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Clinical Features and Upper Airway Symptoms in Association with Severity and Outcome in Patients with COVID-19

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Abstract

Objectives: To assess the relationship between the early occurrence of upper respiratory tract symptoms and the severity of SARS-COV-2 infection.

Methods: A cohort observational study had been conducted on a total of 140 patients [60 mild, 40 moderate, 40 severe], diagnosed with SARS-CoV-2 between 4th of August and 31 of October 2020. Patients diagnosed by PCR or chest CT scan or both of them. A full history was taken from the patients and data including the age of the patient, gender, occupation, residence, height, weight, history of previous comorbidities {cardiovascular, Diabetes mellitus, Hypertension, chronic respiratory disease, chronic renal disease, malignancy, and other diseases}. Smoking and alcoholic history were also taken, clinical features {loss of smell/taste, sore throat, rhinorrhea, fever, cough, shortness of breath, headache, fatigue, myalgia, arthralgia, diarrhea, and vomiting} and temperature, SPO_2, investigations, the need for respiratory support {O_2, non-invasive ventilation, invasive ventilation} and any complications developed during illness.

Results: Mean age of the patients was 51 (range: 17–82) Males were dominant; (57.1%) with male to female ratio of 1.33 to one, out of the 140 COVID-19 patients, 63 (45%) had upper respiratory symptoms. Regarding biomarkers of severity only S. LDH was significantly lower in cases who did have compared to those who did not have upper respiratory symptoms, 1.3 ± 1.4 vs. 1.7 ± 1.3, respectively. The mean SPO_2% was significantly higher in patients with upper respiratory symptoms compared to those without. Percent of Pulmonary damage was significantly lower in patients with upper Respiratory symptom compared to those without. Mortalities were significantly lower in patients with upper respiratory symptoms compared to those without; among the 113 patients with upper respiratory symptom compared only 7 (6.2%) died compared to 7 out of 27 (25.9%) patients with no upper respiratory symptom.

Conclusion: Early occurrence of upper respiratory tract symptoms predicts less severe form of the disease.

Keywords: COVID-19, Anosmia, SARS-CoV-2, Pandemics, Iraq

Introduction

In the early of December 2019, SARS-COV-2 was discovered in China, Wuhan and leads to an ongoing pandemic disease.[1,2,3] Corona viruses are RNA viruses and there are four groups of coronavirus virus, are identified; alpha coronavirus, beta coronavirus, gamma coronavirus and delta coronavirus, of these alpha and beta coronaviruses are known to infect the human being.[4] SARS-CoV-1 was identified in 2002 in China and MERS-COV was identified in 2013 in Saudi Arabia both are beta COV.[5,6]

SARS-CoV-2 enters the human cells through angiotensin converting enzyme 2 receptors.[7,8] SARS-CoV-2 transmitted between humans by respiratory droplet of infected person [symptomatic or asymptomatic] coming in close (1 meter) or [aerosol particles] contact with person who are not infected with the virus, but this is not the only route of transmission indirect contact can also transmit the virus as touching surfaces contaminated with the virus and contact with mucous membranes of the mouth, nose or eye.[9,10,11,12]

The symptomatology of SARS-COV-2 infection is wide and reflect different systems involvement, general symptoms as fever, malaise, fatigue, bone pain and back pain are prominent, respiratory symptoms like cough, chest tightness and dyspnea are the most important clinical manifestation, upper respiratory symptoms like loss of smell, loss of taste, sore throat and rhinorrhea are occurring next in order, other systems are not an exception, neurological like headache and confusion, gastrointestinal like anorexia, diarrhea and vomiting, ophthalmic like conjunctivitis and retinitis, cardiovascular like acute myocardial injury and atrial fibrillation, rheumatological like arthralgia.[9] Fever, cough and fatigue are the three most common manifestation of SARS-CoV-2.[13,14] Isolated sudden onset loss of smell is the fourth most common manifestation of the disease.[15,16]

Surprisingly; sudden loss of smell/taste sense occurs without usual nasal symptoms {as sneezing, rhinorrhea, nasal obstruction and facial pain}, unlike other respiratory diseases caused by respiratory viruses {as influenza, rhinovirus, adenovirus}.

There are well described but not fully understood cause of anosmia which is post viral olfactory disorder {PVOD}, some physicians thought it is an inflammatory reaction of nasal mucosa while others thought the virus may damage the olfactory neuroepithelium or central olfactory pathway and transmitted to the brain directly {central nervous system including olfactory bulbs and olfactory cortex} with the development of micro vascular phenomenon and injury as micro bleeding and blood brain barrier break as demonstrated by MR imaging of patients with SARS-CoV-2 infection.[17]

Patients with SARS-CoV-2 may have mild symptoms as fatigue, loss of smell with no radiological manifestation or moderate as fever, dry cough but no dyspnea with radiological manifestations less than 50% or severe as having respiratory symptoms of dyspnea, hypoxia, cough, with radiological manifestation that is more than 50%.[9]

The diagnosis of SARS-CoV-2 is done by the detection of the virus by mean of real time-polymerase chain reaction {RT-PCR} assay from nasopharyngeal swab of infected patients,[18,19] false negative results may occur. Chest radiography is used as initial imaging method while the computed tomography {CT-scan} is very important in the diagnosis, prognosis and management plan of the disease as it found more sensitive than RT-PCR for detecting SARS-CoV-2 {98% vs. 71%}.

Other laboratory tests are helpful in the assessment of severity and complications including: complete blood picture {CBC}, coagulation profile {D-Dimer}, inflammatory markers {C-reactive protein, ferritin}, lactate dehydrogenase, creatine kinase, cardiac troponin and procalcitonin.[20]

Increase white blood cell count, increase neutrophil count, decrease lymphocyte count, increase lactate dehydrogenase, increase creatinine, increase D-dimer, increase C-reactive protein, CT invasion of more than 50%, SPO_2 of less than 93%, are associated with severe disease, unfavorable outcomes and complications.[20] Also being old {>65 year}, male sex, BMI >35 kg/m^2, have previous comorbidities {as hypertension, cardiovascular, diabetes mellitus, etc.} are also associated with severe disease.

All these factors were included in our study to assess the severity of the disease and its association with the clinical features and upper respiratory symptom.

Aim of Study

In this study we assess the relationship between the early occurrence of upper respiratory tract symptoms and the severity of SARS-CoV-2 infection.

Patients and Methods

A cohort observational study had been conducted on a total of 140 patients {hospitalized and non-hospitalized} hospitalized patients in Al-Sadder teaching hospital in Najaf Ashraf province diagnosed with SARS-CoV-2 between 4th of August and 31 of October 2020. Patients diagnosed by PCR or chest CT scan or both of them.

A full history was taken from the patients including the age of the patient, gender, occupation, residence, height, weight, history of previous comorbidities {cardiovascular, Diabetes mellitus, Hypertension, chronic respiratory disease, chronic renal disease, malignancy, and other diseases}. Smoking and alcoholic history were also taken, clinical features {loss of smell/taste, sore throat, rhinorrhea fever, cough, shortness of breath, headache, fatigue, myalgia, arthralgia, diarrhea, and vomiting} and temperature, SPO_2, the need for respiratory support {O_2, non-invasive ventilation, invasive ventilation} and any complications developed during illness.

Chest CT scan was done for symptomatic patients either before confirming the diagnosis with PCR or after confirming the diagnosis with PCR to assess the severity of the disease and treat the patient accordingly.

The patients were classified according to clinical presentations into:[9]

1-Mild: the clinical symptoms were slight and no signs of pneumonia on radiological imaging.

2-Moderate: symptoms of fever and respiratory tract symptoms and signs of pneumonia on radiological imaging.

3-Severe: patients meet any of the following criteria: a-respiratory distress {respiratory rate > = 30 breath/min. b-blood oxygen saturation <93%. c-lung infiltrate >50% of lung field on radiological imaging.

Very few patients with moderate, or severe disease confirmed by CT scan refuse PCR, so, PCR was not done for these patients.

Patients were sent for CRP, CBP {neutrophils, lymphocytes}, renal functions test, ferritin, lactate dehydrogenase and D-dimer.

Normal values of these biomarkers are: CRP = <10 mg/l, ferritin = 20–230 ng/ml

D-dimer = <400 ng/ml, LDH = 140–280 U/L.

The duration of hospitalization and the outcome of the patients whether recovered or died was followed.

Ethical consideration: Ethically this study was approved by the ethical committee of the Iraqi Board for Medical Specialization.

Statistical Analysis

Data of the studied group were entered managed and analyzed using the statistical package for social sciences (SPSS) version 25. Descriptive statistics presented as mean, standard deviation, frequencies and percentages according to the type of variables. To assess the relationship between categorical variables and severity of SARS-COV-2, chi square test was applied. As an alternative, Fisher's exact test used when chi square was inapplicable. Analysis of variances (ANOVA) test used to compare means across the severity categories, Kruskal-Wallis analysis used when ANOVA test couldn't be applied (variable did not follow statistical normal distribution), Student's *t* and Mann-Whitney tests when applicable, used to compare parameters according to presence of respiratory symptoms. Level of significance, *P*. value, of 0.05 or less considered significant.

Result

A total of 140 SARS-COV-2 patients were enrolled in this study with a mean age of 50.9 ± 15.1 (range: 17–82) Males were dominant; (57.1%) with a male to female ratio of 1.33 to one, other demographic characteristics and distributions are shown in (Table 1 and Figure 1).

Table 1. **Demographic characteristics of the studied group**

Variable		
Age	Mean (SD)	50.9 (15.1)
	Range	17–82
Gender *n* (%)	Male	80 (57.1)
	Female	60 (42.9)
Occupation *n* (%)	Employed	55 (39.3)
	Unemployed	85 (60.7)
Marital status *n* (%)	Married	130 (92.9)
	Unmarried*	10 (7.1)
Smoking *n* (%)	Smoker	24 (17.1)
	Non-smoker	116 (82.9)
BMI category *n* (%)	Normal	35 (25.0)
	Overweight	71 (50.7)
	Obese	34 (24.3)

SD: standard deviation. Mean (SD) BMI = 27.9 (4.1) (kg/m^2).

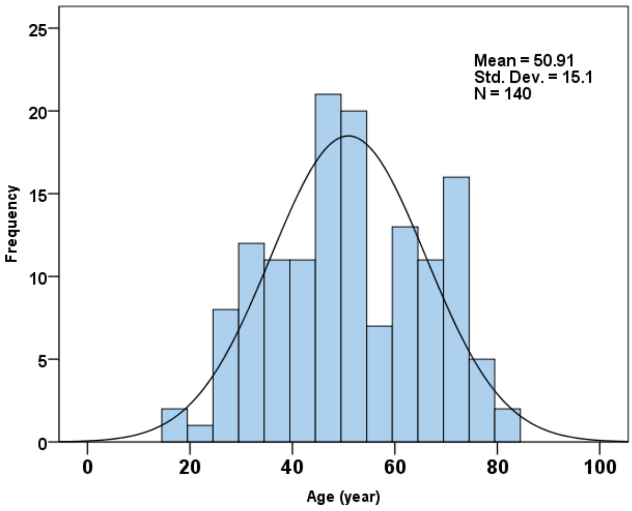

Fig. 1 **Age distribution of the studied group.**

Table 2. **History of chronic diseases reported among the studied group (*N* = 140)**

Chronic diseases and medication use	Total cases	Severity						*P*. value (chi-square test/ Fisher's)
		Mild (*n* = 60)		Moderate (*n* = 40)		Severe (*n* = 40)		
		No.	%	No.	%	No.	%	
Hypertension	50	15	30.0	16	32.0	19	38.0	0.057 NS
DM	37	8	21.6	17	45.9	12	32.4	
CVD	30	14	46.7	5	16.7	11	36.7	0.235 NS
Respiratory disease	7	2	28.6	2	28.6	3	42.9	0.640 NS
Renal disease	5	2	40.0	2	40.0	1	20.0	0.827 NS
Malignancy	2	0	0.0	0	0.0	2	100.0	0.079 NS
Hypothyroidism	2	0	0.0	1	50.0	1	50.0	0.467 NS
Rheumatoid arthritis	2	0	0.0	0	0.0	2	100.0	0.079 NS
Chronic use of medications	52	11	21.2	24	46.2	17	32.7	< 0.001 sig

* Some patients had more than one comorbidity.
sig: significant association (0.05 or less), NS: not significant.

Of those 140 patient, 40 had severe disease, 40 had moderate disease and 60 had mild disease.

The association between chronic diseases from one side and severity of SARS-COV-2 on the other side, no significant association was found between them, in all comparisons, *P*. value > 0.05), with exception of DM where significant association were found, among 37 patients with DM, only 8 had mild disease compared to 17 moderate and 12 severe disease, ($P = 0.016$).

Conversely, chronic use of medication was significantly associated with more severe disease where among 52 chronic medications users (anti-hypertensive, oral hypoglycemic agent, anti-ischemic…) only 21.2% had mild disease compared to 46.2% moderate and 32.7% severe disease, ($P < 0.001$), (Table 2).

Table 3. **Frequency distribution of reported symptoms of the studied group according to severity of COVID-19 (*N* = 140)**

Symptom*	Severity						*P*. value (chi-square test/Fisher's)
	Mild (*n* = 60)		Moderate (*n* = 40)		Severe (*n* = 40)		
	No.	%	No.	%	No.	%	
Fever	58	96.7	38	95.0	37	92.5	0.645 ns
Cough	56	93.3	38	95.0	35	87.5	0.415 ns
Headache	56	93.3	22	55.0	19	47.5	< 0.001 sig
Shortness of breath	23	38.3	36	90.0	36	90.0	< 0.001 sig
Sore throat	46	76.7	24	60.0	20	50.0	0.019 sig
Loss of smell	38	63.3	25	62.5	15	37.5	0.023 sig
Rhinorrhea	5	8.3	3	7.5	1	2.5	0.481 ns
Fatigue	44	73.3	19	47.5	25	62.5	0.032 sig
Myalgia	49	81.7	14	35.0	9	22.5	< 0.001 sig
Vomiting	19	31.7	8	20.0	5	12.5	0.072 ns
Arthralgia	8	13.3	8	20.0	13	32.5	0.068 ns
Diarrhea	3	5.0	7	17.5	2	5.0	0.058 ns

*Majority of patients had more than one symptom.
sig: significant association (*P* = 0.05 or less), NS: not significant.

Table 4. **Mean values standard deviation (SD) and range of measured temperature and SPO_2 of the studied group (*N* = 140)**

Parameter	Statistics	Severity			*P*. value (ANOVA test)
		Mild (*n* = 60)	Moderate (*n* = 40)	Severe (*n* = 40)	
Spo_2 (%)	Mean ± SD	97.2 ± 1.1	92.7 ± 1.2	74.8 ± 11.3	< 0.001 sig
	Range	95–99	90–94	50–88	
Temperature (°C)	Mean ± SD	38.1 ± 0.5	38.7 ± 0.7	38.7 ± 0.9	< 0.001 sig
	Range	37.0–39.0	37.0–40.0	37.0–40.0	

SD: standard deviation.
sig: significant association (*P* = 0.05 or less), NS: not significant.

Among symptoms, presence of headache, sore throat, loss of smell, fatigue and myalgia was significantly associated with mild disease, ($P < 0.05$), while presence of shortness of breath was significantly associated with more severe disease, (*P*. value < 0.001), other symptoms did not show significant associations, ($P > 0.05$), 0020 (Table 3).

A significant inverse association was found between SPO_2 level and severe disease; patients with mild disease had the higher SPO_2 levels with a mean of 97.2 ± 1.1% compared to 92.7% ± 1.2% in moderate disease patients and 74.8% ± 11.3% in severe disease patients, (*P*. value < 0.001).

Similarly, lower temperature was significantly associated with mild disease, 38.1 ± 0.5°C compared to 38.7°C in moderate and severe cases, ($P < 0.001$), (Table 4).

As shown in Table 5, CT-scan performed in 118 patients, among them a highly significant difference was found in percent of pulmonary damage reported by CT-scan, where mild cases had the lowest pulmonary damage (mean: 20.5% ± 8.8%) followed by moderate (mean: 36.9% ± 8.5%) and the larger percent of pulmonary damage in severe cases with a mean

Table 5. **Radiological findings of the studied group according to disease severity (*N* = 140)**

Parameter	Statistics	Severity			*P*. value
		Mild (*n* = 60)	Moderate (*n* = 40)	Severe (*n* = 40)	
CT scan (percent of pulmonary damage)*	Mean ± SD	20.5 ± 8.8	36.9 ± 8.5	64.6 ± 11.3	< 0.001 sig ANOVA
	Range	10–35	20–50	50–85	
Chest X-ray Finding no (%)	Infiltrate	21 (35.0)	14 (35.0)	15 (37.5)	< 0.001 sig Fisher's
	Normal	28 (46.7)	0 (0.0)	0 (0.0)	
	Not available	11 (18.3)	26 (65.0)	25 (62.5)	

SD: standard deviation, sig: significant difference
Fisher's exact test, chi square couldn't be applied
*CT scan performed in 118 patients only
sig: significant association (*P* = 0.05 or less), NS: not significant.

Table 6. **Frequency distribution of hospitalization, duration of hospital stays and need for respiratory support among patients with moderate and severe disease**

	Moderate (*n* = 40)	Severe (*n* = 40)	*P*. value
Hospitalization no. (%)	27 (67.5%)	40 (100.0)	< 0.001 sig Chi square
Duration hospital stay (day) Mean ± SD (range)	4.3 ± 2.1 (2–8)	13.8 ± 8.2 (3–55)	< 0.001 sig *t* test
Respiratory support no. (%)	23 (57.5)	40 (100.0)	< 0.001 sig Chi square

SD: standard deviation, sig: significant difference
sig: significant association (*P* = 0.05 or less), NS: not significant.

Table 7. **N Hematological WBC differential count regarding neutrophils & lymphocyte in pt. with COVID-19 (*N* = 140)**

Parameter		Severity						*P*. value Fisher's test
		Mild (*n* = 60)		Moderate (*n* = 40)		Severe (*n* = 40)		
		No.	%	No.	%	No.	%	
Neutrophil count	High	18	30.0	31	77.5	32	80.0	< 0.001 sig
	Normal	42	70.0	9	22.5	8	20.0	
Lympho-cyte count	High	2	3.3	0	0.0	0	0.0	
	Low	17	28.3	31	77.5	32	80.0	< 0.001 sig
	Normal	41	68.3	9	22.5	8	20.0	

sig: significant (0.05 or less).
*Result taken at presentation (before management).

Table 8. **Distribution of blood urea and serum creatinine levels according to disease severity of among studied group (*N* = 140)**

Parameter		Severity						*P*. value Chi square test
		Mild (*n* = 60)		Moderate (*n* = 40)		Severe (*n* = 40)		
		No.	%	No.	%	No	%	
Blood urea	High	6	10.0	8	20.0	16	40.0	0.002 sig
	Normal	54	90.0	32	80.0	24	60.0	
S. Creatinine	High	4	6.7	3	7.5	5	12.5	0.570 ns
	Normal	56	93.3	37	92.5	35	87.5	

sig: significant association (*P* = 0.05 or less), NS: not significant.

Table 9. **Distribution of biomarkers according to disease severity (*N* = 140)**

Parameter		Severity			*P*. value
		Mild (*N* = 60)	Moderate (*N* = 40)	Severe (*N* = 40)	
CRP	Mean ± SD	3.0 ± 1.7	4.1 ± 3.5	7.3 ± 4.8	< 0.001 sig
	Range	1–10	2–28	3–28	
S. Ferritin	Mean ± SD	1.2 ± 1.0	1.1 ± 1.1	4.2 ± 2.6	< 0.001 sig
	Range	1–3	1–5	1–10	
S. LDH	Mean ± SD	1.0 ± 1.0	1.0 ± 1.0	2.6 ± 1.4	< 0.001 sig
	Range	1.0–2.0	1.0–3.0	1.0–6.0	
D-Dimer	Mean ± SD	1.3 ± 0.9	2.2 ± 1.6	9.0 ± 4.1	< 0.001 sig
	Range	1–6.0	1–11.0	1–34	

CRP: C-reactive protein, S. LDH: serum lactate dehydrogenase, all parameters presented in mean folds elevated than normal, sig: significant association (*P* = 0.05 or less), NS: not significant.

percent of pulmonary damage of (64.6% ± 11.3%), (*P*. value < 0.001). With regard to chest X-ray findings, none, of the cases with moderate or severe disease form had normal X-ray findings, compared to 46.7% of mild cases (*P*. value < 0.001).

Hospitalization needed in 67.5% of moderate cases and all severe cases, (*P* < 0.001). The mean duration of hospital stay was significantly longer in severe cases, 13.8 ± 8.2 days, than moderate disease group, (4.3 ± 2.1 days), (*P* < 0.001).

All cases with severe disease needed respiratory support compared to 57.5% of moderate cases, (*P* < 0.001), it is worth mentioned that none of mild cases hospitalized or needed respiratory support, (Table 6).

Neutrophil count was significantly higher in severe cases while Lymphocyte count was significantly lower in severe cases, (*P* < 0.001), (Table 7).

A significantly higher blood urea reported in severe cases (*P* = 0.002), where 40% of severe cases had elevated blood urea compared to 20% of moderate cases and 10% of mild ones. No significant differences were reported in S. Creatinine (*P* > 0.05), (Table 8).

The comparison of biomarkers according to disease severity revealed that severe cases had significantly higher CRP, S. ferritin, S. LDH and D-dimer, in all comparisons, (*P* < 0.001), (Table 9).

All mild and moderate cases recovered, however, only 2 moderate cases developed complications and recovered later, among severe cases complications occurred in 50%, and unfortunately, 14 (35%) died, the differences in outcomes, were statistically significant, (Table 10).

The mean S. LDH level was significantly lower in cases who did have compared to those who did not have upper respiratory symptoms, 1.3 ± 1.4 vs. 1.7 ± 1.3, respectively, (*P*. value = 0.011). Neither CRP, S. Ferritin nor D-Dimer level significantly different across the presence of upper respiratory symptoms, (*P* > 0.05), (Table 11).

Table 10. **Outcomes of moderate and severe Covid-19 patients**

Outcome	Moderate (*N* = 40)		Severe (*N* = 40)		*P*. value Chi square test
	No.	%	No.	%	
Recovered	40	100.0	26	65.0	< 0.001 sig
Complications developed	2	5.0	20	50.0	< 0.001 sig
Died	0	0.0	14	35.0	< 0.001 sig

Table 11. **Relationship between Upper Respiratory symptom and markers of diseases severity**

Parameter	Upper Respiratory symptom		*P*. value
	Yes (*N* = 113)	No (*N* =27)	
	Mean ± SD*	Mean ± SD	
CRP level	4.4 ± 3.2	5.0 ± 3.8	0.552 ns
S. LDH	1.3 ± 1.4	1.7 ± 1.3	0.011 sig
S. Ferritin	1.8 ± 2.1	3.0 ± 2.6	0.175 ns
D-Dimer	2.8 ± 1.7	5.1 ± 3.4	0.070 ns

SD: standard deviation.

Table 12. **Relationship between of Upper Respiratory symptom with SPO_2 and CT scan findings of the studied group**

Parameter	Upper Respiratory symptom				*P*. value
	Yes		No		
	Mean	SD	Mean	SD	
Spo_2 (%)	90.7	9.7	84.3	15.5	0.007 sig
Chest CT scan (%) of pulmonary damage	34.6	20.2	49.1	21.2	0.001 sig

Table 13. **Relationship between of Upper Respiratory symptom with complication and mortality of COVID-19 patients (*N* = 140)**

		Upper respiratory symptoms				*P*. Value
		Yes (*n* = 113)		No (*n* = 27)		
		No.	%	No.	%	
Complications	Yes	15	13.3	7	25.9	0.105 Ns
	No	98	86.7	20	74.1	
Outcome	Recovered	106	93.8	20	74.1	0.002 Sig
	Died	7	6.2	7	25.9	

sig: significant association (*P* = 0.05 or less), NS: not significant.

The mean SPO_2% was significantly higher in patients with upper respiratory symptom compared to those without, (P = 0.007). Percent of Pulmonary damage was significantly lower in patients with upper Respiratory symptom compared to those without, (P = 0.001), (Table 12).

No significant association was found between complications and presence of upper respiratory symptom, (P > 0.05). Mortalities were significantly lower in patients with upper respiratory symptom compared to those without; among the 113 patients with upper respiratory symptom compared only 7 (6.2%) died compared to 7 out of 27 (25.9%) patients with no upper respiratory symptom, (P = 0.002), (Table 13).

Discussion

The clinical manifestations associated with SARS-COV-2 share some features with other respiratory viral infection but there are many areas of differences including the absence or minimal occurrence of rhinorrhea, severe and distressing cough and marked involvement of lung with severe destruction observed in many patients.[21,22]

Radiographic imaging has a significant role in confirmation of diagnosis and the assessment of severity of pulmonary damage and this helps in early recognition of critically ill patients to prevent unnecessary delay in intensive management and consequently increasing mortality.[23–30]

The present study is planned to assess the clinical features, in particular, upper respiratory symptoms and their association with CT findings and severity of disease in group of Iraqi patients.

In this study there was no significant association between having chronic diseases and severity of SARS-COV-2, with the exception of diabetic patients and chronic medication users had significantly more severe disease. Similar findings were also reported in previous studies; in large scale case-control study, Yan et al. found that chronic drug users had significant higher susceptibility and severity of disease,[31] Erener S documented that diabetic patients at high risk of infection and poor glycemic control are a major risk factor for infection and contributed that to the alteration in the immune function in diabetic patients.[32] On the other hand, other studies reported strong correlation between comorbid chronic disease and severity of SARS-COV-2;[33] Wang et al. found that comorbid chronic disease and acute organs injury was strongly and significantly associated with severe disease and higher mortality among patients with SARS-COV-2.[34]

Expectedly, in the present study, lower SPO_2% was significantly associated with more severe disease, similar findings reported in many other studies;[35–37] Xie et al. found a significant association between hypoxemia and higher mortalities.[35] Rubin et al. supported these findings.[36] Li et al.[37] found that oxygen saturation of less than 93% was significant predictor of poor prognosis and higher body temperature on admission was significantly associated with more severe disease.

Petrelli et al.[38] found that body temperature on admission was good predictor for viral infection and that higher temperature of 38°C or more would be good diagnostic indicator implies severe and critically ill patients, on the other hand, Petrelli et al.[38] documented higher proportion of patients with severe disease with temperature of more than 38°C compared to those with milder disease and non-hospitalized patients.

Conversely, Guan et al.[39] from China studied the clinical characteristics of 1909 SARS-COV-2 patients, among their findings no significant difference in the mean body temperature on admission between cases with non-severe and severe disease. The differences between studies could be due to the criteria that depended for admission and classification of disease severity in different countries, where in most studies, clinician not much rely on body temperature as indicator of severe disease, but some authors stated that patients with severe or critical illness, had significantly longer duration of

higher body temperature than the mild or non-severe cases. Furthermore, the duration of high body temperature in patients who transferred to ICU was almost 31 days compared to 9 days in other patients.[40]

The present study found that higher CT scan percent of pulmonary damage associated with severe disease this finding supported that in other studies,[41,42] where these studies documented that CT-scan detected pulmonary damage was significantly associated with disease severity and the proportion of pulmonary damage increased with severity.

In the current study, presence of infiltrate on chest x-ray was significantly associated with severe disease. It had been adopted that Chest-X-ray findings is helpful in monitoring the course and severity of SARS-COV-2.[43] Yasin and Gouda from Egypt found that severity score was significantly associated with abnormal X-ray findings and concluded that radiographic findings were good predictor for long term monitoring of SARS-COV-2 cases.

In the current study, patients with severe disease needed longer duration of hospitalization than the cases with moderate disease and all patients with severe disease needed respiratory support compared to only 57.5% of moderate cases, these findings were not unexpected due to nature of disease, and similar findings reported in most other studies,[36,38,40–42,44] in the present study none of mild cases were admitted, and this is according to the management recommendations of MOH in Iraq that mild cases send for home quarantine and followed up.

The blood count results of this study show increase neutrophils count and decrease lymphocytes count was found in severe cases compared to moderate and mild cases, Knong et al. reported that higher neutrophil and lower lymphocyte counts as demonstrated by higher neutrophil to lymphocyte ratio (NLR) was significantly associated with severe form of SARS-COV-2 and that patients with increased NLR should be admitted to an isolation ward with respiratory monitoring and supportive care.[45]

A meta-analysis conducted by Li et al.[46] proved good value of NLR in prediction of severe and critical disease. Another study indicated that high neutrophil and lower lymphocyte counts had good prognostic implications in SARS-COV-2, the higher NLR has been hypothesized to be associated with underlying endothelial dysfunction which favor cellular damage and then endothelial cell death particularly in patients with pre-existing endothelial dysfunction.[47]

Biomarkers including CRP, S. ferritin, S. LDH and D-Dimer were all significantly and proportionately increased with severity of SARS-COV-2; patients with severe disease had significantly higher mean values of these biomarkers than those with moderate disease while the level in mild cases were the lowest and these findings were consistent with other studies.[24,25,48–50]

Regarding the association between symptoms and severity of disease, the present study found that patients with headache, sore throat, loss of smell, fatigue and myalgia had significantly milder disease and those with shortness of breath had significantly more severe disease, while other symptoms did not show significant associations with severity of SARS-COV-2, the patients with upper respiratory symptoms had lower levels of CRP, S. ferritin, S. LDH and D-Dimer, higher SPO_2% and lower CT scan percent of pulmonary damage, these findings indicated less severe disease in patients with upper respiratory symptoms compared to those without.

Although the exact pathophysiology of post-viral anosmia is unclear, it is believed that damage to the receptor cells of the olfactory neuroepithelium is one of the probable causes.

Objective assessment of loss of smell was not done because of risk of infection transmission.

Conclusion

Early occurrence of upper respiratory tract symptoms predicts less severe form of the disease and good outcome of the patient.

Conflicts of Interest

None.

References

1. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. "The continuing 2019-nCoVepidemic threat of novel coronaviruses to global health—The latest 2019 novel corona virus outbreak in Wuhan, China". International Journal of Infectious Diseases. (February 2020) 91:264–266.
2. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study [published correction appears in Lancet. 2020 Feb 4;]. Lancet. 2020;395(10225):689-697.
3. Helmy YA, Fawzy M, Elaswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 pandemic: a comprehensive review of taxonomy, genetics, epidemiology, diagnosis, treatment, and control. J Clin Med 2020; 9(4): E1225.
4. Paules CI, Marston HD, Fauci AS. Coronavirus infections — more than just the common cold. JAMA 2020;323:707-8.
5. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8): 523-534. doi: 10.1038/nrmicro.2016.81PubMedGoogle ScholarCrossref
6. Song, Z., Xu, Y., Bao, L., Zhang, L., Yu, P., Qu, Y., ... & Qin, C. (2019). From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses, 11(1), 59.
7. Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2. Am J Physiol Renal Physiol. 2020;318(6):F1454-F1462. doi:10.1152/ajprenal.00160.2020.
8. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends onACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271-280.e8
9. Baj, J., Karakuła-Juchnowicz, H., Teresiński, G., Buszewicz, G., Ciesielka, M., Sitarz, R., & Maciejewski, R. (2020). COVID-19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. Journal of Clinical Medicine, 9(6), 1753.
10. CW Lu, XF Liu, ZF Jia. 2019-nCoV transmission through the ocular surface must not be ignored. Lancet, 395 (2020), p. e39,10.1016/S0140-6736(20)30313-5.
11. WG Carlos, CS Dela Cruz, B Cao, S Pasnick, S Jamil. Novel Wuhan (2019-nCoV) coronavirus. Am J Respir Crit Care Med, 201 (2020), pp. P7-P8, 10.1164/rccm.2014P7.
12. J Xia, J Tong, M Liu, Y Shen, D Guo. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol (2020 Feb 26), 10.1002/jmv.25725.
13. Fu L.; Wang B.; Yuan T.; Chen X.; Ao Y.; Fitzpatrick T.; Li P.; Zhou Y.; Lin Y.-F.; Duan Q.; et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J Infect 2020;80:656–665.
14. Sun P.; Qie S.; Liu Z.; Ren J.; Li K.; Xi J. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: a single arm meta-analysis. J Med Virol 2020;92:612–617.

15. Gane S.B.; Kelly C.; Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? Rhinology 2020;58:299-301. doi:10.4193/Rhin20.114.
16. Tong J.Y.; Wong A.; Zhu D.; Fastenberg J.H.; Tham T. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: a Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg 2020;163:3-11.
17. Aragão, M. D. F. V. V., Leal, M. C., Cartaxo Filho, O. Q., Fonseca, T. M., & Valença, M. M. (2020). Anosmia in COVID-19 associated with injury to the olfactory bulbs evident on MRI. American Journal of Neuroradiology, 41(9), 1703-1706.
18. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med 2020;382:1199-1207 DOI: 10.1056/NEJMoa2001316.
19. https://www.researchgate.net/publication/340447353_The_Laboratory_Diagnosis_of_COVID-19_Infection_Current_Issues_and_Challenges.
20. https://www.researchgate.net/publication/339627510_Laboratory_abnormalities_in_patients_with_COVID-2019_infection
21. Novel CPERE. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi. 2020;41(2):145.
22. Giesen C, Diez-Izquierdo L, Saa-Requejo CM, Lopez-Carrillo I, Lopez-Vilela CA, Seco-Martinez A, et al. Epidemiological characteristics of the COVID-19 outbreak in a secondary hospital in Spain. Am J Infect Control. 2020;
23. Velavan TP, Meyer CG. Mild versus severe COVID-19: laboratory markers. Int J Infect Dis. 2020;
24. Keddie S, Ziff O, Chou MKL, Taylor RL, Heslegrave A, Garr E, et al. Laboratory biomarkers associated with COVID-19 severity and management. Clin Immunol. 2020;221:108614.
25. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting disease severity and outcome in COVID-19 patients: a review of multiple biomarkers. Arch Pathol Lab Med. 2020;144(12):1465–74.
26. Ieong CM, Xu X, Kong SC, Luo L. Evaluation of chest CT and clinical features of COVID-19 patient in Macao. Eur J Radiol Open. 2020;7.
27. Jin C, Tian C, Wang Y, Wu CC, Zhao H, Liang T, et al. A Pattern Categorization of CT Findings to Predict Outcome of COVID-19 Pneumonia. Front Public Heal. 2020;8(September).
28. Matos J, Paparo F, Mussetto I, Bacigalupo L, Veneziano A, Perugin Bernardi S, et al. Evaluation of novel coronavirus disease (COVID-19) using quantitative lung CT and clinical data: prediction of short-term outcome. Eur Radiol Exp. 2020;4(1).
29. Zhong L, Zhang S, Wang J, Zhao X, Wang K, Ding W, et al. Analysis of Chest CT Results of Coronavirus Disease 2019 (COVID-19) Patients at First Follow-Up. Can Respir J. 2020;2020.
30. Leonardi A, Scipione R, Alfieri G, Petrillo R, Dolciami M, Ciccarelli F, et al. Role of computed tomography in predicting critical disease in patients with covid-19 pneumonia: a retrospective study using a semiautomatic quantitative method. Eur J Radiol. 2020;130(April):1–7.
31. Yan H, Valdes AM, Vijay A, Wang S, Liang L, Yang S, et al. Role of drugs used for chronic disease management on susceptibility and severity of COVID-19: a large case-control study. Clin Pharmacol Ther. 2020;108(6):1185–94.
32. Erener S. Diabetes, infection risk and COVID-19. Mol Metab. 2020;101044.
33. Liu H, Chen S, Liu M, Nie H, Lu H. Comorbid Chronic Diseases are Strongly Correlated with Disease Severity among COVID-19 Patients: A Systematic Review and Meta-Analysis. Aging Dis. 2020;11(3):668.
34. Wang X, Fang X, Cai Z, Wu X, Gao X, Min J, et al. Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: a systemic review and meta-analysis. Research. 2020;2020:2402961.
35. Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association between hypoxemia and mortality in patients with COVID-19. In: Mayo Clinic Proceedings. Elsevier; 2020.
36. Rubin SJS, Falkson SR, Degner NR, Blish C. Clinical characteristics associated with COVID-19 severity in California. J Clin Transl Sci. 2020;(Table 2):1–4.
37. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol [Internet]. 2020;146(1):110–8. Available from: https://doi.org/10.1016/j.jaci.2020.04.006
38. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369.
39. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. Clin Charact coronavirus Dis. 2019;1708–20.
40. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020;80(2020):e1–6.
41. Xia L, Chen J, Friedemann T, Yang Z, Ling Y, Liu X, et al. The course of mild and moderate COVID-19 infections-the unexpected long-lasting challenge. Open Forum Infect Dis. 2020;7(9):1–7.
42. Matsumura K, Toyoda Y, Matsumoto S, Kawai Y, Mori T, Omasa K, et al. Comparison of the clinical course of COVID-19 pneumonia and acute respiratory distress syndrome in 2 passengers from the cruise ship diamond princess in February 2020. Am J Case Rep. 2020;21:1–6.
43. Yasin R, Gouda W. Chest X-ray findings monitoring COVID-19 disease course and severity. Egypt J Radiol Nucl Med. 2020;51(1).
44. Turcotte JJ, Meisenberg BR, MacDonald JH, Menon N, Fowler MB, West M, et al. Risk factors for severe illness in hospitalized Covid-19 patients at a regional hospital. PLoS One. 2020;15(8):e0237558.
45. Kong M, Zhang H, Cao X, Mao X, Lu Z. Higher level of Neutrophil-to-Lymphocyte is associated with severe COVID-19. Epidemiol Infect. 2020;0–5.
46. Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. Crit Care [Internet]. 2020;24(1):1–10. Available from: https://doi.org/10.1186/s13054-020-03374-8
47. Jimeno S, Ventura PS, Castellano JM, García-Adasme SI, Miranda M, Touza P, et al. Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. Eur J Clin Invest. 2021;51(1):1–9.
48. Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ evidence-based Med. 2020;
49. Benotmane I, Perrin P, Vargas GG, Bassand X, Keller N, Lavaux T, et al. Biomarkers of cytokine release syndrome predict disease severity and mortality from COVID-19 in kidney transplant recipients. Transplantation. 2020;105(1):158–69.
50. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020;8(1):1–11.