ORIGINAL ARTICLE

Relationship between Duration of Symptom Onset and Hospital Admission with other Variables Among COVID-19 Patients

Yoganathan Chidambaram, Sujith Kumar S, Saravanan T, *Merlin Veronika

Abstract

Background: Recent infections caused by Coronavirus disease 2019 (COVID-19) have been reported worldwide, which makes complete understanding of the associated factors essential. **Objectives:** To assess the relationship between duration between symptom onset and hospital admission (SOT) with inflammatory markers, oxygen requirement, duration of hospital stay, and outcome among COVID-19 patients. **Methods:** A retrospective observational study was conducted among patients admitted in a tertiary healthcare center located in Coimbatore. Patients were selected based on the inclusion and exclusion criteria. The medical records of all the selected participants were retrieved, and data related to the demographic and clinical variables were analysed. **Results:** The distribution of participants showed that 52.41% were males and had a mean age of 55.48±19.09 years. Common symptom reported was fever (63.45%), followed by cough (58.32%), myalgia (23.79%), and breathlessness (14.93%), with the most prevalent comorbidity being diabetes (36.7%). Results also show that there were significantly increased odds of needing oxygen requirement, remdesivir and steroid treatment, and increased D-dimer levels ($p<0.05$) with increased SOT. **Conclusions:** The results of this study suggest that the duration between SOT in COVID-19 patients can influence variables such as duration of hospital stay, symptoms, comorbidities, oxygen requirement, D-dimer levels, and treatment efficacy.

Key Words

COVID-19, Symptoms, Outcomes, Association, Treatment

Introduction

At the end of 2019, Wuhan City in China recorded pneumonia cases of unknown origin which was termed as Coronavirus disease 2019 (COVID-19), also referred to as SARS-CoV-2 [1]. The World Health Organization's (WHO) update from September 2023 reported over 1,800 deaths and more than 1.4 million new COVID-19 cases globally in contrast to the previous 28 days [2].

Research has revealed multiple circulating double- and triple-mutant strains of SARS-CoV-2 in diverse locations of India, which exhibit more pathogenicity than the original strains signifying the virus's evolution [3]. The widespread immunization of a significant portion of the worldwide populace has saved more lives than any other preventative or treatment approach for any disease in history. Nevertheless, COVID-19 infections persist, resulting in hospital admissions and prolonged stays in intensive care units (ICUs) [2,4-6]. Recent variants have resulted in significant increases in cases, with a notable percentage,

Department of General Medicine, PSG Institute of Medical Sciences & Research, Peelamedu, Coimbatore, Tamil Nadu. *PSG center for molecular medicine and therapeutics, PSG Institute of Medical Sciences and Research, Coimbatore, India.

Correspondence to: Yoganathan Chidambaram, Department of General Medicine, Tamil Nadu Dr MGR Medical University, Peelamedu, Coimbatore, Tamil Nadu, India.

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especially among the elderly and individuals with comorbidities, experiencing severe diseases. Multiple extrapulmonary complications, affecting the neurological, gastrointestinal, dermatological, and cardiovascular systems, can be markedly severe [7].

In combination with diabetes, cardiovascular diseases (CVDs), and Chronic obstructive pulmonary disease (COPD), SARS-CoV-2 exposure damages the lungs, heart, kidneys, and liver, causing mucus formation and inflammation [8]. The underlying issues cannot be altered in the short term, rendering the development of improved strategies to mitigate the progression of moderate COVID-19 cases to severe disease essential for controlling a new outbreak.

Helping hospitalized COVID-19 patients avoid excessive mortality by advocating early examination and admission requires understanding the association between symptom onset time and clinical outcomes. The primary objective of the present study was to assess the relationship between time of symptom onset to hospital admission with inflammatory markers, oxygen requirement, duration of hospital stay and outcome.

Material and Methods

A retrospective observational study conducted among patients diagnosed with COVID-19 admitted at a tertiary healthcare center located in Coimbatore. The study was conducted after obtaining approval from the Institutional Human Ethics Committee (PSG/IHEC/2024/Appr/Exp/073).

Participants were included in the study if the patient was above 15 years of age, diagnosed with COVID-19 using Reverse transcription polymerase chain reaction (RT-PCR) test or radiologically, and admitted to the study hospital in January 2022. Patients were excluded from the study if they were discharged against medical advice or if their medical records were missing. The medical records of all selected participants during the month of January 2022 were retrieved and scrutinized, the records of 643 patients were included in the final analysis.

Data related to demography, comorbidities, presenting symptoms, IL-6 (pg/ml) levels, D-dimer (mg/L FEU) levels, oxygen requirement, treatment details [use of remedisvir (200 mg stat on first day and 100 mg IV q 24 hours from day 2 to total of 3 to 5 days), steroids (IV methylprednisolone 1-2 mg/kg per day), anticoagulants (Low molecular weight heparin 1mg/kg q12 hourly)], number of days in hospital, and outcome (discharge or death) were collected. The D-dimer measurement method used in the study was an immunoturbidimetric assay using Innovance D dimer (Siemens), and quality control was performed using Innovance D dimer controls, which are used for the assessment of precision and analytical bias in the normal and pathological range. IL-6 was measured using Chemiluminescent Immunoassay using Elecsys IL-6 (Roche Diagnostics), and quality control was performed using Precicontrol Multimarker.

Data analysis: Data analysis was performed using R i386 3.6.3 with continuous variables presented as mean ± standard deviation/median and categorical variables presented as frequencies. Non-normal continuous data were compared using the Kruskal–Wallis test followed by pairwise Mann-Whitney U-test with Bonferroni adjustment. Categorical data were compared using the Exact Binomial/Chi square/chi square test with simulation. Statistical significance was set at $p<0.05$.

Results

The gender distribution of the study participants showed that 52.41% participants were men and the participants had a mean age of 55.48 ± 19.09 years. The distribution of subjects based on duration of symptoms differed significantly between genders ($p=0.0033$). A significant difference in median age across different levels of symptom duration was observed ($p<0.0001$), it was also found that the median age was significantly higher for subjects with a symptom onset time (SOT) of "8 & above days" followed by "3 to 7 days" ($p=0.0041$) and "2 or less than 2 days" ($p<0.0001$). (Table 1)

The predominant symptom was fever (63.45%) followed by cough (58.32%), myaliga (23.79%), breathlessness (14.93%) and sore throat (13.84%). Fever, cough, myalgia, sore throat, fatigue, pregnancy, and loss of smell, were significantly associated with SOT ($p<0.05$). (Table 2) The most prevalent comorbidity was diabetes (36.7%), followed by hypertension (33.9%), coronary artery disease (11.2%), and acute kidney injury or chronic kidney disease (5.29%). (Table 3).

Oxygen requirement was significantly associated with symptom duration ($p=0.0440$), the odds of oxygen requirement for subjects with a symptom duration of "8 and above days" were found to be 2.97 times higher than for those with "2 or less than 2 days." Similarly, median D Dimer level was found to be significantly higher for subjects with a symptom duration of "8 and above days" compared to "3 to 7 days" ($p=0.017$). Additionally, it was established that remdesivir treatment was significantly associated with symptom duration ($p=0.0006$), the odds of remdesivir treatment for subjects with a symptom duration of "3 to 7 days" were 1.96 times higher than "2 or less than 2 days."A significant association was reported between steroid treatment and

Table 1 : Characteristics of Subjects by Demographic Details

Factor		Duration of symptoms on presenting to PSG (SOT)			Grand Total	p-value
		2 or less than 2 (n=320)	3 to 7 days (n=304)	8 and above (n=19)		
Gender	Male	150 (44.51%)	172 (51.04%)	15 (4.45%)	337 (52.41%)	0.0033[CS]
	Female	170 (55.56%)	132 (43.14%)	4 (1.31%)	306 (47.59%)	
Age (in years)	Mean ± SD	52.07 ± 19.59	58.13 ± 18.11	70.42 ± 10.40	55.48 ± 19.09	<0.0001[KW]
	Median [Q1,Q3]	53[34,69]	61[46.75,72]	72 [66.50,78.50]	59 [40,71]	
	Less than or equal to 30	67 (68.37%)	31 (31.63%)	0 (0%)	98 (15.24%)	
	31-45	62 (59.62%)	42 (40.38%)	0 (0%)	104 (16.17%)	
	46-60	66 (47.14%)	70 (50%)	4 (2.86%)	140 (21.77%)	
	61-75	87 (42.23%)	110 (53.4%)	9 (4.37%)	206 (32.04%)	
	Above 75	38 (40%)	51 (53.68%)	6 (6.32%)	95 (14.77%)	

Note: [CS]: Chi square with simulation; [KW]: Kruskal Wallis test

Table 2: Distribution of Subjects by Presenting Symptoms

Factor		Duration of symptoms on presenting to PSG (SOT)			Grand Total	p-value
		2 or less than 2 (n=320)	3 to 7 days (n=304)	8 and above (n=19)		
Presenting Symptoms	Fever	187 (58.44%)	206 (67.76%)	15 (78.95%)	408 (63.45%)	0.0195[C]
	Cough	153 (47.81%)	208 (68.42%)	14 (73.68%)	375 (58.32%)	<0.0001
	Myalgia	74 (23.13%)	79 (25.99%)	0 (0%)	153 (23.79%)	0.0299[CS]
	Breathlessness	43 (13.44%)	47 (15.46%)	6 (31.58%)	96 (14.93%)	0.0805[CS]
	Sore throat	36 (11.25%)	53 (17.43%)	0 (0%)	89 (13.84%)	0.0165[CS]
	Fatigue	16 (5%)	34 (11.18%)	0 (0%)	50 (7.78%)	0.0105[CS]
	Pregnancy	44 (13.75%)	6 (1.97%)	0 (0%)	50 (7.78%)	0.0005[CS]
	Diarrhoea	16 (5%)	16 (5.26%)	1 (5.26%)	33 (5.13%)	>0.99[CS]
	Loss of Appetite	7 (2.19%)	12 (3.95%)	2 (10.53%)	21 (3.27%)	0.0780[CS]
	Loss of Smell	3 (0.94%)	13 (4.28%)	0 (0%)	16 (2.49%)	0.0260[CS]
	loss of taste	3 (0.94%)	10 (3.29%)	0 (0%)	13 (2.02%)	0.0930[CS]
	Altered mental status	6 (1.88%)	2 (0.66%)	0 (0%)	8 (1.24%)	0.4348[CS]
	Seizures	6 (1.88%)	1 (0.33%)	0 (0%)	7 (1.09%)	0.2429[CS]
	Limb weakness	3 (0.94%)	2 (0.66%)	0 (0%)	5 (0.78%)	>0.99[CS]

Note: [CS]: Chisquare with simulation

symptom duration (p=0.0003) with the odds of steroid treatment for subjects with a symptom duration of "3 to 7 days" being 1.81 times higher than "2 or less than 2 days." Moreover, the odds of steroid treatment for subjects with a symptom duration of e" "8 days and above" were 3.05 times higher than "2 or less than 2 days." (Table 4)

Discussion

The duration between symptom onset and hospital admission in COVID-19 patients is associated with various risk factors and symptoms such as age, comorbidities, oxygen requirement, D-dimer levels, and

Table 3: Distribution of Subjects by Presenting Comorbidities

Factor		Duration of symptoms on presenting to PSG (SOT)			Grand Total	p-value
		2 or less than 2 (n=320)	3 to 7 days (n=304)	8 and above (n=19)		
Co-morbidities	Chronic Liver disease	5 (1.56%)	6 (1.97%)	0 (0%)	11 (1.71%)	0.4931 [CS]
	Rheumatoid Arthritis	2 (0.62%)	1 (0.33%)	0 (0%)	3 (0.47%)	0.8243 [CS]
	Diabetes	111 (34.69%)	118 (38.82%)	7 (36.84%)	236 (36.7%)	0.5644 [C]
	Hypertension	97 (30.31%)	112 (36.84%)	9 (47.37%)	218 (33.9%)	0.1028 [C]
	Coronary artery disease	35 (10.94%)	32 (10.53%)	5 (26.32%)	72 (11.2%)	0.1004 [CS]
	Hypothyroidism	25 (7.81%)	20 (6.58%)	0 (0%)	45 (7%)	0.4468 [CS]
	AKI/ CKD	16 (5%)	18 (5.92%)	0 (0%)	34 (5.29%)	0.5512 [CS]
	Bronchial asthma	12 (3.75%)	9 (2.96%)	0 (0%)	21 (3.27%)	0.5932 [CS]
	Dyslipidaemia	7 (2.19%)	11 (3.62%)	0 (0%)	18 (2.8%)	0.3633 [CS]
	COPD	9 (2.81%)	7 (2.3%)	2 (10.53%)	18 (2.8%)	0.1259 [CS]
	Stroke	7 (2.19%)	6 (1.97%)	1 (5.26%)	14 (2.18%)	0.6257 [CS]
	Seizure disorder	3 (0.94%)	5 (1.64%)	0 (0%)	8 (1.24%)	0.6197 [CS]
	Cancer	3 (0.94%)	1 (0.33%)	0 (0%)	4 (0.62%)	0.6472 [CS]
	Renal transplant	1 (0.31%)	3 (0.99%)	0 (0%)	4 (0.62%)	0.4608 [CS]
	Liver transplant	1 (0.31%)	1 (0.33%)	0 (0%)	2 (0.31%)	>0.99 [CS]

Note: [CS]: Chisquare with simulation

treatment with remdesivir and steroids [7,8].

The gender distribution showed an almost equal number of men and women with a mean age of 55.48±19.09. The duration of symptoms differed significantly by gender, with males reporting to the hospital after longer durations (p=0.0033). There was also a significant difference in median age, as older patients exhibited longer symptom onset durations (p<0.0001). Research indicates that older patients tend to seek medical care later than younger patients, resulting in delayed hospital admissions [9,10]. Notably, patients aged 75 years and above have a shorter delay between symptom onset and hospital admission than younger individuals [11]. However, a study by Peng et al. found no association between the disease onset-admission interval and mortality or length of stay for severe-to-critical patients [12]. Moreover, the timing of hospital admission is an independent predictor of mortality in COVID-19 patients, with each additional day between symptom onset and hospital admission linked to a 1% increase in mortality risk [13].

Fever was the most common symptom reported, followed by cough, myalgia, breathlessness, and sore throat; these symptoms were significantly associated with SOT (p<0.05). A study by Dananche et al. reported that weakness, cough, ageusia, and anosmia were associated with longer delays between symptom onset and hospital admission, partly aligning with the present study's results [11]. The inflammatory response to the initial infection likely explains why fever is the most common symptom. Diabetes was the most prevalent comorbidity reported, followed by hypertension, coronary artery disease, and kidney issues; however, none were associated with SOT (p>0.05). While certain comorbidities have been linked to COVID-19 severity in other studies, they were not directly connected to delays in hospital admission [11].

A significant association existed between oxygen requirement and SOT (p=0.0440), with subjects experiencing "8 days or more" of symptoms having 2.97 times higher odds of requiring oxygen compared to those with "2 days or fewer." Previous studies indicated a median duration from symptom onset to supplemental oxygen need of 8 days, shorter in ICU patients, reinforcing current findings [14]. Additionally, another study noted median durations of 6 days in one group and 8 days in another for initial oxygen requirements based on clinical characteristics [15,16].

The median D-dimer level was significantly higher for

Table 4: Distribution of Subjects by Other Factors

Factor		Duration of symptoms on presenting to PSG (SOT)			Grand Total	p-value
		2 or less than 2 (n=320)	3 to 7 days (n=304)	8 and above (n=19)		
Hospital stay	Mean ± SD	5.28±2.91	5.71±3.32	6.16±2.73	5.51±3.11	0.0855[KW]
	Median [Q1, Q3]	5 [4,6]	5 [4,6]	5 [4,7]	5 [4,6]	
	1-3	61 (55.45%)	47 (42.73%)	2 (1.82%)	110 (17.11%)	
	4-7	221 (50%)	208 (47.06%)	13 (2.94%)	442 (68.74%)	
	8-14	33 (43.42%)	39 (51.32%)	4 (5.26%)	76 (11.82%)	
	Above 14	5 (33.33%)	10 (66.67%)	0 (0%)	15 (2.33%)	
Oxygen Requirement		43 (13.44%)	56 (18.42%)	6 (31.58%)	105 (16.33%)	0.0440[CS]
RTPCR +ve		308 (96.25%)	293 (96.38%)	17 (89.47%)	618 (96.11%)	0.3483[CS]
IL- 6	Mean ± SD	126.84±514.74	147.32±615.26	109.83±260.87	136.02±558.87	0.0998[KW]
	Median [Q1, Q3]	20.50 [8.23,60.11]	19.30 [2.27,62.11]	39.90 [27.01,83.69	20.82 [7.86,62.42]	
D Dimer	Mean ± SD	2.16 ± 4.17	1.97 ± 4.37	2.97 ± 4.81	2.09 ± 4.28	0.0112[KW]
	Median [Q1, Q3]	0.82 [0.38,1.89]	0.63 [0.38,1.29]	1.32 [0.66,3.19]	0.70 [0.39,1.65]	
Treatment	Remedisvir	199 (62.19%)	232 (76.32%)	14 (73.68%)	445 (69.21%)	0.0006[C]
	Steroid	133 (41.56%)	171 (56.25%)	13 (68.42%)	317 (49.3%)	0.0003[C]
	Anticoagulants	210 (65.63%)	205 (67.43%)	17 (89.47%)	432 (67.19%)	0.0981[C]
Outcome	Discharge	309 (96.56%)	291 (95.72%)	18 (94.74%)	618 (96.11%)	0.8891[CS]
	Death	11 (3.44%)	13 (4.28%)	1 (5.26%)	25 (3.89%)	

Note: IL-6: Interleukin-6, C: Chi-square test, KW: Kruskal Wallis test.

subjects with "8 days or more" of symptoms compared to those with "3 to 7 days" (p=0.0112). Evidence shows that D-dimer levels increase with COVID-19 severity, being higher in non-survivors than survivors. Elevated D-dimer levels correlate with increased mortality odds and serve as a prognostic marker for in-hospital outcomes [17-19].

Remdesivir treatment was significantly associated with symptom duration (p=0.0006), with odds of needing it being 1.96 times higher for those with longer symptoms. A study by Alonso-Navarro R et al. found that patients receiving remdesivir within 5 days from symptom onset had reduced ICU admission risk, highlighting the importance of timely administration for hospitalized COVID-19 patients [20]. Remdesivir has proven effective in reducing hospitalization risk for non-hospitalized patients with mild to moderate COVID-19 when given within 7 days of symptom onset for a 3-day course. It also shortens recovery time for hospitalized patients requiring supplemental oxygen [21,22].

A significant association between steroid treatment and symptom duration was observed; odds of steroid treatment were 1.81 times higher for subjects with longer symptoms. Specifically, those with "8 days or more" had odds 3.05 times higher than those with "2 days or fewer." A previous study indicated that steroid treatment beyond 3 days linked to decreased in-hospital mortality hazard showed that 72.1% of individuals received steroids and revealed a crude hospital mortality rate of 15.3% [23]. Steroid use has been effective in treating COVID-19 patients [24]. However, a systematic review suggested that using steroids in non-oxygen-requiring COVID-19 patients may increase disease progression risk and death odds, indicating that timing and patient selection for steroid treatment are critical factors [25].

The retrospective nature of the study can be considered a limitation along with no clear sample size calculated. The strengths of the study include the diverse number of variables that were tested for associations among patients from different age groups. Early

recognition of the severity of COVID-19 can lead to the difference between complete recovery and mortality, and the results of the present study can help improve the clinical management of such patients.

Conclusion

It can be ascertained that longer duration between onset and admission can result in increased need for oxygen, treatment with remdesivir or steroids as well as increased levels of D-dimer which is an indicator of COVID-19 severity. Timely intervention and understanding of these associations are vital for improving COVID-19 patient management.

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