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Original Article

Predictors and clinical outcomes of silent hypoxia in COVID-19 patients, a single-center retrospective cohort study



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ARTICLE INFO

Article history:

Received 28 May 2021

Received in revised form 6 September 2021

Accepted 12 September 2021

Keywords:

SARS-CoV-2

COVID-19

Hypoxia

Silent hypoxia

Mortality

Risk factors

ABSTRACT

Background: Patients with COVID-19 usually present with fever and respiratory symptoms such as cough, sputum production, and dyspnea. However, they may suffer from severe hypoxemia without a clinical correlation with the respiratory symptoms, also known as silent or apathetic hypoxia. The aim of the study was to assess the predictors and clinical outcomes of COVID-19 patients without dyspnea.

Methods: A single-center retrospective cohort study, based on data extracted from the electronic hospital information system, with COVID-19 patients over a 10-month period in Riyadh, Saudi Arabia.

Results: Of the COVID-19 patients presenting at the Emergency Department with a SpO₂ < 90%, 13% had silent hypoxia. The majority of the patients required BiPAP, 34% were intubated and 60% were admitted to an intensive care unit. There was no association between dyspnea and gender, age group, body mass index, or comorbidity. Cough, fever, and chronic cardiac diseases were predictive for dyspnea in a regression analysis. There was no difference in the clinical outcome between patients with silent dyspnea or dyspnea. Age and obesity were significantly associated with a decrease in survival, and an increase in the initial SpO₂ increased survival.

Conclusion: Patients with cardiac disease are more likely to present with silent hypoxia. The SpO₂ saturation in COVID-19 may be an independent predictor of survival. Silent hypoxia in COVID-19 patients does not appear to have an association with increase in mortality.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19, has become a global threat in a short period of time. COVID-19 is a positive sense, single-strand enveloped RNA virus belonging to the family Coronaviridae, which have an extensive range of natural hosts [1]. The emergence of SARS-CoV-2 marked the third introduction of a highly pathogenic coronavirus since the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [2]. The World Health Organization declared the novel coronavirus COVID-19 outbreak a global pandemic on

March 11, 2020 [3]. As of 1st of September 2021, there are over 217 million confirmed cases globally and over 544 thousand cases locally [4]. SARS-CoV-2 transmission occurs through direct means (droplets, human-to-human transmission) or indirect means (contaminated objects and airborne contagion) [5]. Respiratory droplets when a patient sneezes, coughs, or talks can be transmitted up to six feet [5]. In addition, the virus is suspended in the air for 3 h [5].

A patient with COVID-19 usually presents with fever and respiratory symptoms such as cough, sputum production and dyspnea [6]. Upper airway symptoms, including sore throat and nasal congestion occurs in mild disease [6]. In addition, the patient may present with extra-respiratory manifestation including gastrointestinal, olfactory, cardiac, renal, hepatic, cutaneous and ocular symptoms [6]. A patient with COVID-19 may have severe hypoxemia without a clinical correlation of respiratory symptoms, known as silent or apathetic hypoxia [7]. In COVID-19 patients, respiratory failure usually develops 8–14 days following the onset of

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symptoms, if combined with silent hypoxia and tachypnea [7]. A case report from Oslo University hospital in April 2020 described a COVID-19 case of a man in his sixties who initially developed fever and cough. The patient was deeply cyanotic but not agitated or in distress, although the oxygen saturation was 66%, and the respiratory rate 36 per minute [7]. In May of 2020, another case report was published about a 72-year-old obese male with a history of diabetes and hypertension, who presented at the Emergency Department (ED) with minimal respiratory symptoms but a low oxygen saturation [8]. Within a few days, the patient's condition worsened and he died [8]. In 2020, the University of Chicago Stritch School of Medicine, US reported three patients with hypoxia with minimal respiratory symptoms. All denied any difficulty in breathing, and was comfortable without any apparent respiratory distress [9]. In September 2020, an Indian case report described a 56-year-old male smoker with diabetes, presenting with low-grade fever, dry cough, fatigue, and loss of appetite, but he denied having dyspnea although the oxygen saturation was 78% on room air [10]. In addition, a 2020 US study concluded that home pulse oximetry, telemonitoring, and earlier institution of oxygen supplementation for hypoxemic COVID-19 outpatients could be beneficial [11]. However, since the novel virus is not fully understood, the current study aimed to assess the predictors and clinical outcomes of COVID-19 patients without dyspnea.

Methods

Study setting and design

This was a single-center retrospective cohort study based on data extracted from an electronic hospital information system (BESTCare) of patients presenting at a tertiary academic medical center in Riyadh, Saudi Arabia. The hospital has a bed capacity of 1501 with more than 100 emergency beds. All patients who present at the ED are triaged by the emergency staff, depending on the condition and vital signs which are manually entered in the BESTCare system.

Study participants and data collection

The study included all pediatric and adult patients admitted from March 24, 2020 to December 31, 2020 through the ED with an initial pulse oximeter reading, oxygen saturation (SpO₂), <90% at room air and a positive COVID-19 polymerase chain reaction (PCR) test. The study excluded patients with a missing initial SpO₂ at room air (2 patients). The data included demographic information (age, gender, body mass index (BMI), and initial vital signs), symptoms, comorbidities, initial blood gas, and the clinical management.

Statistical analysis

Data were analyzed with the Statistical Package for the Social Sciences (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY). The demographic information and baseline characteristics were summarized and are reported in frequency and proportion, and the comparison between dyspnea and silent hypoxia cases was done with a Chi-square test. The prevalence was calculated with a 95% confidence interval (CI). A model was run for a binary logistic regression including cough, fever, nausea, vomiting, diarrhea, sore throat, comorbidities, and medication. The model was run twice to assess the predictors for presenting with silent hypoxia and the predictors for mortality. The 95% CI and odds ratio (OR) were reported. All tests were considered significant with a *p*-value less than 0.05.

Table 1
Baseline characteristics of the sample.

Variable	Category	N	%
Gender	Male	133	68
	Female	62	32
Age (years)	<45	32	16
	45–54	29	15
	55–64	55	28
	65–74	42	22
	>= 75	37	19
	Underweight	8	4
Body mass index	Normal	25	13
	Overweight	58	30
	Obese	104	53
	Shortness of breath	170	87
Triage symptoms	Cough	150	77
	Fever	133	68
	Nausea & vomiting	7	4
	Diarrhea	5	3
	Sore throat	29	15
	Other	11	6
	Shortness of breath	154	79
Physician symptoms	Cough	133	68
	Fever	136	70
	Nausea & vomiting	18	9
	Diarrhea	9	5
	Sore throat	12	6
	Other	50	26
	Hypertension	102	52
	Diabetes	97	50
	Dyslipidemia	35	18
	Cancer	7	4
Comorbidity	Chronic respiratory disease	11	6
	Chronic heart disease	31	16
	Chronic kidney disease	10	5
	Obesity	104	53
	Bronchial asthma	16	8
	Epilepsy	6	3
	Other comorbidities	41	21
Bilevel positive airway pressure (BiPAP)	56	29	
Intubation	66	34	
ICU admission	116	60	
Month of presentation	March	1	1
	April	3	2
	May	18	9
	June	103	53
	July	27	14
	August	14	7
	September	8	4
	October	6	3
	November	10	5
	December	5	3
	<4	18	16
	ICU length of stay (days)	4–7	28
8–14		31	27
>14		39	34
Heparin		175	90
Medications	Azythromycin	50	26
	Steroid	110	56
	Hydroxychloroquine	5	3
	Zinc	31	16
	Vitamins	36	19
Clinical outcomes	In-hospital death	51	26
	Alive	144	74

Results

This study included all the patients presenting at the ED with a SpO₂ < 90% from March 24, 2020 to December 31, 2020. Of 195 patients, 133 (68%) were male. The highest proportion (n = 163, 84%) of the sample were in the 45 years and above age group. For the BMI, more than two thirds of the sample (n = 162, 83%) were in the overweight or obese categories. The most frequent triage symptoms were dyspnea (n = 170, 87%), cough (n = 155, 77%) and fever (n = 133, 68%). The physician identified symptoms were almost similar to the triage symptoms, with dyspnea (n = 154, 79%), cough (n

Table 2
Clinical characteristics of the sample by dyspnea status.

Variable	Category	No dyspnea (N = 25)		Dyspnea (N = 170)		p-Value
		N	%	N	%	
Gender	Male	18	72	115	68	0.663
	Female	7	28	55	32	
	<45	5	20	27	16	
Age (years)	45–54	2	8	27	16	0.827
	55–64	8	32	47	28	
	65–74	6	24	36	21	
	> = 75	4	16	33	19	
	Underweight	3	12	5	3	
Body mass index	Normal	2	8	23	14	0.126
	Overweight	9	36	49	29	
	Obese	11	44	93	55	
	Cough	10	40	140	82	
Triage symptoms	Fever	10	40	123	72	<0.01
	Nausea & vomiting	1	4	6	4	0.906
	Diarrhea	0	0	5	3	0.385
	Sore throat	3	12	26	15	0.666
	Other	1	4	10	6	0.703
	Shortness of breath	16	64	138	81	0.049
	Cough	17	68	116	68	0.981
	Fever	14	56	122	72	0.109
	Nausea & vomiting	2	8	16	9	0.82
	Diarrhea	0	0	9	5	0.239
Physician symptoms	Sore throat	0	0	12	7	0.17
	Other	9	36	41	24	0.204
	Hypertension	14	56	88	52	0.692
	Diabetes	12	48	85	50	0.852
	Dyslipidemia	5	20	30	18	0.775
	Cancer	0	0	7	4	0.301
	Chronic respiratory disease	1	4	10	6	0.703
	Chronic heart disease	8	32	23	14	0.018
	Chronic kidney disease	2	8	8	5	0.486
	Obesity	11	44	93	55	0.316
Comorbidity	Bronchial asthma	2	8	14	8	0.968
	Epilepsy	1	4	5	3	0.775
	Other comorrbidities	4	16	37	22	0.509
	Bilevel positive airway pressure (BiPAP)	4	16	52	31	0.132
	Intubation	3	12	63	37	0.013
	ICU admission	9	36	107	64	0.007
	March	0	0	1	1	
	April	1	4	2	1	
Month of presentation	May	2	8	16	9	0.815
	June	15	60	88	52	
	July	1	4	26	15	
	August	2	8	12	7	
	September	1	4	7	4	
	October	0	0	6	4	
	November	2	8	8	5	
	December	1	4	4	2	
	<4	2	22	16	15	
	ICU length of stay (days)	4–7	3	33	25	
8–14		2	22	29	27	
>14		2	22	37	35	
Heparin		21	84	154	91	0.311
Medications	Azythromycin	5	20	45	27	0.489
	Steroid	11	44	99	58	0.18
	Hydroxychloroquine	1	4	4	2	0.627
	Zinc	3	12	28	17	0.568
	Vitamins	2	8	34	20	0.149
	In-hospital death	2	8	49	29	
Clinical outcomes	Alive	23	92	121	71	0.027

= 133, 68%) and fever (n = 136, 70%). Almost half had hypertension (n = 102, 52%) and diabetes (n = 97, 50%).

Regarding the management, the highest proportion of the sample required either bi-level positive airway pressure (BiPAP) (n = 56, 29%) or intubation (n = 66, 34%). More than half of the sample required admission to an intensive care unit (ICU) (n = 116, 60%). Of the ICU group, only 18 (16%) were admitted for less than 4 days. Heparin (n = 175, 90%), azithromycin (n = 50, 26%), and steroids (n = 110, 56%) were the most frequently administered treatment. In

terms of survival, 74% (n = 144), survived. The baseline characteristics for the sample is listed in [Table 1](#).

According to [Table 2](#), the majority of the sample (68%, n = 115) with dyspnea were male, and in the group with no dyspnea, 72% (n = 18) were male. Age and BMI were not statistically significant between the two groups. The group with silent hypoxia had significantly less cough (40%) and fever (40%) compared to the group with dyspnea (cough 82% and fever 72%), (p = <0.01 and 0.001). Hypertension, diabetes, dyslipidemia, cancer, chronic respiratory disease, chronic kidney disease, obesity and bronchial asthma were

Table 3
Forward stepwise logistic regression for the predictors of dyspnea.

Variables	p-Value	OR (95% CI)
Cough	<0.001	6.26 (2.47–15.9)
Fever	0.007	3.63 (1.43–9.26)
Chronic heart disease	0.055	0.36 (0.12–1.02)

OR, odds ratio; CI, confidence interval.

Table 4
Forward stepwise logistic regression for the predictors of survival.

Variables	p-Value	OR (95% CI)
Increase in age	<0.001	0.94 (0.92–0.97)
Increase in BMI	0.029	0.95 (0.92–0.99)
Increase in initial SaO ₂	0.008	1.05 (1.03–1.02)

OR, odds ratio; CI, confidence interval.

not significant between the two groups. Chronic cardiac disease were more prevalent ($n = 8$, 32%) in the silent hypoxia group compared to 14% ($n = 23$) in the dyspnea group ($p = 0.018$). Intubation and ICU admission were higher in the dyspnea group (37% $n = 63$, 64% $n = 107$, respectively) than the silent hypoxia group (12% $n = 3$, 36% $n = 9$, respectively), (p -value = 0.013 for intubation and 0.007 for ICU admission).

There was no relationship between dyspnea and gender, age group, body mass index, or comorbidity. Cough, fever, and chronic heart diseases were predictive for dyspnea in a regression analysis (Table 3). There was a significant association between cough and dyspnea (OR 6.26; 95% CI 2.47–15.9). Fever was also strongly associated with dyspnea (OR 3.63; 95% CI 1.43–9.26). In addition, patients with a chronic heart disease were more likely to experience silent dyspnea than patients with chronic kidney disease (OR 0.36; 95% CI 0.12–1.02).

The current study indicated no association between survival and gender, triage symptoms, or comorbidities. However, age was significantly associated with a decrease in survival (OR 0.94; 95% CI 0.92–0.97), and similarly, patients with a high BMI were strongly associated with a decrease in survival (OR 0.95; 95% CI 0.92–0.99). An increase in the initial SpO₂ was associated with increased survival (OR 1.05; 95% CI 1.03–1.02). Interestingly, there was no difference in the clinical outcome in the groups with silent dyspnea and dyspnea. The regression for the predictors of survival is summarized in Table 4.

Discussion

In all countries affected by COVID-19 in early 2020, EDs and ICUs admitted mostly COVID-19 patients. There was a global increase in the reported infection rate and mortality [3,12,13]. However, literature reported many patients with COVID-19 presenting with silent hypoxia [14–16]. It is important to know the risk factors and the causes contributing to the presentation of silent hypoxia in COVID-19 patients. The purpose of this study was to identify the factors and the outcomes in COVID-19 patients presenting at a tertiary academic hospital with an initial SpO₂ < 90.

One of the distinctive features of patients diagnosed with COVID-19 is the presence or absence of dyspnea (“silent” or “happy” hypoxia), in relation to their level of oxygen saturation [17]. Experiencing dyspnea is a subjective feeling reported by the patient [18]. According to the American Thoracic Society “dyspnea per se can only be perceived by the person experiencing it” [19]. A study by Busana et al. reported the prevalence of silent hypoxia in 213 patients as 31.9%, with 68.1% of patients dyspneic hypoxemic [17]. The prevalence of hypoxia in the COVID-19 patients was similar to what have been reported in the USA [20], China [21] and Italy [22]. In France, the prevalence of silent hypoxia and dyspnea were

64.7% and 35.3%, respectively [23], and an Indian study with 1370 patients reported that 78% had hypoxia [24]. A Peruvian study with COVID-19 cases concluded that 64.4% were hypoxic, similar to a Chinese study by Xie et al. indicating the prevalence of dyspnea as 64.71% [25]. In the current study, the prevalence of silent hypoxia was 13%, which is lower than reported in literature.

In the current study, most of the group (68%) with dyspnea were male. A similar study conducted in France reported the prevalence of dyspnea in males as 42.5% [23], and in the Indian study, 58.2% of the male patients were hypoxic [24]. In Milan, the prevalence of silent hypoxemia in females was 63.2%, which is inconsistent with the current study indicating that the majority of the silent hypoxia group (72%) were male. Most of the group (72%) with silent hypoxia in this study were older than 54 years, in contrast to a study by Brouqui et al. reporting that 57.3% of the silent hypoxia patients were less than 55 years [23]. However, a European study reported the mean age for the patients with silent hypoxemia as 67.8 [17]. In the current study, 55% of the group with dyspnea were obese (BMI of 30 kg/m² and above), higher than the 5.2% reported in Italy [17]. The rate of admission to ICU for silent and dyspneic hypoxemic patients was 36% vs 64% in the current study compared to 26.5% vs. 38.6% reported in Italy [17]. In France, only 5.1% of the silent hypoxia cases was admitted to ICU [23]. In the current study, 37% of the dyspneic group were intubated, compared to a study reporting that 8% of COVID-19 patients with dyspnea were intubated [24]. In the Brouqui et al. study regarding the effect of chronic cardiac disease on silent hypoxia in COVID-19 patients, reported an increased risk in chronic cardiac disease patients, similar to the current study [23]. However, the Brouqui et al. study found that chronic respiratory disease increased the risk of silent hypoxia, not supported by the current study.

COVID-19 patients may present with a decreased oxygen saturation due to the ongoing respiratory tract infection, with the body attempting to compensate for the decreased oxygen level through several physiological mechanisms. An important consideration is whether the oxygen saturation at the initial presentation has a prognostic value or not. The current study indicated that a decrease in the oxygen saturation in the initial presentation is associated with a poorer outcome which is consistent with a study by Dillon et al. suggested that the pre-hospital lowest recorded oxygen saturation may be a predictor of mortality in COVID-19 patients [26]. Similarly, a study from the United Kingdom reported that the oxygen saturation at room air as a strong predictor for patient outcome and mortality [27], also supported by a Peruvian study reporting that an oxygen saturation lower than 90% on admission was an important predictor of in-hospital mortality in patients with COVID-19 [28]. Another study concluded that a low level of oxygen on admission was strongly associated with more critical illness and mortality [20].

Locally in Saudi Arabia, on 2 March 2020, the first case of the COVID-19 pandemic was confirmed by the Ministry of Health, followed by a restriction on international travel the next day. By the 21st of May, a lockdown was mandated with other measures to control the pandemic. Although the government took early precautionary measures by enforcing the restriction of movement and travel, the number of daily cases gradually increased. On June 16, the number of new daily cases peaked at 4919 positive cases. However, due to the early intervention and availability of medical equipment, including oxygen and ventilators, the mortality rate was of the lowest compared to other countries. By the beginning of July, the curve in Saudi Arabia reached the peak with a total number of confirmed cases exceeding 100,000 [29]. The majority of the cases of silent hypoxia in the study occurred during the peak. The absence of dyspnea in the initial assessment of a COVID-19 patient should be not be interpreted as a mild case. The current study and

other studies recommend a SpO₂ pulse oximetry for all patients with symptoms of COVID-19 to detect silent hypoxia cases.

The current study is the first local study to identify the predictors of silent hypoxia in COVID-19 patients and the clinical outcomes. However, the study was a retrospective study, done in a single academic tertiary center, rather than multiple centers. Another limitation is that not all potential cofactors were available in the electronic system.

Conclusion

The results suggest that cardiac disease patients are more likely to present with silent hypoxia. The SpO₂ saturation in COVID-19 patient may be an independent predictor of survival. However, silent hypoxia in COVID-19 patients was not associated with increase in mortality. The current study investigated an aspect of silent hypoxia and highlights the need for accurate international and national databases to adequately assess and predict silent hypoxia in COVID-19 patients.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Ethical approval for the study was obtained from the Institutional Review Board, King Abdullah International Medical Research Center, National Guard-Health Affairs, Riyadh, Saudi Arabia, protocol number RC20.624.R.

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