Original Article

A clinico-epidemiological profile, coinfections and outcome of patients with Influenza Like Illnesses (ILI) presenting to the emergency department during the COVID-19 pandemic

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Abstract

Background: During the COVID-19 pandemic, many patients presented to the emergency department (ED) with features of Influenza-like illnesses (ILI) and with other atypical presentations. This study was done to determine the etiology, co-infections, and clinical profile of patients with ILI. **Methods:** This prospective observational study included all patients presenting to the ED with fever and/or cough, breathing difficulty, sore throat, myalgia, gastrointestinal complaints (abdominal pain/vomiting/diarrhea), loss of taste and altered sensorium or asymptomatic patients who resided in or travelled from containment zones, or those who had contact with COVID-19 positive patients during the first wave of the pandemic between April and August 2020. Respiratory virus screening was done on a subset of COVID-19 patients to determine co-infection. **Results:** During the study period, we recruited 1462 patients with ILI and 857 patients with the non-ILI presentation of confirmed COVID-19 infection. The mean age group of our patient population was 51.4 (SD: 14.9) years with a male predominance (n-1593; 68.7%). The average duration of symptoms was 4.1 (SD: 2.9) days. A sub-analysis to determine an alternate viral etiology was done in 293 (16.4%) ILI patients, where 54 (19.4%) patients had COVID 19 and co-infection with other viruses, of which Adenovirus (n-39; 14.0%) was the most common. The most common symptoms in the ILI-COVID-19 positive group (other than fever and/or cough and/or breathing difficulty) were loss of taste (n-385; 26.3%) and diarrhea (n- 123; 8.4%). Respiratory rate (27.5 (SD: 8.1)/minute: p-value < 0.001) and oxygen saturation (92.1% (SD: 11.2) on room air; p-value < 0.001) in the ILI group were statistically significant. Age more than 60 years (adjusted odds ratio (OR): 4.826 (3.348-6.956); p-value: <0.001), sequential organ function assessment score more than or equal to four (adjusted OR: 5.619 (3.526-8.957); p-value: <0.001), and WHO critical severity score (Adjusted OR: 13.812 (9.656-19.756); p-value: <0.001) were independent predictors of mortality. **Conclusion:** COVID-19 patients were more likely to present with ILI than atypical features. Co-infection with Adenovirus was most common. Age more than 60 years, SOFA score more than or equal to four and WHO critical severity score were independent predictors of mortality.

Keywords: Adenovirus, atypical COVID-19 presentation, co-infection, COVID-19 infection, influenza-like illness, mortality

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Introduction

Since its inception in Wuhan, China in the later half of 2019, the Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV2)

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has created a pandemic that has thrown our lives into disarray and has left lasting impacts on the economical, psychosocial, and political conditions of the world. The World Health Organization (WHO) declared the pandemic in March 2020, and as information regarding the droplet transmission of this virus came to light, countries scrambled to heighten their safety measures, develop rapid methods of viral detection, and enforce isolation through lockdowns and quarantines.[1,2] At the time, the symptomatology of this disease was largely unknown, but most cases presented as an influenza-like illness (ILI) with fever and respiratory symptoms of cough and shortness of breath.[3,4] However, several cases were also later reported to have atypical non-respiratory presentations such as abdominal pain, loose stools, vomiting, loss of appetite, fatigue, and altered sensorium.[3,5,6] Many cases of co-infection of SARS-CoV2 were reported of which Adenovirus, Influenza virus A (H1N1), Dengue, and Malaria were common.[7-9] Hazra *et al.* reported a case of COVID-19 co-infection with Scrub Typhus as well.[10]

Recent systemic reviews and meta-analysis have shown that as many as 19% of COVID-19 patients had chances of added co-infections.[11] However, there was and still is a dearth of data and information on co-infection or superinfection of COVID-19 by viral or bacterial agents. This highly variable presentation, aided by our ignorance in the early stages of the pandemic, contributed to several missed or delayed diagnoses of cases, and furthered the spread of the virus. In any case, most of these presentations were seen in emergency departments (ED) across the country, giving the healthcare workers (HCW) here a bird's eye view of the pandemic. Our study began in the ED of a large tertiary care referral centre in South India, and these patients were then followed up to measure various outcomes of interest.

At the time of this study, the lack of evidence-based protocols made it challenging for clinicians to recognize and tackle this infection or associated co-infection. Our goal was to provide comprehensive characterizations of COVID-19 patients and to aid in establishing sound management strategies for the same. Currently, as we have surpassed the fourth wave, primary physicians should consider other viral and bacterial differentials for a flu-like syndrome other than COVID-19, as it is now the new norm. This is a prospective study comparing the demographics, clinical profile, co-infection with other viruses, and predictors of mortality in COVID-19 patients presenting with typical symptoms of an ILI to those with atypical symptoms and would help our primary care physicians in managing such cases with limited resources.

Methodology

Study design and setting: This prospective observational cohort study was done in the COVID-19 suspected zone of an ED of a large tertiary care centre in South India. This zone was segregated structurally from the rest of the ED at the start of the pandemic. It included patients with symptoms of COVID-19 or those who were at high risk of infection.[12]

Study period: This study was conducted over 5 months (1 April 2020-31 August 2020).

Participants: Inclusion criteria: All patients presenting with fever and/or cough, breathing difficulty, sore throat, myalgia, gastrointestinal complaints (abdominal pain/vomiting/diarrhea), loss of taste and altered sensorium or asymptomatic patients who resided in or travelled from containment zones, or those who had contact with COVID-19 positive patients were included in the study.

Exclusion criteria: Patients or relatives who denied informed consent, patients who denied investigations/reverse transcriptase polymerase chain reaction (RT-PCR) COVID-19 testing, and patients with a history suggesting COVID-19 infection but who were brought dead were excluded from the study.

Variables: At the beginning of the study, a proforma with several variables was prepared, that included age, sex, symptoms and their duration, comorbidities, vitals at presentation, and the requirement of respiratory and ionotropic support in the ED. Patients were classified in our study as "healthcare workers" if they worked in a hospital setting in any capacity, and this included not just doctors, nurses, and technicians, but also security personnel, medical students and other ancillary staff. Secondary variables namely the WHO severity index and the Sequential Organ Failure Assessment (SOFA) score were calculated based on the primary variables. These details were later recorded in a data extraction sheet.

Sub-analysis: A sample of patients were selected to determine alternate viral etiology and co-infection rate.

Method of sampling: The convenience sampling method was used to determine the infection rates of multiple respiratory viruses (MRV). The first two patients presenting to the ED with ILI on the Monday and Thursday of each week were included in the sub-analysis. This part of the study was undertaken solely with the financial backing of our institute, and it is due to these budget constraints that this sampling method was adopted.

Sample processing and respiratory viruses scanned: Respiratory samples (nasal/throat/nasopharyngeal swabs in a viral transport medium) were transported to the laboratory in cold conditions. In the lab, viral RNA was extracted using a QiaCube HT-automated extractor. RNA extracts were tested in a multiplex real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) using primers and probes targeting 15 common respiratory viruses with internal control. Adenovirus, Bocavirus, Enterovirus, Metapneumovirus, Influenza A, Influenza B, Human Coronavirus-NL63, Human Coronavirus-229E, Human Coronavirus-OC43, Parainfluenzavirus 1-4, and Rhinovirus and Respiratory syncytial virus were the viruses screened with Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as the internal control.

Outcome variables: Rates of hospital admission, Intensive Care Unit (ICU) admission, and mortality were recorded for analysis.

Statistical analysis: Data were entered into a standard data abstract sheet (Microsoft Excel-version 16.53. Thereafter, analysis was done using Statistical Package for Social Sciences for Windows (SPSS Inc. Released 2015, version 23.0. Armonk, NY, USA). The continuous variables were presented as mean with standard deviation (SD) and categorical and nominal variables were presented as percentages. Factors associated with outcome measures of RT-PCR—positive COVID-19 patients, both ILI and atypical presentations, respiratory support with outcomes of patients presenting with ILI and non-ILI and predictors of hospital mortality in this group were determined by bivariate followed by multivariate logistic regression analysis and their 95% confidence intervals were calculated. For all tests, a 2-sided *P* value less than 0.05 was considered statistically significant.

Ethical considerations: This study was approved by the Institutional Review Board before the commencement of the study, and approval from the Institutional Review Board Ethical Committee was obtained (IRB Min no: 12746; dated 09.04.2020). Patients were recruited after obtaining informed written consent. Patient confidentiality was maintained using unique identifiers and password-protected data entry software with restricted users.

Results

During the 5-month study period, our ED received a total of 23,416 patients, of which 8,052 (34.4%) were triaged into the COVID-19 suspected zone. Based on their symptomatology, 1790 (22.2%) were classified into the ILI category, whereas 2114 (26.3%) presented with atypical features. Among the ILI category, majority (n-1462; 81.7%) were tested positive for COVID-19 infection, whereas about one-third (n-857; 39.7%) from the atypical presentation category were tested positive. Sub-analysis to determine alternate viral etiology or co-infection in patients presenting with ILI was done in 293 participants. [Figure 1]

Baseline characteristics: The mean age group of our patient population was 51.4 (SD 14.9: years and had a male predominance (n- 1593; 68.7%). Irrespective of the symptoms, their duration upon presentation was found to be significantly higher (p-value < 0.001) in the COVID-19 positive ILI group with 4.6 (SD: 2.8) days as compared with the atypical presentation group with 3.2 (SD: 3.0) days. On admission to the ED, the respiratory rate in the ILI group was significantly higher (p-value < 0.001), i.e., 27.5 (SD: 8.1)/minute than the atypical presentation group, i.e., 25.7 (SD: 7.7)/minute. Additionally, the oxygen saturation in the ILI group was significantly lower (p-value < 0.001), i.e., 92.1% (SD: 11.2) on room air, as compared to the other group at 93.9% (SD: 10.2). Details of clinical presentation and vital signs, along with the calculated WHO severity index and the SOFA score are categorized and presented in Table 1. Adjusted and unadjusted analyses of respiratory supports and outcomes of patients presenting with ILI and non-ILI are given in Table 2. This reveals oxygen requirement (adjusted odds ratio (OR): 2.77 (1.98-3.86); p-value: <0.001), non-invasive ventilation (NIV) requirement (adjusted OR: 1.48 (1.08-2.01); p-value: 0.014) and ICU stay (adjusted OR: 1.06 (0.75-1.50); p-value: 0.729) to be significantly higher in the ILI group as compared with the atypical presenting group.

Sub-analysis to determine alternate viral etiology or co-infection: Of the patients presenting with ILI, 293 patients were included in a sub-analysis. Among this group, 279 patients tested positive for COVID-19, of which 54 (19.4%) showed co-infection with one other virus (Adenovirus being the most common). Of those who tested negative for COVID-19, 5 patients were infected with Adenovirus, while the rest remained negative for a viral etiology. These details are shown in Figure 2.

Predictors of mortality: Based on their physiological status after initial management in ED, 2225 (95.9%) patients were admitted to different medical ICU, medical high-dependency units, or general wards. One-tenth (n-245; 11.01%) of patients died during the hospital stay. Independent predictors of mortality, as determined by bivariate and multivariate logistic regression analysis, showed age more than 60 (adjusted OR: 4.826 (3.348-6.956); p-value: <0.001), SOFA score more than or equal to four (adjusted OR: 5.619 (3.526-8.957); p-value: <0.001), and WHO critical disease (adjusted OR: 13.812 (9.656-19.756); p-value: <0.001) to be significant, details of which are given in Table 3.

Discussion

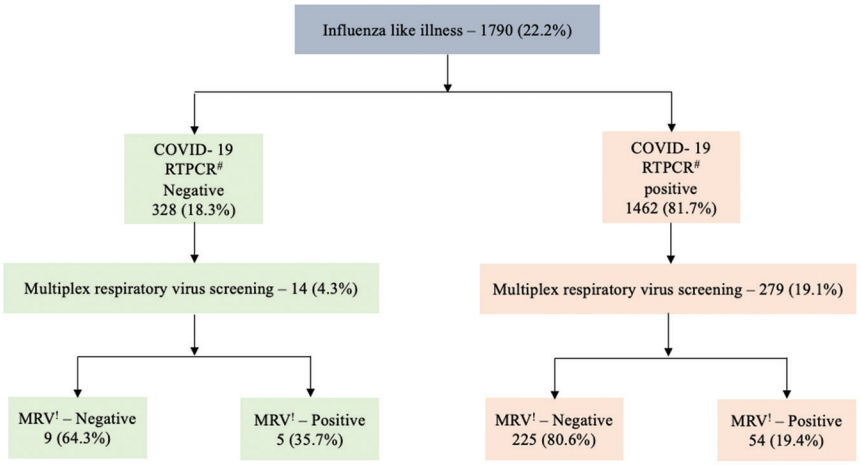
Our study showed that COVID-19 infection manifested in several different forms in patients—the most common being ILI. It also presented as myriad atypical and seemingly unrelated symptoms. This study was done at a time when COVID-19 had just reared its head, during the first wave of the pandemic, when it was starting to be noticed. In our study population, as mentioned, the duration of symptoms at presentation was longer amongst the ILI group. The reason for this could be that ILI symptoms in most patients tend to be typically mild and less alarming in that they mimic the ubiquitous flu. This may deter them from seeking immediate medical attention, as opposed to more alarming and less familiar symptoms such as altered sensorium or loss of taste. It is important to note, that though some atypical symptoms were present in both groups; however, as postulated the respiratory symptoms were predominant in the ILI group. Studies show that the neurological symptoms of COVID-19, affecting both the central and peripheral nervous systems, could be due to the expression of the ACE2 receptor in this region.[13,14] Additionally, the presence of the same receptor in the gut could explain the gastrointestinal symptoms that afflict COVID-19 patients.[15,16]

Our study included a sub-analysis done on a small sample of the population to examine rates of alternate viral etiology and co-infection in patients with ILI, wherein Adenovirus was found to be the most common. According to numerous reports, co-infection with other viruses is associated with certain differences in clinical, lab and imaging findings, and must be suspected when findings cannot be solely explained by

Table 1: Baseline characteristics with influenza-like illness and atypical presentation of COVID-19 infection

Variables	Total *n*=2319 (%)	COVID-19 Influenza-like illness *n*=1462 (63.0%)	COVID-19 Atypical presentation *n*=857 (37.0%)	p-value
Age >60 years	760 (32.8)	286 (33.4)	474 (32.4)	0.638
Male sex	1593 (68.7)	1047 (71.6)	546 (63.7)	<0.001
Healthcare workers	150 (6.5)	80 (5.5)	70 (8.2)	0.011
Duration of symptoms (SD#) days	4.1 (2.9)	4.6 (2.8)	3.2 (3.0)	<0.001
Diarrhea	223 (9.6)	123 (8.4)	100 (11.7)	0.010
Myalgia	179 (7.7)	106 (7.3)	73 (8.5)	0.270
Loss of taste	685 (29.5)	385 (26.3)	300 (35.0)	<0.001
Altered sensorium	28 (1.2)	14 (1.0)	14 (1.6)	0.150
More than 2 comorbidities	716 (30.9)	456 (31.2)	260 (30.3)	0.668
Diabetes Mellitus	995 (42.9)	650 (44.5)	345 (40.3)	0.048
Hypertension	814 (35.1)	516 (35.3)	298 (34.8)	0.799
Vital signs at presentation				
Systolic blood pressure (SD#) mmHg	118.71 (SD: 20.4)	118.5 (SD: 18.8)	119.2 (SD: 22.2)	0.040
Heart rate (SD#) beats/minute	99.6 (SD: 17.4)	101.1 (SD: 18.8)	99.0 (SD: 16.9)	0.006
Respiratory rate (SD#) per minute	26.34 (SD: 7.6)	27.5 (SD: 8.1)	25.7 (SD: 7.7)	<0.001
O_2 Saturation (SD#) %	93.3 (SD: 10.1)	92.1 (SD: 11.2)	93.9 (SD: 10.2)	<0.001
WHO& Severity				
WHO& severity score 0	791 (34.1)	426 (29.1)	365 (42.6)	0.012
WHO& severity score 1 (Mild)	689 (29.7)	436 (29.8)	253 (29.5)	
WHO& severity score 2 (Moderate)	458 (19.7)	336 (23.0)	122 (14.2)	
WHO& severity score 3/4/5 (Critical)	381 (16.4)	264 (18.1)	117 (13.7)	
SOFA* score ≥4	166 (7.5)	102 (7.3)	64 (7.7)	0.701

SD#: Standard Deviation; WHO&: World Health Organization; SOFA*: Sequential Organ Failure Assessment



COVID-19* - Corona Virus Disease -2019; RTPCR# - Reverse Transcription Polymerase Chain reaction; Multiplex respiratory virus! – MRV

Figure 1: STROBE diagram

a COVID-19 infection.[11,17-19] This becomes important when the treatment of the secondary virus can improve outcomes in such patients. Larger and more thorough analytical studies need to be performed to further explore the effect of infection with other respiratory viruses on the clinical course and management of COVID-19 infection.

Hypoxia in COVID-19 patients can be due to several causes, ranging from fulminant pneumonia to a severe, potentially lethal acute respiratory distress syndrome. Either the ACE2 receptors in the lungs or the cytokine storm secondary to infection are thought to be responsible for these manifestations.[20-22] A third mechanism wherein certain viral surface proteins and glycoproteins form complexes with porphyrin that attack heme on hemoglobin and decrease its capacity for gas exchange has also been proposed.[23] Patients in the ILI group in our study had some expected complications over the atypical group, notably hypoxemia and increased work of breathing, leading to a significantly higher requirement for oxygen and NIV.

The requirement of inotropic support showed no significant differences between the two groups in our study and was

Table 2: Adjusted and unadjusted analysis of respiratory supports and outcomes of patients presenting with ILI and non-ILI

Variables	Total *n*=2319 (%)	COVID-19 Influenza-like illness *n*=1462 (63.0%)	COVID-19 non-Influenza-like illness *n*=857 (37.0%)	Unadjusted odds ratio			Adjusted odds ratio		
				OR#	95% CI%	p-value	OR#	95% CI%	p-value
Oxygen requirement in a hospital	969 (41.8)	723 (49.5)	246 (28.7)	2.43	2.03-2.91	<0.001	2.77	1.98-3.86	<0.001
Requirement of NIV%	308 (13.3)	214 (14.6)	94 (11.0)	1.39	1.08-1.80	0.012	1.48	1.08-2.01	0.014
Ionotropic support	45 (1.9)	28 (1.8)	17 (2.0)	0.97	0.53-1.77	0.908	-	-	-
Hospital admission	2221 (95.8)	1406 (96.2)	815 (95.1)	1.29	0.86-1.95	0.216	-	-	-
ICU! Admission	836 (36.1)	617 (42.2)	221 (25.8)	2.10	1.75-2.53	<0.001	1.06	0.75-1.50	0.729
In hospital mortality	245 (10.6)	167 (11.4)	78 (9.1)	1.20	0.97-1.71	0.079	-	-	-

NIV%: Non-invasive ventilation, ICU!: Intensive Care Unit, OR#: Odds Ratio, CI%: Confidence Interval

Table 3: Predictors of in-hospital mortality in patients with COVID-19 infections

Variables	Total patients *n*=2225 (%)	COVID-19 alive *n*=1980 (%)	COVID-19 dead *n*=245 (%)	Unadjusted odds ratio			Adjusted odds ratio		
				OR#	95% CI%	p-value	OR#	95% CI%	p-value
Age >60 years	715 (32.1)	544 (27.7)	171 (69.8)	6.1	4.56-28.15	<0.001	4.826	3.348-6.956	<0.001
Sex - Males	1523 (68.4)	1340 (67.7)	183 (74.7)	1.41	1.04-1.91	0.026	0.759	0.514-1.121	0.166
Healthcare workers	150 (100.0)	150 (100.0)	0 (0.0)	-	-	<0.001	-	-	-
ILI^ Presentation	1398 (62.8)	1231 (62.2)	167 (68.2)	0.77	0.58-1.02	0.067	-	-	-
Diabetes Mellitus	953 (42.8)	807 (40.8)	156 (59.6)	2.14	1.64-2.81	<0.001	1.068	0.738-1.547	0.727
Hypertension	779 (35.0)	647 (32.7)	132 (52.9)	2.41	1.84-3.15	<0.001	1.179	0.816-1.704	0.381
Chronic Kidney disease	64 (2.9)	47 (2.4)	17 (6.9)	3.07	1.73-5.43	<0.001	0.547	0.244-1.227	0.143
Obstructive airway disease	134 (6.0)	109 (5.5)	25 (10.2)	1.95	1.24-3.08	0.004	1.100	0.592-2.042	0.764
SOFA* ≥4	166 (7.5)	66 (3.3)	100 (40.8)	20	14.04-28.49	<0.001	5.619	3.526-8.957	<0.001
WHO& Critical disease	351 (15.8)	178 (9.0)	173 (70.6)	24.32	17.75-33.33	<0.001	13.812	9.656-19.756	<0.001
Non-invasive ventilation	293 (13.2)	149 (7.5)	144 (58.8)	17.52	12.92-23.75	<0.001	-	-	-

ILI^ : Influenza like illness; SOFA*: Sequential Organ Function Assessment score; WHO&: World Health Organization, OR#: Odd ratio; CI%:: Confidence interval

relatively rare compared to other studies.[24,25] The Surviving Sepsis Campaign (SSC) guidelines were followed wherever applicable, in patients with septic shock. Management of patients in both groups was mainly supportive and based on established institutional guidelines that were continually revised based on newer evidence.[26-29]

Despite differences in the requirement of support and intensive care management in the two groups, our study did not demonstrate a significant difference in mortality rates between them. The independent predictors of mortality were found to be patient age of more than 60 years, SOFA score of more than 4 and WHO index suggesting critical disease. This is in keeping with several other such studies, depicting particularly the SOFA score to be a consistent predictor of in-hospital mortality.[22,28-30]

Limitations

In our study, many potential participants had to be excluded due to a lack of adequate consent. Our study also determined COVID-19 positivity solely through an RT-PCR and did not employ other tests of detection. Additionally, the MRV screen could only be performed on a small sample of the population, due to budget constraints, limiting our ability to examine these relationships in detail. For other etiologies of these clinical symptoms, evaluation done was not included or analyzed in our study.

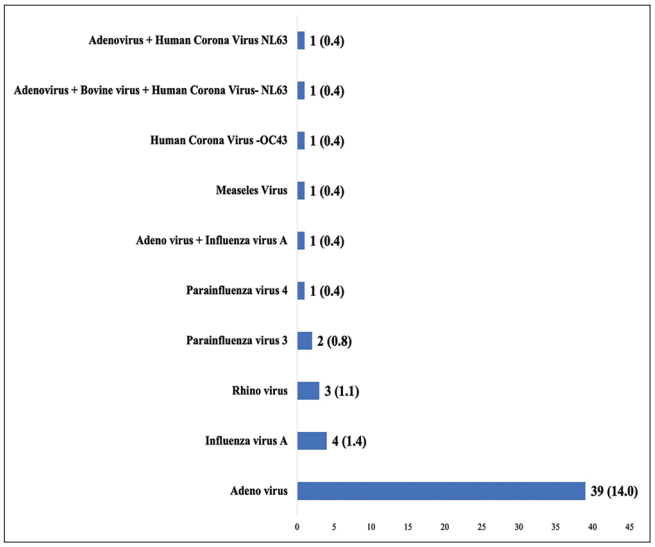


Figure 2: Sub-analysis to determine alternate viral etiology in typical COVID-19 patients

Strengths and scope of further research: This is a large pioneering study on typical and atypical presentations of COVID-19 pneumonia, wherein we have also analyzed viral co-infections rates in a small subgroup. As we have completed the fourth wave and COVID is here to stay, the primary physicians need to realize that COVID is one of many viruses and bacteria causing disease in the population and differentials and evaluation have to be broad. A multicentric assessment of etiology of ILI

will give us the spectra of current etiological diagnosis, which will help in the management of the same.

Conclusions

Our study found ILI to be the more common presentation of COVID-19 in comparison to atypical presentations. Sub-analysis showed several cases of co-infection with Adenovirus and other respiratory pathogens, and the consequences of this require further exploration. Patients with ILI had significantly higher odds of requiring oxygen therapy, NIV support, and ICU stay. There was no difference in mortality rates between the ILI and the atypical group. Age more than 60 years, SOFA score more than or equal to four, and WHO critical disease were found to be independent predictors of mortality.

Research Quality and Ethics Statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is IRB Min no: 12746; dated 09.04.2020. The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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