Original Article

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Clinical predictors of long COVID-19 and phenotypes of mild COVID-19 at a tertiary care centre in India

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SUMMARY A variable proportion of patients develop persistent/prolonged symptoms of Coronavirus Disease 2019 (COVID-19) infection (long COVID). We aimed to study the clinical predictors of persistent symptoms in patients with mild COVID-19 at 30 days post discharge (long COVID-19). We also tried to identify symptom clusters among mild COVID-19 patients. Fifty-seven patients admitted at a tertiary care centre after a positive RT-PCR report over a period of 2 months, were enrolled in the study. Details of presentation, history of illness, laboratory investigations and disease outcomes were recorded from documented medical records and discharge slip. The patients were contacted (telephonically) at 30 days after discharge and enquired regarding persistent symptoms, if any. Follow up data at 30 days post-discharge was available for 53 patients. Among them, the most common persistent symptom was fatigue (22.6%), followed by cough (9.4%) and myalgias (7.5%). There was a significant association of persistent symptoms with diarrhoea at presentation [OR 14.26 (95% CI 2.30-142.47; p = 0.009] and gap between symptom onset and admission [OR 1.40 (95% CI 1.08-1.93; p = 0.020] on multivariate logistic regression analysis. On cluster analysis, three phenotypes of mild COVID-19 were identified, which may have implications on monitoring and management. There appears to be a positive association of diarrhoea as a presenting manifestation and gap between symptom onset and admission with the persistence of symptoms classified as long COVID-19, even in mild illness. We also identified multiple phenotypes of mild COVID-19 illness, which warrant further exploration.

Keywords COVID-19, long COVID, phenotypes, predictors

1. Introduction

The Coronavirus Disease 2019 (COVID-19) has caused significant global health loss, undermining economy and destabilising society (*1*). COVID-19 manifests as a broad clinical spectrum, ranging from asymptomatic illness to a flu-like illness to severe viral pneumonia, culminating in Acute Respiratory Distress Syndrome (ARDS) (*2*). The most common symptom is fever (92.0%) followed by symptoms such as cough (53.0%), shortness of breath (40.8%) and fatigue (39.9%) (*3*), with some studies claiming digestive symptoms to be present in about 50.5% patients including loss of appetite, diarrhoea, vomiting, abdominal pain, *etc.* (*1*).

Clinically, SARS-CoV-2 infection can be categorised into mild, moderate, and severe based on parameters such as respiratory rate (RR) and saturation (SpO_2). As per the clinical management guidelines by Ministry of Health & Family Welfare ,India (MoHFW) a patient with RR < 24/min and room air $SpO_2 \geq 94\%$ is categorised as mild COVID, while a RR ≥ 24/min and room air $SpO_2 < 94\%$, as moderate COVID, and RR ≥ 30/min and $SpO_2 < 90\%$ as severe COVID. The classification is simple and clinically based, easily applicable even in resource limited setting, with management being mainly observation and supportive care. Moderate and severe cases should receive oxygen supplementation along with steroids and anti-coagulation.

The most prominent laboratory abnormalities seen are lymphopenia (47.9%), decreased eosinophils (58.4%), elevated C-reactive protein (CRP) (73.6%), followed by hypoalbuminemia (62.9%), elevated erythrocyte sedimentation rate (ESR) (61.2%), increased interleukin-6 (IL-6) (53.1%), and lactate dehydrogenase (LDH) (46.2%) (*4*). Data regarding difference between laboratory parameters suggests that cases with severe

disease had higher leukocyte and neutrophil counts, lymphopenia, higher neutrophil-to-lymphocyte ratio (NLR). Inflammatory markers in the severe cases as compared to the non-severe cases demonstrated raised serum biomarkers, including procalcitonin, ferritin, CRP and IL-6 (*5*).

"Long covid" is a term used for illness in people who have either recovered from COVID-19 but still report lasting symptoms of the infection or have had the usual symptoms for a duration far longer than expected (*6*). While there are no agreed upon definitions, Greenhalgh *et al.* defined "post-acute COVID-19" as illness extending beyond 3 weeks and "chronic COVID-19", beyond 12 weeks from symptom onset (*7*). The reason for prolonged illness in some patients is largely unknown. It may be due to prolonged viremia, immune responses or mental health of the patient.

There exists a paucity of literature on long term follow up among patients with COVID 19 after discharge, especially in the mild illness subset, from a resource-limited setting, such as ours. It was our aim to follow up patients with mild COVID-19 at a tertiary care centre, for persistent symptoms at 30 days after discharge and to study clinical predictors for the same.

2. Materials and Methods

2.1. Study setting

The study was conducted in a designated COVID ward of a tertiary care centre in India. Individuals included were healthcare workers and their direct dependents who had mild symptoms. Fifty seven patients admitted after a positive reverse transcription polymerase chain reaction (RT-PCR) for severe acute respiratory coronavirus-2 (SARS-CoV2) over a period of 2 months were enrolled in the study. Details of presentation at admission, history of illness along with duration and progression, laboratory investigations and outcome of disease were recorded from documented medical records and discharge slip. Case definitions of severity were as provided by the MoHFW. The patients were contacted (telephonically) at 30 days after discharge using the details provided in medical records and enquired regarding persistent symptoms, if any. The study was approved by the Institute's ethics committee.

2.2. Tools and definitions

Long COVID-19 has been defined as symptoms of COVID-19 extending beyond 4 weeks.

2.3. Statistical analysis

Baseline characteristics of the study subjects were summarized. Shapiro-Wilk test of normality was used to assess the variable for data distribution. Continuous variables were reported as mean (± standard deviation) if they were normally distributed, otherwise reported as median (Inter Quartile Range). Categorical variables were reported as counts (percentages). To observe the difference, with assumed normality, two categories student's *t* test was performed; if otherwise, Wilcoxon-Rank sum test was used. To establish the association between categorical variables Pearson Chi square test/Fisher's exact test was used. Correlation between continuous variables was performed using Pearson's correlation or Spearman's rank correlation test (for non-normal distribution) depending upon the normality of bivariate joint distribution. Logistic regression was performed to find the risk of the standardized parameters (with penalisation, shown in **Appendix A**). Effect sizes were labelled according to Chen's (2010) recommendations. A value of $p \leq 0.05$ was considered statistically significant. The statistical analysis was done using R software version 3.5.2.

3. Results

3.1. Baseline characteristics

In this study, a total of 57 patients were enrolled. Of these, 50 (87.7%) were healthcare workers while 7 (12.3%) were their direct dependents (spouses/children). The mean age for our patients was 34.90 ± 12.09 years. The baseline characteristics were as summarised in the Table 1. The most common comorbid conditions were hypertension and hypothyroidism (10.5% each) followed by diabetes (7%), heart disease (5.3%) and respiratory disease (1.7%). Apart from these, a small minority of patients (5.3%) had arthropathies, transient ischemic attacks (TIA) and dyslipidaemia.

3.2. Clinical presentation and course

The commonest presenting symptom was fever (63.2%), followed by myalgias (50.9%), cough (49.1%), sore throat (49.1%), diarrhoea (21.1%), *etc.*, as summarised in Table 2. Two patients (3.5%) were asymptomatic at presentation and throughout hospital stay. Only 31.6% patients gave a history of contact with a confirmed COVID-19 case. 26.3% patients were working at a COVID-19 area at the time of exposure. 11 patients had taken weekly pre-exposure prophylaxis with hydroxychloroquine (HCQ) for a mean duration of 6.4 ± 1.4 weeks.

93% patients were managed as mild COVID-19 while 4 patients (7%) worsened during hospital admission and were managed as moderate illness. Two patients had to be transferred to a step-up facility with the institution. Laboratory profile of the patients was as summarised in Table 3. Distribution of laboratory parameters by disease severity has been depicted in Table 1.

Table 1. Baseline demographic characteristics and comorbidities

Characteristic	*N* (%)
Sex	
Male	30 (52.6)
Female	27 (47.4)
Co-morbidities	
Diabetes	4 (7.0)
Hypertension	6 (10.5)
Hypothyroidism	6 (10.5)
Respiratory Disease (Asthma/COPD)	1 (1.7)
Heart Disease (CAD, RHD)	3 (5.3)
Others	3 (5.3)
Symptoms at presentation	
Fever	36 (63.2)
Myalgia	29 (50.9)
Cough	28 (49.1)
Sore throat	28 (49.1)
Diarrhoea	12 (21.1)
Rhinitis	12 (21.1)
Dyspnea	9 (15.8)
Fatigue	8 (14.0)
Others	9 (15.8)
Contact History	
Contact with a confirmed COVID-19 case	18 (31.6)
Healthcare worker at a COVID-19 area	15 (26.3)
Healthcare worker at a non-COVID-19 area	26 (45.6)
Residing at or visiting a hotspot	15 (26.3)
History of Hydroxychloroquine (HCQS) prophylaxis	
Patients taking HCQS pre-exposure prophylaxis	11 (19.2)
Severity of COVID-19	
Mild	53 (93.0)
Moderate	4 (7.0)
Severe	0 (0.0)
Treatment	
HCQS	44 (77.2)
Doxycycline	20 (35.1)
Ivermectin	13 (22.8)
Outcome	
Discharged	55 (96.5)
Transferred	2 (3.5)

Table 2. Baseline laboratory profile

Laboratory Parameter	Median [IQR]
Total Leukocyte Count (per cu mm)	5875 [4887.5-6940.0]
Neutrophils (%)	52.9 [45.4-60.5]
Lymphocytes (%)	33.5 [28.5-42.7]
Neutrophil-Lymphocyte Ratio (NLR)	1.70 [1.04-1.96]
CRP (mg/dL)	0.20 [0.10-0.69]
CPK (mg/dL)	95.0 [59.0-95.0]
Procalcitonin (ng/mL)	0.02 [0.01-0.04]
Ferritin (ng/mL)	78.10 [28.30-156.40]
D dimer (ng/mL)	0.36 [0.12-0.51]
Aspartate Transaminase (AST)	25.0 [21.0-34.0]
Alanine Transaminase (ALT)	26.0 [18.8-40.5]
Alkaline Phosphatase (ALP)	195.5 [176.8-214.8]

Table 3. Laboratory profile distribution by severity of disease

Laboratory Parameter	Mild disease (*N* = 53) [Median Value]	Moderate disease (*N* = 4) [Median Value]
Ferritin	80.00	57.65
CRP	0.28	2.12
CPK	105.00	94.50
Procalcitonin	0.02	0.01
NLR	1.69	2.55

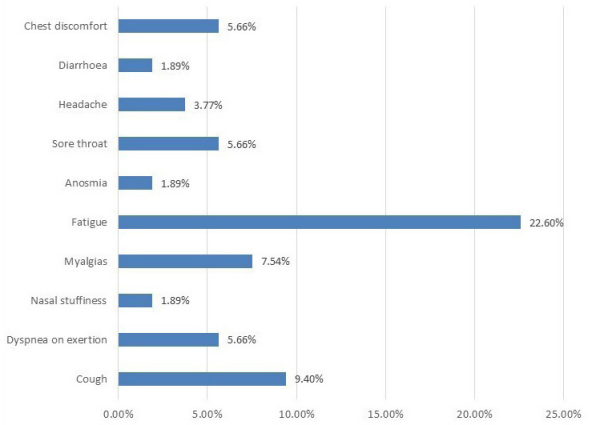

Figure 1. Persistent symptoms at 30 days (*n* = 53).

3.3. Persistent symptoms at 30-day follow up

After discharge, all patients were followed up telephonically at 30 days from date of discharge, for persistent symptoms, if any. While 2 patients could not be reached, 2 refused to participate in the study. A total of 53 patients were included in the analysis. 25 patients (47.17%) reported persistent symptoms at 30 days post discharge. The most common symptom reported was fatigue (22.60%), followed by cough (9.60%), myalgias (7.54%), chest discomfort, sore throat, dyspnea on exertion (5.66% each) and diarrhoea, anosmia, nasal stuffiness (1.89% each) (Figure 1). There was a significant association of persistent symptoms among patients who had diarrhoea at presentation [χ^2 (1, N = 53) = 6.687; p = 0.010 by chi square analysis]. There was no significant association with other symptoms at presentation or comorbidities. For multivariate logistic regression analysis, we fitted a logistic model (estimated using maximum likelihood) to predict long COVID (persistent symptoms at 30 days post discharge) with age, female gender, fever, dyspnea and diarrhoea at presentation, gap between symptom onset and admission (Figure 2). The model's explanatory power is substantial (Tjur's R^2 = 0.36). The model's intercept is at -2.83 (standard error (SE) = 1.35, 95% confidence interval (CI) [-5.77, -0.40], $p < 0.05$). Within this model, the individual components have been shown in the Table 4 given below. Therefore, diarrhoea at presentation and gap between symptom onset and admission were positively correlated with persistent symptoms at 30 days post discharge.

3.4. Symptom clusters: COVID-19 phenotypes

We performed K nearest neighbour cluster and

exploratory factor analysis. We found 3 clusters. 2 Dimensions (principal component 1 and principal component 2 explained up to 48% of variability addition of other dimensions had minimal incremental effect). Hence, this principal component analysis (PCA)-biplot was made showing effect of dimensions, component and contribution of symptom variable to various dimensions of our factor analysis. Dimension 1 and 2 denote the principal component (1 and 2 of exploratory factor analysis). Narrow angle of vector and longer vector length indicate closer association and effect size to a dimension. Colours denote clusters based on K nearest neighbour classification.

Cluster analysis revealed three possible phenotypes of mild COVID illness: Cluster 1 (diarrhoea, rhinitis, myalgias, and sore throat, majorly upper respiratory tract involvement), cluster 2 (fever and fatigue, comprising constitutional symptoms), and cluster 3 (dyspnea and cough, majorly lower respiratory tract involvement) (Figure 3). On exploratory factor analysis, most vectors follow their clusters except for rhinitis that may not be aligning with its cluster due to the small sample size in our study.

4. Discussion

Our study recruited 57 Health care workers (or their dependents) admitted with mild COVID-19 of which 53

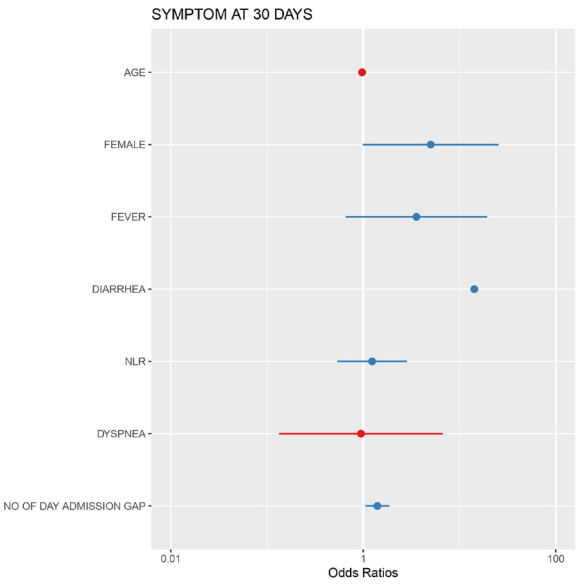

Figure 2. Forest plot for multivariate regression analysis for persistent symptoms. [Covariates: Age, sex, fever, dyspnea and diarrhea at presentation, neutrophil lymphocyte ratio and gap between symptom onset and admission; all except age and dyspnea (marked in red), showing varied association with long COVID-19].

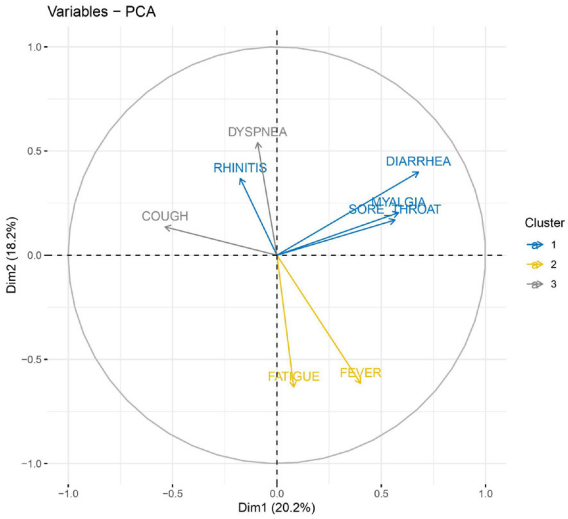

Figure 3. Symptom cluster analysis: 3 phenotypes of mild COVID-19. Narrow angle of vector and longer vector length indicate closer association and effect size to a dimension. Three phenotypic clusters identified: cluster 1 (diarrhea, rhinitis, myalgia, sore throat); cluster 2 (dyspnea and cough); cluster 3 (fever and fatigue). PCA, principal component analysis; Dim 1, Dimension 1; Dim 2, Dimension 2.

Table 4. Analysis for persistent symptoms at 30 days

Characteristic	Persistent symptoms absent ($N = 28$)	Persistent symptoms present ($N = 25$)	Odds Ratio (univariable)	Odds Ratio (multivariable)
Age (years), Mean (SD)	32.2 (12.74)	37.28 (11.37)	1.04 (0.99-1.09; $P = .139$)	0.97 (0.90-1.05; $P = .484$)
Sex				
Male (%)	18 (64.3)	10 (40.0)	2.70 (0.90-8.48; $P = .080$)	5.02 (1.07-29.63; $P = .049$)
Female (%)	10 (35.7)	15 (60.0)		
Days between symptom onset and admission, Mean (SD)	2.96 (1.89)	4.64 (3.59)	1.24 (1.01-1.58; $P = .051$)	1.40 (1.08-1.93; $P = .020$)
Neutrophil-Lymphocyte Ratio (NLR), Mean (SD)	1.6 (0.6)	2.0 (1.3)	1.54 (0.87-3.13; $P = .175$)	1.24 (0.57-3.17; $P = .614$)
Fever at admission				
Absent	13 (46.4)	8 (32.0)	1.84 (0.61-5.83; $P = .286$)	3.57 (0.72-23.07; $P = .141$)
Present	15 (53.6)	17 (68.0)		
Dyspnea at admission				
Absent	25 (89.3)	19 (76.0)	2.63 (0.61-13.76; $P = .209$)	0.95 (0.13-7.38; $P = .957$)
Present	3 (10.7)	6 (24.0)		
Diarrhoea at admission				
Absent	26 (92.9)	16 (64.0)	7.31 (1.63-52.14; $P = .018$)	14.26 (2.30-142.47; $P = .009$)
Present	2 (7.1)	9 (36.0)		

patients were included in the final analysis for persistent symptoms at 30-day follow up. The most common persistent symptom reported by far, was fatigue, followed by cough and myalgia. There was a significant association of persistent symptoms with diarrhoea at presentation, and gap between symptom onset and admission on multivariate logistic regression analysis. On cluster analysis, three phenotypes of mild COVID-19 were identified, which may have implications on monitoring and management.

Tenforde *et al.* followed up 292 COVID-19 outpatients in the US, telephonically for up to 14-21 days from symptom onset (median 16 days) (*8*). They reported the persistence of cough, fatigue and breathlessness in 43%, 35%, and 29% patients, respectively, at 14-21 days from symptom onset. These findings would suggest that post-COVID-19 is an entity with implications even in mildly affected individuals.

Carfi *et al.* followed up 143 patients admitted with COVID-19 at a hospital in Italy at 60 days after onset of first symptom, for persistent symptoms, if any (*9*). The mean age of the study participants was 56.5 ± 14.6 years and 53 patients (37%) were women. Only 18% patients were found to be asymptomatic at follow up, while 55% had at least 3 symptoms. The symptoms reported most often was fatigue (53.1%), as seen in our study. Other common symptoms were shortness of breath (43.4%), arthralgia (27.3%) and chest pain (21.7%). The overall proportion of patients with persistent symptoms was lower (47.17%) in our population, probably because we included a major proportion of mild (93.0%) and moderate (7.0%) cases, and no severe COVID cases. On the contrary, Carfi *et al.* recruited 21 patients (15.0%) who had been on non-invasive ventilation and 5 patients (7.0%) who had been on invasive ventilation during hospital stay, which may explain the higher prevalence of persistent symptoms. Around 44.1% participants reported a worsened quality of life at follow up, as per the EuroQoL questionnaire.

There is a paucity of data on predictors of persistent symptoms in COVID-19 infection. Chen *et al.* reported significant impairment in physical and psychological health among 361 COVID-19 patients at one-month post discharge, using the HRQoL questionnaire (*10*). It was seen that the more severe the condition of patients, the worse the impact on physical, emotional as well as mental health. There was a significant association between higher body-mass index (BMI) and poorer physical health outcomes.

Our study revealed a possible association of persistent symptoms with diarrhoea at presentation. A retrospective single-centre analysis by Wei *et al.* reported longer duration of illness (fever and dyspnea) among patients presenting with diarrhoea than those without (10.5 ± 4.7 days *vs.* 7.6 ± 3.4 days, $p < 0.005$; 8.1 ± 3.2 days *vs.* 4.7 ± 2.3 days, $p < 0.002$, respectively) (*11*). The hospital stay duration was longer in diarrhoea group than in non-diarrhoea group (16.5 ± 5.2 days *vs.* 11.8 ± 5.6 days; $p < 0.001$). It was also seen that patients with diarrhoea were more likely to complain of headache, myalgia or fatigue, cough, nausea and vomiting than those without diarrhoea.

Shang *et al.* retrospectively studied the implications of diarrhoea among 564 hospitalised COVID-19 patients in China (*12*). They categorised the 157 diarrhoea patients among two groups: 38 patients with diarrhoea alone (group A) and 119 with both diarrhoea and respiratory symptoms (group B). They reported worse clinical outcomes among group B patients than group A patients and group C (respiratory symptoms alone) in terms of higher levels of inflammatory activity (higher ferritin and CRP levels), longer hospital stay (27.5 *vs.* 23.0 *vs.* 22.0 days, $p < 0.029$). Group B patients also had an odds ratio of mortality of 3.2 compared to group A patients. This was attributed to possible higher viral loads and in turn, a stronger inflammatory response in patients with both respiratory and gastrointestinal involvement, though the exact mechanism is not known. Group A patients had a longer time from onset of symptoms to admission (14.5 *vs.* 11.0 days, $p < 0.04$) but an overall milder illness.

As per the report of the WHO-China Joint Mission on COVID-19, diarrhoea is an important manifestation of COVID-19 with public health implications due to prolonged faecal shedding of the virus, creating a potential for faecal-oral transmission (though not proven to be significant so far). It has been shown that angiotensin-converting enzyme-2 (ACE 2) receptors are present not only in the lung, but also in the gastrointestinal tract (stratified cells of the oesophagus and enterocytes in the ileum and colon) (*13*). SARS-CoV2 may directly damage the epithelial barrier leading to diarrhoea, and mucosal inflammation and cytokine release. This may even promote translocation of pathogens. Moreover, intestinal mucosal barrier injury could affect the mucosal immune response of the lung, thereby, worsening the pneumonia and may give rise to a cytokine storm through the 'gut-lung axis' (*14*).

Therefore, our study brings forth certain important observations. It is important to consider gastrointestinal symptoms as an important presentation of COVID-19. As demonstrated in our cluster analysis, these symptoms may occur in the absence of typical symptoms of fever or cough. Therefore, a high suspicion for COVID-19 is paramount in patients with diarrhoea. This is highlighted by the fact that diarrhoea at presentation may portend worse clinical outcomes in the form of prolonged symptoms, such as fatigue, myalgias, chest discomfort, *etc.* This is an outcome with important implications and should prompt further research into the matter. It is also of concern to note that patients with a longer gap between symptom onset and admission are more likely to complain of persistent symptoms at follow up. Therefore, it is important to recognise symptoms of

COVID-19 (respiratory and gastrointestinal), especially in mild illness, so that patients are brought to medical attention at the earliest. Prolonged duration of symptoms also indicates a need for "post-COVID" rehabilitation services (yoga, meditation, breathing exercises, adequate nutrition, *etc.*) (*7*) to ensure speedy return to usual state of health. We also identified specific phenotypic clusters which could possibly lead us to further observation in large population and then developing as a tool for prognosis.

There are certain limitations to our study. Firstly, the sample size was small and definite conclusions about predictors of clinical outcomes could not be formed. Secondly, most patients had mild COVID-19 illness, which may introduce a bias in our findings.

5. Conclusion

It can be concluded that there may be a positive association of diarrhoea as a presenting manifestation and gap between symptom onset and admission with the persistence of symptoms classified as long COVID, even in mild illness. There also appear to be multiple phenotypes of mild COVID-19 illness, which warrant further exploration.

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Appendix A

Logistic regression showing the risk of the standardized parameters

Items	Coefficient	S.E.	Wald Z	Pr (> | Z |)
Intercept	-2.1520	1.1038	-1.95	0.0512
AGE	-0.0045	0.0280	-0.16	0.8733
Female = 1	0.8461	0.5628	1.50	0.1327
Fever = 1	0.5983	0.5754	1.04	0.2984
Diarrhoea = 1	1.3170	0.6272	2.10	0.0358
NLR	0.2509	0.3209	0.78	0.4342
Dyspnea = 1	0.1133	0.6587	0.17	0.8634
Number of days between admission & symptom onset	0.2144	0.1075	1.99	0.0462