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Original Article

Internal Medicine Section

Predictors of Length of Hospital Stay in Patients with COVID-19: A Retrospective Study

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ABSTRACT

Introduction: Known independent predictors of extended Length Of Stay (LOS) in Coronavirus Disease 2019 (COVID-19) included older age, chronic kidney disease, elevated maximum temperature, and low minimum oxygen saturation. Additional known predictors of prolonged hospitalisation included male sex, chronic obstructive pulmonary disease, hypertension, and diabetes. Elevated levels of C-Reactive Protein (CRP), creatinine, and ferritin are proven determinants of hospitalisation and LOS. Determining predictors of LOS will aid in triaging and management of COVID-19 patients.

Aim: To assess the clinical, biochemical and radiological profile of admitted COVID-19 patients and determine the predictors of prolonged length of stay at hospital.

Materials and Methods: It was a retrospective, cross-sectional observational, record-based study included hospital records of 544 confirmed COVID-19 patients, above age of 18 years admitted at Bharati Vidyapeeth Medical College and Hospital, Pune, Maharashtra, India, during February 2021 to June 2021. Possible determinants of LOS were studied including their demographic, epidemiological, clinical and radiological characteristics. The patients were divided into two groups as per median LOS i.e, group I with LOS <10 days (n=277) and group II with LOS ≥10 days (n=267). Statistical analysis was done using Chi-square test, proportion test, Z test, Mann-Whitney U test, regression analysis by Statistical Package for the Social Sciences (SPSS) software version 23.0.

Results: Mean age in group I and II was 47.83±16.34 years and 53.21±15.63 years (p-value <0.0001), respectively. The fatigue was significantly more in group II than group I (p-value=0.018). Diabetes mellitus was more (p-value=0.026) and severity of illness (p-value <0.0001) was significantly higher in group II than group I. In univariate analysis, mean Neutrophil/Lymphocyte ratio (p-value <0.0001), serum LDH (p-value <0.018), blood urea level (p-value <0.0001), random blood sugar (p-value=0.003), glycated haemoglobin (HbA1c) (p-value=0.072) and serum creatinine (p-value=0.41) were significantly more in group II. Median CRP (p-value <0.0001), D-dimer (p-value <0.0001), serum ferritin (p-value <0.0001), procalcitonin (p-value <0.0001), Serum Glutamic Oxaloacetic Transaminase (SGOT) (p-value=0.002) was significantly higher in group II. Lung involvement {chest radiograph or High-Resolution Computed Tomography (HRCT) chest} was significantly (p-value <0.0001) more in group II.

Conclusion: Fatigue, older age, diabetes mellitus, severity of illness, mean neutrophil/lymphocyte ratio, CRP, D-dimer, serum ferritin, serum Lactate Dehydrogenase (LDH), procalcitonin, blood urea, SGOT were associated with prolonged LOS among hospitalised COVID-19 patients.

Keywords: Coronavirus disease 2019, C-reactive protein, Diabetes, D-dimer, Fatigue

INTRODUCTION

During Coronavirus Disease 2019 (COVID-19) pandemic healthcare almost collapsed in developed as well as developing countries. A large number medical and paramedical staff, along with a huge number of hospital beds were required to treat confirmed COVID-19 cases. This led to overburdening and exhaustion of healthcare systems all over world.

Advanced age [1], male sex, fever, chronic kidney disease or liver disease before admission and increasing creatinine levels are some of the known factors for prolonged Length Of Stay (LOS) [2]. Diabetes [3], raised inflammatory markers like C-Reactive Protein (CRP), D-dimer, Lactate Dehydrogenase (LDH) [1] are also some of the known factors associated with prolonged length of stay. So, it is important to know predictors of length of hospital stay in hospitalised COVID-19 cases. Determining risk factors on admission, to predict length of hospital stay, can help treating physician for triaging the patients and to monitor vulnerable patients more closely and will be helpful for manpower management also. This will consequently reduce cost, complications and mortality.

Average hospital stay for admitted COVID-19 cases varies across countries. For instance, meta-analysis on 52 studies revealed the average time of hospital stay from China was 14 days and 5 days outside of China [4]. A study from Patna, India found that presence of breathlessness at admission, co-morbidities, Chronic Obstructive Pulmonary Disease (COPD)/asthma, deranged diastolic blood pressure, and higher quick Sequential Organ Failure Assessment (qSOFA) score at admission were associated with greater duration of hospitalisation [5].

Projecting future demand requires an estimate of, length of hospital stay at different care levels required by patients with COVID-19. A study done in Greece, involving type 2 diabetic patients showed that hospitalisation was significantly prolonged in patients with glucose>180 mg/dL than those with lower levels on admission [6].

A study from Cisanello hospital of Pisa, Italy showed subjects with obesity with COVID-19 require prolonged hospitalisation [7]. A study done in Sichuan Province of China, found that patients ≥45 years old, having severe illness, living in areas with fewer healthcare workers per 1000 people and being admitted to higher grade hospital had longer LOS [8]. Another study from Hefei, China found female gender, presence of fever on admission, pre-existing Chronic Kidney Disease (CKD) or liver disease to prolong hospital stay [2]. A study from New York, showed that age, CKD, temperature, oxygen saturation, elevated levels of CRP, creatinine, and ferritin was associated with prolonged LOS [9].

India has seen 28, 173, 655 cases till 31st May 2021. Among Indian patients highest number of cases during second COVID-19 wave were recorded in Maharashtra with a 20.3% share of all Indian cases as of 31st May 2021. In Maharashtra, the Pune city had a huge number of cases with shortage of beds. From March 2020 to 31st May 2021 Pune District was worst affected with 10, 17, 154 cases and 12, 507 fatalities [10].

There are many studies on predictors of prolonged LOS from outside India but Indian studies and data on the same are lacking, hence, this study was conducted.The aim of the present study was to study the clinical, biochemical and radiological profile of admitted COVID-19 patients and to determine the predictors of prolonged length of stay at hospital.

MATERIALS AND METHODS

The retrospective observational study was conducted at Bharati hospital and Medical College, Pune, Maharashtra. Data belonging from the period February 2021 to June 2021 was collected. The analysis and interpretation was done from March 2022 to May 2022. This study was approved by ethics committee of Bharati Vidyapeeth (deemed to be university) Medical College and Hospital (ref: BVDUMC/IEC/20B, Dt.25/04/2022).

Inclusion criteria: All patients with confirmed COVID-19 above 18 years of age admitted to COVID-19 wards.

Exclusion criteria: Patient staying in hospital for lack of facility for isolation (as mentioned in discharge records).

A total of 544 records were retrieved. Discharge and admission criteria were applied as per guidelines of Maharashtra's COVID-19 task force [11].

Admission criteria

These were as follows:

1. Age >60 years, diabetes mellitus, hypertension/ischaemic heart disease, COPD/chronic lung disease, immunocompromised state, immunosuppressive drugs, chronic kidney disease, obesity, chronic liver disease.
2. Symptomatic patients with any of the following signs (irrespective of co-morbidity)- Fever >100.4° F, respiratory rate >22/min, Systolic Blood Pressure (SBP) ≤100 mmHg, respiratory distress, cyanosis, change in mental state.

Discharge criteria

These were as follows:

1. Mild disease- No fever for three days.
2. Moderate disease- Fever resolved within three days and oxygen saturation maintained without support for consecutive three days.
3. Severe disease- Discharge only after clinical recovery, patient tested negative once by Reverse Transcription-Polymerase Chain (RT-PCR).

Categorisation of patients was done as per the following clinical staging system [11]-

1. Mild- Mild/early infection.
2. Moderate- Pulmonary involvement without hypoxia.
3. Severe- Pulmonary involvement with hypoxia with sepsis/ shock/multiorgan dysfunction syndrome.

Study Procedure

Epidemiological, demographic, clinical and laboratory data for each patient were extracted from the medical record section as per predesigned proforma. Symptoms on admission and other parameters on admission were recorded. The records during admission were checked for complete blood count, random blood sugar level, liver function test, kidney function test, C-reactive protein level, D-dimer, procalcitonin, LDH, serum ferittin, Glycated haemoglobin (HbA1c). All patients had undergone either chest radiograph or High-Resolution Computed Tomography (HRCT) chest.

There are no definite guidelines defining prolonged LOS among hospitalised COVID-19 patients. Hence, stay of more than 10 days was taken as prolonged LOS depending on the median LOS in this study, which was 10 days.

Group I: Length of stay <10 days and

Group II: LOS ≥10 days.

STATISTICAL ANALYSIS

Statistical analysis was done using Chi-square test, proportion test, Z test, Mann–Whitney U test, regression analysis by Statistical Package for Social Sciences (SPSS) software version 23.0.

RESULTS

The present study included 544 patients. The characteristics of patients are listed in [Table/Fig-1].The mean age of patients was 47.83 vs 53.21 for group I and II (p-value <0.0001), respectively. There were more males in the group II (176, 65.92%). Among all patients, the most common symptoms on admission were fever, cough and shortness of breath followed by fatigue, myalgia and sore throat. Co-morbidities were present in almost 60% of patients with hypertension (69.24%) and diabetes (64.5%) being the most common co-morbidity. Clinical symptoms on admission showed no significant association with LOS. Only patients with loss of smell had LOS ≥10 days, (p=0.05). Out of total 544 patients, 277 patients had length of stay <10 days and remaining 267 patients had LOS ≥10 days. Mean age was significantly more in the group with LOS ≥10 days. Fatigue was significantly more in LOS ≥10 days; fever, cough, shortness of breath, nausea/vomiting, sore throat, myalgia,

Parameters	Group I (n=277)	Group II (n=267)	Z-value/χ^2 value	p-value
Age (years)	47.83±16.34	53.21±15.63	3.93	<0.0001
Gender				
Male	171 (61.73%)	176 (65.92%)	1.03	0.31
Female	106 (38.27%)	91 (34.08%)		
Chief complaints				
Fever	213 (76.89%)	204 (76.40%)	0.14	0.89
Cough	209 (75.45%)	204 (76.40%)	1.27	0.21
Shortness of breath	160 (57.76%)	157 (58.80%)	0.25	0.81
Fatigue	98 (35.38%)	121 (45.32%)	2.38	0.018
Nausea/vomiting	22 (7.94%)	24 (8.99%)	0.44	0.66
Sore throat	30 (10.83%)	38 (14.23%)	1.20	0.23
Myalgia	88 (31.77%)	93 (34.83%)	0.76	0.45
Headache	8 (2.88%)	14 (5.24%)	1.39	0.16
Loss of smell	4 (1.44)	11 (4.12)	1.89	0.058
Loss of taste	14 (5.05%)	12 (4.49%)	0.31	0.76
Diarrhoea	16 (5.78%)	25 (9.36%)	1.58	0.11
Runny nose	7 (2.53%)	3 (1.12)	1.23	0.22
Haemoptysis	3 (1.08%)	5 (1.87%)	0.76	0.45
Co-morbidity				
DM	77 (27.80%)	98 (36.70%)	2.23	0.026
HTN	87 (31.41%)	101 (37.83%)	1.58	0.11
IHD	13 (4.69%)	17 (6.37%)	0.85	0.39
CKD	6 (2.17%)	11 (4.12)	1.30	0.19
BA/COPD	1 (0.36%)	6 (2.25%)	1.93	0.053
Severity of illness				
Mild	102 (36.82%)	4 (1.50%)	135.72	<0.0001
Moderate	38 (13.72%)	13 (4.87%)		
Severe	137 (49.46%)	250 (93.63%)		

[Table/Fig-1]: Demographic and clinical laboratory characteristic of COVID-19 patients according to hospital length of stay in study group.
DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischaemic heart disease; CKD: Chronic kidney disease; BA: Bronchial asthma; COPD: Chronic obstructive pulmonary disease

headache, loss of taste, diarrhea, runny nose, hemoptysis were observed almost equally in both the groups. DM and severity of illness was significantly more in LOS ≥10 days than LOS <10 days [Table/Fig-1].

In the univariable analysis, fatigue, diabetes mellitus and severity of illness were significantly associated with prolonged LOS. Loss of smell and bronchial asthma/COPD were associated with prolonged LOS but the association was not significant [Table/Fig-2].

Parameters	OR	95% CI	p-value
Gender (Male vs female)	1.20	0.84-1.70	0.31
Chief complaints			
Fever	0.96	0.64-1.43	0.83
Cough	1.05	0.71-1.56	0.79
Shortness of breath	1.04	0.74-1.47	0.81
Fatigue	1.51	1.07-2.14	0.018
Nausea/Vomiting	1.14	0.63-2.10	0.66
Sore throat	1.37	0.82-2.28	0.23
Myalgia	1.15	0.80-1.64	0.45
Headache	1.86	0.77-4.51	0.16
Loss of smell	2.93	0.92-9.33	0.057
Loss of taste	0.88	0.40-1.95	0.76
Diarrhoea	1.69	0.88-3.23	0.11
Runny nose	0.44	0.11-1.71	0.22
Haemoptysis	1.74	0.41-7.37	0.44
DM	1.51	1.05-2.16	0.026
HTN	1.33	0.93-1.89	0.12
IHD	1.38	0.66-2.90	0.39
CKD	1.94	0.71-5.32	0.19
BA/COPD	6.34	0.76-53.06	0.051
Disease severity	15.03	8.72-25.91	<0.0001

[Table/Fig-2]: Risk factors associated with prolonged hospital length of stay.
DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischemic heart disease; CKD: Chronic kidney disease; BA: Bronchial asthma; COPD: Chronic obstructive pulmonary disease

Mean N/L, WBC, LDH, BUL, serum creatinine, random blood sugar, HbA1c was significantly more in LOS ≥10 days than LOS <10 days (p-value <0.0001). Median CRP, D-dimer, serum ferritin, procalcitonin, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT) was significantly more in LOS ≥10 days than LOS <10 days. Chest X-ray or Computed Tomography (CT) findings were significantly associated with prolonged LOS [Table/Fig-3].

Parameters	Group I (Mean±SD/Median (Range)	Group II (Mean±SD/Median (Range)	Z-value (Mann-Whitney U test)	p-value
N/L	4.21±2.44	5.22±3.05	4.25	<0.0001
Haemoglobin	13.43±1.57	13.29±1.61	0.98	0.33
WBC	6465.07±2703.15	7749.62±3602.29	4.72	<0.0001
Platelets	234227.80± 84190.06	245814.23± 96794.71	1.49	0.14
CRP	25.30 (6.13-63.26)	63.40 (23-119)	6.96	<0.0001
D-dimer	252 (162-462)	461 (253-911)	7.30	<0.0001
Serum ferritin	214 (96.31-454.73)	392 (210-662)	6.17	<0.0001
LDH	482.65±222.141	634.62±328.546	6.34	<0.0001
Procalcitonin	0.04 (0.02-0.08)	0.07 (0.04-0.18)	5.98	<0.0001
BUL	26.44±15.762	31.27±20.292	3.10	0.002
Serum creatinine	0.92±0.423	1.02±0.520	2.41	0.016
RBS	151.39±67.910	169.08±73.424	2.92	0.004
HbA1c	6.42±1.484	6.74±1.712	2.38	0.018
SGOT	32 (23-45)	37 (27-54)	3.93	<0.0001
SGPT	27 (17.50-42)	32 (22-47)	3.17	0.002
Serum bilirubin	0.53 (0.32-0.80)	0.57 (0.40-0.80)	1.90	0.058
HRCT chest findings present	125 (45.13%)	133 (49.81%)	-	<0.0001
CXR findings present	72 (25.99%)	114 (42.70%)	-	<0.0001
HRCT chest/ CXR findings absent	80 (28.88%)	20 (7.49%)	-	<0.0001

[Table/Fig-3]: Laboratory and Radiological characters of COVID-19 patients according to hospital length of stay.
N/L: Neutrophil lymphocyte ratio; WBC: White blood cells; CRP: C reactive protein; LDH: Lactate dehydrogenase; BUL: Blood urea level; RBS: Random blood sugar; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; HRCT: High resolution computed tomography; CXR: Chest X-ray

In the univariate analysis, N/L ratio, CRP, D-dimer, serum ferritin, LDH, procalcitonin, BUL, random blood sugar, SGOT were significantly associated with prolonged LOS [Table/Fig-4].

Parameters	OR	95% CI	p-value
N/L	2.90	1.95-4.32	<0.0001
Haemoglobin	1.07	0.72-1.60	0.74
WBC	1.26	0.87-1.81	0.22
Platelets	1.08	0.63-1.84	0.77
CRP	4.55	2.51-8.24	<0.0001
D-dimer	2.87	1.99-4.15	<0.0001
Serum ferritin	1.92	1.35-2.71	<0.0001
LDH	3.21	1.16-8.90	0.018
Procalcitonin	2.14	1.52-3.01	<0.0001
BUL	1.96	1.39-2.76	<0.0001
Serum creatinine	0.85	0.55-1.25	0.41
RBS	1.67	1.19-2.35	0.003
HbA1c	1.39	0.97-1.99	0.072
SGOT	1.73	1.23-2.42	0.002
SGPT	1.54	0.95-2.49	0.079
Serum Bilirubin	1.16	0.83-1.63	0.38

[Table/Fig-4]: Risk factors associated with prolonged hospital length of stay in study group.
N/L: Neutrophil/Lymphocyte; WBC: White blood cell; CRP: C reactive protein; LDH: Lactate dehydrogenase; BUL: Blood urea level; RBS: Random blood sugar; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase

DISCUSSION

The study aimed to determine all factors for prolonged length of stay and all patients were discharged as per guidelines advocated at that time as per Maharashtra's COVID-19 Task Force policy.

The [Table/Fig-5] showed variation of median length of stay and factors associated with prolonged LOS at various places of different countries, the stay more than median length of stay was considered prolonged. In the present study, the average age of patients with a prolonged LOS was higher than that of patients with normal LOS, (47.83±16.34) vs. (52.21±15.63) which was statistically significant. In a study by Grasselli G et al., among admissions of COVID-19 patients in ICU, majority were older men [19]. A retrospective study in Vietnam showed age and residence were significantly associated with longer duration of hospitalisation in patients with COVID-19 during second wave [16]. Hassan Alwafi H et al., in their study found that age has significant impact on LOS [1]. Fever (76.84% vs. 76.4%), cough (73.65% vs. 76.4%), shortness of breath (57% vs. 58%) were most common symptoms, observed in this study in LOS <10 days vs. LOS ≥10 days, but were not statistically significant. In some studies, high fever was associated with severe COVID illness and ARDS [20]. Wu S et al., also found that having fever before admission was associated with increased LOS [17]. However, in

Author and year of publication	Place of study	Number of subjects	Median length of stay	Factors associated with longer length of stay		
				Co-morbidities	Clinical finding	Laboratory findings
Present study, 2023	Pune, India	544	10	Diabetes	Severity of illness	N/L ratio, CRP, LDH, Ferrittin, D-dimer
Kinge KV et al., 2020 [12]	Mumbai, India	2883	6 to 15 days	Hypertension		
Wu Y et al., 2020 [13]	China	125	14 days	Coronary artery disease	Bilateral pneumonia	Lymphocytopenia Hypocalcaemia, hypochloraemia
Thiruvengadam U et al., 2021 [14]	India	730	7 days	Multiple co-morbidities (more than two)		High D-dimer, ferritin and N/L Ratio
Liu X et al., 2020 [15]	China	99	22 days		Use of steroids	Lymphopaenia
Wang Z et al., 2022 [8]	China	538	19days	Age >45 years	Severity of illness	
Guo A et al., 2021 [2]	China	75	17 days	Male sex, pre-existing liver or kidney disease	Fever	Increased creatinine
Thai PQ et al., 2020 [16]	Vietnam	133	21 days	Age	Sources of contamination	
Alwafi H et al., 2021 [1]	Saudi Arabia	706	6 days	End-Stage Renal Disease (ESRD)	Low oxygen saturation	Increased D-dimer, elevated ferritin and procalcitonin
Wu S et al., 2020 [17]	China	136	10.3 days	DM	Fever, bilateral pneumonia	
Birhanu A et al., 2022 [18]	Eastern Eutopia	394	12 days	-	Difficulty in breathing	Decreased leucocyte, blood urea nitrogen

[Table/Fig-5]: The factors associated with prolonged length of stay in various studies compared to present study [1,2,8,12-18].

this study, fatigue instead of fever, was most common symptom associated with increased LOS and was statistically significant. In this study of COVID-19, patients with prolonged LOS presented with shortness of breath (58.27%), fever (76.40%), cough (76.40%), but haemoptysis was less common. It was found in only 1 to 2% of all patients, which was similar to study of Tang X et al., [21]. In this study males (63.78%) were affected more than females (36.21%). Like many other studies males had prolonged LOS (65.92%) than females (34.08%) though not statistically significant. The possible explanation for more infection in males is, they are more susceptible to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection than females [22]. The gene responsible for ACE2 expression lies in the X chromosome.The females have two copies and thereby double the amount of Angiotensin-Converting Enzyme 2 (ACE2), which may compensate for SARS-CoV-2 mediated down regulation of ACE2 cell surface expression [23]. Bai F et al., found that female gender is associated with long COVID-19 syndrome [24]. Epidemiological data from many studies confirms more severe disease in males [25].

Presence of DM was significantly more in LOS ≥10 days (36.70%) than LOS<10 days (27.80%), and was statistically significant, which was similar to study of Alkundi A et al., and Alahmari AK et al., [26,27]. Hypertension (37% versus 31%), IHD (17% versus 13%), CKD (11% versus 6%), bronchial asthma (6% versus 1%) were more in LOS ≥10 days but not statistically significant. Wu S et al., found that DM was associated with prolonged LOS [17].

In the study by Alwafi H et al., D-dimer >0.5, white blood cells >10,000, CRP >0.3 mg/dL, LDH >230 U/dL were associated with increased LOS [1]. In this study, by univariable analysis, high Neutrophil-Lymphocyte ratio, CRP, D-dimer, serum ferritin, LDH, procalcitonin, BUL, random blood sugar, SGOT were significantly associated with prolonged LOS.

The leucocyte count increment, decreases hospital length of stay by 0.95 among COVID-19 patients. Studies showed that leucocytosis is a biomarker of COVID-19 severity clinical stages [28-30]. This could be indirectly because increment of leucocyte, aggravates the clinical outcome of the patient that results in shortening of length of stay by ending up the stay with death. In contrast this study showed leucocytosis was statistically significantly associated with prolonged LOS.

In the present study, increase in BUN was significantly associated with prolonged LOS.The study by Qu J et al., suggests BUN could be independent factor for predicting the severity of COVID-19 [31]. BUN is one of the indices that may predict the patients at high risk of in-hospital mortality. This finding can be justified by the fact that increment of serum BUN predicts the severe clinical stages which may result the shortening of patient's hospital stay due to death. In contrast, in this study increased BUN was associated with prolonged LOS.

Liu X et al., found lymphopenia as a marker for prolonged length of stay [15]. In the present study increased N/L ratio was statistically significantly more in LOS ≥10 days vs LOS <10 days (5.22 versus 4.21). This may be related to more severity of illness, which was similar to findings of Ghaharamani S et al., [32] and Gayatri T et al., [14]. The disease severity was associated with prolonged LOS and was statistically significant (p-value <0.0001). In contrast Guo A et al., found that a longer LOS was associated with milder disease [2].

High CRP and LDH levels have been previously associated with a severe clinical course and prolonged hospitalisation [30]. Buyukaydin B, found that CRP, LDH, ferritin at the time of hospitalisation were among the other factors affecting LOS [33]. Chest radiograph findings of consolidation were significantly more in LOS ≥10 days than LOS <10 days.

Limitation(s)

It is a retrospective study with small sample size, done at one centre. LOS may vary due to difference in admission and discharge criteria at various COVID-19 centres.

CONCLUSION(S)

The COVID-19 pandemic continues to affect the world with increasing cases and mortality. In the present study predictors of length of stay in COVID-19 were determined. Factors like fatigue, older age, diabetes mellitus, severity of illness, neutrophil/lymphocyte ratio, CRP, D-dimer, serum ferritin, serum LDH, procalcitonin, random blood sugar, blood urea level, SGOT are some of the factors associated with prolonged length of stay among hospitalised COVID-19 patients. Future studies are needed to confirm the above factors for their association with prolonged length of stay.

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