensive and Non-Hypertensive patients, independent two sample t-test was applied.

Results

In the study, a total of 245 asymptomatic siblings were analysed, 140 (57.1%), of whom were females and 105 (42.9%) males.

Analysis of data showed that 7.6% male siblings and 4.3% female siblings were known hypertensives, 17% and 6.4% were known diabetics and 9.5% and 9.3% were known cases of dyslipidaemia on some form of treatment. 11% of the study subjects were already on treatment for dyslipidaemia. 11% of the study subjects were already on some form of passive smoke, 25% of male siblings and 21.9% were currently using tobacco. Among non-smokers in both sexes, as many as 36% were exposed to some form of passive smoke, 25% of female and 54.9% of male siblings reported passive smoke exposure on a regular basis either at home or at the workplace.

In addition to risk factor assessment, a comparison of study parameters between Hypertensive’s and Non Hypertensive’s were also done as per the JNC 8 criteria. Analysis showed that siblings found to have higher blood pressures also had an increased incidence of abnormal waist to hip ratio (53.3%) as compared to females (20.7%).

With respect to lab parameters like fasting plasma glucose and lipid profile 150 siblings (75 male siblings and female siblings respectively) were analysed. 11% of the study subjects were known diabetics, already on some form of treatment. Fasting plasma glucose profiles were similar in male and female siblings with both groups showing 22.7% of people with abnormal levels. A similar pattern was found in relation to low density lipoprotein levels and triglycerides with (17.3%) male siblings and (18.7%) female siblings found to have elevated levels of Low Density Lipoprotein (LDL), whereas 20% males and 21.3% females were found to have elevated Triglycerides. With respect to total cholesterol however, there was a significant difference with almost half of the female siblings (41.3%) and only a quarter of male siblings (25.3%) having abnormal levels on testing with 9.4% already on treatment for dyslipidaemia. Awareness of lipid levels was low in siblings of both genders.

Statistically significant results were obtained with respect to Body Mass Index (BMI) with almost one third of the study population i.e. 30.5% of male siblings and 20% female siblings being overweight and 19.1% and 21.4% obese. The majority among the study population had an abnormal abdominal girth (73.3% male siblings and 85.7% female siblings). Among siblings males were however found to have increased incidence of abnormal waist to hip ratio (53.3%) as compared to females (20.7%).

Fig. 2: Association between Gender and Hypertension

- Out of 254 subjects (105 males and 140 females respectively), 50 (47.6%) males and 50 (35.7%) females were found to have abnormal blood pressure levels. There was no significant difference with respect to blood pressure between males and females. (p value 0.061)
factor status was poor among the CAD. In addition awareness of risk factors for premature atherosclerotic CVD in sibling of individuals identified with premature CVD was low among both male siblings and female siblings. This was in accordance with a community based study done in Kerala itself in the year 2010 where only one third of the subjects were aware of their risk factors and an even less number obtained treatment.18

Study Limitations

Major confounders in estimation of lipid profile, namely dietary habits and physical activity, were not extensively studied. A limitation of the study was that exercise could not be quantified or classified in this study population due to lack of accurate information during the screening process. No prospective follow up of the siblings was done. Bias due to under reporting of habits like consumption of alcohol and tobacco use due to social undesirability was also considered.

Conclusions

The study demonstrates the distribution of potentially modifiable and non-modifiable risk factors among siblings of patients with premature CAD at prevalence rates considerably higher than in the general adult population. Previously undetected risk factors were found to be highly prevalent.

Significant number of male and female siblings was found to be hypertensive and at the same time not aware of their abnormal blood pressure levels. More number of males were found to be aware than females (40.8%), high cholesterol (33.3%), diabetes (11%) and smoking (21.9%) of the adult population (>20 years). While our study revealed a prevalence of hypertension (40.8%), high cholesterol (33.3%), diabetes (11%) and smoking (21.9% among male siblings) all of which are higher than the prevalence in the general adult population.

The reported prevalence of diabetes in our study was higher than that reported in majority of the prior studies. Diabetes and impaired glucose tolerance also showed increasing trend with age which was previously proven in a study done in 2001 by Ramachandran et al. In the study, in addition to the increasing trend, subjects under 40 years of age had a higher prevalence of impaired glucose tolerance than diabetes (12.8% vs 4.6%, p < 0.0001). This was also similar to findings of a cross-sectional survey of 1123 subjects by Gupta et al in an urban population of Jaipur in 2002 where Diabetes was prevalent in 12.2% of the subjects.16

A study done by Ramachandran et al in September 2004 from Chennai, showed that for a given BMI, Asian Indians have higher central adiposity. Majority of siblings, males (73.3%) and female (85.7%) were found to have increased abdominal girth which is a cause of concern considering its impact on health of especially the younger subgroup of the population. Males (53.3%) were however reported to have higher prevalence of waist to hip ratio than female (20.7%) siblings. A risk factor study done on Asian Indians in 1993 by Jha et al also showed the importance of obesity in addition to conventional risk factors.9

Awareness regarding important risk factors and the need for regular screening was low among both male siblings and female siblings. This was in accordance with a community based study done in Kerala itself in the year 2010 where only one third of the subjects were aware of their risk factors and an even less number obtained treatment.18

Table 2: Comparison of Study Parameters Among Hypertensives and Non Hypertensives

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypertensive</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>25.37</td>
<td>5.37</td>
<td>0.871</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>100</td>
<td>25.48</td>
<td>5.47</td>
<td></td>
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<tr>
<td>Abdominal Girth</td>
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<td>145</td>
<td>93.28</td>
<td>7.98</td>
<td>0.888</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>100</td>
<td>93.13</td>
<td>8.77</td>
<td></td>
</tr>
<tr>
<td>W : H</td>
<td>No</td>
<td>145</td>
<td>0.87</td>
<td>0.09</td>
<td>0.415</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>100</td>
<td>0.88</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>No</td>
<td>90</td>
<td>101.08</td>
<td>34.66</td>
<td>0.121</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>60</td>
<td>110.39</td>
<td>37.61</td>
<td></td>
</tr>
<tr>
<td>T. CHOL</td>
<td>No</td>
<td>90</td>
<td>179.36</td>
<td>44.20</td>
<td>0.518</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>60</td>
<td>184.19</td>
<td>45.62</td>
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<tr>
<td>TGL</td>
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<td>48.97</td>
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<td>Yes</td>
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<tr>
<td>FBS</td>
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<td>90</td>
<td>100.08</td>
<td>20.35</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Yes</td>
<td>60</td>
<td>131.88</td>
<td>66.54</td>
<td></td>
</tr>
</tbody>
</table>

Out of 245 subjects (105 males and 140 females respectively), mean Fasting Blood Sugars of Hypertensives were found to be higher (131.88) than Non Hypertensives (100.08). With respect to other parameters like Body Mass Index, Abdominal Girth, Waist to Hip Ratio, Low Density Cholesterol, Total Cholesterol and Triglycerides, there was no significant in the mean levels between Hypertensives and Non Hypertensives.

ANNEXURE 1: Association between Gender and Awareness

<table>
<thead>
<tr>
<th>Gender</th>
<th>Yes</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td>Female</td>
<td>21.4</td>
<td>78.6</td>
</tr>
<tr>
<td>Male</td>
<td>38.1</td>
<td>61.9</td>
</tr>
</tbody>
</table>

- Out of 245 subjects (105 males and 140 females respectively), 40 (38.1%) males and 30 (21.4%) females were already aware of risk factors for premature coronary artery disease. More number of males were found to be aware than females.

LDL and Triglycerides were all higher in hypertensive siblings none of which reached statistical significance when compared to non-hypertensive siblings in the cohort (Table 2).

An important aspect that the study highlighted was the widespread lack of awareness about the existence of risk factors and the need for screening methods for early identification of the same. Only 38.1% of male and 21.4% of female siblings were aware of health/disease status (annexure 1). Even fewer numbers were on regular treatment and follow up.

Discussion

The study results suggest a high prevalence of risk factors for atherosclerotic CVD in sibling of individuals identified with premature CAD. In addition awareness of risk factor status was poor among the siblings in the study population.

The Global Burden of Disease (GBD) data for India (2016) reports a prevalence of hypertension (21.1%), high cholesterol (23%), diabetes (7.7%) and smoking (8.6%) of the adult population (>20 years). While our study revealed a prevalence of hypertension (40.8%), high cholesterol (33.3%), diabetes (11%) and smoking (21.9% among male siblings) all of which are higher than the prevalence in the general adult population.
levels. Fasting blood sugar levels were also found to be higher in these siblings than those with normal blood pressure levels.

Other modifiable risk factors like obesity, alcohol consumption, tobacco use, passive smoking, lack of exercise were also found to be significantly high in the study subjects.

An important aspect that the study highlighted is the widespread lack of awareness about the presence of risk factors and underlying disease status among the study subjects, who part of the young and working population in the most literate state of our country. Screening of these risk factors in younger age group among the high risk population, along with health education, will therefore play a key role in primordial prevention of premature CAD, thereby reducing disease burden, morbidity and mortality.

References


TB prevalence have suggested that up to 46% of patients may not be currently reported. There are many reasons why people in India seek care from the private sector. These include poor knowledge about TB, poor knowledge about services available through the national programme, the convenience of services, a desire for confidentiality, a desire for personalized care. Many quantitative studies have investigated risk factors associated with poor adherence to ATT. However, few studies have examined the relationship between socio-economic determinants of treatment adherence in the field of social epidemiology.

Some studies have reported that previous history of TB, including number of previous TB episodes and previous treatment interruptions were the major risk factors for current adherence. However, previous TB history may not be causal but simply an indicator of vulnerability. Conceptually, we may consider treatment-related factors, including previous history, as effect modifiers, and previous TB history may affect the association between socio-psychological factors and TB patients. The second objective of this study was to determine whether this association differs in treated and untreated persons.

**Methods**

**Population Study and methods**

Data were extracted from Pune district Maharashtra state, India. The original study protocol aimed to identify predictors of unfavourable treatment outcomes among new and previously treated TB cases. Total 104 patient samples were selected from the population; criteria covered age group of 25 to 60 years along with their education and economic background. Trained study nurses then collected baseline information from consenting participants using a questionnaire. The study team collected clinical information by regularly reviewing medical records and/or by phone during the treatment period and follow up was taken for up to 40 months after they get cured.

**Measures**

The main outcome variable was poor adherence or loss to follow-up (LTFU), defined as treatment interruption for at least two consecutive months and not restarting the same regimen within 6 months. The history of patients was studied by using the variables like history of disease in family, genetic diseases, bad habits (smoking, alcohol) and low diet profile. We analyzed their accommodation types and the variables such as; clean and fresh house, suffocated house situated in the high density population zone as well as home in the high traffic zone of the city. We collected information about the behaviour of relatives, family and friends towards patient during and/or after treatment. The psychological conditions were studied by using variable like loneliness, social gatherings and phobia. This study in
itself has got number of limitations; we omitted direct costs, including health care cost of treating ordinary TB cases and that resulting from longer hospital stays for individuals with resistant infections with MDR-TB and XDR-TB.

Results and Discussion

*Mycobacterium tuberculosis* patients were selected on random sampling basis. These patients were selected from Pune, the study area and registered for treatment at Government hospital and medical college, Pune. Patients were initially not responded to the surveyors due to fear about the disease and prestige issues. Total 104 patients registered for the treatment of tuberculosis. Out of 104 patients, 36 patients were being treated whereas 68 were found to be cured. Patients those were under treatment patients were mainly new infections with multiple drug resistance or extensive drug resistance strains, distribution is shown in figure 1.

The statistically significant discrepancy was calculated from patients drug resistance data. Physicians in India have identified a form of incurable tuberculosis, raising further concerns over increasing drug resistance to the disease. The percentage of drug resistance in the cured patients was found higher than the untreated (Figure 1).

Health status of these patients was found encouraging for patients fight against disease.
and chicken pox. Although significant patients received vaccination against TB, it seemed that either the latent infections emerged after vaccinations were activated or in remaining patients they were acquired from some other source. Out of 104 only 28 patients had factors as genetic disease, smoking habit or contagious disease, possibility suggests that in the case of remaining 76 patients infection was due to poor health support depicted in Figure 2.

As this region has been known to suffer moisture stress (draught), increasing temperatures in summer, the possibility of having adverse effect of environment on the health of individuals within this region could not be ruled out.

Diet plays an important role in the tuberculosis patients’ recovery. Before the advent of ATT, a diet rich in calories, proteins, low fats, minerals, and vitamins was generally considered to be an important, if not a critical factor while treating tuberculosis. Introduction of specific antituberculosis drugs have radically altered the management of the disease when followed the diet plan thus role of diet should be considered in the light of the advances in treatment. Among 104 patients 52% patients were vegan while 48% patients followed mixed Vegetarian and non-vegetarian diet. After disease diagnosis, 88% patients were observed strictly prescribed diet plan by the nutritionist. All of the patients agreed on their irregular food habits, improper sleep before the infection onset. The lack of exercise was found within 48% patient’s schedule (p<0.0001) shown in Figure 3. Earlier studies indicate that incidence of tuberculosis is unusually high among malnourished people.

The meta-analysis by Lin and colleagues is important for two reasons. It evaluates the evidence concerning exposure to combustion-derived air pollution and tuberculosis (TB), and it quantifies the risk of TB associated with three important sources of exposure: tobacco smoking/ environmental tobacco smoke, and indoor solid fuel burning. Their analysis invites speculation about the possible role of another combustion source: outdoor urban air pollution, a growing problem in developing countries where the burden of TB disease is greatest. Only one study of outdoor air pollution and tuberculosis has been reported. We found that 76% patients lived in residential surroundings those were suffocating. About 18% patients resided in area with heavy shown in Figure 4.

A good very clean and fresh environment observed near 16% patients’ residence. These observations suggest that there exist an influence of the environment on patients’ health.

Several authors found frequent co-morbidity of TB and common mental disorders. Few studies have investigated common mental disorders in TB patients from low and middle income countries (LMICs) and have found high rates of CMDs in Pakistan 46.3 %–80 %, Nigeria 27.7 %–30 %, Ethiopia 64 %, India 76 %, South Africa 46 %, and Turkey 19 %–26 %. The psychological effect on the patients were studied by using variables such as tension namely; unknown fear, increased heartbeats, infection phobia, under stress, loss of interest, persecution and their public relations. Data presented in Figure 5 shows that about 98% patients reported suffering of unknown fear, while 88 % patients with increased heartbeats. The fear about the any disease was identified in 76% patients, leading to stress among these patients. The psychological conditions of these patients were disturbed and 16% patients expressed desire to live alone and/ or lost their interest in daily routine shown in Figure 5.

Disease phobia was identified in 96% patients; they were tensed about health concerns, placing them at high risk for stress induced diseases such as; anxiety, eczema, diabetes, anorexia and bulimia.

Despite knowing that Psychological distress could exert strong effect on TB patients’ general health and treatment outcomes studies on psychological conditional and factors associated are not much studied from under developed and etiological countries including Ethiopia. Social relations of patients

Patients were surveyed to investigate on their social life. About 21% patients were not interested in disclosing about infection within the society whereas majority of them were either neutral or had no issue in disclosing infection. Interestingly, only 23% patients were accepted by society with TB status as depicted in Figure 6.

However, 77% patients suffered discouragement by the society. In discouragement by the society members included persecuting patients, which at times extended up to persecuting patients family members. Perhaps, for the sake of family name and societal pride 21% patients denied for disclosing about infection within society. This aggravates stress both on patient and on family member and in turn the TB spread risk.

The care giving family member plays many roles when looking after a TB patient that includes the assessment of adverse effects of medication; such as deafness, gastrointestinal upset, skin rashes, hypertension/ hypotension and many other medical problems. In addition, the caregiver should also monitor patient’s adherence to prescribed medication regimen. The caregiver should also ensure that the patient practices safe hygiene and consumes a nutritious diet. Caregivers should also supervise the patient’s levels of activity and ensure that scheduled appointments with care providers are kept in order. These duties and experiences pose challenges and exert pressure on family members who are caring for TB patients at home. Besides the pain of watching a loved one suffer, family members may experience shame, resentment and guilt. It may be very difficult for family members to accept the illness and adjust to the fact that despite their efforts to care for them, sometimes condition of their loved ones might become worse.

The patients were found to respond to behavior of their family members. After diagnosed with disease patients experience included hidden stress due to their close relative and family members shown in Figure 7.

Patients were found to be ridiculed and sometime keen, family members and friend started to avoid patients as if they are the infectious agent. In a few cases patients were kept in isolation even within their home, ultimately making them emotionally weak. The emotional weakness could take a toll on patient psychology, making at times vulnerable to secondary infection. Patients were found to be interrogated by their relatives repeatedly about
their medication, repeated questioning on treatment effects was found to be discouraging the patients (30.34%) shown in Figure 8.

The general myths about the treatments and disease persisted in discouragement of patients. Psychological counseling on how to handle such situation was found to be undertaken by only 10% patients. Studies noticed that patients got cured those were complying to prescribed regime, regular health check up along with balanced diet. Even after getting cured about 44% patients were found to avoid by their friends and were kept away from friends gathering while the society members shown in Table 1 avoided 16% patients in social gatherings. Despite long time programs on public awareness by the central and state government it seems majority of society members have still not clearly understood that once got cured is likely to be immune towards tubercule bacillus.

After being cured off the disease, patients could share their clothes or utensils of their family members. Although psychological effects were found to be decreasing over the time, the social distance maintained by friends and relatives was found to be same during infection and after being cured off the TB. As cured patients grow with time, their fighting spirit against this deadly disease was found to be on rise. This was exemplified from their enhanced desire to live long with joy and happiness along with diverse plans.

Conclusion

As, much efforts have been made to improvise diagnostic methods for the detection of TB. There is a dire need to stress upon societal factors to augment socio-psychology and psycho-physiology of patients, which in turn would impressively impact success rate of ATT. Cured off patients were found to have improved fighting sprit against deadly disease.

References

5. Satyanarayana S. “From where are Tuberculosis patients accessing treatment in India? Results from a cross-sectional community based survey of 30 districts”, PLoS one.
33. Smeltzer SC, Bare BG. 2003, Textbook of Medical-Surgical Nursing, 9th edn., Lippincott Williams & Wilkins, Philadelphia.
34. South African Depression and Anxiety Support Group, 2008, Spectravision Medical Aid Update, 3rd edn.
# Key Parameters of Combination

<table>
<thead>
<tr>
<th></th>
<th><strong>Allegra-M</strong></th>
<th>Levocetirizine + Montelukast</th>
<th>Bilastine + Montelukast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioequivalence published data</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Synergistic effect</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HTH efficacy data in Indian patients</td>
<td>Yes</td>
<td>Yes</td>
<td>No HTH data</td>
</tr>
<tr>
<td>HTH efficacy (TNSS)</td>
<td>92.5%</td>
<td>85.6%</td>
<td>No HTH data</td>
</tr>
<tr>
<td>HTH safety data (Sedation)</td>
<td>9.6%</td>
<td>23.2%</td>
<td>No HTH data</td>
</tr>
</tbody>
</table>

**References:**
2. This dissolution study compares Allegra-M, Allegra, Singulair and one Fexofenadine + Montelukast fixed dose combination available as a monolayered tablet in India. Data on File, 2012 (b).

**API Link:**

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* Indian Journal of Pharmaceutical Sciences
Risk Factors and Outcomes of Acute Cardio-renal Syndrome in a Tertiary Care Setting in South India

Kevin Fernando1, Rajeevalochana Parthasarathy1, Milly Mathew1, Georgi Abraham1,*, Nancy Lesley1, A Muruganathan3, Ajit Mullaseri2

Original Article

Abstract

Aims and Objectives: To study the incidence, risk factors and in hospital mortality of Type I Cardiorenal syndrome (CRS1). To study the incidence of hyperkalemia in patients receiving ACEi, ARB’s or MRA

Materials and Methods: Prospective observational cohort study done between June and December 2015 in Madras Medical Mission, Chennai. Consecutive patients admitted with ACS/ADHF were studied and clinical, biochemical and laboratory data was collected. The development of CRS1 was determined by KDIGO criteria. Statistical analysis was done using IBM SPSS version 21.

Results: Among 460 patients studied, 153 (34%) developed CRS 1 according to KDIGO criteria. The number of diabetics and patients with pre-existing CKD was significantly higher in the CRS 1 group (p=0.00). Mortality was significantly higher in the CRS 1 group (20.2% vs. 7.8% p=0.00). The presence of CKD, Diabetes mellitus, inotropic requirement and eGFR, 60 ml/min/1.73 m² were significant predictors of CRS 1. Among patients with CRS1, 55 patients (23.5%) needed renal replacement therapy (15.6 % acute peritoneal dialysis, 20.2% SLED). There was no significant difference in the incidence of hyperkalemia in patients who were on prior ACEi, ARBs and MRA.

Conclusion: There is a high incidence of CRS 1 in our setting and the mortality is significantly higher in this group of patients. Early nephrology referral and prompt stoppage of nephrotoxic agents can significantly reduce the incidence and risk of CRS1

Background

Cardiorenal syndrome Type 1 (CRS 1) / Acute cardio renal syndrome is defined as acute deterioration of renal function resulting from an acute worsening of cardiac function. This definition encompasses all patients who develop renal dysfunction in the setting of a primary cardiac event. If not detected early, it can result in permanent renal damage, making it important for physicians to vigilantly monitor renal functions in high risk cardiac patients. This study focuses on the identification of risk factors and mortality affected with CRS-1 to understand this syndrome better and prevent long term complications in a tertiary care referral center in a developing country.

Other objectives included assessment of the in-hospital mortality in patients who developed acute cardiorenal syndrome and the risk of hyperkalemia (serum potassium >5.5 meq/L) in patients receiving ACE inhibitors (Acei), Angiotensin receptor blockers(ARB) / Mineralo corticoid antagonists (MRA)

Materials and Methods

After obtaining Institutional Ethics committee clearance, a prospective observational cohort study was performed in the cardiac intensive care in Madras Medical Mission, Chennai.

Between June and December 2015, consecutive patients admitted with acute coronary syndrome (ACS) and/or acute decompensated heart failure (ADHF) in the cardiac intensive care of Madras Medical Mission were studied at admission and during the course of hospital stay.

Standard demographic, clinical, and physiological data were collected. Clinical data included primary diagnosis, co morbidities like diabetes mellitus, hypertension, and chronic kidney disease (CKD), previous coronary artery disease, and smoking history.

In patients who underwent transthoracic echocardiography, we included data regarding global systolic function, wall motion abnormality and ejection fraction.

The following treatment parameters were recorded: inotropes used the need for ventilation and type of renal replacement therapy and length of hospital stay.

Medications given during the hospital stay, laboratory parameters which included a complete blood panel, serum urea, serum creatinine (sCr), serum electrolytes and urine analysis were recorded.

Adult patients more than 18 years of age with ACS/ADHF were included in the study. Patients with known malignancy, sepsis, urinary infections, CKD stage V, pregnancy and documented chronic heart failure were excluded from the study.

Assessment of Kidney Function

Acute kidney injury (AKI) was classified based on sCr, as proposed by the KDIGO Criteria.

Chronic kidney disease was determined in patients with an estimated glomerular filtration rate

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(eGFR) of < 60 ml/min/1.73 m² for 3 months, based on the guidelines of the National Kidney Foundation.¹

In patients who developed AKI, the recovery, the need and type of renal replacement therapy and the time of recovery of AKI were noted.

Heart failure and ST elevation

Table 1: Baseline characteristics of patients with/without CRS1

<table>
<thead>
<tr>
<th></th>
<th>With AKI Group 1 N=153</th>
<th>Without AKI Group 2 N=307</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>111(72.5)</td>
<td>204(66.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>65±12</td>
<td>62±12</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>99(64.5)</td>
<td>175(57)</td>
<td>0.13</td>
</tr>
<tr>
<td>Diabetes mellitus(%)</td>
<td>103(67.3)</td>
<td>175(57)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>12(7.8)</td>
<td>18(5.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>CKD(%)</td>
<td>28(18.3)</td>
<td>10(3.3)</td>
<td>0.00</td>
</tr>
<tr>
<td>Coronary artery disease(%)</td>
<td>80(52)</td>
<td>151(49)</td>
<td>0.554</td>
</tr>
<tr>
<td>ACE-I(%)</td>
<td>20(13)</td>
<td>42(13.6)</td>
<td>0.798</td>
</tr>
<tr>
<td>ARB(%)</td>
<td>36(23.5)</td>
<td>75(24.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Diuretics(%)</td>
<td>80(52.2)</td>
<td>114(37.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Metformin(%)</td>
<td>35(22.8)</td>
<td>74(24.1)</td>
<td>0.817</td>
</tr>
<tr>
<td>Hyperkalemia (%)</td>
<td>61(39.8)</td>
<td>56(18.2)</td>
<td>0.00</td>
</tr>
<tr>
<td>Ejection fraction &lt; 50%</td>
<td>39±13</td>
<td>47±13</td>
<td>0.00</td>
</tr>
<tr>
<td>Wall motion abnormality on echocardiogram (%)</td>
<td>119(77)</td>
<td>58(18.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Systolic BP (mmHg)*</td>
<td>128±35</td>
<td>129±25</td>
<td>0.61</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)*</td>
<td>77±22</td>
<td>77±14</td>
<td>0.88</td>
</tr>
<tr>
<td>Death</td>
<td>31(20.2%)</td>
<td>24(7.8)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Mean ±Standard deviation; **Potassium > 5.5 meq/L; ***Expressed as Median (Interquartile range)

Table 2: Laboratory parameters

<table>
<thead>
<tr>
<th></th>
<th>With AKI Group 1 N=153</th>
<th>Without AKI Group 2 N=307</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.7±2.5</td>
<td>12±2.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Random Blood Sugar (mg/dL)*</td>
<td>168±73</td>
<td>162±70</td>
<td>0.383</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)*</td>
<td>23±5</td>
<td>25±4.5</td>
<td>0.00</td>
</tr>
<tr>
<td>Albumin (g/dL)*</td>
<td>3.1±0.7</td>
<td>3.1±0.7</td>
<td>0.928</td>
</tr>
<tr>
<td>HbA1C</td>
<td>7.8±2.2</td>
<td>7.6±2.2</td>
<td>0.434</td>
</tr>
<tr>
<td>Trop T (ng/ml)***</td>
<td>0.180(03-1.19)</td>
<td>0.05(0.01-0.23)</td>
<td>0.007</td>
</tr>
<tr>
<td>NT Pro BNP (pg/ml)***</td>
<td>8350(2447-20800)</td>
<td>692.1(979-5742)</td>
<td>0.028</td>
</tr>
<tr>
<td>eGFR (Baseline) mL/min per 1.73m²</td>
<td>77±14</td>
<td>88±11.1</td>
<td>0.00</td>
</tr>
<tr>
<td>eGFR (Presentation) mL/min per 1.73m²</td>
<td>65±10</td>
<td>88±11.3</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Mean ±Standard deviation; **Potassium > 5.5 meq/L; ***Expressed as Median (Interquartile range)

myocardial infarction (STEMI), non ST Elevation MI (NSTEMI) and unstable angina (UA) were defined according to standard ACC/AHA guidelines.²⁸

Classification of Cardio renal Syndromes¹

Type 1 CRS (CRS 1) reflects an abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury.

Type 2 CRS describes chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease.

Type 3 CRS consists in an abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia).

Type 4 CRS describes a state of chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events.

Type 5 CRS reflects a systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 21. Continuous variables were compared using Student t Test/ Anova tests and categorical variable were analysed using chi-square test. A p value of less than 0.05 was considered significant. Cox logistic regression analysis was used to determine the predictors of AKI. The survival analysis was done using Kaplan Meier survival curve.

Results

A total of 460 patients with ACS/ADHF were included in this observational cohort study. Among these 153 patients (34%) developed CRS1 (Group 1) and 307 patients did not develop CRS1 (Group 2) according to KDIGO Criteria. The baseline characteristics of these patients are shown in Table 1.Diabetics were 67% in Group 1 compared to 57% in Group 2 (p=0.03). Patients with pre-existing CKD was 18.3% in Group 1 when compared to 0.3 % in Group 2 (p<0.00). The laboratory parameter of the patients with and without CRS 1 is shown in Table 2. Presence of pre-existing CAD was not statistically significant for the development of CRS 1 between the 2 groups (p=0.5). Mean ejection fraction was significantly lower

Fig. 1: (a) Mortality chart; (b) Kaplan Meier Survival Analysis determining the median time of survival in patients with and without CRS 1
Interventions like coronary angiogram, and percutaneous revascularisation procedures were done in limited number of patients with CRS 1, hence statistical significance was not observed (p=0.168). Inotropic, IABP and ventilatory requirements were significantly higher in the CRS group. (p=0.00). The therapeutic interventions and the course in hospital are depicted in Table 3.

Among patients with CRS 1, 28 % were in KDIGO stage 1 and 2 of AKI and 41.8 % were in stage 3 of AKI. The median time of development of CRS was a day. As shown in Table 3, 55(23.4%) required RRT (15.6 % acute peritoneal dialysis, 20.2% SLED). Recovery of CRS 1 was seen in 75 patients. (49%)

Mortality was significantly higher in Group 1 compared to group 2. (20.2% vs. 7.8% p=0.00). Median time of survival (in days) with 95% confidence interval was 21 days in patients with AKI and 26 days in patients without AKI (p=0.242) (Figure 1B). Mortality was higher in patients undergoing PD compared to SLED. (15 vs. 10).

After cox regression analysis, presence of DM, CKD, eGFR<60ml/min/1.73 m2 and requirement of inotropes were significant risk factors of CRS 1.

Discussion

Cardiorenal syndrome is not uncommon and it is of critical importance to analyse the risk factors, incidence and outcome for understanding the overall burden of disease, including the natural history, morbidity and mortality. We consecutively studied a cohort of 460 patients who presented at the cardiac emergency with ACS or ADHF, in whom 34% developed CRS 1.

Treatment of CRS 1 includes stabilizing both the cardiac and renal function which is a challenge to the treating team. Initial treatment is aimed at maintaining the renal perfusion and cardiac function and treat the fluid overload status. This includes the use of diuretics, non-invasive ventilation and if the patient is not responding there is a need for ultrafiltration for fluid overload. Diuretic use is a double edged sword which has to be used with caution. A fluid challenge maybe tried if there is no signs of left ventricular systolic function impairment or volume overload status but should always be done with caution and with continuous monitoring of the urine output. In case of low output states, the use of vasopressors, digitalis and other supportive drugs to maintain the renal perfusion has to be tried. In resistant cases, intra aortic balloon pump and elective ventilation can be considered in order to maintain the renal perfusion. Various other vasodilator agents like nitroprusside and nitrates are also considered where there is not much hemodynamic compromise. Newer agents like recombinant BNP, recombinant relaxin etc are in the pipeline for the treatment of ADHF and are yet to show positive results in CRS-1.

The incidence of CRS 1 may be higher as it is a tertiary care center, with most patients being referrals, and the application of a more sensitive KDIGO definition to identify it. Many studies have described the development of CRS 1 and have used the term worsening renal function to describe the changes in kidney function. Incidence estimates of AKI associated with ACS and ADHF range from 9-19% and 20-45% respectively. This wide variation is due to the inherent problem of the lack of a consensus definition. In a retrospective study done by Eren et al in Turkey, data of 289 patients with acute cardiac events was collected over 3 years and 24.5% were found to have CRS 1 by the AKIN Criteria. This analysis by Eren et al of the ACS and ADHF groups separately found CRS 1 in 50.7% and 49.2% respectively as was observed in our study

In another study from Portugal, the prevalence of CRS 1 was 70.3 %.The definition used in this study was an increase in serum creatinine of ≥26.5 micromol/l (0.3 mg/dl) compared to baseline values.

Though no single criteria has been recommended to detect CRS 1, a retrospective cohort study with 1498 patients with acute coronary syndrome done by Li Z et al concluded that KDIGO criteria identified significantly more CRS type 1 episodes than RIFLE or AKIN. By the KDIGO definition which was used in our study, only an absolute Scr increase of 0.3 mg/dL within 48 hours is sufficient for an AKI diagnosis. Small changes in Scr have also been associated with higher early and long-term mortality in cohorts of ACS patient.

Elderly patients and males were more at risk at developing AKI in this study. The pathophysiology of CRS 1 which involves hemodynamic and neurohormonal mechanisms are often exaggerated as there is a lack of compensatory response in the elderly. This might explain the higher incidence of CRS 1 in the elderly as demonstrated by both Eren et al and the Portugal study where the mean age in the CRS group was 60 years as shown in our study.

The presence of Diabetes mellitus and chronic kidney disease predisposed patients to CRS 1 as seen in our cohort. A lower median eGFR at admission was significantly associated with the development of CRS 1 in our study. The median eGFR measured by the CKD EPI formula was 70.67 ml/min in the AKI group when compared to 88.24 ml/min in the non AKI group. Our study had 42 patients with Chronic kidney disease of which 90.2% developed CRS 1 and majority of them were in CKD stage 2. This illustrates that a preexisting CKD has a strong predilection for CRS 1 and helps in prognosticating the outcome in this subgroup of patients. Atherosclerotic changes, platelet dysfunction, contrast-induced nephropathy, and diuretic-resistant states have been reported to contribute to the higher risk of CRS 1 in CKD.

The median levels of Troponin T and NT -Pro BNP were significantly higher in the CRS 1 group in the present study. These markers basically reflect higher degree of cardiac damage resulting in renal dysfunction. This was also reported by Eren et al and Caetano et al.

The requirement of inotropes, IABP, mechanical ventilation and the the occurrence of arrhythmias was higher in our CRS 1 group similar to the observation made by Eren et al and Caetano et al.

Forman et al examined risk factors for worsening renal function defined as rise in Scr of >0.3mg/dL among 1,004 consecutive patients admitted for a primary diagnosis of HF. The highest risk of CRS 1 was associated with elevated creatinine at admission. The presence of diabetes (adjusted hazard ratio [HR] 1.40) and a systolic blood pressure >160 mmHg (adjusted HR 1.37) were associated with a comparable risk.
Hospital stay was significantly higher (p=0.242). The median duration of Meier Analysis, median time of survival did not develop CRS 1. Using Kaplan was 38.3% in the CRS 1 group when therapy in our center was based on the stage 3 with the median duration of cases, and it was associated with a higher risk for mortality and longer hospitalization. Patients who developed CRS 1 had longer hospital stay, were treated with higher daily doses of intravenous furosemide, and more often required inotropic support and renal replacement therapy. They had higher in-hospital and 30-day mortality, and multivariate analysis identified CRS 1 as an independent predictor of in-hospital mortality similar to our study.  

This study has several strengths because of the number of patients with significant comorbidities including diabetics and multidisciplinary approach. One of the reasons for lower risk of hyperkalemia is the combined efforts and involvement by nephrology and cardiology teams especially in patients on Acei/ARB/MRA where early nephrology referral was given leading to prompt discontinuation of the drugs CRRT in critical care units in India is not cost effective being a developing country and our results with SLED (Slow Low Efficiency Dialysis) and peritoneal dialysis(PD) highlights the positive aspect of patient care in terms of renal replacement therapy and cost saving. The study also has its limitations because of the inherent constraints of an observational study and the lack of a long term follow up.

Acute kidney injury (AKI) in the setting of acute cardiac events is high. Mortality is higher in patients with CRS1. This study emphasizes that with early detection and management, the rate of CRS 1 is comparable to that of developed countries. This highlights the fact that a multi tasking team from the early part of care can provide better outcomes as shown in our study.

References
3. KDIGO. Summary of recommendation statements: Kidney Int

Table 4: Renal functions and renal replacement therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>No of patients with CRS 1=153 Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIDIGO Stage</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44 (28.7%)</td>
</tr>
<tr>
<td>2</td>
<td>45 (28%)</td>
</tr>
<tr>
<td>3</td>
<td>64 (41.8%)</td>
</tr>
<tr>
<td>Median time of CRS 1 in days (Interquartile range)</td>
<td>1(0-12)</td>
</tr>
<tr>
<td>Oligoanuria</td>
<td>38 (24.8%)</td>
</tr>
<tr>
<td>Renal Replacement therapy</td>
<td>55 (23.4%)</td>
</tr>
<tr>
<td>Acute peritoneal dialysis (APD)</td>
<td>24 (35.6%)</td>
</tr>
<tr>
<td>Slow low efficiency dialysis (SLED)</td>
<td>31 (20.2%)</td>
</tr>
<tr>
<td>Median time of RRT requirement In days (Interquartile range)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Number of recovered CRS 1</td>
<td>75 (49%)</td>
</tr>
<tr>
<td>Median time of recovery of CRS 1 in days(Interquartile Range)</td>
<td>4 (3-5)</td>
</tr>
</tbody>
</table>

Table 5: Independent Risk Factors of CRS 1 by Cox Regression Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio (Confidence Interval of 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>1.554 (1.076-2.245)</td>
</tr>
<tr>
<td>eGFR&lt;60 ml/min at presentation</td>
<td>1.81 (1.07-3.064)</td>
</tr>
<tr>
<td>CKD</td>
<td>1.461 (0.941-2.27)</td>
</tr>
<tr>
<td>Inotropic requirement</td>
<td>1.521 (0.945-2.448)</td>
</tr>
</tbody>
</table>

1 was reported to develop in 25% of cases, and it was associated with a higher risk for mortality and longer hospitalization. Patients who developed CRS 1 had longer hospital stay, were treated with higher daily doses of intravenous furosemide, and more often required inotropic support and renal replacement therapy. They had higher in-hospital and 30-day mortality, and multivariate analysis identified CRS 1 as an independent predictor of in-hospital mortality similar to our study.  

In the present study, there was a higher number of patients in KIDIGO stage 3 with the median duration of development of CRS 1 being one day. The type of renal replacement therapy in our center was based on the hemodynamic stability of the patient, the indication for dialysis and the cost involved. The higher mortality seen in the patients who underwent acute PD was probably because of worse hemodynamic status.

We found the short term mortality was 38.3% in the CRS 1 group when compared to 10 % in the patients who did not develop CRS 1. Using Kaplan Meier Analysis, median time of survival was 2.1 days in patients with CRS 1 and 26 days in patients without CRS 1 (p=0.242). The median duration of hospital stay was significantly higher in patients who developed CRS 1 (7.5 versus 4 days P<0.001).

Smith et al. published a systematic review of 16 studies including 80,098 hospitalized and non-hospitalized CHF patients, and found that mortality increased by 7% for every 10 ml/min reduction in baseline eGFR.

Damman et al. 21 evaluated the relationship between worsening renal failure and mortality in 18,634 patients enrolled in 8 studies. CRS

References
3. KDIGO. Summary of recommendation statements: Kidney Int

2013; 3 (Suppl):5.
Capsular Warning Syndrome - A Case Series and Discussion on Management Dilemmas

Uma Sundar1*, Pramod Darole2, Ashank Bansal3, A Wadal4, S Gosavi5, Anagha Joshi6

Abstract

Background: The term ‘Capsular warning syndrome (CWS)’ refers to recurrent, stereotypical transient ischemic attacks, either motor, sensory or both, without cortical symptoms or signs. Of these patients, 42-71% go on to develop infarcts. There are no defined treatment guidelines for this lesser known entity.

Methods: We studied 9 patients who presented over last 2 years to our hospital with recurrent and stereotypical transient ischemic attacks suggestive of capsular warning syndrome. Their clinical characteristics, neuroimaging findings, relevant etiological investigations, management and outcomes were studied.

Results: Seven out of 9 patients were under 40 years of age. The commonest presentation in our series was a pure motor syndrome. The duration of neurologic deficits ranged from 5 minutes to 20 minutes with complete recovery in between episodes. Three patients had concordant abnormalities on CT brain angiography. Five out of 9 patients received IV thrombolysis with t-PA. One patient worsened neurologically post thrombolysis, whilst the others improved clinically.

Discussion: Despite multiple hypotheses, the pathogenesis and management of CWS has not been established clearly. Due to fluctuating neurological symptoms with complete recovery in between the episodes, there is a dilemma concerning treatment of such patients with intravenous thrombolysis. However, intravenous thrombolysis appears to be safe in CWS as in acute ischemic stroke, followed by treatment with antiplatelet agents.

Introduction

The Capsular warning syndrome (CWS) is defined as the occurrence of at least three recurrent stereotyped transient ischemic attacks in 24 hours, being purely motor, sensory or both, involving 2 of the 3 regions of face, arm and leg.1 No cortical symptoms or signs should be present. Among these patients, 42-71% go on to develop a capsular infarct.1,2 The pathogenesis of this syndrome is largely hypothetical, with mention of hemodynamic impairment, vasoospasm, artery-to-artery embolism, peri-infarct depolarization, and cardio-embolic source as putative etiologies.1,2 Hence, optimal treatment in acute stage as well as for further prevention of strokes, is controversial. Herein, we report our experience of 9 cases of CWS and discuss the management conundrum.

Patients and Methods

We describe 9 cases that fulfilled the definition of CWS that were treated at our centre in the past 2 years (Table 1). CT brain and CT angiography were done at time of presentation to look for intracranial bleed and occlusion of a large vessel whilst MRI brain was done 24 to 48 hours later for most of the patients. To determine the etiology, patients underwent further investigations like 2D Echo, thromophilia profile, sickling test, etc. Seven patients were treated with intravenous thrombolysis with tPA. This was followed by treatment with dual antiplatelet agents starting 24 hours post thrombolysis, after ruling out intracerebral hemorrhage on repeat CT brain. Written informed consent was obtained from all patients/relatives for data collection and publication.

Case 1

A 38 year old male was brought at 12 noon to Emergency room with a 3 hour history of right hemiparesis. He had no prior TIAs, HT, DM or cardiac history, was not a substance abuser, and was on no medications. His BP in left UL was 120/88 mm Hg, and he had a regular pulse rate of 110/m. He was alert, fully oriented, dysarthric due to right UMN facial weakness, and had Rt hemiparesis of Gd 0. His NIHSS was 14 at 3 hrs 15 min after onset of symptoms. CT brain and angiography were normal and ASPECTS score was 10. He was thrombolysed at 12.54 pm with IV tissue plasminogen activator (tPA). Within 20 minutes, his power improved to Gd 4, and facial weakness resolved. However, in the next 20 minutes, power fluctuated twice from Gd 4 to 0 and back again to Gd 4. We repeated a CT brain and Angiogram, and performed a 2D Echo, all of which were normal. At 1 hour post-thrombolysis, power was Gd 0 on the hemiparetic side.

MRI done at that point showed showed a left gangliocapsular infarct (DWI-ADC concordant), with FLAIR images already showing concordant signal abnormalities (Figure 1). No bleeding was seen.

Patient had a complete hemorheological investigation including sickling test, thromophilia workup, and homocysteine level, and had a bubble Echo study performed, all of which were normal. He made a complete recovery over 2 weeks and was discharged on double antiplatelets with statins.
Table 1: Clinical and Imaging features, treatment and in-hospital outcome in 9 patients with Capsular Warning Syndrome

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Time to Presentation after last episode (hrs)</th>
<th>Deficit</th>
<th>NIHSS No. of Fluctuations/Time Period hours</th>
<th>CT Brain</th>
<th>CT/MR Angio</th>
<th>MRI</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38/M</td>
<td>3</td>
<td>Rt hemiparesis</td>
<td>14/3/4.5</td>
<td>N</td>
<td>N</td>
<td>LGC* infarct</td>
<td>IV thrombolysis at 4 hours</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>18/F</td>
<td>2.5</td>
<td>Lt Hemiparesis</td>
<td>8/15/48</td>
<td>N</td>
<td>N</td>
<td>R Post IC** infarct</td>
<td>IV thrombolysis at 3 hrs</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>13/M</td>
<td>8</td>
<td>Rt Hemiparesis</td>
<td>6/128</td>
<td>N</td>
<td>N</td>
<td>L CS* post IC</td>
<td>Standard</td>
<td>Partial Recovery</td>
</tr>
<tr>
<td>4</td>
<td>21/F</td>
<td>24</td>
<td>Lt Faciobrachial</td>
<td>2/8, 6 mths ago</td>
<td>22/72</td>
<td>N</td>
<td>Abnormal</td>
<td>Standard</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>17/F</td>
<td>Not acute</td>
<td>Rt Hemiparesis</td>
<td>0/2/3, 1 mth ago</td>
<td>12/24, 8</td>
<td>N</td>
<td>Standard</td>
<td>L CR* acute infarct</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>50/M</td>
<td>Ongoing</td>
<td>Rt Hemiparesis</td>
<td>11/5/12</td>
<td>N initially, Rt GC</td>
<td>N</td>
<td>Not done</td>
<td>IV thrombolysis 1 hr after onset</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>30/M</td>
<td>Ongoing</td>
<td>Rt Hemiparesis</td>
<td>0-6/3, 4/24, a week ago</td>
<td>22/72</td>
<td>Left SC* infarct</td>
<td>Left IC complete block</td>
<td>Not done</td>
<td>Thrombolysed 1 hour after episode</td>
</tr>
<tr>
<td>8</td>
<td>64/M</td>
<td>Ongoing</td>
<td>Rt Hemiparesis</td>
<td>7-8/8/14</td>
<td>N</td>
<td>N</td>
<td>L GC infarct 6 days later</td>
<td>Heparin</td>
<td>Aspirin</td>
</tr>
<tr>
<td>9</td>
<td>28/M</td>
<td>4 hrs</td>
<td>Lt Faciobrachial</td>
<td>3/4/7 hrs</td>
<td>N</td>
<td>N</td>
<td>L IC acute infarct</td>
<td>IV thrombolysis</td>
<td>No change</td>
</tr>
</tbody>
</table>

Key: *- Gangliocapsular; **- Internal Capsule; ≠- Centrum Semiovale; Ω- Corona Radiata; ∑- Striatocapsular

Case 2

An 18 year old girl was brought with recurrent left hemiparesis, totalling 14-15 episodes over 2 days, each episode lasting 5-8 mins. She had had no recent viral exanthematous fevers or vaccinations. At presentation to us, she had Left hemiparesis of 3/5 power with a left UMN facial weakness, NIHSS score being 8. Her vital parameters were normal, including cardiac examination and carotid pulsations.

ASPECTS score was 10 on CT brain with a normal angiography. She recovered to normal power in 20 mins. She was thrombolysed with tPA at 3 hours after her last episode. Repeat CT at 24 hours, and Echocardiogram were normal.

MRI showed diffusion restriction with concordance on ADC, in right posterior limb of internal capsule (Figure 2).

All hemorheological, and structural causes were ruled out on investigation. She continued to be asymptomatic over the next 3 weeks, on antiplatelets and statins.
Case 3

A 13 year old boy presented to us with 5 episodes 5 days ago, and 1 episode on day of presentation, comprising headache, body pain progressing to Right hemiparesis, and slurred speech lasting 5 minutes each time. He had no past history of migraine or seizures, and had had no recent vaccinations or exanthematous fevers. His blood pressure was 100/70 mm Hg and pulse was regular at 80/m. He had a widely split S2.

Possible diagnoses considered were CWS, hemiplegic migraine, or seizures with Todd’s palsy. While his CT brain and Angiography were normal, MRI showed an acute infarct in left Centrum semiovale and posterior limb of Internal capsule (Figure 3). He was managed conservatively with antiplatelets, and continued to have 1 daily episode of weakness lasting a few minutes, while in the ward. He was detected to have a Bicuspid Aortic valve with commissures at 10 and 4 O’clock positions. Thrombophilia workup showed no abnormality.

Case 4

A 20 year old woman presented with 2 episodes of left faciobrachial weakness, lasting 6-8 minutes, over 8 hours. Six months before this presentation, she had had 15-20 similar episodes of left faciobrachial weakness, Gd 0-2, lasting 5-8 mins, over a period of 3 days. She had taken treatment at that time, but had not continued any medications.

Clinically, her vital parameters and neurological examination were normal, except for mild torticollis to the right. Her CT and MRI brain were normal. MR angiography showed long-segment narrowing of left vertebral artery, narrowing of left internal carotid in cavernous portion, and absence of left A1 segment of ACA. MRI brain stroke protocol was normal.

Case 5

A 17 year old girl presented with 2 episodes of left Hemiparesis without facial involvement, in Jan 2020, lasting 6 minutes each, over 3 hours. She had had...
2 prior episodes in the previous month, each lasting 5-15 minutes, over 4 hours. She had had no recent vaccinations or exanthems.

At presentation, she was on Aspirin 150 mg daily for the previous 2 wks. All investigations, including sickle testing, bubble echo, Lipoprotein levels, and thrombophilia workup, were normal. MRI done the previous month had shown an acute infarct in deep white matter on the right side, with some restricted diffusion in right frontal cortex, and a possible M2 narrowing (Figure 5). However, at present episode, CT brain and angiography and MRI were normal.

She had a history of migraine without aura, of 2-3 years duration. A combination of Aspirin and Clopidogrel was started, and Flunarizine was added. She continued to be asymptomatic over the next 3 months.

**Case 6**

A 50 yr old man presented with a flurry of 5 episodes of left sided hemiparesis with UMN facial weakness over the past 12 hours. During presentation, he had an NIHSS score of 11, but the deficit recovered fully within 10 minutes. CT brain and CT angiography were normal, and the patient was thrombolysed with tPA at 1 hour post the last episode. He remained asymptomatic till discharge 4 days later. Repeat CT at 24 hours post thrombolysis showed a gangliocapsular infarct on the right side (Figure 6).

**Case 7**

A 30 yr old male, newly detected to have hypertension, presented with 3 TIAs over 3 hours, each lasting 5-10 mins. He had had a similar episode a week ago. The deficit included a right hemiparesis with facial weakness. At presentation, his NIHSS fluctuated from 0-6. His ECG showed inferolateral
A 28 year old man presented with recurrent right faciobrachial weakness, having had 4 episodes over 7 hours, lasting 5-7 minutes each time. His NIHSS was 3 during 1 such episode in the emergency room. CT brain and CT angiography were normal. His Hb was 17 gm %, with no clinical signs of dehydration. He was thrombolysed at 4 hours after the last episode. The decision to thrombolysse despite low NIHSS was taken in view of dominant upper limb being involved, and young age of patient. MRI brain done at 14 hours after thrombolysis showed a left Internal Capsule acute infarct (Figure 9). He had recovered partially at discharge, with no further episodes.

**Discussion**

Pathogenesis, and hence, management of CWS are debatable. It has been proposed that even as early as 48 hrs post-stroke, patients with subcortical infarction engage bilateral prefrontal, ipsilateral posterior parietal and bilateral sensorimotor cortices during a finger-sequencing task. The fluctuations that are observed in CWS may represent perturbation of this complex network, in some patients. However, it is surprising that fluctuations persist, even after infarction has occurred, as seen in our patients.

There are anecdotal reports of focal arterial pathology causing CWS. It has been proposed that when there is a single dominant Lenticulostriate artery supplying the deep motor tracts, instead of multiple small penetrating vessels, then a proximal MCA stenosis can result in this syndrome. Additionally, atherosclerotic plaques on the ventral wall of MCA at the origin of the lenticulostriate arteries, demonstrated by high resolution MRI, have been proposed as the causation of CWS. There has also been an anecdotal report of Anterior choroidal artery stenosis causing CWS.

In our series, 7/9 patients were under 40 years of age, a finding which is different from other larger series (In Paul et al’s series, the mean age was 73 years). The presence of this fluctuating vascular subcortical syndrome in the young, throws up the possibility of an immature supplementary network that fails to function during the episodes.

Since the majority of our patients were young, without traditional vascular risk factors, it was important to investigate fully for a cause, despite the infarcts being subcortical. Cerebral CT angiography, 2D Echocardiogram (Transesophageal Echo may be required), cardiac rhythm recording, and hemorrhheology would be mandatory in younger patients. Among our 9 patients, 3 had definite concordant angiographic abnormalities on CT angiography. Patient no. 5 had been documented to have a concordant M2 narrowing at a previous episode. She also had a history of migraine, and had had the present episode while on Aspirin. It was possible that migraine induced vasoospasm, or Reversible vasoconstriction syndrome was the cause of her deficit, although CT angiography at the present episode was normal. Flunarizine was added to the Aspirin- Clopidogrel combination at the present episode for this patient.

All except one patient had a normal Echocardiogram, the single exception being patient 3, who had a bicuspid aortic valve, with no arrhythmia.

The commonest presentation in our series was a pure motor syndrome, which was consistent with the reports by He et al and Hawkes et al. An infarct was almost always seen on CT/MRI in our patients in the first few hours after presentation (even while the patient was fluctuating clinically), or on a repeat CT at 24 hours, but the patients continued to do well clinically. Site of infarct was distributed between Striatocapsular area, posterior limb of Internal capsule, Corona radiata and Centrum semiovale in our patients. In He et al’s series, internal capsule was the commonest area of involvement.

Treatment of this syndrome is controversial. There are anecdotal reports of successful stenting of the proximal arterial stenosis with a good outcome. However, this pathology is rarely demonstrated, and in the majority of cases, the question is whether to thrombolysse or not, in the fluctuating scenario. Tassi et al, in a retrospective analysis of ischemic strokes over a 5 year period, found that 18/967 patients had a ‘Stroke warning syndrome’, and that 9 of them received IV tPA, with a good outcome in one third of these patients at 3 months; however, 55% in the ‘no tPA group’ of this subset also had a good outcome. Another group has reported a short case series of 4 patients with CWS who received IV tPA within 4 hours of onset, with ¼ patients
showing complete clinical recovery, and a normal MRI, at 1 week. Overall, IV thrombolysis appears to be as safe in CWS as in general acute ischemic stroke. Intravenous thrombolysis was done in 5/9 patients in our series, with excellent clinical outcome in most patients. In case 7, thrombolysis was done despite CT showing an infarct, as the patient was clinically fluctuating, the infarct appeared to be evolving, and there was a concordant large artery thrombosis. In fact, a conventional angiography was planned to be done at the earliest for this patient for any further intervention, but he worsened rapidly and was discharged against medical advice. It is possible that his worsening may have been part of the ongoing fluctuations, with later improvement. Among the patients who were not thrombolysed, one patient was seen a few months after the episodes and was doing well on Aspirin, while another refused thrombolysis but was stable on Aspirin; the third patient, as mentioned above, was treated for possible migraine induced vasospasm and continued to do well.

Various case reports have mentioned efficacy of individual or combinations of antiplatelet agents in the treatment of CWS. Fahey et al found a loading dose of Clopidogrel to be efficacious in 2 patients who were ‘Aspirin resistant’.13 Kawano et al, and Asil et al, in separate case reports, also reported combination antiplatelet agents to be of benefit.13,14 Jiao et al reported favorable outcome in CWS with combination of clopidogrel, aspirin, heparin and a plasma expander.15 Lalive et al, reporting on 6 patients with Lacunar syndrome preceded by TIAs, suggest that frequent BP monitoring, and pharmacological raising of BP if necessary, is key to a good outcome.16 Wei Li et al have used intravenous Tirofiban in combination with standard medications and demonstrated reduction in early fluctuations and shortening of duration of functional deficits in CWS.17 It should be noted that these are all reports of acute period treatment of CWS.

Even in all lacunar strokes, it has been noted that 18.5% patients had a preceding TIA, with the interval between TIA and stroke being under 24 hours in 87.9%.16 The CWS may be an exaggerated and recurrent phenomenon of such TIAs preceding a lacune, due to attendant peculiar arterial pathology or blood pressure fluctuations. Following the reported data from the Austrian stroke registry which shows equal benefit of intravenous thrombolysis in lacunar and non-lacunar strokes, there should be no hesitation in thrombolysing lacunar syndromes.17 Thus, as a large percentage of patients with CWS will end up with a disabling stroke if not thrombolysed, there should be no hesitation in thrombolysing a fluctuating CWS either, if other standard criteria are met. As in our patients, fluctuations can recur even after thrombolysis, prompting an early repeat CT.

There is no definite recommendation on the role of Heparin in CWS, or a definite recommendation on secondary prophylaxis in these patients. In a recent study by Hawkes et al, 17 patients with stuttering lacunar syndrome (SLS) were treated with double antiplatelet therapy, comprising 300 mg of Clopidogrel with aspirin, resulting in resolution of symptoms in 11/17 patients.8 In a retrospective multicentre analysis by He, Xu et al, analysing treatment effects in CWS, the difference in therapeutic effects between the rt-PA, single and double antiplatelet groups was not statistically significant.9 Our patients are on single or double antiplatelets and statins, with a plan to modify treatment after 3 months.

In conclusion, the pathogenesis of CWS continues to be debated. It is essential to look for any underlying angiographic, cardiac or hemorheological factors, especially in younger patients with no vascular risk factors. Intravenous thrombolysis is safe and should be done early, despite ongoing clinical fluctuations, to prevent a resultant disabling stroke.

References

Diabetes in Pre-independence India: Rediscovering a Forgotten Era

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Abstract
Around 300-400 AD, ancient Indian physicians described a condition akin to diabetes mellitus which was called “Madhumeha”. Sushrutha and Charaka, are also credited with describing two types of diabetes which would roughly correspond to type 1 diabetes and type 2 diabetes. However, little is known about the history of diabetes in India between the first and 19th century AD. A thorough search of literature revealed a large number of publications on diabetes from India in the 1800s and early 1900s, mostly from Calcutta and the Madras Presidency, suggesting that the prevalence of diabetes was high in these two places. Building on the observations made by a number of English physicians, Chunilal Bose in 1907 suggested the link between diabetes and lifestyle in India. Amazingly, India did not have to wait long after the discovery of insulin by Banting and Best at Toronto in 1921, to get its own supply. Around this time, Dr. J.P. Bose, eminent physician and diabetologist from Calcutta made remarkable contributions to the study of diabetes in India. He was also the first to describe the dramatic effects of insulin administration to children with type 1 diabetes in India. All these facts have remained largely forgotten which prompted the authors to delve deep into the history of diabetes in pre-independence India. This has led to the unearthing of several pearls of knowledge which are presented in this article as a fitting tribute to the 100th year of Insulin Discovery.

The year 2021 represents a very important milestone in the history of diabetes, as it marks the centenary of one of the most dramatic advances in medicine – the discovery of insulin by a group of Canadian scientists. While the story of the discovery of insulin and its near-magical effects on individuals with diabetes in Canada, the United States and the United Kingdom is well-known, there is little information available on what was going on in the management of diabetes in India, which at that time was home to nearly a sixth of the global population. When did insulin come to India? Which were the first recorded cases of children with type 1 diabetes in India whose lives were saved by insulin? Little is known about these important details.

We conducted a thorough study of diabetes in pre-independence India and found some fascinating articles which have been largely forgotten. In this article, we try to piece together the historical events related to diabetes treatment before the discovery of insulin, through the 1920s when insulin became commercially available, up to the time of India’s independence in 1947. We believe this important aspect of diabetes research in India is not widely known and that it deserves wider attention.

Diabetes in ancient India
Over 3000 years ago, the ancient Egyptians mentioned a condition which closely resembles what we refer to today as diabetes. In ancient India (circa 300-400 AD), people discovered that they could detect diabetes by presenting urine to ants. If ants were attracted to the urine, it was a sign that it contained sugar. They called the condition as “Madhumeha”, meaning “honey urine”¹. Most authors begin with Hippocrates and the “Golden Age” of Greece before mentioning Galen and the contributions from Rome when discussing the history of diabetes. However, this approach has omitted the information from the ancient civilizations of India which flourished before and during the emergence of Mycenaen cultures. Sushrutha and Charaka, the ancient Indian physicians are also credited with the description of two types of diabetes which would correspond to type 1 diabetes and type 2 diabetes today.² They described that some people with diabetes were young and thin and had a more severe form of diabetes characterised by progressive wasting – corresponding to type 1 diabetes. They also described a second form of diabetes seen in obese, wealthier people, associated with gluttony and decreased physical activity – characteristic of type 2 diabetes of modern days.¹ Sushrutha was also known to include exercise in his prescription for treating obesity and diabetes.¹ It may not be out of place to mention here that Sushrutha and Charaka also described diabetes insipidus, where the patients did have polyuria just like diabetes mellitus but the urine passed by them was tasteless (insipid) and not sweet as in the former condition; they termed this condition as udakmeha, meaning excessive passage of tasteless urine.

Diabetes in pre-independence India
There are hardly any references to diabetes in Indian literature between the first and the 19th century AD. One of the earliest references to diabetes in India in modern times was reported

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by Dr William Martin, Professor of Ophthalmic Surgery in the Calcutta Medical College in 1858. In his article on “Illustrations of hospital practice”, he recorded the case details of patients he treated at the Calcutta Eye Infirmary. One of the cases he described was of a patient aged 46, who had suffered from impaired vision for about a year and had diabetes which had impaired his general strength and caused great exhaustion. In 1867, Dr Baboo Kamaksh Nath Acharyee reported 2 cases of diabetes among wealthy individuals in Calcutta (modern day Kolkata) whom he described to be “fat and immoderately fond of sweets”. He reported his findings in the Indian Medical Gazette which was perhaps the most important medical journal during the pre-independence era and which showcased the important medical practices in India at that time. Indeed, many physicians across India used the journal as a tool to communicate with each other, reporting new cases, sharing scientific ideas for best management and treatment methods based on their experience.

In 1871, the editors of the Indian Medical Gazette reported that among the upper and middle classes of Indians in Calcutta, almost every family had lost one or more of its members to diabetes. Such instances of diabetes being prevalent among Indians have been well recorded throughout the late 1800s in the Indian Medical Gazette. Several reports of treatment of diabetes using western and Indian medicines were also recorded during this time. A case illustrating the effect of skimmed milk treatment for diabetes was reported in 1872 by Dr LD Spencer at Bhurtpore. He reported how rapidly skimmed milk had improved the patient’s condition; the patient was no longer weak and had regained considerable strength within 6 weeks. Other reports of use of codeina, codine and pepsine for treating diabetes have also been reported in India. BD Basu’s “Dietetic Treatment of Diabetes” was a popular text that went through seven editions. His principles of diet involved use of various fruits, cereal grains and vegetables including jambul and coconut that were easily available in India. David Arnold, a retired Professor of History at Warwick University wrote a detailed account of Diabetes in the Tropics in which he recorded key information about doctors in India and how they treated diabetes. Another Indian surgeon, KP Gupta, delivered a lecture in 1881 on diabetes at the Calcutta Medical Society and stated that diabetes had “greatly increased of late years”, but there were little to no statistics available to prove this point. In 1893, Bolai Chunder Sen, who also worked on diabetes claimed that diabetes in Bengal was growing “by leaps and bounds”. Since at that time, there was no tests to differentiate type 1 diabetes and type 2 diabetes, reports tended to use the term “acute” form of diabetes to explain the disease in young people that caused early death and a milder, more common “chronic” form that occurs in adults that persisted for many years before leading to death. Although the aetiology of diabetes was not very well understood, doctors tried to point out certain factors that could play a role – like unsanitary conditions, diet that was rich in carbohydrates, early marriage, lack of outdoor exercise and the stressors of modern living. Chunilal Bose in 1907 famously wrote “What gout is to the nobility of England, diabetes is to the aristocracy of India” which probably summed up the etiological factors quite well- sloth and gluttony. He also suggested that diabetes was more commonly found among the English-educated “Bengali babu” who led a sedentary life and “whose girth had a great tendency to increase in direct proportion to any increment in his pay” and was “almost unknown among Hindu widows, who lead a most unexciting life and are not indulged in excess of saccharine or other farinaceous foods”. The question of whether diabetes was common among “rice-eating natives” referring to Indians in Bengal and Madras was raised by Dr TG McGann, a surgeon major from Mysore in 1885. The role of excess carbohydrate in inducing diabetes and how excluding carbohydrate from food could help control the progress of the disease was discussed by Dr Pavy. He describes, in detail, the rationale for treating diabetes, by explaining the mechanism of carbohydrate action and says that “exclusion of carbohydrate principles from the food, will not only check the downward progress occurring, but also bring back health and strength to the patient”.

A European Indian Medical Service (IMS) officer, H Stott, who was Professor of Physiology at Lucknow Medical College, highlighted that diabetes was four times more common among Indians than Europeans and that diabetes was the fifth cause of death in India following influenza, pneumonia, apoplexy and tuberculosis. He also noted that hospital records showed a close correlation between diabetes and rice consumption, since 6.5% of hospital admissions in Madras were for diabetes compared to 4.2% in Bengal and <2.4% in other provinces.

Therefore from the above, it is fairly evident that diabetes was common in pre-independence India and also the prevalence appeared to be more in Bengal and Madras, the two major rice eating regions in India. In an article published in 1895, Sir Kailash Chandra Bose (1850-1927) from Calcutta, described not only the prevalence of diabetes but also deaths due to diabetes. In one street in Calcutta with a population of just over a 1000 people, he recorded 30 people living with diabetes and stated that one tenth of the mortality in Calcutta was due to diabetes. Bose also reported that diabetes was more common in people living in urban areas and among people who are less physically active (e.g. zamindars and talookdars, who lead an “indolent life”). In an article titled “Metabolism of Bengalis” published in 1907, an inference to the cause of diabetes was drawn based on the fact that the diet habits of upper-class Bengalis consisted of excessive carbohydrates (mostly rice) with very little protein. He believed that changes in habits, and increased indulgence in food were responsible, at least to some degree, for the increase in the rates of diabetes in India.

Cases of diabetic retinopathy were also recorded in Bareli and Bengal from clinical notes of ophthalmic and cataract surgery. An article published in 1901 by ML Mitra who performed more than 400 cataract surgeries, stated that diabetes was very common in Bengal. Another report by Dr FP Maynard, a civil surgeon from Patna, stated that of 145 patients with cataract disease who were tested, 3 had diabetes. Dr Krishnamurthy Aiyer, sanitary commissioner from Travancore discussed the differences in the dietary habits between Bengalis and those in the Madras Presidency. He discussed in detail, about the differences in the dietary habits between men and women, the type of meal consumed, the time taken to consume a meal, and how all these factors play a role in...
Among those who were sedentary, 22 Dr. stated that diabetes was more common in people who moved frequently and those who were sedentary, and he pointed out that diabetes is more common in people who move frequently and those who are sedentary.22 Comparison was also made between the development of diabetes during the night than the olden days.

Development of diabetes. Dr. Aiyer also noted that people consumed more rice during the night than the olden days. Comparison was also made between people who moved frequently and those who were sedentary, and he stated that diabetes was more common among those who were sedentary.22 Dr. Muthuswamy, a retired surgeon from Tanjore also recorded in the journal, in 1887, the medicinal properties of some common indigenous plants of southern India. He briefly mentioned how the medicinal properties of some common indigenous plants of southern India. He briefly mentioned how the medicinal properties of some common indigenous plants of southern India. He briefly mentioned how the medicinal properties of some common indigenous plants of southern India.

In 1894, Dr. A. Mitra, Chief Medical Officer of Kashmir, wrote a letter to the Editor of the Indian Medical Gazette (IMG), addressing patients with diabetes and other doctors across India, requesting them to share information about diabetes9 (Figure 1). He published the letter along with a series of questions to collect information systematically. Two years following this publication, Dr. Mitra reported that he had recorded over 350 cases of diabetes in India.20

In 1907, the British Medical Association’s annual conference that was held in Exeter had a dedicated session on “Diabetes in the Tropics” which was one of the first occasions when diabetes in India was given importance in the West. This led Dr. Mitra to write to the IMG in 1908, requesting them to consider including “Diabetes in India” as a topic of discussion during the Indian Medical Congress to be held that year. He was one of the earliest advocates of diabetes research and believed that this topic would be of great interest to practitioners in India.20 However, there seems to have been no follow up to his request, nor has any record been found of his subsequent work in the field of diabetes. There was however a note published in 1927, where the Editors of IMG had mentioned that following his death, Dr. Mitra’s wife had founded a research scholarship in diabetes at the Calcutta School of Tropical Medicine.27

During the pre-independence era, the Calcutta School of Tropical Medicine was a landmark institution from where several research works, particularly on diabetes were carried out. This was mainly possible because of the “Mitra Memorial Research Scholarship in Diabetes for Indians”. One of the first recipients of this scholarship was Dr. Jyoti Prokash (JP) Bose, who made invaluable contributions to the study of diabetes in pre-independence India.

Discovery of insulin and its introduction in India

It was around the same time as Dr. JP Bose started his work on diabetes in India, that a major event of historical importance was taking place in far off Canada. In the spring of 1921, a young doctor, Dr. Fredrick Banting with the help of a medical student Charles Best and Dr. J.J. Mcleod, Professor of Physiology at the University of Toronto and a chemist James Bertram Collip discovered insulin. For this epoch-making discovery, the Nobel Prize for medicine was awarded to Banting and Mcleod in 1923.

Insulin was soon manufactured by Eli Lilly in the US under the license provided by the University of Toronto. Soon after Canada and the U.S. received insulin, major drug houses in Britain such as Allen & Hanbury’s, British Drug House Ltd and Boots Pure Drugs Ltd. also received their licence to sell insulin. Following the preparation of insulin in their labs and after undergoing rigorous testing, the AB brand insulin (so called because it was produced by Allen & Hanbury’s and the British Drug House) was proved to be stable over many months of storage without loss of activity.28 This was the first insulin to come to India.

As a Mitra Research Scholar on Diabetes, Dr. JP Bose was one of the first to use insulin in India, as early as 1923, just two years after its discovery. Indeed, it is fair to state that he was in the right place, at the right time. This enabled him to publish several of his research works on diabetes. One of the first articles by Dr. JP Bose on insulin was published in December 1923 where he succinctly described the various details of insulin, right from how it is produced, its storage properties, its action, indications for use of insulin, contraindications, symptoms of overdose of insulin etc. He also explains in the article, the effect of insulin on non-diabetic individuals, including the results of an experiment that he conducted on himself.29

Several publications on the deterioration in the potency of insulin in the hot, humid climate of India emerged and Dr. J. Taylor at Pasteur Institute of Burma was the first to report this.30,31 He explained that some insulin preparations that were imported did not come with labels and emphasised how it was important to re-standardize insulin after importing it into India. He also addressed the
need for bringing in strict measures to control its distribution. Subsequently, reports started coming in from other physicians across India. Dr JP Bose performed experiments on rabbits and made an interesting observation that the effect of insulin was closely correlated to the color of the animal tested.

Some reports also suggested that consignment of insulin that was maintained in proper cold storage was found to retain its full potency. Bose tested the AB brand of insulin and reported that certain batches of the AB insulin only retained one fourth of their original potency. As these issues were being addressed by physicians across India, the company themselves performed several tests, even sending a consignment from London to India and then back to London. After two and a half months of testing, they reported that their insulin did indeed retain its potency.

It is thus heartening to note that, following the discovery of insulin in Canada, there was very little delay in insulin coming to India. Despite the initial issues pertaining to storage and stability, there was no doubt that physicians in India accepted insulin as a life saving drug for treating diabetes. During the 1927 congress of the Far Eastern Association of Tropical Medicine, H Stott remarked that insulin was a “gift to humanity” and that it was one of the most outstanding scientific achievements of the decade. In the following years, especially around the time of the Second World War, there appears to have been some shortage of insulin in India. Details of how these issues were ultimately resolved after the war, have unfortunately not been recorded.

Meanwhile, Dr Bose continued his research on diabetes. In 1928, he explained that the importance of testing blood sugar only increased after the introduction of insulin as a treatment for diabetes. He acknowledged that the process that was used then to estimate blood sugar required a fully functional laboratory and a trained technician to perform the test, which might be easy in a city like Calcutta, but not in small towns and villages of India. He therefore, devised an alternate, simplified method for estimating the blood sugar that was authenticated and was shown to produce accurate results. He consistently worked on several issues related to diabetes including basal metabolism of Indians, arterial versus venous blood sugar differences, insulin anaphylaxis, protamine zinc insulin, role of vitamin B in treating diabetes and hypoglycemia due to prolonged insulin administration.

Perhaps one of the important contributions of Dr JP Bose in the context of insulin relates to his work on type 1 diabetes. He published case notes about children suffering from type 1 diabetes. He explained in detail the case of an extremely weak child, who presented with typical symptoms of type 1 diabetes including severe burning sensation over the whole body and an insatiable thirst, all of which subsided after treatment with insulin, and the patient subsequently gained weight. Bose heavily advocated the use of insulin in treating children with type 1 diabetes and continued to publish several papers with clinical photographs as evidence to show the marked improvement of children’s growth after starting insulin. He mentioned that the improvement was so marked that the child was hardly recognizable, barely 6 weeks after starting the treatment. Figures 4 and 5 show the dramatic improvement in children with type 1 diabetes after treatment with insulin. These remarkable pictures pay a rich tribute...
not only to the discoverers of insulin, but also to Dr Bose for meticulously recording the dramatic and miraculous recovery of these children in India shortly after the discovery of insulin.

Table 1 outlines the major contributions of Indian physicians in the field of diabetes in the pre-independence era.

Conclusion

This article describes a forgotten chapter in India’s diabetes literature - diabetes in pre-independence India. Available records show that researchers in pre-independence India were able to build on ancient knowledge to describe the pathophysiology, classification and management of diabetes. They also show that contrary to common belief, India was not a “late starter” in the treatment of diabetes with insulin. We believe this article would be of interest to all those who wish to know about diabetes in the colonial period – most of which is now forgotten and not easily accessible. This article is just a small tribute we can pay to the pioneering efforts of our forefathers in diabetology in India as we celebrate the centenary of insulin discovery.

Acknowledgements

We acknowledge the assistance of Dr. TK Mukherjee and Dr. Ayan Mukherjee in accessing the records at the School of Tropical Medicine.
Spontaneous Internal Carotid Artery Dissection presenting as Stroke

Sankar J

19 year old male presented with history of sudden onset weakness of left half of the body associated with asymmetry of face lasting for 3 min followed by spontaneous recovery. He denied any history of preceding trauma. On examination he was hemodynamically stable with no focal neurological deficit. He underwent an urgent magnetic resonance imaging and angiography of the brain, revealed right internal carotid artery dissection with right middle cerebral area (MCA) infarct (Figures 1 and 2). He was managed as a case of spontaneous internal carotid artery dissection and stroke with antiplatelets and anticoagulants. Repeat magnetic resonance angiography of the brain after 04 weeks revealed normal study. Spontaneous Internal carotid artery dissection is an uncommon cause of stroke that occurs in the setting of trauma, but can rarely occur spontaneously. Management options include thrombolysis, anticoagulation, antiplatelet therapy and surgical or endovascular intervention. Majority of carotid artery dissections heal spontaneously over time. Spontaneous dissection of the carotid artery is an often missed, increasing cause of stroke in young adults, hence cervicocephalic arterial dissection should be considered in the differential diagnosis of causes of stroke in young.

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Military Hospital, Chennai, Tamil Nadu
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Peripheral Gangrene Associated with Disseminated Tuberculosis - a Rare Manifestation

Aswin Geo Jacob¹, Jency Maria Koshy², Divya Deodhar², Mary John³

Abstract
With global resurgence of M. tuberculosis infection, cases of extra pulmonary TB have also shown an increase. Tuberculosis is a major cause of morbidity and mortality in India. Although disseminated tuberculosis can affect most of the organs, vasculitis presenting as peripheral gangrene as a manifestation of tuberculosis is very rare. We report the case of a 70 years old male who presented with gangrene of left leg complicating disseminated tuberculosis.

Introduction
India has the highest burden of TB (tuberculosis). According to the World Health Organization (WHO), the estimated TB prevalence in India for 2013 was 2.6 million.¹ It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB. The clinical spectrum of TB is complicated with varied manifestations. Peripheral gangrene as a manifestation of tuberculosis is very rare.

Case Report
A 70 year old businessman with no other co morbidities presented to the emergency department with complaints of intermittent low grade fever for 2 months, breathing difficulty for 2 months, pain and blackish discoloration of his left leg for 15 days prior to presentation.

On general physical examination he was conscious, oriented to time place and person. There was no pallor, icterus, cyanosis, clubbing or lymphadenopathy. He had tachycardia with a pulse rate of 120/min, blood febrile with a temperature of 100.2 F and maintained a saturation of 98% on room air. Left popliteal, bilateral dorsalis pedis and posterior tibial pulses were absent. Local examination revealed blackish discoloration of the left foot suggestive of gangrene (Figure 1). Dull percussion note and decreased breath sounds were noted over the infrascapular area bilaterally, JVP was raised 7 cms above sternal angle and S1 S2 were muffled. A clinical diagnosis of pericardial effusion, bilateral pleural effusion and arterial gangrene of left foot was made. Chest X-ray done in the emergency department revealed cardiomegaly with loss of cardiac silhouette (Figure 2). Echocardiography confirmed the diagnosis of a massive pericardial effusion with a diastolic collapse of RA and RV. Pericardial tap was done under cardiac monitoring which drained 800ml of thick pus. Pericardial fluid analysis revealed RBC of 1640/mm³ and WBC of 5340/mm³ (polymorphs 44%, lymphocytes 34% and unidentified cells 34%). LDH in the pericardial fluid was 8751 U/L with a corresponding serum LDH of 1398 U/L, Protein was 6.1g/dl which was suggestive of an exudative fluid; ADA in pericardial fluid was 4.5 U/L.

In the presence of exudative pleural effusion and gangrene differentials considered were tuberculosis, malignancy and connective tissue disorder. Smear for acid fast bacilli, fungal and malignant cytology were negative.

On doppler study occlusion of left anterior tibial artery, posterior tibial artery, and left popliteal arteries with low volume mono phasic flow in right leg arteries were noted. CT angiography of the lower limbs confirmed the above findings. It also revealed bilateral superficial femoral artery thrombosis extending into popliteal arteries. High resolution computed tomography of chest was done which showed B/L pleural effusion with pericardial effusion (Figure 3), large right upper lobe nodule with break down which may represent a small tuberculoma and an incidental large splenic abscess. (Figure 4).

Mean while his vasculitic work up came negative. C-ANCA and PANCA were 2.9 U/ml (< 12u/ml) and 1.6 u/ml (<12u/ml) respectively. ANA, anti ds DNA, anti cardiolipin antibody, antiphospholipid antibody and rheumatoid factor were negative. C3 was 48mg/dl (90-180mg/dl) and C4 was 11mg/dl (10-40). Pericardial fluid Tb PCR came positive for mycobacterium tuberculosis. Hence a final diagnosis of disseminated TB with pericardial effusion, pleural effusion, pulmonary TB, splenic abscess and left foot gangrene due to tubercular vasculitis was made. The patient was initiated on anti tubercular therapy, anticoagulation and steroids. On treatment his pleural effusion and pericardial effusion decreased and peripheral gangrene did not progress.

Discussion
The mode of onset and progression...
of symptoms in our patient suggests that he acquired tubercular infection through inhalational route which primarily affected his lungs from where it spread hematogenously involving pericardium, spleen and eventually causing gangrene of the lower limb as a sequela.

Peripheral gangrene resulting from tuberculosis is uncommon. Only few cases have been reported in the literature of gangrene associated with tuberculosis. Itin, et al2 described symmetrical peripheral gangrene in a patient with disseminated tuberculosis. Vasculitis is a clinicopathologic process characterized by blood vessel wall inflammation, which can be primary or secondary to other systemic diseases. Vasculitis can affect blood vessels of all sizes in any organ, and these result in a wide variety of signs and symptoms in clinical presentation. Vasculitis secondary to TB was first described by Parish and Rhodes in 1967.3 TB could result in granulomatous arteritis and affect the aorta and its branches, thereby mimicking large-vessel vasculitis.4 TB also was considered a cause of small-vessel vasculitis, such as leukocytoclastic vasculitis.5 The mechanism of injury proposed for vasculitis is deposition of immune complexes in the vascular wall rather than direct aggression of M. tuberculosis.6 Many of the manifestations seen in tubercular meningitis are also due to vasculitis of the intracranial blood vessels. Our patient presented with disseminated tuberculosis and peripheral gangrene.

**Conclusion**

With global resurgence of M. tuberculosis infection, cases of extrapulmonary TB have also shown an increase. Peripheral gangrene and vasculitis are seldom associated with TB. The purpose of this case report is to highlight this uncommon manifestation of disseminated tuberculosis, which is a common condition in our country.

**References**

Dengue and COVID-19 Coinfection- A Double Trouble

Amandeep Kaur¹, Navneh Samagh², Nimish Singh³, Navdeep Kaur⁴

Abstract
COVID 19 since its onset in Wuhan in 2019 has overburdened our existing health resources and infrastructure. Dengue virus has been endemic in Asian countries since decades. Both being viruses with similar clinical profile and overlapping laboratory parameters has posed a great challenge for Asian countries to combat a co epidemic, creating a double burden. We, as clinicians must be more vigilant in diagnosing the patients so that dengue is not missed in this covid pandemic era and does not progress to life threatening dengue shock syndrome. More importantly, we should emphasize on preventive measures for prevention of dengue so that we can reduce the burden on health care system.

Introduction
The world is still facing the challenges of combating the coronavirus since its onset in Wuhan China. The coronavirus is a respiratory illness caused by SARS-CoV2 and manifests a variety of clinical symptoms varying from fever, cough, headache, myalgias, nausea, vomiting to more severe pneumonia, ARDS, septic shock and multiorgan failure. Dengue virus has been endemic for decades in Asian countries. Dengue virus having a similar clinical profile as the COVID 19 has made it even more challenging for the Asian countries to combat a co epidemic, thus creating a double burden on both the resources and health systems. We present a case series where the patients presented with symptomatology consistent with COVID 19 but the investigations prompted us to look for Dengue NS1 antigen. We found it pertinent to bring these cases to light so that dengue is not missed and it does not progress to dengue shock syndrome masquerading as COVID 19.

Case 1
16-year-old male presented with chief complaint of fever associated with headache for 2 days. Associated history of recurrent vomiting’s with pain abdomen was present. The patient tested positive for SARS -Cov 19 by rapid antigen test. On presentation, his vital signs showed a temp of 97.7, blood pressure 100/70, PR 92/min and blood oxygen saturation of 98% at room air. Initial investigations revealed thrombocytopenia (platelet count 33000) and leukopenia (2800). Renal function tests revealed serum creatinine of 1.8 with slightly raised liver enzymes (aspartate aminotransferase 63 U/L and alanine aminotransferase 36 U/L). CRP was raised (79.4 mg/L), serum LDH was raised (989 IU/L), with raised D dimer levels of 1585.76 ng/ml) and serum ferritin levels (>1200 ng/mL). Dengue serology was positive for NS1 antigen. During hospitalisation, patient was started on symptomatic treatment. Gradually the platelet count improved along with resolution of clinical symptoms and the patient was discharged in a satisfactory condition.

Case 2
30-year-old male with no significant past medical history presented with fever and generalised malaise for 4 days. The patient had no respiratory or gastrointestinal complaints and no history of contact with COVID positive patient. The patient tested positive for SARS-COV 19 by rapid antigen test. On presentation, his vital signs showed a temp of 97.7, blood pressure 100/70, PR 92/min and blood oxygen saturation of 98% at room air. Initial investigations revealed thrombocytopenia (platelet count 33000) and leukopenia (2800). Renal function tests revealed serum creatinine of 1.8 with slightly raised liver enzymes (aspartate aminotransferase 63 U/L and alanine aminotransferase 36 U/L). CRP was raised (79.4 mg/L), serum LDH was raised (989 IU/L), with raised D dimer levels of 1585.76 ng/ml) and serum ferritin levels (>1200 ng/mL). Dengue serology was positive for NS1 antigen. During hospitalisation, patient was started on symptomatic treatment. Gradually the platelet count improved along with resolution of clinical symptoms and the patient was discharged in a satisfactory condition.

Case 3
67-year-old female with previous history of hypertension on medication presented with chief complaint of fever associated with generalised malaise for 3 days. The patient had no history of respiratory complaints. She tested positive for COVID-19 with a rapid antigen test and was admitted to the hospital immediately in view of high risk. At presentation, the patient was afebrile with blood pressure of 128/80, PR 96/min and blood oxygen saturation of 97% at ambient room air. Initial investigations revealed thrombocytopenia (platelet count 8000) with normal total leucocyte count (10000). Patient did not have any bleeding manifestations despite severe thrombocytopenia. Liver function tests were abnormal with raised liver enzymes (aspartate aminotransferase 744 U/L and alanine aminotransferase 295 U/L). Further investigations revealed CRP(4.24mg/L), serum LDH (1233 IU/L), with raised D dimer levels of 1170.81 ng/ml) and serum ferritin levels (>1200 mg/mL). The

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One of the easiest ways to diagnose either of the disease is through the available rapid tests. Due to the pandemic COVID 19 protocol, the patients were tested for coronavirus initially when they presented to the hospital with complaints of fever. On admission, investigations revealed severe thrombocytopenia and raised liver enzymes. Being an endemic country for dengue with spikes of dengue fever each year, the patients were tested for dengue virus which came out to be positive for NS1 antigen. It has been hypothesized that antigenic similarities between SARS-Cov 2 and dengue virus may result in the false positive results resulting in misdiagnosis of either disease.

Thrombocytopenia being characteristic feature of dengue infection has also been observed in COVID-19 patients. Thrombocytopenia is associated with severity of COVID-19. Chen N et al in his study observed thrombocytopenia is more prevalent (12% vs 4%) in COVID-19 patients compared to thrombocytosis. Another study of COVID-19 patients showed 36.2% of them developed thrombocytopenia. In dengue endemic countries, health care workers are facing difficulty trying to distinguish between both the viruses and further managing the diseases. More emphasis should be laid on preventive measures for such endemic diseases so that we can effectively control these diseases and further reduce the burden on the health care workers.

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COVID Philately Part-III

Jayant Pai-Dhungat

COVID-19 second wave has swept through India at a pace that has staggered us all. It has been unbelievably aggressive with an enormous mortality in many healthy young adults, making us realize how vulnerable we are.

During last one year we have learned a great deal many more things of concern, like increased risk of vascular involvement and resulting cardiac, cerebrovascular insults; severe pulmonary involvement with late manifestations leading to high mortality. There have been covid related long term organ damage and unusual complications like virus triggered diabetes- which would not have been otherwise expected; second is invasive mucormycosis associated with covid which may result in serious visual and brain involvement.

With fresh escape mutation mutant covid B.617.2 now has lead to delta plus or AK.1 ‘variant of great concern’. This variant is responsible for infectious and virulent second wave; what is more alarming is its detection in 25 more countries at present.

Virulence of present wave compels one to compare covid 19 pandemic with a Century old Spanish flu of 1918-19, pandemic which was due to H1N1 influenza mostly of avian origin. Nature of virus was unknown and apart from quarantine and other public health measures nothing was available in diagnostic and therapeutic fields. There was no concept of intensive care. However, rapid global travel was limited then and many countries escaped. Initial spring wave (March–June 1918), was clinically mild. The second, autumn wave (late August–December 1918), was extremely virulent with an enormous mortality in those aged 25–40 year accounting for 40% of deaths. The third pandemic phase started in January 1919 and fourth wave lasted approximately from 1 December 1919 to 30 April 1920. Pandemic killed 50-100 million people. It is said that mortality was more than combined two world wars WW-I (17 million) WW-2 (60 million) put together.

The 1918 influenza mostly killed patients from secondary bacterial pneumonia, while victims of COVID-19 mostly died from an overactive immune response resulting in multi organ failure.

The experience of the past teaches us that battle against pandemic is linked to a rapid, constant, and lasting application of scientific knowledge. Fortunately, today, knowledge in medicine particularly in the field of therapies and vaccination has greatly improved when compared to earlier pandemic.

Sir Macfarlane Burnet wrote prophetically in 1956-

“in dealing with virus particle we are dealing with matters of life and death…. it would also make it possible to let loose, maliciously or by accident, another pandemic like 1918 spread unchecked through civilized and uncivilized countries…….it would be a bitter irony if its further development in science bring man made plagues even more lethal than the natural epidemics in the past”

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SUGAR FREE, SUGAR FREE, SUGAR FREE, SUGAR FREE
Consensus Statement on Holistic Management of Angina

Tiny Nair1, Uday M Jadhav2, KP Suresh Kumar3, PC Manoria4, Devanu Ghosh Roy5, Jabir Abdullakutty6, Sameer Shrivastav7, Ashwani Mehta8, Arindam Pande9, Ravikant Patil10

Abstract
Worldwide, coronary heart disease (CHD), have assumed epidemic proportions. Increasing use of interventional therapy and a higher adherence to medical therapy have led to a 33% reduction in cardiac deaths at 5 years after hospital discharge. Angina pectoris is a common symptom of ischemic heart disease. The goals of anti-ischemia therapy in patients with stable coronary artery disease (CAD) include relieving angina symptoms, improving duration of exercise and quality of life, improving prognosis and preventing cardiovascular (CV) events. The consensus statement was devised with the help of multiple meetings held across India. Ten regional advisory board e-meetings were held in Mumbai, Delhi, Chennai, Kolkata, Ahmedabad, Cochin, Trivandrum, Lucknow, Bhopal and Varanasi. These meetings were attended by ten eminent experts from the field of cardiology from each region. Extensive literature review, intense discussions, and feedback from the cardiologists led to the development of the following consensus statements on definition, diagnosis, and management of angina, which have been reported in this article.

Introduction
Coronary artery disease trends in India
Coronary heart disease (CHD), have assumed epidemic proportions worldwide.1 Globally, cardiovascular disease (CVD) led to 17.5 million deaths in 2012.2 According to the office of the Registrar General of India (RGI) in 1980s and 1990s, CVD was reported to be the cause of 15%-20% of deaths in the country. In India, more than 10.5 million deaths occur annually, and CVD led to 20.3% of these deaths in men and 16.9% of all deaths in women.3

The Global Burden of Diseases, Injuries, and Risk Factors study has reported that deaths as well as disability from CHD have more than doubled in India in the last 30 years.4 In developing countries such as India, premature CHD is an increasing concern.5 According to Million Death Study, a high premature mortality due to CVD has been reported in India.4 Women have less obstructive CAD, but a higher prevalence of coronary microvascular dysfunction than men, as shown in the Women’s Ischemia Syndrome Evaluation (WISE) study.7 Obesity is a more potent risk factor for angina in women than in men.8 Microvascular angina affects 30% of stable angina patients with non-obstructive coronary arteries.9 It has been estimated that nearly 40% of the angina patients have vasospastic angina.10

Increasing use of interventional therapy and a higher adherence to medical therapy have led to a 33% reduction in cardiac deaths at 5 years after hospital discharge.11 Diabetes mellitus (DM) itself is an independent risk factor for atherosclerosis, and CAD is a frequent cause of morbidity and mortality in the diabetic population.12,13 Patients with DM tend to have more extensive coronary disease and worse survival after acute myocardial infarction (AMI) compared to those without DM.14-17 However, studies suggest patients with DM tend to have asymptomatic (or “silent”) ischemia.18-20 Various studies have indicated a higher burden of angina among patients with DM compared to those without DM after an AMI.21,22

Definition
The 2019 European Society of Cardiology (ESC) guidelines have replaced the term “stable CAD” with “chronic coronary syndrome.”23 CAD is dynamic in nature and can manifest as multiple clinical presentations, which can be categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS).24

Diagnosis
Non-invasive functional imaging for myocardial ischemia, coronary computed tomography angiography (CTA) is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone. Invasive coronary angiography is recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood, severe symptoms refractory to medical therapy or typical angina at a low level of exercise, and clinical evaluation that indicates high event risk.24

In Europe and the US, each year approximately 4 million elective coronary angiograms are performed.25,26 Patients with diabetes and atypical symptoms are nearly twice as likely to be diagnosed with angina compared with non-diabetic patients.27 However, 50% of patients who undergo elective coronary angiography with symptoms and/or signs of ischemia have no obstructive epicardial CAD. This large group includes patients with microvascular angina (MVA),

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Holistic treatment of angina

Worldwide, ischemic heart disease is major cause of morbidity and mortality. Moreover, angina pectoris is a frequent symptom manifestation. The goals of anti-ischemia therapy in patients with stable CAD are:

1. relieving angina symptoms, improving duration of exercise and quality of life, and
2. improving prognosis and preventing CV events.

A. Pharmacotherapy
   ● Beta-blockers
   
   Beta blockers reduce myocardial oxygen demand by reducing the major determinants of myocardial oxygen demand like heart rate, blood pressure and myocardial contractility. 
   
   ● Ivabradine
   
   Ivabradine selectively reduces heart rate by reducing slope of the slow diastolic depolarization phase of the action potential in sinus node cells. Ivabradine not only maintains exercise-related coronary dilatation but also reduces heart rate. Additionally ivabradine also increases coronary flow reserve and collateral perfusion, promotes formation of coronary collaterals and maintains endothelial function.

   The mortality-mortality Evaluation of the I(f) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) trial evaluated effects of ivabradine in 10,917 patients with stable CAD and left ventricular dysfunction. Treatment with Ivabradine could reduce myocardial infarction in those patients with HR at entry >70 bpm or angina at baseline.

   ● Verapamil and diltiazem
   
   Non-dihydropyridines calcium channel blockers such as verapamil, and diltiazem help in reducing heart rate. Verapamil and diltiazem have an effect on calcium channels of the myocytes as well as of the cardiac pacemaker and atroventricular conduction cells thereby causing negative inotropic effect and reduction of heart rate.

   Verapamil was also demonstrated to have vasodilator properties. Following verapamil administration, decrease in myocardial oxygen consumption, with or without a decrease in coronary sinus blood flow, has regularly been observed.

   ● Dihydropyridine calcium channel blockers
   
   Dihydropyridines are responsible for inhibiting calcium influx in the smooth muscle of the arterial wall, which leads to smooth muscle relaxation.

   Findings from the International Multicenter Angina Exercise trial showed that both nifedipine and metoprolol were equally effective in reducing angina frequency and improving exercise tolerance.

   ● Nitrates
   
   Nitrates act by relaxing the vascular smooth muscle. At low doses, nitrates reduce preload and venous return, moreover at elevated doses nitrates dilate peripheral coronary arteries which results in reduction of myocardial oxygen demand and afterload.

   Combining nitrates with β-blockers can be useful to block tachycardia, leading to a synergetic anti-ischaemic effect.

   ● Nicorandil
   
   Nicorandil results in the dilatation of the coronary arteries with an increase of myocardial blood flow. Therefore, nicorandil improves the balance of oxygen demand and delivery.

   Results from the Impact of Nicorandil in Angina (IONA) study showed that, nicorandil reduced the composite of CV death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac pain at a median of 1.6 years.

   In a propensity score-matched analysis of 5,116 Japanese patients with CAD, nicorandil reduced the frequency of angina attacks compared to sustained release nitroglycerine.

   ● Trimetazidine
   
   Trimetazidine acts on the heart by reducing oxidation of free fatty acids, increasing anaerobic glucose utilization and anaerobic energy production from the cytosol. These effects were confirmed when trimetazidine treatment for 3 months improved myocardial levels of high-energy phosphates by 33% in heart failure patients.

   In a meta-analysis of 23 randomized trials, trimetazidine improved angina compared with placebo or other antianginal therapies. In a Cochrane meta-analysis, the antianginal effects of trimetazidine were similar to those of other antianginal agents. In patients presenting with history of myocardial infarction, or diabetes, or left ventricular dysfunction, antianginal efficacy of trimetazidine has been demonstrated.

   A clinical study, in diabetic patients with ischemic heart disease showed a beneficial effect on left ventricular volumes and left ventricular ejection fraction compared to placebo. This may be due to virtue of cardiac glucose utilization due to trimetazidine. In another study, trimetazidine reduced serum myocardial enzyme, improved liver function and cardiac function in type 2 diabetic patients with AMI undergoing percutaneous coronary intervention (PCI).

   ● Ranolazine
   
   Ranolazine is an active piperazine derivative that is structurally related to trimetazidine. Its metabolic effects are similar to trimetazidine. Ranolazine as monotherapy or combination therapy, not only improves symptoms but also increase exercise tolerance.

   One randomized, controlled trial involving 823 patients with coronary artery disease and taking BBs and CCBs as antianginal therapy demonstrated that the addition of ranolazine 750 mg or 1000 mg two times per day decreased the frequency of anginal attacks, reduced nitroglycerin use, and increased exercise capacity.

B. Revascularization

Coronary artery revascularization is performed to relieve symptoms, improve quality of life, and prevent cardiovascular death. Revascularization can offer survival benefits in high-risk, stable-angina patients, who are formally defined as those with multivessel coronary artery involvement or left main CAD, LVEFs <0.35, and myocardial ischemia affecting more than 15-20% of the left ventricular myocardium.

However, according to a large retrospective study from the Mayo Clinic, majority of patients treated with PCI show an improvement in angina episodes, but 30% and 20% patients still report recurrent angina and severe recurrent angina respectively. The causes of recurrent angina after PCI may be either structural (“stretch pain”, in-stent restenosis, in-stent thrombosis, incomplete revascularization, progression of coronary atherosclerosis) or functional (microvascular dysfunction, epicardial
coronary spasm). Pharmacological treatment options for management of recurrent angina after PCI include nitrates, β-blockers, calcium channel blockers, angiotensin converting enzyme (ACE)-inhibitors, statins, trimetazidine, nicorandil, ivabradine, and ranolazine. Further, the Indian population displays a higher trend of presenting with atypical symptoms of angina, which may result in a missed diagnosis. Indian Consensus on OPtimal Treatment of Angina, OPTA, provides screening tools such as a checklist for screening of angina. It also provides a treatment algorithm guide for management of suspected angina cases. Moreover, there is also a questionnaire which will help the clinicians stratify the severity of the condition and individualize the treatment.

**Methodology**

The consensus statement was devised with the help of multiple meetings held across India. Ten regional adboard e-meetings were conducted across the county i.e., Mumbai, Delhi, Chennai, Kolkata, Ahmedabad, Cochin, Trivandrum, Lucknow, Bhopal and Varanasi. The meetings were attended by ten eminent experts from the field of cardiology from each region. Extensive literature review, intense discussions and feedback from the cardiologists led to the development of the following consensus statements on definition, diagnosis and management of angina.

**Consensus statement**

**Expert group recommendation 1: Definition**
- The terminology of stable angina/stable CAD has been replaced with CCS.
- **Coronary syndromes** are categorized into CCS and ACS.
  - ACS is further classified as ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable angina
  - CCS is further classified as:
    - Stable angina
    - New heart failure (HF) and suspected CAD
    - Stabilized symptoms for less than a year post ACS or PCI
    - Stabilized symptoms for more than a year post initial diagnosis
    - Patients with angina and suspected microvascular disease
    - Asymptomatic CAD detected at screening

**Expert group recommendation 2: Diagnosis (Table 1)**
- Microvascular angina and vasospastic angina are diagnosis of exclusion (Figure 1).
- If ischemia is present on resting electrocardiogram (ECG) and echocardiogram (ECHO) as well as stress tests, proceed to angiography.

**Expert group recommendation 3: Management**

**Heart rate (Figure 2)**
1. Pharmacotherapy (Table 2)
2. Additional therapies
   - Counselling, ACE inhibitors, anxiolytics, control of lipids and anemia are equally important in the management of CSA.
   - Statins have shown to prevent secondary events as well as improve the chest pain in non-obstructive angina
   - Both aspirin and statins are indicted for microvascular dysfunction and show the most benefits
   - In certain individuals, anxiolytics have demonstrated to relieve chest pain
3. Revascularization (Table 3)
4. Angina management in special population

**Angina in hypotension and bradycardia patients**
- Approximately 10% of patients develop hypotension and bradycardia, which leads to negative outcome
- Prescribing nitrates or beta blockers to elderly patients can lead to hypotension/bradycardia
- To manage hypotension, adjust the doses of the prescribed antianginal drugs and assess if there is deterioration

**Table 1: Diagnostic techniques**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional Flow Reserve (FFR)</td>
<td>FFR provides functional evaluation of the stenosis.</td>
</tr>
<tr>
<td>Invasive coronary angiography</td>
<td>It plays an important role in diagnosing non-obstructive angina; however, it is an expensive procedure. One of the advantages is that, if coronary obstruction is diagnosed, angioplasty can be performed at the same time.</td>
</tr>
<tr>
<td>Coronary artery calcium scoring</td>
<td>It is a cheaper mode of investigation compared to computed tomography angiography with less exposure to contrast dose and radiation. Coronary artery calcium scoring should be conducted prior to CT angiography and invasive angiography.</td>
</tr>
</tbody>
</table>

*CFR, computed tomography; FFR, fractional flow reserve*
A consensus statement was arrived at under the guidance of expert cardiologists, for improving angina management in comparison to the latest available evidence. Drug therapy should combine drugs that prevent CV events (statins, antiplatelets and ACE inhibitors/angiotensin receptor blockers) along with anti-anginal therapy. Pharmacological agents for angina management are known to possess anti-anginal properties besides anti-anginal effect which could benefit both angina and coexisting comorbidities.

Hence, it is suggested that personalized approach to invasive testing helps to diagnose during patients’ index presentation. This approach helps stratify medical therapy leading to improved patient health and quality of life.

Table 2: Treatment options for management of chronic stable angina

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>Nitrates do not alter the mortality rate or left ventricle function.</td>
<td>Discontinue or reduce the dose of beta-blocker if heart rate is &lt; 50 bpm.</td>
</tr>
<tr>
<td></td>
<td>Nitrates is used for symptom relief though there is no evidence of mortality benefit.</td>
<td>If patient develops bradycardia or hypotension, reduce the beta-blocker dose; however, avoid sudden stoppage of the drug.</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Beta-blockers are prescribed when the heart rate is &gt;60 bpm.</td>
<td>One of its most common side effects is headache.</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers are useful in left ventricular dysfunction and post myocardial infarction.</td>
<td>Generally avoided as it causes reflex tachycardia.</td>
</tr>
<tr>
<td></td>
<td>If heart rate is maintained at 50-60 bpm, without experiencing dizziness, continue the beta-blockers.</td>
<td>Decreases contrast enhanced nephropathy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preferred over ranolazine in hepatic impairment.</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>Nicorandil is an effective antianginal agent.</td>
<td>Twice daily is more commonly prescribed compared to once daily.</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Nifedipine can be used to relieve nocturnal angina.</td>
<td>Once daily dosage of sustained release formulation, decreases pill burden and improve compliance</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>Provides ischemic preconditioning, useful in LV dysfunction, recurrent angina post revascularization and patients not responding to traditional antianginal agents.</td>
<td>Avoid in elderly, Parkinson’s disease, tremor disorders, CKD.</td>
</tr>
<tr>
<td></td>
<td>Prescribing trimetazidine before or post revascularization decreases ischemia reperfusion injury.</td>
<td>Not recommended for elective PCI as there is insufficient clinical data.</td>
</tr>
<tr>
<td></td>
<td>Shows survival benefit when added post revascularization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shown improvement in heart failure patients as well as in chronic coronary syndrome patients with erectile dysfunction on sildenafil.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In patients where microvascular angina is associated with heart failure, trimetazidine is preferred over ranolazine.</td>
<td></td>
</tr>
<tr>
<td>Ivasbradine</td>
<td>Should be used only when the heart rate is &gt; 60 bpm or in angina with low ejection fraction.</td>
<td>Adverse effects include constipation and QT prolongation at higher doses, hence should be used with caution.</td>
</tr>
<tr>
<td></td>
<td>Since it does not affect heart rate or blood pressure, mostly preferred when the patient develops low blood pressure.</td>
<td>Although it causes QT prolongation, it can be used for the management of atrial fibrillation.</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Ranolazine, a metabolic modulator, is prescribed in diabetes patients with angina.</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Revascularization

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indications for revascularization are:</td>
<td>• If patient complains of chest pain post revascularization procedure then rule out:</td>
</tr>
<tr>
<td>o Multiple risk factors,</td>
<td>o Obstructive causes</td>
</tr>
<tr>
<td>o Occlusion in mid left anterior descending artery.</td>
<td>o Assess the compliance of the patient as they become noncompliant after a year.</td>
</tr>
<tr>
<td>o When more than 10% of myocardium tissue is damaged.</td>
<td>o Rule out anemia, tachycardia.</td>
</tr>
<tr>
<td>• To decrease peri-procedural myocardial injury during emergency procedures, trimetazidine 70mg + 80 mg atorvastatin/40mg rosuvastatin + antiplatelets are prescribed</td>
<td></td>
</tr>
<tr>
<td>• For an elective revascularization, initiate trimetazidine 2 weeks prior to the procedure.</td>
<td></td>
</tr>
<tr>
<td>• Due to presence of side branch occlusion and distal vessel stenosis, 20-30% patients may be diagnosed with recurrent angina post revascularization</td>
<td></td>
</tr>
</tbody>
</table>

of left ventricular function

• Trimetazidine and ranolazine can be prescribed as it does not alter the blood pressure.

Angina in diabetes patients

• Almost 50% of angina patients are diagnosed with diabetes.
• In patients with DM who have diabetes, intense diabetes control decreases both micro as well as macrovascular complications.

Newer therapies

• Preference should be given to newer emerging antianginal therapies especially trimetazidine
• Preference should be given to newer emerging antianginal therapies especially trimetazidine

Conclusion

Optimal management of known or suspected angina starts with establishing the correct diagnosis. Almost 50% patients are without obstructive coronary disease as majority may have microvascular and/or vasospastic angina. This consensus statement was arrived under the guidance of expert cardiologists, for improving angina management in comparison to the latest available evidence. Drug therapy should combine drugs that prevent CV events (statins, antiplatelets and ACE inhibitors/angiotensin receptor blockers) along with anti-anginal therapy. Pharmacological agents for angina management are known to possess similar efficacy; hence, it is difficult to recommend which drugs should be the first choice. It is also evident that certain drugs possess pleotropic properties besides antianginal effect which could benefit both angina and coexisting comorbidities.

Acknowledgement

Authors gratefully acknowledge the following experts across India who gave their expert opinion in the advisory board meetings; Dr Anuj.
Hypertension in the Young: Remember the Rare Causes

Rudrajit Paul
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Sir,

Hypertension is one of the commonest non-communicable diseases in India. A recent study has shown that the current prevalence of hypertension among adults in this country may be as high as one in three. A significant number of newly diagnosed hypertensives belong to the young adult age group. While essential hypertension is the commonest cause, there are many secondary causes of hypertension too. A clinician needs to exclude such causes, especially when dealing with hypertension in the young. An extremely rare cause of hypertension in the young is reported here.

A 31 year old female came to the clinic with uncontrolled hypertension. She had been diagnosed with hypertension five years ago and put on four different medications. However, the blood pressure was not controlled and at the clinic this time, B.P. was still recorded at 180/110 mm of Hg in both upper limbs. There was no other symptom like palpitation, chest pain, fever, pedal edema or visual impairment. Pulses were well palpable in all four limbs. General survey and cardiovascular systemic examination was also normal. The patient’s father had died more than two decades ago from some unidentified disease (no available records) and her mother was normotensive.

Initial blood reports revealed hemoglobin concentration of 10.2 gm/dl with total leucocyte count of 5240/cumm and normal platelet count and ESR. Urea/Creatinine were 45/2.04 mg/dl respectively. Urine had RBC 7-8/HPF and 2+ albumin. Pus cells were absent. Rest of blood biochemistry parameters were normal. Thyroid profile and serum cortisol levels were also normal. Urine ACR was 1997.5 µ g/mg of creatinine. Blood ANA (indirect immunofluorescence) and ANCA (Immunofluorescence assay) were also negative. Ultrasonography showed bilateral renal parenchymal disease with altered CMD. Kidney sizes were normal.

In view of the renal parameters, after controlling the blood pressure to 130/80 mm of Hg, a renal biopsy was done. This showed variable mesangial expansion with increased cellularity. Around 40% of the glomeruli (10/25) were globally sclerosed with tubular atrophy and inflammatory infiltrates in the interstitium. Glomerular necrosis or basement membrane thickening was absent. Immunofluorescence staining showed predominant C3 deposits (3+) in the mesangium. No appreciable staining was seen for IgM, IgG or Clq. Thus, the microscopic findings were indicative of C3 glomerulopathy.

C3 glomerulopathy is an extremely rare variety of nephropathy, characterized by complement dysregulation and C3 deposition in the glomeruli and mesangium. Two major subgroups of this disease are dense deposit disease and C3 glomerulonephritis (C3GN). It is mainly a dysregulation of the complement alternative pathway.

The entity of C3GN is a newly described entity, with Servais et al giving the first proper description in 2007 only. While some cases have a genetic basis, there are still other instances of autoantibodies targeting the regulator components of C3 or C5 convertase which are responsible for pathogenesis of the condition. Thus, C3 glomerulopathy is a highly heterogeneous disease from the point of view of pathogenesis.

The main presenting features are proteinuria and hematuria. Renal function is relatively preserved till late in the disease. The disease usually manifests in young adults, as in our case. Hypertension (as in our case) is a rare manifestation of this rare disease. Another rare clinical feature, which may give a clue to the underlying renal pathology, is partial lipodystrophy (caused by complement mediated lysis of adipocytes).

C3 glomerulopathy has only rarely been reported from India. In a retrospective study from Rajasthan, out of 514 samples, only six were diagnosed as C3 glomerulopathy. The mean age of patients was 26 (our patient was 31) and all patients had microscopic hematuria (as in our case). Hypertension was documented at presentation in four out of the six cases.

We present this case to sensitize clinicians about this rare renal disorder. Thus, hypertension in the young, especially if difficult to control, must be investigated further for underlying sinister causes.

References

An Unusual Course of Weakness in Neurotoxic Snake Bite

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Dear editor,

Snakebite is a common form of envenomation encountered in our country as a significant proportion of the population is involved in agriculture. Local and systemic manifestations vary with the species of snake. A neurotoxic snakebite can cause weakness due to its effect on the neuromuscular junction. This weakness is usually rapid in onset and is flaccid in type starting from extraocular and facial muscles progressing to involve the bulbar, neck, respiratory and limb muscles. Once the toxin is neutralized with anti-snake venom or as the effect of the toxin wanes, muscle weakness begins to reverse. This recovery process is generally completed within a few days. But in some patients, prolonged weakness and persistent electromyographic abnormalities are also reported.

This correspondence
is about a neurotoxic snake bite patient who exhibited an unusual recurrence of weakness after recovering completely.

A 16-year-old boy presented to our casualty with an alleged history of snakebite over the dorsum of his left foot. The snake was not captured, and the species could not be identified. An hour later, he developed difficulty in swallowing, inability to vocalize and pooling of oral secretions. There was no bleeding manifestations or decreased urine output. He was taken to a nearby hospital where he was intubated for inadequate respiratory efforts. Twenty vials of Antiven Venom were given. He was then referred to our hospital, which is a tertiary care centre, where he was admitted in the intensive care unit. On examination, his sensorium was normal, and vitals were stable except tachycardia of 130 beats per minute. Local examination revealed prominent fang marks and minimal swelling with discoloration at the bite site. The overall clinical picture was consistent with a cobra bite.

Complete hemogram showed hemoglobin of 15.1 g/dl, total leukocyte count of 12000/mm³ with 83% neutrophils and platelet count of 3.8 Lakhs/mm³. Prothrombin time and INR were 13 seconds and 1.08, respectively. Renal parameters were within normal limits. Liver function parameters were also normal. Serum sodium and potassium levels were 137 and 4.2 mEq/L. Creatine phosphokinase level was elevated with a value of 1391 IU/L. Electrocardiogram showed sinus tachycardia. He was observed overnight and was extubated the next morning after neck holding was deemed adequate and post-Exubation there was no CO₂ retention. Vitals remained stable, and he was ambulatory without assistance.

On the second day of hospitalization, he was found to have new-onset ptosis and neck weakness with inability to hold his neck off the bed for more than a second, about 18 hours after extubation. Weakness was observed in both upper and lower limbs with the power of 3/5. Deep tendon reflexes were normal. As there were clear signs of neuromuscular weakness, we decided a trial of neostigmine challenge. There was a dramatic response to 1mg of neostigmine given after premedication with atropine 0.6mg. Ptosis resolved, and he could sit up from the bed without the support and hold his neck. However, weakness reappeared after 30 min for which neostigmine was repeated twice followed by long-acting pyridostigmine 60mg, four times a day. Over the next two days, he was closely monitored for signs and symptoms of neuromuscular weakness. Pyridostigmine was tapered and stopped after four days. He was observed for two more days and then discharged.

There is a paucity of literature on the kinetics of snake venom, and any study on venom kinetics is difficult as it is a mixture of different proteins. A possible explanation for the recurrence of weakness could be venom’s unusual kinetics with both an initial and a subsequent release from the bite site. Venom entering systemic circulation immediately after bite could have been neutralized by the anti-snake venom and caused initial muscle power improvement. The subsequent systemic release of residual venom might have caused the recurrence of weakness, which was successfully tackled with the parasympathomimetic drugs, neostigmine and pyridostigmine. Alternative explanations for the recurrence of weakness, like reperfusion after an initial episode of hypotension, the release of tourniquet applied proximal to bite site or use of aminoglycosides, were absent in our case. Hence, we believe that the release of neurotoxic snake venom from the depot can rarely show a second wave with delayed-release.

This communication highlights the distinctive course of weakness that can occur following a neurotoxic snakebite. It also underscores the importance of monitoring the patients for recurrence of neuromuscular symptoms even after a period of apparent complete recovery.

References

endpoints. We suggest that instead of conducting gene sequencing randomly in cluster groups, gene sequencing should be carried out in patients with specific indications like:

1. Those infected after 2 doses of the vaccine.
2. Moderate to serious illness requiring hospitalization after one dose of the vaccine
3. In all deaths due to COVID pneumonia.

Along with these, data on the type of vaccine given and time interval between vaccination dose and RT-PCR positivity should be captured too.

Vital information on the strain pattern and correlating this information with the vaccination details on a real-time basis is likely to provide the vaccine industry, epidemiologists, microbiologists and the treating physicians the timely advantage to review, reassess and reinforce their strategies.

The enormity, rapidity and severity unmasked by this pandemic has posed unprecedented challenges in terms of assessing the efficacy of the vaccines administered. Time tested methods of assessing humoral and cell mediated responses pose logistical issues in terms of time lags, resources constraints and there has always been the contention that neutralizing antibodies might not be the single factor predicting immune response.

Real world assessment of the vaccine efficacy with respect to prevailing strain patterns needs to be unearthed and speedily analyzed. Key primary outcome measures like mortality, moderate severe pneumonia, reinfections and transmission status in the vaccinated group is a goldmine of information that will keep us a step ahead of the wily virus in this protracted battle of wits.

References


Diabetic Dysglycemia During Lockdown an Unsung Journey (DDLJ) – An Online Survey

NK Singh, Prabhat Kumar Agrawal, Ashish Gautam, Nikhil Pursnani, Awanitka Parihar, Paramjeet

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Sir,

We did an online survey among physician and endocrinologist to know the reasons of their patients for diabetic dysglycemia during lockdown. This online survey was conducted from 26th June 2020 to 06th July 2020. A self designed questionnaire was prepared and shared with physicians/endocrinologist via WhatsApp/email to know the ways people are coping with their diabetes during lockdown. Informed consent was obtained from participants and it was disclosed that the identity will be kept confidential and data will be used for research purpose. The questionnaire was mainly focused on reasons of diabetic dysglycemia during lockdown (Table 1). Total 161 Physician/Endocrinologist participated in this survey but 3 responses were incomplete therefore responses of only 158 participants were analyzed.

We did the analysis which was provided by treating physician/endocrinologist comparing the pre and post lockdown blood sugar level and HbA1c(if possible) of the patients. Out of the 158 responses, 46.8% considered the unavailability of Insulin and OHA’s, 73.4% patients were unable to contact their physician, 55.7% patients found difficulty in buying a glucometer and test strips for monitoring their blood sugar levels. 45.6% of patients considered that during lockdown they found difficulty to get diabetic diet. Majority of the patients 86.1% found the decline in physical activity to be the reason for diabetic dysglycemia. 92.4% patients found over eating/improper diet to be the reason for the poor control of blood sugar levels. This is because staying at home with sedentary lifestyle, frequently munching most of the times made them eat more. A vast majority (91.1%) of patients considered the stress due to various reasons such as their work or the fear of the pandemic to be a reason for their insomnia and anxiety which ultimately caused Diabetic dysglycemia. Due to the closing of pathology centre 50.6% of patients not able to monitor their glucose. 77.2% patients found that COVID panic created by social media was the cause of dysglycemia. 72.2% of patients had no money to buy their drugs/glucometer and test strips due to loss of job. Many respondents concluded that it was multi-factorial.

Few other reasons as stated by the patients for dysglycemia are loss of interest in maintaining health, indoor life for long periods, indiscipline in life, non-compliance for drugs/food, due to ineffective Insulin due to loss of cold chain maintenance, lack of motivation, unexpectedly long lockdown, patient education, natural calamities, social stigma, over controlling of administration to the public safety, no moderation of alcohol intake etc., depression, monotony, lack of drive, preoccupied with COVID news & dwindling source of income, just worries of losing jobs how to earn daily bread and butter and the misbehavior by police, lack of education regarding SMBG and guidance of doctor during lock down also of panic, change in sleep/wake cycle, priority change, more attention to corona / supply of essentials leading to less attention on diabetes and other health issues.

In India nationwide lockdown was implemented on March 25, 2020 in

Table 1: Reasons of dysglycemia

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Non availability of drugs/insulin</td>
<td>74 (46.8%)</td>
<td>84 (53.2%)</td>
</tr>
<tr>
<td>2.</td>
<td>No consultation/contact from physician</td>
<td>116 (73.4%)</td>
<td>42 (26.6%)</td>
</tr>
<tr>
<td>3.</td>
<td>Non availability of glucometer strips</td>
<td>88 (55.7%)</td>
<td>70 (44.3%)</td>
</tr>
<tr>
<td>4.</td>
<td>No exercise/physical activity</td>
<td>136 (86.1%)</td>
<td>22 (13.9%)</td>
</tr>
<tr>
<td>5.</td>
<td>Over eating/improper diet</td>
<td>146 (92.4%)</td>
<td>12 (7.6%)</td>
</tr>
<tr>
<td>6.</td>
<td>Due to non availability of diabetic diet</td>
<td>72 (45.6%)</td>
<td>86 (54.4%)</td>
</tr>
<tr>
<td>7.</td>
<td>Due to stress/anxiety/insomnia</td>
<td>144 (91.1%)</td>
<td>14 (8.9%)</td>
</tr>
<tr>
<td>8.</td>
<td>Due to closing of pathology centre</td>
<td>80 (50.6%)</td>
<td>78 (49.4%)</td>
</tr>
<tr>
<td>9.</td>
<td>Due to social media panic</td>
<td>122 (77.2%)</td>
<td>36 (22.8%)</td>
</tr>
<tr>
<td>10.</td>
<td>Due to no work/no money for drugs</td>
<td>114 (72.2%)</td>
<td>44 (27.8%)</td>
</tr>
<tr>
<td>11.</td>
<td>Any other reason</td>
<td>Mentioned in text</td>
<td></td>
</tr>
</tbody>
</table>
order to limit the spread of the disease. In this first of its kind survey, it showed substantial increase in hyperglycemia during lockdown. Measures we must take to limit the spread of the virus lead to big changes to the way we live our lives. It is very important to focus without neglecting the comorbidities facilitating the virus related morbidities and mortality. Uncontrolled Diabetes Mellitus has been as one of the important and major risk factors for the mortality in patients with COVID-19.1

Therefore it is of paramount importance to achieve as well as maintain good glycemic control for short as well as long term benefits during this pandemic.2 Common factors responsible for dysglycemia during lockdown are no contact from physician, not doing any exercise/physical activity, overeating/improper diet, stress/anxiety/insomnia and social media panic in this survey. Another factor responsible for dysglycemia emerged from this survey was irregular/limited supply of medications/glucometer or access to pathology lab. However this situation may be poorer in smaller towns or suburban areas.

In our knowledge most probably this is first survey to know the causes of diabetic dysglycemia during lockdown and COVID pandemic amongst physician and endocrinologist.

References

Hyperhomocysteinemia a Independent Risk Factor for Acute Ischemic Stroke in South Kerala: A Case Control Study

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1. Assistant Professor of Biochemistry, Government Medical College, Ernakulam, Kerala; 2. Professor & Head of Neurology, Government Medical College, Thrivunanthapuram, Kerala; 3. Professor & Head of Biochemistry, Government Medical College, Kozhikode, Kerala

Sirs,

We do not know if hyperhomocysteinemia (HHcy) is an independent risk factor for stroke in southern Kerala. A case-control study was conducted with 70 subjects in each arm: neuroimaging confirmed ischemic stroke survivors one to six months after the ictus between the ages of 45 and 65 years and age and gender-matched control subjects without stroke. The recruitment started after the approval from Institutional ethics committee (IEC No.05/30/2010/ MCT). In addition to the demographic characteristics, and conventional risk factors for stroke, we estimated the fasting plasma homocysteine (Hcy) using Globe Diagnostics Homocysteine Enzymatic test kit based on a series of enzymatic reactions causing a decrease in absorbance value due to NADH Oxidation to NAD+. The statistical analysis was performed using SPSS version 17.0 for windows. Continuous variables were expressed as mean and standard deviation or median and interquartile ranges. Differences in proportion were tested by the chi-square test or Fisher’s exact test. T-test and ANOVA compared group means and a p-value of <0.05 was considered significant. In multivariate analysis, the multiple logistic regression method was used to select independent variables for ischemic stroke.

There was a significant difference in the proportion of patients with HHcy between controls [4(5.7%)] and stroke cases [66(94.3%)]. The plasma levels of Hcy were higher among the cases [20.2 (3.9) µmol/L] than among the controls [10.4(3.4) µmol/L] (p<0.001). The Hcy levels correlated with the NIHSS score (Pearson correlation coefficient r = 0.692 p<0.001). When adjusted for age, sex, smoking, diabetes mellitus and hypertension, for every 1µmol/L increase in homocysteine, homocysteine was an independent risk factor in ischemic stroke. Hcy levels also correlated with LDL -C levels (Pearson correlation r=0.298 p<0.001). Hcy levels >15 (µmol/L) were associated with higher LDL cholesterol levels (p=0.004). Comorbidities like hypertension, diabetes mellitus, hypercholesterolemia, elevated LDL cholesterol and hypertriglyceridemia were higher in stroke patients than controls. Logistic regression showed that HHcy with an odds ratio of 2.30 (95% CI, 1.4 - 3.8) (p-value <0.001) and elevated LDL cholesterol with an odds ratio 1.1 (95% CI 1.03, 1.18) to be independent risk factors for ischemic stroke.

A nested case-control study involving 864 Japanese men and women has shown high Hcy levels associated with the increased risk of stroke, specifically ischemic stroke and lacunar infarction.3 Kalita et al., showed Hcy concentration to correlate with the Vitamin B12 levels and, 41.4% of their patients were vegetarian.4 Our study’s limitation is that we did not include the participants’ nutritional status and did not assess the association between folic acid, vitamin B12 and homocysteine. Hcy is an endothelial toxin, and hyperhomocysteinemia (HHcy) (>15 micromole/L) is associated with small vessel disease (SVD) particularly lacunar infarcts and leukoaraiosis.5 A recent population-based primary prevention trial among patients with hypertension showed benefit with folic acid supplementation among high-risk group patients with low platelet count and HHCy.4

References

Perceived Stress among Healthcare Workers in COVID-19 Pandemic

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2. Sir,

The COVID-19 pandemic has put immense pressure on all the healthcare resources and workers worldwide. When all the citizens were supposedly at homes, doctors, nurses, cops and some unsung heroes were working tirelessly in the frontline. Long duty hours wearing personal protective equipments, fear of getting
Table 1: Comparison of PSS score between HCW and NHCW

<table>
<thead>
<tr>
<th></th>
<th>Healthcare workers (n=115)</th>
<th>Non-healthcare workers (n=100)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress severity (PSS) wise distribution</td>
<td></td>
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<tr>
<td>Mild (1-13)</td>
<td>15.65%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Moderate (14-26)</td>
<td>78.26%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Severe (27-40)</td>
<td>6.09%</td>
<td>3%</td>
<td></td>
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<tr>
<td>Gender wise PSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18.38±5.31, n=87</td>
<td>12.16±5.20, n=42</td>
<td>P=0.003</td>
</tr>
<tr>
<td>Female</td>
<td>15.96±3.83, n=28</td>
<td>13.45±5.96, n=58</td>
<td>P=0.887</td>
</tr>
</tbody>
</table>

infected and being a source of infection for family members could lead to significant stress and anxiety among the healthcare workers. The Perceived Stress Scale (PSS) developed by Sheldon Cohen in 1983 is a popular tool used to understand how different situations affect our feelings and our perceived stress.1

We conducted a cross-sectional observational study in August-September 2020 at Government Medical College, Kota to compare the perceived stress among healthcare workers, who had worked in COVID dedicated hospital in past 1 month, and non-healthcare workers, randomly selected people not closely related to medical profession from general population, using perceived stress scale. Subjects who had suffered from any major illness over the past one month and those with pre-existing psychiatric illness were excluded. 215 subjects including 115 healthcare workers (90 doctors and 25 nursing staff) and 100 non-healthcare workers were assessed. Proportion of healthcare workers under low (PSS 1-13), moderate (PSS 14-26) and severe (PSS 27-40) stress was 15.65%, 78.26% and 6.09% respectively while that of non-health care workers was 57%, 40% and 3% respectively. The mean PSS score was significantly higher among healthcare workers (17.79 ± 5.08) as compared to non-healthcare workers (12.91 ± 5.67) (p=0.00001). The mean PSS score of male healthcare workers (18.38 ± 5.31, n=87) was higher than females ones (15.96 ± 3.83, n=28) (p=0.0034). In both the groups no subject reported the PSS score of zero indicating 100% prevalence of stress in both the groups. The perceived stress however did not differ with age (Table 1). Among HCWs, the mean PSS score of doctors was 18.21 ± 5.40 and that of nursing staff was 16.28 ± 3.42 (p = 0.15).

The prevalence of moderate to severe stress is significantly high in healthcare workers (84.4%) as compared to non-health care workers (43%). Aiyer A et al.2 also found an elevated stress level (PSS-4 of >8) in 49% healthcare workers (n=569) during COVID-19. High stress levels among healthcare workers could lead to decreased work efficiency, prescribing errors, interpersonal relationship difficulties, sleep disturbances, mood disturbances, depression, anxiety and even suicide. We recommend routine screening of psychological problems in COVID-19 healthcare workers along with early interventions at their work place to alleviate their stress and promote mental well-being.

References


Additional Course of Dexamethasone Therapy in Oxygen Dependent COVID-19 Patients

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As glucocorticoids may flare up infections, they are best avoided unless the inflammatory response to infection is deleterious as in the case of tuberculosis meningitis. In a similar vein, low-dose dexamethasone was tested in the RECOVERY trial and has shown benefits in moderate to severe COVID-19. Specifically, a choice of a low-dose for ten days was chosen, as the aim of therapy was to reduce the degree of exuberant inflammation and not complete immunosuppression with steroid pulse.1 However, the option for an additional course of low-dose dexamethasone therapy beyond ten days in patients who continue to be oxygen dependent needs to be evaluated. We want to share our experience of dramatic response observed in selected severe COVID-19 patients in whom an additional brief course of dexamethasone 6mg daily was given after a brief interruption of about 48 hours (Table 1). The additional course of dexamethasone may shorten the duration of oxygen therapy, which is highly pertinent when the capacity of health care systems is overwhelmed.

Hyponxia manifests only when the cardiopulmonary reserve is compromised by COVID-19 related tissue injury, which may take the form of direct viral-mediated injury, antiviral inflammatory response-related tissue injury, thromboembolic manifestations, or secondary infections. In COVID-19, there is a delayed but robust antiviral response, with release of a significant amount of proinflammatory cytokines (IL-1, IL-6, TNF alpha), which may cause hypoxia and multiorgan dysfunction. However, unlike other causes of cytokine storm, in severe COVID-19, the degree of IL-6 elevation is lesser, IFN-gamma levels are normal, the occurrence of thromboembolic events is more and lymphopenia is observed.2 In addition to cytokine storm, another major determinant of disease severity is widespread endotheliitis which manifests as endothelial viral inclusion bodies, vascular monocyte infiltration, and microvascular thrombosis (Immune thrombosis).3,4 Occasionally, persistent inflammation may manifest as organizing pneumonia.5 Thus, the substantial benefits of dexamethasone in COVID-19 may be explained by the generalized anti-inflammatory activity that curtails both direct injury from cytokine storm and the indirect injury of endotheliitis as compared to therapies targeting specific cytokines wherein the response is minimal, if not,
inconsistent.

However, starting dexamethasone in patients without hypoxia is not beneficial.1 Steroids also delay the healing process. In all our patients, dexamethasone was restarted after about two days. It is plausible that this brief period of interruption along with subsequent dexamethasone therapy would have tipped the balance of cytokine milieu in favour of rapid recovery.

Hence, we feel that for patients who remain oxygen-dependent, with evidence of inflammation (persistently high CRP, ground glass opacities or peribronchial consolidation in HRCT lung) and lesser chances of infection, an additional course of dexamethasone therapy beyond ten days should be considered.

### References


<table>
<thead>
<tr>
<th>Course of Steroid Therapy</th>
<th>Initial 10-day course of</th>
<th>Off steroid therapy</th>
<th>Additional course of daily 6mg</th>
<th>dexamethasone therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
<td>D5</td>
<td>D10</td>
<td>2 to 3 days*</td>
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<tr>
<td>P1 (A-a)DO₂</td>
<td>58</td>
<td>552</td>
<td>454</td>
<td>460</td>
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<tr>
<td>CRP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18</td>
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<tr>
<td>P2 (A-a)DO₂</td>
<td>48</td>
<td>332</td>
<td>121</td>
<td>480</td>
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<tr>
<td>CRP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>P3 (A-a)DO₂</td>
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<td>148</td>
<td>152</td>
</tr>
<tr>
<td>CRP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
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<td>46</td>
<td>528</td>
<td>467</td>
<td>477</td>
</tr>
<tr>
<td>CRP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
</tr>
</tbody>
</table>

After an initial 10-day course of dexamethasone, four patients who remained oxygen dependent were given an additional brief course of dexamethasone in view of elevated CRP with high resolution computed tomography (HRCT) lungs showing ground-glass opacities. One patient improved in 48 hours, and the other three patients improved in 72 hours of steroid therapy. P1-4 refers to patients 1 to 4. *average (A-a) DO₂ gradient during the period when the patient was off steroids.*
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