The risk factors and related hospitalizations for cases with positive and negative COVID-19 tests: A case-control study

Mostafa Ghanei [a,*], Hossein Keyvani [b], Aliakbar Haghdoost [c], Hassan Abolghasemi [a,d], Ghasem Janbabaei [e], Hamdi Reza Jamshidi [f], Amir Hosein Ghazale [g], Seyed Hassan Saadat [h], Mohammad Gholami Fesharaki [i], Mehdi Raei [j]

[a] Chemical Injuries Research Center, Systems Biology and Poisoning Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[b] Department of Virology, Faculty of Medicine, Iran University of Medical Science, Tehran, Iran
[c] Associate Professor of Epidemiology, Kerman University of Medical Sciences, Kerman, Iran
[d] Department of Applied Microbiology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[e] Gasterointestinal Cancer Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[f] Secretary of the National Headquarters of Fighting Corona Virus, Iran
[g] Student Research Committee, Baqiyatallah University of Medical Sciences, Tehran, Iran
[h] Behavioral Sciences Research Center, Lifestyle Institute, Baqiatallah University of Medical Sciences, Tehran, Iran
[i] Department of Biostatistics, School of Medical Sciences Tarbiat Modares University, Tehran, Iran
[j] Baqiyatallah Research Center for Gastroenterology and Liver Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: The aim of this study was to evaluate the risk factors for hospitalizations of cases with positive and negative COVID-19 tests.
Methods: In this case-control study, the case and control groups consisted of 292 COVID-19 patients and 296 non-COVID-19 patients. Patients who referred to a reference laboratory in Tehran (Iran) in March 2020 were selected and interviewed. The patients were contacted by telephone and data were recorded through a questionnaire.
Results: The sample of this study consisted of 588 patients (349 [59%] females, 239 [41%] males) with a mean age of 42 ± 15. The results of this study showed that comorbidities like diabetes (OR = 7.42), hypertension (OR = 4.85), asthma and respiratory diseases (OR = 5.64) in addition to symptoms including fever (OR = 6.67), chills (OR = 11.2), anorexia (OR = 11.3), dyspnea (OR = 4.8), weakness and lethargy (OR = 5.7) were the most predictive variables for hospitalization of non-COVID-19 cases. Furthermore, demographical variables like male gender (OR = 3.71), high age (>50; OR = 3.12), BMI (>25; OR = 2.37), travel (OR = 2.79), comorbidities including diabetes (OR = 5.26), hypertension (OR = 3.7) and underlying immunosuppressant patients receiving corticosteroid therapy (OR = 3.62) in addition to symptoms like anorexia [OR = 2.55] and dyspnea (OR = 6.99) tend to increase the risk of hospital admission in COVID-19 patients, suggesting their predictive values for hospitalization of COVID-19 patients.
Conclusion: Our results indicated that different factors tend to increase the odds of hospital admission in patients with positive and negative COVID-19 tests, suggesting their predictive values for hospitalization.

1. Introduction

1.1. Background

The outbreak of COVID-19 disease in Wuhan (China) in late 2019 led to the World Health Organization (WHO) announcing a new pandemic in the world [1]. According to the WHO report until May 12, 2021, millions of people had been infected and died respectively duo to COVID-19 infections around the world [2]. In Iran, since the first two cases of COVID-19 were reported on February 19, 2020 [3]; until May 12, 2021 [2], >2.5 million have been infected and >75 thousand people have died of COVID-19 disease.

The clinical features of COVID-19 are varied, ranging from asymptomatic states or mild upper respiratory tract infections to severe pneumonia with respiratory failure (acute respiratory distress syndrome [ARDS]) in the early stages or even death [4–5].

Major symptoms like fever, cough, dyspnea [4] and minor symptoms such as loss of taste and smell, gastrointestinal symptoms and cutaneous manifestations [6–9] are common clinical features of this disease. Booth et al. [10] in a *meta*-analysis study comprising of 76 studies across 14 countries demonstrated that commonly reported variables including age > 75, male sex, severe obesity, active cancer, crucial measure (e.g., respiratory rate and SpO2) as patient characteristics contributing to an increased risk of severe COVID-19 infection .

In a national cohort study of 88,747 cases tested for SARS-CoV-2, Loannou found that older age, high regional coronavirus disease 2019 burden, higher Charlson Comorbidity Index score [11], fever, dyspnea, and abnormal results in many routine laboratory tests are significant risk factors for mortality, while other factors such as chronic obstructive pulmonary diseases, obesity, smoking and hypertension were not found to be linked to mortality [12]. A nationwide study reported that age, sex, and comorbidity are generally associated with severe COVID-19 [13].

As far as patient management is concerned, there is substantial interest in examining risk factors associated with hospitalization, severe illness, and mortality in case series. Exploration of the epidemiology, details of the clinical characteristics (e.g., respiratory symptoms, etc.), laboratory and CT scan results, comorbidities, and clinical outcomes of patients are essential in this regard [14–16]. Some cases are discharged earlier, whereas others needed longer hospitalization; therefore, risk factor estimation and definitive outcomes need to be clarified. Since its outbreak, there have existed myriad uncertainties about COVID-19 especially in different communities as well. Given most COVID-19 studies have been performed on hospitalized patients rather than those receiving pre-hospital care, this study was aimed at evaluating the
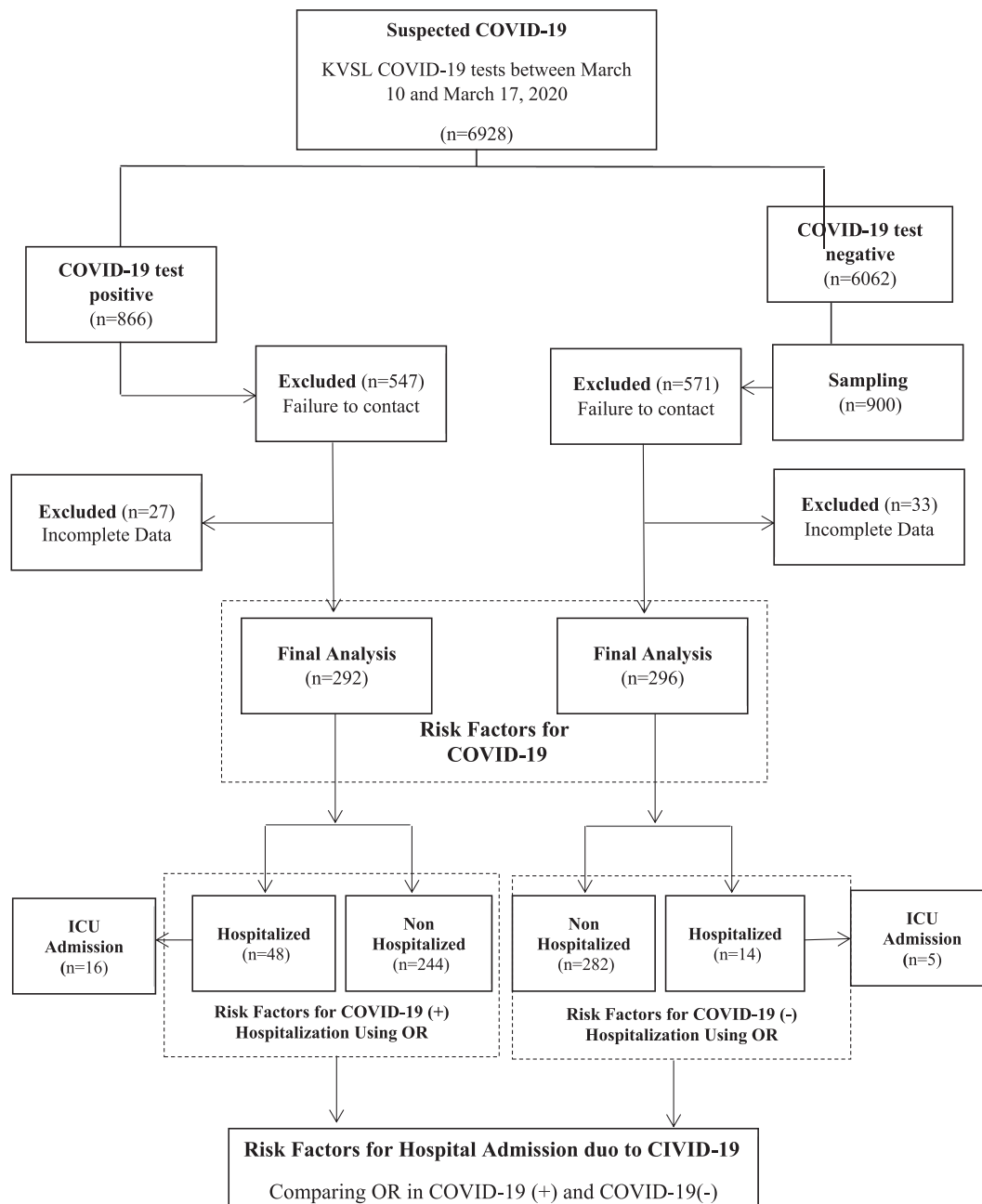

Fig. 1. Flow diagram of study and Analysis.

risk factors for hospitalizations among individuals with positive and negative COVID-19 tests.

2. Materials and Methods:

The front-line data of the present retrospective case-control study were obtained from Keyvan Virology Specialty Laboratory (KVSL) in Tehran, Iran. The KVSL was one of the main referral laboratories for screening suspected COVID-19 cases in Tehran.

The inclusion criteria in this study were: $18 \leq age \leq 90$, willingness to participate, reference to KVSL form 10 March to 23 March 2020, registration of correct information at the time of admission, and detection of COVID-19 virus through RT–PCR. Patients' refusal to participate and failure to complete the interview were the exclusion criteria. The flow diagram of the study is presented in Fig. 1. A total of 6928 suspected COVID-19 cases referred to KVSL form 10 March to 23 March 2020. Based on the positive or negative RT-PCR of throat-swab specimens, 866 confirmed COVID-19 patients and 6062 negative COVID-19 cases were included and followed up. Finally, 292 and 296 cases who tested positive and negative for SARS-CoV-2 respectively were contacted.

Study participants responded to a 40-item telephone-based interview checklist including demographic information, current diseases, clinical outcomes, signs and symptoms, designed by a team of specialists (i.e., epidemiologists, statisticians, pulmonologists and infectious disease specialists) who were treating or studying COVID-19 disease. The content and face validity of this checklist were approved with Content Validity Ratio (CVR) > 0.7. The time interval between the referrals of and phone calls to patients was minimum 10 days (Min = 10, Max = 16).

2.1. Ethical considerations:

In this study, the principle of information confidentiality was observed and participants would have willingly participated in this study. The research procedure was entirely consistent with the Human Ethics Committee of the Baqiyatallah University of Medical Sciences, and was implemented with an ethical number (IR.BMSU. REC.1399.044).

2.2. Statistical analysis

Categorical variables were compared by Chi-square (χ2) tests or Fisher's Exact Test and presented as n (%), whereas continuous variables were compared using the Mann-Whitney *U* test and were reported as median (Inter Quartile Range). In this study, logistic regression (OR with 95% confidence interval) was used to explore the risk factors related to COVID-19 and hospital admission. The SPSS software (version 18) and P-value<5% were used for statistical inferences and statistical significances, respectively.

3. Results

The data were obtained from 292 laboratory-confirmed COVID-19 patients and 296 non-COVID-19 patients referring to the KVSL in Tehran, Iran, during the study period. The mean age was 44.42 years (SD: 14.87; range: 19–90; IQR: 21), and 39.57 years (SD: 14.12; range: 18–85; IQR: 19) for COVID-19 and non-COVID-19 cases, respectively.

The most common comorbidities in this study were hypertension [n = 63,10.7%], diabetes [n = 53, 9.0%], asthma and respiratory diseases [n = 29, 4.9%], radiotherapy [n = 19, 3.2%], autoimmune diseases [n = 17, 2.9%], heart failure [n = 14, 2.8%], stomach problems [n = 14, 2.8%], pregnancy [n = 9, 1.5%], coronary arteries [n = 8, 1.3%], cancer [n = 7, 1.1%], open-heart surgery [n = 5, 0.8%], chemotherapy [n = 3, 0.5%] and history of dialysis [n = 2, 0.3%].

The demographics, baseline features, and symptoms of patients with and without COVID-19 are presented in Table 1, where diseases with a

Table 1
Demographics, baseline features, and symptoms of patients with COVID-19 and non-COVID-19.

Demographic variables	COVID-19		OR 95% CI	P-value
	Positive (n = 292) N (%)	Negative (n = 296) N (%)		
Gender (Male)	180(%62)	169(%57)	1.21 (0.87–1.68)	0.226
Age (>50)	88(%30)	63(%21)	1.50 (1.09–2.30)	0.018
BMI (>25)	191(%66)	148(%51)	1.87 (1.34–2.61)	<0.001
Smoking (yes)	25(%9)	46(%16)	0.51 (0.31–0.85)	0.001
Trips out of town(yes)	38(%13)	42(%14)	0.90 (0.56–1.45)	0.719
Current disease Diabetes (yes)	40(%14)	13(%4)	3.45 (1.81–6.61)	<0.001
Hypertension (yes)	45(%15)	18(%6)	2.81 (1.59–4.99)	<0.001
Asthma and respiratory diseases (yes)	24(%8)	5(%2)	1.57 (0.81–3.01)	0.192
Corticosteroid therapy (yes)	18(6%)	6 (2%)	3.17 (1.4–8.12)	0.012
Sign and symptom				
Fever (yes)	164(%56)	111(%38)	2.13 (1.53–2.97)	<0.001
Cough (yes)	140(%48)	91(%31)	2.07 (1.48–2.91)	<0.001
Sore throat (yes)	45(%15)	63(%21)	0.67 (0.44–1.03)	0.07
Muscle and body pain (yes)	112(%38)	63(%21)	2.30 (1.59–3.31)	<0.001
Headaches (yes)	67(%23)	34(%12)	2.29 (1.46–3.59)	<0.001
Diarrhea (yes)	20(%7)	14(%5)	1.48 (0.73–2.99)	0.293
Nausea(yes)	37(%13)	22(%7)	1.81 (1.04–3.15)	0.039
Dyspnea (yes)	77(%26)	44(%15)	2.05 (1.35–3.10)	<0.001
Tachycardia (yes)	13(%5)	12(%4)	1.01 (0.495–2.46)	0.840
Sweating (yes)	30(%10)	23(%8)	1.36 (0.77–2.40)	0.315
Chills (yes)	101(%35)	48(%16)	2.73 (1.85–4.04)	<0.001
Runny nose (yes)	29(%10)	43(%15)	0.65 (0.39–1.07)	0.109
Anorexia (yes)	56(%19)	30(%10)	2.04 (1.31–3.39)	<0.001
Weakness and lethargy	94(%32)	49(%17)	2.39 (1.62–3.54)	<0.001
Outcomes				
Hospital admissions	48(16%)	14(5%)	3.96 (2.13–7.36)	<0.001
ICU admissions	16 (6%)	5 (2%)	3.37 (1.22–9.33)	0.014
Deaths	12 (4%)	2 (1%)	6.30 (1.40–28.4)	0.006

OR: Odds Ratio, 95% CI: 95% Confidence Interval

frequency of occurrence lower than 20 are not reported.

The findings indicated that risk factors such as high age and BMI, smoking, diabetes, hypertension, and corticosteroid therapy can increase the risk of COVID-19 (Table 1). As shown in Table 1, the findings revealed that signs and symptoms like fever, cough, and muscle pain/ body pain, headaches, dyspnea, chills, anorexia, weakness and lethargy were more frequent in COVID-19 patients compared with non-COVID-19 patients. Based on the findings presented in Table 1, COVID-19 cases appear to be at increased risk for hospitalization, ICU hospitalization, and mortality. The risk factors for hospital admissions of COVID-19 and

non-COVID-19 patients are presented in Table 2 (i.e., signs and symptoms, demographic variables, and current disease status). The results revealed that comorbidities like diabetes, hypertension, asthma and respiratory diseases in addition to some symptoms such as fever, chills, dyspnea, anorexia, weakness and lethargy were the most predictive variables accounting for non-COVID-19 cases' hospitalization. Moreover, demographical variables such as gender, age, BMI, travel, comorbidities including diabetes, hypertension and corticosteroid therapy and symptoms like anorexia and dyspnea were found to be the most predictive variables for hospitalization of COVID-19 patients.

4. Discussion

Numerous COVID-19 studies in Iran and other countries have been performed based on patients admitted to the hospital with moderate-to-severe coronavirus diseases, but the present study aimed to evaluate the risk factors affecting positive and negative COVID-19 test results. The aim of this retrospective case control study was to provide preliminary data on the risk of hospitalization among COVID-19 patients.

In the current study, the main clinical symptoms of COVID-19 patients were fever (56%), cough (48%), muscle and body pain (38%), weakness and lethargy (32%), and dyspnea (26%), while minor symptoms included runny nose (10%), diarrhea (7%), and tachycardia (5%). These findings are more or less consistent with *meta*-analysis studies performed by Li et al. [17], Zhu et al. [18], Li et al [19], Qiu et al. [20], Pormohammad et al. [21] and Olumade et al. [22], indicating that individuals with clinical features linked to the disease should be monitored closely.

Our results also showed that signs and symptoms such as chills [OR = 2.73], weakness and lethargy (OR = 2.39), muscle and body pain [OR = 2.3], headaches [OR = 2.29], fever [OR = 2.13], cough [OR = 2.07] and dyspnea [OR = 2.05] were more frequent in COVID-19 patients compared with non-COVID-19 cases. Among the clinical symptoms recorded in our study, variables such as chills, fever, cough, fatigue or muscle pain, and headaches were not significant predictors of hospitalization, when the symptoms were separately considered in the model to evaluate the impact of the factors on the patients' hospitalization.

Therefore, regarding the risk of hospitalization, these symptoms could not be considered as general predictors. However, the present model identified dyspnea and anorexia as the most important symptoms associated with odds of hospitalization in COVID-19 patients, while anorexia was found to increase the odds of hospitalization in non-COVID-19 patients.

Based on a systematic review and *meta*-analysis, the clinical manifestations such as fever [OR = 0.56] and shortness of breath or dyspnea [OR = 4.16] have attested to their association with the progression of the disease [23]. Another *meta*-analysis study reported that dyspnea [OR = 4.52], chest tightness [OR = 2.50], hemoptysis [OR = 2.00], expectoration [OR = 1.52] and fatigue [OR = 1.27] were significantly associated with increased risk of mortality in COVID-19 patients [24], indicating their values as independent predictors of death. Based on the data presented herein, older age [OR = 1.5] and obesity [OR = 1.87] were found to be more frequent in COVID-19 patients when compared with non-COVID-19 cases. This result was in line with previous studies. Yang et al. in a *meta*-analysis study [25] showed that obesity was linked to a higher risk of COVID-19 disease [OR = 1.39] and severity of COVID-19 (hospitalization rate [OR = 2.45], severe cases [OR = 3.74], need for intensive care unit admission [OR = 1.30], need for invasive mechanical ventilation [OR = 1.59] and mortality [OR = 1.65]).

We also found that a remarkable proportion of the patients admitted to hospital had a history of diabetes and/or BMI > 25 when all variables were separately considered in the model. Risk of hospitalization was higher among COVID-19 patients who had BMI>25 and diabetes.

Xiang et al. [26] showed that the age of patients (age ≥ 60) is associated with in-hospital deaths [OR = 4.94]. Data from initial studies in China also indicated that case fatality ratio could be markedly elevated with age [27].

This study presented that the most commonly comorbidities of COVID-19 infections were diabetes [OR = 3.45], hypertension [OR = 2.81] and corticosteroid therapy (in immunosuppressed patients) [OR = 3.17]. Hypertension [OR = 2.29] and diabetes, etc. [OR = 2.47] have been reported to be independent risk factors linked to COVID-19 severity by Wang et al. [28], suggesting their use for early medical management of COVID-19 disease.

Table 2
The risk factor for hospital admission in COVID-19 and non-COVID-19 patients.

Demographic variables	COVID-19 (Positive)			COVID-19 (Negative)		
	Hospitalized (yes) (n = 48) N (%)	Hospitalized (no) (n = 244) N (%)	OR 95% CI	Hospitalized (yes) (n = 14) N (%)	Hospitalized (no) (n = 282) N (%)	OR 95% CI
Gender (Male)	40 (83%)	140(57%)	3.71**(1.67–8.27)	5(36%)	164(58%)	0.4(0.13–1.22)
Age (>50)	23(48%)	63(26%)	3.12**(1.65–5.89)	6(42%)	57(20%)	2.93(0.97–8.79)
BMI (>25)	37(80%)	154(63%)	2.37*(1.09–5.15)	6(50%)	142(51%)	0.95(0.30–3.04)
Smoking (yes)	3(6%)	22(9%)	0.67(0.19–2.34)	2(14%)	44(16%)	0.90(0.19–4.17)
Trips out of town (yes)	12(25%)	26(10%)	2.79*(1.29–6.03)	4(29%)	38(13%)	2.5(0.76–8.60)
Current disease						
Diabetes (yes)	17(35%)	23(9%)	5.26**(2.5–10.94)	3(21%)	10(3%)	7.42*(1.7–30.8)
Hypertension (yes)	16(33%)	29(12%)	3.7*(1.81–7.57)	3(21%)	15(5%)	4.85* (1.22–19.26)
Asthma and respiratory disease (yes)	5(10%)	19(8%)	1.37 (0.49–3.88)	3(21%)	13(5%)	5.64* (1.40–22.17)
Corticosteroid therapy (yes)	7(15%)	11(4%)	3.62* (1.32–9.87)	1 (7%)	5 (2%)	4.2 (0.46–39.2)
Sign and symptom						
Fever (yes)	26(46%)	138(57%)	0.91(0.49–1.69)	11(79%)	100(35%)	6.67**(1.82–24.5)
Cough (yes)	26(46%)	114(47%)	1.35(0.72–2.51)	4(29%)	87(31%)	0.90(0.27–2.94)
Muscle or body pain (yes)	16(33%)	96(39%)	0.77(0.40–1.48)	6(43%)	57(20%)	2.96(0.99–8.87)
Headache (yes)	10(21%)	57(23%)	0.86(0.40–1.84)	1(7%)	33(12%)	0.58(0.07–4.58)
Nausea(yes)	38(79%)	10(21%)	2.11(0.95–4.73)	2(14%)	20(7%)	2.18(0.45–10.43)
Dyspnea (yes)	30(62%)	47(19%)	6.99**(3.6–13.59)	6(43%)	39(13%)	4.8**(1.58–14.65)
Chills (yes)	19(40%)	82(34%)	1.29(0.68–2.44)	9(64%)	39(14%)	11.2**(3.57–35.2)
Anorexia (yes)	16(33%)	40(16%)	2.55**(1.28–5.08)	7(50%)	23(8%)	11.3**(3.63–34.2)
Weakness and lethargy	28(58%)	20(42%)	1.64(0.86–3.09)	7(50%)	42(15%)	5.7**(1.96–17.13)

ARD: Asthma and respiratory disease, COT: Corticosteroid Therapy, **: P-value < 0.01, *: P-value < 0.05

In the present study, the odds of hospitalization were found to be higher in males [OR = 3.71]. In a systematic review and *meta*-analysis, male gender [OR = 1.76] has been shown to have contributed to a higher risk of developing into critical or mortal conditions among COVID-19 patients [23]. This result can be justified by more risky behaviors in males and stronger immune responses of females [29].

It has been also reported that older age along with co-morbidities may be an important predictor of mortality resulting from COVID-19, SARS and MERS [30–32]. Therefore, in the initial screening; older patients who are immunocompromised should be considered as having a higher risk for developing moderate to severe form of the disease.

The limitations of this study included the lack of some clinical and laboratory findings due to the design of study, access to KVSL information only in the period from 10 March to 23 March 2020 and not using CT scan usage for increasing the accuracy of COVID-19 detection [33].

5. Conclusion

Based on the results presented herein, having included Covid-19 negative and positive cases, our data exhibited increasing odds of hospital admissions associated with demographic variables like male gender, high age, BMI, travel, comorbidities including diabetes, hypertension and underlying immunosuppressant patients receiving corticosteroid therapy in addition to symptoms like anorexia and dyspnea, indicating that motoring these indicators could have predictive values for such patients.

The findings of this study may provide a framework in clinical practice. However, additional large samples are required to verify the findings.

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