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Systematic Review

Influential Factors on the Hospitalization Length of COVID-19 patients: A Systematic Review

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Abstract

Introduction: The COVID-19 pandemic has led to rising demand for hospital beds and the shortage of medical equipment and supplies. It is necessary to identify the factors that influence the length of stay of COVID-19 patients to accurately predict the number of beds needed at each level of care. This study systematically reviewed influential factors on the hospitalization of COVID-19 patients to provide evidence for risk classification and improvement of clinical outcomes and recommendation solutions for reducing the length of stay.

Methods: With the appropriate keywords and a clearly defined search strategy, relevant databases such as PubMed, Embase, and Cochrane Library were searched for cohort studies and randomized control trials to November 10, 2020. The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of studies. Data including influencing factors length of stay, age, sex, country were extracted based on a checklist developed by the researchers. Data obtained due to differences in measurement criteria were qualitatively analyzed.

Results: The systematic search resulted in 48 relevant studies. Dependence of the severity of disease on age and comorbidities is the principal determinant of increased length of stay. Secondary bacterial infections, obesity, diabetes, and uncontrolled hyperglycemia in COVID-19 patients are likely to increase their length of stay. Special attention to liver damage has also been recommended in SARS-CoV-2 infections since pharmacological factors are independent risk factors for liver damage in non-severe patients. Neurological complications at presentation or during the hospital stay significantly increase the risk of prolonged hospitalization. Shortage of re-sources could decrease stay among COVID-19 patients, which indicates that intensive care is either delayed, deferred, or abbreviated.

Conclusion: Overall, demographic and epidemiological factors, dietary factors and diabetes, neurological conditions, liver damage, acute cardiovascular diseases, and social factors contribute to the length of hospital stay in COVID-19 patients. The present results can provide insights for policymakers regarding the factors that influence the length of stay of COVID-19 patients and practical solutions that can be employed to manage these factors.

Keywords: SARS-CoV-2; COVID-19; Length of Stay; Hospitalization.

Introduction

COVID-19 is a highly contagious disease that can cause a lethal respiratory syndrome in humans[1]. The Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Version 6) classifies it as mild, moderate, severe, or critical [2-4]. This pandemic has changed the level of care in hospitals[1]. Early reports suggest a 2-14-day incubation period[5-7]. Health systems are challenged due to the influx of COVID-19 patients in late December 2019 [8,9]. This pandemic causes an increase in the demand for hospital beds and a lack of medical equipment and supplies[10]. Most individuals infected with SARS-CoV-2 experience mild to moderate symptoms (cough, fever, and dyspnea) and do not need hospitalization. However, patients with severe pneumonia symptoms require clinical care.

The severity of Covid-19 among hospitalized patients can be temporally described in terms of the length of stay in the intensive care unit (ICU), duration of mechanical ventilation, and the possibility of death [11]. The rapid increase in Covid-19 cases raises severe concerns about the potential impact of this pandemic on resource-limited health systems in low- and middle-income countries (LMICs).

Predicting the demand for hospital beds and required types of equipment and staff provides crucial evidence for decision-making and contingency planning [12,13]. These requirements estimate the number of patients that need to be hospitalized and the duration of hospital care required for each patient. Since COVID-19 occurs at different levels of severity, hospital care may be provided in general wards for patients with mild symptoms, high dependency units for patients that require oxygen support, or ICUs for patients with intubated mechanical ventilation [12-14].

Due to changes in COVID-19 care guidelines, length of stay (LOS) depends on the level of care and the geographical setting [15,16]. Evolving knowledge about effective treatments and clinical pathways and availability of staff, beds, and equipment are also likely to influence the required duration and level of care. Patient characteristics such as age and comorbidities also affect the severity of the disease [16-18], which is possible to affect LOS [9,19]. Among the treatment methods used, studies have shown that prescribing angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) was associated with reduced LOS. Prompt discharge may indicate a better improvement of the disease or unmeasured factors that accelerate the discharge process by normalizing oxygen levels [20]. Corticosteroid therapy (CST) was not associated with a reduction in short-term mortality but possibly with a delay in viral clearance in patients hospitalized with COVID-19 of different severities [21]. In case of significant differences in patient characteristics, capacity planning can be applied to predict the number of beds required at each level of care.

Various studies have provided an estimate of LOS, but they often report a summary of statistics instead of direct results. Nonetheless, many studies have been conducted on the epidemiological and clinical characteristics of COVID-19 patients, including LOS [22-24]. This study systematically was reviewed influential factors on the hospitalization of COVID-19 patients to provide evidence for risk classification and improvement of clinical outcomes and recommendation solutions for reducing the length of stay.

Methods

Protocol

The present research was a systematic review of all cohort studies and randomized control trials on factors in the LOS of COVID-19 patients. This systematic review was conducted based on a predefined protocol and following the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.

Search strategy

The most important and relevant medical databases were systematically searched, including Cochrane Library, Google Scholar, Embase, PubMed, and Clinical Trials, govto November 10, 2020. In addition, the reference lists of the identified articles were reviewed to find more relevant papers. According to PRISMA, the study population was coronavirus patients, the factors affecting the length of stay were intervention, and the outcome was the length of stay. Searched keywords were SARS-CoV-2, 2019 novel coronavirus, coronavirus disease, COVID-19, length of stay, LOS, and admission duration. The sample search strategy of one of the data-bases: ((COVID-19) or

(SARS-CoV-2 Virus) or (Severe acute respiratory syndrome coronavirus 2) or (2019 novel coronavirus) or (2019-nCoV) or (Wuhan coronavirus)) AND ((length of stay) or (LOS) or (admission duration) or (admission length)) AND ((randomized controlled trial) or (cohort analysis)).

Eligibility criteria

The inclusion and exclusion criteria were as follows:

- Inclusion criteria: All studies published (as pre-print or publication) between January 1, 2020, and November 10, 2020, about the length of stay and underlying factors in COVID-19 patients.
- Exclusion criteria: Studies that reported LOS for individuals that had been hospitalized for reasons other than COVID-19 were excluded. In addition, studies on patients with chronic comorbidities, studies on non-human samples, systematic reviews, and studies not published in English were also excluded.

Study selection

Endnote Manager software was used to identify duplicates, categorize data, and screen studies from different databases. The title and abstract of the articles were screened independently by two reviewers based on some criteria (study design, language, studied factors, and human samples), and discrepancies were resolved by a third reviewer. The full texts of relevant articles were also reviewed by two reviewers, and a checklist developed by the researchers was used for data extraction. Discrepancies were again resolved by a third reviewer. Finally, the total number of patients evaluated during treatment was obtained.

Quality assessment

The quality of the included studies was assessed based on the Newcastle-Ottawa Scale (NOS). This checklist consists of three domains, including selection, comparability, and outcome, with eight items that can be rated with a maximum of one star in the selection and outcome do-mains and a maximum of two stars in the comparability domain. The quality of each study was assessed based on the total number of awarded stars. Studies with up to three stars are considered poor quality [25-27], those with three to five stars are regarded as fair quality [28-31], and those with higher than five stars are regarded as good quality [32-34].

Outcome measurement

In addition to identifying the factors influencing the LOS of COVID-19 patients, the results of studies were also reported by average age, country, and LOS. Most studies reported the median LOS of COVID-19 patients in a specific sample along with factors that influence it. Studies that did not report the mean or median were included in the comparative graph, but their results were not summarized.

Statistical analysis

The results of the studies are provided in a comparative table by the mean and median LOS of COVID-19 patients and factors such as age, sex, and comorbidities. Given the differences in measures of outcome (mean, median, HR), the results are qualitatively analyzed.

Results

Overall, 1,332 studies were extracted, and after removing redundant cases, 1,266 were screened by title. After screening the abstracts, 58 studies were included in the full-text review and, finally, 48 articles were included in the present research. Among the studies reviewed, two studies were accepted and one study was in press. The obtained data are the results of cohort and observational studies. The screening procedure is displayed using a PRISMA flow diagram (Fig. 1).

The evaluated studies are displayed in Fig. 1. Overall, 48 articles were included in the final phase of the research, of which 42 were retrospective cohort, and six were prospective cohort studies. Overall, 15,149 COVID-19 patients were examined in these studies. Of this number, 4,228 were in the treatment groups, and 10,921 were in the control groups. All studies provided the factors influencing LOS in COVID-19 patients in the average between control and treatment groups. In addition, the number of patients is provided by sex and average age. (Table 1 provides the characteristics of the included studies.)

Studies were conducted especially on adults aged 21-74 years. Generally, further men were studied than women (65% men vs. 35% women). One study examined children with an average age of 6 years. In most studies, LOS was investigated as a secondary outcome concurrently with the factors influencing it. In terms of geographical situation, most studies were conducted in China (48%) and the United States (27%). Two studies were performed in the United Kingdom, two in Italy, one in France, one in Texas, one in India, one in Turkey, one in Australia, and one in Brazil. Two studies did not focus on a specific country. All studies are retrospective cohorts that can affect the quality of the data obtained.

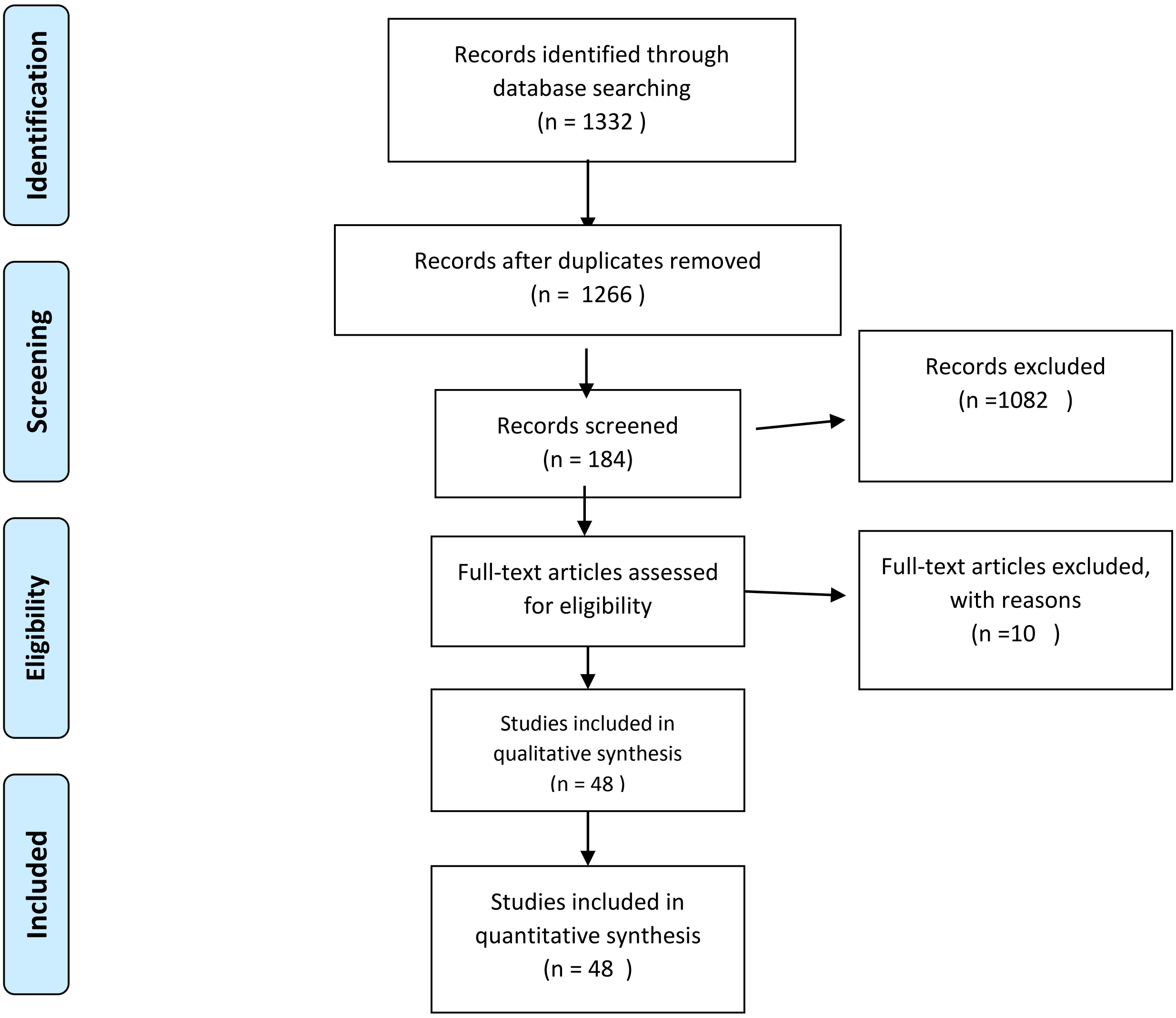

Figure 1: Diagram of the process of searching and studying articles

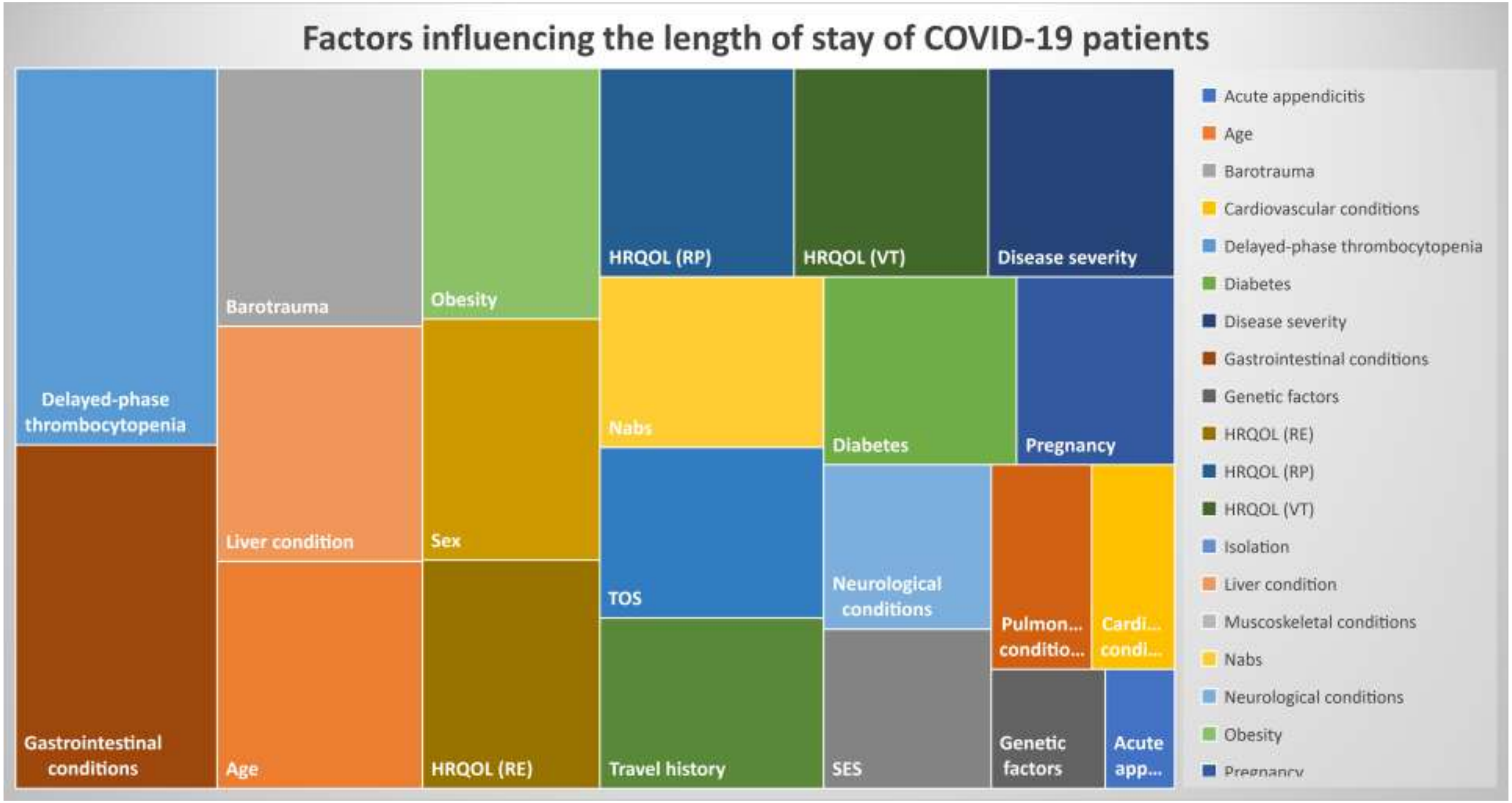

Figure 2: Factors influencing LOS in COVID-19 patients (Based on the average length of stay).

Table 1: The characteristics of the included studies.

Ref	Ref	Authors	Year	Country	Type of Study	Risk factor	Number of patients		Gender (Male/Female)		Age-year (mean ± SD)/IQR		LoS (Days, mean ± SD)/IQR		P
							Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	
03	(Al-Salameh et al., 2020)	Abdallah Al-salameh	2020	France	Observational cohort	Diabetes	115	317	73/42	165/152	72 ± 14.3	70.6 ± 16.4	17.1 ± 11.7	13.5 ± 9.1	
04	(Alkundi et al., 2020)	Alamin Alkundi	2020	England	Retrospective cross-sectional	Diabetes	87	145	63/24	82/63	71.4 (13.1)	69.9 (17.1)	14.4 (SD ± 9.6)	9.8 (SD ± 17.1)	< 0.0001
43	(Yan et al., 2020)	Yongli Yan	2020	Hubei, China	Retrospective cohort	Diabetes	48	145	33/15	81/64	70 (62 to 77) IQR	60 (43 to 71) IQR	10 (6 to 13) IQR	13 (9 to 18) IQR	0.001
19	**(Bode et al., 2020)**	**Bruce Bode**	2020	U.S.	Retrospective observational	Diabetes and/or uncontrolled hyperglycemia	451	671	268/183	356/315	65 (24-95)	61 (18-101)	5.7 (1.1-24.6) IQR	4.3 (1.0-21.2)	<0.001
13	(Li et al., 2020)	Juyi Li	2020	Wuhan, China	Retrospective cohort	Ketosis	42	616	16/26	281/335	47.0 (38.0–70.3)	58.0 (43.0–67.0)	19.0 [12.8–33.3] IQR	16.0 [10.0–24.0] IQR	
						Ketosis± diabetes	15	27	3/12	13/14	56.0 (49.0–73.0)	41.0 (30.0–56.0)	33.0 (20.0–39.0)	17.0 (10.0–22.0)	
10	(Liu et al., 2020)	Gaoli Liu	2020		Retrospective cohort	Nutritional risk (NRS 2002)	120	21	59/61	9/12	71.9 ± 6.0	70.5 ± 4.6	32.7 ± 11.8	17.0 ± 9.6	
						Nutritional risk (MUST)	58	83	29/29	39/44	70.6 ± 65.1	72.5 ± 6.2	31.5 ± 11.9	29.5 ± 13.3	
						Nutritional risk (MNA-sf)	109	32	54/55	14/18	72.0 ± 5.9	70.8 ± 5.7	31.9 ± 12.1	25.0 ± 13.6	
						Nutritional risk (NRI)	101	40	54/47	14/26	71.7 ± 5.7	71.6 ± 6.2	33.0 ± 11.1	23.7 ± 14.2	
29	(Moriconi et al., 2020)	Diego Moriconi	2020	Pisa, Italy	Retrospective, observational cohort	Obesity	29	71	12/17	40/31	70 ± 15	69 ± 17	21 ± 8	13 ± 8	0.0008
09	(Hu et al., 2020)	Xiang Hu	2020	Zhejiang, China	Retrospective, single-center	Overweight/obesity	29	29					17.4 ± 6.1	20.4 ± 4.4	
						Abnormal liver function (ALF)	17	41					22.8 ± 6.5	17.7 ± 4.2	
						Sex	36 M	22 F	36	22	48.7 ± 14.4	50.0 ± 10.9	20.2 ± 6.1	17.5 ± 3.6	
39	(Xie et al., 2020a)	Hansheng Xie	2020	Wuhan, China	Retrospective cohort	Liver injury	29	50	21/8	22/28	62.0 (46.0-67.0)	56 (45.5-65.0)	15.4 (11.0-16.8)	11.4 (8.5-14.0)	.01
27	*(Jiang et al., 2020b)*	*Saiping Jiang*	2020	Zhejiang, China	Retrospective observational	Liver injury	104	27	52/52	18/9	47.2 (13.3)	67.0 (16.2)	15.8 (5.1)	19.8 (7.1)	-
16	**(Gu et al., 2020)**	**Xuexiang Gu**	2020	Huai'an, China	Retrospective	Liver condition (levels of aspartate aminotransferase (AST))	66	23	35/31	22/11	43 (33-53)	44 (35-50)	*Correlation; r* = 0.334		0.007
05	(Chen et al., 2020b)	Liping Chen	2020	Shanghai, China	Retrospective, single-center	Hepatitis B virus (HBV)	20	306	13/7	155/151	52.5 (44-62.8)	50.5 (36-64)	14 (10-19)	14 (11-19)	
15	(Garcez et al., 2020)	Flavia B. Garcez	2020	Sao Paulo, Brazil	Longitudinal observational cohort	Delirium	234	473	143/91	261/212	70 (±11)	64 (±10)	13 (8–20)	10 (6–15)	<0.001
17	(Wu et al., 2020)	Fan Wu	2020	Shanghai, China	Cohort	Level of neutralizing antibodies (nabs)	29 high	52 low	13/16	19/33	63 [44-68]	38 [31-53]	18 [15-22]	14.5 [12-19.5]	-
20	(McGuinness et al., 2020)	Georgeann McGuinness	2020	New York	Retrospective	Barotrauma	89	512	65/24	361/151	58 (54-61)	64 (62-65)	25 (22-28)	18 (17-19)	<0.001
21	(O'Reilly et al., 2020)	Gerard M O'REILLY	2020	Melbourne, Australia	Prospective cohort	Isolation (association between ED LOS and isolation)	123	324	74/49	200/124	57 (23)	49 (21)	259 (210–377) min	204 (126–297) IQR	-
22	(Zheng et al., 2020a)	Hua Zheng	2020	Wuhan, China	Cohort	Sex	924	868	924/0	0/868	62 yr (IQR, 51-70; range, 0-95 yr)		28 (20-42)	28 (20-40)	-
						Age	208	150	108/100	78/72	<40 yr	80 yr or over	22 (14-31.3) IQR	34 (24-43.8) IQR	-
11	(Peng et al., 2020)	Hui Peng	2020	Hubei, China	Retrospective	Age (children)	75		44/36		6.06 ± 4.78		10.57 ± 3.22		
24	**(Zheng et al., 2020b)**	**Jiazhen Zheng**	2020	Guangdong, China	Prospective cohort	Redetectable as positive, RP	27	258	12/15	116/142	44.0 (32.0–62.0)	49.0 (35.0–62.0)	18.0 (13.0–24.0)	18.0 (13.0–25.0)	0.822

25	(Ramachandran et al., 2020b)	Preethi Ramachandran	2020	New York	Retrospective cohort	Aminotransferases	20	125	10/10	69/56	59.5 (46,70.8)	63 (53.5, 74)	7 (4.3,10.3) IQR	7 (5,10)	0.78
26	(Spoldi et al., 2020)	Chiara Spoldi	2020	Lombardy, Italy	Retrospective cross-sectional	Olfactory cleft mucosal thickening (OCMT)	16	47	9/7	30/17	74.74±21.01 (43–89)	77.82± 16.65 (45–95)	16± 4 (12–24)	9±14.5 (1–44)	.009
28	(Chachkhiani et al., 2020)	David Chachkhiani	2020	Louisiana	Retrospective cohort	Neurological complaints	34	216	15/19	98/118	68 ± 14	59 ± 15	HR = 1.7, (1.1,2.5, p = 0.0001)		-
30	(Zhang et al., 2020a)	Jiancheng Zhang	2020	Wuhan, China	Retrospective, single-center cohort	Sleep quality (good/poor)	60	75	40/20	38/37	61 (51–68) IQR	64 (56–70)	25.0 (20.5–36.5) IQR	33.0 (23.0–47.0)	0.0116
37	(Abbaspour Kasgari et al., 2020)	Hyunjoong W. Kim	2020	U.S.	Retrospective cohort	Oxygen saturation	184	226	92/92	114/112	63	55	HR=1.0509 (CI=1.0089–1.0946)		0.0170
						X-ray grade (>1, 0)	184	226	92/92	114/112	63	55	HR=0.6125 (CI=0.5134–0.7307)		< 0.001
34	(Turcotte et al., 2020)	Justin J. Turcotte	2020	U.S.	Retrospective, observational case series	Disease severity	48	69	26/22	36/33	70.2 ± 12.1	62.6 ± 16.9	18.36 ± 11.86	9.26 ± 7.53	-
06	(Wei et al., 2020)	Yiping Wei	2020	Hubei, China	Single center descriptive	Disease severity	14	262	10/4	145/117	65.0 (60.0–72.8)	50.0 (39.0–57.0)	21.5 (14.0–21.0)	18.0 (15.0–24.0) IQR	0.44
38	(Wang et al., 2020a)	Dawei Wang	2020	Wuhan, China	Retrospective cohort	Disease severity	36	102	22/14	53/49	66 (57-78) IQR	51 (37-62)	8.0 (4.5-10.0) IQR	6.0 (3.0-7.0) IQR	.009
46	(Xu et al., 2020b)	Jiqian Xu	2020	Wuhan, China	Retrospective cohort	Disease severity	92	147	53/39	90/57	57.5 ± 13.5	65.7 ± 12.2	26.5 [19–46.5] IQR	12 [8–18] IQR	< 0.001
14	**(Mishra et al., 2020)**	**Vinayak Mishra**	2020	Karnataka, India	Retrospective cohort	Severity of symptoms	30	360	21/9	254/105	21–40	21–40	15.3 (3-17)	17 (15-20)	
						Travel history	123	267	87/36	189/78	21–40	21–40	18 (15-21)	17.5 (15-20)	
35	(Li, 2020)	BinBin Li	2020	Yongjia, China	Retrospective	Time of symptom onset (TOS)	12	26	IRR F= 1.133	IRR F=1.078	IRR=1.016	IRR=1.007	IRR= 0.997; CI (0.984-1.010)	IRR= 0.980; CI (0.967-0.993)	0.633 /0.003
23	(Jabri et al., 2020)	Ahmad Jabri	2020	Northeast Ohio	Retrospective cohort	Stress cardiomyopathy	20	6	7/13	3/3	67 [57-75]	67 [59-74] IQR	8 (6-9)	4 (3-4)	0.006
45	(Zhang et al., 2020b)	Lijuan Zhang	2020	Wuhan, China	Retrospective cohort	Stroke	49	602	33/16	259/343	70 (67–84)	55 (37–67)	34 (27–48) IQR	23 (15–32) IQR	<0.001
49	(Bhatt et al., 2020)	Ankeet S. Bhatt	2020	U.S.	Retrospective longitudinal trends	Acute cardiovascular conditions	231	404	128/103	233/171	70.3 15.1	71.1 13.8	4.8 (2.4–8.3)	6.0 (3.1–9.6)	0.003
40		Nicolas Hellmuth Dreifuss	2020		Prospective cohort	Acute appendicitis	15	65	6/9	32/33	39·4 (16-80)	41·8 (16-83)	3·9 (1-17)	1·9 (1-30)	0·11
31	(Xu et al., 2020a)	Hai Xu	2020	New York	Retrospective cohort	Pulmonary embolisms (PESI risk stratification≤ >85)	35	66			62 (± 15)	62 (± 15)	9.7 (± 5.4)	14.3 (± 11.6)	0.030
32	(Kwok et al., 2020)	Benjamin Kwok	2020	New York	Retrospective cohort	Pulmonary embolism response teams (pert)	22	60	8/14		64±15.3	58.1 ± 16.2	7.7± 7.7	13.2±12.7	0.02
41	(Agarwal et al., 2020)	Shashank Agarwal	2020	New York	Retrospective cohort	Leukoencephalopathy and/or Cerebral Microbleeds	35	80	29/6	53/27	61 (50–66) IQR	69 (59.75–75.25) IQR	42.1(9.9)	20.9 (18.1)	<0.001
47	(Ye et al., 2020)	Cong Ye	2020	Tongji	Retrospective cohort	Rheumatic disease	21	2305	F 81%	F 50%	>40 y= 90%	>40 y= 89%	>20 d= 57%	>20 d= 47%	-
48	(Chen et al., 2020d)	Wanxin Chen	2020	Wuhan, China	Retrospective cohort	Delayed-phase thrombocytopenia	32	239	21/11	124/115	67.00±12.86	56.52±13.93	35.84±11.20	31.07±10.74	0.021
50	(Ramachandran et al., 2020a)	Preethi Ramachandran	2020	New York	Retrospective cohort	Gastrointestinal symptoms	31	119	19/12	64/55	57.6 (17.2)	63.3 (14.6)	7.8 (4.4)	7.9 (4.7)	0.87
51	(Egol et al., 2020)	Kenneth A. Egol	2020	New York	Prospective cohort	Hip fracture care	17	107	12/5	34/73	82.4 ± 9.6	83.4 ± 10.4	9.8 ± 5.2	5.0 ± 2.6	,0.001
01	(Ikitimur et al., 2020)	Hande Ikitimur	2020	Istanbul, Turkey	Retrospective	Genetic factors	29	52	16/13	29/23	58.86 ± 19.02	53.37 ± 16.64	6.4	3.4	0.000
12	(Qiancheng et al., 2020)	Xu Qiancheng	2020	Wuhan, China	Retrospective	Pregnancy	28	54	0/28	0/54	30 (26.75–32)	31.00 (28.00–35.00)	14 (12–22.25)	18 (10.25–22)	
33	(Chen et al., 2020a)	Ke-Yang Chen	2020	Zhejiang,China		HRQOL (role physical (RP))	361		186/175		47.22(13.03)		-1.167, -0.221 CI	19.13 (7.60)	0.004

						HRQOL (role-emotional (RE))	361		186/175		47.22(13.03)		-1.515, -0.357	19.13 (7.60)	0.002
						HRQOL (vitality (VT))	361		186/175		47.22(13.03)		0.023,0.461	19.13 (7.60)	0.040
07	(Hong et al., 2020)	Yucai Hong	2020	Zhejiang, China	Retrospective cohort	History of traveling to Wuhan (procalcitonin, initial symptom, comorbidities)	25	50	11/14	30/20	44.12±11.33	47.50±14.21	16 (IQR, 15–17	7 (IQR, 4–11)	
08	(Yue et al., 2020b)	Hongmei Yue	2020	Gansu, China	Retrospective cohort	History of epidemic exposure	44	42	23/21	15/27	42.5 (31.3–53.8)	40.5 (29.0–55.3) IQR	19.0 (16.0–23.0)	11.0 (9.0–12.0)	
02	(Ali et al., 2020)	Kiran Ali1	2020	Texas	Retrospective cohort	Prison population	5	15	5/0	10/5	56 ± 9.0	67.4 ± 15.1	12.6 ± 8.9	8.6 ± 6.5	-
36	(Khan et al., 2020)	Khurram Shahzad Kha	2020	Scotland, UK	Prospective cohort	Socioeconomic status (SES) (good /poor)	55	117	38/17	70/47	≤70yr= 24	≤70yr= 62	10	17	.018

Disease severity

The severity of COVID-19 has been identified in five studies as a critical factor in LOS. However, due to applying of different levels of disease severity in these studies, no definitive conclusions can be drawn from it. More severe cases with higher oxygen requirements at admission and those with comorbidities such as insulin-dependent diabetes or chronic kidney disease are more likely to have a longer LOS[32]. Older patients with comorbidities are at increased risk for more severe illness from COVID-19 infection[3]. Early identification of these patients may cause improved clinical outcomes[32].

Disease symptoms

COVID-19 cases without symptoms of severe acute respiratory illness (SARI) at the time of hospitalization and those without a travel history have significantly shorter LOS than their peers [35]. Moreover, time of symptom onset (TOS) is negatively associated with LOS in patients without an epidemiological trace that is, patients with later TOS have relatively shorter LOS[36]. Oxygen saturation and chest X-ray grade are significantly associated with LOS. Patients with lower alveolar opacity in their X-rays have shorter LOS. Therefore, a chest X-ray can be a useful diagnostic tool for the manage suspected COVID-19 patients especially when hospital beds are limited and demand is high[33].Gastrointestinal (GI) symptoms are commonly observed in hospitalized COVID-19 patients. However, it is not significantly associated with a higher mortality rate or secondary outcomes such as longer LOS and increased mechanical intubation[37]. A large number of COVID-19 patients manifest detectable positivity (RP). These patients are expected to return to true negative and are unlikely to be re-infected. Prolonged viral shedding during the first hospital admission is a risk factor for RP events that have implications for future virology research[38].

Diabetes

Studies suggest that COVID-19 patients with diabetes are at a greater risk of developing complications such as acute respiratory distress syndrome (ARDS), chronic kidney disease, and ICU admission. In addition, the average LOS is longer in COVID-19 patients with diabetes than in those without diabetes[39,40]. These patients exhibit severe inflammatory responses. Also, diabetes can be a risk factor for death in patients with severe COVID-19. Overall, mechanical ventilation, ICU admission, and the mortality rate are higher in critically ill COVID-19 patients with diabetes[41]. COVID-19 infection may cause ketosis, ketoacidosis, and diabetic ketoacidosis (DKA) in diabetic patients. Subsequently, the LOS and mortality rate are increased. However, the mechanism of DKA from COVID-19 requires further research[42].

Nutritional risk and obesity

A study of COVID-19 patients as a nutritional risk group shows that longer LOS, loss of appetite, and more significant weight loss in these patients are significantly associated with nutritional risk. This highlights the importance of nutritional screening of hospitalized patients and providing nutritional support to improve clinical outcomes[2]. With body mass index (BMI) and alanine aminotransferase (ALT) as measures of overweight and obesity, it has been shown that overweight/obese patients have more extended hospital stays (17.4 ± 6.1 vs. 4.4 ± 4.4 days; $P = 0.046$) and constitute a plenty proportion of prolonged hospitalization (62.1%vs. 26.1%; $P = 0.010$)[28]. Obtaining a negative oropharyngeal or nasal swab and achieving oxygen weaning take longer in obese patients, which increases their LOS. Moreover, these patients require more time for SARS-COV-2 shedding COVID-19 patients with Obese have higher c-reactive protein (CRP) and tumor necrosis factor

(TNF) levels. Further research is required to find whether the pro-inflammatory state observed in obese patients can lead to more severe clinical presentation and evolution of SARS-CoV-2 infection[43].

Liver damage

Patients with liver damage have higher white blood cells, neutrophils, c-reactive protein (CRP), and CT score and are more likely to have a more extended hospital stay[27]. On the other hand, liver damage widely occurs in COVID-19 patients and is associated with prolonged hospital stay and increased viral shedding duration. Critically ill patients experience the earlier occurrence of liver injury with greater severity and slower recovery[44]. There is a significant positive correlation between serum aspartate aminotransferase (AST) and LOS in COVID-19 patients based on analysis of liver blood tests. Elevated AST levels in COVID-19 patients indicate relatively severe liver and myocardial damage, which may be one of the reasons for a more extended hospital stays among these patients[29]. Abnormal liver enzymes are observed in hospitalized COVID-19 patients, and elevated AST levels have been associated with a non-significant increase in the rate of mechanical ventilation, but they are not associated with higher mortality rates or more extended hospital stays. There is no evidence that SARS-CoV-2/HBV coinfection could aggravate liver damage or increase the length of hospital stay[45].

Antibody levels

A study of the relationship between LOS and antibody titers indicates that variable levels of SARS-CoV-2 neutralizing antibodies (NAbs) are observed at discharge. NAbs are detected in 4 to 6 days and peak in 10 to 15 days after the onset of the disease. The positive correlation between NAbs and blood CRP level at discharge and their negative correlation with lymphocyte count at admission suggest that high levels of NAbs are likely to be an inflammatory or innate immune response. Further research is needed for understanding the clinical consequences of different antibody titers against future infection and their relationship with LOS[46].

Barotrauma

Barotrauma occurs at a higher rate in COVID-19 patients who require mechanical ventilation. It is associated with increased LOS and is a risk factor for death. Barotrauma is especially dangerous for critically ill patients that are managed by staff who are not familiar with ventilator use[26].

Isolation

One study has shown that isolation is independently associated with a 23% increase in LOS of COVID-19 patients in emergency departments and doubles the likelihood of staying for more than 4 hours. A statistically significant association is reported between LOS and isolation in admitted patients ($p = 0.003$), while no significant association is observed in those who are not admitted ($p = 0.35$)[47].

Age

LOS is age-dependent and ranges from about 22 days for people aged 40 years or older to 34 days for those aged 80 years or older[48]. One study finds no association between the studied factors and LOS or SARS-CoV-2 clearance time in children, suggesting that infected family members are the principal cause of COVID-19 in children[49].

Mental and neurological complications

Delirium is associated with adverse outcomes in hospitalized COVID-19 patients, reducing their functional and cognitive ability. However, its long-term effects that that cause severe cardiovascular and pulmonary damage are still unknown. Delirium is associated with increased LOS, ICU admission, ventilator utilization, and in-hospital death[69]. Regarding sleep quality, it has been shown that absolute lymphocyte count (ALC) is lower, and its recovery rate is slower in COVID-19 patients with poor sleep. Also, the increased neutrophil-to-lymphocyte ratio in these patients increases the need for ICU care. Length of stay increases in patients with poor sleep than those with good sleep (33 days vs. 25 days; P = 0.0116)[51].

Neurological complications at admission and during hospitalization are associated with longer LOS, increased likelihood of intubation, and a higher risk of death in COVID-19 patients. Age and hypertension are significant demographic/clinical predictors of LOS in these patients[52]. Olfactory cleft mucosal thickening (OCMT) affects one in four SARS-CoV-2 patients that need to be hospitalized. Patients with OCMT require invasive ventilation and have more extended hospital stays. This issue is accurate regardless of age, sex, and diffusion of lung lesions, but OCMT is not associated with a higher mortality rate[53].

Altered mental state (AMS) is another common neurological complication in COVID-19 patients that results in a prolonged hospital stay. Patients with AMS and those who suffer seizures during their hospital stay are more likely to require incubation However; further research is required to determine the nature, incidence, and relevance of these neurological conditions[70].

Leukoencephalopathy and/or cerebral micro bleeds in COVID-19 patients are associated with critical illness, worse outcomes, and higher mortality. These complications are observed in critically ill COVID-19 and cause increased ventilator utilization, extended hospital stays, thrombocytopenia, and higher D-dimer levels. Although the relationship between leukoencephalopathy and cerebral micro bleeds and SARS-CoV-2 is unclear. The possible mechanisms for complications are endothelin with thrombotic microangiopathy, prolonged respiratory failure, and hypoxemia and hypoxemia are possible mechanisms for the incidence of these complications in COVID-19 patients[54].

Acute coronary syndrome

There has been a significant increase in the incidence of stress cardiomyopathy during the coronavirus pandemic, and the length of hospital stay has been significantly longer for cardiomyopathy patients hospitalized during this period. However, one study has found no cases of COVID-19 infection in a sample of patients with stress cardiomyopathy, which suggests that the increased incidence of the disease could be the result of indirect, psychological, and socioeconomic stress caused by COVID-19[55].

Length of hospital stay and hospitalization costs are higher in patients with myocardial infarction (with a crucial ratio of 65%). It is higher than the 5% critical ratio in COVID-19 patients[56]. On the other hand, given the concerns for exposure to COVID-19 in healthcare settings, there may be pressure from patients and clinicians for early discharge, which could be facilitated by a reduction in waiting time for specific essential procedures due to the decrease in elective cardiovascular methods. This decrease in hospitalization highlights the need for educating and guiding high-risk patients about when to seek emergency care[57,67].

Other acute diseases

Significant increases in consultation delay, rates of severe peritonitis, and rates of complicated appendicitis, as well as non-significant increases in rates of postoperative intra-abdominal abscess, readmissions, reoperations, and LOS, have been observed in COVID-19 patients. It indicates that the COVID-19 crisis has changed healthcare systems in many respects[58]. Acute pulmonary embolism is also recognized as a complication of active COVID-19 infection. Higher pulmonary severity index (PESI) scores are a predictor of a higher rate of ICU admission, more extended hospital stays, and a higher mortality rate[30]. Pulmonary embolism response teams (PERT) activation is associated with reduced LOS and fewer bleeding events[34].

No significant difference has been observed in hospitalization time and mortality rate between rheumatic and non-rheumatic COVID-19 patients[59]. Delayed-phase thrombocytopenia in COVID-19 patients is significantly associated with increased LOS and a higher mortality rate[60]. COVID-19 infection in patients with hip fractures is associated with increased mortality rate, longer LOS, higher rate of main complications, and greater postoperative need for ventilators[61]. The results of a study on pregnant and non-pregnant women with SARS-CoV-2 indicate no significant association between pregnancy and disease severity, virus clearance time, and LOS. There is no evidence for vertical transmission of the disease in the late stage of pregnancy as a vaginal delivery. However, further research is required to reach definitive conclusions about the lack of vertical transmission of SARS-CoV-2[62].

Other environmental and socioeconomic factors

A study of genetic factors has shown that COVID-19 patients with the genetic association in a large family cluster have more severe disease and worse clinical course compared to unrelated COVID-19 patients. LOS and ICU admission rates are also shown to be significantly higher in genetically related patients. Where recognized risk factors of COVID-19 such as age, sex, cardiovascular diseases, and chronic comorbidities do not account for differences in clinical presentation, genetic factors could help explain those differences[63]. LOS in COVID-19 patients has a negative association with role emotional and role physical, and there is a positive association with vitality[64].

A comparative study of COVID-19 during the first wave of the disease showed that prisoners had respiratory and gastrointestinal symptoms. The patients had more comorbidities, often required mechanical ventilation, had more extended ICU stays and had the same mortality rate as community-based patient’s despite being a decade younger on average[65].

It has been shown that socioeconomic status does not affect the outcome in hospitalized patients with COVID-19. However, it is negatively associated with LOS that hospital stays are significantly longer for underprivileged patients, which can have importance for hospitals in more deprived regions. Health inequities may have a significant impact on health outcomes in COVID-19 patients on a global scale[25].

Quality of the studies

Based on the NOS checklist, the reviewed studies were examined in terms of selection, comparability, and outcome. These were cohort studies, and results of the quality assessment indicate that 48 studies had good quality, 33 studies had acceptable quality, and ten studies had poor quality. There were two accepted studies and one study in press[44,61,64].

Discussion

Identifying the factors influencing length of stay (LOS) in patients with COVID-19 is key to developing solutions for reducing LOS, which both increases patient satisfaction and helps reduce hospital costs. This study was a systematic review of published literature on LOS and its determinants in COVID-19 patients. The average LOS range is from 3.9 days to 35.8 days, irrespective of the type of discharge in different studies depending on the underlying factors. To our knowledge, this is the first review of factors influencing LOS in COVID-19 patients.

Studies have been conducted to predict the number of beds required for covid-19patients[66,67], to investigate the distribution of length of stay of corona-virus patients, potential sources affecting the difference between the length of stay, and possible bias in the estimates[69]. The results can be effective in modeling the forecast of required bed occupancy based on the capacity of hospitals, together with predicting the incidence of the disease. And it plays a vital role in preparing for the following stages of the dis-ease. The present research, conducted to identify and examine the factors influencing LOS in COVID-19 patients, shows that most reviewed studies have examined LOS as a secondary out-come. However, given the progression of the disease worldwide and the rising demand for healthcare resources, a study of LOS and factors influencing can be effective for the optimal allocation of resources.

The results indicate variations in LOS in different countries but it must be noted that most studies have been conducted in China and that the measures of patient admission and dis-charge can have a significant role in these variations. Varying guidelines may explain the discrepancies in the results of various studies by geographic location. On the one hand, China was the first country to be affected by this disease, and other countries have used the experiences and the knowledge gained to reduce LOS more. The present study considers the total duration of hospital stay. A previous review study reported that there was no significant difference be-tween China and other countries in the distribution of LOS for intensive care. However, there may be differences in intensive care in China compared to other countries[71]. Therefore, further research is required to examine the effect of the characteristics of intensive care on LOS in COVID-19 patients.

There were few differences between the results of different studies in terms of sex and age group. However, there is not enough evidence to draw definitive conclusions about the effect of these factors on LOS; since age and sex distributions have mostly been incidental and not planned. In addition, studies have shown that disease severity is a critical factor in the LOS of COVID-19 patients. It must be noted that the definition of the levels of disease severity varies in different studies, and no definitive conclusions can be drawn. Moreover, the disease has been estimated to be less severe outside the core epidemic region, and modeling of prolonged hospital stay has shown good discrimination[69]. It is likely that the dependence of dis-ease severity on age and comorbidities ultimately determines LOS[48]. In addition, the time between the onset of symptoms and SARS-CoV-2 RNA-negative conversion and its relationship with the severity of illness must be taken into account in the treatment of COVID-19 patients and requires further investigation[77].

Secondary bacterial infections may lead to prolonged hospital stays. Therefore, clinicians must be alert to patients with a history of infection, even if they do not have a fever or other symptoms[22]. Patients with near-total or total involvement of the lungs are at a greater risk of poor clinical outcomes, a higher rate of intubation, and more extended hospitalization[33]. On the other hand, as the pandemic spreads, the recovery time of hospitalized COVID-19 patients may become shorter. However, this has only been observed in cases without an epidemiological trace, indicating that the course of the disease is affected by the mode of transmission[36].

Diabetes and uncontrolled hyperglycemia are prevalent comorbidities in hospitalized COVID-19 patients. These comorbidities are related to a prolonged hospital stay and higher mortality[73].

COVID-19 patients with obesity require prolonged hospitalization and more intensive oxygen treatment. They may also need more time to clear from SARS-CoV-2 shedding[28]. Special attention to liver injury during SARS-CoV-2 infection is recommended.

Drug factors were independent risk factors for liver injury of non-critically ill patients. Also, drug interference together with concomitant drugs should be closely monitored. Healthcare workers should monitor the medications during hospitalization and adjust the drug treatment promptly[44].Abnormal results of the liver blood test are typical in COVID-19 patients. The serum level of AST measured on admission may be helpful to identify patients with COVID-19 and predict the length of their hospital stay[29]. The results indicate that AST levels can be proper in detecting COVID-19, evaluating of treatment, and predicting LOS[45].

A study showed that delirium is not associated only with in-hospital death. But is related to a higher rate of ICU admission and ventilator utilization[69]. In addition, poor sleep quality in hospitalized COVID-19 patients is associated with slower recovery and increased need for intensive care[51]. Neurological complications are common in COVID-19 patients at presentation or during hospitalization and cause a greater risk of prolonged hospital stay. AMS is the most common complication and a significant predictor of longer LOS, death, and intubation. Future studies must examine the underlying causes of AMS and determine whether it is the result of SARS-CoV-2 infection or is caused by another disease that leads to worse outcomes in these patients[52].

The rate and length of hospitalization in patients with acute cardiovascular diseases de-creased significantly during the first phase of the COVID-19 pandemic, indicating that intensive care may have been delayed, deferred, or abbreviated[57]. This could suggest that the "stay at home" policy and people's fear of the hospital setting may have contributed to the progression of the disease. Therefore, the medical community and health officials must in-form people about the risks of delaying medical care[58]. In addition, more re-search is required on the effect of socioeconomic inequalities to minimize the impact of the next wave of COVID-19 or even the next pandemic[25].

Limitations of the study

Given that most published studies are geographically centered around China, they contribute most to the findings of this review study, and there is a possibility of bias in the data. In addition, the relatively lower number of studies conducted outside China makes geographical comparisons more difficult. The pandemic is an active constant worldwide, and some studies are being done in various countries. Some studies have been published after the cutoff date in this review and are not included. Therefore, it is essential to replicate this review study with a larger body of research on various geographical locations.

In this study, the total length of hospital stay was examined without differentiating stays in regular wards and ICU stays. However, disease severity and admission of patients at different levels of care can have a significant effect on their LOS. Moreover, hospital capacity and the level of demand can contribute to prolonged hospital stays, since as the disease progresses, a larger number of people will require care, especially intensive care, which may not be possible to provide due to limited resources as a well-limited individual and organizational capacity. The present study does not examine the course of the disease and its effect on the LOS of patients. Another limitation of the research is that it does not account for follow-up, which could intro-duce bias since the information related to patients without complete followed-up are not included and may not reflect the actual LOS. Another limitation of this study is that of the studies studied, three studies have not yet been published and may affect the quality of the results obtained.

Conclusion

The present study conducted a review of the literature on factors influencing LOS in COVID-19 patients. In general, it has presented the effect of the studied factors in the field of demographic and epidemiological factors, nutritional factors and diabetes, neurological problems, liver problems, acute heart and lung diseases, and social factors. Given that about 50% of the re-viewed studies are centered around China, the effect of situational factors on the results must be taken into account. Given that the present study only identifies the factors affecting the length of stay, the results can be a guide for clinicians and policy makers to provide useful solutions to reduce the length of stay of COVID-19 patients. For this purpose, considering different treatment methods along with the factors identified during this study, can be effective. The results of the present study can help policymakers recognize and evaluate factors that influence LOS in COVID-19 patients and develop effective solutions for managing them. However, given the limited data and studies available for drawing definitive conclusions about the effect of some of these factors, it is recommended for policymakers to exercise caution in making decisions based on the extant literature, and further research with larger samples and longer follow-up periods is needed to obtain more conclusive evidence.

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Conflict of Interest Disclosures

The Author(s) declare(s) that there is no conflict of interest.

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