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EDITORIAL

Post COVID-19 Mucormycosis in the Second Wave—Realities, Uncertainties and Myths

Rajeev Soman¹, Ayesha Sunavala²

After our last editorial on COVID-19-associated mucormycosis (CAM) in the Jan 2021 issue of this journal, there has been an exponential rise in CAM from nearly every part of the country. Although the true incidence is difficult to estimate given the rampant second COVID-19 surge and the ambiguity of a true denominator, the socioeconomic impact on the population and the health system has been devastating. The sensationalized misnomer of ‘black fungus,’ although taxonomically incorrect, paints a symbolic picture of the diabolical nature of invasive mucormycosis.

Myriad hypotheses have been generated for the inordinate number of cases in our country. Higher fungal spore counts in our tropical climate especially around heaps of garbage, construction of makeshift COVID 19 facilities, contamination of oxygen supplies, respiratory equipment, reused face masks and zinc supplements are some of the theories that have been deliberated upon inconclusively. The most convincing risk factors appear to be unrecognized, uncontrolled diabetes compounded by the indiscriminate use of steroids at high doses for prolonged periods, even in non-hypoxic patients. Such patients have spent most time in the community with all the heavy exposures that go with it. These cases may be considered as ‘Never in the frying pan, straight into the fire.’

A multicenter study of 187 cases of CAM after the first COVID wave, noted a 2.1-fold increase in the cases of mucormycosis during the peak COVID-19 period as compared to pre-COVID-19 time. Uncontrolled diabetes was noted in 62.7% of cases. COVID-19 was the only risk factor in 32.6% CAM patients among whom 78.7% received glucocorticoid treatment for COVID-19 management. Inappropriate glucocorticoid use was independently associated with late CAM.¹ Lymphocytopenia with prolonged depletion of T cell subsets is an important feature in COVID-19.² This is a known risk factor for opportunistic infections including invasive mucormycosis. Additionally hyperglycemia due to affection of the β-cells of the pancreas by SARS-CoV-2 may be a contributing factor.³

While rhino-orbito-cerebral involvement has been the most common manifestation even in pre-COVID times,⁴ dental pain, loosening of teeth and involvement of the jaw appear to be common features of CAM observed in the present outbreak.¹ Pulmonary CAM is less common, appears to affect patients with severe COVID 19 infection and poses significant diagnostic difficulties. Mixed infections with septate and aseptate moulds, both in the sinuses and lungs have also been reported.⁵

Radical and often repeated surgical debridement has been the cornerstone of management for invasive mucormycosis. The benefits appear to be time sensitive and have dramatically improved survival in various studies, albeit limited by their observational, retrospective nature and small numbers.⁵ The aggressive approach to remove necrotic tissue and afford better antifungal penetration and oxygenation to the affected sites, forms the justification for radical surgery although resulting in mutilation and functional impairment. The advent of more effective treatment options like liposomal Amphotericin B (LAmB) and the newer oral Azoles, have emboldened treating teams to sometimes steer away from aggressive surgical approaches. Functional endoscopic sinus surgery for both tissue diagnosis and thorough debridement of sino-nasal disease remains the mainstay of surgical management. However, in cases with limited orbital involvement and preserved vision, medial orbital wall resection with orbital decompression and retrobulbar Amphotericin B (AmB) injections have shown initial encouraging results. Organ and tissue sparing approaches are difficult decisions, requiring multidisciplinary expertise and close monitoring. Needless to emphasize that orbital exenteration is warranted in cases with extensive initial orbital involvement or with worsening of disease after attempted conservative management.⁶

AmB has been grand-fathered into the treatment of invasive fungal infections when there was no other drug available. All subsequent drugs have been compared to this standard. Over the years, AmB deoxycholate has been replaced by lipid formulations, in particular LAmB, in resource rich settings. Although LAmB is an advance in overcoming challenges of toxicity and penetration, the expense and need for intravenous treatment remains an issue. In resource limited settings as also in the current situation, where LAmB is scarcely available, clinicians have to re-learn the best ways to use AmB deoxycholate and certain other products about which adequate data is hard to find.

Better outcomes is of course an unmet clinical need and the question arises whether the new Azoles can meet expectations as initial or step-down treatment for mucormycosis. Some Mucorales species have high minimum inhibitory concentrations (MICs) to AmB or to the newer Azoles indicating a degree of intrinsic resistance. AmB is definitely not a drug of choice for Aspergillus which appears as a co-infection in some patients. Additionally, the penetration of AmB into certain sites like CNS is suboptimal. The inability to have intravenous (IV) to oral switch, toxicity, cost and prolonged duration of treatment are other shortcomings.

Isavuconazole has a labelled indication for Mucormycosis on the basis of the VITAL trial.⁷ However it involved relatively small number of patients, was a single arm, open label

¹Jupiter Hospital Pune, Maharashtra; ²Hinduja Hospital, Mumbai, Maharashtra

As regards transitioning treatment from AmB to the Azoles, it has been recommended as step down in patients who have improved and as step up (salvage therapy) in those who have not. This creates uncertainty in judging the exact place of the Azoles in treatment.

Combination treatment of AmB and Azoles is fraught with even greater uncertainties. There is no plausible reason for synergy, but pathogen coverage could be widened by a combination. If indeed there is a benefit of combination, it would be best realized in patients at the highest risk of poor outcome. However in order to demonstrate superiority, a very large randomized trial is needed. This could have been done in this epidemic, which seems to be a lost opportunity. The role of the second drug may not be for synergy, but can be viewed as that of a supporting drug due to interruptions in AmB therapy caused by various factors including toxicity, cost and erratic availability.

Given the stark realities of drug treatment in the current state, the role of surgery and adequate debridement assumes even more importance. Adjuvant therapy with Caspofungin, hyperbaric oxygen, statins, aspirin and deferasirox also needs to be considered more seriously. However there are issues of expense, availability, uncertain efficacy and toxicity with these agents.

The question of prophylaxis for mucormycosis often comes up considering the large number of cases seen at tertiary care hospitals. However, this is most likely a referral bias as the denominator is unknown. We do not think routine prophylaxis is advisable at this stage. This is based on our unpublished observation of low incidence (about 0.5 to 1%) of mucormycosis developing in COVID-19 cases that were admitted to hospitals where we work. For perspective, prophylaxis for mould infections is recommended for certain groups of hematologic-malignancy patients in whom the incidence is about 6%. The lack of sufficient supplies of these drugs also have to be factored in while deciding about offering prophylaxis. It may be far more important to emphasize discretion in the use of steroids, and monitoring and treating hyperglycaemia as preventive strategies.

In conclusion CAM appears to be a consequence of misinformation, nonchalance and uncontrolled access to drugs used to treat COVID-19, especially steroids. Emphasis on awareness of early warning signs in both patients and care givers is important. Multicentre randomized studies are urgently needed to overcome the myriad uncertainties in managing this difficult mould infection.

References

In Hypertension Management

Olsertain
Olmesartan Medoxomil 20 mg & 40 mg
SURE-SHOT BP Drop

In T2DM patients

Glimy
Glimepiride 1/2/3/4 mg Tablets

Sureshot BP drop – Nearly 80% patients treated with Olmesartan 40 mg reached target blood pressure < 130/80 mm Hg.


T2DM: Type 2 diabetes mellitus
BP: Blood pressure
Clinical Study of Use of Remdesivir and Tocilizumab in Severely Ill COVID-19 Patients

Vishal Gupta¹, Sushrut Ingawale²*, Amit Bhondve³, Wasim Khot⁴, Santosh Salagre⁵, Archana Sonawale⁶, Kavita Joshi¹, Meghna Vaidya¹, Smrati Tiwari¹, Kaustubh Salagre¹, Yogesh Pawade⁶, Juhi Kawale⁷, Nilakshi Sabnis⁷

Abstract

Introduction: Remdesivir and Tocilizumab are two experimental drugs used in severely ill COVID-19 patients. Various clinical trials studying these drugs are giving conflicting results. Our aim is to study these two drugs and share the experience in our setting.

Methods: Our Study is a retrospective analysis of Clinico-laboratory details and outcome of three groups of patients who were given either (i) Remdesivir or (ii) Tocilizumab or (iii)both Remdesivir and Tocilizumab. We compared the outcome of these patients with other patients who did not receive either of these drugs, when it was not available or not introduced as experimental drugs earlier in treatment guidelines.

Results: Out of a total of 521 patients, in the above three groups who received either or both Remdesivir or Tocilizumab, 334 survived. Out of 214 patients who did not receive any of the two drugs only 74 survived. The outcome was better individually for all the three groups of patients receiving either or both of the drugs as compared to neither of the drugs. (p < 0.01)

Conclusion: Remdesivir and Tocilizumab were useful drugs in treatment of severely ill COVID-19 patients as compared with the patients who did not receive any of the above drugs.

Introduction

Over time various drugs have been proposed as potential treatment for COVID-19; These include: (i) Hydroxychloroquine,¹ (ii) Lopinavir-Ritonavir,² (iii) Favipiravir, Remdesivir and Ribavirin; nucleoside analogues which may block viral entry, cause lethal mutagenesis and inhibit nucleotide synthesis;³ (iv) Corticosteroids, by their anti-inflammatory action;⁴ (v) Tocilizumab, Siltuximab, Sarilumab; anti-Interleukin-6 agents, by preventing T cell and macrophage activation to manage cytokine storm complications;⁵ (vi) Interferon, to inhibit viral replication;⁶ (vii) Convalescent serum,⁷ (viii) Vitamins C and D, by boosting general immune system functioning;⁸ and (ix) BCG vaccine, an anti-tuberculosis vaccine used in children, by an unknown mechanism in COVID-19.⁹

Many of the above mentioned drugs now are no longer recommended even as experimental therapies as there is enough evidence to suggest lack of benefit and in some cases potential harm. Various centers and societies have used and are continuing to use antivirals like Remdesivir and IL-6 antagonists like Tocilizumab. There has been a conflicting evidence from various studies about the benefit of these drugs The time of introduction of Remdesivir and Tocilizumab as potential therapy was not same. Tocilizumab was introduced earlier. Also availability and supply of these two drugs was not constant. Thus we were able to form three different treatment groups of severely ill Covid-19 patients who received: (i) Remdesivir, (ii) Tocilizumab, and (iii) Both Remdesivir and Tocilizumab. The outcome of these three groups was compared with the outcome of a fourth group of severely ill patients who had not received either of the drugs earlier (when these drugs were not available or not included in the treatment guidelines.)

Materials and Methods

Our study was a single-center, retrospective, observational study conducted in COVID wards of a public tertiary care hospital. Patients admitted between 1st June, 2020 to 30th September, 2020 who have had an outcome (discharge or death) and satisfying the inclusion and exclusion criteria were included by complete enumeration. Inclusion criteria were: (i) Laboratory confirmed COVID-19 adults (Age > 18 years), (ii) SpO2 less than 94% (Severe and Critical Category as per NIH Clinical spectrum for SARS-CoV-2 infection),¹⁰ (iii) Received any of the following drugs alone or in combination: Remdesivir, Tocilizumab. Suspected COVID-19 patients (but RT-PCR negative report), Positive patients with SpO2 94% and above, Pregnant/Lactating patients and patients with Mortality within 24 hours of admission were excluded. A total of 521 patients were included. Study commenced only after Institutional Ethics Committee (IEC) approval [Ref no: EC/OA-132/2020] and we had sought CTRI registration [Reg no: CTRI/2021/01/030341].

Due to unavailability of similar studies in the past it was decided to

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A total of 521 patients satisfied the above criteria. The available clinical and laboratory details of these patients were retrieved from the indoor case papers and electronic records. The data was recorded in a case record form. A case record form was designed which included the following details: (1) Demographic details i.e. age, gender, comorbidities; (2) Symptomatology; (3) Vitals: Heart rate, respiratory rate, blood pressure, oxygen saturation (SpO2 by Pulse Oximetry); (4) Laboratory values: Complete hemogram, liver and renal function tests, random blood sugar, CRP etc. (5) Oxygen therapy: mode of oxygenation, SpO2, (6) Use of Remdesivir and Tocilizumab. (7) Other Treatment details. (8) Data related to monitoring change in WHO ordinal scale like: mode of oxygen therapy, need for renal replacement therapy, need for vasopressors.11

TOOLS: World Health Organization Ordinal Scale Score (WHO- OSS)11 for clinical improvement is a freely available public domain 9 pointer scale ranging from scores 0-8. The Scores allotted are as follows:

0’ - for the uninfected (no clinical or virological evidence of infection),

‘1’ for the ambulatory infected patients with no limitation of activities,

‘2’ for the ambulatory infected patients with limitation of activities,

‘3’ for the hospitalized patients with no oxygen therapy.

‘4’ for the hospitalized patients with oxygen therapy by mask or nasal prongs,

‘5’ for the hospitalized patients with non-invasive ventilation or high-flow oxygen,

‘6’ for the hospitalized patients with intubation and on mechanical ventilation

‘7’ for the hospitalized patients with mechanical ventilation plus additional organ supports: pressors, renal replacement therapy, ECMO

‘8’ for the death of a patient.

Outcome was measured in terms of:
(1) Death or Discharge, (2) Duration of Hospitalization, (3) Duration of Oxygen therapy and (4) Duration to bring an improvement in the WHO-OSS.

Survival outcome was compared with existing data of 214 severely ill Covid positive patients of the time (23rd March, 2020 to 31st May, 2020) when both these drugs were not available for treatment.

Statistical Analysis

The data was compiled, tabulated using Microsoft Excel 2010. Statistical analysis was conducted with SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Results for Quantitative Variables like age, duration of hospitalisation, duration of oxygen therapy, WHO- OSS score, duration between Admission and initiation are presented with mean (±SD), median(IQR). Results for Qualitative Variables like Gender, comorbidities, outcome of patients, no of patients in each group, number of patients on various O2 therapies, need of vasopressors are presented with frequency and percentage. The association between outcome and drugs used and need of vasopressor is calculated using the Chi-Square test. After establishing the Non-Normality of data with Shapiro Wilk test, comparison between all the three treatment groups is done using Kruskal Wallis H test. The comparison between two treatment groups is done using Mann-Whitney U Test.

The binary logistic regression analysis was conducted to predict the factors predicting the outcome with all the predictor variables by backward elimination method where 12 steps were taken to reach the current model at every step variables with p value <0.1 was omitted. For binary logistic regression and comparative analyses, odds ratios (OR) and 95% confidence intervals (CI) will be reported, with p-values; a p-value <0.05 was considered statistically significant.

Results

Patients demography: (Table 1)

A total of 521 patients had received either Tocilizumab/Remdesivir or both. We compared them with severe covid patients admitted earlier in ICUs when these drugs were not available. Most of the patients were >55 Years (54.1 %) with median age (56.18 years). More than 62% of the patients were males. Diabetes (41.9%) and DM with HTN (23.03%) were common comorbidities in all the patients (Table 1). Demographics of all the groups are shown in Table 1.

Outcome (Discharge vs Death): (Table 2)

Out of 521 patients who received either/both Remdesivir and/or Tocilizumab 334 survived. The discharge percentage amongst the patients without any of these drugs was 34.6 % whereas amongst the patients who received Remdesivir, Tocilizumab and both are 66.4%, 80.6%, 47.4% respectively. The association as compared with none of the drugs was statistically significant (Table 2).

Oxygen status: (Table 3)

Oxygen requirements of all the groups were noted and classified as per WHO OSS criteria. Details in Table 3. Only 12 patients in the discharge group had presented without oxygen for admission. 141 patients were admitted with nasal prongs or face masks, 178 admitted with either NRBM or HFNC. 3 patients in the discharge group had come intubated, who were successfully
exhusted. Only 5 patients required supplemental oxygen on discharge while 329 patients were discharged without oxygen.

**Duration of Hospitalization, Oxygen therapy and Change in WHO-OSS:** 
(Table 4)

As shown in Table 4 we used Kruskal Wallis H Test comparison between all three treatment groups and duration of hospitalization and oxygen therapy and WHO-OSS. Before the drug initiation all the patients were comparable on WHO-OSS scale (p>0.1). (Median, IQR: 5.0,1.0). The most important observation which is seen in this study was statistically significant variation in the hospital stay in ICU and out of ICUs amongst all three treatment groups. The duration of hospitalisation was maximum in Tocilizumab Group (47,15) whereas it was 14 and 10 days in only Remdesivir and Remdesivir and Tocilizumab groups respectively. (14,10 and 10,12.8). The duration of Oxygen therapy (days) was also significantly different between all three groups. (14,10 & 7.5,10)and no statistically significant variation which is seen in this study was statistically significant variation in the hospital stay in ICU and out of ICUs amongst all three treatment groups. The duration of hospitalisation was maximum in Tocilizumab Group (47,15) whereas it was 14 and 10 days in only Remdesivir and Remdesivir and Tocilizumab groups respectively. (14,10 and 10,12.8). The duration of Oxygen therapy (days) was also significantly different between all three groups. (14,10 & 7.5,10)and no statistically significant variation which is seen in this study was statistically significant variation in the hospital stay in ICU and out of ICUs amongst all three treatment groups. The duration of hospitalisation was maximum in Tocilizumab Group (47,15) whereas it was 14 and 10 days in only Remdesivir and Remdesivir and Tocilizumab groups respectively. (14,10 and 10,12.8). The duration of Oxygen therapy (days) was also significantly different between all three groups. (14,10 & 7.5,10)and no statistically significant variation which is seen in this study was statistically significant variation in

**Need for Vasopressors:** (Table 5)

Of 26 patients requiring vasopressors only 8(2.4%) survived while 326(97.6%) out of 495 patients not requiring vasopressors survived, indicating significant correlation.

**Factors Predicting Outcome:** (Tables 6, 7 & 8)

On performing the univariate analysis, it was decided to predict the factors responsible for survival amongst three drug groups differently. All the variables were used to predict the model. The binary logistic regression analysis is conducted by Backward elimination method where 12 steps were taken to reach the current model. At every step variables with p value <0.1 was omitted. It was a statistically significant model (Remdesivir, p=0.792, Tocilizumab, p=0.945, Remdesivir and Tocilizumab, p=0.913) by Hosmer-Lemeshow goodness of fit test.

Amongst the patients who received Remdesivir (n=416) it was observed that the odds of discharge of the males are 0.59 times less than that of the females patient (OR=0.59, P=0.04, 0.35-0.99). Age was found to be significant predictor patients with age <55 Years had 2.9 times more likely to get discharge. (OR=2.976, P<0.001), The odds of discharge are 0.59 times lesser, if TLC before drug initiation is >11.0 × 10 9/L. Oxygen intervention at admission was the most determining factor for discharge of the patient. Comparing with patients on Invasive ventilation, the odds of discharge are 34 times higher amongst the patients who required Face mask or nasal prongs [OR=34.3, CI (5.26-225) P<0.001], 6.08 times higher amongst the patients who required NRBM or HFNC [OR=26.1, CI (1.14-32.6) P<0.001]. The patients who came off o2 were not found to have significant predictor value probably because of low sample size in that group (n=11).

Amongst the patients who received Tocilizumab (n=31) none of the factors found to be predicting the discharge (Table 7).

Amongst the patients who received both Remdesivir and Tocilizumab (n=76) only Respiratory Rate (RR) at admission was found to be positive. The odds of discharge were 1.27 times higher if RR at admission is <20/min. (OR=1.27, CI (1.05-1.54), p<0.01) (Table 8).

**Discussion**

In our study, on comparing the outcome of the critically-ill patients
who had received either Remdesivir or Tocilizumab or both with those who had not received any of these drugs (prior to availability of these drugs), significant improvement was observed (p < 0.001). Positive results were also seen with the individual groups receiving Remdesivir only, Tocilizumab only and both Remdesivir and Tocilizumab.

In our study the median age of patients was (56,18) with male predominance (62%) with diabetes mellitus (218) and hypertension (221) being the most common comorbidities. 76.5 % of patients had at least one comorbidity. The overall survival was 64.1%. In a similar Indian study, the demographic data on age (58+-13.2) and Gender (70.8%) was comparable, nevertheless the at least 1 comorbidity data was much lower (40.56%) as compared to (76.5%) in our study and survival amongst the critical patients was 52.3%.\(^1\)

Various randomized clinical trials showed varying outcomes with Tocilizumab. In the COVACTA trial\(^1\) involving hospitalized patients with severe Covid-19 pneumonia, Rosas et al stated that the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days. However, REMAP-CAP trial\(^2\) investigators showed that in critically ill patients with Covid-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab improved outcomes, including survival. RECOVERY trial\(^3\) had emphatically proved that glucocorticoids improve outcome. However, in COVACTA it was noted fewer patients received glucocorticoids. In EMPACTA trial\(^4\) Salama et al showed treatment with tocilizumab in patient not receiving mechanical ventilation reduces the likelihood of progression to mechanical ventilation but there was no impact on survival. In the randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) studying various treatment options, 4116 patients were included in assessment of tocilizumab, which included patients on corticosteroids also. It was noted that 621 (31%) of the 2022 patients allocated tocilizumab and 729 (35%) of the 2094 patients allocated to usual care died within 28 days. Also patients not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death.\(^3\) Thus this study shows improved survival and other clinical outcomes with Tocilizumab in addition to steroids usage. In our study out of 31 who received tocilizumab, 25 patients survived. None of the survived patients needed mechanical ventilation and were discharged without supplemental oxygen. Tocilizumab given at appropriate times can have better survival and reduced need for mechanical ventilation. However these patients also required oxygen therapy for longer time (47 days, median), maximum time to bring down WHO-OSS score (45 days, median), maximum time to bring down invasive ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death.\(^3\) Thus this study shows improved survival and other clinical outcomes with Tocilizumab in addition to steroids usage. In our study out of 31 who received tocilizumab, 25 patients survived. None of the survived patients needed mechanical ventilation and were discharged without supplemental oxygen. Tocilizumab given at appropriate times can have better survival and reduced need for mechanical ventilation. However these patients also required oxygen therapy for longer time (47 days, median), maximum time to bring down WHO-OSS score (45 days, median), and duration of hospitalization was also highest (50 days); which may be secondary to higher nosocomial infections in this group.

WHO Solidarity trial\(^5\) showed that death occurred in 301 of 2743 patients receiving remdesivir and in
303 of 2708 receiving its control (P=0.50) showing no survival benefit. Neither initiation of mechanical ventilation or duration of hospitalization was better as compared to control. Beidel et al in the ACTT-I trial9 showed improvement in the time to recover and also clinical improvement at the end of 15 days. This study also showed no mortality benefit. In our study, a total of 226 patients survived out of 414 who received Remdesivir without tocilizumab. The survival was statistically better than those who did not receive any treatment of these two drugs. (p<0.0001).

Patients in this Remdesivir group in our study required oxygen therapy for 12 days (median), and 12 days (median) to reduce the WHO OSS grade, which was shortest in all three groups. Total duration of stay was 15 days (median) for those who survived in the Remdesivir group. 11 patients in this group were on mechanical ventilation before initiation of Remdesivir, out of which only 2 survived. With acute shortage, inconsistent supply of Remdesivir and financial burden, need for Remdesivir in already mechanically ventilated patients needs to be studied further. As inferred from Binary regression, younger patients, no leukocytosis, better oxygen saturation and lower WHO-SS score on presentation fares better in Remdesivir group. For those who survived in this group, the median duration between Illness onset and Admission was 4 days (IQR=4days) and median duration between Admission and initiation was 2 days (IQR=4days). Thus, suggesting early initiation may be beneficial.

There is limited data globally on combined use of Remdesivir and Tocilizumab together. REMDACTA phase-III trial30 is underway comparing the use of Remdesivir with Tocilizumab and Remdesivir with placebo in severe COVID-19 pneumonia. In our study, in the third group of 76 patients who received both Remdesivir and Tocilizumab during the said period, 36 survived. As compared to the group who did not receive either of these drugs, p value was significant (p = 0.04) for survival. The combination has subsequently been used frequently and is in various protocols for management advised by various societies and task forces including the Maharashtra Task Force Guidelines dated 7th April, 2021. In our study, the median duration of hospitalization (15 days), median duration of oxygen therapy (12 days) and the median duration to reduce WHO-SS score (12 days) in patients receiving both Remdesivir and Tocilizumab, was significantly lower than compared to Tocilizumab alone (p<0.001). Thus, it may be better to use a combination of Antivirus and an anti-inflammatory drug rather than an anti-inflammatory drug alone.

Therefore we can say with our study giving Remdesivir and Tocilizumab can have better clinical outcome. However, a larger multi centric trial is needed. While administering these drugs it is noteworthy that the guidelines and protocols issued by government authorities are followed.

Our study had limitations being an observational retrospective study. No control group available due to guidelines recommending Remdesivir in all severe patients. Hence we have to use a retrospective control before introduction of these drugs. We could not correlate the outcome with inflammatory markers: CRP, LDH, IL-6 etc due to limited data. Further study would be essential.

Acknowledgement

We are grateful for the support of Dr. Hemant Deshmukh (Dean). Dr. Milind Nadkar (HOD & Academic Dean) thank the unprecedented support of the entire Department of General Medicine, the Residents, the Administration, the other departments working in COVID, the paramedical staff and other Healthcare providers of our hospital.

References

In high grade fever & pain

Nise
Nimesulide 100 mg tablets

Get well. Sooner...

STARTS ACTION WITHIN
15 MINUTES

References

Nise (Nimesulide Tablets 100mg)

Name of Medicine Product: NISE (Nimesulide). Dosage form and Strength: Each coated tablet contains: Nimesulide BP 100 mg Therapeutic Indication: In the short-term treatment of inflammatory conditions including joint disorders such as rheumatoid arthritis, osteoarthritis and post-operative painful conditions and fever. Dosage and Administration: The usual adult dose is 100 mg twice daily, orally, given in Special Precautions: Patients with renal impairment. Patients with renal impairment should use nimesulide with caution. Patients with severe renal impairment should preferably avoid using nimesulide. Patients with hepatic impairment. Nimesulide should not be administered in moderate to severe hepatic impairment. Use in Asthmatic Patients: As with any NSAID, caution should be exercised when using nimesulide in patients with bronchial asthma. Pregnant and Lactating Women: Safety and efficacy of nimesulide in pregnancy and lactation have not been established. Therefore, nimesulide is not indicated for use in pregnant and lactating women. Contra-indications: Known hypersensitivity to nimesulide. History of hypersensitivity reactions (bronchospasm, rhinitis, urticaria) to aspirin or other NSAIDs. Patients with active peptic ulcer disease. Patients with hepatic or renal impairment. Pregnancy and lactation. Precautions: Caution is advised when administering warfarin and nimesulide concurrently. Undesirable effects: Among the adverse events reported with nimesulide, the common ones are gastrointestinal disturbances (epigastric pain, heartburn, nausea, diarrhoea, vomiting), skin reactions (itch, pruritus) and CNS effects (dizziness, somnolence, headache). Nimesulide has been reported to cause hepatic adverse events, ranging from mild to moderate liver function to severe liver injuries including fatal hepatic failure in a few cases. Most of these patients were elderly women. It is reported that this adverse event appears to be idiosyncratic or immunological in nature. Overdose: No information is available on overdose with nimesulide.

Date: 30 Apr 2018

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Association of SARS CoV-2 Cycle Threshold (Ct) with Outcomes in COVID-19: Hospital-Based Study

Sonali Sharma¹, Arvind K Sharma², Gaurav Dalela³, Prahalad Dhakar⁴, Teja Veer Singh⁵, Vaseem Naheed Baig², Sudhanshu Kacker⁵, Raja Babu Panwar⁶, Rajeev Gupta⁶*

Abstract
Background and Objective: Burden of SARS-CoV-2 estimated by PCR cycle threshold (Ct) may have prognostic importance. To evaluate association of COVID-19 Ct with clinical features and outcomes we performed a hospital based study.

Methods: Successive virologically confirmed patients were recruited and demographic and clinical details recorded. Cohort was classified according to Ct into three: Group 1 >30.0, Group 2 25.0-29.9 and Group 3 <25.0. Descriptive statistics are presented.

Results: 873 adults (men 651, women 222) were enrolled. The mean age in men was 38.2±18y and women 41.2±19y. Group 3 patients were significantly older (42.4±19y) than Group 2(39.5±18) and Group 1(39.3±17y). Co-morbidities-hypertension, diabetes, obstructive lung disease- were more in Group 3 as were shortness of breath at admission and lymphopenia. In Group 3 vs. Group 2 and Group 1, the average time to virus negativity (9.8±4.1 vs 8.6±3.3 and 8.4±3.4 days) and duration of hospitalization (10.5±5.4 vs 9.8±3.7 and 9.5±3.3 days) were greater. Odds ratios and 95% confidence intervals (OR, 95% CI) in Groups 2 and 3 vs. Group 1 for oxygen requirement were 5.47(CI 2.98-10.07) and 4.48(1.69-11.91), non-invasive ventilation 3.43(1.47-8.05) and 9.81(2.93-32.76), and invasive ventilation 10.81(4.68-24.79) and 63.10(16.90-235.52) (p<0.001). Multivariate analyses showed that compared to Group 1, mortality was significantly greater in Group 2(OR 8.78, 1.95-39.63) and Group 3(OR 34.71, 7.01-171.78) and in Group 3 vs. Group 2(OR 2.27, 1.66-3.12).

Conclusions: Hospitalized COVID-19 patients with low SARS CoV-2 cycle threshold are older, have greater comorbidities and lymphopenia. They have greater need for oxygenation, non-invasive and invasive ventilation and have significantly greater mortality. Ct values provide important prognostic information.

Introduction
Nucleic acid amplification tests, such as real-time reverse transcription polymerase chain reaction (RT-PCR) for identification of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) in respiratory samples, are the investigations of choice for its diagnosis. This test allows qualitative as well as quantitative information of virus load. RT-PCR cycle threshold (Ct) values represent the number of amplification cycles required for the target gene to exceed a threshold level. The Ct values are inversely related to viral load and each 3.3 increase in Ct value reflects a 10-fold reduction in virus burden. It has been reported the highest viral loads are detected at the time of symptom onset and generally decrease within one to three weeks. It has also been suggested that the viral load of SARS CoV-2 may be important in disease transmission and prediction of disease severity.

Controversy exists regarding prognostic value of SARS-CoV-2 Ct counts. Previous studies involving other viruses have reported inconsistent association of viral load with disease severity and acute respiratory syndromes. Some studies in COVID-19 have also reported non-significant associations of viral load and illness severity. On the other hand, recent studies have reported significantly lower Ct values in patients with severe disease as compared to those with mild and moderate disease. A systematic review of clinical utility of Ct values in COVID-19 observed correlation between Ct value and disease severity in more than two-thirds of studies among hospitalized patients, although no correlation was shown in studies that included patients with COVID-19 who were not hospitalized. India has one of the largest burden of COVID-19, but almost no data are available on association of Ct level and disease burden. We analysed the association of COVID-19 RT-PCR Ct values with baseline clinical features and hospital outcomes in successive patients presenting to a dedicated COVID-19 hospital in India.

Methods
This is a hospital based prospective observational study conducted on patients with laboratory confirmed COVID-19 admitted at a 1200-bed dedicated COVID-19 government hospital from April to mid-September 2020. This hospital serves as covid-19 quarantine, isolation and treatment centre designated by the state government in Rajasthan, India. Initial data on patients have been reported earlier. The study has been approved by the college administration and
Table 1: Demographic and Clinical Characteristic of the Study Cohort

<table>
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<tr>
<th>Variables</th>
<th>Men (n=651)</th>
<th>Women (N=222)</th>
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<tr>
<td>Don’t know</td>
<td>160 (24.6)</td>
<td>65 (29.3)</td>
<td></td>
</tr>
<tr>
<td>Medical co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>131 (20.1)</td>
<td>47 (21.2)</td>
<td>0.74</td>
</tr>
<tr>
<td>Asthma</td>
<td>36 (5.5)</td>
<td>15 (6.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>66 (10.1)</td>
<td>19 (8.6)</td>
<td>0.49</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>13 (2.0)</td>
<td>7 (3.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>13 (2.0)</td>
<td>8 (3.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>9 (1.4)</td>
<td>22 (9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>41 (6.3)</td>
<td>12 (5.4)</td>
<td>0.63</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>6 (0.9)</td>
<td>3 (1.4)</td>
<td>0.58</td>
</tr>
<tr>
<td>Presenting symptoms</td>
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</tr>
<tr>
<td>Fever</td>
<td>290 (44.5)</td>
<td>93 (41.9)</td>
<td>0.49</td>
</tr>
<tr>
<td>Sore throat</td>
<td>30 (4.6)</td>
<td>13 (5.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Running nose</td>
<td>24 (3.7)</td>
<td>5 (2.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cough</td>
<td>65 (10.0)</td>
<td>23 (10.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>176 (27.0)</td>
<td>75 (33.8)</td>
<td>0.05</td>
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<tr>
<td>Headache</td>
<td>51 (7.8)</td>
<td>14 (6.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Muscle ache/body ache</td>
<td>50 (7.7)</td>
<td>13 (5.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52 (8.0)</td>
<td>21 (9.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Altered taste</td>
<td>48 (7.4)</td>
<td>22 (9.9)</td>
<td>0.23</td>
</tr>
<tr>
<td>Altered smell</td>
<td>48 (7.4)</td>
<td>23 (10.4)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percent; *n=857; 16 patients were less than 7 yrs old (m=10, f=6)

Results

We enrolled 873 successive adult patients (men 651, women 222) with laboratory confirmed COVID-19 and available Ct counts presenting to our hospital from April to mid-September 2020. Salient sociodemographic and clinical details in men and women are provided in Table 1. The mean age in men was 38.2±18 years and in women 41.2±19 years. One-third of men and a quarter of women were <30 years of age and more than half >60 years. Almost three-quarters lived in a large family. Illiteracy was more among women while tobacco use was more in men. Hypertension (men 20.1%, women 21.2%) and diabetes (men 10.1%, women 8.6%) were major comorbidities. Details of various symptoms are also reported with fever (men 44.5%, women 41.9%) being the most common. Almost all the patients had multiple symptoms at presentation.

The cohort was divided into 3 groups based on Ct counts, Group 1 >30.0, Group 2 25.0-29.9 and Group 3 <25.0. Important demographic, clinical features and comorbidities in the three groups are shown in Table 2. The mean age in Group 3 (42.4±19y) is significantly greater than Group 2 (39.5±18y) and Group 1 (39.3±17y) with greater proportion of older individuals. Sex distribution is identical. There are more smokers or tobacco users in Group 3. Shortness of breath as presenting symptom is more frequent in Group 3. Medical comorbidities- hypertension, type-2 diabetes, coronary heart disease and chronic kidney disease, are significantly greater in Group 3. Total leukocyte count, lymphocyte-neutrophil ratio and absolute lymphopenia are significantly greater in Group 3. In Group 3 vs. Group 2 and Group 1, the average time to virus negativity (9.8±4.1 vs 8.6±3.3 and 8.4±3.4 days) as well as days of hospitalization (10.5±5.4 vs 9.8±3.7 and 9.5±3.3 days) are significantly greater (Table 2).

Clinical outcomes (need for oxygenation, non-invasive ventilation, invasive ventilation) and deaths are significantly greater in Group 3 as compared to the other two (Figure 1). Univariate ORs and 95% CI in Groups 2 and 3 compared to Group 1 for oxygen requirement are 5.47 (2.98-10.07) and 4.48 (1.69-11.91), non-invasive
Table 2: Demographic and Clinical Characteristics in Groups Based on SARS-CoV-2 Cycle Threshold (Ct)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1: Ct &gt;30.0 (n=338)</th>
<th>Group 2: Ct 25.0-29.9 (n=316)</th>
<th>Group 3: Ct &lt;25 (n=219)</th>
<th>χ² test, p-value Group 1 vs. 2</th>
<th>χ² test, p-value Group 1 vs. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30y</td>
<td>104 (30.8)</td>
<td>106 (33.5)</td>
<td>69 (31.5)</td>
<td>0.462</td>
<td>0.864</td>
</tr>
<tr>
<td>30-49</td>
<td>118 (34.9)</td>
<td>98 (31.0)</td>
<td>56 (25.6)</td>
<td>0.281</td>
<td>0.023</td>
</tr>
<tr>
<td>50-69</td>
<td>91 (26.9)</td>
<td>82 (25.9)</td>
<td>65 (29.7)</td>
<td>0.772</td>
<td>0.472</td>
</tr>
<tr>
<td>≥70</td>
<td>25 (7.4)</td>
<td>30 (9.5)</td>
<td>29 (13.2)</td>
<td>0.33</td>
<td>0.023</td>
</tr>
<tr>
<td>Men</td>
<td>260 (76.9)</td>
<td>232 (73.4)</td>
<td>159 (72.6)</td>
<td>0.302</td>
<td>0.254</td>
</tr>
<tr>
<td>Family members/house</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>82 (24.3)</td>
<td>75 (23.7)</td>
<td>50 (22.8)</td>
<td>0.852</td>
<td>0.682</td>
</tr>
<tr>
<td>5-9</td>
<td>227 (67.2)</td>
<td>215 (68.1)</td>
<td>137 (62.6)</td>
<td>0.801</td>
<td>0.261</td>
</tr>
<tr>
<td>≥10</td>
<td>29 (8.6)</td>
<td>26 (8.2)</td>
<td>32 (14.6)</td>
<td>0.854</td>
<td>0.027</td>
</tr>
<tr>
<td>Ever tobacco/smoking</td>
<td>38 (11.2)</td>
<td>56 (17.7)</td>
<td>65 (29.7)</td>
<td>0.019</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BCG Vaccination:</td>
<td>179 (53.0)</td>
<td>144 (45.6)</td>
<td>89 (40.6)</td>
<td>0.168</td>
<td>0.010</td>
</tr>
<tr>
<td>Medical co-morbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>46 (13.6)</td>
<td>61 (19.3)</td>
<td>71 (32.4)</td>
<td>0.049</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
<td>18 (5.3)</td>
<td>22 (7.0)</td>
<td>41 (18.7)</td>
<td>0.383</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Type-2</td>
<td>16 (4.8)</td>
<td>30 (4.7)</td>
<td>39 (17.8)</td>
<td>0.017</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>12 (3.6)</td>
<td>22 (7.0)</td>
<td>19 (8.7)</td>
<td>0.050</td>
<td>0.010</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>7 (3.2)</td>
<td>0.961</td>
<td>0.005</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>131 (38.8)</td>
<td>152 (48.1)</td>
<td>100 (45.7)</td>
<td>0.016</td>
<td>0.106</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>95 (28.1)</td>
<td>80 (25.3)</td>
<td>76 (34.7)</td>
<td>0.421</td>
<td>0.099</td>
</tr>
<tr>
<td>Altered taste and altered smell</td>
<td>21 (6.2)</td>
<td>24 (7.6)</td>
<td>32 (14.6)</td>
<td>0.485</td>
<td>0.001</td>
</tr>
<tr>
<td>Investigation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White cell count (10⁹ cells/L)</td>
<td>6.32±4.1</td>
<td>7.08±5.1</td>
<td>8.3±5.4</td>
<td>0.035</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocytes/neutrophil ratio</td>
<td>0.58±0.2</td>
<td>0.59±0.2</td>
<td>0.61±0.2</td>
<td>0.643</td>
<td>0.212</td>
</tr>
<tr>
<td>Lymphocytes &lt;1000x10⁹/L (%)</td>
<td>13(3.8)</td>
<td>56 (17.72)</td>
<td>82 (37.44)</td>
<td>0.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virus negativity (days)</td>
<td>8.4±3.4</td>
<td>8.6±3.3</td>
<td>9.8±4.1</td>
<td>0.362</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization days</td>
<td>9.5±3.3</td>
<td>9.8±3.7</td>
<td>10.5±5.4</td>
<td>0.274</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percent. Numbers + indicate 1 SD.

Fig. 1: Clinical outcomes in various SARS-CoV-2 cycle threshold (Ct) groups shows significantly greater adverse outcomes in Group 3. Ct levels in Group 1 >30.0, Group 2 25.0-29.9, Group 3 <25.0.

Discussion

Higher SARS-CoV-2 virus load, as determined by low cycle threshold (Ct), is more prevalent in older individuals, with smoking or tobacco use and comorbidities including hypertension, diabetes, and chronic respiratory, cardiovascular and renal diseases. This is associated with more severe symptoms, greater need for oxygenation, non-invasive and invasive ventilation, longer hospital stay and more time to virus negativity. Among patients with Ct counts <30.0 and especially <25.0, there is significantly greater mortality even after adjustment for age, sex and comorbidities suggesting that low Ct count is an independent risk factor for adverse outcomes and mortality in COVID-19.

Emerging importance of quantitative SARS-CoV-2 viral load still remains understated.8,9 Our results are similar to findings of multiple recent studies that have reported that SARS-CoV-2 genomic load is an independent predictor of adverse outcomes in patients admitted to the hospital with COVID-19 pneumonia and may be used to risk stratify patients.18-27 Studies have reported a significant difference in survival probability between those with high viral load and those with low viral load, with a mean follow-up of 13 days and a maximum follow-up of 67 days.19 It has been found that admission SARS-CoV-2 viral load, as was determined by the Ct value, is an important surrogate epidemiological marker of infectivity that was independently associated with mortality among the patients hospitalized with COVID-19.20 Our results are in accordance with these studies.

In the present study, age has emerged as one of the predictors of severe disease and poor clinical outcomes and older adults have been shown to have a 10-fold increased risk for progression to severe and critical states.
with higher rates of adult respiratory distress syndrome and intensive care unit admission than the younger adults similar to previous studies. These findings have been attributed to immunosenescence, which could impair innate and adaptive immune responses. In our study cohort almost 75% of the patients were men similar to the previous reports. A broad array of non specific symptoms have been reported in hospitalised adults with covid-19 with fever and cough being the most commonly reported symptom. However, absence of fever in a largely geriatric cohort has been reported. The most common presenting symptoms in the patients of our study cohort based on Ct counts were fever, shortness of breath and altered taste and altered smell which is similar to previous reports. Lower Ct values are associated with lower lymphocyte levels in our study, this is similar to previous studies and suggests that lymphopaenia is an important marker of greater disease severity. In the present study, we have observed lower Ct counts in patients with comorbidities including hypertension, obstructive lung disease, type 2 diabetes, cardiovascular disease and chronic kidney disease. Greater presence of comorbidities have been reported among patients with severe COVID-19 in studies from China, UK, Europe and USA. A significant proportion of patients in the present study with Ct count <25.0 required oxygen supplementation (24.7%), non invasive ventilation (12.8%) and invasive ventilation (11.4%) (Table 2). Greater mortality has also been observed in patients with low Ct values as compared to patients with higher Ct values. Our findings on mortality of patients with high viral load in this cohort are supported by studies that reported that low Ct value correlated with higher risk of admission to hospital, intensive care units and death. Mechanistic studies have suggested that greater SARS CoV-2 viral load is associated with activation of inflammatory reactions and coagulation leading to alteration of integrity of vessel barrier, promoting pro-coagulant state, inducing endothelial inflammation and mediating leukocyte infiltration. These factors are mediated by a number of cytokines, endothelial activation and dysfunction, vascular inflammation, increased permeability and endothelial cell apoptosis. There is also an imbalance of renin-angiotensin-aldosterone and kallikrein-kinin systems, and oxidative stress and endothelial dysfunction due to reactive oxidative species, high-mobility group box-1, receptor for advanced glycation products, interleukin-6, interleukin-6 receptors, complements, vascular-endothelial growth factors and C-reactive protein, etc. All these lead to pulmonary and vascular abnormalities that are typical of COVID-19.

This study has multiple limitations. This is a single centre cohort study with a relatively small sample size and external validation of our finding is required using larger multicentric studies. Secondly, although the RT-PCR assays were performed using India government approved kits, the results could be different with other commercially available reagents, primer/probe concentrations, and cycling conditions. Thirdly, since the quality of collected samples directly affects the viral load, so the assay may affect low concentration samples. Very high odds ratios of mortality in Groups 3 and 2 compared to Group 1 suggest unmatched comparison. However, on comparison of Groups 3 with 2 also shows doubling of risk of mortality and the results are therefore valid. Lastly, a probability of incomplete capture of baseline characteristics exists as the time from onset of symptoms to specimen collection was not noted. There is lack of data on other prognostic biomarkers such as C-reactive protein levels, d-dimer, fibrinogen and interleukin-6 due to paucity of funds and is an important study limitation. Long-covid has emerged as an important clinical problem prevalent in more than a third of patients. Lack of long term follow-up data and its association with baseline Ct counts is also a study limitation.

In conclusion, findings from this study provides evidence that low Ct counts on RT-PCR, suggestive of greater SARS CoV-2 viral load at admission to hospital, are associated with significantly greater adverse outcomes. The study provides important prognostic information for clinicians for identification of patients for risk stratification and triage.

References
Post-COVID Interstitial Lung Disease – The Looming Epidemic

Ashish Kumar Singh1, Om Prakash Kumar1, Priya Bansal2*, Subha Laxmi Margekar3, Ramesh Aggarwal1, Lekh Raj Ghotekar4, Ankit Gupta5

Abstract

Introduction: As India recovers from the two waves of the Covid-19 pandemic, its sequelae are posing a new challenge to the physician. These may vary from fatigue and myalgia to persistent, and even worsening breathlessness, due to pulmonary fibrosis. Management of post-COVID-19 pulmonary fibrosis is currently limited to symptomatic management and largely an unexplored aspect.

Objectives: To draw attention to the imminent threat of post-COVID-19 interstitial lung disease (PC-ILD) in COVID survivors through a case series.

Methods: A retrospective analysis of data was done in patients admitted with severe COVID in December 2020 at our tertiary care hospital, and who had a prolonged stay with symptoms and signs suggestive of pulmonary fibrosis. HRCT was done to make a diagnosis of pulmonary fibrosis or ILD. Three such patients were identified.

Results: All the three cases were laboratory proven SARS CoV-2 positive cases and had developed pulmonary fibrosis, with traction bronchiectasis, termed here as PC-ILD (Post Covid-Interstitial Lung Disease). Two of them survived and had improved oxygen saturation on room air at three-month follow-up, while one patient had developed arrhythmia and died.

Conclusion: PC- ILD is one of the emerging complications of COVID-19 pneumonia. A proactive follow-up programme should be undertaken to identify and manage this looming epidemic.

Introduction

Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), the virus behind one of the most tragic pandemics of the century, is leaving a trail of devastating pulmonary fibrosis amongst the disease survivors. There is a lot of ongoing research to understand its pathophysiology, clinical course and management, with a particular focus on treatment modalities. Treatment of post-COVID-19 pulmonary fibrosis is currently limited to symptomatic management, and is largely an unexplored aspect, especially, the role of anti-fibrotic therapy. This review attempts to draw attention to the problem of post-COVID-19 interstitial lung disease (PC-ILD), a condition likely to be more frequently encountered in the future. We describe three cases of Covid-19 with post-COVID-19 fibrosis that were managed at our tertiary care hospital.

Case 1

A 45-year-old woman, non-smoker, known case of hypertension and hypothyroidism, presented with fever, dry cough and breathlessness of ten days duration. Her oxygen saturation was 77 % on room air, and was normal on high-flow oxygen through face-mask. Physical examination revealed decreased air entry at the lung bases with bilateral basal crepitations. The patient did not have limb edema, and jugular venous pressure was normal. A chest X-ray showed bilateral inhomogeneous opacities involving middle and lower zones, and blunting of bilateral costo-phrenic angle suggestive of bilateral pleural effusion. Patient’s routine blood profile and biochemistry were normal except raised serum C-reactive protein (CRP) and

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**Lactate dehydrogenase (LDH).** Her SARS-CoV-2 nasopharyngeal reverse-transcriptase polymerase chain reaction (RT-PCR) was found to be positive. The patient was treated on lines of the institutional protocol for severe COVID-19 infection with ivermectin, azithromycin, dexamethasone and low-molecular-weight heparin. Patient was given high-flow nasal oxygen, intermittent BiPAP therapy and prone ventilation for maintenance of saturation. 2D-ECHO was done, and found to be normal with left ventricular ejection fraction of 60%, and normal chamber dimensions.

Despite improvement in symptoms of fever and cough, patient required continuous oxygen and BiPAP therapy. High-resolution computed tomography (HRCT) imaging of chest done at three weeks showed multiple ground-glass opacities (GGOs) bilaterally, and interstitial thickening with traction bronchiectasis involving the middle and lower lobe of the right lung. The patient was started on anti-fibrotic therapy – oral Pirfenidone 400mg thrice a day. Repeat 2D-ECHO was also done at three weeks, which showed dilated RA (right atrium) and RV (right ventricle) suggestive of cor pulmonale. Patient was kept on continuous BIPAP, anti-coagulation and anti-fibrotic therapy for four weeks, but she eventually succumbed to arrhythmia and cardiac arrest.

**Case 2**

A 61-year-old male non-smoker, with alcohol use disorder, diabetes and hypertension, presented with complaints of dry cough and fever, and abdominal pain and distension, since 10 days, followed by shortness of breath since 7 days. His vitals were stable but for severe hypoxemia on room air (SpO₂ of 78%). On chest examination use of accessory muscles of respiration was present, respiratory rate was 26/minute, and coarse crepitations were present on both sides. On laboratory investigation he had normal total leukocyte count with lymphopenia, elevated LDH, raised CRP, and elevated D-dimer levels. Initial chest radiograph revealed peripheral multiple inhomogeneous opacities in bilateral lung fields. His RT-PCR nasal and oropharyngeal swab for COVID-19 came out to be positive. Initially, he was managed conservatively with supplemental oxygen and non-invasive ventilation (NIV)/ BiPAP support, low-molecular-weight heparin, dexamethasone, and antibiotics for super-added bacterial infection. He symptomatically improved, but continued to have mild hypoxemia and requirement of supplemental oxygen support, even after two weeks of treatment, and negative repeat COVID-19 RT-PCR test. HRCT of the chest showed architectural distortion, peri-bronchial, interstitial and interlobar septal thickening and traction bronchiectasis, which are features suggestive of fibrotic lung disease. He was treated with anti-fibrotic agent Pirfenidone starting with 200 mg three times a day a day titrated up to maximum dose of 600 mg three times a day, along with low-flow supplemental oxygen therapy for the next three weeks. After three weeks of treatment, he improved symptomatically, and the supplemental oxygen requirement decreased. He was discharged on intermittent home oxygen therapy. At three months of follow-up patient is able to do all his activities, without any limitation due to respiratory compromise.

**Case 3**

A 58-year-old male patient, with history of systemic hypertension, presented to the emergency department with complaints of dry cough, fever, and throat pain since seven days, followed by shortness of breath since two days. The breathlessness was insidious in onset and gradually progressive, and associated with orthopnea. On examination his blood pressure was 120/80 mmHg, pulse rate – 120 beats per minute, respiratory rate - 26/minute, SpO₂ on room air - 65% and use of accessory muscle of respiration was present. Bilateral course diffuse crepitations were present on lung auscultation; rest of the systemic examination was unremarkable. On laboratory investigation he had leukocytosis with lymphopenia, elevated LDH, CRP and D-dimer levels. Initial chest radiograph revealed multiple inhomogeneous opacities in bilateral lung fields. His RT-PCR nasal and oropharyngeal swab for COVID-19 came out to be positive. The patient was managed on lines of severe covid-19 with severe acute respiratory distress syndrome (ARDS) and type-1 respiratory failure with high flow supplemental oxygen therapy and NIV, low-molecular-weight heparin, dexamethasone, and other supportive treatment. He symptomatically improved and repeat RT-PCR for COVID-19 came out to be negative after two weeks of treatment. However, he continued to have hypoxemia on room air and became NIV dependent. HRCT chest was performed and it showed diffuse bilateral GGOs with extensive irregular peribronchial, interstitial and interlobar septal thickening, and parenchymal bands, suggestive of post COVID-19 lung fibrosis. He was started on tablet pirfenidone 200 mg three times a day, up-titrated to 600 mg three times a day, along with supplemental oxygen and NIV. He improved over the next ten days, supplemental oxygen requirement decreased, and he was discharged on low-flow home oxygen therapy. Pirfenidone was continued for a total duration of three months along with supplemental oxygen therapy. On third month follow-up patient’s lung condition had improved; he has now been able resume his routine activities.

**Discussion**

Post-COVID-19 manifestations fall in wide range of symptoms varying from low-critical symptoms like fatigue, headache, arthralgia, and myalgia to more critical conditions such as stroke, myocarditis, renal failure and pulmonary fibrosis.1

The etiology of post-COVID-19 pulmonary fibrosis is multifactorial and depends on age, smoking, viral infection, drug exposure, and genetic predisposition. SARS-CoV-2 uses angiotensin-2-converting enzyme (ACE-2) receptor, a cell receptor in humans for cellular entry, and causes interstitial lung damage. Chronic inflammation which may result in epithelial damage and fibroblast activation is considered as the main cause of pulmonary fibrosis. Dysregulated release of matrix metalloproteinases, together with other mediators - Transforming growth factor β1 (TGF-β), vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and vascular dysfunction, contribute to progression of fibrosis.2

Other viral infections that have been seen to progress to development of ILDs are Epstein–Barr virus (EBV), Cytomegalovirus, Human herpesvirus-8 (HHV-8), adenovirus,
Hepatitis C, Torque-Teno (Transfusion-Transmitted) Virus, Human Immunodeficiency Virus (HIV), Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). \( ^3 \) Like COVID-19, ACE-2 receptor dependent cellular entry and IL-6 driven hyper inflammation were seen in SARS. Studies conducted among SARS survivors showed that 36% of patients developed fibrotic features. The more phylogenetically related MERS also caused fibrosis in 33% of patients.\(^4\)

Our patients showed evidence of persistence of lung function impairment within three weeks of their in-patient stay itself. Impaired diffusion-capacity, decrease in respiratory muscle strength, and lung imaging abnormalities have been demonstrated, in early convalescence phase, in more than half of the COVID-19 patients in a study from China.\(^5\) In the prospective multicentric study named CoVILD, patients were reviewed at 60 and 100th day. Impaired lung function was seen in 42% and 36% of patients respectively, while CT abnormalities were detected in 77% and 63% of patients.\(^4\)

Patients affected with pulmonary fibrosis complain of dry cough, fatigue, dyspnea, decreased functional capacity and loss of weight.\(^2\) In a study of Italian COVID-19 pandemic survivors, on two month follow-up after the onset of the first COVID-19 symptom, worsened quality of life was observed among 44.1% of patients. A high proportion of individuals complained of fatigue (53.1%), dyspnea (43.4%) and chest pain (21.7%).\(^6\)

In a follow-up study of COVID-19 survivors in China, three months after discharge, radiological abnormalities were detected in 70.91% of patients, and in half of the patients (54.55%) more than one lung segment was involved. Twenty-four percent patients showed bilateral involvement on chest HRCT scans. Pure GGOs (7.27%), interstitial thickening (27.27%), and crazy paving (5.45%) were the most common CT features found. These features were seen in our patients as well.\(^7\)

For management of post-Covid ILD, drugs such as steroids, antifibrotics, and anticoagulation have been under study but definitive treatment is yet to be approved. After the results of the RECOVERY trial in June 2020 steroids became the standard of care in hypoxic patients in ICUs across the world.\(^8\) However, long-term use of steroids in patients with COVID-19 to prevent potential pulmonary fibrosis requires more robust data.\(^9\)

The role of antifibrotic drugs in post-covid fibrosis is unclear currently. A large proportion of patients with idiopathic pulmonary fibrosis (IPF) are treated with one of the two available antifibrotic drugs, pirfenidone and nintedanib. These have been shown to slow the rate of lung function decline. There is a clear rationale for use of these drugs in post-Covid fibrosis, as many of the epidemiological risk factors and biological processes that lead to viral-induced ARDS and fibrosis are shared with IPF.\(^10\) It is suggested that pirfenidone might be a beneficial therapeutic strategy in Covid-19 disease management as it can inhibit apoptosis, downregulate ACE receptors expression, decrease inflammation and ameliorate oxidative stress, thereby protecting pneumocytes and other cells from COVID-19 invasion, and cytokine storm simultaneously. Novel antifibrotic drugs for the treatment of severe COVID-19 that are in experimental stage target TGF-β pathway, IFN-β and IFN-γ. Rapamycin, an mTOR inhibitor, could also be a useful repurposed drug as mTOR (viral replication pathway) may be a useful anti-SARS-COV-2 target.\(^10\) All our patients were given pirfenidone and seen to have variable outcomes.

As the pathophysiology and the prevalence of post-Covid fibrosis have been seen to be similar to SARS and MERS, we can predict the prognosis of post-COVID fibrosis based on previous evidence. A 15-year follow-up study of 71 patients with moderate to severe SARS showed that the rate of interstitial abnormalities remarkably declined within the first 2 years of recovery to only 4.6% of patients. Similar findings were reported for MERS also. It is hoped that while the problem of PC-ILD is likely to be more frequently encountered in comparison to SARS and MERS due to the sheer scale of the pandemic, the majority of the patients will stabilize over time.

**Conclusion**

In conclusion, PC-ILD is one of the emerging complications of COVID-19 pneumonia and ARDS. As the world recovers from this pandemic, a proactive follow-up programme should be undertaken to evaluate and manage its sequelae, and resources optimally utilised to study and treat this looming epidemic of pulmonary fibrosis.

**References**

49th ANNUAL MEETING OF RESEARCH SOCIETY FOR THE STUDY OF DIABETES IN INDIA (RSSDI 2021)

11th – 14th NOV, 2021

Organised by

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Org. Chairman - RSSDI 2021

Dr. Ch. Vasanth Kumar
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Effect of Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on COVID-19 outcome: A Record Based Observational Study in West Bengal

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Abstract

Background: Since its first identification in December 2019, in WUHAN (CHINA), SARS-COV-2, causative agent of Corona virus pandemic, has affected millions of people worldwide, causing thousands of death. There is much speculation about the interplay between ACEI/ARB and Corona virus infection, as for internalization into host cell SARS-COV-2 binds through S spike protein to ACE-2, aided TMPRSS2.

Methods: A record based observational study has been conducted (data obtained from the clinics of fourteen physicians) in two worst affected districts of West Bengal, to find out the association of ACEI/ARB on patients, suffering from Corona virus infection. The study-protocol has already been approved by Clinical Research Ethics Committee of Calcutta School of Tropical Medicine. (IEC Ref. No: CREC-STM/2020-AS-37)

Results: Increasing age, male sex and presence of co-morbidities (viz. Diabetes, COPD) are significantly associated with the occurrence of moderate and severe disease. Drugs (viz. ACEI/ARB), though are associated with less severe disease, have not achieved statistical significance, in the present study.

Conclusion: Drugs, like ACEI/ARB, should be continued in patients suffering from COVID-19 infection, (if they are already on these drugs).

Introduction

The Covid-19 pandemic (declared by WHO in March 2020), also known as Corona virus Pandemic, is an ongoing pandemic, caused by severe acute respiratory syndrome Coronavirus-2 (SARS-COV-2) and since its first identification in December 2019, in WUHAN, HUBEI (CHINA), it has affected millions of people worldwide and as on 15th December, 2020, Covid-19 pandemic has been attributed to 70 million cumulative cases and 1.6 million deaths globally. As WHO declared the outbreak a “Public health Emergency of International Concern”, in January 2020, India recorded its first case of Covid-19 in Kerala on 30th January, 2020 and on 3rd Feb, 2020, there were three cases (all were students returning from WUHAN). Again on 4th march twenty-two new cases were reported, including fourteen infected members of Italian tourist group, and thereafter the transmission grew after several people (who acted as super spreaders), with travel history to affected countries and their contacts and people attending different religious congregations and family get-together, and thus travelling from one place to another fell ill and tested positive.

As the SARS-COV-2 virus is mainly airborne and it is transmitted from one person to other by their close proximity, recommended preventive measures include wearing a mask, hand-washing, and social distancing. In addition to all these measures, to prevent migration of people, Govt. of India also imposed a strict “Lock-Down” (which had been much debated) on and from 24th March till 1st June (when Govt. started unlocking the country-barring the containment zones). Insipite of all these measures, India recorded more than nine million cases with more than hundred thousand deaths (till 15th December, 2020).

Though the Covid-19 pandemic was first confirmed in the state of West Bengal, in Kolkata, on 17th March, 2020; by 9th December, 2020 West Bengal recorded 510951 confirmed cases, 8867 deaths with 478434 recoveries with 23650 active cases (with north 24 pgs. and Kolkata being two of the worst affected districts).

For the infection to occur (i.e. for virus-host interaction), the polybasic cleavage protein in the spike protein of novel corona virus binds to the Angiotensin converting enzyme 2 receptor (ACE-2) and this ACE-2 is expressed abundantly in the lung alveolus cells (which cause primary respiratory presentation) and also in
the brain, gut, kidney, gallbladder, testes, adrenal glands (thus causing systemic illness also). The virus can affect people of all age groups, but older people and people with pre-existing medical conditions [Diabetes mellitus, Heart disease, Asthma/ COPD (chronic obstructive pulmonary disease), Cancer, Obesity, Chronic kidney disease etc.] appear to be more vulnerable to becoming severely ill with COVID-19 infection. So there are concerns that ACEIs/ARBs may affect the severity and mortality of COVID-19 illness. The concerns regarding harmful effects of these group of drugs are based on considerations of biological plausibility, and the observation that there is an overrepresentation of patients with hypertension and other cardiovascular co morbidities among patients with Covid-19 who have poor outcomes. Millions of people around the world are on treatment with ACEIs/ ARBs for hypertension, heart failure, coronary artery, diabetes mellitus and kidney disease. Speculation about worse outcomes among patients, on these medications during Covid-19 pandemic has caused widespread anxiety among patients and their care-givers. On the other hand, the harms of indiscriminate withdrawal of these medications on cardiovascular outcomes are well documented. There is also widespread speculation about the potential benefits of ACEIs/ARBs, based on biological plausibility arguments and animal data and small clinical studies on patients with other viral respiratory infections.

One meta-analysis (published from China) showed no significant increase in the risk of Covid-19 infection in patients receiving ACEIs/ARBs, and ACEIs/ARBs therapy was associated with a decreased risk of severe Covid-19 and mortality. Another study, in which data were collected from 169 hospitals in Asia, Europe and North America, showed no potential harmful association of ACEIs/ARBs with in-hospital deaths. In the BRACE CORONA trial, in which 659 patients were enrolled, eligible patients were randomized to temporary suspension of ACEIs/ARBs (n=334) versus continued use of ACEIs/ARBs (n=325) and the trial showed that suspending ACEIs/ARBs compared with continuing them did not improve the days alive and out of the hospital. In another study published in BMJ in July 2020, the authors showed that ACEIs/ARBs were associated with reduced risks of Covid-19 disease after adjusting for a wide range of variables (data were collected from 1205 general practices). This study also shows that, neither ACE inhibitors nor ARBs are associated with significantly increased risks of receiving ICU care.

**ACEI/ARB and Pathogenesis of Covid-19**

For internalization into the host cell, SARS-COV-2 binds through the S spike protein to ACE-2, which is again aided by TMPRSS2 protease. The high infectivity of the virus may be related to the mutation in the receptor binding domain and acquisition of a furan cleavage site in the S spike protein. The interaction of the virus with ACE2 may downregulate the anti-inflammatory function and heighten the Angiotensin II effects in predisposed persons. ACE2, which is widely present in the lung, tongue and in type1 and type2 alveolar epithelial cells of lower part of human lungs, acts as functional receptor for SARS-COV-2.

Angiotensin converting enzyme, located primarily on luminal surface endothelium, converts Angiotensin I to Angiotensin II and metabolizes bradykinin to inactive products. Though, pulmonary vasculature being the largest area of endothelium, is important in regulating circulating levels of Angiotensin II, the activity of endothelial Angiotensin converting enzyme in systemic vessels may be more important in determining the concentration of Angiotensin II and bradykinin reaching blood vessel wall. Endothelial cells can synthesize rennin and its substrate and it therefore seems as though the enzymatic machinery for a complete rennin-angiotensin system is present within the vessel wall.

The activity of rennin-angiotensin system is important in cardiovascular diseases viz. hypertension and heart failure and the relative importance of local compared with systemic regulation of Angiotensin II production is a matter of concern. Furthermore, the vasodilator action of Angiotensin converting enzyme inhibitors in certain blood vessels is partly due to accumulation of bradykinin (which stimulates nitric oxide) and is probably due to the fact that, endothelial angiotensin converting enzyme has got a role in bradykinin metabolism.

Angiotensinogen, a circulating glycoprotein of 452 amino acids, is synthesized primarily in the liver as preangiotensinogen and Ang I is cleaved by rennin from the amino terminus of angiotensinogen. Throughout the vasculature, the activity of membrane bound ACE on the luminal surface of endothelial cells facilitates the rapid conversion of Ang I to Ang II in plasma. ACE has large amino-terminal extracellular domain, a short carboxy-terminal intracellular domain and a 17-aminoacid hydrophobic region, that anchors the ectoenzyme to the cell membrane and circulating ACE represents membrane ACE, that has undergone proteolysis. ACE cleaves dipeptides from substrates and the preferred substrates have only one free carboxyl group in the carboxy-terminal amino acid (proline must not be the penultimate amino acid) and thus ACE does not degrade Ang II [Angitensin II or Angiotensin 1-8 (NH₂-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-COOH)]. ACE also inactivates bradykinin and other potent vasodilatorpeptides. Ang II is more potent than Ang I, by its action on smooth muscle, heart and adrenal cortex and Ang III or Angiotensin (2-8) is less potent than Ang II in elevating blood pressure or stimulating adrenal medulla. Angiotensin(1-7) is formed by multiple pathways and ACE inhibitors increase tissue and plasma levels of Angiotensin (1-7), as increased amount of Ang I are diverted away from Ang II formation [ACE also helps in plasma clearance Angiotensin (1-7)]. Angiotensin(1-7) does not cause vasoconstriction, aldosterone release or facilitation of noradrenergic neurotransmission and it actually releases vasopressin, stimulates prostaglandin biosynthesis, dialates some blood vessels, inhibits proliferation of vascular smooth muscle cells and thus it has been proposed that Angiotensin (1-7) serves to counterbalance the effects of Ang II and the effects of Angiotensin (1-7) may be mediated by a specific Angiotens (1-7) receptor. Angiotensin IV [Angiotensin (3-8)] is another biologically active angiotensinpeptide, which also appears to counteract the effects Ang II.

Angiotensin act through two specific GPCRs-AT₁ and AT₂. Losartan (and related bipheryl tetrazole derivatives) has got high affinity for AT₁ and low
Table 1: Distribution of the Covid 19 cases according to various attributes (N=386)

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (completed years)</td>
<td></td>
</tr>
<tr>
<td>18-39</td>
<td>90 (23.3)</td>
</tr>
<tr>
<td>40-59</td>
<td>183 (47.4)</td>
</tr>
<tr>
<td>≥60</td>
<td>113 (29.3)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>219 (56.7)</td>
</tr>
<tr>
<td>Female</td>
<td>167 (43.3)</td>
</tr>
<tr>
<td>Residence (district)</td>
<td></td>
</tr>
<tr>
<td>Kolkata</td>
<td>229 (59.3)</td>
</tr>
<tr>
<td>North 24 pgs.</td>
<td>157 (40.7)</td>
</tr>
<tr>
<td>Severity of disease</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>275 (71.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>78 (20.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>33 (8.5)</td>
</tr>
<tr>
<td>a. Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>150 (38.9)</td>
</tr>
<tr>
<td>Present</td>
<td>236 (61.1)</td>
</tr>
<tr>
<td>One</td>
<td>129 (33.4)</td>
</tr>
<tr>
<td>Two</td>
<td>85 (22.0)</td>
</tr>
<tr>
<td>≥3</td>
<td>22 (5.7)</td>
</tr>
<tr>
<td>b. Types of Co-morbidities (Overlapping)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>198 (51.3)</td>
</tr>
<tr>
<td>DM</td>
<td>105 (27.2)</td>
</tr>
<tr>
<td>CVD</td>
<td>23 (6.0)</td>
</tr>
<tr>
<td>COPD</td>
<td>22 (5.7)</td>
</tr>
<tr>
<td>Others*</td>
<td>18 (4.7)</td>
</tr>
<tr>
<td><strong>(Stroke, CVD, Cancer, Hypothyroidism &amp; Obesity)</strong></td>
<td></td>
</tr>
<tr>
<td>Use of anti-hypertensive drugs</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>174 (45.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>212 (55.0)</td>
</tr>
<tr>
<td>Both groups</td>
<td>62 (16.1)</td>
</tr>
<tr>
<td>One group</td>
<td>150 (38.9)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>96 (24.9)</td>
</tr>
<tr>
<td>‘Others’</td>
<td>54 (14.0)</td>
</tr>
<tr>
<td>[Duration of use (Years) - Mean 3.7 Sd 3.7 Min 0.1 max 25]</td>
<td></td>
</tr>
<tr>
<td>Use of anti-hypertensive drugs</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>174 (45.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>212 (55.0)</td>
</tr>
<tr>
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<td>96 (24.9)</td>
</tr>
<tr>
<td>‘Others’</td>
<td>54 (14.0)</td>
</tr>
<tr>
<td>[Duration of use (Years) - Mean 3.7 Sd 3.7 Min 0.1 max 25]</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>7 (1.8)</td>
</tr>
</tbody>
</table>

Table 2: Associations of Severity of disease (Moderate & Severe) with selected variables (N=386)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Moderate &amp; Severe disease No (%)</th>
<th>Significance* Chi Square/Exact P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-39</td>
<td>90</td>
<td>18 (20)</td>
<td>25.8</td>
</tr>
<tr>
<td>40-59</td>
<td>183</td>
<td>40 (21.9)</td>
<td>0.000</td>
</tr>
<tr>
<td>≥ 60</td>
<td>113</td>
<td>53 (46.9)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>167</td>
<td>39 (23.4)</td>
<td>4.19</td>
</tr>
<tr>
<td>Male</td>
<td>219</td>
<td>72 (32.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolkata</td>
<td>229</td>
<td>59 (25.8)</td>
<td>2.46</td>
</tr>
<tr>
<td>North 24 pgs.</td>
<td>157</td>
<td>52 (33.1)</td>
<td>0.137</td>
</tr>
<tr>
<td>Co-morbidities (Number)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>150</td>
<td>26 (17.3)</td>
<td>28.6</td>
</tr>
<tr>
<td>One</td>
<td>129</td>
<td>35 (27.1)</td>
<td>0.000</td>
</tr>
<tr>
<td>Two</td>
<td>85</td>
<td>37 (43.5)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>22</td>
<td>13 (59.1)</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities (Type)</td>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>188</td>
<td>39 (20.7)</td>
<td>11.48</td>
</tr>
<tr>
<td>Yes</td>
<td>198</td>
<td>72 (36.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>281</td>
<td>67 (23.8)</td>
<td>12.17</td>
</tr>
<tr>
<td>Yes</td>
<td>105</td>
<td>44 (41.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>363</td>
<td>98 (27.0)</td>
<td>9.20</td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>13 (56.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>364</td>
<td>96 (26.4)</td>
<td>17.70</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>15 (68.2)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*Chi square/Fisher’s Exact test done as applicable

Ang II to ACE2 derived peptides like Ang (1-7)(which counteracts the effects of Ang II). Thle imbalance between the action ACE1 and ACE2 may aggravate the pathology. Blunting the ACE1-Ang-II-AT1R enhances the action of ACE1-AngII-AT1R, thus ACE2-Ang (1-7)-AT2R or the ACE2-Ang (1-7) probably protecsts from ARDS, triggered infecting pathogens viz. coronaviruses. ACE2 is expressed at apical plasma membranes of epithelial cells, including those of respiratory origin, the primary location of SARS-COV infection. After attachment of viral spike proteins with ACE2, the amount of ACE2 expressed on cell-surface, is reduced and this ACE2 receptor downregulation provokes a worsening effect of lung failure. Barring the lung alveolar cells, ACE2 is also expressed in other organs viz. kidney, heart and gut and thus, acute kidney injury(AKI),cardiac damage, abdominal pain are the most common co-morbidities of COVID-19.

India, a country with a of population more than 130 crore, bears a large diabetic (77 million as per IDF-International Diabetes Federation) and hypertension burden. Both ACE 1 and ACE2 cleave angiotensin peptidase. ACE1 cleaves Angiotensin1 and generates Angiotensin II, which causes vasoconstriction, bronchoconstriction.

Increases vascular permeability, inflammation and fibrosis and enhance the development of acute respiratory distress syndrome(ARDS) and lung failure in patients with SARS-COV-2 infection. ACE1 generated AT1receptor function is the key mediator of Ang II action and opposes the action of ACE2 derived peptides. ACE2, a carboxypeptidase, responsible for Ang II degration to Ang (1-7), produces effects that oppose the action of Ang II mediated by AT1. The SARS-COV-2 infects alveolar pneumocytes by binding to ACE2, leading to decreased conversion of Ang II to ACE2 derived peptides like Ang (1-7)(which counteracts the effects of Ang II). Thle imbalance between the action ACE1 and ACE2 may aggravate the pathology. Blunting the ACE1-Ang-II-AT1R enhances the action of ACE1-AngII-AT1R, thus ACE2-Ang (1-7)-AT2R or the ACE2-Ang (1-7) probably protecsts from ARDS, triggered infecting pathogens viz. coronaviruses. ACE2 is expressed at apical plasma membranes of epithelial cells, including those of respiratory origin, the primary location of SARS-COV infection. After attachment of viral spike proteins with ACE2, the amount of ACE2 expressed on cell-surface, is reduced and this ACE2 receptor downregulation provokes a worsening effect of lung failure. Barring the lung alveolar cells, ACE2 is also expressed in other organs viz. kidney, heart and gut and thus, acute kidney injury(AKI),cardiac damage, abdominal pain are the most common co-morbidities of COVID-19.

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India, a country with a population...
Diabetes Federation-2020)\textsuperscript{24} and hypertensive (29.8% prevalence-FEB 2016-Ministry of health and family welfare-Govt. of India)\textsuperscript{25} population and ACEI/ARB occupies a very important position in managing these patients.

So, to address the above mentioned issues and uncertainties, an observational study has been conducted among the patients attending clinics of conveniently selected physicians (about 16/17 in number) with a positive diagnosis of Covid-19 infection (from 01/10/2020 to 31/12/2020) of North24pgs and Kolkata districts of West Bengal (two of the worst affected districts of India) with the objectives of identifying the association between severity of SARS COV-2 illness and use of ACEIs/ARBs.

**Materials and Methods**

Present clinic based study was conducted among diagnosed adult (≥18 years) COVID 19 patients (RT PCR/RAT positive) hailing from Kolkata and North 24 pg district of West Bengal attending private clinics of a group of physicians between October to December 2020. A total of 386 such patients were included in the study who gave consent and received care either in home isolation or in hospital inpatient. Patients were followed up once after 28 days of contact to confirm their disease status [mild, moderate and severe classified as per guideline detailed in “Clinical management protocol: COVID-19” (GOI-MOH&FW)]\textsuperscript{26} and final outcome (recovery or death).

**Study variables included** were age (completed years), sex (male, female), residence (district; Kolkata and North 24 pg districts) of the patients did not achieve statistical significance. The association of disease severity with the use of anti-hypertensive drugs has been shown in Table 3. It shows that although, overall, it is associated with less severe disease (P<0.01) but upon stratified analysis in different age groups and duration of drug use, it did not achieve statistical significance e.g. disease severity does not appear to be associated with use of anti-hypertensive drugs.

To identify the individual role of variables associated with moderate & severe disease, logistic regression analysis was done (Table 4). It shows that age ≥60 years [AOR 2.45, 95% CI 1.45-4.13; p 0.001], male sex [AOR 1.74, 95% CI 1.06-2.87; p 0.029], presence of diabetes [AOR 1.98, 95% CI 1.15-3.40; p 0.013] and COPD [AOR 5.09, 95% CI 1.86-14.0; p 0.002] are significantly associated with moderate & severe disease when all other variables remaining constant. Although did not achieve statistical significance and there is chance of overlap. patients with CVD [AOR 2.43, 95% CI 0.93-6.32; p 0.070] and Hypertension [AOR 1.82, 95% CI 0.59-5.59; p 0.294] are observed to have more risk of moderate & severe disease. On the contrary, patients receiving antihypertensive drugs [ACEI: AOR0.503, 95% CI 0.22-1.16; p 0.106; Other Drugs: AOR 0.87, 95% CI 0.41-1.83; p 0.710] are observed to have less risk of moderate & severe disease but did not achieve statistical significance.

There is much speculation about...
### Table 3: Associations of Severity of disease (Moderate & Severe) with use of anti-hypertensive drugs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Drugs</th>
<th>Total</th>
<th>Moderate &amp; Severe disease No (%)</th>
<th>Significance Chi square/Fisher’s Exact test done as applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Nil</td>
<td>174</td>
<td>35 (20.1)</td>
<td>12.58</td>
</tr>
<tr>
<td></td>
<td>‘Other’</td>
<td>54</td>
<td>22 (40.7)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>ACEI/ARB</td>
<td>96</td>
<td>34 (35.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>62</td>
<td>20 (32.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>386</td>
<td>111 (28.8)</td>
<td></td>
</tr>
</tbody>
</table>

In different age groups:

- **18-39 years**
  - Nil: 71 (15.5) 5.08
  - ‘Other’: 5 (02 (40.0) 0.123
  - ACEI/ARB: 8 (03 (37.5) 0.322
  - Both: 6 (02 (33.3) 0.25
  - Total: 90 (18 (20.0) 0.025

- **40-59 years**
  - Nil: 78 (12 (15.4) 4.36
  - ‘Other’: 27 (09 (33.3) 0.225
  - ACEI/ARB: 43 (11 (25.6) 0.15
  - Both: 35 (08 (22.9) 0.13
  - Total: 183 (40 (21.9) 0.002

- **60 years +**
  - Nil: 25 (12 (48.0) 0.21
  - ‘Other’: 22 (11 (50.0) 0.967
  - ACEI/ARB: 45 (20 (44.4) 0.22
  - Both: 21 (10 (47.6) 0.16
  - Total: 113 (53 (46.9) 0.001

With different duration of drug use:

- **0.1-1 year**
  - ‘Other’: 27 (13 (48.1) 1.5
  - ACEI/ARB: 30 (10 (33.3) 0.466
  - Both: 26 (14 (46.2) 0.24
  - Total: 83 (35 (42.2) 0.106

- **1.1-5 years**
  - ‘Other’: 15 (05 (33.3) 1.42
  - ACEI/ARB: 43 (14 (32.6) 0.523
  - Both: 25 (05 (20.0) 0.294
  - Total: 83 (24 (28.9) 0.029

- **> 5 years**
  - ‘Other’: 12 (04 (33.3) 0.908
  - ACEI/ARB: 23 (10 (43.5) 0.725
  - Both: 11 (03 (27.3) 0.013
  - Total: 46 (17 (37.0) 0.001

### Table 4: Logistic Regression analysis for Moderate & Severe disease with relevant variables (N=386)³⁴

<table>
<thead>
<tr>
<th>Variables</th>
<th>Prevalence (%) of Moderate &amp; severe disease</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td></td>
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</tr>
<tr>
<td>18-59</td>
<td>21.2</td>
<td>3.27 (2.05-5.38)</td>
<td>0.000</td>
<td>2.45</td>
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<tr>
<td>≥ 60</td>
<td>46.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23.4</td>
<td>1.61 (1.02-2.54)</td>
<td>0.041</td>
<td>1.74</td>
</tr>
<tr>
<td>Male</td>
<td>32.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20.7</td>
<td>2.18 (1.38-3.44)</td>
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<td>1.82</td>
</tr>
<tr>
<td>Yes</td>
<td>36.4</td>
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</tr>
<tr>
<td>Diabetes</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>23.8</td>
<td>2.30 (1.43-3.70)</td>
<td>0.000</td>
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</tr>
<tr>
<td>Yes</td>
<td>41.9</td>
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<tr>
<td>COPD</td>
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<tr>
<td>No</td>
<td>26.4</td>
<td>2.30 (1.43-3.70)</td>
<td>0.000</td>
<td>5.09</td>
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<tr>
<td>Yes</td>
<td>68.2</td>
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<tr>
<td>CVD</td>
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<tr>
<td>No</td>
<td>27.0</td>
<td>3.51 (1.49-8.28)</td>
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<tr>
<td>Yes</td>
<td>65.6</td>
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<td></td>
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<tr>
<td>ACEI/ARB use</td>
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<td></td>
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<tr>
<td>No</td>
<td>25.0</td>
<td>1.56 (0.99-2.43)</td>
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<td>0.503</td>
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<tr>
<td>Yes</td>
<td>34.2</td>
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<tr>
<td>Other Drugs</td>
<td></td>
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<tr>
<td>No</td>
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<td>1.65 (1.04-2.64)</td>
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<tr>
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<td>36.2</td>
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</table>

³⁴Chi square/Fisher’s Exact test done as applicable

### Conclusion

In this record based observational study, though most of the patients have suffered from mild disease, there is statistically significant association of moderate and severe disease with increasing age of the patient, male sex and co-morbidities esp. diabetes and COPD. Although, did not achieve statistical significance, presence of hypertension increases the risk of more severe disease and use antihypertensive drugs, like ACEIs/ARBs, are associated with less severe disease. So, it may be concluded, that if any person, who is on ACEI/ARB, suffers from COVID-19, the drugs should be continued.

### Limitations

- a. As the study includes patients from selected clinics of physicians, it won’t be the representative of all such patients of the district and results cannot be generalized.

- b. The study deals with persons, who are already infected, and thus it cannot predict the effects of ACEI/ARB on the susceptibility to COVID-19.

### Ethical Issues

Informed consent has been taken from every patient and the identities of covid-19 positive patients are not disclosed (these information are with the treating physicians). The study-protocol has already been approved by Clinical Research Ethics Committee of Calcutta School of Tropical Medicine-IEC Ref.No:CREC-STM/2020-AS-37.

Statistical analysis has been done by Prof. (Dr.) Sanjoy Kumar Sadhukhan.
Characteristics of COVID-19 Patients Admitted to a Tertiary Care Hospital in Pune, India and Predictors of Requirement for Intensive Care Treatment

Urvi Bhooshan Shukla¹, Sharvari Rahul Shukla², Sachin Bhaskar Palve³, Rajiv Chintaman Yeravdekar⁴, Vijay Madhusoothan Natarajan⁵, Pradeep Tiwari⁶, Chittaranjan Sakerlal Yajnik⁷

Abstract

Objectives: 1. To study associations of severity of COVID-19 disease with clinical features and laboratory markers. 2. To develop a model to predict the need for ICU treatment.

Methods: This is an analysis of clinical course in 800 consecutive patients from a dedicated COVID-19 tertiary care hospital in Pune, India (8th April to 15th June 2020). We obtained clinical and laboratory information, severity grading and progress from hospital records. We studied associations of these characteristics with need for ICU management. We developed a predictive model of need for ICU treatment among first 500 patients and tested its sensitivity and specificity in the following 300 patients.
Results: Average age was 41 years, 16% were <20 years of age, 55% were male, 50% were asymptomatic and 16% had at least one comorbidity. Using MoHFW India severity guidelines, 73% patients had mild, 6% moderate and 20% severe disease. Severity was associated with higher age, symptomatic presentation, elevated neutrophil and reduced lymphocyte counts and elevated inflammatory markers. Seventy-seven patients needed ICU treatment: they were older (56 years), more symptomatic and had lower SpO2 and abnormal chest X-ray and deranged hematology and biochemistry at admission. A model trained on the first 500 patients, using above variables predicted need for ICU treatment with sensitivity 80%, specificity 88% in subsequent 300 patients; exclusion of expensive laboratory tests (Ferritin, C-Reactive Protein) did not affect accuracy.

Conclusion: In the early phase of COVID-19 pandemic, a significant proportion of hospitalized patients were young and asymptomatic. Need for ICU treatment was predicted by simple measures including higher age, symptomatic onset, low SpO2 and abnormal chest X-ray. We propose a simple model for referring patients for treatment at specialized COVID-19 hospitals.

Introduction

India reported its first case of COVID-19 on 30th January, 2020 in Kerala. As of 30th September 2020, according to the Ministry of Health and Family Welfare (MoHFW) more than 6 million COVID-19 cases have been reported in India, with 95,000 deaths. India is now 2nd only to United States in the number of cases. Maharashtra is one of the worst affected states in this pandemic. As of 30th September, Maharashtra has in total 1.4 million cases with 38,000 deaths. COVID-19 cases in Pune have exceeded those in Mumbai. There is considerable load on the health care system to accommodate COVID-19 patients which is met by opening specialized centers for mild patients. Guidelines for triaging patients for hospitalization who may need subsequent Intensive Care Unit (ICU) treatment will be useful.

Symbiosis University Hospital and Research Center is a state of the art hospital. The management offered 500 isolation and 30 ICU beds for COVID-19 patients to the local authorities on 24th March 2020.

We narrate our experience of managing the initial 800 consecutive patients admitted with confirmed COVID-19 positive status. We described the demographic, clinical and biochemical characteristics, and developed a model of predictors for ICU admission.

Methods

COVID-19 patient admissions began on 8th April 2020, patients were referred by the Pune Municipal Corporation with a positive RT-PCR test for SARS-CoV2 done at the National Institute of Virology, Pune. The test was advised for symptoms suggestive of COVID-19 or because of close contact with COVID-19 patients.

All patients were screened at admission for severity of the disease by the MoHFW Clinical Guidelines for the management of COVID-19, dated 30th March 2020. Screening included: demographic details, history of symptoms, comorbidities and their medication, clinical examination including respiratory rate, blood pressure, pulse oximetry (SpO2) and chest X-ray. Clinically asymptomatic patients with SpO2 >94% on room air and without any radiographic abnormality were classified as mild. Patients with lung infiltrates on chest X-ray were classified as having moderate disease if SpO2 was 90-94%, and severe if SpO2 was <90%.

A venous blood sample was collected for following laboratory measurements: Complete blood count (CBC) with absolute neutrophil count (ANC), absolute lymphocyte count (ALC), liver and kidney tests, serum C-reactive protein (CRP), serum ferritin (as an acute phase reactant). Patients with comorbidities had appropriate additional tests (glucose, HbA1c etc).

A baseline ECG was recorded for any abnormalities and specifically for QTc, in anticipation of hydroxychloroquine (HCQ, 400mg BD on day 1, and 200mg BD x 4 days) treatment which was not given for those with prolonged QTc, G6PD deficiency and those younger than 16 years of age. HCQ treatment was not prescribed for those patients admitted from June 2020 based on updated evidence on its efficacy in the treatment of COVID-19. Pre-admission treatment for co-morbidities was continued or adjusted as necessary.

Laboratory tests were repeated as necessary and usually on day 5 for stable patients. Those who showed deterioration in clinical state, fall in SpO2 or worsening chest X-ray were

---

**Fig. 1: Flowchart of study participants**

**Duration March-June 2020**

**Severity grading**

- Mild=587 (320 Male, 267 Female)
- Moderate=49 (31 Male, 18 Female)
- Severe=164 (89 Male, 75 Female)

**Progression**

- Continued in observation Mild=582, Moderate=41, Severe=100
- Shifted to ICU mild=5, Moderate=8, Severe=64

**Outcome**

- Discharged=723
- Discharged=52
- Deaths=25
Table 1: Demographic, clinical characteristics and comorbidity of patients by severity grading

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mild n (%)</th>
<th>Moderate n (%)</th>
<th>Severe n (%)</th>
<th>p</th>
<th>p1</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>587 (73.4)</td>
<td>49 (6.1)</td>
<td>164 (20.5)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>37.3 (19.1)</td>
<td>52.7 (19.1)</td>
<td>54.9 (15.5)</td>
<td>&lt;.001</td>
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</table>

Age categories (y)*

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<tr>
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<th>≤ 10</th>
<th>10-20</th>
<th>20-40</th>
<th>&gt;60</th>
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<th>71</th>
<th>231</th>
<th>156</th>
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<td>(8.5)</td>
<td>(12.1)</td>
<td>(39.4)</td>
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<td>(13.5)</td>
<td>(19.1)</td>
<td>(17.1)</td>
<td>(13.5)</td>
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Sex*

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<td>267</td>
<td>45.5</td>
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<td>(45.5)</td>
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<th>Number of symptoms at admission*</th>
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<table>
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<td>(57.9)</td>
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<th>31</th>
<th>18</th>
<th>7</th>
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<td>(63.5)</td>
<td>(36.7)</td>
<td>(14.8)</td>
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Symptoms*

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<tr>
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<th>Fever</th>
<th>Cold-Cough</th>
<th>Sore Throat</th>
<th>Breathless</th>
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<td>130</td>
<td>180</td>
<td>66</td>
<td>16</td>
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<td>(22.1)</td>
<td>(21.0)</td>
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<td>(13.4)</td>
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<th>Duration of symptoms (days)</th>
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<tr>
<th>Comorbidity*</th>
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<tbody>
<tr>
<td>T2DM</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>IHD/CABG</td>
</tr>
<tr>
<td>Asthma/COPD</td>
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<table>
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<tr>
<td>One</td>
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<tr>
<td>More than one</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
</tr>
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<td>---------------------------</td>
</tr>
<tr>
<td>Systolic BP</td>
</tr>
<tr>
<td>Diastolic BP</td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
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<td>Biochemical characteristics</td>
</tr>
<tr>
<td>Day 1 (n=778)</td>
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<td>Hemoglobin (g/L)</td>
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<table>
<thead>
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<th>127</th>
<th>126</th>
<th>126</th>
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<tbody>
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<td></td>
<td>(114-141)</td>
<td>(106-139)</td>
<td>(115-139)</td>
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<thead>
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<th></th>
<th>6.1</th>
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<td>(4.7-7.6)</td>
<td>(4.8-7.5)</td>
<td>(4.9-8.7)</td>
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</table>

Day 5 (n=581)*

<table>
<thead>
<tr>
<th></th>
<th>Hemoglobin (g/L)</th>
<th>TLC (x10^9/cmm)</th>
<th>Platelet count (x10^9/cmm)</th>
<th>ANC (x10^9/cmm)</th>
<th>S. Ferritin (pmol/l)</th>
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<tbody>
<tr>
<td>Normal</td>
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<td>259</td>
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<td>Abnormal</td>
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<td>291</td>
<td>4.1</td>
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<td>Chest X-ray *</td>
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<td>1.01</td>
<td>1.01</td>
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<td>156.91</td>
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<tr>
<td>Unilateral infiltrates</td>
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<td>--</td>
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<td>4.18</td>
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</table>

Note: values are Median (IQR) and p by ANOVA, p1 adjusted for age and sex. *number (%) and p by χ²-test. T2DM: Type-2 Diabetes Mellitus, IHD:Ischemic heart disease, CARG-Coronary artery bypass graft, COPD: Chronic obstructive pulmonary disease, TLC-Total Leucocyte count, ANC-Absolute Neutrophil Count, ALC-Absolute lymphocyte count, CRP- C-Reactive protein, PT- Prothrombin time, INR- International normalized ratio.

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transferred to the Intensive Care Unit (ICU) for necessary treatment. Patients with a stable course were discharged between days 15-18 after two consecutive negative tests for SARS CoV-2 Ag. In these initial 800 patients there were no height and weight measurements during admission. We were able to obtain this data during a telephonic follow up 6 weeks after discharge (n=219).

All patients signed a written informed consent at the time of admission which permitted use of anonymized data for research. The Independent Ethics Committee of Symbiosis Medical College for Women gave necessary approvals.

**Statistical Methods**

We have presented data of clinical and laboratory characteristics of the initial 800 patients by sex, severity of disease and for those admitted to ICU. We have also shown data for those who were asymptomatic at admission. For statistical analysis, variables with skewed distributions were log-transformed to satisfy assumptions of normality. Differences in clinical and biochemical characteristics between groups of patients were tested by ANOVA adjusting for age and sex or by Chi-square test. Significant associations generated in this analysis were used as predictors to build a multivariate logistic regression model to test independent associations with the outcome of need for ICU treatment. These are presented as ROC curves. Analyses were carried out using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA).

A Random Forest model was also built to predict ICU admission requirement using significant clinical and laboratory features from the above analysis. The model was trained on the first 500 patients and tested on subsequent 300 patients for its accuracy which is reported as sensitivity, specificity, positive predictive value.
8th April to 15th June, 402 patients were tested for SARS-CoV2 because they had suggestive symptoms and others because of close contact with a case (Figure 1). There were 440 males and 360 females. Our cohort of COVID-19 patients is relatively young: 49% of patients were below 40 years of age (16% less than 20 years), only a fifth (n=155) were beyond 60 years of age. Majority of patients belonged to lower-middle socio-economic classes.

At admission, 50% of patients had no symptoms, 31% had one symptom, 14% had two symptoms and only 6% had more than two symptoms. The commonest symptoms were fever (26%) and cough (26%); other symptoms included sore throat (13%) and breathlessness (11%). The average duration of symptoms before hospitalization was 3.4 days.

Diabetes (17%) and hypertension (15%) were the commonest comorbidities which were more common in females. None of the patients had a previous diagnosis of tuberculosis, HIV or other immunocompromised state. We were able to calculate BMI in 219 patients from self-reported height and weight data to be 25.0 ± 6.0 kg/m² (age 45.4 ± 16.8 years, 52% males).

Asymptomatic patients were younger (38.9 vs 44.7 years), less likely to have comorbidities (23 vs 28%), and had lower prevalence of moderate and severe disease (15% vs 39% respectively) compared to those symptomatic at the time of hospital admission. Only 3% of asymptomatic patients needed ICU treatment and 4 died compared to 16% ICU admissions and 21 deaths in symptomatic group. When comparing (PPV) and negative predictive value (NPV). The data on subsequent 300 patients was shared for validation after the model was available. We also had no symptoms, 31% had one symptom, 14% had two symptoms and only 6% had more than two symptoms. The commonest symptoms were fever (26%) and cough (26%); other symptoms included sore throat (13%) and breathlessness (11%). The average duration of symptoms before hospitalization was 3.4 days.

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Results

Of the initial 800 consecutive COVID-19 patients admitted to Symbiosis University Hospital between 8th April to 15th June, 402 patients were tested for SARS-CoV2 because they had suggestive symptoms and others because of close contact with a case (Figure 1). There were 440 males and 360 females. Our cohort of COVID-19 patients is relatively young: 49% of patients were below 40 years of age (16% less than 20 years), only a fifth (n=155) were beyond 60 years of age. Majority of patients belonged to lower and lower-middle socio-economic classes.

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laboratory tests, lymphopenia was more common in symptomatic and severely ill patients compared to asymptomatic patients, and inflammatory markers were also higher. As a group, mild and asymptomatic patients had near normal biochemical tests, normal chest X-ray (95%) that remained normal over the course of illness.

Table 1 describes characteristics of patients by the clinical severity at admission. Out of 800 patients, 587 (73%) had mild disease, 49 (6%) moderate and 164 (21%) severe disease. Twenty-four severely ill patients needed immediate ICU admission (for hypoxemic respiratory failure, others were admitted in the isolation wards. Moderate and severely ill patients were older than those with mild disease, had larger number of symptoms at presentation and for longer duration. Twenty-four percent of patients with severe disease had more than one comorbidity (35% had diabetes and 31% had hypertension). Expectedly, SpO2 was lower in moderate and severe cases. Chest X-ray was normal in 72%, and showed unilateral or bilateral infiltrates in 28% patients which were mostly seen in moderate and severe groups. Pulse rate and blood pressure were similar across groups.

Hemoglobin, total leucocyte count and platelet count were similar across three severity groups. There was increasing neutrophilia and lymphopenia with increasing severity which reflected in increasing ANC/ALC ratio. Markers of inflammation i.e., serum C-reactive protein (CRP) and serum ferritin progressively increased with severity of the disease. The haematological and inflammatory markers remained stable and near normal in mild cases (on second measurement 3-5 days after admission) but continued to be elevated or deteriorated in severe patients.

When demographic and clinical characteristics were compared by sex, females had similar age, symptoms and severity grading but had higher rate of co-morbidities compared to males. Mortality was higher in males.

HCQ was prescribed to 395 patients. It was stopped in 12 patients who developed QTc prolongation on ECG. Seventy-seven patients also received Azithromycin and 86 Oseltamivir, based on treating physician’s preference.

A total of 77 patients needed ICU treatment (Table 2) (24 directly admitted, 53 shifted from isolation ward due to clinical deterioration). These patients had a mean age of 57 years (min 25 and max 90 years) and 44 were males. Majority of these patients were symptomatic at admission, had longer duration of symptoms and about half of these patients had at least one comorbidity (29 diabetes and 26 hypertension). They had higher ANC (median 5.3 vs 3.2), lower ALC (median 1.0 vs 1.8), and higher ANC/ALC ratio (median 5.3 vs 1.9) compared to those who did not require ICU treatment. Similarly, CRP and serum ferritin concentrations were also higher.

Ten of these patients had cardiac
Table 3B: Random forest model for ICU admission, trained on first 500 patients and tested on subsequent 300 patients

<table>
<thead>
<tr>
<th>Models</th>
<th>Data Dimension</th>
<th>Training Accuracy N=500 (Discovery Data)</th>
<th>Validation Accuracy N=300 (Validation Data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Main Model</td>
<td>N=465(500), 9 Features, 35 No-ICU samples with NA removed</td>
<td>72.72</td>
<td>95.01</td>
</tr>
<tr>
<td>Model (Age&gt;20)</td>
<td>N=396, 9 features, 69 samples less than age&gt;20 removed</td>
<td>72.72</td>
<td>94.31</td>
</tr>
<tr>
<td>Model Excluding CRP and Ferritin</td>
<td>N=465(500), 7 Features, 35 No-ICU samples with NA removed</td>
<td>75.00</td>
<td>93.11</td>
</tr>
<tr>
<td>Model Excluding Ferritin</td>
<td>N=465(500), 8 Features, 35 No-ICU samples with NA removed</td>
<td>72.72</td>
<td>94.04</td>
</tr>
<tr>
<td>Model Excluding CRP</td>
<td>N=465(500), 8 Features, 35 No-ICU samples with NA removed</td>
<td>70.45</td>
<td>94.53</td>
</tr>
<tr>
<td>Model (Age&gt;20) excluding CRP and Ferritin</td>
<td>N=396, 7 features, 69 samples less than age&gt;20 removed</td>
<td>77.27</td>
<td>92.04</td>
</tr>
</tbody>
</table>

arrhythmias, 37 required invasive mechanical ventilation, 12 had acute kidney injury (KDIGO stage 1 and above) and 25 developed circulatory failure. Twenty-five patients died in the ICU: four because of refractory hypoxemia and 19 due to multi-organ failure, 2 due to sudden cardiac death. Patients who died were older (mean age 64.7, min 36-max 90 years) compared to those who survived, and predominantly male 18/25. Fifty-two patients were discharged from ICU; the average duration of ICU stay was 12 days.

We found that the following factors were significantly related to ICU admission on univariate analysis: higher age, larger number of symptoms at diagnosis, more than 1 co-morbidity, abnormal chest X-ray, low SpO2 (<94%), higher ANC/ALC ratio, CRP and Serum ferritin concentrations.

Table 3A describes the multivariate logistic regression to predict ICU treatment. Significant predictors were: higher age (OR 1.05, 95% CI 1.04 to 1.06), symptomatic presentation (OR 6.13, 95% CI 3.14 to 11.96), abnormal chest X-ray (OR 20.14, 95% CI 8.79 to 46.16) and low SpO2 < 93% (OR 12.67, 95% CI 6.36 to 25.23). Two indicators of lung involvement (low SpO2 and abnormal chest X-ray) had an overriding prediction. The laboratory tests (ANC/ALC ratio, CRP, S. Ferritin) were significantly related but did not make an additional contribution to the prediction (Figure 2). The overall prediction was high (AUC 0.951), and the model suggests that simple clinical, radiological and SpO2 predict requirement for ICU treatment quite reliably. Of the laboratory tests, the simple hematological test of CBC made an equal contribution compared to the costlier markers of inflammation. HCQ treatment did not reduce the need for ICU treatment.

A Random forest model was constructed on initial 500 patients using sex and eight features found to be significant in univariate logistic regression. The model was able to predict ICU admission with high accuracy on subsequent 300 patients (sensitivity 80%, specificity 88%, PPV 47%, NPV 97%). CRP, SpO2 and chest X-ray were the top three important predictors. A model without CRP and ferritin was comparable (sensitivity 77%, specificity 86%, PPV 43% and NPV 96%), further excluding younger patients (<20 years of age) only marginally improved the accuracy.

Seven hundred and seventy-five patients (96.8%) were discharged from the hospital after 15-18 days of hospitalization.

Discussion

This is one of the largest case series of COVID-19 patients from a dedicated COVID-19 hospital from Pune, India. It describes patients from the early phase of the epidemic and given a liberal hospital admission policy at the time includes a large number of asymptomatic (50%) and mild (73%) cases. Sixteen percent of patients needed ICU management, 3% died and 97% were discharged in satisfactory condition. We developed and validated a predictive model to identify patients requiring ICU admission with high accuracy using mainly clinical parameters and two commonly used markers of respiratory involvement. This supports the current policy to triage patients needing hospitalization and the usefulness of simple clinical and bed-side measurements in such a decision. This will be important in resource-limited settings.

We report on a large number of asymptomatic cases who were younger and had minimally deranged laboratory findings. Majority of them remained with mild disease and did not need any further intervention. Severe disease was associated with higher age, multiple symptoms and comorbidities, and abnormal laboratory tests. The latter included higher neutrophil (ANC) and lower lymphocyte (ALC) count leading to higher ANC/ALC ratio, and higher levels of CRP and serum ferritin concentrations, but not coagulation parameters. Mild cases had stable clinical and laboratory course while severe cases deteriorated in both. Patients who required ICU treatment were older (mean age 57 years), more symptomatic and had more comorbidities compared to those who did not require ICU treatment. Those who died were the oldest (mean age 64.7 years) and predominantly men (18/25). Our death rate of 3% is lower than the rate in Pune at that time (4.5%), probably due to preponderance of young patients with mild or asymptomatic disease.

We used both a conventional multiple logistic regression and the random forest technique to predict the need for ICU admission with high accuracy. Overriding importance of clinical and simple bedside predictors of respiratory compromise makes our model highly effective in a resource limited set-up. Our results highlight the importance of having at least a basic x-ray machine in primary COVID care centers. We encourage other researchers to validate and improve our model using their data to increase its generalizability. A high negative predictive value means that the model...
accurately predicts those who are unlikely to need ICU admission, and raises confidence in selecting patients for home quarantine, thus helping to avoid overcrowding of specialized COVID-19 hospitals.

A large number of papers have been published on epidemiology, clinical and biochemical characters of COVID-19 patients and some models to predict serious outcomes. They are mainly from China, Italy, Spain, USA and UK. These countries have a different demographic and socio-economic profile compared to India. Their COVID-19 patients were older, more obese and with substantially more co-morbidity. This reflected in higher morbidity and mortality, especially in the geriatric and the deprived sections of the population. There are only a few reports from India: 1) Gupta et al. reported on 22 young patients with mild disease from a tertiary hospital in Delhi, two-thirds having a history of travel abroad. 2) Tambe et al. reported on 197 patients (mean age 45 years) from the largest public hospital from Pune, with a high mortality rate of 29.4%, probably due to a referral bias. In other reported studies, the risk of ICU treatment varied from 8-15%. Saluja et al also reported (n=406) a profile of relatively young, predominantly male patients. Their figures of 8% ICU requirement and 1.9% mortality are not very different to our case series. We have also reported our experience of critically ill ventilated patients and outcomes.

Strengths of our study include: a large number with a mix of symptomatic and asymptomatic patients, a uniform protocol of clinical and laboratory measurements, severity classification, and ICU transfer. Inclusion of data on a large number of asymptomatic and mild patients provides an assurance that they can be managed at home or in a peripheral facility. For hospitalized patients, we developed a useful predictive model for ICU requirement from simple clinical measurements and validated it in subsequent group of patients. This has guided us to improve our treatment practices and make them pragmatic. Unfortunately, we do not have measurements of height, BMI and admission glucose concentrations in these patients, and therefore are not able to comment on their contribution to bad outcomes.

In summary, we describe clinical features of COVID-19 patients from early phase of epidemic in India and the first validated model to predict ICU requirement. This will be useful for the clinicians and the policy makers.

Contributors

CY, VN conceptualized this paper and drafted it with contributions from US. SS analyzed the data and other authors reviewed the study findings and contributed to the interpretation of results. All authors agreed and saw the final version of this manuscript.

Acknowledgement

We are further grateful to all participants for giving us consent to use this data for research. This research study was funded by Symbiosis International (Deemed University), Pune through its internal funds and partially funded by DST/SERB File Number: MSC/2020/000063. We gratefully acknowledge the contribution of Dr Supriya Londhe, Dr Afreen Pathan, Dr Pravin Anpat, Dr Mayur Yewale, Dr Urvashi Panchal for their contribution to data collection. We thank Dr Mohan Gupte, Dr Satyajeet Rath and Dr Sanat Phatak for useful discussions and advice. The content of this paper is solely the responsibility of the authors.

References

A Prospective Study of the Course and Outcome of COVID-19 Patients with Acute Kidney Injury Admitted in an Intensive Care Unit

Shreyas D Wajekar1*, Shreepad M Bhat2, Niraj B Birajdar3, Dileep B Kadam4

Abstract

Background: COVID-19, caused by SARS-COV-2, has been a health emergency of great concern throughout the world. Acute Kidney Injury was reported in a considerable amount of patients suffering from COVID-19, especially in those admitted in the ICU setting. This study was undertaken to study the clinical profile, incidence, severity, requirement of renal replacement therapy, and the outcomes of COVID-19 patients with Acute Kidney Injury admitted in the Intensive Care Unit.

Materials and Methods: A prospective observational study was conducted at a tertiary hospital recognized as Dedicated COVID Hospital during the period of May 2020 to September 2020. 218 patients hospitalised in the Intensive Care Unit during this period were monitored for the development of Acute Kidney Injury. The clinical profile, laboratory findings, requirement of invasive ventilation and renal replacement therapy, and outcomes of such patients were recorded. Data was analysed using the SPSS software.

Results: Among all the patients enrolled in the Intensive Care Unit during the study period, 27.06% developed Acute Kidney Injury. 67.79% of these patients developed AKI during the first five days of hospitalisation. 76.27% of the patients with AKI required invasive mechanical ventilation, while 28.81% required renal replacement therapy. There was a significant association between the development of Acute Kidney Injury and the requirement of invasive mechanical ventilation (p = 0.0000015). 44.68% of the deaths among the 218 patients were associated with COVID-19 related AKI (p = 0.0000003).

Conclusion: Acute Kidney Injury was found to be common among the hospitalised COVID-19 patients in our Intensive Care Unit. AKI occurs early, often in a temporal association with respiratory failure, and portends a dire prognosis.

Introduction

Coronavirus Disease 2019 (COVID-19) is a severe acute infectious respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).1 Initially detected in the Wuhan province of China in December 2019, it later spread to other parts of the world, and was later declared as a pandemic by the World Health Organisation (WHO) in March 2020.2,3 The clinical spectrum of patients presenting with COVID-19 infection is varied – ranging from asymptomatic to having mild symptoms, to developing acute hypoxic episodes, or having a full-blown acute respiratory distress syndrome.4-11 Although COVID-19 primarily involves the respiratory system, there might be other systemic involvement as well. Initial reports indicated that the involvement of kidneys in COVID-19 was not common.1-3 As the disease reached a stage of pandemic, various other studies noted that the incidence of Acute Kidney Injury (AKI) in COVID-19 patients was alarming, particularly among patients in the Intensive Care Unit.5-10 However, the incidence of AKI reported among COVID-19 patients varies widely. Hence, this study was undertaken to study the clinical profile, incidence, severity and outcomes of patients of COVID-19 with Acute Kidney Injury admitted in the Intensive Care Unit of a Dedicated COVID Hospital in India.

Aims and Objectives

The primary objective of this study was to determine the incidence of Acute Kidney Injury in patients with COVID-19 admitted in an Intensive Care Unit, and to study their baseline characteristics and the laboratory parameters associated with its development. The secondary objective of the study was to determine the severity of Acute Kidney Injury, the need for renal replacement therapy in such patients, the renal recovery, and to find out the outcomes associated with Acute Kidney Injury in COVID-19.

Materials and Methods

This prospective observational study was conducted at a tertiary hospital recognized as Dedicated COVID Hospital at Pune. The study included all the patients admitted in the period of five months from May 2020 to September 2020, who met the following criteria –

Inclusion Criteria: All hospitalised COVID-19 patients (above 12 years of age) admitted in the Intensive Care Unit with laboratory confirmed diagnosis of COVID-19.

Data collection: All patients who met the above criteria were included in the study. The diagnosis of COVID-19 was confirmed by RTPCR or Rapid Antigen test or CB-NAAT for COVID-19.
on any of the respiratory specimen as per ICMR guidelines in all patients. COVID-19 patients who were known cases of Chronic Kidney Disease requiring maintenance hemodialysis were excluded from the study. Details regarding the demographics, presenting clinical symptoms, prior comorbidities, prior level of renal function, fluid intake and output, and the in-hospital laboratory data were noted. Laboratory data consisted of complete blood count, renal and liver function, creatinine kinase, lactate dehydrogenase, and inflammatory markers including C-reactive protein (CRP), ferritin, and D-dimer. Normal range of these parameters was provided by the laboratory.

All patients received treatment as per the standard protocol by the treating physicians. Patients’ clinical course was observed for the progression of symptoms, development of new symptoms or physical findings, on admission of the patient. X-axis represents various age groups (in years) while the Y-axis represents the number of patients. A majority of patients fall under the 50 to 70 years age group.

**Table 1: Baseline characteristics and comorbidities of patients of AKI with COVID-19 in the ICU setting**

<table>
<thead>
<tr>
<th>Patients with AKI (n=59)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>65.2±13.18</td>
</tr>
<tr>
<td>Minimum age (years)</td>
<td>36</td>
</tr>
<tr>
<td>Maximum age (years)</td>
<td>92</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>3.21:1</td>
</tr>
<tr>
<td>Fever</td>
<td>50 (84.74%)</td>
</tr>
<tr>
<td>Cough</td>
<td>46 (77.97%)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>43 (72.88%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>22 (37.29%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (44.07%)</td>
</tr>
<tr>
<td>Old CVA</td>
<td>02 (3.39%)</td>
</tr>
<tr>
<td>Old IHD</td>
<td>03 (5.08%)</td>
</tr>
<tr>
<td>COPD</td>
<td>05 (8.47%)</td>
</tr>
</tbody>
</table>

**Table 2: Baseline laboratory parameters of patients of AKI with COVID-19 in the ICU setting at the time of admission**

<table>
<thead>
<tr>
<th>Patients with AKI (n=59)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Hb (g/dl)</td>
<td>12.2±2.72</td>
</tr>
<tr>
<td>Mean TLC (cells/mm³)</td>
<td>8786.81±4389.35</td>
</tr>
<tr>
<td>Mean N:L Ratio</td>
<td>6.49±4.50</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>05 (9.47%)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>16 (27.12%)</td>
</tr>
<tr>
<td>Neutrophils &gt;3.5</td>
<td>42 (71.19%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (27.12%)</td>
</tr>
<tr>
<td>Elevated Blood Urea</td>
<td>45 (76.27%)</td>
</tr>
<tr>
<td>Mean Blood Urea (mg/dl)</td>
<td>78.66±48.69</td>
</tr>
<tr>
<td>Elevated Serum Creatinine</td>
<td>46 (77.97%)</td>
</tr>
<tr>
<td>Mean Serum Creatinine (mg/dl)</td>
<td>2.3±1.94</td>
</tr>
<tr>
<td>Elevated Serum Ferritin</td>
<td>39 (66.10%)</td>
</tr>
<tr>
<td>Elevated CRP</td>
<td>58 (98.30%)</td>
</tr>
<tr>
<td>Elevated CPK-MB</td>
<td>11 (18.64%)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>51 (86.44%)</td>
</tr>
<tr>
<td>Elevated D-dimer</td>
<td>54 (91.52%)</td>
</tr>
<tr>
<td>Mean D-dimer (mcg/ml)</td>
<td>3.28±3.53</td>
</tr>
</tbody>
</table>

The timing of the initial development of AKI with respect to the day of hospital admission is shown in Figure 2. Most cases developed early in the course, with 25.42% of the patients either presenting with AKI or developing it with 48 hours of admission. 42.37% of the patients developed AKI between the third to fifth days of hospitalisation. Of the 59 patients who developed AKI, 32 (55.24%) had Stage 1 AKI, 7 (11.86%) had Stage 2 AKI, and 20 (33.90%) had Stage 3 AKI (based on KDIGO Staging of AKI).

The relationship of the worsening of respiratory failure and development of AKI is shown in Figure 3. There is a substantial overlap of AKI events around the time of intubation and mechanical ventilation. Of the 59 patients who developed AKI, 76.27% required mechanical ventilation. The mean values of Blood Urea and Serum Creatinine on the day of intubation were 149.6±82.65 mg/dl and 3.84±2.69 mg/dl. 28.81% of the patients required renal replacement therapy during the course of hospitalisation, while 20.34% underwent multiple sessions of renal replacement therapy.

From May 2020 to September 2020, 218 patients were admitted in the Intensive Care Unit with a diagnosis of COVID-19 present on admission or made during the hospitalisation. Of these 218 patients, 59 patients (27.06%) developed Acute Kidney Injury during hospitalisation. AKI was seen commonly in the age group of 50 to 70 years as shown in Figure 1. The mean age of the 59 patients who developed AKI was 65.22 ± 13.18 years, with the minimum and maximum ages being 36 years and 92 years respectively. The baseline characteristics and laboratory parameters of COVID-19 patients with AKI are shown in Tables 1 and 2.

The results showed a significant development of medical complications especially Acute Kidney Injury, and requirement of organ support like non-invasive or invasive ventilation, haemodialysis etc. Their outcome in the form of discharge or death was noted.

Statistical analysis: We performed descriptive statistics including means and standard deviations for normally distributed continuous measures. Data was analysed using Chi-Square test, Fisher exact tests, unpaired t-test, etc. with the help of SPSS software. All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant.

**Results**

From May 2020 to September 2020, 218 patients were admitted in the Intensive Care Unit with a diagnosis of COVID-19 present on admission or made during the hospitalisation. Of these 218 patients, 59 patients (27.06%) developed Acute Kidney Injury during hospitalisation. AKI was seen commonly in the age group of 50 to 70 years as shown in Figure 1. The mean age of the 59 patients who developed AKI was 65.22 ± 13.18 years, with the minimum and maximum ages being 36 years and 92 years respectively. The baseline characteristics and laboratory parameters of COVID-19 patients with AKI are shown in Tables 1 and 2.

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The relationship between requirement of invasive mechanical ventilation and the development of AKI is shown in Table 4. Among the 218 patients who were hospitalised during the study period, 108 (49.54%) required mechanical ventilation. Among the patients who required mechanical ventilation, 41.67% developed AKI as compared with 12.73% in non-ventilated patients. The majority of patients with severe (Stage 3) AKI (18.52%) and all patients requiring dialytic support were on mechanical ventilation.

Among the 218 patients who were admitted during the study period, 42 (44.68%) of the deaths (p value = 0.0000003) were attributed to COVID-19 related Acute Kidney Injury. 42 (71.9%) out of 59 patients who developed Acute Kidney Injury had death as an outcome. Among the 17 people who required dialysis, 13 (76.47%) died. Renal recovery was noted among 17 (28.81%) patients who developed Acute Kidney Injury. Based on the severity of COVID-19-AKI, the mortality was 53.12%, 87.71% and 85% in patients with AKI Stages 1, 2, and 3 respectively (as shown in Figure 4).

### Discussion

Since its initial detection in the Wuhan province of China in December 2019, the Coronavirus Disease 2019 (COVID-19) has affected the entire world, and was declared a pandemic in March 2020. The novel coronavirus was named as the Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) due to its high homology (~80%) to SARS-CoV, which caused acute respiratory distress syndrome (ARDS) and high mortality during 2002-03. The disease itself is rapidly evolving and expanding, with a varied spectrum of effects - from mild, self-limiting respiratory tract illness to severe acute respiratory distress syndrome (ARDS), multiple organ failure, and death.

The primary involvement of the lung with diffuse alveolar damage and respiratory failure has been commonly seen in patients with COVID19; however, recent reports reveal that kidney injury is also relatively common and is associated with increased morbidity and mortality. The renal involvement in COVID-19 is frequently observed since the virus enters the cell through the angiotensin-converting enzyme 2 (ACE2), which is expressed, in addition to pulmonary type 2 alveolar cells, on renal proximal tubular cells, glomerular visceral and parietal epithelium, and the cytoplasm of the distal tubules and collecting ducts. COVID-19 also causes hemodynamic instability and cytokine storm, which, in addition to direct renal infection, may lead to acute tubular necrosis (ATN).

The incidence of AKI seen among the COVID-19 patients admitted in the ICU in our study was 27.06%. A study conducted by Wang Y et al. among 344 COVID-19 patients admitted in eight ICUs had an almost similar incidence of AKI (25.0%). Another study conducted by Yu Y et al. among 226 COVID-19 patients admitted in 19 ICUs in Wuhan reported the incidence of AKI to be 25.2%.

As observed in our study, AKI developed within the first 8 days of admission with the peak corresponding to the day of intubation and initiation of mechanical ventilation. A study carried among 704 patients with COVID-19 by Cheng et al. similarly noted that most AKI developed within 7 days of admission. A multicentre study carried in New York among 5449 patients by Hirsch et al. observed that AKI seems to develop soon after hospitalization, with a characteristic spike around the time of requiring intubation.

28.81% of the patients with AKI in our study required renal replacement therapy, and 20.34% required multiple sessions of renal replacement therapy. Similar studies carried out by Hirsch et al. in Northwell, Mohamed et al. in Ochsner, and Cummings et. al in Columbia noted that the need for renal replacement therapy was related to AKI severity.

### Table 3: Clinical Course in patients of AKI with COVID-19 in the ICU setting

<table>
<thead>
<tr>
<th>Patients with AKI (n=59)</th>
<th>Mean Day of AKI</th>
<th>Mean Day of Intubation</th>
<th>Number of patients on mechanical ventilation with AKI</th>
<th>Mean Blood Urea on the Day of Intubation (mg/dl)</th>
<th>Mean Serum Creatinine on the Day of AKI (mg/dl)</th>
<th>Number of patients requiring Renal Replacement Therapy</th>
<th>Number of patients requiring multiple sessions of Renal Replacement Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.90±3.45</td>
<td>4.07±3.49</td>
<td>45 (76.27%)</td>
<td>149.64±82.65</td>
<td>3.84±2.69</td>
<td>17 (28.81%)</td>
<td>12 (20.34%)</td>
</tr>
</tbody>
</table>

The outcomes of the patients admitted during the study period based on the severity of AKI (KDIGO Staging).

![Fig. 3: The relationship between the day of mechanical ventilation and the day of AKI](image)

![Fig. 4: Outcomes based on the severity of Acute Kidney Injury](image)
replacement therapy in COVID-19 patients with AKI admitted to a critical care unit is at least 25%, 20-23. Out of the patients who developed Acute Kidney Injury during the study period, 71.9% patients died. 76.47% of those requiring renal replacement therapy succumbed during the course of illness. Studies conducted by Zhou et al., Chen et al., Ruan et al., and data from ICNARC report had similar observations that COVID-19 related Acute Kidney Injury is associated with worse outcomes. 24-27 Additionally, ICNARC data and Zhou et al. observed a higher mortality among the patients requiring renal replacement therapy.

**Conclusion**

Renal involvement following SARS-CoV-2 infection is more common than initially thought. Patients requiring mechanical intubation are at an increased risk of developing Acute Kidney Injury, and there seems to be a temporal association between the development of AKI and the requirement of invasive mechanical ventilation. The development of AKI among critical COVID-19 patients portends a dire prognosis. Unfortunately, renal replacement therapy provided little survival benefit. Thus, early detection of Acute Kidney Injury in such patients, initiation of renal replacement therapy at the apt time, and supportive treatment is of utmost importance. Policy changes and planning in preparation for this high incidence of AKI in COVID-19 patients are necessary at the local and national levels.

**Limitations of the Study**

Our study was a single centre observational study including a limited number of patients admitted in the Intensive Care Unit spread over a period of approximately 5 months. Therefore, the results will be applicable to a similar group of patients. Data for urine examination and the renal parameters on ultrasonography were also extremely limited due to the limited resources during the surge of COVID-19 cases, despite current clinical interest and their potential to affect clinical outcomes. A large multicentre study including patients admitted in both general wards and intensive care units will definitely be helpful to improve the medical understanding on this topic.

**Statement of Ethics**

Study was approved by the Ethical Committee of the Dedicated COVID Hospital, Pune.

**References**


4. "Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected" WHO interim Guidance, March 2020


A Retrospective Analysis of Fixed Combination of Empagliflozin and Linagliptin in Addition to the Existing Treatment for its Clinical Effectiveness in Adults with Type 2 Diabetes: A Real-World Clinical Experience

Abhinav Gupta¹, Pavan Malhotra², Vinu Jamwal¹, Maneesha Khalse³*

Abstract

Background: The efficacy and safety of empagliflozin and linagliptin (Empa/Lina), is demonstrated in adults with T2DM in the various trials. The study was planned to investigate the clinical effectiveness and safety of Empa/Lina in a more representative population of the Indian outpatient setting.

Methods: The study was conducted in poorly controlled T2DM patients being treated with Empa/Lina once daily (25/5mg) as an add on in a tertiary care institute in Jammu, India. Various efficacy and safety parameters were assessed prior to the initiation of Empa/Lina and thereafter at periodic intervals until week 12. Appropriate statistical tests were applied.

Results: In a total of 347 eligible patients, the mean age (SD) was 57.84 ±7.3 years, Males were 49%, average body weight was 79.81 ±9.72 kg. The median duration of diabetes was 6.42 ±2.05 years. Empa/Lina as an add on therapy to other glucose-lowering treatment was associated with a significant lowering in HbA1c (-1.1 ±0.64 mg/dl), FPG level -47.11 (±20.42) mg/dl, PPG level (-71.32 ± 26.56), body weight -2.64 (±1.97) kg and blood pressure parameters (systolic BP -7.68 ±5.2 and Diastolic BP -3.16 ±1.7) from baseline at 12 weeks. A total of 47.55 percent of patients responded to Empa/Lina (25/5mg) added in conjunction with other antidiabetes agents. There was no significant difference in glycemic parameters of various subgroups assessed based on concurrent antidiabetes drugs. However, a significant reduction in body weight of subjects on insulin therapy was noticed. There was an improvement in eGFR level which was maintained across the study period. Genital mycotic infection was reported in 8.6% of patients. Empa/Lina as an add on therapy was well tolerated with less hypoglycemic events.

Discussion and Conclusion: Thus, the combination of empagliflozin and linagliptin (25/5 mg) significantly improved the glycemic and non-glycemic measures in combination with one or more commonly prescribed antidiabetic drugs in inadequately controlled diabetes patients and is well tolerated.

Introduction

Type 2 diabetes mellitus (T2DM), which is a chronic disease with multiple metabolic defects is highly prevalent condition around the globe. Developing countries like India are rapidly becoming the epicenter of this pandemic. Associated comorbidities like hypertension and obesity may further lead to worsening of the complications rendering the management more challenging with optimum glucose control. Furthermore, the chronic and progressive nature of the disease makes the maintenance of recommended glycemic targets with monotherapy rarely possible after a few years; invariably need combination therapy. There is a clinical unmet need for an effective antidiabetic treatment that can ameliorate the risk of progression to major complications, with a lower propensity to hypoglycemic events and weight gain, common with conventional antidiabetes therapy. Combination therapies that may target various stages of the disease with more favorable safety profiles and simplified drug dosing, may have a role in improving patient adherence and quality of life.

Current guidelines on diabetes encourage the early adoption of oral combination therapies at treatment initiation while simultaneously underscoring the importance of individualized treatment. 1 Empagliflozin/linagliptin (Empa/Lina) (10/5 mg, 25/5 mg) once-daily tablet is the novel, first-in-class, fixed combination of sodium glucose co-transporter-2 inhibitor (SGLT2 inhibitor) and dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor). Potential benefit on glucose control and beyond offered by this combination may translate a better patient outcome in a more diverse clinical setting of India. Therefore, with an objective to evaluate the clinical effectiveness and safety of the recently approved single-pill combination of EMPA/LINA we planned to conduct the present study.

Methods

Study design: Data from the electronic medical records of tertiary care hospital ‘Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, India’ was retrieved from February 2019 to October 2019. The study data consists of adult
Type 2 diabetes mellitus (T2DM) aged 18-70 years with uncontrolled glycaemia (N=986) either on single or multiple antidiabetes agents from February 2019 to October 2019.

Aged <18 years, patients currently being treated with SGLT2i, receiving four or more drug regimen were excluded (N=294)

Patients started on Empa/Lina once daily 25/5 mg (index case) as add on in combination of other drugs. (N=641)

Incomplete data on baseline HbA1c or any variables, history of recurrent genitourinary tract infection. Discontinued due to side effects, non-adherent to therapy, switched to other SGLT2i, not on stable dose of antidiabetes drug, amputation or major adverse events or deteriorating renal impairment (estimated GFR ≤45 ml/min/1.73 m²) were excluded (N=294)

Patients started on Empa/Lina once daily 25/5 mg with at least 3 months data on glycemic, metabolic and laboratory data of patients (N=347)

Fig. 1: Patient flow chart

patients aged between 18 to 70 years diagnosed with type 2 diabetes mellitus (T2DM) with uncontrolled glycaemia using anti-diabetic medications (more than 7 percent within 2 weeks or at the initiation). The study conformed to ethical principles of the Declaration of Helsinki during analysis of the patient records. Because of the unidentified nature of patients’ data, informed consent was not obtained.

Study population: Patients with inadequately controlled T2DM were eligible for study inclusion before initiating Empa/Lina once daily 25/5 mg as add on to one or more anti-diabetes medication for at least one month. The individuals were required to be on the stable optimum dose of anti-diabetes therapy before being intensified on the Empa/Lina combination and then follow-up visits over 12 weeks. The patient flow in the study is described in Figure 1. Information from 347 eligible patients whose HbA1c was found to be between >7≤10.5% were incorporated in this study.

Patients previously treated with SGLT2i, aged <18 years, type 1 diabetes and secondary diabetes, incomplete data on baseline HbA1c or any variables, receiving four or more drug regimen, having history of recurrent genitourinary tract infection, lower limb amputation or bone fracture or diabetic ketoacidosis or severe renal impairment (estimated GFR ≤45 ml/min/1.73 m²) were excluded from the study.

The anthropometric measurements were recorded using standardized procedures and body mass index (BMI) was calculated for each weight measurement (baseline as week 0 and follow up visits). We obtained the data from patient records of self-glucose monitoring. The study subjects also underwent various laboratory tests, such as

- Blood tests for glycaemic profile at baseline, subsequently on every visit and at the end of 12 weeks (week 0,1,3,5,7,9,12) were examined in OPD records. Self-monitoring of blood glucose monitoring was advised to all participants.
- The patient’s vital parameters including blood pressure and body weight were also recorded.
- Routine urinalysis and renal function test (eGFR) at baseline and on every visit till 12 weeks using Cockcroft-Gault equation
- Patient diaries were examined for occurrence of hypoglycaemia symptoms during each follow-up visit

The visit dates were mentioned for each patient on the prescription/file and they attended the clinic accordingly. A semi-structured, close-ended proforma was used to record the socio-demographic parameters, observations of physical examination, and results of biochemical tests.

Assessment of study outcomes: The primary endpoint was the change in HbA1c from baseline (last observation before the initiating Empa/ Lina) to week 12. Key secondary endpoints were the change from baseline in FPG, PPG, and body weight at week 12. Additional endpoints included change from baseline in blood pressure (SBP and DBP), eGFR measurement at week 12. Safety assessments included recording the occurrence of hypoglycaemia episodes along with any signs of urinary infection.

Statistical analysis: Data were processed in Excel-sheet and analyzed using the GraphPad prism (Version: 8.4) software. Quantitative variables were summarized using mean and standard deviation. The student’s t-test or dependent sample t-test was used for testing the significance of differences between the mean values of two continuous variables. Binary endpoints of the likelihood of achieving target HbA1c level in group comparison was analysed using a logistic regression model, to obtain odds ratios. The categorical values were described by frequencies and percentages and the chi-square test was applied at alpha level = 0.05.

Ethics committee clearance: The study received clearance from the ethics committee of the institution (registration no: ASCOMS/IEC/ RP&T2019/401).

Results

Baseline demographics and characteristics of subjects involved in the observational study are depicted in Table 1. The mean age (SD) of the participants was 57.84 ±7.3 years and 49% were males. Average body weight was 79.81±9.72 kg. Median duration of diabetes was 6.42±2.05 years. At baseline, the BMI of participants was 30.86 ±4.16 kg/m² indicating mainly overweight or obese patients taking present medication. Hypertension (61.1 %) was the common co-morbidity present in study groups followed by dyslipidemia (50.3%) while combined hypertension and dyslipidemia were also common among the subjects.

Later, individuals who were initiated on Empa/ Lina (25/5 mg) once daily were categorized into four groups based on the ongoing antidiabetes medication (Group I: Metformin monotherapy, Group II: Dual therapy on metformin
and sulfonylureas/ DPP-4 inhibitors TZD/ alpha-glucosidase inhibitor (AGI), Group III: Triple therapy with (Metformin, Sulfonylureas and TZD/ DPP-4 inhibitors/ AGI) and Group IV: Insulin therapy [Basal insulin 31.46%, prandial insulin 25.84% and premix insulin 42.70%]. Majority of subjects on Empa/Lina (25/5 mg) were present in Group II (33%) followed by Group III (28%) and then Group I (metformin) suggesting rather a late initiation of this class of molecules in the overall treatment approach. Most of the subjects were uncontrolled on glycemic profile with baseline HbA1c from 7.2% to 8.5% (77%). Of note, 20 percent of patients in Group IV is noted to have a baseline HbA1c level of more than 8.5 percent. Subjects in group I (13%) were relatively younger, with short duration disease, overweight and with better renal function compared to the other three treatment regimens (not shown).

At week 12, there was a significant lowering of mean HbA1c from the baseline (-1.1 ±0.64, p <0.0001) when Empa/Lina (25/5mg) was initiated on ongoing medications (Table 2). Groupwise, group III shows glycemic decrement [mean (SD) -1.3±0.72 from 8.2% at baseline] the most with no major intergroup variation. (p=0.064) Similarly, a significant mean reduction in FPG level -47.11 mg/dl (±20.42) and PPG level (-71.32 ±26.56) were noticed which was similar across treatment groups (P=0.92). There were 47% of patients who responded to therapy by achieving the recommended A1C target with a greater number of patients in group III (50.51%). (Table 2). When we compared the probability of achieving the target in patients according to background therapies, there was no significant correlation with patient proportion achieving target HbA1c (<7%) and background therapies (Table 5). Patients who were initiated on Empa/Lina (25/5mg) in conjunction with concurrent therapy demonstrated glycemic improvement from as early as 1st week of the treatment period and then maintained over 12 weeks (Figure 2).

The combination led to a net weight loss of 2.3 to 2.6 kg in OADs group over 12 weeks of treatment.

### Table 1: Baseline characteristics at the initiation of Empagliflozin and linagliptin combination (N=347)

<table>
<thead>
<tr>
<th>Baseline Parameters</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>57.84 ±7.3</td>
</tr>
<tr>
<td>Male: Female n (%)</td>
<td>171 (49)</td>
</tr>
<tr>
<td>Body weight in Kg, (SD)</td>
<td>79.81±9.72</td>
</tr>
<tr>
<td>BMI in kg/m², (SD)</td>
<td>30.86 ±4.16</td>
</tr>
<tr>
<td>HbA1c in % (SD)</td>
<td>8.2±±0.81</td>
</tr>
<tr>
<td>FPG, mg/dl (SD)</td>
<td>167±28</td>
</tr>
<tr>
<td>PPG, mg/dl (SD)</td>
<td>246±36</td>
</tr>
<tr>
<td>Median duration of diabetes, years(SD)</td>
<td>6.42±2.05</td>
</tr>
</tbody>
</table>

- Metformin monotherapy: 3.67 ±0.93
- Dual therapy: 5.77 ±1.24
- Triple therapy: 6.98 ±1.41
- Insulin therapy: 8.08 ±2.05
- Co-morbidities, n(%):
  - Hypertension: 210 (61)
  - Dyslipidemia: 140 (40)
  - Hypertension and Dyslipidemia: 78 (22)

Concomitant anti-diabetes drugs, n (%):
- Metformin monotherapy: 45 (13)
- Dual therapy: 116 (33)
- Triple therapy: 97 (28)
- Insulin therapy: 89 (26)
- SBP (SD), mm of Hg: 145±11
- DBP (SD), mm of Hg: 91.55±8.5
- eGFR (SD), ml/min/1.73m² (Cockcroft-Gault equation): 81 ± 8.1

Data are presented as mean ± standard deviation or as n (%). Abbreviations: BMI: Body Mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated hemoglobin A1c; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose; CI, p value significant p<0.0001 at all timepoints.

### Table 2: Mean reduction in glycemic parameters post administration of Empa/Lina as an add-on treatment at 12 weeks (N=347)

<table>
<thead>
<tr>
<th>Concomitant anti-diabetes agents</th>
<th>Glycemic parameters after Empa/Lina as an add-on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Overall (n=347)</td>
<td>8.2±0.81</td>
</tr>
<tr>
<td>Group 1 (n=45)</td>
<td>8.2±0.80</td>
</tr>
<tr>
<td>Group II (n=116)</td>
<td>8.1±0.67</td>
</tr>
<tr>
<td>Group III (n=97)</td>
<td>8.2±0.90</td>
</tr>
<tr>
<td>Group IV (n=89)</td>
<td>8.2±0.86</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation otherwise mentioned. Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated haemoglobin A1c; PPG, postprandial plasma glucose; p<0.05 versus Group 1, p<0.0001 versus baseline.

### Abbreviations:
PFG: Fasting plasma glucose; PPG: Postprandial plasma glucose; HbA1c, glycated haemoglobin A1c; CI, p value significant p<0.0001 at all timepoints.

**Fig. 2: Mean change (SD) in FPG and PPG levels (in mg/dL) from baseline post-initiation of Empa/Lina (25/5 mg) over 12-week treatment period (n=347)**
Table 3: Relationship between categories of baseline characteristics and proportion of subjects achieving target HbA1c with Empa/Lina (25/5 mg) as an add on (n=347)

<table>
<thead>
<tr>
<th>Demographic and clinical parameters</th>
<th>Total number of subjects</th>
<th>Proportion of subjects achieved HbA1c target</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-25 years</td>
<td>158</td>
<td>79 (46.20)</td>
<td></td>
</tr>
<tr>
<td>≥26 years</td>
<td>176</td>
<td>81 (46.02)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>171</td>
<td>79 (46.20)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>176</td>
<td>81 (46.02)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥23-25</td>
<td>18</td>
<td>11 (61.11)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥25-30</td>
<td>158</td>
<td>90 (56.96)</td>
<td>0.012</td>
</tr>
<tr>
<td>&gt;30</td>
<td>171</td>
<td>59 (34.50)</td>
<td>0.16</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td></td>
<td></td>
<td>0.184</td>
</tr>
<tr>
<td>≤5</td>
<td>112</td>
<td>44 (39.29)</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>169</td>
<td>89 (52.66)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI Body mass index, HbA1c glycated haemoglobin, p value significance <0.05%, p value 1 BMI 23-25 versus 25-30; p value 2 BMI 25-30 versus >20

Table 4: Change in efficacy endpoint from baseline after administration of EMPA/LINA as an add-on treatment at 12 weeks (N=347)

<table>
<thead>
<tr>
<th>Concomitant antidiabetes medication</th>
<th>Efficacy endpoint after Empa/Lina as an add-on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>Systolic BP</td>
</tr>
<tr>
<td>Baseline</td>
<td>Δ</td>
</tr>
<tr>
<td>Group I (n=45)</td>
<td>80.82±9.65</td>
</tr>
<tr>
<td>Group II (n=116)</td>
<td>81.47±8.16</td>
</tr>
<tr>
<td>Group III (n=97)</td>
<td>78.96±9.98</td>
</tr>
<tr>
<td>Group IV (n=89)</td>
<td>80.21±10.11</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or as n (%). Abbreviations: SBP Systolic blood pressure, DBP Diastolic blood pressure, eGFR estimated glomerular filtration rate. *p<0.05 versus baseline, ^p<0.05 versus group 1

Table 5: Association between group-wise concurrent Oral Antidiabetes Drugs (OADs) and reaching HbA1c <7.0% with treatment with Empa/Lina (25/5 mg) (N=347)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ΔHbA1c (95% CI)</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Higher 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Reference</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group II</td>
<td>1.06 (0.00-2.11)</td>
<td>1.575</td>
<td>0.38</td>
<td>6.63</td>
<td>0.528</td>
</tr>
<tr>
<td>Group III</td>
<td>1.26 (1.12-1.410)</td>
<td>0.955</td>
<td>0.16</td>
<td>5.10</td>
<td>0.956</td>
</tr>
</tbody>
</table>

Abbreviations: ΔHbA1c change in glycated haemoglobin, OADs: Oral Antidiabetes Drugs, CI, confidence interval; HbA1c glycated haemoglobin; OR, odds ratio derived from Logistic regression with 95% confidence interval (CI)

Discussion

Though the highest level of evidence is provided by randomized controlled studies (RCTs) in clinical medicine, in real-life settings, variations in outcomes may be observed due to considerable heterogeneity in the diabetes population. As there is limited data on empagliflozin and linagliptin combination which is a novel treatment option available since 2017 in India, the present study was planned to investigate the glycemic improvement and effect on metabolic risk factors in more representative population settings.

Empagliflozin (USFDA approved 2014) is an aryl C-glycosides with the higher selectivity for high-capacity, low-affinity sodium-glucose cotransporter-2 receptor (SGLT2) present in S1 segment of the renal proximal tubule. It mediates its glucose-lowering effect by blocking SGLT2 transporter proteins responsible for reabsorption of 90% glomerularly filtered glucose and thereby, increasing glucose excretion in urine and osmotic diuresis and natriuresis. Linagliptin (USFDA approved 2011), an inhibitor of widely expressed proteases enzyme Dipeptidyl peptidase-4 in human body exerts its glucose lowering effect by preventing the degradation incretin hormones resulting in augmenting the glucose-dependent insulin secretion from pancreatic beta cells and inhibiting the pancreatic alpha cell-mediated glucagon release.

Single pill combination of empagliflozin and linagliptin is unique in its class of SGLT2 inhibitor and DPP-4 inhibitor due to the complementary mode of action of both agents providing good glycemic control with less intrinsic...
The glycemic decrement in HbA1c in than corresponding monotherapies. Additionally, early achievement of the glycemic control at 12 weeks was yielded a robust control of glycemic and metabolic parameters in combination with various ongoing antidiabetes regimes. In contrast to conventional anti-diabetes agents, this combination demonstrated moderate weight loss attributed to urinary calorie loss which is consistent with a large randomised trial (~3.1 kg) at 52 weeks. Moreover, the effect of body weight loss was evident in insulin-treated patients implying a meaningful outcome of potential interest in large number of insulin-treated subjects. The EMPA-REG study showed that patients on empagliflozin 25 mg lost a mean of around 3 kg of body weight and blood pressure control, speculating to be one of the contributing factors for remarkable benefit of cardiovascular protection seen with SGLT2 inhibitor. In another Asian study a composite endpoint of (decreases from baseline in HbA1c ≥ 0.5%, SBP > 3 mm Hg and body weight > 2%) was reported to be of considerable significance in empagliflozin and linagliptin group (31.9% vs 2.2%, P < .0001).7 and SBP reduction (~3.6 at 130.9 mm of Hg at 52 weeks) from baseline.

Similarly, clinically relevant lowering of both systolic and diastolic blood pressure was consistent with other major trials.8 Asian study with 132 nonobese elderly population highlighted the potential relevance of the BP-lowering effect of SGLT2i which reported a significant mean reduction in daytime SBP from baseline 9.5 mmHg in the empagliflozin group as add on to ARB therapy in diabetes patients with uncontrolled nocturnal hypertension study.9

The favourable trend in eGFR was consistent with several large clinical trials indicating that SGLT2i class of drugs slowed the progression of kidney function decline in patients with T2DM providing a noteworthy renoprotective effects in diabetes patients.10 However, no data for albuminuria were available in our study. The risk of hypoglycaemia, an important parameter affecting the selection of the add-on therapy, given its close link to increased risk of morbidity and mortality was less in oral medications which were consistent with the low risk reported in major controlled studies.5,11,12 Similarly, the present study demonstrated no significant increased risk of hypoglycaemia in OAD group with improved glycaemic control. However, patients reported hypoglycaemia events in concomitant insulin group, which is an expected outcome. The clinical strategy of adding SGLT2 inhibitor in subjects with inadequately managed on insulin therapy is a fascinating approach as reported by wide range clinical evidence to avoid the risk of rise in hypoglycaemia, and dose-dependent increase in weight gain which are considered as key barriers for patient adherence to insulin therapy.13,14 Dose titration of complex insulin regimen will be major challenge for this approach.

The reported rate of genital mycotic infection was consistent with major trials showing less infections in the combination arm as compared to SGLT2i monotherapy arm. It is important to emphasize early awareness of these manageable side effects. Personal hygiene advice may also help prevent this issue. There was no significant risk of major AEs such as DKA and amputation reported in the present study.

The limitations of the study need to be acknowledged while interpreting the study results such as retrospective nature prone for multiple bias, EMR records may not provide details of baseline variables leading to less control over unobserved confounders. There is also lack of a matching cohort which would have provided the opportunity of sound methodologic consideration. Furthermore, relatively short follow-up duration has limited ability to inform on long term effects of outcome. Also, unlike clinical trials where drug
administration is supervised, patients in the current study were responsible for their own medication.

Conclusion
To summarise, the present study provides promising evidence on suitability of use of fixed combination of empagliflozin and linagliptin in wide range of population due to its beneficial clinical effects on glycemic and metabolic risk factors in addition to various coexisting background diabetes therapies supporting its distinctive place in pharmacotherapeutic range of antidiabetes agents in the progressive course of diabetes.

References

Serum Retinol Binding Protein-4 Levels in Prediabetics – Novel Biomarker of Insulin Resistance and Atherosclerosis

Ajay Chauhan1*, Ayushi Singhal2, Parul Goyal3, Anil Taneja4

Abstract
Background: Atherosclerotic cardiovascular diseases are the leading cause of morbidity and mortality in both diabetics and prediabetics. In insulin resistant states, increased levels of various adipose derived cytokine (adipokine) have been found to have an important role in the process of atherosclerosis. One such novel adipokine is RBP4, (belonging to lipokalin family) which also by exerting an inflammatory process has a role in the pathogenesis of insulin resistance and CVD. Early detection of all these inflammatory cytokines may immensely help us in prognosticating the pace of disease besides instituting early interventional maneuvers.

Objective: The aim of the study was to compare serum levels of RBP4 in prediabetics and controls and to correlate levels of RBP4 with HOMA-IR and CIMT.

Methods: 60 prediabetic patients and 60 age, sex, BMI matched controls were employed in the case control study. In both cases and controls serum levels of fasting and postprandial blood glucose, glycated hemoglobin (HbA1c) and fasting insulin levels were measured. HOMA-IR values in both the groups were calculated using fasting glucose and insulin levels. Serum RBP4 levels were measured using ELISA. The values obtained were compared between cases and controls. CIMT was only measured in cases using B-mode ultrasonography.

Results: Median (IQR) of fasting plasma insulin levels (µU/ml) in cases was 11.3 (10.175–13.505) versus that of controls which was 5.73 (4.3-7.1). HOMA-IR median (IQR) in cases and controls was 3.12 (2.73-3.595) and 1.21(0.918-1.505) respectively. Median (IQR) for RBP4 in cases was 67.4 (46.166–111.088) which was significantly higher as compared to controls 33.92 (23.902-52.45). Significant positive correlation was seen between RBP4 with both, HOMA-IR and mean CIMT with correlation coefficients of 0.3693 and 0.621 respectively. On performing univariate linear regression analysis it was found that with increase in serum RBP4 levels by 1 mg/L, HOMA-IR and mean CIMT significantly increased by 0.007 units and 0.001 mm respectively.

1Professor of Medicine, 2PG Resident of Medicine, 3Professor of Biochemistry, 4Professor of Radiodiagnosis, ABVIMS and Dr. RML Hospital, New Delhi; *Corresponding Author
Received: 27.08.2020; Accepted: 19.01.2021
Conclusion: Prediabetics have been found to have more risk of cardiovascular events as compared to normoglycemics. Early assessment of the same with the use of novel biomarkers like RBP4 can be considered for early detection of atherosclerosis in prediabetic individuals. It may further help in early intervention and thus prevention from future complications.

Introduction

Diabetes Mellitus is a chronic condition occurring due to inadequate production or inadequate action of insulin, ultimately leading to hyperglycemia. Prediabetes, regarded as a predecessor of diabetes, is a condition with elevated plasma glucose above normal levels but below that of clinical disease. According to American diabetes association it encompasses fasting plasma glucose of 100-125 mg/dl OR 2 hour postprandial blood glucose of 140-199 mg/dl OR HbA1c of 5.7-6.4%. As per data published in international diabetic federation (IDF) diabetes atlas 2019, number of people living with impaired glucose tolerance was 25.2 million with age adjusted comparative prevalence of 3.3%.

Atherosclerotic cardiovascular diseases contribute to the world’s largest disease burden and are a leading cause of morbidity and mortality in both diabetics and prediabetics, accounting for about two third of mortality in diabetics. All components of metabolic syndrome have been found to be associated with increased risk of cardiovascular disease (CVD). In prediabetes increased risk of cardiovascular disease is multifactorial with etiologies including insulin resistance, hyperglycemia, dyslipidemia, hypertension, systemic inflammation and oxidative stress.

Risk factors leading to prediabetic state are often associated with increased expression of inflammatory cytokines and also infiltration of immune cells in adipose tissue which lead to an insulin resistance state and problems linked with this state like dyslipidemia (due to non storage of triglyceride by insulin resistant cells), hypertension, hypercoagulability and atherosclerosis. Increased levels of adipose derived cytokine (adipokine) apart from having immunological role, also have role in insulin resistant states and the process of atherosclerosis. One such novel adipokine is RBP4 (belonging to lipokalin family) which also by exerting an inflammatory process has its effect in the pathogenesis of insulin resistance and CVD.

For assessing these atherosclerotic changes in both peripheral and coronary arteries, intima-media thickness (IMT) is currently being used as a marker. Most commonly used among these is Carotid Intima-Media Thickness (CIMT), usually performed by a B-mode ultrasonographic scan as it is a non invasive, inexpensive and reproducible method.

Materials and Methods

The study was conducted in the Departments of Medicine, Biochemistry and Radiology at Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi.

Study Design: A Cross sectional observational study

Study Size: The study group consisted of 60 consecutive patients of prediabetes and 60 control subjects from Medicine OPD, Medicine wards and Medicine Emergencies of ABVIMS and Dr. RML Hospital, after fulfilling all inclusion and exclusion criteria and matched for age, sex and ethnicity.


Calculation of Sample Size

Primary Objective
To compare serum levels of RBP4 in prediabetics and controls.

To achieve the primary objective the input for statistical sample size calculation was taken from the study by Pandey GK et al, 2015.

Patient with Impaired Glucose Tolerance showed a mean (± SD) for RBP4 of 10.5± 3.2 while those with Normal Glucose Tolerance had mean of 8.7± 2.5.

Taking these values as reference, the minimum required sample size with 90% power of study and 5% level of significance is 54 patients in each study group. To reduce margin of error, total sample size taken was 120 (60 patients per group).

Formula used was:
For comparing mean of two groups

\[ N = \frac{2(SD)^2 \times (Z_\alpha + Z_\beta)^2}{(\text{mean difference})^2} \]

Where \( Z_\alpha \) is value of \( Z \) at two sided alpha error of 5% and \( Z_\beta \) is value of \( Z \) at power of 90% and mean difference is difference in mean values of two groups.

Pooled standard deviation = \( \sqrt{(S_1^2 + S_2^2)/2} \)

Where \( S_1 \) is standard deviation of 1 group and \( S_2 \) is standard deviation of other group.

Calculations of sample size for RBP4

Pooled standard deviation = 2.87

\[ N = \frac{(2(2.87)^2)(1.96 + 1.28)^2}{(1.8)^2} \]

\[ N >= 53.37 \approx 54 \text{(approx.)} \]

Inclusion Criteria

- 60 consecutive cases of Prediabetes of age 30-60 years as defined by fasting plasma glucose between 100 to 125 mg/dl OR 2-hour postprandial glucose/2-hour OGTT (after 75 gm of glucose solution ingestion) between 140 to 199 mg/dl. OR HbA1c =5.7-6.4% (ADA 2016).
- 60 control subjects, matched for age, gender, ethnicity and body mass index and with fasting blood glucose of less than 100mg/dl and 2-hour postprandial glucose of less than 140 mg/dl and HbA1c less than 5.7% with no known co-morbidities as per exclusion criteria.

(An informed bilingual written consent was taken from each of the patient/relatives for inclusion).

Exclusion Criteria

- Known hypertensive
- Known diabetics
- Known cases of chronic liver disease
- Known cases of non alcoholic fatty liver disease
- Known cases of myelodysplastic syndrome
- Patient on maintenance hemodialysis
- Known cases of coronary heart disease
- Known case of cerebrovascular
BMI (mean ± SD) 25.33 ± 2.65 24.93 ± 2.22 0.844  
Females 53.33% (n= 32) 51.67% (n= 31)

Diastolic Blood Pressure (mean ± SD) 74.97 ± 5.17 73.43 ± 4.97 0.079  
Waist Circumference (mean ± SD) 84.57 ± 7.3 82.62 ± 8.7 0.287

measurements. Plain (Red) vials were for glycated haemoglobin (HbA1c) 
Samples were taken in EDTA vial 
was collected after venipuncture.

• Fastings protein 4 were imported from 
Principle of test
The ELISA test used was for quantitative determination of RBP/ RBP4 in plasma, urine and serum. In first incubation step, RBP/ RBP4 in samples bound to polyclonal rabbit anti RBP/ RBP4 antibodies, immobilized on microtitre plate. A peroxidase (where tetramethylbenzidine used as a peroxidase substrate) conjugated anti RBP/RBP 4 antibody is used for detection and quantification. A dose response curve of absorbance unit (optical density at 450 nm) versus concentration was generated using the values obtained from standard and using this curve values of RBP/ RBP 4 were directly determined.

Test procedure
1. All the reagent and samples were bought to room temperature (15-30°C) and mixed well. 
2. Position of standard/ control/ samples were marked on a protocol sheet. 
3. Samples were diluted by 1:5000 in sample dilution buffer. 
4. Before use, wells were washed 5 times with 250 μl wash buffer and after final washing step, residual wash buffer was removed by firmly tapping the plate on absorbent paper. 
5. 100 μl of standard/ controls/ diluted samples were added in respective wells.

6. Strips were covered and incubated for 1 hour at room temperature (15-30°C) on a horizontal shaker.  
7. Content of each well was discarded and washed 5 times with 250 μl wash buffer. After final washing step, residual wash buffer was removed by firmly tapping the plate on absorbent paper. 
8. 100 μl conjugate (diluted CONJ) was added in each well. 
9. Strips were covered and incubated for 1 hour at room temperature (15-30°C) on a horizontal shaker.  
10. Again, content of each well was discarded and well was washed 5 times with 250μl wash buffer. After final washing step residual wash buffer was removed by firmly tapping the plate on absorbent paper.  
11. Then 100μl substrate (SUB) were added in each well. 
12. Incubation was done for 10-20 minutes at room temperature in dark. 
13. Finally, 100 μl stop solution

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cases (n = 60)</th>
<th>Controls (n = 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>45.68 ± 8.78</td>
<td>44.48 ± 7.44</td>
<td>0.439</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>0.835</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>46.67% (n = 28)</td>
<td>48.33% (n = 29)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>53.33% (n = 32)</td>
<td>51.67% (n = 31)</td>
<td></td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>25.33 ± 2.65</td>
<td>24.93 ± 2.22</td>
<td>0.844</td>
</tr>
<tr>
<td>Waist Circumference (mean ± SD)</td>
<td>84.57 ± 7.3</td>
<td>82.62 ± 8.7</td>
<td>0.287</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mean ± SD)</td>
<td>116.23 ± 6.66</td>
<td>116.93 ± 8.13</td>
<td>0.541</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mean ± SD)</td>
<td>74.97 ± 5.17</td>
<td>73.43 ± 4.97</td>
<td>0.079</td>
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<td>86 (79-91.25)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Postprandial Blood Sugar</td>
<td>168 (156- 184.25)</td>
<td>125 (117-130)</td>
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<tr>
<td>HbA1c</td>
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<td>4.9 (4.6-5.125)</td>
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<td>HOMA-IR Index</td>
<td>3.12 (2.73-3.595)</td>
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<td>&lt; 0.001</td>
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<tr>
<td>Serum RBP4</td>
<td>67.4 (46.166-111.088)</td>
<td>33.92 (23.902-52.45)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
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Lab investigations
Around 10 ml of fasting blood sample was collected after venipuncture. Samples were taken in EDTA vial for glycated haemoglobin (HbA1c) measurements. Plain (Red) vials were used to take samples for biochemical profile and separately for RBP4.

Investigations done on the patients were:
• Fasting plasma glucose
• 2 hour postprandial plasma glucose
• Glycated haemoglobin (HbA1c) measurement by Immuno turbidimetry method on Vitros dry chemistry analyser by NSGP guidelines.

Methods
All the cases and controls underwent following examinations and tests:

Clinical Examination
• Anthrometric measurement: The study participants were called to the Department of Medicine, Dr. RML hospital and asked to fill a pre-determined questionnaire which included baseline data about age, sex, race, ethnicity and family history of diabetes or hypertension. Then they underwent a detailed clinical examination including measurement of height (using stadiometer), weight (using a weight measurement scale) and waist circumference (using a standard measuring tape). Body Mass Index was calculated as weight in kilograms divided by height in square meters.
• Resting systolic and diastolic blood pressures were recorded twice using an automated sphygmomanometer after a 5-min rest. A mean of these two readings were taken.

Laboratory Investigations
Around 10 ml of fasting blood sample was collected after venipuncture. Samples were taken in EDTA vial for glycated haemoglobin (HbA1c) measurements. Plain (Red) vials were used to take samples for biochemical profile and separately for RBP4.

Investigations done on the patients were:
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Table 1: Demographic and anthropometric characteristics among cases and controls

Table 2: Biochemical parameters among cases and controls
An ELISA reader (BIO RAD analyzer in Biochemistry Laboratory, ABVIMS and Dr. RML Hospital, at 450 nm (against 620 nm or 690 nm as a reference) was finally used to determine absorption immediately.

- Strips were shaken at 550 rpm (rotation per minute) with an orbit of 450 nm (STOP) was added in each well and values obtained were converted into µg/L.
- Coated Reference range for kit was 20-75 mg/L.
- Reference range

### Plasma or serum

- Adults: 20-75 mg/l
- Newborn: 11-34 mg/l
- Age 6 months: 18-50 mg/l

Ultrasoundographic Examination:

(only performed in cases)

All cases underwent high-resolution B-mode ultrasonography with a 7.5 MHz linear probe, in Department of Radiology, ABVIMS and DR RML Hospital, New Delhi. CIMT was measured as distance between two echogenic lines (representing intima and media). All scans and image measurements were carried out by the same investigator, blinded to the risk factor status of the participants.

#### Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Qualitative variables were compared using Independent t test/ Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were compared using Chi-Square test. Spearman rank correlation coefficient was used to assess the correlation of mean carotid intima media thickness with retinol binding protein 4. A p-value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

### Results

The aim of the study was to assess the serum levels of Retinol binding protein 4 (RBP4) in patients with prediabetes, compare the same in normoglycemics and to correlate its levels with carotid intima media thickness (CIMT) and HOMA IR in prediabetics. It was an observational case-control study and after calculating the sample size (of 54 for RBP4) as per statistical analysis, a total of 120 patients were enrolled (60 cases and 60 controls). Matching with respect to age, sex, blood pressure and BMI was ensured. The following observation was made (Tables 1, 2, 3).

Significant difference was seen in levels of fasting plasma insulin (uIU/ml) between cases and controls (p value <0.05). Median (IQR) of fasting plasma insulin level (uIU/ml) in cases was 11.3(10.175-13.505) which was significantly higher as compared to controls (5.73(4.3-7.1)) (Tables 2, 4, Figure 2). Fasting plasma insulin levels (uIU/ml) were =&gt;9 in 83.33% of cases as compared to controls where it was 11.67% (Figure 3). HOMA-IR Index in our study showed median (IQR) values of 3.12(2.73 ± 3.595) in cases and 1.21 (0.918 ± 1.505) in controls which

### Table 3: Descriptive statistics of mean carotid intima media thickness (mm) of study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Median(IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean carotid intima media thickness (mm)</td>
<td>0.61 ± 0.1</td>
<td>0.6(0.5-0.7)</td>
<td>0.4-0.8</td>
</tr>
</tbody>
</table>

### Table 4: Comparison of fasting plasma insulin level (uIU/ml) between cases and controls

<table>
<thead>
<tr>
<th>Fasting plasma insulin level (uIU/ml)</th>
<th>Case (n=60)</th>
<th>Control (n=60)</th>
<th>Total</th>
<th>P value</th>
<th>Test performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>11.97 ± 3.53</td>
<td>5.77 ± 1.95</td>
<td>8.87 ± 4.22</td>
<td>&lt;.0001</td>
<td>Mann Whitney test; 175.5</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>11.3(10.175-13.505)</td>
<td>5.73(4.3-7.1)</td>
<td>(5.675-11.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4.8-21.9</td>
<td>1.5-9.6</td>
<td>1.5-21.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5: Comparison of homeostasis model assessment of insulin resistance (HOMA-IR) between cases and controls

<table>
<thead>
<tr>
<th>HOMA-IR</th>
<th>Case (n=60)</th>
<th>Control (n=60)</th>
<th>Total</th>
<th>P value</th>
<th>Test performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>3.26 ± 0.97</td>
<td>1.21 ± 0.41</td>
<td>2.23 ± 1.27</td>
<td>&lt;.0001</td>
<td>Mann Whitney test; 61</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>3.12(2.73-3.595)</td>
<td>3.595</td>
<td>1.21(0.918-1.505)</td>
<td>3.12</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1.25-5.77</td>
<td>0.29-2.02</td>
<td>0.29-5.77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Fig. 1: Descriptive statistics of mean carotid intima media thickness (mm) of study subjects

#### Fig. 2: Box-whisker plot showing comparison of fasting plasma insulin level (uIU/ml) between cases and controls

#### Fig. 3: Comparison of fasting plasma insulin level (uIU/ml) between cases and controls with a cutoff of 9 mIU/l
was statistically significant (p value < 0.0001) (Tables 2, 5). Moreover, around 91.67% of cases and 1.67% of controls had HOMA-IR > or equal to 2 (Table 6). Median (IQR) of RBP4 level (mg/L) in cases was 67.4 (46.166-111.088) which was significantly higher as compared to control [33.92(23.902-52.45)] (p value <0.0001) (Table 2 and 7, Figure 4). Mean value of mean CIMT (mm) of study subjects was 0.61 ± 0.1 with median (IQR) of 0.6(0.5-0.7). It is shown in Table 3, Figure 1. The correlation of RBP4 and HOMA-IR Index and mean CIMT was found to be statistically significant with a correlation coefficient of 0.3693 and 0.621 respectively and p value of 0.0037 and <0.0001 respectively (Figure 5 and 6). Univariate linear regression analysis showed that with increase in levels of RBP4 by 1 mg/L, HOMA-IR, Fasting plasma insulin and mean CIMT significantly increased by 0.007 units, 0.025 uIU/ml and 0.001 mm respectively (Table 8).

**Discussion**

The study showed evidence of increased levels of RBP4 in prediabetes as compared to normoglycemics. A significant positive correlation was found between RBP4 with HOMA-IR Index (marker of insulin resistance) and mean CIMT while moderate positive correlation between RBP4 and fasting plasma insulin. It proved, the diagnostic and prognostic significance in hyperglycemia associated cardiovascular disease assessment due to alteration in the levels of the same in these states. It would thus help in early intervention to prevent any future complications.

Insulin resistance along with impairment of insulin signaling, hyperinsulinemia, and hyperglycemia by increasing glycosylation and oxidation of lipoproteins like LDL and VLDL (Very Low-Density Lipoprotein) leads to decrease in vascular compliance and also promote atherosclerosis. These vascular changes due to atherosclerosis are characterized by arterial wall lesion and endothelial dysfunction, ultimately leading to vessel wall hypertrophy which later contributes to increased risk of strokes, MI and TIA.

One of the novel adipokines that has been found to be elevated in insulin resistant states is Retinol Binding Protein 4 (RBP4). It is secreted from liver (major fraction) and adipocytes. It carries retinol in blood from liver to peripheral tissues. RBP4 itself also seems to affect the insulin signaling cascade leading to insulin resistance.

In a prospective study done in 2014 by Ram J et al, it was found that participants who developed T2DM had higher levels of serum RBP4 as compared to non-progressors, indicating prognostic utility of RBP4 as a marker which can predict subjects who will progress from prediabetes to frank diabetes mellitus. In another study by Meisinger C et al, higher levels of RBP4 levels were found to be associated with metabolic risk factors, such as body mass Index (BMI), waist circumference, hypertension, and lipid parameters which in turn are linked with development of resistance to insulin. In another study by Kwanbunjan K et al, RBP4 levels were found to be associated with insulin resistance in stroke and...
heart disease. A positive correlation between serum levels of RBP4 and CIMT (correlation coefficient of 0.623) observed in our study was correlating with other studies as well but those were done in diabetic patients only. Our study is thus the first study correlating levels of RBP4 with insulin resistance and HOMA-IR in prediabetics.

RBP4 has been found to be elevated in serum before the onset of overt diabetes and it has also been correlated with components of metabolic syndrome. Various studies suggest important role of RBP4 as a direct trigger of insulin resistance and subclinical inflammation, leading to premature development of CVD and diabetes.16-19 Like these studies our study too suggests measurement of serum RBP4, a noninvasive, accessible method can be used as an early predictor for assessing the risk of CVD in prediabetic patients. It has been considered as more convenient and inexpensive test compared to vascular ultrasound for early detection and hence early intervention in vascular complications.19

### Conclusion

- In prediabetic patients levels of RBP4 may be considered as a surrogate marker for early atherosclerosis and can be used as an early predictor for the same. It may cause carotid artery atherosclerosis through the influence on insulin sensitivity, lipid metabolism, and the body oxidative stress. This molecule, when combined with other atherosclerotic markers can improve the predictive value of cardiovascular risk assessment. These patients can also be targeted for medical management with cardioprotective drugs like aspirin, statins and metformin for insulin resistance. Thus, CIMT along with RBP4, used to detect atherosclerosis in cardiovascular diseases can be employed at a much earlier stage in patients with prediabetes to estimate future CVD risk as they indicate subclinical atherosclerosis. Also RBP4 alone can be used in early detection and intervention of vascular complication as more convenient and inexpensive compared to vascular USG.

### Table 8: Univariate linear regression to find out effect of serum RBP 4 levels (mg/L) on Fasting plasma insulin level (uIU/ml)

<table>
<thead>
<tr>
<th>RBP4 (mg/L)</th>
<th>Fasting plasma insulin level (uIU/ml)</th>
<th>HOMA-IR</th>
<th>Mean CIMT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta coefficient</td>
<td>0.025</td>
<td>0.007</td>
<td>0.0001</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.009</td>
<td>0.002</td>
<td>0.0002</td>
</tr>
<tr>
<td>Standardized coefficient</td>
<td>0.364</td>
<td>0.004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lower bound (95%)</td>
<td>0.008</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>Upper bound (95%)</td>
<td>0.042</td>
<td>0.012</td>
<td>0.0003</td>
</tr>
<tr>
<td>Equation</td>
<td>$9.838 + 0.025 \times \text{RBP4 (mg/L)}$</td>
<td>$2.662 + 0.007 \times \text{RBP4 (mg/L)}$</td>
<td>$0.49 + 0.001 \times \text{RBP4 (mg/L)}$</td>
</tr>
<tr>
<td>$R^2$</td>
<td>13.27%</td>
<td>13.64%</td>
<td>38.41%</td>
</tr>
</tbody>
</table>

### References

14. Tramontana L, Bossone E, Angiolillo DJ, Papi C, Verani MS, Maccario M, et al. Atherosclerotic markers can improve the predictive value of cardiovascular risk assessment. These patients can also be targeted for medical management with cardioprotective drugs like aspirin, statins and metformin for insulin resistance. Thus, CIMT along with RBP4, used to detect atherosclerosis in cardiovascular diseases can be employed at a much earlier stage in patients with prediabetes to estimate future CVD risk as they indicate subclinical atherosclerosis. Also RBP4 alone can be used in early detection and intervention of vascular complication as more convenient and inexpensive compared to vascular USG.
Abridged Prescribing Information: **COMPOSITION:**

- **Glycomet GP 0.5:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 1 mg. 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 2 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 1 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 8mg 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, chew, or break for easy swallowing. Water should be given immediately after taking the tablet and may be repeated after every dose. The dose of Glycomet GP is to be increased at the discretion of the physician and may be increased at intervals of not less than 1 week up to a maximum of 2 tablets once daily.

**CONTRAINDICATIONS:**

- In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, metformin or any of the excipients of Glycomet GP.
- In patients with a history of or who are at risk for ketoacidosis, including patients with severe renal impairment (serum creatinine >5 mg/dl) or with a serum creatinine level of 3-5 mg/dl in the presence of one or more of the following conditions: moderate to severe diabetic autonomic neuropathy, advanced age, malnutrition, alcoholism, hypovolemia, severe sepsis, trauma, or surgery.
- In patients with symptomatic CHF, diabetes mellitus in severe metabolic decompensation, or with a history of diabetic coma or ketoacidosis.
- In patients with acute or chronic conditions that may cause tissue hypoxia (myocardial infarction, shock, cardiac/respiratory failure) hepatic insufficiency, acute alcohol intoxication, alcoholism.

**WARNINGS:**

- Keep out of reach of children. Patient should be advised to report promptly exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate and a temporary change to insulin may be necessary to maintain good metabolic control. In case of lactic acidosis, patient should be hospitalized immediately.

**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. Glycomet GP should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal. Use of Glycomet GP should be discontinued 48 hours before any surgical procedure.

**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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Let Glycomet be part of journey of every Insulin Resistant patient either alone or in combination

Immediate release SKUs

- Glycomet-500
- Glycomet-850
- Glycomet-250

Sustain release SKUs

- Glycomet-S.R. 500
- Glycomet-S.R. 850
- Glycomet-1 gm S.R.
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**Ghar Ghar BP Care**

**120/80**

**India’s one of the largest patient education initiative**

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- Awareness via social media & e-pharmacy

**Screening**

**Education**
- Our aim is to provide patients with an interactive learning platform on Awareness, Management & Prevention of Hypertension

**Monitoring**
- Motivating patients for Home BP Monitoring by providing additional discount on availing BP monitor

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Comparison in Outcome of Patients with Post TB-Destroyed Lung and COPD Admitted with Respiratory Failure

Swapnil Manaji Thorve1*, Nilkanth T Awad2, Jairaj P Nair3, Siddharth R Waghmare1, Ganapriya GP4, Gayatri S Nair1

Abstract

Introduction: The term post TB sequelae is usually used to describe the destructive lung parenchymal changes due to pulmonary tuberculosis, which occur over years, and cause chronic airway obstruction as well as restriction. Furthermore, post TB sequelae and COPD are common causes of acute exacerbation with respiratory failure in Indian setting.

Aim of the study: To compare the outcome of patients with post TB sequelae and COPD admitted with respiratory failure

Methods: 62 Post TB sequelae and 79 COPD patients admitted in respiratory failure were treated as per standard ICU protocols. Outcome of these patients in these groups were compared with respect to mortality, morbidity and requirement of type ventilatory support.

Results: It was observed that duration of stay, morbidity and mortality in these groups was comparable and difference was not statistically significant.

Conclusion: The presentation and outcome of COPD and Post TB destroyed lung patients is similar, so Post TB Destroyed lung patients should be treated as per COPD guidelines.

Introduction

The term post TB sequelae is usually used to describe the destructive lung parenchymal changes due to pulmonary tuberculosis, which occur over years, and cause chronic airway obstruction as well as restriction. TB is a major pulmonary disease and clinical manifestations of post TB sequelae can be similar to those of chronic obstructive pulmonary disease (COPD) with manifestations of dyspnea due to airway obstruction. Furthermore, post TB sequelae may be a common cause of acute exacerbation with respiratory failure; but there are few predictive factors to suggest differences in the prognosis between patients with post TB sequelae and those with COPD when patients with dyspnea, caused by aggravation of airway obstruction, are admitted to intensive care unit (ICU).

Although several published studies have focused on patients with active pulmonary TB and respiratory failure, few studies have attempted to identify the difference between patients with Post TB sequelae and COPD who have respiratory failure symptoms. Thus, the aim of this study was to identify differences in outcome between patients with post TB sequelae and COPD who were admitted to ICU with respiratory failure.

Aim and Objective

To compare the outcome of Post-TB sequelae patients and COPD admitted with respiratory failure

Materials and Methods

All patients admitted in intensive respiratory care unit of Lokmanya Tilak Municipal General Hospital in respiratory failure from 02/01/2017 till 30/09/2017 with a clinical diagnosis of COPD or Post TB sequelae were included in study. Patients having associated OSA, Bronchial asthma, ILD, Kyphoscoliosis, CHD, Valvular heart diseases etc acting as a confounding factor for respiratory failure were excluded. Clinical history was noted and patient was examined in detail with emphasis on past history of pulmonary tuberculosis, history of previous admissions and smoking.

Patients were treated as per standard ICU protocols and GOLD guidelines for management of acute exacerbation of COPD. The total duration of stay in hospital, stay in ICU, need of mechanical ventilation, need of oxygen supplementation, need of ionotropic support and long term oxygen treatment was noted in detail for each patient.

The study group was divided into two groups, COPD and Post TB sequelae and outcome was compared in two groups.

Results

A total of 141 patients admitted with respiratory failure in intensive respiratory care unit satisfying the inclusion and exclusion criteria were included in the study. Out of 141 patients, 62 patients were of post TB sequelae and 79 patients were of COPD. Mean age of Post TB sequelae patients was 51.5 years and COPD was 63 years. Out of 62 Post TB sequelae patients 65% were males and 35% were females. Out of 79 COPD patients 71% were males and 29% were females.

14.5% post TB sequelae and 20.3% COPD patients were in type 1 respiratory failure and 85.5% post TB sequelae and 79.7% COPD patients were in type 2 respiratory failure at
Table 1: Types of Respiratory failure in both study groups

<table>
<thead>
<tr>
<th></th>
<th>Post TB sequelae</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Respiratory failure</td>
<td>9 (14.5%)</td>
<td>16 (20.3%)</td>
</tr>
<tr>
<td>Type 2 Respiratory failure</td>
<td>53 (85.5%)</td>
<td>63 (79.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>79</td>
</tr>
</tbody>
</table>

Table 2: Outcome of patients and need of mechanical ventilation

<table>
<thead>
<tr>
<th></th>
<th>Post TB sequelae</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only managed with Oxygen and bronchodilators</td>
<td>48.4%</td>
<td>44.3%</td>
</tr>
<tr>
<td>Only Non invasive mechanical ventilation</td>
<td>24.2%</td>
<td>26.6%</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>27.4%</td>
<td>26.6%</td>
</tr>
</tbody>
</table>

Table 3: Mean duration of hospitalisation in study groups

<table>
<thead>
<tr>
<th></th>
<th>Post TB sequelae</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean hospitalisation days</td>
<td>10 days</td>
<td>11.42 days</td>
</tr>
</tbody>
</table>

Table 4: Mortality in study groups

<table>
<thead>
<tr>
<th></th>
<th>Post TB sequelae</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>24.19%</td>
<td>18.98%</td>
</tr>
</tbody>
</table>

Table 5: Outcome of mechanically ventilated patients

<table>
<thead>
<tr>
<th></th>
<th>Post TB sequelae</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged</td>
<td>53.12%</td>
<td>64.28%</td>
</tr>
<tr>
<td>Died</td>
<td>46.88%</td>
<td>35.72%</td>
</tr>
</tbody>
</table>

that the prevalence of COPD is higher in those ≥ 40 years of age compared to those < 40, and in men compared to women. The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) examined the prevalence of post-bronchodilator airflow limitation among persons > 40 years in one major city from each of five Latin American countries – Brazil, Chile, Mexico, Uruguay, and Venezuela. In each country, the prevalence of COPD increased steeply with age, with the highest prevalence among those > 60 years.

The mean age of the post TB sequelae patients in our study was similar to to a study conducted in burla, in which the mean age was 53.39 years. The age difference in COPD and post TB sequelae patients was not statistically significant.

It was observed that 14.5% post TB sequelae and 20.3% COPD patients were admitted with type 1 respiratory failure. 85.5% post TB sequelae patients and 79.7% COPD patients were admitted with type 2 respiratory failure. The difference of presentation of respiratory failure in post TB sequelae and COPD patients was not statistically significant.

A similar study conducted by YK Seo et al. TB-destroyed lung and COPD in ICU showed that the mean PaCO2 was 54.9 and 44.7 in post TB sequelae and COPD respectively. This was not in accordance with our study where most of the patients were in type 2 respiratory failure.

In our study, 48.4% post TB sequelae and 44.3% COPD patients were managed with oxygen and bronchodilators while 51.2% post TB sequelae and 55.7% COPD patients required mechanical ventilation for management. The need for mechanical ventilation (non-invasive and invasive amongst two groups was not similar and difference was not statistically significant.

Similarly, the study conducted by Seo et al. concluded that 50% post TB

Discussion

The mean age of the COPD patients in our study was 63 years and post TB sequelae was 51.5 years. Prevalence of both COPD and post TB sequelae was more in males than in females.

This was similar to various studies conducted for estimating the prevalence of COPD. A systematic review and meta-analysis, including studies carried out in 28 countries between 1990 and 2004, provided evidence the time of admission. The p-value is .375976. This result is not significant at p < .05.

48.4% post TB sequelae and 44.3% COPD patients were managed with bronchodilators and oxygen supplementation. The rest requires mechanical ventilation for management. 24.2% post TB sequelae patients and 26.6% COPD patients required non invasive mechanical ventilation, while 27.4% post TB sequelae and 26.6% COPD patients required intubation and mechanical ventilation. The p-value is 0.48. The result is not significant at p < .05.

Out of 141 patients, 111 survived. The mean duration of hospitalisation days in Post TB sequelae patients was 10 days and COPD patients was 11.42 days.

15 out of 62 i.e. 24.19% post TB patients died while 15 out of 79 i.e. 18% COPD patients died during the course of treatment. The p-value is .433403. This result is not significant at p < .05.

46.88% post TB sequelae patients and 35.72% COPD patients who required mechanical ventilation died during their hospital stay. The p-value is 0.33. This result is not significant at p < .05.

The mean duration of hospitalisation amongst two groups was not statistically significant.

In the study conducted by Seo et al. hospitalisation duration was 11.3 days and 8.3 days in Post TB sequelae and COPD patients respectively. Similarly, in this study also the difference of hospital duration for management was not statistically significant.

The mortality of patients admitted with respiratory failure in Post TB sequelae group was 24.2% and COPD group was 18.9%. The difference in the mortality was not statistically significant. The mortality amongst the ventilated patients in post TB sequelae and COPD group was 46.88% and 35.72% respectively.

In a study conducted by Seneff et al. the mortality rate was 24% amongst those admitted in ICU. In a review by Weiss and Hudson of 11 studies, the combined mortality rate was 20.3% and ventilation rates were 9.8–67.6%.

In our study it was observed that there was no difference in patient profile, presentation of Respiratory failure, mortality, survival and need for long term oxygen therapy in post TB and COPD patients admitted in intensive care with respiratory failure.

Recommendations

Various pathological changes that occur during the healing of tuberculosis infection after proper treatment lead to development of sequelae and obstructive airway disease. These obstructive airway disease leads to respiratory failure, exacerbation and recurrent admissions in critical care units. Many studies and guidelines consider post TB sequelae/obstructive airway disease as a part of COPD group. Our study also finds no difference in patient profile, type of respiratory failure and outcome of both groups.
Exhaled Breath Temperature and Systemic Biomarkers for Assessment of Airway Inflammation in Asthmatics

Bhupendra Singh Yadav¹, Geetanjali Bade², Randeep Guleria³, Anjana Talwar²*

Abstract

Objectives: Asthma is characterised by chronic airway inflammation and remodelling. Inflammation may alter the thermal balance of the affected tissues secondary to changes in the blood flow. Measurement of exhaled breath temperature (EBT) is a simple, safe and non-invasive technique to detect airway inflammation. The objective of this study was to measure EBT in asthma patients and compare it with healthy controls and also to correlate it with serum biomarkers of inflammation and remodelling.

Methods: 24 male asthma patients and 23 age and gender matched healthy controls were recruited in the study. EBT and core body temperature were recorded followed by spirometry to measure forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR). Serum levels of interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) were quantified by ELISA.

Results: Asthmatics had significantly lower FEV1 % predicted compared to healthy subjects. EBT in asthma patients was significantly higher as compared to healthy controls while rate of rise of EBT was not significantly different. Serum biomarker of inflammation i.e. IL-6 and of tissue remodelling i.e. VEGF, MMP-9 and TIMP-1 were significantly raised in asthma patients while the ratio of MMP-9/TIMP-1 was comparable between two groups. But no correlation was observed between EBT and serum biomarkers.

Conclusion: EBT may be used as an adjunct tool for non-invasive assessment of airway inflammation and remodelling in asthma patients.

Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough with variable and often reversible expiratory airflow limitation. Of about more than 300 million sufferers, around 2.5 million patients die every year from the asthma worldwide.¹ Prevalence in Indian adults is about 2.05% and is growing over time with increased urbanisation and rapidly changing lifestyle.²

Earliest descriptions of significant changes in airways of asthma patients were provided via histopathology from autopsy studies of patients who died of asthma. These autopsies revealed airway inflammation, inspissated mucus, epithelial desquamation, thickening of the subepithelial basal lamina and hyperplasia or hypertrophy of goblet and airway smooth muscle cells. These persistent changes in composition, organisation and functions of the structural cells in the airways along with enhanced turnover of extracellular matrix components are collectively defined as “airway remodelling”.³ Airway inflammation is central to the pathogenesis of asthma, chronic inflammation increases tissue vascularity and induces airway remodelling. This inflammation and remodelling of airways is also reflected systemically as raised serum biomarkers in asthma patients.⁴

Bronchoscopy with bronchoalveolar lavage (BAL) and endobronchial biopsy are considered the gold standards for assessing airway inflammation and remodelling in asthma but, being invasive methods, they have a limited use in the clinical setting. Also the discomfort, inconvenience and risk involved in performing these invasive procedures limit their use. Evaluation of the exhaled breath temperature (EBT) has recently been suggested as a simple, safe and valid non-invasive technique to detect inflammatory process in the conducting airways which can be repeated to monitor the airway inflammation. The cardinal signs of inflammation are redness, pain, swelling and increased heat production.

References


¹Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh; ²Department of Physiology, ³Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences New Delhi; ⁴Corresponding author

Received: 23.03.2020; Revised: 13.01.2021; Accepted: 24.02.2021
Asthma patients were recruited from inhalation) were recruited in this study. 10-15 min after 400 mcg salbutamol expiratory volume in one second (FEV₁) positive bronchodilator reversibility according to the Global Initiative for Asthma (GINA) guidelines and having asthma patients who were clinically diagnosed according to an alpha error of 0.05 power at 0.90. required sample size was n=23 for each group considering an alpha error of 0.05 powered at 0.90.

24 male mild and moderate asthma patients who were clinically diagnosed according to the Global Initiative for Asthma (GINA) guidelines and having positive bronchodilator reversibility test (>12% and 200-mL increase in forced expiratory volume in one second (FEV₁) 10-15 min after 400 mcg salbutamol inhalation) were recruited in this study. Asthma patients were recruited from Department of Pulmonary, Critical Care and Sleep Medicine OPD after obtaining written informed consent and with prior approval of Ethics Committee of All India Institute of Medical Sciences, New Delhi, India (Ref. No. IESC/T-303/03.08.2012). 23 age and gender matched healthy controls were also recruited in this study.

Patients who were smokers or having severe and exacerbated asthma, associated respiratory illness (tuberculosis, pneumonia), associated systemic illness (fever, malignancy) and any previous lung volume reduction surgery were excluded from the study to avoid confounding effect, if any.

**Material and Methods**

This study was conducted at the Respiratory Research Laboratory, Department of Physiology, All India Institute of Medical Sciences, New Delhi, India.

Sample size was calculated based on previous studies where in authors have compared exhaled breath temperature of asthma patients with healthy controls. Using difference of mean exhaled breath temperatures of 0.8°C and pooled standard deviation 0.9°C, the required sample size was n=23 for each group considering an alpha error of 0.05 powered at 0.90.

Thus it is very likely that inflammation would alter the thermal balance of the affected tissues in respiratory diseases due to changes in the blood flow of their walls and adjacent structures. EBT has been reported to be related to the degree of airway inflammation in asthma patients.⁵

So the objective of the present study was to measure EBT in asthma patients and to compare it with healthy controls. We have also investigated correlation between EBT and serum biomarkers of inflammation and remodelling.

**Spirometry**

Spirometry was performed according to ATS-ERS guidelines. Forced expiratory volume in 1 second (FEV₁), Forced vital capacity (FVC) and FEV₁/FVC were estimated using a dry rolling spirometer (Spiroair, Medisoft, PK Morgan Ltd., Kent, UK).

**Measurement of exhaled breath temperature**

EBT was measured in a room with temperature maintained between 24-27°C using a multiple breath portable hand held device X-halo (Delmedica Investments Pvt Ltd, Singapore).⁶ After giving 15 minutes rest, subjects were instructed to hold the device with their two hands, purse their lips around the mouth piece, inhale through the nose and exhale freely into the device at a rate and depth suiting their normal tidal breathing pattern. The subject exhales continuously into the thermal chamber of the device until temperature of heat sink reaches a plateau indicating that a thermal equilibrium has been reached inside the closed system. The final stable temperature is picked up by thermal sensor and reflected on the LCD screen of the device. X-Halo stores data that can be transferred to computer for offline analysis of temperature curve (Figure 1A).

**Analysis of exhaled breath temperature**

As discussed in our previous study, two parameters of EBT were studied:

1. Plateau (stable) temperature achieved
2. Rate of rise of temperature (slope of EBT curve)

As the curve showed exponential rise, the point in time at which the EBT raised to 63% from baseline temperature (plateau temperature minus ambient temperature), was chosen to study the slope of the curve as it represents two time constants of the maximal temperature change. Slope of the curve at that point in time was calculated by ΔT/Δt, where ‘T’ is temperature in degree Celsius and ‘t’ is time in seconds (Figure 1B). A better intra-session and intersession variability has been observed by Paredi et al by using this method.⁷

**Measurement of core body temperature**

Core body temperature was measured by Omron gentle temp instant ear thermometer (model-MC150). It detects the infrared heat given off by the ear drum and surrounding tissue.

**Estimation of systemic biomarkers by ELISA**

Enzyme linked immunosorbent assay (ELISA) was performed for the estimation of biomarkers of inflammation and remodelling from stored serum samples of patients and controls collected at the time of recording EBT. Serum levels of interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) were quantified by ELISA kits (RayBiotech, USA) and vascular endothelial growth factor (VEGF) by human ELISA kit [Boster Biological Technology Co. Ltd, (USA)]. ELISA was performed according to the manufacture’s guidelines. The absorbance of the colour complex was measured by Benchmark plus microplate reader (BioRad, USA).
Table 1: Demographic characteristics and spirometric parameters of asthma patients and healthy controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Asthma Patients (n=24)</th>
<th>Controls (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>33.24±9.80</td>
<td>31.99±6.83</td>
<td>0.401</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>64.4±13.18</td>
<td>72.08±16.92</td>
<td>0.085</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168±4±5.98</td>
<td>170.5±6.94</td>
<td>0.432</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.62±4.07</td>
<td>24.78±3.28</td>
<td>0.045</td>
</tr>
<tr>
<td>FVC (% of predicted)</td>
<td>76.25±4.68</td>
<td>92±13.69</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV₁ (% of predicted)</td>
<td>62.73±19.22</td>
<td>85.3±18.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>83.5±16.52</td>
<td>95.9±11.68</td>
<td>0.004</td>
</tr>
<tr>
<td>PEFR (% of predicted)</td>
<td>65.32±21.09</td>
<td>88.6±28.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values given are mean ± SD; p<0.05 statistically significant; BMI: Body mass index, FEV₁: Forced expiratory volume in one second, FVC: Forced vital capacity, PEFR: Peak expiratory flow rate.

Table 2: Exhaled breath temperature parameters and core body temperature in asthma patients and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Asthma patients (n=24)</th>
<th>Controls (n=23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plateau EBT (ºC)</td>
<td>34.21±0.57</td>
<td>33.7±0.84</td>
<td>0.024</td>
</tr>
<tr>
<td>Slope of EBT (ºC/Sec)</td>
<td>0.122±0.36</td>
<td>0.113±0.03</td>
<td>0.49</td>
</tr>
<tr>
<td>Core body temperature (C)</td>
<td>36.46±0.25</td>
<td>36.34±0.27</td>
<td>0.113</td>
</tr>
</tbody>
</table>

Values given are mean ± SD; p<0.05 statistically significant; EBT: exhaled breath temperature.

Table 4: Correlation between serum biomarkers and plateau exhaled breath temperature in asthma patients and controls

<table>
<thead>
<tr>
<th>Serum Biomarkers</th>
<th>Plateau EBT (ºC)</th>
<th>r value</th>
<th>p value</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/mL)</td>
<td>-0.18</td>
<td>0.38</td>
<td>-0.11</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>VEGF (pg/mL)</td>
<td>-0.01</td>
<td>0.97</td>
<td>-0.21</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>MMP-9 (ng/mL)</td>
<td>-0.04</td>
<td>0.85</td>
<td>-0.09</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>TIMP-1 (ng/mL)</td>
<td>-0.16</td>
<td>0.42</td>
<td>-0.22</td>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>

*Pearson, *spearman correlation coefficient; EBT: Exhaled breath temperature, IL-6: Interleukin-6, VEGF: Vascular endothelial growth factor, MMP-9: Matrix metalloproteinase-9, TIMP-1: Tissue inhibitor of matrix metalloproteinase-1.

Statistical analysis

All the parameters were expressed as the means ± standard deviation or median (min-max) depending upon their distribution. Intra group and intergroup comparisons of the spirometry, EBT parameters, core body temperature and levels of biomarkers were performed using unpaired t test for parametric and Mann–Whitney U-test for non-parametric variables. Correlations between various parameters were tested by Pearson or Spearman correlation tests based upon distribution of variables. A value of p <0.05 was considered as significant difference. All statistical analysis was performed using the software GraphPad Prism (version 8).

Table 3: Serum biomarkers of inflammation and remodelling in asthma patients and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Asthma patients (n=24)</th>
<th>Controls (n=23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/mL)</td>
<td>2.56 (0.58, 8.16)</td>
<td>1.30 (2.2, 4.55)</td>
<td>0.005</td>
</tr>
<tr>
<td>VEGF (pg/mL)</td>
<td>96.21 (47.9, 379.9)</td>
<td>73.5 (13.21, 121.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>MMP-9 (ng/mL)</td>
<td>215.9±50.09</td>
<td>168.3±44.31</td>
<td>0.001</td>
</tr>
<tr>
<td>TIMP-1 (ng/mL)</td>
<td>462.5 (348, 1040)</td>
<td>395 (179, 1120)</td>
<td>0.01</td>
</tr>
<tr>
<td>MMP-9 to TIMP-1 ratio</td>
<td>0.47 (0.16, 0.8)</td>
<td>0.41 (0.15, 1.84)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Values given are either mean ± SD or median (minimum, maximum range); p<0.05 statistically significant; IL-6: Interleukin-6, VEGF: Vascular endothelial growth factor, MMP-9: Matrix metalloproteinase-9, TIMP-1: Tissue inhibitor of matrix metalloproteinase-1.

Fig. 2: Correlation between A) TIMP-1 and FEV₁, B) Post bronchodilator FEV₁ reversibility (% change) and duration of asthma (years); TIMP-1: Tissue inhibitor of metalloproteinase-1

Results

Demographic characteristics and spirometric parameters of asthma patients and controls are presented in Table 1. All spirometric parameters i.e. FEV₁ % predicted, FVC % predicted FEV₁/FVC and peak expiratory flow rate (PEFR) % predicted were significantly decreased in asthma patients as compared to healthy controls.

We also observed that post bronchodilator FEV₁ reversibility (% change) correlates negatively with duration of asthma (Figure 2).

The plateau temperature of EBT was significantly higher in asthma patients as compared to controls but median slopes of EBT curves were comparable between the two groups. The mean core body temperatures recorded from the tympanic membranes were also comparable between the two groups (Table 2).

Serum levels of IL-6, VEGF, MMP-9 and TIMP-1 were significantly higher in asthma patients as compared to control group but ratio of MMP-9 to TIMP-1 was comparable between both the groups (Table 3).

Significant negative correlation was observed between FEV₁ (% predicted) and serum level of TIMP-1 in asthma patients (Figure 2).

We have also investigated the correlation between EBT and serum biomarkers of inflammation and remodelling but observed no significant correlation between these parameters (Table 4).

Discussion

The aim of the present study was to assess the airway inflammation and remodelling in asthma patients, non-invasively by measuring EBT and also to correlate it with systemic biomarkers of inflammation and remodelling. Bronchial biopsy and bronchoalveolar lavage remained principal techniques to study airway inflammation and remodelling until technique of sputum induction using hypertonic saline emerged over past few decades. But induction of sputum also poses the risk of bronchoconstriction in sensitive individuals and fails frequently to induce sputum in healthy controls. In the present study we evaluated measurement of EBT as a novel non-invasive tool for assessment of underlying airway inflammation in asthma patients and studied its...
T cells. Studies suggest that IL-6 in asthma patients compared to controls which is in line with previous reports while insignificant difference in the rate of rise of EBT curve (slope) between two groups which is in contrast to that reported previously.5,6

In asthma patients airway inflammation results into increased bronchial blood flow which may cause increased heat exchange in the airways of the asthma patients. This increased heat exchange in the airways when measured as exhaled breath temperature (EBT) may reflect the degree of underlying airway inflammation.6,7

Out of these two parameters, plateau of EBT seems to be more reliable as compared to slope of EBT curve which varies with rate and depth of tidal breathing. It also shows high inter and intra individual variations in asthma patients.8

Temperature of tympanic membrane is a good measure of core body temperature, and we found it to be comparable in both the groups. Also lack of correlation between exhaled breath temperature (EBT) and body temperature measured at tympanic membrane further supports our observation that the raised exhaled breath temperature is due to underlying airway inflammation and not confounded by body temperature.10

In the present study we observed significantly raised levels of serum IL-6, VEGF, MMP-9 and TIMP-1 in asthma patients as compared to control group. IL-6 plays an important role in the pathophysiology of asthma by regulating differentiation of CD4+ T cells into specific effector cells and also by promoting the differentiation of T helper type 2 (Th2) cells by enhancing endogenous IL-4 production by CD4+ T cells.11 Studies suggest that IL-6 synergizes with IL-18 to promote Th17 differentiation which secretes IL-17. IL-17 is an inflammatory cytokine which plays very important role in pathogenesis of asthma. Thus, IL-6 may be a key factor in determining the balance of CD4+ T cells in becoming Treg which regulate inflammation or inflammatory Th17 cells. There are reports of elevated IL-6 levels in exhaled breath condensate, BALF, induced sputum and serum in asthma patients.12 The raised serum levels of IL-6 in our study are in agreement with earlier reports.12,13 Thus besides airway inflammation, serum markers of systemic inflammation are raised in asthma patients, suggestive of systemic reflection of inflammatory process.14

Persistent airway inflammation causes changes in the structural components of the airways leading to thickened airway wall and compromised lumen in asthmatics. The mechanisms involved in this airway remodelling are incompletely understood but are thought to involve vascular endothelial growth factor (VEGF), matrix metalloproteinases and one or more isoforms of transforming growth factor-β (TGF-β). VEGF which was originally described as vascular permeability factor based on its ability to cause tissue edema, is now known to be a multifunctional angiogenic regulator.15 VEGF plays a crucial role in the remodelling of airway vasculature contributing to the airway edema and thickness both directly by increasing leakiness of vessels and indirectly by new vessel formation. Other than being an important player in the airway remodelling, VEGF also increases expression of other mediators of airway remodelling. MMP-9 expression had been shown to be raised in ovalbumin-induced mice model of asthma and the same was downregulated following inhibition of VEGF receptor.16 This increased expression of MMP-9 in vascular smooth muscle cell is believed to be mediated via VEGF receptor-fit-1.17 We observed significantly raised serum VEGF in asthmatics over healthy controls which further substantiate the findings of Yoo et. al. but unlike them we did not find significant correlation between serum VEGF levels with disease severity (FEV1, % predicted).18

Matrix metalloproteinases is a large family of calcium-dependent zinc-containing endopeptidases, which are able to degrade extracellular matrix (ECM) and thus play a role in cell migration and tissue remodelling. Moreover, they can splice and inactivate cytokines and chemokines, thereby influencing the recruitment and function of inflammatory cells. Out of about 26 members, MMP-2 and MMP-9 are specific for collagen-IV and are referred to as gelatinase A and B respectively. Of these MMP-9 plays significant role in the pathophysiology of asthma being proinflammatory and promoting airway remodelling.19 MMP-9 has been reported to be raised in serum, BALF, sputum and transbronchial biopsy specimens of the individuals with asthma.20

Tissue inhibitor of matrix metalloproteinases (TIMPs) binds with MMPs in 1:1 molar ratio and are capable of inactivating all MMPs. Of the various subtypes TIMP-1 has high specificity for MMP-9 and thus crucial in airway remodelling in asthma patients as they are important in maintaining the balance between extra cellular matrix (ECM) deposition and degradation. The imbalance between MMP-9 and TIMP-1 may lead to increased turnover of ECM, an excess of TIMP-1 over MMP-9 has been proposed to favour airway remodelling in chronic asthma21 which may explain the negative correlation observed between serum level of TIMP-1 and FEV1 in the present study. We found serum MMP-9 and TIMP-1 levels significantly higher in asthma patients as compared to controls. We did not find statistically significant difference in MMP-9/TIMP-1 ratio between asthma patients and control group. Raised serum levels of all these biomarkers suggest that inflammation and remodelling processes of the airways are also reflected systemically in bronchial asthma. Zeiger at el reported pre and post bronchodilator FEV1 (% predicted) to be correlating with disease duration and disease severity in asthma patients.22 In our study we observed that post bronchodilator FEV1 reversibility (%) change) correlates negatively with duration of disease in asthma patients which may suggest greater airway remodelling with prolonged illness.

We also investigated the correlation between EBT and serum biomarkers of inflammation and remodelling. To the best of our knowledge, this is the first study in which the correlation between exhaled breath temperature and serum biomarkers is investigated. Even though these serum biomarkers are elevated in asthma patients, they don’t correlate significantly with exhaled breath temperature, summary of the same is presented in table no. 4. We have recruited heterogeneous group of asthma patients and did not categorised them into different
inflammatory phenotypes, it could be a probable cause for not finding significant correlation between these parameters. Airway remodelling causes permanent changes in airway architecture which may minimise variations in bronchial circulation and hence EBT. Further, serum biomarkers specific to particular inflammatory phenotypes may be compared and their correlation to EBT can be investigated.

The major limitation of the present study is the small sample size. Also serum cytokine profiling by a whole panel of biomarkers involved in the pathobiology of asthma would be better to assess the underlying inflammation and remodelling and could be better predictor of disease exacerbation and response to treatment. Further studies with large sample size from heterogeneous population and with improvised technique are necessary to establish clinical utility of the EBT for routine screening of asthma patients as the same needs to be proven in outpatient setting.

Acknowledgements
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Author Contribution Statement
AT and BY conceived and designed research. BY conducted experiments. RG provided patients. BY and GB analysed data. BY and GB wrote the manuscript. All authors read and approved the manuscript.

References
Effectiveness of Nimesulide in Acute Fever Management in Adults: Retrospective Electronic Medical Records Database Study Outcome in Outpatient Department

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Abstract

Background: Various clinical trials have established anti-inflammatory and antipyretic properties of Nimesulide in a controlled setting, however, the fever management in real-world settings is quite different.

Objective: To assess the effectiveness of Nimesulide in acute fever management in real-world clinical practice.

Methodology: A retrospective, multicenter study was conducted on electronic medical records (EMR) of 302 patients visiting out-patient departments at three centers between Jan 2016 and Jan 2020 and were prescribed Nimesulide for acute fever. The effectiveness of Nimesulide was analyzed as a change in fever from baseline to follow-up visit within 14 days and tolerability as the number of side effects captured post-Nimesulide ingestion.

Results: The provisional diagnosis at the baseline visit reported major complaints like fever, fever with abdominal pain, body-ache, cough and myalgia. The mean baseline body temperature was 103.2±1.5°F with a mean duration of 4.4±2.8 days significantly (p<0.0001) decreased to 99.7±1.8°F on the administration of Nimesulide. The liver and the renal profiles were found to be normal on records, and the side effects such as nausea and dyspepsia were reported only in 2% of patients.

Conclusion: Nimesulide was found to be well-tolerated and effective as an antipyretic for acute fever management in adults during short-term use in real-world clinical practice.

Introduction

The International Statistical Classification of Diseases, American College of Critical Care Medicine, and Infectious Diseases Society of America define fever as a core temperature of 38.3°C/100.94°F or higher.¹

The major issues associated with fever are discomfort, febrile seizures, cognitive impairment, morbidity and mortality, and decreased outcome in patients with stroke or brain injury. A common justification for suppressing fever is the relief from discomfort.² The fever originates due to known or unknown reasons, which can further be classified as pyrexia of unknown origin (PUO) and acute undifferentiated fever (AUF). Continuous or sustained fever, intermittent, and remittent fever are the three major types of fever. Continuous fever fluctuates around 1.5°F (1°C) for 24 hrs but never touches normal. In comparison, intermittent fever is present only for several hours in a day. Remittent fever is the fever with daily fluctuations of more than 2°C, and no time touches the normal.³

AUF is one of the common causes of patients seeking healthcare in India. AUF or acute febrile illness (AFI) refers to the fevers not extending beyond a fortnight and is characterized by a lack of localizable or organ-specific clinical features. The unspecific sign and symptoms, along with a lack of accurate diagnostic methods, pose a challenge to the health workers.⁴ The AUFs which have a duration of illness longer than three weeks are considered as PUO. The empirical treatment for AUF must be broad enough to avoid untimely mortality.⁵

Fever management includes antipyretic for symptomatic relief and empiric or specific therapeutic arsenal. Pharmacological methods of antipyresis include the administration of antipyretic drugs.⁶ Antipyretic drugs reduce fever primarily by inhibiting the formation of prostaglandin E2 (PGE2) in the brain.¹ The physical methods of antipyresis include sponging with cold water or alcohol, application of ice packs and cooling fans along with sponging.¹² The effect of fever may include metabolic effects such as increased heart rate and respiration, which can pose a challenge, especially in the elderly. Antipyretics may improve the accompanying responses and reduce the discomfort.⁸

Several antipyretic drugs, like Aspirin, Paracetamol, Nimesulide, Ibuprofen, Mefenamic Acid etc., are available and have been used for the management of fever for a long time.²,⁴ Nimesulide inhibits prostaglandin synthesis weakly and has varied mechanisms of action. Nimesulide inhibits platelet-activating factor as well as the release of oxidants.

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from activated neutrophils, decreases histamine release, and scavenge the hypochlorous acid.\textsuperscript{10,11} The greater affinity of Nimesulide for selective inhibition of Cyclooxygenase-2 (COX-2) corresponds to higher anti-inflammatory, analgesic, and antipyretic activity. In India, Nimesulide has been used for the treatment of acute pain, osteoarthritis, dysmenorrhea, fever, and acute tendinitis for patients \textgreater 12 years of age.\textsuperscript{12}

Most of the studies which have provided evidence on the antipyretic effect of Nimesulide in the adult population date back to two decades.\textsuperscript{8,10,12} There is a paucity of most recent data depicting the role of Nimesulide in controlling acute fever in adults from real-world clinical practice in India.

The current retrospective study was conducted to assess the effectiveness of Nimesulide in acute fever management in Indian adults in a real-world clinical setting.

**Methodology**

The current retrospective, multicenter study was conducted on anonymized aggregate patient data captured in the EMR records of patients who visited the out-patient department (OPD) of clinics located in Delhi, Kolkata, and Bongaigaon (Assam) between Jan 2016 and Jan 2020. The EMR records were based on the provisional diagnosis of fever which was managed with Nimesulide 100 mg BID dose or whenever necessary (SOS). This being a retrospective study using anonymized patient EMR data, without any prospective components for research purposes.\textsuperscript{13} Accordingly, independent ethics committee approval was taken for the study along with the patient consent waiver.

The patients satisfying the inclusion criteria: adults aged 18-75 years, body temperature $\geq 38.3^\circ{C}/100.94^\circ{F}$, and the patients who were prescribed Nimesulide for fever with medical records of the follow-up visits within 14 days from the baseline visit, were reviewed and included in the analysis. The exclusion criteria were any history of allergy to the study drug and if any antipyretic or similar drugs consumed eight hours before the baseline visit. The recorded complaints and the laboratory values were also considered. The data points taken into consideration were demographics, medical history, type of fever, duration of illness, baseline body temperature, liver and renal profile reports, and concomitant medications.

For analysis, the patients were divided, based on age, as following three groups -

1. Young adults (<40 years)
2. Middle-aged adults (40-59 years)
3. Old adults (>60 years)

The effectiveness of Nimesulide was assessed as reduction in fever from the baseline temperature to temperature as recorded in the follow-up visit within 14 days duration. The normal (oral) temperature may vary from 96.3 to 99.3$^\circ{F}$, however, for the analysis purpose, the temperature, 98.6$^\circ{F}$ was considered as normal in the manuscript. The tolerability was analyzed from the number of patients reported side effects post-ingestion of Nimesulide as captured by the clinician in EMR.

All outcomes were presented using descriptive statistics. Continuous data were expressed as mean, and SD and categorical data were presented as numbers and percentages. The comparison of mean differences of data was analyzed by T-test and categorical variables by the Chi-square test. A $p$-value of $<0.05$ was considered statistically significant. The calculations were performed using software RStudio V1.2.5033.

Medical records were screened as per inclusion and exclusion criteria and out of which, 302 were considered for the final analysis (Figure 1). The record of one patient was excluded from the study due to the unavailability of demographic data.

**Results**

The demographic analysis of 302 medical records had shown the mean (±SD) age as 50.2 (11.8) years wherein middle-aged adults were 50%, followed by old age (27%) and young adults (18%). The mean (±SD) weight was 69.1 (8.2) kg, and males were 57.6%, as shown in Table 1. The overall mean (±SD) duration of fever was 4.4 (2.8, 2-10) days, wherein young adults had a fever for a longer period, 5.9 days.

The provisional diagnosis was based as per the discretion of the treating clinician wherein reported major complaints viz. viral fever (22.8%), pharyngitis (17.9%), upper respiratory
More than 40% of the patients were administered antibiotics as concomitant medications, namely, Penicillins, Macrolides, Cephalosporins, and Ciprofloxacin, which were the major class of antibiotics given. Multivitamins and povidone-iodine gargles were prescribed to 21.5% and 11.6% of patients as concomitant medications, respectively.

The mean baseline body temperature was 103.2±1.5°F with a mean duration of 4.4±2.8 days decreased to 99.7±1.8°F on the administration of Nimesulide 100 mg BID dose or whenever necessary (SOS) (Table 3). This reduction in fever was statistically significant (p-value <0.0001).

After the administration of Nimesulide, the body temperature reduced to ≤98.6°F in 44% of patients, while 56% of patients still had a temperature >98.6°F. The percentage of male and female patients recovered from fever (≤98.6°F) were comparable with 22.8 and 21.5%, respectively.

Age-wise, the body temperature was subsided to ≤98.6°F in 24.8% middle-aged, 11.6% in young and 7.9% in old adults, after administration of Nimesulide. The statistical significance (p-value <0.05) depicted that there is a difference in associated temperatures across the age groups. The average temperature difference was found to be the same among all the adults (Table 4).

The investigations of liver enzymes were performed for 43 patients, and the mean laboratory values of SGOT and SGPT were 24.2±4.1 U/L and 19.0±1.9 U/L, respectively. Total leucocyte count (TLC) was measured for 55 patients and was found to be 11040.7±3229.2 mm³. The detailed information regarding timing (pre and post treatment with Nimesulide) of conduct of these investigations were not captured in EMR.

The majority of patients, 88% (266), had not reported any side effects, only 2% (5) complained nausea and dyspepsia, and for remaining 10% (31), no data on side effects was available.

Discussion

In India, with limited resources, most of the physicians in OPD are trying to diagnose fever typically based on the clinical judgment, which includes signs, symptoms, epidemiology of the disease, and so on. The pattern of fever in case of malaria, pyogenic infections, tuberculosis, schistosomiasis, lymphomas, leptospirosis, borrelia, kala-azar, or septicemia corresponds to intermittent fever. Remittent fever is often associated with infectious diseases such as infective endocarditis, rickettsia infections, brucellosis, and the rest. In general, Indian patients suffer from AUF during the period between June and September.14 AUF patients can be managed initially with antipyretics in case of the self-limiting fever while for other fever types, antibiotics and/or specific medicines can be managed initially with antipyretics before investigating for specific conditions. The success story of any effective medication lies in the active translation of its efficacy from clinical
trials to clinical practice. The evidence of efficacy from the clinical trials of Nimesulide established it as antipyretic while evidence from the current real-world study on 302 patients will further supplement this evidence.

A post-marketing surveillance study conducted on 401 patients with fever and painful inflammatory states with Nimesulide 100 mg twice a day dose for seven days. The efficacy and tolerability were assessed as reported by the study clinicians as 91.3% and 94% of the cases had good to excellent effect and tolerability of treatment with Nimesulide, respectively. The corresponding percentages, according to patients, were 87.5% and 67.8%, respectively. The study reported nausea (normal SGOT and SGPT values) post the treatment with Nimesulide. In our study, 44% had shown a decrease in temperature (≥98.6°F) wherein middle-aged adults (24.8%) had comparatively been shown better effectiveness of Nimesulide treatment than young (11.6%) and old adults (7.9%). The effectiveness of Nimesulide, assessed as reduction in fever ≤98.6°F, was equivalent between male (22.8%) and female (21.5%) patients.

Goyal PK et al. reported that Nimesulide (2 doses per 9.8 hours) significantly decreased the mean temperature with a fewer number of doses as compared to paracetamol (2 doses per 8.21 hours). In our study, Nimesulide significantly (p <0.0001) decreased fever with an average temperature difference of 3.5°F from the mean baseline temperature with 100 mg twice daily dose. Cunietti et al., evidenced the better efficacy of Nimesulide than Paracetamol in the treatment of pyrexia in elderly patients (≥65 years age). However, in our study, higher percentage (25%) of effectiveness was observed in the middle-aged adults (>40–60) compared to older (>60 years) and young adults (<40 years). While the average temperature difference was found to be the same among all age groups in our study.

The higher values of TLC (>11000) count gave a clue of viral or bacterial infection, and further clinical diagnosis showed that the continuous fever was characterized as typhoid and other fever associated with infection as upper/lower respiratory infections and urinary tract infection. Another type of fever reported was intermittent fever characterizing malaria. Viral fever was diagnosed in the maximum number of patients in the study.

Cunietti et al. in a comparative study of Nimesulide with Paracetamol also observed Nimesulide as an active and safe antipyretic. In the current study, the lab investigations of SGOT and SGPT were suggested by the investigators to 67 and 50 patients respectively, of which only 43 and 42 patients went for these tests, respectively. Amongst those patients who had given the tests, the SGOT, SGPT values, and urine analysis resulted within the respective normal ranges, however, conclusive interpretations cannot be made due to lack of EMR details on timing (pre or post-Nimesulide) of the test done. Comparable inferences can be drawn from a post-marketing study of Nimesulide on Indian population which reported SGOT and SGPT and serum bilirubin values post the treatment with Nimesulide had not changed.

The safety and tolerability of Nimesulide has well been established in double-blind, multicenter studies. Nimesulide decreased the fever with comparable effect across the age groups 18-75 years. Overall, Nimesulide for fever management in adults with acute fever was found to be effective with rather good tolerability. The study outcomes provide the necessary real-world evidence to physicians to consider Nimesulide as an alternative drug of choice to symptomatically manage the acute fever when treating a patient in out-patient department along with other definitive treatments like antibiotics as needed.

Limitation

In this retrospective EMR database study, data of out-patients with follow-up visits were captured, therefore, the time data for measuring temperature after Nimesulide ingestion was not homogeneous and the time duration of Nimesulide treatment was not available. The diagnoses of fever were based on the clinical judgment of the treating physicians rather based on the investigation. Additionally, Nimesulide with other medications was prescribed empirically, which may have a confounding effect. Further studies in a prospective manner where time-correlated reduction of fever with Nimesulide and other NSAIDs need to be explored.

Conclusion

Nimesulide decreased the fever with comparable effect across the age groups 18-75 years. Overall, Nimesulide for fever management in adults with acute fever was found to be effective with rather good tolerability. The study outcomes provide the necessary real-world evidence to physicians to consider Nimesulide as an alternative drug of choice to symptomatically manage the acute fever when treating a patient in out-patient department along with other definitive treatments like antibiotics as needed.

References


The Nature of Autoimmune Diseases

Lopa Mehta

Abstract
There are innumerable theories proposed for the cause of autoimmune diseases. Repeatedly it is stated that it is multifactorial inheritance, i.e., polygenes and environment factors together are responsible. That is another way of saying that the cause is not known. None of the causes proposed so far can satisfy the basic requirement that the cause should always precede and be consistently present for the occurrence of a given disease.

A concept is presented here that there is no cause for autoimmune diseases. They are, in reality, an integral part of cell program. It is an established fact that the cell doubling capacity in vivo and in vitro is finite. What is proposed here is that on exhaustion of that capacity one of the preprogrammed alternatives for the cells is to alter their morphology of “identity as self” within the body in such a manner that invites immune system to react on them as foreign elements. This is the basis of all varied autoimmune diseases in the body which can be put together under one heading as autoimmune disease group in the same way as it is done for cancer or vascular diseases. This preprogrammed alteration in morphology can involve any cell system of body including those of immune system. This phenomenon is cell specific and hence can manifest as organ specific disease or system specific disease depending on the type of cell involved. This built-in program makes autoimmune disease group a time-governed intrinsic, senescent process. This concept accounts for all the common features of varied autoimmune diseases in the group of autoimmune disease.

They are seen in the cellular systems in plant and animal kingdoms. In humankind, they are universal and democratic. They affect all the races and both sexes. Their incidence progressively increases with age. In a given population, the distribution, the incidence, and varied features of any given autoimmune disease follow normal distribution curves. Each normal distribution curve of any one characteristic of a given autoimmune disease is independent of their other characteristics and their normal distributions. This makes each autoimmune disease unique. The total incidence of autoimmune disease group remains fixed in a given population. The herd determines its random distribution at individual level. Therefore, one can predict total incidence of autoimmune disease group in a given population but at an individual level – who, when, where, what, why and how – can be predictable only in terms of probability. The features of its being chronic, acute exacerbation and/or constant deterioration can also be accounted by being a cellular built-in program.

All the varied types of autoimmune diseases show these common features. These observations establish that they are an integral part of the biological trajectory and follow biological principles in their manifestations. The autoimmune disease group operates at bio-cosmic level displaying order in apparent chaos and making it a trans-science and trans-technique phenomenon.

Introduction
The autoimmune diseases occur at all ages in life - childhood, early adult life, mature adult life, and old age. Immune-senescence with increasing age is seen as a reduction in immune response. There is an increase in the inflammatory and oxidation background response and a production of autoantibodies. There is an increase in autoimmunity with age. A percentage of that population develops autoimmune diseases. They cause morbidity and mortality in 5-10% of the world population. There are about 80-100 variants listed under autoimmune diseases. There is no cell, fibre, organ or system immune from autoimmune diseases. An autoimmune disease affects one or more organ or tissue types involving destruction of tissues and dysfunction of the organ/system. They vary depending on the cell/tissue/organ/system affected and accordingly carry different labels. Each disease involves a specific age group and shows selective preponderance for a gender. They are a major contributor of chronic diseases and high morbidity. Unlike cancer autoimmune diseases are not grouped under a common label with common causal mechanism and hence they are looked upon as distinct entities and treated by all medical specialities. They are global phenomena, and evenly distributed. There is democracy in the prevalence of autoimmune diseases.

The common refrain regarding the exact cause of autoimmune disorders is that it is not known. There are innumerable theories suggested. They are diverse, contradictory at times and incomplete. All the proposed theories surmise that they have complex pathologies and multifactorial etiologies. The disease is triggered in genetically susceptible individuals by exposure to environmental factors such as bacteria, viruses, drugs or nutritional factors. Some factors are identified and many are hypothesized. Besides them, adaptive and innate immunity and gender play roles. A co-occurrence of autoimmune diseases is also well known fact. There is alteration in antigen processing. So far there is no existing theory which provides integration of all these factors. The cause and effect remain an unproven
link in autoimmune diseases, and therefore therapies used have no specific basis.

Any proposition that a given factor causes a particular autoimmune disease is invalidated by the latter occurring without, and refusing to occur despite, the former. This *conundrum of an autoimmune-causalist* could be expressed as follows: X causes Y, but why does Y occur without, and not occur despite, X? No autoimmunogenic factor has yet proved the *causa sine qua non* of any particular disease, in humans or in animals, *in vivo* or *in vitro*. The earmark of causality, an *invariant relationship* of events in which the cause must *precede* its effect and the effect must follow its cause, in time is absent. ‘It is this sense of *must* which distinguishes causal connection from coincidence.’1

There is no definite cause linked with autoimmune disease group.

Occam’s razor or Law of Parsimony is the problem solving principle that states that “Entities should not be multiplied without necessity; the simplest solution is most likely the right one.” In science it is used in the development of theoretical models for “simpler theories are preferable to more complex ones.”

In 1973, Dr. Manu Kothari and the present author wrote a 1000-page book, *The Nature of Cancer.*2 In that we had presented a concept that cancer is an intrinsic, time governed senescent process. It is a cellular phenomenon and it occurs at the end of completion of finite cell doubling capacity (FCDC). This concept has held true till today.3−7 We further showed that heart attack and stroke are also cellular phenomena. They are result of massive apoptosis on completion of the life time of the cells of heart and brain respectively. They are intrinsic, time governed senescent processes.8 The present article is to present a concept that the autoimmune diseases also are a part of built-in cellular program. The different diseases listed under this group are only varied manifestations depending on the type of cell involved. The autoimmune disease group is similar to cancer and vascular disease. It is an intrinsic, time governed senescent process. It is a manifestation of the integral part of last phase of life cycle of cells on completion of FCDC. It involves preprogrammed disease inducing morphological changes in self-identity which invites reactivity from the defense wing of immune system. To put it succinctly, cancer, heart attack, stroke and autoimmune disease group are all alternative manifestations of built-in senescence program in a cell which comes into play only after the cell has exhausted its finite cell doubling capacity. These processes follow well defined biological laws which we outlined in our earlier publications *Trans-science aspects of disease*9 and death and *Trans-technique aspects of disease and death.*10 In our bio-cosmic world there is order amidst apparent chaos and uncertainty of behavior of all these diseases.

**Basis of concept**

In the biological kingdom a cell is the structural and functional unit of life. Development, growth, decay and death of any organism occur with predictable precision. It is dependent on the cellular program. A cell, in a metazoic organism, has its own individual development, finite lifetime, senescence and death. Cytomorphosis is a series of successive changes undergone by a dividing cell in a metazoic organism. It consists of phases *in vitro* and stages *in vivo*.

Hayflick11−15 showed *in vitro* study of dividing cells a series of events that are seen while culturing normal diploid dividing cells from humans and animals. He showed that there is finite capacity for division of cells that has been termed the Hayflick Limit. We have termed it as the Finite Cell Doubling Capacity (FCDC). He has shown that at the end of completing the capacity of division the cells enter phase of senescence which is characterized by the appearance of chromosomal abnormalities, sluggishness of cell division, heterogeneity in the length of growth cycle. The morphological alterations of cells arise predominantly in this degenerative phase. It is shown that lack of any essential metabolite, or presence of any toxic material, infection by viruses or mycoplasms are not responsible for the cellular degeneration. According to him, it is an intrinsic character of cells. These observations are verified and accepted by others.16

Similar changes are seen *in vivo* in all organisms. This Finite Cell Doubling Capacity (FCDC) is a built-in, species-specific, individual-specific, and cell-specific characteristic of dividing cells that plays a pivotal role in determining the lifespan of a species, the life-expectancy of an individual, the lifetime of an organ or a cell, and such processes as growth, development and senescence. The term *lifetime* applies to a cell; organ or a system in an individual; *life-expectancy* applies to an individual; *lifespan* applies to a species wherein the maximal life-expectancy is equal to lifespan. The only noticeable clock in the body is the sequential expenditure of the FCDC or Hayflick Limit. The expense of the FCDC triggers the discernible changes in the biologic trajectories, at the cellular level, organ level, system level or an individual level.

The dividing cell at end of its FCDC enters stage III. It has various options. It can predictably and presumably apoptosis to vanish. The built-in capacity of repair including immune system operates to take care of structural and functional homeostasis of the body. That is how non-pathogenic autoimmune bodies are seen normally in an individual. However, a fixed number of cells in a given population are pre-programmed to develop morphological changes in such a manner that their alteration of the self-identity stamp invites reactivity of rejection. This pre-endowed capacity of morphological change of self-identity which invites self-destructive reactivity is termed as autoimmune genome as an operational mechanism. At the end of its FCDC-run that cell with autoimmune genome shifts its gene towards somatic metamorphosis which invites reactivity.

The human body is made of up trillions of cells. However they can be broadly classified into static cell populations, expanding cell populations and renewing cell populations.17−19

The static cell population comprises of nerve, both central and peripheral, sensory receptors and muscle (SNM) cells of body. They essentially complete their cell divisions in intrauterine and early stage of life. They therefore remain in post-mitotic phase of cell division in postnatal life. They only increase in the sizes of the cells as the individual grows. SNM cells are fated to end in degeneration or death, as in some cases seen in the form of various degenerative disorders of the neuromuscular system if their
lifespan falls short of the lifespan of the host. One other alternative is if they have built-in program to undergo metamorphosis so as to invite pathogenic autoimmune reaction due to presence of autoimmune genome. That forms the basis of autoimmune disease affecting the neuromuscular system.

Expanding cell populations (ECP) comprise the glands and visera like liver and kidney, wherein mitosis occurs only on demand. In the renewing cell populations (RCP), the same goes on ceaselessly to refurnish the cells lost regularly in areas such as lining of the skin, mucosa or bone marrow producing various component cells of the blood.

In expanding cell populations and renewing cell populations the constancy of the desired cell number is maintained by the differential cell divisions undergone by the stem cells housed in the individual organ/system. They produce differentiated daughter cells to carry on with the function of that organ. These stem cells follow their own FCDC quanta.

It is the stem cells, in the ECP and RCP that are the seat of an autoimmune metamorphosis at its predetermined appropriate time. The stem cells of ECP and RCP progressively deplete their quota of FCDC. With progressive march towards the depletion, the age-related changes are also concurrently seen. Once the limit of a given stem cell is over, it brings an end of clone which was being maintained to replenish the cells to maintain the fixity of cell numbers. The end result is seen as atrophy which is seen in form of aging and various age-related dysfunctions in the body. But it has an option of undergoing metamorphosis inducing autoimmune reactivity. The decision rests with the stem cell cytoplasm to switch on the autoimmune inducing genome when present to manifest changes inviting pathogenic autoimmune reactivity. Basically therefore no differences are noted in the stem cells of the normal organ and that of autoimmune reactivity arising from that organ or system.

The FCDC quantum is a direct function of, and in turn determines the lifespan of a species. Within a particular species at one end of the mortality curve shows a low life-expectancy as against others at the other end of the curve exhibiting maximal life-expectancy equal to the species-specific lifespan, the entire gradation being a function of the varying FCDC quanta. At an individual level, every individual, short-lived or long-lived, possesses some cells with high FCDC and, therefore, a long lifetime and other cells with a short lifetime because of low FCDC quanta. This concept of varying FCDC of exhibiting a normal distribution, even in the cells of the same tissue, accounts for a number of biologic phenomena at the ontogenic level such as increasing levels of autoantibodies with increasing age including increasing number of autoimmune diseases and progressive decline of cell number with increasing age. For a particular tissue (e.g., fibroblast in musculoskeletal system, skin, hematopoetic cells), the FCDC quantum in its constituent cells follows a normal distribution. The distribution of autoimmune genome to cells with different lifetime in different individuals would account for the age distribution curve of a given autoimmune disease. Simultaneous metamorphosis of cells from a clone would account for acute exacerbation of disease periodically.

Transformation of a cell to invite autoimmune reactivity is not a cellular response but a stage in the life cycle of a cell that comes to the fore irrespective of the postulated factors causing autoimmune disease. It must be pointed out that autoimmune genome as postulated here only connotes a certain intrinsic operational intracellular mechanism that determines whether the cell will invite reactivity spontaneously or in presence of external agents or whether it would refuse to do so in the face of all those agents. There will not be any structural basis such as the genes or the autoimmune genome of the cell. The reason for this is the biological principles described later governing this phenomenon.

The site/s of distribution of autoimmune genome cannot be predicted. Probability-wise the human females have greater chance of having it for some diseases. For the other diseases the probability remains equal in males and females. The endocrine organs, the skin, the blood and skeletal-musculo-fibrous system have greater probability of having this operational genome.

Viruses, chemicals, irradiation, hormones, miscellaneous other known and unknown agents, built-in low FCDC, heredity, act to effect an early entry of the target cell/s into the senescent stage by reducing the FCDC quantum or promoting its accelerated expenditure. Further, the process once “initiated” continues unabated in the absence of these agents.

**Integrity, immunity, reactivity and autoimmune disease**

Every individual biologically is a unique entity - a biocosmic phenomenon. Every individual has a blueprint or subtle body which carries the details of the entire biological configuration of the person and is in communication with all other persons - past, present and future. Non-repetition of finger print and iris print are classic examples to prove this point. Every individual has a distinct unique ID stamp of ‘self’ written on every cell. Maintaining the uniqueness in terms of its wholeness and integrity is a wonderful mechanism which operates in toto. Integrity of each body is maintained by immunity, reactivity and restorativity.

The integrity – non-quarrelling togetherness – amongst the galactic number of human cells, microbes, and other elements is maintained by two forces immunity and reactivity. Immunity etymologically connotes imm = not + munis = service and therefore meaning freedom from having to act or from acting. Immunity is neither for defence nor for offence. The tolerance that the immune system exerts against its trillion microbial symbionts, against cells chimerically derived, implants and so on is the true role of immunity. Immunity connotes a sense of peace between self and not-self.

Integrity, as a distinct noumenal entity like the subtle body, is the overall director of the so-called immunologic orchestra. Integrity is the mind, soul and the total body in abstraction. It knows what should or should not be where and why, and how. It is cosmically conscious of all other lives past, present and future so that the entry of any such alien element is greeted with appropriate orders to act. It orders immunity, again as an abstract force, to desist from any reactivity; in fact, integrity orders immunity to maintain peace through no-war, a form of somatostasis. On detecting
the presence of non-self from without, and occasionally from within, it orders reactivity to go all hog to eliminate the nonself factors, and follow up with reparativity, and restorativity. Integrity is keen to put a halt to reactivity as soon as the need is over and extends the same braking mechanism to reparitivity, so that 99,000 of 100,000 surgical wounds heal without keloiding. Integrity, as it works, maintains and restores somatostasis structurally and homeostasis functionally. The other name for somatostasis is immunity.

If reactivity is power, immunity is the brake, the precise finely tuned passivity that keeps the ever-active reactivity mechanism held in a perpetual, no-nonsense restraint. The word reactivity stems from the root react meaning “to act in return on an agent or influence,” or “act reciprocally upon each other,” or “to act in opposition, as against some force.” Reactivity steps in when alienity/alienism seems imminent from without or within. Every threat is treated on its own merits. Reactivity seen as inflammation is at the heart of non-age-related pathology. An important role of the reactivity mechanism is to treat the body’s own mutated cellular/fibral/proteinaceous elements as not-self to set up a mutiny or civil war. Reactivity directed against the sui-elements themselves, creates auto immune diseases. The other problem is of hyperreactivity comprising reactivity of mild, moderate or severe degree diseaseing the individual through gentle allergy to lethal anaphylaxis or the so-called hyperphylaxis.

Reactivity can be defined as cellular-humoro-vascular activity comprising focal, local and systemic formation and presence of extraneous specific and non-specific cells and humours (antibodies and other agents) that aim at restoration of the body’s integrity as near to status quo ante as possible. The reactivity response gets excited by disturbances in the integrity of the body due to the presence of (i) damaged, dead or de-selfed sui-cytes/sui-elements, (ii) any inanimate material (iii) microbes, or (iv) allo-cytes/allo-elements, the entire process passing through the phases of recognition, reaction, removal of the disturbing cells/elements, and restitution to status quo ante with the help of such processes as replication of missing cells (e.g., epithelial cells, liver cells), vascularization, devascularization, and contracture of the matricial fibrous tissue. Nature’s masterstroke vis-a-vis reactivity was to ask the ubiquitous fibroblast to provide the fibrous scaffold for any reactive focus, so that the inherent contractibility of the fibrous tissue would help eventually to reduce the focus to the smallest possible size, on completion of the job.

The reactivity of the immune system is protective in infectious diseases. However, reactivity of the immune response in autoimmune inflammatory disease is a major feature of all immune diseases. One of the common features of reactivity in entire group of autoimmune diseases is production of autoimmune bodies. The immune response usually involves activation of both T and B cells, the latter producing antibodies that can be detected in the sera and can be used to guide the clinical management of certain diseases.

Autoantibodies are frequently observed in healthy individuals. However, in a minority of these individuals, they lead to manifestation of autoimmune diseases, such as rheumatoid arthritis or Graves’ disease. Overall, about 5% of the population who have predetermined programmed genome to induce reactivity is affected by autoantibody-driven autoimmune disease. Pathways leading to autoantibody-induced pathology greatly differ among different diseases, and autoantibodies directed against the same antigen, have varied effects. Depending on the type of autoantibodies they can mimic receptor stimulation, can block neural transmission, induct altered signaling, trigger uncontrolled microthrombosis, bringing about cell lysis, activate neutrophils or induce inflammation.21

Biological laws governing autoimmune disease

CHAOS theory is accepted in modern science. Chaos theory presents a universe that is deterministic, obeying fundamental physical laws, but with a predisposition for disorder, complexity and unpredictability. The science of chaos is chaology. This theory also operates in the biological world as shown by its propounder James Gleik in his tome - CHAOS – Making a New Science. In the biologic world where Chaos theory prevails supreme there are a number of biologic principles which operate governing all the biologic phenomena and their characteristics ranging from sub-molecular component of an organelle of a cell to any organism. They hold good for all intrinsic diseases. The immunologic disorder group is not an exception. The CHAOS needs to be reread as Cosmic Harmony Ahead Of Science. There is surprising order in the autoimmune diseases group. Heisenberg, in 1927, declared that Uncertainty is the only certainty. Randomness is Nature’s quendom of orderedness divinity of distribution. Whenever a large sample of chaotic elements are taken in hand and marshaled in the order of their magnitude, an unsuspected and most beautiful form of regularity proves to have been latent all along. The distribution shows a perfect bell-shaped Gaussian curve. This is the cosmic power of normal distribution. The constellation comprising the universality, the vertebrateness, the time-relatedness and the intrinsicality of the autoimmune disease group make them trans-science and trans-technique. Trans-science questions are those that can be asked of science, but cannot be answered by science. Epistemologically, these are questions of facts presentable in the language of science but to which science has no rational answers; such questions transcend science. For example, about the ‘why?’ of the invariable variability of a person, from birth through death, questions have been asked of medical science, but have not been answered by medical science. Technique in medicine is whatever a doctor does to a patient, be it diagnosing, treating or prognosing. It admits of the simplest transcendent technique. Trans-science questions transcend science. For example, about the ‘why?’ of the invariable variability of a person, from birth through death, questions have been asked of medical science, but have not been answered by medical science. Technique in medicine is whatever a doctor does to a patient, be it diagnosing, treating or prognosing. It admits of the simplest transcendent techniques. Trans-technique aspects of disease and death are those innate, ordinary, day-to-day features of human diseaseing and dying that technique can in no way modify to a patient’s advantage. Modern medicine, in its ostensibly scientific and technical optimism, has not accorded due consideration to biological factors that are not only trans-modern-medicine but trans-any-science and trans-any-technique. These biological factors are Temporality, Uncertainty, Relativity and Normality (TURN), as also Systemicity, Uniqueness, Cellularity,
The pathological features of autoimmune diseases have unpredictable and unalterable distributions on the normal curves. They are independent of all other features. Because of this it is difficult to make out what, when why of any of autoimmune diseases. That is why uncertainty operates at the level of the individual patient regarding autoimmune diseases.

The human body is composite collection of cells. The advanced cytological techniques have revealed that a cell’s behavior, in health or disease, can hardly be trifled with. Because of the self-sameness of all body cells any attempt to diagnose early or selective destruction of undesired cells flooding the body with anti-abnormal-cell-agents fail.

Systemicity of a disease implies its presence in wide areas of the body. Autoimmune diseases are in reality a disease of the whole organism. The systemicity of a disease rules out its being either diagnosed early or removed or destroyed completely.

Uniqueness, variability, it is said, is the only invariant law of biology, a natural propensity that unfailingly varies from one autoimmune disease to the other. Uniqueness of every individual extends to the uniqueness of every disease. This is the unsolved and unsolvable problem of medicine. There are as many different diseases as patients. Even ‘identical’ twins differ in their individual disease patterns. The presumed identically of the genotype in such twins is unable to circumvent this code of individuality. Naturally occurring autoimmune diseases are extremely diverse even when they carry the same diagnostic label. No two cases of auto-immune disease are identical either in their presentation or in their progress. The behavioral uniqueness of a disease, with its unpredictability, forms the basis for unexpected successes and equally unexpected failures, given the same treatment. This makes prognostication difficult. In most diseases, what the doctors can prognosticate is based on group statistics that obviously have no bearing on an individual case. All technological marvels, deal with the appearances and assumed correlations of a human being’s disease; none, as yet, knows or can know of the behavioral uniqueness of such a biological entity. It is a one-to-one encounter where the uniqueness of the individual, his disease, his very biological trajectory is unpredictable, unalterable, and overwhelmingly important.

Herdity is a corporate program subserved by individual performance. Unlike the other biologic forces discussed thus far which are innate to an individual; herdity is a force that the human herd exerts on the individual. Mankind was, and is a single inclusive population and is endowed with a single corporate genotype, a single gene pool. In the physical world quantum physics reveals a basic oneness of the universe in which, at fundamental level, the seemingly separate parts of the universe are connected in an intimate and immediate way, in a complicated web of relations between the various parts of the whole. In similar way in biological world an individual’s body, and his diseases, his autoimmune disease - each unfailingly unique is a spatiotemporal manifestation of a cosmic order. This is reflected in clinical, bedside reality demonstrating the role of herdity in distribution of disease in any given group. As general statistics go, the incidence of probability of pathological events is a function of a corporate herd program that finds expression at the level of an individual who has crossed a critical genetic threshold. Herdity, thus, is a reciprocal relationship between an individual and his herd, what
consequence of axioms must be freedom is controlled to the extent can be proposed as a solution, any confirmation by experience. The freedom is not of a novelist, but of the person who solves a crossword puzzle. Any word can be proposed as a solution, but there is only one that fits the puzzle in all parts.

Einstein


Enhancing Physician’s Toolkit: Integrating Storytelling in Medical Practice

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Abstract
Traditional communication of medical literature using evidence-based terminologies are inadequate as the body of COVID-19 literature increases thereby requiring alternate methods of communication like podcasts, webinars, social media. A common theme in all these alternate forms of communication is the art of storytelling that allows physicians to make a connection with a patient by understanding their perspectives. Apart from few situations where story telling can be distracting in many situations where the patient’s history is complex and require great listening skills and empathy. Learning to be a good storyteller can help the physician help patients be a great change agent for them. Communicating with these patients can be done effectively using standard communication tools and using effective storytelling techniques can reinforce the patients trust in the provider and strengthen patient physician relationship. This could have a salutary result both for the patient by increasing patient satisfaction and compliance with treatment and physician satisfaction by increasing to understand their patient’s true concerns.

Introduction
COVID-19 pandemic has brought to the forefront stories of loss, relentless struggles of patients, health care providers and policy makers. These stories have been forged by the recent experiences of the inpatients with SARS-COV2 infection, the emotions of their families and health care providers. Experiences that cover all aspects of human lives being played out on a daily basis in the patients homes, their work places, in the communities they live in, in hospital clinics and wards and in the confines of hospital management. Stories of shortage of personal protective devices, ventilators, overworked staff, team work and supply chain issues, became common place issues during the COVID-19 pandemic. 1

Physicians, health care leaders, patients and their stakeholders have all been struggling to make sense of the uncertainty that surrounded each aspect of COVID-19 management as most evidence –based guidelines fell short of delivering the desired benefit to the patients.2 However there has been an increasing needs to bring to the forefront the rapidly evolving body of medical literature in areas of COVID-19 diagnostic tests, therapeutics, effective preventive strategies and patient experience. Traditional communication of medical literature using evidence-based terminologies (relative risks, absolute risks, number to treat, sensitivity and specificity) are inadequate even in absence of a pandemic and as the body of COVID-19 literature increases alternate methods of communication like podcasts, webinars, social media (twitter, blogs).3 A common powerful theme in all these alternate forms of communication is the art of storytelling. 4 5 In this review we describe the role of storytelling using narratives to explain complex information in simpler terms to the patient. We also include examples of story lines use to explain various themes and resources required by physicians for developing skills in storytelling.

What is storytelling and why is it important?
Story telling by physician leaders and patient advocates have been used more than in any other time in history to bring in the reality of coping with COVID-19 and understanding the emerging efforts of physician, health care teams, pharmaceutical research in using repurposed drugs, vaccinology, tied to patient unique life situation and social determinant of health.4 There is an increasing need for physicians to be able to peruse medical and social information and bring these information to the patient in the form of powerful stories.

The stories of our patients give us a glimpse to their social determinates of health and leads us to ponder what they are silent about. The hidden message (the real reason of visit) of many patients are their concerns of fear, pain and loss of functions. Very often these three concerns are left unspoken till the very end of the patient’s visit. Being an active listener of patients stories led to understanding these very aspects that patient’s often shy away from discussing. Stories are excellent platforms of explaining complexity of medical care, team work while expressing empathy of the patients situation.6 Storytelling brings to life mundane details buried in medical graphs and charts which stressing need for patient compliance. Physicians convey by their stories and acknowledgement that they respect and have understood the patient’s unique story and perspectives.

Storytelling has been described as making a connection with a patient and opening a window into their world by understanding their perspectives and changing our own. Storytelling remains
an ancient art much forgotten in current day medical school curriculum.

What is narrative medicine?

Recent efforts by physician champions like Dr. Rita Charon\textsuperscript{9,10} and Dr. Abraham Verghese\textsuperscript{6} have led to the emergence of ‘narrative medicine’. Narrative medicine has been described as medicine practiced with narrative competence. Despite the emergence of evidence based medicine and challenge to improve numeracy among physicians and patients,\textsuperscript{11} it has been increasingly recognized that the practice of medicine needs every student to be competent in understanding narratives of the patients.\textsuperscript{9}

Programs that enhance the competence of physicians in narrative medicine stress the development of 3 kinds of skills, namely (i) textual skills - understanding the structure and multiple perspectives of the story as well as identify metaphors, (ii) creative skills – being curious and able to interpret the stories while creating multiple possible options for the patient and (iii) affective skills-appreciating and tolerating uncertainty of the patients stories.

Storytelling and narrative medicine curriculum has been documented to be of high relevance even when taught to highly technical learners.\textsuperscript{12} In a study involving introduction of a yearlong communication skills curriculum for Oncology fellows that included attending in monthly 1-hour seminars lead to improvement in reflective skills, mindfulness and empathy. Fellows rated their curriculum to be of high relevance and value when it came to their abilities for storytelling.\textsuperscript{12}

Examples of narratives that can be used for story telling

Patients all over the world have share common values. Patient management issues often need patients and their relatives to accept change.\textsuperscript{13} In preparation for change management both physicians and patients need to understand the principles of how to initiate changes and the skills required for successful change management namely - listening skills and understanding patient stories, keeping our emotions under check, being resilient and flexible to accept change, hope and kindness, taking a pause to reflect our next step, how to communicate effectively and managing uncertainty. We describe here narratives that we share with our patients that help to convey our understanding of the above values. Several of these narratives can be converted and used for storytelling to convey these ideas to patients. We have been able to apply the same principles across patients across different cultures, speaking different languages working with medical interpreters.

Narratives on- Listen to understand perspectives

COVID-19 situation has put all of us in a bind. We might think that we understand what our friends are going through. However based on our unique situation we will respond differently to economic hardship due to our individual perspective. Great sensitivity is required during this period as we interact with each other. Patience and deep listening of each perspective is a time tested strategy.

Ernesto Sirolli\textsuperscript{14} in his often watched TED talk- ‘Want to help sometime? Shut up and listen!’ tells an interesting story. As a young Italian NGO he and his colleagues landed in Zambia and started a farm growing tomatoes and zucchini. His team wanted to demonstrate to the local people how easy it was to grow food in the fertile land. The local people didn’t seem to interested I helping them. The tomatoes were growing beautifully and the night before the harvest 200 hippos came from the Zambezi river and wat all the vegetables! Ernesto was horrified and he asked the locals why they had not warned them about the hippos. The local said,’ Well you didn’t ask! You presumed we were lazy! That is why we don’t farm next to the Zambezi river!’ Mr. Sirolli now spends his whole career sitting one to one with individuals understanding their unique perspective. He does not suggest any big solutions.

Narratives on- Controlling one’s emotions

One of the author’s (AG) spent 6 years in Southern India where there the temperature fluctuates between warm to hot. Imagine his rude awakening when he experienced the first winter in Minneapolis in 1993! He was frustrated and complained to his mentor, ‘I wish someone had told me how bad it gets in Minnesota during winter?’

His mentor smiled and sprung a question, ‘Are you a thermostat or a thermometer? ‘You see’, he continued, “A thermometer is reactive and just reads high or low temperature; a thermostat both reads and adjusts to keep the temperature even! People living in Minnesota we are thermostats, we don’t react like thermometers!” We keep meeting colleagues and patients who remind us the advantages of being stoic like a thermostat! They don’t overreact to any adverse news.

Hence when it comes to managing emotions one should behave more like a thermostat and not like a thermometer.

Narratives on- Being flexible and resilient

The fable goes as follows. Once upon a time there was a giant majestic looking Oak tree. He was very proud of his strength, his looks and his huge spread of leaves. Needless to say the Oak tree was proud and didn’t miss a chance to blow his horn. The Oak tree would often make fun of the Willow tree standing next to it. ‘Look at you,’ the Oak would say to the Willow tree, ‘you get all ruffled with each wind that blows over. While look at me I stay upright, defiant and don’t bend to any pressure!’ The Oak would look down at the Willow and the this went on for a while.

As it would so happened one day there was a massive hurricane. While the Willow tree was more plaint and bent with the force of the howling winds, the Oak tree was no match to the mighty hurricane and was uprooted.

Surprisingly I find this tendency in my patients. Patients who are flexible and ready to work with their providers do well inspite of their medical problem. However patients who are inflexible do poorly. They follow their own course much to their own detriment. This has led me to often tell them the story of Oak versus Willow tree and emphasize, ‘Mr. Dutta I want you to flexible as a willow tree.” Sometimes the story catches on the Mr. Smith’s overall condition improves as he follows instructions and makes good decision.

Narratives on Hope and kindness

The famous American Novelist, Edith Wharton wrote “There are two ways of spreading light: to be the candle or the mirror that reflects it.”
What a profound quote that applies so well to us.  

So how do we do good things in our community? Do we spread goodness by doing some act of kindness ourselves or be part of team and following an act of leader who is doing good herself?

Light illuminates our environment. It doesn’t matter if there is considerable darkness all around us as long as we have a source of light around us we feel safe. Interestingly the sources of light are many- it can be a candle, a torch, a lamp, a matchstick and so one. It doesn’t matter if the light is created by lighting a lamp, turning on a switch, sliding the side switch of torchlight or making a bonfire. The light destroys darkness regardless of the source of the light! Positive message destroys ignorance and removes cobwebs from my minds.

A mirror can also reflect and make the light stronger and spread to a longer distance and cover a larger area. A chandelier with reflecting mirrors makes the light so much brighter and more beautiful. Mirrors have been used over centuries to reflect light to long distances.

What has candle and mirrors got to do with current times? There is a lot of confusion and misinformation around us. There is unhappiness and distress due to furloughs and layoffs. We can each be a source of light by spreading a positive message, being a friend, lending an ear, and helping with resources if we are blessed to have an excess amount of inventory of any kind.

We can also be like a mirror by speeding cheer, positivity, lending our shoulder to carry a community burden, pass on a helpful resource that we find through online source.

**Narratives on- Taking a pause to reflect**

**what we are doing- pressing on our brakes**

Are the brakes not there to slow the car down? Brakes are there so that we can accelerate when we want! This concept runs opposite to our current idea about brakes.

Let us explain our point. If the brakes were not there we would drive our car at 10 mph for fear of collision. Since our car has brakes we feel confident. We can slow down and accelerate at will of course with an eye on the rear view mirror for flashing lights. Having brakes help us to know when to accelerate and not slow down!

Brakes are very essential in life. There are many useful examples where the analogy of hitting the brakes can be used in our daily lives!

1. Communication: If we didn’t control the way we speak and told whatever comes in our minds we all know we will be in trouble.

2. Relationship: If we don’t put a brake on our bad habits we know our relationship with ur significant other will dissolve

3. In Medicine: if he don’t put a brake on our habits (lack of exercise, increase food intake, alcohol intake) our health will fail (I use this example with my patients all the time).

4. COVID-19: ability of understand the smoothening of the curve helps us to predict when to open up businesses and resume normalcy

At each step brakes help us to momentarily slow down and then accelerate (of course without breaking any laws).

It takes great planning, intelligence and restraint to know when to apply the brakes and when to accelerate. Knowing when to press the brake and slow down are hallmarks of a wise person, great institution and strong society. The better the driver the better they know how to apply brakes in their daily life. A rash driver will only accelerate (speed up, shoot his mouth, not check harmful habits) and might get in trouble.

One of life’s most important lesson - Brakes help us reach our destination faster.

**Narratives on how to communicate effectively**

Even though we communicate every day we pay little attention on how we say things and how we interpret information presented to us. What we say matters! Like the toothpaste squeezed out of a tube can’t be put back into the tube- what we say often can’t be taken back. The old adage – ‘Think before you speak!’ remains very true.

We need to put several filters before we translate our thoughts to words. Filters like (i) Intention- Am I saying this to cause alarm? (ii) Choices- can this be interpreted differently by people, (iii) Listening- Did I listen what was said, (iv) Embarrassment – Will what I say embarrass someone?, (v) Empathy- will my words convey empathy. Statements that have not been vetted properly can cause pain to others and diminish our credibility. In worse case scenarios damage our reputation irreparably. ’The tongue has no bones, but it is strong enough to break a heart, Proverbs 15:1’ So be careful with your words. Very true!

**Narratives on how to negotiate through period of uncertainty**

What we learnt during a pandemic is that - there are no straight forward issues during period of uncertainty. Philosophers and leaders have called this phenomenon as the ‘fog of uncertainty’. When a driver is negotiating a tough and narrow pass in a steep hill which suddenly became engulfed by fog a passenger has to trust the driver’s competence in getting them safely to their destination. No written handbook can deliver that safety.

More than evidence people pay attention to a communication of that evidence from a trusted source during moments of uncertainty. Since the evidence is often evolving and data is not straightforward leaders need to be transparent about the sources of the data and trusted to be followed by their team. Two things are important to generate trust; competence and communicating with empathy. Miss one and there is lack of trust.

Another aspect of dealing with uncertainty is having discussions on effective trade-offs. More important than knowing how to deliver a message, it is important to weigh the pros and cons and spell out the trade-offs. There is a trade-offs for each of the recommendations that are expected from us during COVID-19 including masking, social distancing, using hand sanitizers and social responsibility.

Planning how to deal with a crises emerging from an uncertain crises like a pandemic or natural disaster needs preparedness. Uncertainty is unavoidable and doesn’t need to be paralyzing. Not preparing for uncertainty however is always anxiety provoking. Building a strong community of trust and teamwork during regular times helps tremendously during periods of uncertainty. Sharpening skills like empathetic communication, working on strategic priorities (identifying and resolving disparities,
supply chain improvement, crises management, etc.) are some example of preparedness.

We realize that in crisis statements that are over-optimistic or over-pessimistic are both suspected to be partially true. Reviewing the evidence and knowing how to say it need constant practice. The truth remains that problems caused by COVID-19 will cease with time – history has shown that they always do.

**What are the components of an effective storytelling?**

Physicians can learn storytelling by making a deliberate effort to take time of and pay attention to how to constructive and tell stories. Narrative can be easily converted to stories by paying attention to 3 essential components of compelling storyteller – the story (the real message you want to convey), the characters in your story (the patient, family, friends, nurses, you) and their unique personality and traits and use to relevant metaphors that summaries complex stories in few words. Powerful metaphors make the patients realize that we truly understand their situations and are walking in their shoes.

There are multiple resources to learn about narrative medicine and storytelling. These includes books, key articles, websites and workshops. Practicing writing narratives of patients can help bring out the life of the story. Physicians can become effective storytellers if they take the time to review several these resources and practice story telling among their colleagues.

**When should storytelling techniques not be used?**

There is however few problems with story telling that the reader needs to be aware of. In a work place sometime we have found that using a story to relay a key message can be confusing to the listeners. Our diverse and inclusive workforce comes with a solid set of skills and knowledge. Using a story to convey a message that they are not immediately familiar with carries a risk of losing their attention. Metaphors too however should be culturally appropriate as they may not be understood by someone living in a different country due to lack of awareness of the terms used in the metaphor.

A term called ‘wobbling on your logic’ has been used to describe this situation. The trouble is that for the story teller lack of preparation, rigor or knowledge is never an issue. If anything they are over prepared and have researched their topic well. The problem lies in the perception of their logic being wobbly than the reality of it! So how can someone used to storytelling communicate effectively? Fortunately there are good recommendations from experts.

Firstly speak only speak about things you know with absolutely certainty and then the hard part - stop speaking. Don’t let the ‘go on’ looks from your audience lure you into talking excessively or telling stories to make your point. You will lose them.

Secondly unlike a story teller who uses a story and weaves in the elements of the story to make the argument before coming to the final message do the following. Try changing your style and this needs practice. Imitate what newscaster’s do- deliver your main message first as a headline. Then build your case by delivering supporting evidence that will reinforce your main point. This approach will enforce your command of the problem and clear logic to the listeners. As you have already mentioned your key message first that listeners not be distracted by the rest of your talk.

In conclusion physicians get to hear numerous patient stories in their career. Many of these stories are straightforward and can be dealt promptly. Apart from few situations where story telling can be distracting in many situations where the patient’s history is complex and require great listening skills and empathy storytelling becomes an essential skill. Communicating with these patients can be done effectively using standard communication tools though many a times techniques using effective storytelling techniques can reinforce the patients trust in the provider and strengthen patient physician relationship. This could have a salutary result both for the patient by increasing patient satisfaction and compliance with treatment and physician satisfaction by increasing to understand their patient’s true concerns.

**References**

An Unusual Posterior Mediastinal Mass - Ectopic Thyroid within the Oesophagus

Padmanabhan Arjun1, Shaji Palangadan2, Rachel Abraham3, Azharul Haque4, Rahul Ramachandran4

Abstract

Presence of ectopic thyroid tissue in unusual locations is a rare phenomenon. Herein we present the case of a 55 year old lady, who on evaluation of dyspnoea was detected to have a mediastinal mass. Initial radiological evaluation showed the presence of a mass arising from the wall of the oesophagus which was presumed most likely to be leiomyosarcoma. She underwent surgical resection of the mass, but on histopathological examination, it turned out to be a nodular goiter which was lying within the smooth muscle layer of the oesophageal wall.

Introduction

Ectopic thyroid is defined as functioning thyroid tissue is seen in anatomical sites other than usual location of thyroid gland. It is usually found along the normal path of descent of the thyroid gland. The most common site of ectopic thyroid is the lingual thyroid and next in sequence is the wall of a thyroglossal duct cyst. Rare sites include the mediastinum, heart, esophagus, and diaphragm. Common presentations of ectopic thyroid include an asymptomatic, incidental radiological finding, or functional hypo or hyperthyroidism, and sometimes mass effect. This case is presented to highlight an extremely unusual presentation of ectopic thyroid tissue in a highly atypical location - within the smooth muscle of the wall of the oesophagus.

Case Report

A 55 yr old lady without any co-morbidities presented to our hospital with complaints of progressively increasing breathlessness over a period of six weeks. She had cough with mucoid expectoration. She denied having had chest pain, haemoptysis, or fever. She did not give any history of significant respiratory illness in the past. She had undergone a hemithyroidectomy twenty years back and the histopathology report had come as adenoma thyroid. Her thyroid function status was reported as normal prior to admission in our hospital. There was no relevant family history. General examination was unremarkable and all systems were normal on clinical examination. Routine blood examination revealed a total count of 11400 cells / cu mm with 74% polymorphs and 20% lymphocytes. Her renal and hepatic function tests were normal. Thyroid stimulating hormone level was 3.75 micro U/ml (normal range 0.27 – 4.2). Her chest radiograph revealed widening of the mediastinum in the superior aspect with tracheal shift to the right (Figure 1). The cervicothoracic sign was negative, thereby indicating it to be in the posterior mediastinum. A spirometry was done, which revealed a mild restriction anomaly (FVC 62% predicted). A complete cardiac assessment was done including echocardiogram, which was essentially normal. A contrast enhanced CT scan of the thorax was done which revealed a heterogenous mass in the posterior mediastinum (Figures 2 and 3). The mass was found to be anterior to the oesophagus, possibly even arising from it and displacing the trachea and great vessels anteriorly and to the right. As it was not approachable with CT guided biopsy, an Endoscopic ultrasound (EUS) guided fine needle aspiration (FNAC) was done, but the results were inconclusive. A clinical possibility of a neoplasm arising from the smooth muscle of the oesophagus – either leiomyoma or leiomyosarcoma was considered taking into account

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the radiological appearance. A PET CT was negative for uptake elsewhere and hence she was advised to undergo surgical removal of the mass lesion. She underwent a right posterolateral thoracotomy. The tumour was found to be in the intramuscular plane of the oesophageal wall (Figure 4) and it was enucleated en block from the surrounding tissues. The oesophageal mucosa was intact. She had an uneventful post operative period and recovered well. Very curiously, histopathological examination showed the presence of thyroid tissue composed of colloid filled follicles (Figure 5) and the final pathological diagnosis was nodular colloid goiter. In view of her euthyroid status, she was just kept under follow up and three months after surgery, she is asymptomatic, being totally relieved of dyspnoea. Her TSH value also remains within the normal range (3.85 micro U/ml).

**Discussion**

Approximately 25% of all mediastinal masses are located in the posterior mediastinum. The most common ones are neural tumors like neuroblastoma, ganglioneuroma and nerve root tumours like schwannoma. Less common ones include lymphomas, mesenchymal tumours, oesophageal varices, hematoma, descending thoracic aorta aneurysms and extramedullary hematopoeis.

Ectopic thyroid presenting as a posterior mediastinal mass is an extremely uncommon condition. Ectopic thyroid tissue is a rare developmental abnormality that results from aberrant embryogenesis of the thyroid gland during its migration from the floor of the primitive foregut to pre-tracheal position. Lingual thyroid is the most common site of ectopic thyroid tissue and accounts for 90% of cases. Other rare sites include the mediastinum, esophagus, lung, heart, aorta and abdomen. It is more often seen in females, particularly in Asians. The common presenting symptoms are dry cough, dyspnea and hemoptysis. Rarely, dysphagia or the superior vena cava syndrome can be the initial presentation. In cases of mediastinal ectopic thyroid, orthotopic tissue usually coexists and the patients are euthyroid. It may be seen incidentally in chest radiograph as in our case or on autopsy. Technetium-99m, Iodine-131, or Iodine-123 scintigraphy are the most important diagnostic tools to detect ectopic thyroid tissue, if it is clinically suspected. Thyroid scan can also help identify additional sites of thyroid tissue. Radiological imaging modalities like color Doppler Ultra Sound, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI), are helpful in delineating the extent and location of ectopic tissue. In patients with symptomatic ectopic thyroid, the treatment of choice is surgery. If symptomatic, the intrathoracic goitre is managed surgically. Surgical removal usually necessitates thoracotomy or sternotomy depending on the exact location of the mass inside the thorax.

This case is being presented because of its rarity. There have been a few case reports of ectopic thyroid tissue being found adherent to the outer wall of the oesophagus. We were unable to find any other case similar to ours, where the thyroid tissue was found inside the smooth muscle layer of the oesophagus. To the best of our knowledge, this is the first of such a case to be reported. It also highlights the importance of keeping into consideration all possible differential diagnosis of mediastinal masses, particularly in cases like this, where the patient had previously undergone a thyroid surgery, and then, years later presented with an ectopic thyroid mass in the posterior mediastinum.

**References**

Introduction

The first cases of SARS CoV-2 infection were reported in Wuhan, China in December 2019. The most commonly reported symptoms were respiratory in nature. However, clinical data has demonstrated that gastrointestinal manifestations can be seen in a significant number of patients. Gastrointestinal manifestations such as anorexia, nausea, vomiting, diarrhoea and abdominal pain can be seen in 10-65% of patients. There have been few case reports of acute pancreatitis in Covid-19 infection, which shed some light on the possible mechanisms of pancreatic injury and the clinical spectrum of pancreatitis in Covid-19 infection. Here we are reporting two cases of acute pancreatitis in patients with severe Covid-19 pneumonia.

Case 1

A 28-year-old male with no previous co-morbidities or history of substance abuse, presented with fever and cough for a period of five days, associated with prostration and difficulty in breathing. The patient was found to have Covid-19 infection evidenced by a positive nasopharyngeal RT-PCR test. In view of significant dyspnoea and hypoxia he was shifted to the Intensive Care Unit. He was administered Doxycycline, Remdesivir, Paracetamol, Methylprednisolone, Enoxaparin, Pantoprazole, Baricitinib and Tocilizumab according to the local treatment guidelines.

On the third day of admission, the patient developed severe upper abdominal pain radiating to the back, with vomiting, and stopped passing flatus and stools. In view of the above mentioned clinical features, his serum amylase and lipase were tested, which were grossly elevated. The patient was kept nil per oral, initiated on IV fluids and opioid analgesics, as per routine treatment of acute pancreatitis.

The abdominal pain progressively worsened, and abdominal distension developed.

Laboratory investigations initially revealed marked neutrophilic leucocytosis, but a normal lipid profile, liver and renal parameters. The abdominal ultrasonography study revealed no evidence of cholelithiasis, gall bladder sludge or bile duct dilatation. A computed tomography scan of the abdomen was done, which revealed findings suggestive of acute necrotizing pancreatitis. Serial chest radiographs taken daily, revealed progressively worsening pneumonia. The patient was intubated on the seventh day of admission, and put on ventilatory support. He concurrently developed acute kidney injury with severe metabolic acidosis and was planned for Sustained Low Efficiency Dialysis (SLED). However, shortly after initiating ventilatory support, he went into cardiac arrest and eventually died. The cause of death was attributed to acute respiratory distress syndrome (ARDS) and sepsis.

Case 2

A 45-year-old female presented with the complaints of fever and cough for a period of 5 days. The patient did not have any co-morbidities. The patient tested positive for SARS CoV2 infection by an RT PCR test. Initially the patient was hemodynamically stable and had a peripheral oxygen saturation of 97% in ambient air. The blood panel revealed significantly elevated levels of C-reactive protein, Interleukin-6 and D-dimer. After 2 days of admission, the patient suddenly became hypoxic, after which she was shifted to the critical care unit. A high resolution computed tomography of the chest was done, which suggested moderate lung involvement (16/25 CT score). The patient was administered Doxycycline, Ivermectin, Remdesivir, Dexamethasone, Enoxaparin, Pantoprazole and Paracetamol.
In Covid-19 infection, it has been hypothesized that mechanisms of acute pancreatitis in Covid 19 infection. The expression of ACE2 receptors in pancreatic cells has been well documented, and is a plausible explanation for the involvement of the pancreas in Covid-19 infection. Pancreatic injury may be related to the direct cytopathic effect of SARS CoV2 replication. Pancreatic injury may also be related to direct toxicity of various inflammatory cytokines released during SARS CoV2 infection. Another possible mechanism that can lead to pancreatitis is endothelial inflammation with microthrombosis, which is the cornerstone of the pathogenesis of Covid-19 infection. It is unclear whether drug induced pancreatitis is a possibility in these cases, considering the vast, and often unapproved pharmacological armamentarium used to treat Covid.

Alharmi et al reported a case of moderate acute pancreatitis in a 52 year old female patient with SARS CoV2 infection, where common causes of acute pancreatitis such as alcohol, gall stones and hypertriglyceridemia were ruled out. Pancreatic injury, defined by any elevation in amylase and/or lipase was seen in 17% patients in a study in Wuhan, China. However, none of these cases demonstrated clinically severe pancreatitis[9]. Szatmary et al described various clinical characteristics in 35 patients with acute pancreatitis and SARS CoV2 infection, where other common causes of acute pancreatitis were ruled out. Interestingly, it was noted that all these patients had mild pancreatic edema, without any pancreatic necrosis.

There are relatively few case reports of the same from India. Manoj Kohle et al reported a case of a 19 year old female with severe necrotizing pancreatitis and SARS CoV2 infection, where other causes were ruled out[11]. Ghosh et al reported a case of acute necrotizing pancreatitis in a middle aged diabetic with SARS CoV2 infection[12].

There have been few hypothesized mechanisms of acute pancreatitis worldwide are implicated in acute pancreatitis. The most common causes of acute pancreatitis are alcohol, gall stones and hypertriglyceridemia. The patient was kept nil per orally, and administered intravenous fluids and supportive care. There was no associated organ dysfunction, excluding the pre-existing lung involvement. After two days, the patient’s pain improved, and she started passing flatus. Enteral nutrition was initiated, which she tolerated well. The patient recovered completely in a span of ten days, and was discharged from the hospital.

### Discussion

Acute pancreatitis is defined as an inflammatory process of the pancreas, diagnosed by the presence of at least two of the following criteria: 1) Abdominal pain characteristic of acute pancreatitis, 2) Elevation of serum amylase and/or lipase more than three times the upper limit of normal, and 3) Imaging findings suggestive of acute pancreatitis. The most common causes for acute pancreatitis worldwide are gall stones and alcohol use. Previously, viral infections such as hepatitis viruses (A, B, C, D, E), Coxsackie virus, Echovirus, Hemorrhagic viruses and Cytomegalovirus have all been implicated in acute pancreatitis. The mechanism by which each virus causes acute pancreatitis is different. In Covid-19 infection, it has been demonstrated that the S protein of the virus binds to the ACE2 receptor and facilitates entry of the virus into the host cell.


### References

Bilateral Fungus Ball: An Uncommon Complication Post Severe COVID 19 Infection

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Abstract
COVID 19 is one of the world’s worst hit pandemics. WHO first learned of this new virus on 31 December 2019, following a report of cluster of cases of ‘viral pneumonia’ in Wuhan, China. Covid 19 causes systemic infection but it worst hits the lungs and can cause ARDS (<5%). Bilateral lung fibrosis is a commonly observed sequela after severe Covid 19 infection. Covid 19 pneumonia also acts as a nidus for superadded bacterial and fungal infections. However we haven’t come across fibrocavitation and fungus ball as post Covid 19 sequelae.

We here present a case report of a patient who was diagnosed as ARDS due to SARS CoV2, was treated as per standard Covid 19 protocols, required NIV and discharged on home oxygen. The HRCT on discharge showed bilateral fibrosis. The follow up HRCT after 45 days of discharge showed evidence of Bilateral cavities with Fungus ball.

Introduction
Covid 19 has led to a global pandemic. Severity of Covid 19 can be associated with fever, rising inflammatory markers and signs of systemic inflammation, in the absence of secondary infection. Superadded bacterial or fungal infections can occur due to immune suppression due to viral infection, use of corticosteroids and drugs like tocilizumab, as well as comorbid conditions like diabetes mellitus. Severe Covid 19 infection leads to bilateral lung fibrosis which is evident on HRCT. However, to our knowledge very few cases of fungus ball in a COVID-19 patient’s lungs have been reported. Here we present a case of severe Covid 19 infection who on follow up HRCT showed evidence of Bilateral cavities with fungus ball.

Case Presentation
A 55 Years old male, known case of diabetes Mellitus, hypertension and ischemic heart disease status post percutaneous transluminal coronary angioplasty (PTCA) presented to the emergency department with history of low grade fever, cough with expectoration, progressive increase in dyspnoea and generalized weakness since 1 week. On examination, the patient had a pulse rate of 130/min, was tachypnoeic with a respiratory rate of 36-40 breaths per minute, had a oxygen saturation of 95% on 10 Litres of Oxygen by a non rebreather mask and blood pressure of 130/80 mmHg. The patient was admitted as a COVID 19 suspect and appropriate investigations done. He was diagnosed as SARS CoV2 positive by RT-PCR test of nasopharyngeal swab. His X-ray chest on admission showed Bilateral peripheral patchy opacities consistent with Covid 19 pneumonia. Due to progressive worsening of respiratory distress, the patient was put on CPAP by Non invasive ventilation. Patient was started on Hydroxychloroquine, doxycycline, ivermectin which was the standard treatment protocol at that time. Subsequently the patient also received lopinavir and ritonavir.

Patient was also treated with high dose steroids (injection methylprednisolone 500 mg once a day) and intravenous antibiotics Piperacilline+Tazobactum and azithromycin in view of raised WBC counts. Patient required non invasive ventilation for 3 weeks after which he was shifted to oxygen by nasal prongs. HRCT chest was done 4 weeks after his admission (Figure 1) which showed diffuse areas of ground glass opacities and inter-intra lobular septal thickening in bilateral lung fields and patchy areas of consolidation in bilateral upper lobes. Due to persistent oxygen requirement, the patient was discharged on home oxygen therapy and oral steroids. A follow up HRCT Chest was done (Figures 2a, 2b) after one and a half month of previous CT scan which showed evidence of cavitary lesion in bilateral upper lobes with evidence of fungus ball within.

The patient’s sputum was sent for fungal stain and culture and was subsequently started on oral itraconazole.

Discussion
Coronaviruses are enveloped RNA viruses.1 Six coronavirus species are known to cause human disease.2 Four viruses — 229E, OC43, NL63, and HKU1 — typically cause common cold symptoms in immunocompetent individuals.3 The other two strains are severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).4 SARS-CoV was the causal agent of the severe acute respiratory syndrome outbreaks in 2002 and 2003 in Guangdong Province, China while MERS-CoV responsible for severe respiratory disease outbreaks in 2012 in the Middle East.5 Severe acute respiratory syndrome Coronavirus -2 (SARS CoV2) is responsible for the Covid 19 pandemic.

Secondary infections are a well known complication of viral infections in COVID 19 and are associated with increased mortality.6 Superadded bacterial infections have been reported due to suppression of the immune system and use of corticosteroids.7 Superadded fungal infections due to azole resistant Aspergillus have been reported in immunocompromised patients.8 In our patient, fungal infection was confirmed by HRCT and culture from the lesion in the bilateral lung field.

The follow up HRCT after 45 days of discharge showed evidence of Bilateral cavities with Fungus ball.
Most fungal balls are caused to the cavity wall by granulation and degenerating blood and epithelial amorphous debris, inflammatory cells, Aspergillus niger. A fungus ball consists of both dead and living mycelial elements, fibrin, mucus, amorphous debris, inflammatory cells, and degenerating blood and epithelial elements. The mycelial mass may lie free within the cavity or can be attached to the cavity wall by granulation tissue. Most fungal balls are caused by Aspergillus Fumigatus, rarely by Aspergillus niger.

A secondary fungus ball is caused by the colonization and proliferation of the fungus in a pre-existing pulmonary cavity. The cause of a pre-existing cavity is most commonly prior cavitary tuberculosis. However, it may complicate a wide spectrum of cavitating pulmonary diseases, such as sarcoidosis, histoplasmosis, blastomycosis, AIDS (especially in cases of atypical Pneumocystis jiroveci pneumonia), lung abscess, pulmonary or bronchial cysts, bronchiectasis, cyanotic heart disease, and pulmonary infarction.

Primary fungus ball, which arises within the bronchial tree with the proliferation of Aspergillus leading to a pulmonary cavity, is far less common. The clinical conditions leading to the initiation of a cavitary process and formation of a fungus ball include Invasive pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis (CNPA), and Allergic bronchopulmonary aspergillosis.

Diagnosis is based on fungal cultures of sputum or bronchoalveolar lavage (BAL) from these patients and chest imaging. Most cases of fungus balls are diagnosed incidentally on a chest x-ray or CT scan. Chest radiographs show a solid round mass within a cavity (3–5 cm diameter) partially surrounded by a radiolucent crescent.

CT provides a timely diagnosis or can at least provide more logical differentials. Signs on CT scans constituting clinical evidence for invasive pulmonary disease by the 2008 criteria proposed by the EORTC/MSG include dense, well-circumscribed lesion(s) with or without a surrounding “halo” of ground-glass gray attenuation, air-crescent sign, and cavity formation. Movement of the fungus ball within the cavity may be appreciated when comparing upright and decubitus images.

Sputum culture for aspergillus may be positive for more than half of the patients with fungus ball, it is not a sensitive and specific diagnostic marker. Precipitating antibodies to Aspergillus antigens are present in the sera of more than 95% of patients with aspergilloma; however, some patients receiving corticosteroids may be seronegative.

We report this case of bilateral fungus ball in our patient post Covid 19 infection who did not have any past history of pulmonary tuberculosis, bronchiectasis, sarcoidosis or any preformed cavities to result in fungus ball formation. As depicted in the pictures, prior CT scan images did not show any evidence of a cavity which was later diagnosed at the follow up CT scan suggesting that the fungus ball was a complication after SARS-CoV2 infection. As with any superadded infection, the mortality and morbidity increases due to a secondary infection.

Conclusion
Superadded fungus ball in a cavity can be a complication in patients recovering from SARS-CoV2 infection and can lead to increase morbidity and mortality. By reporting this case, we would like to make our readers aware about such a complication in Covid-19 infection.

References
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James Herrick and IHD

Jayant Pai-Dhungat

James Bryan Herrick (1861-1954) was born in Chicago Illinois. After receiving his BA degree in 1882, he entered Rush Medical College, and earned his medical degree in 1888. Herrick interned at Cook County Hospital, after which he opened a private practice in the Chicago area. Herrick also obtained a part-time teaching position at Rush Medical College, and was appointed as a full professor from 1900-1927. He was also on the staff of Presbyterian Hospital in Chicago from 1895-1945.

His first contributions in medicine came in 1910, when he described an unusual crescent-shaped erythrocytes found in a blood smear from anemic young black Grenada dental student. He also noted tinge of icterus, pigmentation and scars on legs. His description of the student’s disease was known for many years as Herrick’s syndrome (sickle-cell disease).

Herrick’s next contribution is widely acknowledged in coronary heart disease. Although by no means the first to describe, it was he, more than anyone else that made clinicians aware that patient of coronary thrombosis had a characteristic clinical presentation and some patients survived with little lasting damage and the event was not always fatal. He is therefore considered first to describe causes of myocardial infarction as we know today. When Herrick published his initial paper on Clinical features of sudden obstruction of coronary arteries in JAMA (1912), it aroused very little interest.

Herrick then learned use of Einthoven ECG machine with Frank Wilson at Michigan. He published first 6 leads ECG of myocardial infarction in 1918. In his lecture before the Association of American Physicians; he offered concrete ECG documentation in support of his conclusions. In a brilliant presentation, he announced the ability of the electrocardiogram to diagnose the presence of an acute myocardial infarction in a living patient. This was a revelation because. It was the conventional wisdom of the time that an acute myocardial infarction was incompatible with life. Much of Herrick’s documentation was based on experimental work done by Fred Smith, demonstrating the serial ECG changes in the dog following ligation of the coronary arteries. Frank Wilson recorded chest leads with central terminus in 1934. It was only in 1942 when Emanuel Goldberger added augmented unipolar limb leads that 12 lead ECG came into existence.

Herrick died at the ripe old age of 93. Richard S. Ross, of Johns Hopkins University, eulogized him “as a leader in clinical science but “unwilling to let vanish the human values as family doctor.”

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Strategy to Improve Effectiveness of COVID 19 Vaccines and Medicines for Pre-exposure Prophylaxis in Persons with Older Age, Comorbidities, High Exposure

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Background

Dr. K.K. Agarwal, a renowned physician, former President of Indian Medical Association, decorated by Govt. of India with Padmashree recently succumbed to COVID 19. Saddened and alarmed as we are, we noted that he had two doses of COVISHIELD vaccine, surely was following all precautions of masking, social distancing and hand washing, a great promoter of health messages that he was.

Dr. B. Gupta, another well renowned physician, member of many regulatory committees also recently succumbed to COVID.

Why is it that they were not protected from the onslaught of the SARS CoV2 virus? What could (have been) be done?

Comorbidities and risk of COVID

Impact of pre-existing comorbidities on COVID 19 has been extensively reviewed.¹ Older individuals, (age over 60) are more prone to severe COVID 19 and have higher mortality. Covid disease incidence is higher in males. Black, Asian and minority ethnics are at greater risk and have higher mortality. The New York City registry for COVID mortality reported different death rates according to race. They reported 17% death in whites, 22% in Blacks and 31% in Hispanics. While all these aspects need further study, it is reasonable to regard race as a risk factor for COVID mortality.

Autoimmune disease is highest pre-existing comorbidity (82% in Delhi Centre). While higher age is not a risk factor in India, higher age is a major risk factor in the USA, where the population is younger.

COPD, immunosuppression and type 2 diabetes.

In a study from India on hydroxychloroquine (HCQ) pre-exposure prophylaxis in healthcare workers, HCQ reduced probability of COVID positivity by 34%, 48%, 72% with 2-3, 4-5, 6 or more weeks of intake 400 mg BD on day 1 and 400 mg weekly dosing. Median COVID free time was higher in non-diabetics, non-hypertensives and in persons with age below 45 years.

Force of infection

The HCQ study was a multi-centric study. Site was a significant variable for COVID positivity. With logistic regression modeling, it was seen that the site where probability of COVID positivity in HCQ non users was high (82% Mumbai Centre) % reduction in probability of positivity in HCQ users was 32% and was 8% for persons of age over 45 years, with diabetes and chronic respiratory disease. On the other hand, in the site (Bhopal) where probability of COVID positivity in non-users was 23% the reduction was 65% in HCQ users, 58% in HCQ users with age above 45 years with chronic respiratory disease.

Similarly, effectiveness of vaccine also may be lower if overall COVID positivity is high. Kaslow⁴ has reported on force of infection as a determinant of vaccine efficacy. In the Israel study² documented infection was 0.6 per 1000 persons days. At the time of study Israel was facing 3rd wave with test positivity rate of approx. 10%. The study excluded subjects with high variability of infection risk e.g. patients facing health care workers compared to administrative staff.

Thus, for physicians in Delhi with high covid positivity (Delhi facing 2nd wave with positivity rate 35%) during April - May 2021 and with risk factors such as older age and comorbidities, effectiveness of vaccine may not be enough to protect them.

What could be done?

While all these aspects need further studies, it is worth considering studying if under such situations of high overall COVID positivity (high transmission) patients with comorbidities be given an additional booster dose of vaccine.
COVID-19 and Mucormycosis: Time we Answer Questions?

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Sir,

With over 9000 cases as of 23rd May 2021 (according to the ministry of Health and Family Welfare), Mucormycosis caused by a fungus with large, irregular, ribbon like, sparsely septate hyphae, emerged as a disease of immense importance, specially owing to the surge in its number of cases during the current pandemic.

Various factors are being attributed to the sudden burst of cases. While some have a scientific acumen, others are just wild assertions. The authors put forward seven hypothesis which either in isolation or more so in unison might explain the rampant spread of this disease during the second wave of COVID-19 in India.

1) Covid -19, by virtue of causing 1) lymphopenia1 predisposes the host to the development of a number of opportunistic infections, mucormycosis is one of them. The RECOVERY2 trial served as a license to use steroids in patients with COVID-19. However, the benefit was specifically shown with low dose, short duration dexamethasone in moderate to severe illness, a point certainly seemed to have been missed.
2) The use of high doses of and longer duration of corticosteroids, early in the course of the disease is a possible contributory cause.

India is home to millions of diabetics. Poor access to health infrastructure, shortage of medicines and self-monitoring glucose devices coupled with over dependence on alternative form of medicines (example – Ayurveda and Homeopathy) has resulted in a patient population with 3) poor glycaemic control. The stress of severe disease and prolonged ICU stay further lead to dysglycemia and increased the chances of the development of this opportunistic infection. 4) The overzealous use of antibiotics (example Doxycycline and Azithromycin) even without any proven antiviral properties could have led to a flare up this secondary fungal infection by disturbing the natural microbiota of the lung.3

Since the beginning to the pandemic Zinc and Vitamin C were to two medicines which were found on the prescription of almost every doctor. Pre-pandemic scientific literature4 shows how 5) zinc would aid in the fungus infect a host cell and this could possibly be a contributory cause. Although the spores of mucormycosis are ubiquitous, but to hypothesize that a greater concentration of spores could lead to greater chances of a host harbingering the infection is not far-fetched. With the shortage of medical oxygen, industrial oxygen was diverted to hospitals from all over the country. 6) Both the source of production of the industrial oxygen and the tankers used to ferry it to the hospitals could be a breeding ground for the fungi. 7) Use of unsterile tap water in steamers, nebulisers and humidifiers a practise very prevalent, could have also contributed.

The need of the hour is to subject these conjectures to vigorous scrutiny in the form of adequately powered retrospective cross-sectional studies (as a randomised controlled trial in this setting would be both unethical and inappropriate) so that we might get an answer which is scientifically valid and help us alleviate this carnage.

References

Second Episode of Fever as a Sentinel Event in COVID 19 a Retrospective and Prospective Observational Study

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Sir,

COVID 19 is a disease with myriad presentations, so it is of utmost importance to predict a clinical course so as to initiate effective treatment early. We observed that some patients have a period of quiescence after presentation of the first symptom, followed by a second episode of fever, after which they have a sudden accelerated progression in disease severity. We, in our study, explore the second episode of fever after a period of quiescence as a point of inflection in the clinical course of Covid 19, thereby making it a cheap, reliable and easy to observe sentinel event.

In a prospective and retrospective observational study, we analyzed the course of illness of 100 patients, including 62 males and 38 females, who showed the phenomenon of a second episode of fever. Our study aimed to study the changes in level of hypoxia, blood inflammatory markers and HRCT severity score after the second episode of fever as illustrated in Figure 1. Asymptomatic or mildly symptomatic Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) confirmed positive patients above the age of 18, maintaining a saturation >95% on room air, with near normal inflammatory markers and no/minimal symptoms on admission (mild fever not exceeding 101F, body ache, loss of appetite, anemia etc), with an afebrile period of at least 48 hours before second fever spike.

4. Patients maintaining an oxygen saturation at or above 97% on room air.
5. Patients who have been asymptomatic for at least 48 hours.
6. Patients who develop fever >37.2 (AM temp) or >37.7 (PM temp).
7. Patients with near normal initial inflammatory markers
IL6 <15 pg/ml
CRP <15 mg/L
LDH <400 U/L
Serum Ferritin <400 ng/ml (men), <300 ng/ml (women)
(including those with inflammatory markers raised due to pre-existing co morbidities)

Fig. 1: Central illustrative diagram

91% patients had a significant increase in levels of IL6, CRP, LDH. Studying the laboratory findings in the study participants showed a statistically significant difference in levels of Interleukin 6, C Reactive Protein and Lactate Dehydrogenase while levels of Serum Ferritin were not significantly altered after the episode of fever. Percentage increase in inflammatory markers is represented in Figure 4.

(iii) 91% patients had a significant increase in HRCT severity causing new lesions in the lung. Before the second episode of fever, 52% patients had no changes whatsoever for Covid 19 on HRCT while 48% patients showed mild changes in their lungs. After the second fever episode, 9% participants had an

Fig. 4: Percentage change in blood inflammatory markers after the second episode of fever

Diabetes, Hypertension and Ischaemic Heart Disease as illustrated in Figure 3.

A second episode of fever was recorded in the participants after a symptom free period ranging from 3-13 days (mean 7.77 days). We compared the clinical status, laboratory reports and radiological findings of all participants before and after the second episode of fever. Our study showed the following outcomes after this second episode:

21% patients required supplemental oxygen therapy

(ii) 91% patients had a statistically significant increase in one or more blood inflammatory markers - IL6, CRP, LDH. Studying the laboratory findings in the study participants showed a statistically significant difference in levels of IL6, CRP, LDH.

Fig. 5: Radiological (HRCT) changes before and after second episode of fever

Fig. 2 Inclusion and exclusion criteria

Fig. 3 Comorbidities of study participants
HRCT report with no Covid 19 changes, 40% showed mild changes, 44% showed moderate changes and 7% showed severe lung involvement graphically represented in Figure 5.

The study proves that a second episode of fever, after a period of quiescence, in patients of mild or asymptomatic disease at the outset is a simple yet powerful indicator of disease progression in terms of need for supplemental oxygen therapy, increased inflammatory markers and increase in severity on imaging modalities like HRCT. This is also applicable in those without co-morbidities, irrespective of age and gender. By keeping a watch on the temperature, even such patients can be adequately treated at an early stage, much before clinical worsening. This is especially useful in lesser equipped areas, as it does not need expensive blood tests or CT machines.

References

5. The study was registered prior to the study start at the International Clinical Trials Registry-India Plattform (CTRI) (www.ctri.nic.in/Clinicaltrials) under identifier number CTRI/2018/06/014462.

Importance of Self Home Blood Pressure Measurement and its Relevance in the COVID 19 Era

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In times of Corona crisis, blood pressure measurement in the clinic is not feasible and should be avoided. Using the same cuff for many patients is a potential source of contamination. From that perspective, self-measurement of blood pressure may be an alternatively considered and should be popularized in our community. Accurate BP measurement is essential and of crucial importance in diagnosis and management of patients with hypertension hence the need for having a validated method of doing it.

The results of the “Indian Heart Study” were recently published in the Journal of Hypertension. The Study is a collaborative project of 1,237 doctors in 355 cities and 15 states in India. It had the aim of evaluating the agreement between self-blood pressure measurement (SBPM) and Office (clinic) blood pressure measurement (OBPM) for diagnosing hypertension. In total, the study included 18,918 subjects (aged 42.6±11.7 years, 62.7% men) who visited the primary care clinic and who were drug naive at the time of entry. Figure 1 presents an overview of the number of participants together with the average systolic SBPM value per state of India.

The BP was measured according to the usual practice (Mercury sphygmomanometer 69%, Aneroid apparatus 21%) and subjects were asked to perform SBPM at home for one week with a clinically validated automated oscillometer blood pressure monitor (Circa Eris / Watch BP Home A, Microlife AG, Switzerland) as shown in Figure 2. Subjects were carefully instructed how to perform BP measurement appropriately and received a link to an instruction video.

When the patients returned after one week their blood pressure was measured again by their physician by the same method.

Disagreement between SBPM and OBPM was defined as white coat hypertension (WCH), normal SBPM (systolic BP <135 and diastolic BP <85 mmHg) and elevated OBPM (systolic BP ≥140 and/or diastolic BP ≥90 mmHg); or as Masked hypertension (MH), elevated SBPM (systolic BP ≥135 and/or diastolic BP ≥85 mmHg) and normal OBPM (systolic BP <140 and diastolic BP <90 mmHg).

Results showed that, based on 1st visit OBPM and SBPM there were 5,787 (31%) subjects with normotension (NT); 5,208 (28%) with hypertension (HT); 4,485 (24%) with white coat hypertension (WCH) and 438 (18%) with masked hypertension (MH). Thus, a diagnosis contradiction between SBPM and 1st visit OBPM was seen in 9,870 (42%) subjects. Based on 2nd visit OBPM the NT, HT, WCH and MH prevalence values were 7,875 (42%); 4,857 (26%); 2,397 (13%) and 3,789 (20%). There was poor agreement (kappa value 0.37) between OBPM of visit 1 and 2 with a diagnosis difference in 6,027 (32%) subjects. The majority of MH and WCH subjects had BP values close to thresholds.

There is a poor agreement between repeated office BP measurements. Likewise, the agreement between OBPM at both visits and SBPM was poor. SBPM being considered to have a better correlation with patient prognosis should be the preferred method for diagnosing hypertension. It would prevent over diagnosis (White coat hypertension) and underdiagnosis (Masked hypertension) in a significant number of patients and would also be a useful method of BP measurement in the COVID 19 ERA with physical distancing and being indoors at home.

References

A Perfect Beta-Blocker for Kidney: SGLT-2 Inhibitor

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Beta-blockers are one of the most widely used drugs by cardiologists. They are the antagonist of beta-adrenergic receptors that play an important role in maintenance of blood pressure (BP), heart rate (HR), airway reactivity, central nervous processes and metabolic processes. The most common indications of beta-blocker use are: treatment of ischemic heart disease, hypertension, heart failure, arrhythmia, migraine, thyrotoxicosis, glaucoma, essential tremor, anxiety, portal hypertension and others. This drug is so important for cardiologists that no prescription is complete without the use of beta-blockers. For a long time endocrinologists were also in search of a drug like beta-blocker for use in diabetic patients with various comorbidities. Recently SGLT-2 inhibitors have been introduced in management of diabetes mellitus. SGLT2 inhibitors are a newer generation of anti-diabetic drug, which act by blocking glucose reabsorption from the proximal convoluted tubule of kidney and thus control the blood glucose. They reduce the workload of kidney as beta-blocker does for heart. Both SGLT-2 and beta blockers have similar actions such as reduction of BP, HR and sympathetic over activity. Furthermore SGLT-2 inhibitors also reduce weight, uric acid and blood sugar. In contrast, beta-blockers have shown to increase weight, uric acid and blood sugar. This prompts us to think that SGLT-2 might just be the perfect beta-blocker for the kidney, which we shall exemplify with the help of a case study.

A 45-year-old businessman was referred to us for treatment of obesity and raised blood sugar. On examination his BP was 140/86, heart rate (HR) was 74/min, BMI was 32 and weight was 92.5 kg. His laboratory reports were, fasting plasma glucose (FPG): 114 mg/dl, post prandial blood glucose (PPG): 182 mg/dl, glycosylated HbA1c: 6.1%, total cholesterol: 207 mg/dl, LDL: 130 mg/dl, HDL: 48 mg/dl, TG: 235 mg/dl, VLDL: 46.9 mg/dl, creatinine: 0.8 mg/dl, ACR: 210 mg/gm., ECG: normal, Thyroid function test: normal. Since there was obesity, impaired glucose tolerance, micro proteinuria, dyslipidemia and high BP so patient was put on empagliflozine 5 mg OD and statin. Patient was advised to review after 2 week. He was explained about hypovolemia, mycotic infection, polyuria and eguglycemic diabetic ketoacidosis and was explained about corrective measures. After 2 week his FPG, PPG, HR and BP was 90 mg/dl, 140 mg/dl, 70/min and 130/82 mm/Hg respectively. Patient was again advised to come after 3 month. After 3 month his BP, HR, BMI, FPG, PPG and ACR were 134/80, 70/min, 30.4 kg/m2, 92 mg/dl, 148 mg/dl and 52 mg/gm respectively. Patient was advised to continue empagliflozine regularly and follow up regularly. So if we analyze the treatment outcome we find that there is significant reduction in BP, BMI, HR, ACR and blood glucose.

SGLT-2 inhibitors are a newer class of anti-diabetic drugs that not only control blood sugar but also reduce BP, HR, BMI, SGPT and uric acid. Recent CVOT data shows that they also have the potential to reduce major adverse cardiovascular event (MACE), hospitalization for heart failure (HHF), death and major adverse kidney events (MAKE). Recently their role has been extended to non-diabetic heart failure and non-diabetic CKD patients. This case study supports our view that SGLT-2 inhibitors might just be the perfect beta-blockers for the kidney, which also have some added benefits.

References


To Treat or Not to Treat Asymptomatic Hyperuricemia

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Sir

We read with great interest the article by Tiwaskar and Sholapuri on the Knowledge, Attitude, and Practices of Physicians in the Management of Hyperuricemia published in the April issue of JAPI. We would like to highlight three points that emerge from this important study: inadequate knowledge in as many as one-third of the physicians surveyed, the use of journals as a source of information by more than 50% of the physicians, and the approach to asymptomatic hyperuricemia.
Uncovering the knowledge gap is the critical first step towards bridging this gap and the authors are to be congratulated for this pan India study that discusses a contemporaneous issue of practical relevance. The fact that more than half the physicians used journals as their source of information prompts us to use the esteemed columns of JAPI to address the third point, that is, the treatment of asymptomatic hyperuricemia. The authors while reporting the practice habits for patients with newly diagnosed asymptomatic hyperuricemia patients mention that 96.6%, 54.6%, 38.3% of the physicians surveyed recommended low purine diet, short-term urate lowering therapy (ULT) and long-term ULT respectively. We take this opportunity to iterate that diet is one component of the life style measures advocated for asymptomatic hyperuricemia. Exercise, weight optimisation, avoidance of alcohol (especially beer) and carbonated, sweetened beverages are amongst other measures advocated. Given the fact that adherence is an important issue, patient education is indispensable in tackling asymptomatic hyperuricemia. Myths regarding diet abound. Purines are found in all protein foods and it is impossible and impractical to eliminate purines totally. ‘Low purine’ diet in India gets translated into and equated with a ‘low protein diet’. As it is, Indian diet is notoriously ‘protein inadequate’ with protein sources accounting for only 6-8% of calories compared to the 29% in the reference EAT-Lancet diet.2

Of note, purine restriction reduces serum uric acid levels by no more than 1 mg/mL. Also, low purine diets are not palatable. The emphasis, therefore, should be on moderation of portion size rather than a blanket ban. While red meat, organ meat, and some sea foods with large amounts of purine need avoidance, there is no association between purine rich vegetables (peas, tomatoes, lentils, beans, spinach, mushrooms and asparagus) and the development of gout. Low fat dairy is useful since it has a moderate urate lowering effect.3 The recent IDEA consensus is an important initiative in getting all stakeholders in India on one platform.4 Casually worded and loosely offered dietary advice prompts patients to stop all pulses and milk and milk products which is more detrimental than beneficial.

While the survey by Tiwaskar and Sholapuri talks about short and long term ULT, it does not specify the duration of ULT. The institution of short term ULT reflects a knee jerk tendency and is not likely to prevent either crystal arthritis or cardio-metabolic and renal disease. It may transiently correct the biochemical abnormality but is unlikely to provide a tangible clinically meaningful benefit. This pernicious belief, though not backed by evidence, seems to be wide spread and needs to be corrected. Coming to the long term ULT practised by more than one-third of the physicians surveyed, we would like to underline that ‘long term’ in the context of gout is more often than not ‘indefinite’. None of the current recommendations from any of the professional organisations endorse this approach. The putative benefit of treating asymptomatic hyperuricemia to prevent progression of chronic kidney disease (CKD) has been debated endlessly but never proven conclusively. The jury on the relationship between hyperuricemia and CKD- cause, consequence, or coincidence- is still out. A recent publication has drawn attention to the overlooked nuance that asymptomatic hyperuricemia does not affect CKD progression unless uric acid crystallizes in the kidney. Using MALDI-FTICR mass spectrometry, immunohistochemistry, 3D confocal microscopy, and flow cytometry in a novel mouse model of hyperuricemia and chronic uric acid crystal nephropathy with granulomatous nephritis, the authors demonstrated that uric acid crystals trigger M1-like macrophage-related interstitial inflammation and fibrosis.5

The recent IDEA consensus recommends against starting ULT in patients with asymptomatic hyperuricemia and cardiovascular disease until further larger randomized controlled trial reports are available.4

In the context of crystal deposition disease, the current American College of Rheumatology guidelines are explicit in mentioning that in the majority of patients with asymptomatic hyperuricemia (including those with comorbid CKD, cardiovascular disease, urolithiasis, or hypertension), the benefits of ULT would not outweigh potential treatment costs or risks for the large number of patients unlikely to progress to gout.6 Interestingly, they also mention that asymptomatic crystal deposition detected on imaging does not warrant pharmacologic intervention. With greater availability of musculoskeletal ultrasound and dual-energy computed tomography (DECT), a large number of asymptomatic individuals are likely to be inappropriately labelled and treated as gout.

While cautioning against indiscriminate ULT, we do however realise that selected patients with persistent marked asymptomatic hyperuricemia due to inherited defects in purine metabolism or genetic polymorphisms in urate transporter genes may benefit from ULT underscoring the need for individualisation of treatment. A recent systematic review recommends treatment of asymptomatic hyperuricemia only in three situations: a) persistent uric acid levels higher than 13 mg/dL in men or 10 mg/dL in women because these values may carry nephrotoxic risks; allopurinol may slow renal disease progression and prevent nephrotoxic risks b) urinary excretion of uric acid exceeding 1100 mg daily because this is associated with a 50% increase in the risk of developing uric acid calculi, which are prevented by lowering uric acid excretion to 800 mg daily, and c) patients about to receive radiation or chemotherapy to prevent uric acid nephropathy and other manifestations of tumor lysis syndrome.7

The recommendations of today are likely to evolve in light of the new knowledge that becomes available tomorrow. As for now, the overwhelming majority of patients with asymptomatic hyperuricemia need observation and non-pharmacologic intervention rather that ULT. In a way, this is nothing else but reaffirmation of the Oslerian principle of treating the patient and not the laboratory investigation!

References
A 70-year-old male, with known diabetes and hypertension, presented with complaints of increased shortness of breath, cough, and left sided chest pain for five days. He was an ex-smoker and was diagnosed chronic obstructive pulmonary disease (COPD) for last 8 years. He gave a past history of gunshot injury on his chest about 40 years back. On examination, the patient was in respiratory distress with tachypnea, cyanosis, and room air saturation of 68%. His blood pressure was 126/86. Chest pain increased on coughing and radiation to neck and chest. Chest radiology revealed left sided pneumothorax and hyper-resonant note shifted to the right side and decrease chest wall movement with hyper resonant note.

Chest examination revealed trachea shifted to the right side and decrease movement with hyper resonant note and absent breath sound on the left side of the chest. Chest radiology revealed left sided pneumothorax and a 24Fr intercostal chest tube (ICD) was inserted on left side 5th intercostal space in mid-axillary line. There was no bronchopleural fistula. The patient improved and lung expanded partially.

Three days later patient complained of accidental removal of the tube and repeat chest Xray showed complete expansion of lung so re-ICD was not done. But within 24 hour patient developed subcutaneous emphysema on the chest which gradually extended to neck and face. Chest Xray was done (Figure 1A) which showed “Ginkgo leaf” sign. Ginkgo leaf sign is seen with extensive subcutaneous emphysema of the chest wall. Gas outlines the fibers of the pectoralis major muscle (Figure 1A) and creates a branching pattern that resembles the branching pattern in the veins of a ginkgo leaf. (Figure 1B). Chest radiograph (Figure 1A) also shows air in the soft tissues of chest and neck regions and multiple metallic opacities in bilateral lower zones (gunshot pellets).

Subcutaneous emphysema (SE) or surgical emphysema is a clinical condition when air enters into soft tissues under the skin. This can occur in any part of the body but the most common site is under the skin that covers the chest wall or neck. It presents as painless swelling of tissues and has a crackling sensation upon touch. SE can occur mainly by three mechanisms, gas arising internally, gas introduced externally, and gas introduced de novo. Gas arising internally occurs from pneumothorax, pneumomediastinum, or a perforated hollow viscus. Penetrating trauma, postsurgical intervention, and post percutaneous intervention results in introduction of external air. Necrotizing fasciitis caused by gas-producing organisms leads to de novo gas production. Subcutaneous emphysema managed conservatively unless there are compression symptoms or extension into mediastinum or pleura which warrants surgical drainage. Our patient developed extensive surgical emphysema and was managed initially with subcutaneous incisions but later required bilateral subcutaneous drainage.

References


Pathological Fracture & Lytic Lesions: Unusual Suspects!

Sir,

Primary hyperparathyroidism (PHPT) is a relatively common endocrine disorder, with incidence as high as 1 in 500 to 1 in 1000. The clinical presentation of PHPT has evolved over the past 40 years to include three distinct clinical phenotypes: overt target organ involvement, mild asymptomatic hypercalcemia, and high PTH levels with persistently normal albumin-corrected and ionized serum calcium values. Primary hyperparathyroidism (PHPT) in India, unlike in the Western world, is largely a symptomatic disease. Among Indian patients, Bhansali et al. found that 67% had bone disease, 48% had fractures, 21% had stone disease, 23% had psychiatric symptoms and 15% had peptic ulcer.

Parathyroidectomy, the only curative treatment for PHPT, is recommended in symptomatic patients. Surgical intervention is also indicated in following subset of asymptomatic patients: serum calcium ≥1 mg/dl upper limit of normal; osteoporosis (Tscore ≤-2.5) or vertebral fractures; eGFR <60 ml/min, severe hypercalciauria (>400 mg/day), increased risk of stones on a stone risk profile or evidence of occult nephrolithiasis or nephrocalcinosis; and those aged <50 years. Although parathyroid imaging has no role in the diagnosis of PHPT preoperative localization of the abnormal parathyroid tissue guides the surgeon especially if minimally invasive parathyroidectomy is planned. In virtually all cases, the disorder will be benign with a single adenoma (80%) or multiple gland, generally hyperplastic, disease (20%) responsible. Ultrasonography and technetium-99m–labeled sestamibi have been the most popular approaches for preoperative localization; however, more recently, high resolution CT and four-dimensional CT have received positive attention.

A 42 year old male with no comorbid illness was admitted for pathological fracture of right humerus and imaging revealed an expansile lytic lesion over the middle third of humerus (Figure 1).
Evaluation revealed azotemia (1.6 mg/dL); severe hypercalcemia (17.5 mg/dL), hypophosphatemia (2.0 mg/dL), raised alkaline phosphatase 574 U/L, raised intact parathyroid hormone 1840.40 pg/mL (reference range 15–72 pg/ml) & Osborn wave with short QTc(320ms) in ECG (Figure 2). Skeletal survey showed a large lytic lesion with multiple translucent opacities in the calvaria (Figure 3). Ultrasonography neck showed a hypo-echoic lesion 21x23 x 11 mm with peripheral vascularity on posterior-lateral aspect of left lobe of thyroid which was characterised as increased uptake in the left lower parathyroid adenoma on a technetium Tc 99m sestamibi scan (Figure 4). He was managed initially with hydration, loop diuretics and calcitonin and underwent parathyroidectomy on day 4 of admission. He was discharged on day 7 of admission and his parathyroid hormone level on post op day 7 and 30 were 140.40 pg/mL and 11.2 pg/ml. His serum calcium and phosphate levels at 3 months follow up were normal. The fracture segment was stabilized by closed intramedullary locked nailing and he is on three monthly follow up. This patient had primary hyperparathyroidism with osteitis fibrosa cystica and severe hypercalcemia and highlights the importance of screening patients with lytic bone lesions for metabolic bone disease with simple tests such as serum calcium, phosphorus, and alkaline phosphatase besides condescending the more common group of fibro-osseous lesions and occasional skeletal metastases.

References

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References:
5. Data on file

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