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COVID-19 cases and their outcome among patients with uncommon co-existing illnesses: A lesson from Northern India

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ABSTRACT

Introduction: Newer coexisting conditions should be identified in order to modify newer risk factors. Aim was to identify patients with non-classical or less common coexisting conditions in patients infected of COVID 19.
Method: Single centred study from June 2020 to May 2021 at a tertiary centre in North India. A preformed questionnaire was used to record clinical and laboratory parameters and to identify cases which are in addition to CDC list and Indian data.
Results: 0.67% (46) cases out of 6832 patients were identified to have non-classical coexisting illness. It was divided into 2 groups-infections A (60.1%) and non-infections B (39.9%). Group A included-tuberculosis- pulmonary (14.3%) & extra pulmonary (32.9%), bacterial (25.0%) viral infections [dengue, hepatitis B & C] (14.3%), HIV disease (10.7%) and malaria (3.6%). Group B included- organ transplant (27.8%), autoimmune [myasthenia gravis, polymyositis, psoriasis] (22.6%), haematologic [Haemophilia, ITP, Aplastic anaemia, APML, CML] (27.8%), uncommon malignancies [disseminated sacral chordoma and GTN] (11.1%) and snakebite (11.1%). Serum Procalcitonin was not helpful for diagnosis of bacterial infection in COVID-19 disease. Group A had significantly longer duration of illness, hepatitis and elevated CRP. The mortality in group A & B were 32.1% and 43.8% respectively. Death in non-severe COVID cases was in tetanus and snakebite. 30.7% death among tuberculosis patients. More than 70% of deaths were attributable to COVID 19 in both the groups.
Conclusion: In Indian settings, comorbidities like tuberculosis and bacterial infections can precipitate severe COVID 19 unlike other parts of the world where tuberculosis is relatively uncommon.

1. Introduction

COVID-19 affected worldwide after its origin from Wuhan, China. It adversely affected people belonging to high risk group as defined by CDC (**1**) and this was uniformly observed across globe. CDC has laid down risk factors according to available evidences and strongest risk factors includes-cancer, CKD, COPD, cardiac illness, cerebrovascular accidents, smoker, obesity, pregnancy, solid organ or haematopoietic cells transplant and diabetes mellitus. The remaining factors had moderate to low level of evidences for severe diseases (**1**).

As the disease continues to unfold itself new risk groups are expected. One such risk factor established later is tuberculosis as shown by Sarkar et al.[2] We started managing this pandemic since February 2020 and our initial report by D H Reddy et al. shows presence of classical risk group and expected outcome.[3] Over the time during this pandemic we encountered COVID 19 disease with underlying illnesses sparsely described in literature and variable outcomes of this disease. Thereby, we are reporting uncommon co-existing illnesses with COVID19 disease and their outcome in Indian context of this pandemic.

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2. Material and methods

The study was conducted at COVID 19 treatment facility of a tertiary care centre in Northern India from June 2020 to May 2021. The patients admitted to the facility either by self-reporting for testing, contact tracing, positive test from community screening or elsewhere screening. We enrolled consecutive patients admitted with diagnosis of SARS-CoV-2 and evaluated them by pre-formed proforma to record epidemiology, history, examination and investigation. All patients were diagnosed on the basis of Indian Council of Medical Research-National Institute of Virology (ICMR-NIV) criteria[4] and strict screening guidelines levied by the same. The severity of COVID-19 disease was done according to Government of India guidelines on COVID-19 management.[5] The severity of the hypoxemia defines the severity of ARDS: a. mild: PaO2/FiO2 200–300 mmHg or SaO2/FiO2 237–317 mmHg; b. moderate: PaO2/FiO2 100–200 mmHg or SaO2/FiO2 155–237 mmHg; C. severe: PaO2/FiO2 $\leq$ 100 mmHg or SaO2/FiO2 $<$ 155 mmHg. Hyper-inflammation or cytokine response was defined as presence of two or more of the following -serum ferritin >1000 ng/mL; C-reactive protein >150 mg/L; D-dimer > 800 μg/L; Interleukin 6 > 20 pg/mL.[5]

All patients with any suspected or confirmed concurrent illness or recently diagnosed were included in the study. We used CDC criteria to identify comorbidities or coexisting illness.[1] After review of these criteria in Indian context we concluded that the frequency of few diseases or conditions is low and therefore we considered keeping this group among uncommon co-existing condition. This included- Solid organ or blood stem cell transplantation cases, patients on immunosuppressive medications and uncommon cancers.

The mandatory investigations included-complete blood count (CBC), liver function, kidney function test (KFT), serum electrolytes, serum C reactive protein, serum lactate dehydrogenase (LDH), ferritin, rapid testing for HbsAg, Anti-HCV IgG and HIV, EKG and chest x ray. Additional investigations were performed as per case The features positively correlating with infection by COVID-19 include fever with myalgia, fatigue along with dyspnoea, dry cough, absolute anosmia, aguesia. In this background the investigations included-neutrophilic leucocytosis, thrombocytosis, elevated levels of serum LDH, CRP, Pro-BNP, fibrinogen, procalcitonin and, D dimer with normal prothrombin time.[6,7] Serum Procalcitonin was done by ELISA method and all patients sample was sent on day of admission along with other routine investigations.

All suspected or confirmed cases of chronic illness like tuberculosis; rheumatic diseases and malignancy in their active state were included and rest were excluded. Cases of Tuberculosis (pulmonary & extra-pulmonary) with duration of less than 2 months were included as active disease and longer duration were excluded from active co-existing illness. The coexisting illness were categorised as infectious and non-infectious. Death attributable to COVID-19 was adapted from WHO guidelines.[8] All patients were followed up till discharge from hospital or expiry.

3. Statistical analysis

Statistical analysis was performed using SPSS software (version 25.0, IBM, Armonk, NY). Normally distributed data were presented as mean $\pm$ SD and data with a skewed distribution as median (IQR). The between groups differences were determined by using Student's t-test, analysis of variance (ANOVA), and nonparametric tests (Chi-square test) as well as Student's t-test being used for comparison with paired samples. In all statistical results, $P < .05$ was defined as statistical significance. * indicates statistical significance (*$P < .05$, **$P < .01$, ***$P < .001$, ****$P < .0001$).

4. Ethics in research

Ethical clearance was provided by institutional ethical committee.

5. Results

In our study we evaluated 6832 patients admitted in COVID-19 dedicated care and 46 (0.67%) had uncommon or non-classical co-existing illnesses. These are clubbed in 2 groups as infections and non-infections with 63.6% of infections as co-existing illness. Table 1 (Distribution of non-classical co-existing and concurrent illness in patients of COVID-19) shows distribution of coexisting illnesses. The infections group has significantly higher cases of tuberculosis 13 (56.4%) both pulmonary 4 (14.3%) and extra-pulmonary 9 (32.1%) followed by bacterial infections 7 (25%). There were 2 cases of sputum positive with rifampicin sensitive pulmonary tuberculosis (50%) and rest were diagnosed clinico-radiologically. 2 (22.2%) patients of extra-pulmonary tuberculosis were CBNAAT positive and rest were based on clinical, radiological and cytology study. The EPTB cases included- 3 cases of pleural effusion, 2 cases of tuberculous meningitis, 1 each cases of pyothorax, lymph node TB, tuberculoma, and disseminated TB. All suspected tuberculosis patients clinical features of fever with sputum for more than 1 month and in EPTB cases the duration of illness raned between 1 and 3 months. We included cases of more than 1 month of duration of illness so as to prevent over diagnosis of tuberculosis in background of COVID 19. 5 patients were already of antituberculous drugs and 2 were initiated. All bacterial infections diagnosed on basis of positive culture except 2 (pyelonephritis and intra-abdominal sepsis) due to prior antibiotics use. Malaria and 2 dengue cases were diagnosed according to WHO criteria with malaria as uncomplicated illness and each case of dengue as sever and non-severe.

The comparative data of both the groups are depicted in Table 2 (Clinical and laboratory characteristics of the population). There was no significant difference in terms mean age, sex and presence of classical co-morbidities among both the groups. Among clinical features only mean duration of illness was significantly higher among infection group

Table 1
Distribution of non-classical co-existing and concurrent illness in patients of COVID-19.

Co-existing illness: infectious (n = 28)	Co-existing illness: non-infectious (n = 18)
Extra-pulmonary tuberculosis (9) [32.1%]	Transplantation cases (5) [27.8%]
- Central nervous system tuberculosis (7) -Tubercular meningitis ± tuberculoma (6)	- Liver (2)
- Potts' spine (1)	- Renal (2)
- Pleural effusion (1)	- Post bone marrow (1)
- *Abdominal tuberculosis (1)	
Pulmonary tuberculosis (recently diagnosed) (4) [14.3%]	–
HIV/AIDS with opportunistic infections (3) [10.7%]	Autoimmune/Rheumatologic (4) [22.3%]
- *Disseminated tuberculosis (1)	- Myasthenia gravis (2)
- Tuberculoma/toxoplasmosis (1)	- Polymyositis (1)
- without co-infections (Traumatic brain contusion)	- Psoriasis with arthritis (1)
Viral infection (4)- [14.3%]	Uncommon malignancy (2) [11.1%]
- *Dengue (2)	- Disseminated Gestational trophoblastic neoplasm (1)
- Acute hepatitis B (1)	- Disseminated Sacral chordoma (1)
- Asymptomatic Hepatitis C infection without chronic liver disease (1)	
Bacterial infection (7) [25%]-	Haematological conditions (5) [27.8%]
- Pyelonephritis (1)	- Haemophilia (1)
- *Tetanus (1)	- Immune thrombocytopenia (ITP) (1)
- *Ruptured Appendicular abscess{*Kleseilla species*} (1)	- Aplastic anaemia (1)
- Psoas abscess {*Staphylococcus aureus*} (1)	- Acute promyelocytic anaemia (AML) (1)
- *Post-operative biliary sepsis (1)	- Chronic myeloid leukemia (CML) (1)
- *Oesophageal rupture with pyothorax (1)	
- *Purulent bacterial leg cellulitis {*Staphylococcus aureus*} (1)	
Parasitic infection- Malaria (1) [3.6%]	Miscellaneous-Snake bite (2) [11.1%]

*Diagnosis associated with mortality.

Table 2
Clinical and laboratory characteristics of the population.

Indices	Co-existing illness: infectious (n = 28)	Co-existing illness: non-infectious (n = 18)	P value
Mean age	43.62 ± 9.52 (14–76)	37.62 ± 14.88 (10–75)	0.11
Sex- Male	17 (60.8%)	9 (56.3%)	0.8
Female	11 (39.2%)	7 (45.7%)	0.6
Presence of 1 or more classical comorbidities/risk factors	12 (42.60%)	5 (31.25%)	0.46
Presence of 1 or more classical comorbidities/risk factors among expired cases	4 (14.7%)	3 (18.75%)	0.56
Mean duration of illness at admission	15.62 ± 16.54 (7–90)	5.82 ± 4.64 (6–180)	**<0.001**
Clinical features-			
Fever	20 (71.5%)	9 (56.3%)	0.31
Respiratory complaints	17 (60.7%)	9 (56.3%)	0.43
Hypoxia	18 (64.3%)	13 (81.3%)	0.23
Hypotension	5 (17.9%)	2 (12.5%)	0.64
Altered sensorium	7 (25%)	3 (18.75%)	0.63
G I complaints	7 (25%)	2 (12.5%))	0.32
Oliguria	4 (14.7%)	1 (6.50%)	0.42
Others	7 (25%)	5 (31.25%)	0.65
Investigations-			
Neutrophilic leucocytosis	12 (42.60%)	9 (56.3%)	0.38
Lymphocytosis	2 (7.20%)	1 (6.50%)	0.90
Thrombocytopenia	13 (46.60%)	9 (56.3%)	0.64
Anaemia	17 (60.70%)	8 (50%)	0.49
Abnormal liver function test	23 (82.14%)	9 (56.3%)	**0.04**
Abnormal renal function test	10 (35.7%)	3 (18.75%)	0.24
Presence laboratory features of cytokine storm	12 (42.60%)	5 (31.25%)	0.46
Elevated C reactive protein (CRP)	24 (85.7%)	10 (62.5%)	**0.04**
Elevated D-dimer	15 (53.6%)	7 (43.50%)	0.52
Elevated serum fibrinogen	7 (25%)	5 (31.25%)	0.24
Elevated fibrinogen and D-dimer	7 (25%)	4 (22.5%)	0.52
Elevated serum ferritin	13 (46.60%)	8 (50%)	0.83
Elevated serum LDH	20 (71.5%)	10 (62.50%)	0.54
Elevated serum pro-calcitonin	12 (42.60%)	8 (50%)	0.38
[#]Radiologic changes suggestive of COVID-19	17 (60.7%)	9 (56.3%)	0.43
Total deaths	10 (32.1%)	8 (43.8%)	0.44
No of death attributable to COVID-19	7 (70.0%)	6 (75.0%)	0.64
No of Concurrent diagnosed illness	17 (60.70%)	5 (31.25%)	**0.04**

although the longest duration of illness was of 180 days in myasthenia gravis. Among investigations abnormal liver function test (82.2%) and elevation in CRP (85.7%) were significantly higher in infection group. There was no significant difference among mean value of serum pro-calcitonin among bacterial and non-bacterial infections (5.33 v/s 3.23; $p > .05$). Radiological evidence of pulmonary tuberculosis was present in 100% patients with focal consolidation or cavitation, 100% patients of suspected TBM had imaging features of meningo-encephalitis with 1 case of concomitant tuberculoma.1 case of CNS tuberculoma without meningitis. A case of Polymyositis had active disease at presentation with creatine phosphokinase (CPK) levels were 5346 IU/L.

Table 3 (Distribution of stages of COVID-19 infection and mortality among patient groups) shows distribution of case severity and related mortality. Total 18 (39.1%) patients developed severe COVID 19 disease. Death among tuberculosis subjects was seen in 4 (30.7%) cases with 1 each pulmonary tuberculosis, disseminated disease, abdominal and meningo-encephalitis with 75% cause attributable to COVID-19 and rest to tuberculosis. The application of WHO cause of direct death allowed us to differentiate between death directly attributable to COVID 19. Death where immediate causes were unrelated to COVID 19 included-tubercular meningitis, neurotoxic snakebite and oesophageal rupture with secondary pyothorax. Cases where cause death was difficult to delineate from COVID 19 due to overlap features and we placed them in moderate-severe category included-disseminated GTN with pulmonary involvement, acute promyelocytic leukemia with DIC and massive haemorrhage. Dengue fever with warning signs at end of critical phase developed severe COVID pneumonia and expired on 5th day. 3 patients with features suggestive of HLH were subjected to bone marrow study but were inconclusive and diagnosed as cytokine storm.

6. Discussion

Severe form of COVID-19 is usually seen in presence of certain risk factors and they are classical risk factors. We considered the CDC criteria and found few coexisting illnesses apart from classical risk factors. In our study classical risk factors were seen in 38.6% of all patients without any significant differences among both groups. In fact, these factors were present in 15.9% of all cases with sever disease. Additional cases of severe disease were seen in GTN with distant metastasis, tuberculous meningo-encephalitis, and intra-abdominal and biliary sepsis, abdominal tuberculosis, dengue fever and HIV disease. Therefore, it is important to identify other conditions that predispose to development of severe COVID 19 disease or complicate existing COVID-19 infection and increases morbidity and mortality.

In our study, infections constituted 63.3% of coexisting or recently diagnosed illness with tuberculosis (56.4%) as predominant infection. As India homes the highest global burden of tuberculosis, it is expected to cross ways with COVID-19. In our series 56.4% of co-existing infections were tuberculosis. The data in this regard is variable across globe. Two important studies were from Tadolini et al. and Motta et al. had 49 and 69 patients along with 12.3% and 11.6% mortality among individuals with TB-COVID-19 co-infections.[9,10] A recent database from Southern India by M S Kumar et al. found 177 cases of active pulmonary TB-COVID19 co-infection with 15% mortality. Almost all cases of tuberculosis were diagnosed before the diagnosis of COVID 19 infection and more than 50% of mortality was seen among patients without underlying classical comorbidities.[11] A study from N Gupta et al. found 22 cases of tuberculosis with mortality of 27.5%.[12] Similarly, in our series the mortality was 30.7% and 75% attributable to COVID-19 showing role of active tuberculosis as a factor in causing severe COVID-19 disease among patients without underlying classical comorbidities.

Other most common group was bacterial infection and formed 25% of infectious co-existing conditions. There is very sparse data on pre-existing infections on COVID-19 outcome. Study by C G Vidal et al. showed community acquired co-infection was in 3.1% cases and all of them were pneumonia and associated blood stream infection. The organism included- *Staphylococcus, Streptococcus, Haemophilus Influenza* and *Moraxella catarrhalis*.[13] In our study we found 2 cases of *Staphylococcus aureus* in form of blood stream infection and psoas abscess along with each case of *Klebsiella* spp. and *E. coli*. Moliere S et al. found 17.4% cases of COVID-19 among 46 patients with acute symptoms in post-operative period with 25% mortality.[14] We had 2 (7%) post-operative sepsis patients who developed severe COVID 19 disease and died. Our study had 3 (10.8%) cases of tropical infections including 2 cases of dengue and 1of malaria with mortality of 1 dengue by ARDS.

S Sarkar et al. showed only few reported cases of COVID-19 dengue co-infection and dengue as risk factor for severe COVID 19 disease is still under evaluation.[2] 10.7% of all infectious co-existing condition in our study included HIV disease with 1 patient had disseminated tuberculosis developed severe COVID 19 disease and rest recovered from moderate disease. Now CDC considers HIV to be a significant risk factor but our data is sparse to comment.[1]

In our study there were 4 (25.0%) cases of rheumatologic disorders, all of them were on immunosuppression with 75% mortality. A recent review by K L Hyrich et al. showed risk factors for poor prognosis of COVID 19 infected individuals with rheumatological illness were similar to other patients apart from therapy of prednisolone daily dosage more

Table 3
Distribution of stages of COVID-19 infection and mortality among patient groups.

Stage of COVID 19 & outcome	Co-existing illness: infectious (n = 28)	Diseases among infection group	Death as outcome (n = 10)	Co-existing illness: non-infectious (n = 18)	Diseases among non-infection group	Death as outcome (n = 8)
Mild	14 (50%)	1. TBM (1) 2. Potts' spine (1) 3. PTB (3) 4. Pleural effusion (1) 5. Severe Tetanus (1) 6. Hepatitis B & C (1 each) 7. Dengue (1) 8. HIV with traumatic brain injury (1) 9. Malaria (1) 10. *Staphylococcal* abscess (1)	1(10.0%)	5 (27.80%)	1. Myasthenia gravis (1) 2. Neurotoxic snakebite (1) 3. Haemophilia (1) 4. Post bone marrow transplant (1) 5. Renal transplant (1)	0
Moderate	4 (10.7%)	1. TBM (1) 2. PTB (1) 3. Abdominal tuberculosis(1) 4. Pyelonephritis (1)	0	5 (27.80%)	1. Liver transplant (2) 2. Immune thrombocytopenia (ITP) (1) 3. Aplastic anaemia (1) 4. snakebite (1)	1 (12.5%)
Severe	10 (39.3%)	1. TBM (1) 2. TBM (1) 3. Tuberculoma with HIV (1) 4. TB with HIV (1) 5. Cellulitis (1) 6. Dengue (1) 7. Biliary sepsis (1) 8. Bacterial peritonitis (1) 9. Ruptured Appendicular abscess (1) 10. Oesophageal rupture with pyothorax (1)	9(90%)	8 (44.40%)	1. Myasthenia gravis (1) 2. AML (1) 3. Disseminated GTN (1) 4. Psoriasis with arthritis (1) 5. Disseminated sacral chrodoma (1) 6. Polymyositis (1) 7. Renal transplant (1) 8. CML (1)	7 (87.50%)

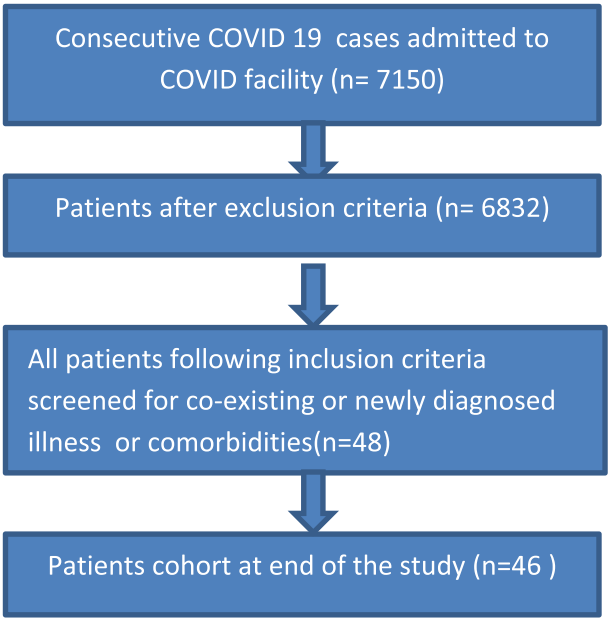
#Diseases marked in red shows cases associated with mortality.

than 10 mg.[15] Last risk factor was present in all patients with 1 of each patients having hypertension and the other had multiple comorbidities.

Solid organ transplant is one of the strongest risk factor for developing severe COVID-19 disease.[1] India has limited reports in this regards. The largest series by M Kumarsenum et al. had 720 kidney transplant recipients and 2.2% developed COVID-19 with mortality of 18.8% and all these patients had at least 1 classical risk factor.[16] Dhampalwar S et al. and Choudhury A et al. had 12 and 6 COVID19 infected liver transplant recipients from India.[17,18] The earlier one had mortality of 18.4% with comorbidities in all of them and later group had no mortality. Most of the mortality occurred in patients with comorbidities. Similarly, in our study both liver transplant recipients recovered from moderate and sever illness whereas the renal transplant recipient succumbed to sever disease. Therefore, our findings are in concordance with current data.

Our series is unique in a way that we are reporting cases not reported in the literature in context of a developing country like India**.** We had 1 case of tetanus that developed sever COVID-19 disease and died. Similarly, 2 cases of snake bite each neurotoxic as well as haematotoxic. The earlier recovered from moderate illness and later eventually developed ARDS and DIC which was not possible to differentiate from COVID as the reason. A moderate COVID-19 complicated newly diagnosed acute hepatitis B that eventually recovered. W A Aldhaleei et al. reported a case of acute hepatitis B with active hepatitis and mild COVID-19 disease.[19] Similarly, 2 cases of myasthenia gravis on immunosuppression and one of them succumbed to sever COVID19 disease while the other recovered a moderate illness. We had a recently diagnosed ITP patient on prednisolone more than 10 mg per day developed progressive thrombocytopenia and moderate COVID disease that responded to pulse methyl prednisolone. American society of haematology **(**ASH**)** mentions ITP as not a risk factor for severe COVID 19 disease.[20] The other unreported case in Indian setting is COVID19 among Haemophilia patients. Since haemophilia is coagulation disorder treatment of COVID 19 coagulation defects poses a challenging task and especially in severe cases as shown by De la Corte-Rodriguez H et al. but fortunately it not a risk factor for severe COVID 19 disease.[21] Our patient recovered a mild illness with complete recovery and no coagulation defect. We report a newly diagnosed untreated case of CML without other comorbidities developed severe COVID disease and recovered. W Li et al. found that CML patients are at higher risk of developing COVID disease with advance illness and comorbidities carries poor prognosis.[22] Similarly, we diagnosed a case of acute promyelocytic leukemia who presented to us with high grade ever with pancytopenia and on evaluation came COVID positive and during stay developed DIC and ARDS. A similar case is reported by Farmer I et al. from London but none from India.[23] We diagnosed 2 cases of GTN with one recovered moderate COVID disease the other with disseminated disease died from ARDS. Bachani S et al. had 1 patient died from GTN post operatively among COVID infected pregnant female.[24]

We found almost no significant difference among laboratory parameters of the patients among both groups showing uniform COVID disease activity among the groups. Procalcitonin as marker of gram negative bacterial infection and it stay elevated in COVID 19 and its levels are directly proportional to the severity of COVID 19 disease.[25] In our study 91% patients with severe disease had elevated levels (0.6–53.8 ng/l) without any significant difference with patients with bacterial infection. About 44% patient had thrombocytopenia and more than 60% of severe thrombocytopenia cases were seen in patients with haematological disorders, and each case of dengue fever, malaria and severe sepsis indicating severe thrombocytopenia as differentiating feature for COVID 19 infection. The unique feature of elevated d-dimer with fibrinogen[6] was seen around 23% cases without any difference amongst the group predominantly in severe disease group showing COVID 19 activity. 37.5% mortality was seen with attributable death of 72.2% evenly distributed in both groups showing COVID disease as predominant cause of death.



Algorithm for patient recruitment in the study.

7. Conclusion

Severe COVID 19 disease is associated with commonly occurring classical risk factors across globe. In Indian context there is possibility of newer coexisting illness that might precipitate severe COVID 19 disease in form of tuberculosis and bacterial infections apart from prolonged immunosuppression and uncommon malignancy as gestational trophoblastic neoplasm, myasthenia gravis and solid organ transplants. These are sparse findings in Indian settings and require close monitoring for severe disease even in absence of classical risk factors. Death attributed to COVID 19 is usually high hence these might be additional risk factors.

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Author statement

S Pandey: Designing the research study, Data collection, Data analysis and report preparation.

D.H Reddy: Designing the research study, Data analysis and report preparation.

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Declaration of competing interest

None.

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None.

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