Fulminant onset COVID-19: predictors and outcome

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ABSTRACT

Purpose During COVID-19 infection, organ dysfunction such as respiratory failure tends to occur towards the second week of illness; however, in a subset, there may be rapid onset of organ dysfunction as early as symptom onset. We define fulminant onset COVID-19 as rapid onset of organ dysfunction such as acute respiratory failure, acute kidney injury, acute encephalopathy or shock within 4 days of symptom onset. Fulminant onset COVID-19 has not yet been systematically studied. We aimed to identify predictors and prognosis of fulminant onset COVID-19.

Methods This retrospective study was carried out on patients admitted to a single referral hospital in South India between June 2020 and January 2022. Patients were categorised into fulminant and non-fulminant onset COVID-19. Candidate predictors for fulminant onset were chosen by an intuitive approach and analysed using logistic regression. Then, the outcome of fulminant onset COVID-19 at 30 days was studied.

Results Out of 2016 patients with confirmed COVID-19, 653 (32.4%) had fulminant onset COVID-19. Age>60 years (a-OR 1.57, 95% CI 1.30 to 1.90, p<0.001), hypertension (a-OR 1.29, 95% CI 1.03 to 1.61, p=0.03) and immune-suppressed state (a-OR 5.62, 95% CI 1.7 to 18.7, p=0.005) were significant predictors of fulminant onset COVID-19. Complete vaccination lowered the odds of fulminant onset COVID-19 significantly (a-OR 0.61, 95% CI 0.43 to 0.85, p=0.004). At 30 days, the fulminant onset COVID-19 group had higher odds of mortality and need for organ support.

Conclusion Fulminant onset COVID-19 is not uncommon and it carries poor prognosis and deserves recognition as a distinct phenotype of COVID-19.

INTRODUCTION

The COVID-19 pandemic has been ongoing since December 2019, claiming at least 6.2 million lives globally as on 20 April 2022.[1] Although the cardinal manifestation of COVID-19 is pneumonia, COVID-19 has a propensity to involve other organ systems such as the heart, liver, brain and kidneys. The COVID-19 illness can be conceptualised to run through three different clinical stages,[2] namely an incubation period followed by a symptomatic phase and subsequently a stage of complications characterised by organ dysfunction such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), shock and death in a subset of patients. The median time to onset of ARDS was found to be 8 days[3] in an observational study, which implies that organ dysfunction such as ARDS could be anticipated towards the second week of illness. However, there is a subgroup of patients who could have a fulminant onset of COVID-19, characterised by incident organ dysfunction as early as symptom onset, which implies that these patients already have an adverse outcome at the time of hospitalisation and that the disease course is stormy and does not conform to a predictable pattern of progression. In the existing literature, the term 'fulminant' COVID-19 has been used to refer to life-threatening forms of organ involvement such as myocarditis,[4] hepatitis[5] and AKI[6] and does not specifically connote rapid onset of organ dysfunction.

We define fulminant onset COVID-19 as rapid onset of organ dysfunction such as acute respiratory failure, AKI, acute encephalopathy or shock within 4 days of symptom onset. Fulminant onset COVID-19 is yet to be systematically studied.

We hypothesise that fulminant onset COVID-19 portends worse outcomes such as mortality and need for organ support compared with non-fulminant onset COVID-19. Identifying predictors of fulminant onset COVID-19 therefore could have prognostic implications. Taking cognizance of an individual's predilection to fulminant onset COVID-19 might aid in triaging of infected patients

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WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Fulminant onset COVID-19 is yet to be studied systematically.

WHAT THIS STUDY ADDS
⇒ Fulminant onset COVID-19 is characterised by rapid onset of organ dysfunction within 4 days of symptom onset.
⇒ About a third of a cohort of 2016 patients presented with fulminant onset COVID-19.
⇒ This study has identified predictors of fulminant onset COVID-19 and observes that vaccination lowers the odds of fulminant onset COVID-19.
⇒ Fulminant onset COVID-19 portends poor prognosis such as mortality and need for organ support.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Suspects of COVID-19, who have risk factors for fulminant onset should be advocated for early testing and hospitalisation and deterred from home isolation.

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who present very early in the course of illness (like the first or second day of illness). Suspects of COVID-19, who have risk factors for fulminant onset COVID-19 must be encouraged to undergo early laboratory testing and hospitalisation and deterred from home isolation.

OBJECTIVES
Our objectives were
1. To find out the proportion of hospitalised patients who had fulminant onset COVID-19.
2. To identify predictors of fulminant onset COVID-19 and assess whether vaccination against COVID-19 could reduce the incidence of fulminant onset COVID-19.
3. To compare the prognosis of fulminant onset with non-fulminant onset COVID-19, in terms of mortality and requirement for organ support.

MATERIALS AND METHODS
Study design, setting and participants
This retrospective study was done by analysing the health records of symptomatic patients admitted to a single referral hospital located in a Southern Province of India from June 2020 to January 2022. Based on the distribution pattern of cases, we arbitrarily divided the study period into three waves. The first wave lasted from June 2020 to March 2021, the second wave lasted from April 2021 to November 2021 and the third wave lasted from December 2021 onwards till January 2022. During the second wave, by May 2021, the nation witnessed a surge of cases due to the B.1.617—delta variant, which was declared as 'variant of concern' by the WHO[7] and during the third wave, by January 2022, there was rampant transmission of the B.1.1.529—Omicron variant.[8]

Our hospital has been a government-authorised tertiary care centre for management of patients infected with COVID-19. Adult patients who were 18 years or older and confirmed to have

COVID-19 infection by reverse transcriptase (RT)-PCR of nasal or oral pharyngeal swab and admitted to our hospital between June 2020 and January 2022 were included in this study. At the time of initial hospitalisation, demographic data, symptom duration, comorbidities such as diabetes mellitus, hypertension, chronic kidney disease (CKD), clinical parameters such as blood pressure, resting oxygen saturation while breathing ambient air, level of consciousness, urine output and laboratory parameters such as haemogram, blood sugar, glycated haemoglobin (HbA1C), urinalysis, renal and liver function tests and inflammatory markers were recorded. The date of onset of symptom was precisely recorded in each case record, which facilitated precise identification of first day of illness. The flow diagram in figure 1 reveals the scheme of participant inclusion and analysis plan.

Diagnosis of fulminant onset COVID-19 in the cohort
Rapid onset of organ dysfunction within 4 days of symptom onset defines fulminant onset COVID-19. Any symptom that was of recent onset and compatible with COVID-19 infection such as fever, cough, sore throat, dysgeusia, unusual fatigue or myalgia, dyspnoea, acute diarrhoea was counted for identifying the first day of illness.

Any patient who had rapid onset of any one or combination of hypoxia, shock, encephalopathy or AKI within 4 days of symptom onset was diagnosed to have fulminant onset COVID-19. Hypoxia was defined as resting oxygen saturation of 94% or lesser while breathing ambient air. Onset of shock of any cause—cardiogenic from fulminant myocarditis, obstructive from pulmonary thromboembolism or distributive from cytokine storm within 4 days of symptom onset led to a diagnosis of fulminant onset COVID-19. Onset of encephalopathy that could be the result of metabolic derangement such as hyponatremia, hepatic failure, or viral encephalitis[9] within 4 days of symptom onset was included as another defining feature of fulminant onset COVID-19. Diagnosis of AKI was based on Kidney Disease:
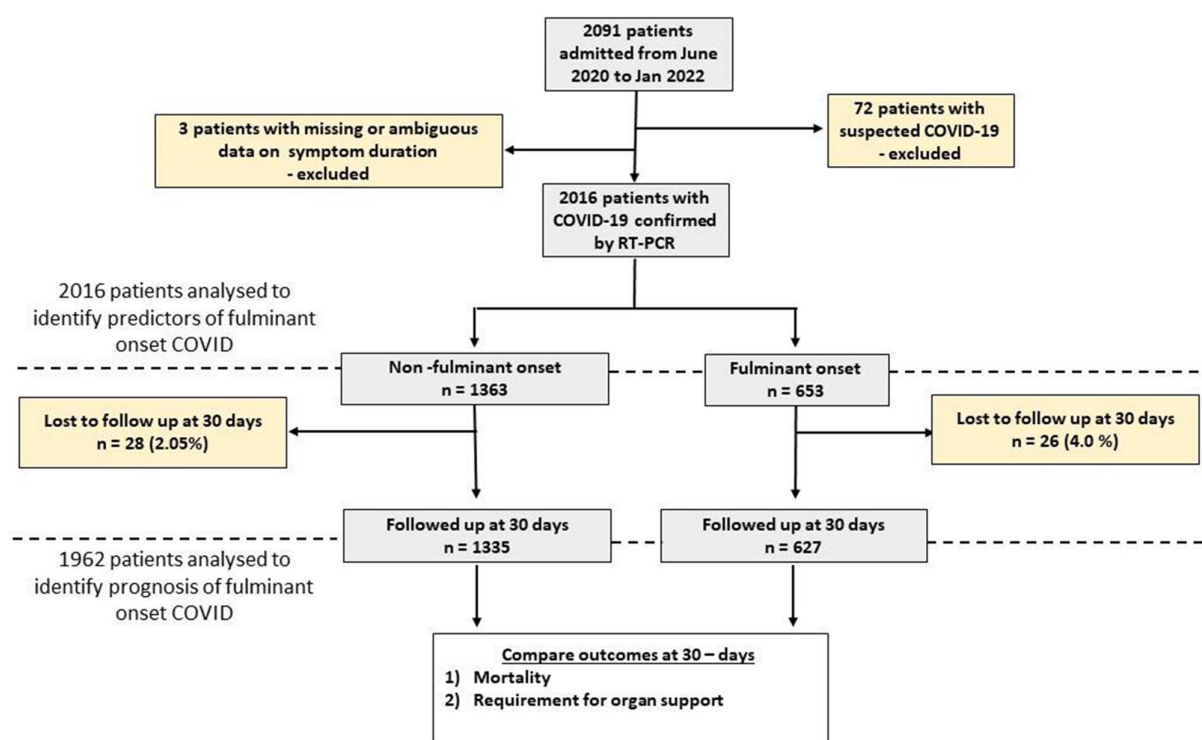
Figure 1 Flow diagram of participant inclusion and analysis plan. RT-PCR, reverse transcriptase polymerase chain reaction.

Improving Global Outcome (KDIGO) criteria[10] and AKI stage-1 or higher was included.

Candidate predictors of fulminant onset COVID-19

Candidate clinical predictors were chosen by an intuitive approach since, as yet no predictors have been established for fulminant onset COVID-19. Age, sex, diabetes mellitus, hypertension, CKD, chronic dialysis, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), bronchial asthma, chronic smoking, immunosuppression and vaccination status were analysed as candidate predictors. Obesity, though appealing as a potential predictor of fulminant onset COVID-19 could not be included in our analysis since body mass index could not be assessed in patients with fulminant onset COVID-19, a majority of whom were non-ambulant. To evaluate whether fulminant onset COVID-19 is a hyperinflammatory state than non-fulminant onset COVID-19, we compared C reactive protein (CRP) and D-dimer at the time of initial hospitalisation between the two groups.

Diabetes mellitus was diagnosed based on self-reported history of diabetes mellitus or antidiabetic medication intake or if the HbA1C was ≥6.5%.[11] Chronic hypertension was diagnosed if the patient reported prior diagnosis of hypertension or intake of antihypertensive drugs. KDIGO definition was used to diagnose CKD.[12] Chronic smoking was defined as at least 5-pack-years of smoking. Participants who had prior myocardial infarction, coronary angioplasty, coronary artery bypass grafting or ischaemic response in provocative testing were ascertained to have CAD. Global initiative for chronic obstructive lung disease 2018 report was used to define COPD.[13] Intake of prednisolone≥10 mg/day has been found to increase the odds of hospitalisation in patients who have underlying rheumatic disease in observational research.[14] Ongoing intake of prednisolone≥10 mg/day or equivalent dose of another steroid for at least 4 weeks or intake of immunosuppressant medications such as calcineurin inhibitors, antimetabolites such as mycophenolate mofetil in the setting of organ transplantation or autoimmune disorder was considered to constitute immune-suppressed state. AIDS due to HIV was regarded as immune-suppressed state.

Two COVID-19 vaccines have been in use in India since 16 January 2021, namely Covishield and Covaxin. Covishield is a recombinant ChAdOx1 nCoV-19 Corona virus vaccine manufactured by Serum Institute of India, Private limited[15], and Covaxin is an indigenously developed whole virion inactivated vaccine—BBV152 manufactured by Bharat Biotech in collaboration with Indian Council of Medical Research.[16] Two doses of either vaccine administered at least 28 days apart are recommended for effective protection. Vaccination status was considered as 'complete' if at least 14 days had lapsed after the second dose of either vaccine and as 'partial' if the individual had received only one dose of either vaccine and crossed 14 days or if less than 14 days had lapsed after the second dose. Any patient who had not received at least one dose of COVID-19 vaccine or had not crossed 14 days after the first dose was considered 'unvaccinated'.

Outcomes

Follow-up at 30 days was recorded. Mortality, ARDS, requirement for organ support and pulmonary thromboembolism by day 30 were the outcomes compared between fulminant onset and non-fulminant onset COVID-19.

The international guidelines for certification and classification of COVID-19 as a cause of death proposed by the WHO[17] was adapted for diagnosis of COVID-19 death. Any individual who had confirmed COVID-19 infection and died due to a compatible illness was diagnosed with COVID-19 death if the death was not attributable to an unrelated event such as polytrauma and if there was no complete recovery between the initial COVID-19 illness and death.

ARDS was diagnosed according to Berlin criteria.[18] ARDS that developed at least 12 hours after hospitalisation was ascertained as outcome while ARDS at initial hospitalisation was excluded. ARDS due to COVID-19 pneumonia was managed sequentially with high-flow nasal oxygen, non-invasive ventilation and ultimately invasive mechanical ventilation (IMV). Hence, IMV that was initiated for ARDS that developed at least 12 hours after hospitalisation was regarded as organ support and compared as outcome between groups.

Patients with AKI were managed with sustained low-efficiency dialysis, intermittent haemodialysis, haemoperfusion or peritoneal dialysis during the pandemic and the choice of renal replacement therapy (RRT) was individualised according to patient's clinical condition by the treating physician. Any form of RRT constituted organ support. Diagnosis of pulmonary thromboembolism was based on definitive identification of thrombus in the pulmonary vasculature by CT angiography.

Statistical methods

Continuous variables were summarised as mean and SD, median and IQR and range. Binary and ordinal data were summarised as proportions. For comparing characteristics between the two groups—fulminant vs non-fulminant onset COVID-19—we used Pearson χ^2 test for proportions, Wilcoxon rank-sum test for medians and t-test for means. Loss to follow-up was anticipated and missing data were dealt with by complete case analysis.

For identifying predictors of fulminant onset COVID-19, candidate predictors such as age, sex, diabetes mellitus, hypertension, CKD, dialysis, CAD, immunosuppressed state, COPD, chronic smoking, asthma and vaccination status were initially tested for their association with fulminant onset COVID-19 using univariate logistic regression and crude OR (c-OR) for each candidate predictor was obtained. If the p value obtained with univariate logistic regression was <0.20, then the candidate predictor was incorporated into a multivariable logistic regression model by a forward selection approach and its association with fulminant onset COVID-19 was measured as adjusted OR (a-OR). Interactions among different predictor variables were tested by adding interaction terms in the regression model. The discrimination and calibration of the multivariable model were interrogated using area under receiver

Table 1 Distribution of COVID-19 cases from June 2020 to January 2022

COVID-19 wave during pandemic	Non-fulminant onset COVID-19 n=1363	Fulminant onset COVID-19 n=653	Total n=2016
June 2020 to March 2021 (wave 1)	638 (46.8%)	343 (52.5%)	981 (48.7%)
April 2021 to November 2021 (wave 2)	660 (48.4%)	281 (43.0%)	941 (46.7%)
December 2021 to January 2022 (wave 3)	65 (4.7%)	29 (4.4%)	94 (4.6%)

Table 2 Baseline characteristics of the COVID-19 cohort according to mode of onset (fulminant vs non-fulminant onset)

Parameter	Total n=2016	Fulminant onset n=653	Non-fulminant onset n=1363	P value for difference
Categorical variables				
Age<50 years	532 (26.4%)	132 (20.2%)	400 (29.3%)	
Age 50–60 years	483 (23.9%)	147 (22.5%)	336 (24.7%)	
Age 60–70 years	550 (27.3%)	186 (28.5%)	364 (26.7%)	<0.001
Age 70–80 years	324 (16.1%)	124 (19.0%)	200 (14.7%)	
Age>80 years	127 (6.3%)	64 (9.8%)	63 (4.6%)	
Male	1376 (68.2%)	460 (70.4%)	916 (67.2%)	0.14
Chronic smoking	23 (1.1%)	5 (0.7%)	18 (1.3%)	0.37
Diabetes mellitus	1044 (51.8%)	370 (56.6%)	674 (49.4%)	0.002
Hypertension	818 (40.6%)	312 (47.8%)	506 (37.1%)	<0.001
CKD	82 (4.1%)	43 (6.6%)	39 (2.8%)	<0.001
Chronic dialysis	27 (1.3%)	12 (1.8%)	15 (1.1%)	0.18
CAD	268 (13.3%)	109 (16.7%)	159 (11.7%)	0.002
Bronchial asthma	74 (3.7%)	25 (3.8%)	49 (3.6%)	0.80
COPD	17 (0.8%)	9 (1.4%)	8 (0.6%)	0.07
Immuno-suppressed	15 (0.7%)	10 (1.5%)	5 (0.4%)	0.004
Vaccination status				
Unvaccinated	1400 (69.4%)	480 (73.5%)	920 (67.5%)	
Partial	135 (6.7%%)	34 (5.2%)	101 (7.4%)	0.01
Complete (two doses)	205 (10.2%)	54 (8.2%)	151 (11.1%)	
Vaccination status missing	276 (13.7%)	85 (13.0%)	191 (14.0%)	0.54
Vaccine type				
Covaxin (partial or complete)	81 (4.0%)	16 (2.4%)	65 (4.8%)	
Covishield (partial or complete)	207 (10.3%)	57 (8.7%)	150 (11.0%)	0.007
Vaccine type missing	331 (16.4%)	104 (15.9%)	227 (16.7%)	0.65
Manifestations at hospitalisation				
Hypoxia (SaO$_2$≤94) at admission	909 (45.1%)	538 (82.4%)	371 (27.2%)	<0.001
ARDS at admission	96 (4.8%)	67 (10.3%)	29 (2.1%)	<0.001
Invasive mechanical ventilation at admission	35 (1.74%)	24 (3.7%)	11 (0.8%)	<0.001
Shock at admission	22 (1.1%)	12 (1.8%)	10 (0.7%)	0.03
AKI at admission	326 (16.1%)	210 (32.1%)	116 (8.5%)	<0.001
AKI—stage 3	31 (1.5%)	18 (2.7%)	13 (1.0%)	0.004
Acute encephalopathy at admission	21 (1.0%)	14 (2.1%)	8 (0.6%)	0.002
Continuous variables				
Age in years mean (SD) median (IQR) range	59.2 (14.2) 60 (50–70) 18–95	62.2 (13.7) 63 (53–72) 20–93	57.8 (14.3) 59 (49–68) 18–95	<0.001
SaO$_2$ at admission mean (SD) median (IQR) range	92.2 (8.5) 95 (91–97) 30–100	87.8 (10.7) 92 (85–94) 30–100	94.3 (6.3) 96 (94–98) 40–100	<0.001
D-dimer ng/mL mean (SD) median (IQR) range	880.5 (1854.3) 300 (100–700) 9.6–16100	1182.8 (2302.5) 400 (140–900) 50–16100	736.3 (1577.6) 240 (100–623) 9.6–14800	<0.001
CRP mg/L mean (SD) median (IQR) range	72.0 (85.7) 41 (12–104) 0.1–943	95.6 (94.1) 64 (25–139) 0.4–630	61.0 (79.2) 32 (10–88.5) 0.1–943	<0.001

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; SaO$_2$, resting oxygen saturation.

operator curve (AU-ROC) and Hosmer-Lemeshow goodness of fit test, respectively.

The two groups, fulminant versus non-fulminant onset COVID-19, were compared for the prespecified outcomes, namely mortality, ARDS, organ support and pulmonary embolism at 30 days. The association of each outcome with the mode of onset of COVID-19 (fulminant vs non-fulminant onset) was measured as c-OR using logistic regression. Statistical analysis was done using STATA V.17 statistical software package.

RESULTS

A total of 2091 adults aged 18 years or older were hospitalised with suspected COVID-19 from June 2020 to January 2022, out of whom 2019 patients were confirmed to have COVID-19 by RT-PCR. The remaining 72 patients with presumptive COVID-19 were excluded. Duration of symptoms at hospitalisation was either missing or ambiguous, thereby precluding categorisation of onset as either fulminant or non-fulminant onset

Table 3 Predictors of fulminant onset COVID-19

Candidate predictor	Univariate model		Multi-variable model	
	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age				
50–60 years	1.32 (1.00 to 1.75)	0.04	1.20 (0.88 to 1.63)	0.26
60–70 years	1.55 (1.19 to 2.02)	0.001	1.40 (1.03 to 1.90)	0.03
70–80 years	1.88 (1.40 to 2.53)	<0.001	1.77 (1.26 to 2.50)	0.001
>80 years	3.08 (2.06 to 4.60)	<0.001	2.76 (1.75 to 4.34)	<0.001
Vaccination status				
Partial	0.64 (0.43 to 1.07)	0.03	0.67 (0.45 to 1.02)	0.06
Complete	0.68 (0.49 to 0.95)	0.02	0.61 (0.43 to 0.85)	0.004
Others				
Male sex	1.16 (0.95 to 1.42)	0.14	1.10 (0.88 to 1.38)	0.39
Diabetes mellitus	1.34 (1.11 to 1.61)	0.002	1.11 (0.89 to 1.38)	0.35
Hypertension	1.55 (1.28 to 1.87)	<0.001	1.29 (1.03 to 1.61)	0.03
CKD	2.40 (1.53 to 3.73)	<0.001	1.77 (0.99 to 3.15)	0.05
Dialysis	1.68 (0.78 to 3.61)	0.18	0.54 (0.17 to 1.72)	0.30
CAD	1.52 (1.16 to 1.97)	0.002	1.25 (0.92 to 1.70)	0.15
COPD	2.37 (0.91 to 6.16)	0.08	1.70 (0.55 to 5.24)	0.36
Immuno-supressed	4.22 (1.44 to 12.41)	0.009	5.62 (1.69 to 18.71)	0.005
Chronic smoking	0.58 (0.21 to 1.56)	0.28	Excluded from multivariable model because of statistical insignificance (p>0.20 in univariate model)	
Bronchial asthma	1.07 (0.65 to 1.74)	0.80		
Vaccine type—Covaxin	0.48 (0.27 to 0.83)	0.009	Excluded from multivariable model because of collinearity with vaccination status	
Vaccine type—Covishield	0.73 (0.53 to 1.02)	0.06		

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

in three patients (figure 1). Among the remaining 2016 patients, 653 (32.4%) had fulminant onset COVID-19 and 1363 (67.6%) had non-fulminant onset. The distribution of cases during the three waves of the pandemic is given in table 1. The proportion of fulminant onset COVID-19 among the three waves were comparable (35% vs 30% vs 31%, respectively, for first, second and third waves, p=0.06).

Table 2 reveals the baseline characteristics of the entire cohort and the baseline differences between the two groups—fulminant versus non-fulminant onset. The fulminant onset group was observed to differ significantly from the non-fulminant onset group (table 2) on account of several baseline characteristics namely, higher mean age of the population (62.2±13.7 vs 57.8±14.3, p<0.001), higher burden of comorbidities such as diabetes mellitus, hypertension, CKD, CAD, COPD and immune-suppressed states. There was lower prevalence of vaccination in the fulminant onset group (8.2% complete vaccination and 5.2% partial vaccination in the fulminant onset group vs 11.1% complete vaccination and 7.4% partial vaccination in non-fulminant group, a significant difference, p=0.01). The

Figure 2 Influence of age and COVID-19 vaccination on the risk of fulminant onset COVID-19. 0 - unvaccinated, 1 - partial vaccination, 2 - complete vaccination.

vaccination status was undocumented in 13% of fulminant onset group and in 14% of non-fulminant onset group (p=0.54), implying missing data of non-differential nature. A significantly greater proportion of patients in the fulminant onset group had hypoxia, AKI, shock and encephalopathy at initial hospitalisation than non-fulminant onset, an effect that could best be regarded as the defining characteristic of fulminant onset COVID-19.

The median symptom duration at hospitalisation was 3 days (IQR 2–4 days) among fulminant onset COVID-19 while that in non-fulminant onset COVID-19 was 5 days (IQR 3–7 days). Hypoxia was the most common mode of onset of fulminant onset COVID-19 (538 of 653, 82.4%), followed by AKI (210 of 653, 32.1%), acute encephalopathy (14 of 653, 2.1%) and shock (12 of 653, 1.8%). Overall, 10.3% of the fulminant onset group had ARDS at initial hospitalisation while 2.1% of non-fulminant onset group had ARDS at initial hospitalisation (p<0.001). Among the fulminant onset group, 3.7% required mechanical ventilation within 12 hours of hospitalisation while 0.8% in the non-fulminant onset group required mechanical ventilation within 12 hours of hospitalisation (p<0.001). Overall, 2.7% in the fulminant onset group had AKI stage-3, whereas 1.0% in the non-fulminant group had stage-3 (p=0.004). None required RRT at admission or within 24 hours of hospitalisation.

For evaluating candidate predictors, univariate and multivariable logistic regression was used to measure c-OR and a-OR (table 3).

By univariate regression, age>50 years, male sex, diabetes mellitus, hypertension, CKD, CAD, COPD and immune-suppressed states were found to be significant predictors of fulminant onset COVID-19, while vaccination, either partial or complete, was found to significantly lower the odds of fulminant onset COVID-19. In the final multivariate model built by a forward selection approach, age>60 years (a-OR 1.57, 95% CI
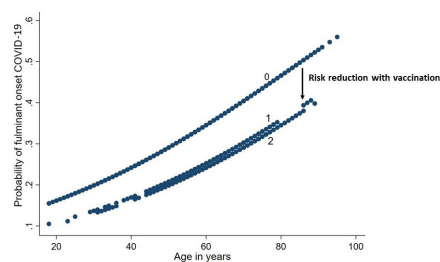
Table 4 Outcomes of COVID-19 according to mode of onset (fulminant vs non-fulminant)

After excluding loss to follow-up	Total n=1962	Fulminant onset n=627	Non-fulminant onset n=1335	P value for difference
30-day mortality risk	181 (9.2%)	108 (17.2%)	73 (5.5%)	<0.001
Pulmonary embolism	8 (0.4%)	5 (0.8%)	3 (0.2%)	0.12
RRT	34 (1.7%)	23 (3.7%)	11 (0.8%)	<0.001
After excluding loss to follow-up and ARDS at initial hospitalisation	Total n=1867	Fulminant onset n=560	Non-fulminant onset n=1307	P value for difference
ARDS after hospitalisation	116 (6.2%)	60 (10.7%)	56 (4.3%)	<0.001
Invasive mechanical ventilation after hospitalisation	74 (4.0%)	40 (7.1%)	34 (2.6%)	<0.001

ARDS, acute respiratory distress syndrome; RRT, renal replacement therapy.

1.30 to 1.90, p<0.001), hypertension (a-OR 1.29, 95% CI 1.03 to 1.61, p=0.03) and immune-suppressed state (a-OR 5.62, 95% CI 1.7 to 18.7, p=0.005) were found to be significant predictors of fulminant onset COVID-19. CKD was observed to be a predictor of fulminant onset COVID-19 almost reaching statistical significance (a-OR 1.77, 95% CI 0.99 to 3.15, p=0.05) After adjusting for other covariates, complete vaccination status was found to lower the odds of fulminant COVID-19 significantly (a-OR 0.61, 95% CI 0.43 to 0.85, p=0.004) and partial vaccination also lowered the odds of fulminant onset COVID-19, but insignificantly (a-OR 0.67, 95% CI 0.45 to 1.02, p=0.06). There was no statistically significant interaction between predictor variables namely age, sex, diabetes mellitus, hypertension and COPD. The discrimination of the final multivariable regression model incorporating these predictors was 62.55% (AU-ROC 0.6255, 95% CI 0.5978 to 0.6531). The Hosmer-Lemeshow goodness of fit test indicated a good fit (p=0.79).

The influence of age and vaccination status on the risk of fulminant onset COVID-19 was evaluated in a bivariate regression model and the result is depicted in figure 2. It could be observed that the increasing risk of fulminant onset COVID-19 associated with advancing age tends to be annulled by vaccination against COVID-19.

CRP and D-dimer at initial hospitalisation were evaluated for their association with fulminant onset COVID-19. Patients with fulminant onset COVID-19 had significantly higher median levels of CRP (64 mg/L vs 32 mg/L, p<0.001) and D-dimer (400 ng/mL vs 240 ng/mL, p<0.001) than non-fulminant onset COVID-19 (table 2). A 100 ng/mL higher D-dimer at initial hospitalisation was associated with a c-OR of 1.012 (95% CI 1.006 to 1.017, p<0.001) and a 10 mg/L higher CRP was associated with a c-OR of 1.05 (95% CI 1.03 to 1.06, p<0.001) for fulminant onset COVID-19.

The difference in the outcome of two groups, fulminant versus non-fulminant onset is shown in table 4.

Table 5 Outcomes of fulminant onset COVID-19—univariate association.

Outcome	Crude OR (95% CI)	P value
30-day mortality	3.60 (2.63 to 4.92)	<0.001
ARDS after hospitalisation	2.68 (1.84 to 3.91)	<0.001
Pulmonary embolism	3.57 (0.85 to 14.98)	0.08
Organ support		
Invasive mechanical ventilation after hospitalisation	2.88 (1.80 to 4.60)	<0.001
RRT	4.58 (2.22 to 9.46)	<0.001

ARDS, acute respiratory distress syndrome; RRT, renal replacement therapy.

It could be observed that, during a follow-up period of 30 days, mortality was significantly higher in fulminant onset group (17.2% vs 5.5%, p<0.001). A significantly greater proportion of patients in the fulminant onset group had other adverse outcomes namely ARDS (10.7% vs 4.3%, p<0.001), requirement for organ support such as IMV (7.1% vs 2.6%, p<0.001) and RRT (3.7% vs 0.8%, p<0.001). The incidence of angiogram proven pulmonary thromboembolism was higher in the fulminant group, but did not reach statistical significance (0.8% vs 0.2%, p=0.12)

In table 5, the c-OR for different outcomes of fulminant onset COVID-19 at 30 days is reported. The fulminant onset COVID-19 group had a c-OR of 3.60 (95% CI 2.63 to 4.92, p<0.001) for mortality, 2.68 (95% CI 1.84 to 3.91, p<0.001) for ARDS, 2.88 (95% CI 1.80 to 4.60, p<0.001) for IMV, 4.58 (95% CI 2.22 to 9.46, p<0.001) for RRT. The c-OR for pulmonary thromboembolism was 3.57 (95% CI 0.85 to 14.98, p=0.08).

DISCUSSION

This study is from a single referral centre and has recognised fulminant onset COVID-19 as a distinct clinical entity and has systematically studied the same. Although retrospective, the longitudinal nature of the study design paved way for identifying both predictors and outcomes of fulminant onset COVID-19 simultaneously. Precise documentation of the exact date of onset of symptoms in the case records facilitated categorisation into two groups—fulminant and non-fulminant onset.

In this cohort of 2016 patients, nearly one-third had fulminant onset COVID-19 and this assumes significance from a public health perspective while recommending home isolation and triage of patients infected with COVID-19 during the early clinical course. Suspects of COVID-19 infection, who have predilection for fulminant onset, shall be recommended for early testing and hospitalisation and deterred from home isolation.

In this cohort, the most common mode of presentation of fulminant onset COVID-19 was hypoxic respiratory failure, which could be due to rapidly progressive pneumonia or ARDS, followed by AKI. The rapid onset of organ dysfunction in these individuals calls for early case detection and implementation of strategies for organ protection such as early antiviral therapy.[19]

While vaccination against COVID-19 is known to reduce the risk of acquiring infection, spreading the infection, progression to severe forms of illness and death,[20 21] this study adds a new dimension to the protective benefits of COVID-19 vaccination. COVID-19 vaccination could have the potential to favourably modulate onset of COVID-19 in the context of breakthrough infection.

Fulminant onset COVID-19 might be due to host susceptibility factors or viral virulence factors or might simply be the result of a long latent infection in the upper respiratory tract that suddenly transitions to an invasive phase producing organ dysfunction. This study has identified predictors of fulminant onset COVID-19 by multivariable logistic regression. The best AU-ROC obtained was a modest 62.55% implying poor discrimination. While the study has identified a few clinical predictors for fulminant onset COVID-19, the modest AU-ROC indicates exclusion of relevant predictors from the model. Fulminant infection in any host may be conceptualised to result from interplay of susceptibility factors in the host and virulence factors in the infectious agent. This implies that there is scope for exploring more host susceptibility factors such as obesity, genetic polymorphisms, immune response determinants. As much as host susceptibility factors, viral virulence factors could have equally contributed to fulminant onset COVID-19. There was no information on the exact viral variant in patients who had fulminant versus non-fulminant onset COVID-19. However, fulminant onset COVID-19 was not confined to any specific wave and the proportion of fulminant onset COVID-19 during the three waves was comparable (table 1) indicating definitive role of host susceptibility factors in the pathogenesis of fulminant onset COVID-19.

The upregulated repertoire of inflammatory markers such as d-dimer and CRP in patients with fulminant onset COVID-19 in this cohort corroborates the hyperinflammatory nature of fulminant onset COVID-19. Exuberant inflammation triggered by infection of monocytes and macrophages has been found to contribute to the pathogenesis of severe COVID-19.[22]

Several prediction models for mortality in COVID-19 exist[23 24] and they have established a multitude of predictors of mortality. However, none of the models have included the rapidity of disease onset as a prognostic marker. In this study, fulminant onset of COVID-19 has been found to portend adverse outcomes such as mortality and need for organ support. Hence, inclusion of fulminant mode of onset into prognostic prediction models may help to stratify a given patient's risk of adverse outcome as early as initial hospitalisation.

While the sample size and modest loss to follow-up at 30 days add strength to this study, the issues of differential loss to follow-up and missing data might rise concerns regarding internal validity of the study. Subjects were lost to follow-up since they left against medical advice or did not return for follow-up. While 2% (n=28) of the non-fulminant onset group were lost to follow-up at 30 days, a higher proportion, that is, 4% (n=26) of the fulminant onset group were lost to follow-up, denoting a significant difference (p=0.01) and informative censoring. The missing information with regard to vaccination status in 13.7% of the whole cohort was found to be a random or non-differential phenomenon with similar proportion of either group having such missing information. Missing data were due to documentation error attributable to lack of specific templates in the case sheets for entering vaccination details when vaccination programme was initially rolled out.

CONCLUSION

Fulminant onset COVID-19 is not uncommon, with approximately one-third of this cohort presenting as fulminant onset COVID-19. After controlling for other covariates, age>60 years, hypertension, CKD and immune-suppressed states were found to be relevant predictors of fulminant onset COVID-19, while complete vaccination was associated with a significantly lower odds of fulminant onset COVID-19. Fulminant onset COVID-19 was associated with worse clinical outcomes such as mortality, ARDS and need for organ support than non-fulminant onset COVID-19.

Fulminant onset COVID-19 therefore deserves recognition as a distinct clinical phenotype and further research exploring more clinical, immunological and genetic determinants of fulminant onset COVID-19 is warranted to unravel its pathogenesis.

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