How to Cite:
Soliman, G. M. M., El –Dessouky, Y. M. M., & Mohamed, R. S. . (2022). Extrapulomnary-extragastrointestinal manifestations in patients with COVID-19. *International Journal of Health Sciences*, *6*(S4), 2831–2842. https://doi.org/10.53730/ijhs.v6nS4.8190

Extrapulomnary-extragastrointestinal manifestations in patients with COVID-19

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***Abstract*---**Background: COVID-19 (coronavirus disease-2019) is a multisystem disorder. In terms of severity, the disease can manifest as mild, moderate, severe, or critical. Depending on the severity of the case, the patient may exhibit extrapulmonary or extragastrointestinal symptoms. Objective: The purpose of this research was to evaluate the extrapulmonary and extragastrointestinal symptoms of COVID-19 infection in patients and to make accurate predictions for follow-up care. Patient and method: This prospective observational study was conducted on (404) COVID-19 infected patients with positive COVID-19 PCR at El-sheikh Zayed Al-Nahyan Hospital from January 1st to June 30th, 2021. Results: There was a statistically significant difference between the clinical severity of illness regrding patient demographic features such as older age, male gender, co morbidities such as diabetes and hypertension; extra pulmonary – extra gastrointestinal manifestations. Conclusion: There is a correlation between COVID-19 illness that is severe and critical and the presence of preexisting conditions such as diabetes and cardiovascular disease, as well as older age, fatigue, anorexia, abdominal pain, diarrhoea, expectoration, dyspnea, chest pain, altered mental status, morbilliform rash, acute kidney injury, acute cardiac injury, and eye manifestations.

***Keywords*---**Clinical severity, COVID-19, Extra-gastrointestinal, Extra-pulmonary.

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 27 March 2022, Manuscript revised: 9 April 2022, Accepted for publication: 18 May 2022

Introduction

However the most common and critical clinical manifestation is secondary to lung engagement (fever, cough), infection with COVID-19 may result in a systemic and multi-organ disorder **(1)**. The method by which GIT symptoms are caused in COVID-19 is dependent on three elements: viral excess, the direct action of SARS-CoV-2 on the ACE2 receptors on the esophageal epithelium or the mucus layer in the stomach and small intestine **(2)**, and the interaction between these two components. Several authors have claimed that SARS-CoV-2 has an indirect influence on renal tissue since ACE2 is expressed in renal tissue. The SARS-CoV-2 virus has the potential to wreak havoc on the ACE2 receptor, which is found in renal tubules 3. The direct action of SARS–CoV-2, which is transported to the cornea and conjunctiva by droplet infection, may cause COVID-19 ocular symptoms to manifest. These symptoms may arise as a consequence of the direct action of SARS–CoV-2. The virus that is contained in the droplets has an interaction with the ACE2 receptors that are located in the conjunctiva and cornea **(3)**.

Cardiac ailment caused by COVID-19 infection-related inflammation **(4)**. In patient populations with COVID-19 infection, a variety of cardiac arrhythmias and ECG abnormalities have been observed, with sinus tachycardia being the most prevalent ECG finding in many study results. **(5)** Antiphospholipid antibodies may explain why thrombosis is more common in people with COVID-19 infection, which has an inflammatory response, coagulopathy and high D-dimer levels **(6)**.

One of the most common findings in COVID-19 infected subjects was liver changes. COVID-19 may cause liver damage. Furthermore, the extent of hepatic injury is proportional to the severity of COVID-19 infection **(7)**. Differences between the sexes in the COVID-19 epidemic should be considered when assessing the disease burden and the dynamics of the health emergency on individuals and populations **(8).**

Patients and Methods

Patients with COVID-19 infection who had a positive COVID-19 PCR and who were admitted to El-sheikh Zayed Al Nahyan Hospital between January 1, 2021 and June 30, 2021 were eligible for inclusion in the study and were randomly assigned to one of three groups after providing written consent and receiving informed consent

Group (1): involved patients with moderate disease, individuals who demonstrated proof of lower respiratory disease all through patient examination or image analysis, and who have oxygen saturation (SpO2) ≥93% on room air at sea level.

Group (2): involved patients with SpO2 <93% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) of 300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50 percent.

Group (3): involved patients with critical illnesses, people suffering from respiratory failure, and people suffering from shock as well as multiple organ dysfunctions.

The criteria for inclusion

The Egyptian COVID-19 Protocol programme was used to add all inclusion criteria. The ages ranged from 18 to 75 years. COVID-19 PCR is positive in all patient populations (moderate, severe and critical cases). Participants were excluded from the study if they met any of the following criteria: Mechanically ventilated patients and patients who have had a past myocardial infarction, congestive heart failure, a past cerebrovascular disease, a past thromboembolic event, or a history of cancer.

Study procedure

All patient groups were subjected to the following tests: complete history taking and extensive clinical examination

Investigations

A complete blood profile, Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), D-dimer, and fibrin degradation products. Inflammation may be measured using many different biomarkers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum ferritin. Liver function tests include total and direct serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and gama-glutamyltransferase (GGT). Kidney function tests include serum urea and creatinine, albumin/creatinine ratio, serum sodium, and serum potassium, hemoglobin A1C, fasting and postprandial blood glucose levels, serum ketones, electrocardiogram, serum lactate, serum troponin, beta-natriuretic peptide, and serum troponin, echocardiography in patients who have shock, heart failure, or a myocardial infarction, computerized tomography (CT) pulmonary angiography in patients with evidence a pulmonary embolism, all patients were subjected to a computerized tomography (CT) chest scan, brain computerized tomography (CT) and magnetic resonance imaging (MRI) in patients with neurological symptoms or a disturbed conscious level, cerebrospinal fluid (CSF) analysis in patients with altered consciousness, encephalopathy, or suspected encephalitis and electroencephalogram in patients with altered consciousness, encephalopathy, or suspected encephalitis.

Ethical Considerations

Protocol approval: The existing protocol was approved by the Committee of Hepato-Gastroenterology and Infectious Diseases Department and the Faculty of Medicine at Al-Azhar University, and then by the Al-Azhar University's ethical committee. Ministry of Health Permission: Permission was obtained from El-sheikh Zayed Al Nahyan Hospital. Patient Consent: All patients that were included in current study had an approved written or verbal consent.

Statistical analysis

The data collected were analyzed with the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). When the distribution was

parametric, the quantitative data were expressed as mean, standard deviation, and ranges (normal). The qualitative data were presented as number and percent. The next tests were carried out: When comparing more than two means, use a one-way analysis of variance (ANOVA). Tukey's test was used for multiple comparisons between different variables in the post-hoc test. To compare proportions between qualitative parameters, the Chi-square (x2) test of significance was used. The confidence interval was set to 95%, and the acceptable margin of error was set to 5%. As a result, the p-value was deemed significant as follows: Possibility (P-value): P-value of <0.05 was deemed significant. P-value greater than >0.05 was deemed insignificant.

Results

The study group consists of 226 males (55.9%) and 178 females (44.1%). Mean age of cases was 61.7 ± 12.5 years and range from 24 to 93 years. Table (1) There were 138 (34.2%) had moderate severity, 154 (38.1%) were severe and 112 (27.7%) were critical. Table (2) Severe and critical illness were more common in older age groups with statistically significant difference (p <0.05). Critical illness was more common in male patients with statistically significant difference (p <0.05). Table (3) Diabetes Mellitus (DM), a kind of diabetes, was found to be more prevalent in severe cases, and this difference was statistically significant (p 0.05). There was a statistically significant difference (p 0.05) in the prevalence of hypertension (HTN) in severe and critical patients. HTN was more prevalent in severe cases. Table (4)

Table (1)
Demographic data of the studied groups

Demographic data		Study group (n=404)
Age (years)	Mean ± SD Range	61.7 ±12.5 24-93
Males Females	N (%) N (%)	226 (55.9%) 178 (44.1%)

Table (2)
Comparing clinical severity in the study group by Chi-square test

Clinical Severity	Study group (n=404)	
	N	%
Moderate	138	34.2
Severe	154	38.1
Critical	112	27.7
Chi square	3.5156	
P. value	0.172	

* P < 0.05 is considered significant

Table (3)
Demographic data of the studied groups according to clinical severity

Demographic data		Clinical severity Moderate (n=138)	Severe (n=154)	Critical (n=112)	P1	P2	P3
Age (years)	Mean ± SD	53.6±10.9	64.5±11.8	67.8±9.8	<0.001*	<0.001*	0.016*
Males Females	N (%) N (%)	68 (49.3%) 70 (50.7%)	84 (54.5%) 70 (45.5%)	74 (66.1%) 38 (33.9%)	0.368	0.008*	0.059

* P < 0.05 is considered significant
P1: P-value in severe group relative to moderate group.
P2: P-value in critical group relative to moderate group.
P3: P-value in critical group relative to severe group.

Table (4)
Risk factors of the studied groups according to clinical severity

Risk factors		Clinical severity Moderate (n=138)	Severe (n=154)	Critical (n=112)	P1	P2	P3
Smoking	N (%)	58 (42%)	50 (32.5%)	49 (43.7%)	0.091	0.784	0.060
DM	N (%)	48 (34.8%)	44 (28.6%)	69 (61.6%)	0.254	<0.001*	<0.001*
HTN	N (%)	36 (26.1%)	115 (74.7%)	77 (68.7%)	<0.001*	<0.001*	0.287

Using: #One Way analysis of variance; ¥Chi-square test
* P < 0.05 is considered significant
P1: P-value in severe group relative to moderate group.
P2: P-value in critical group relative to moderate group.
P3: P-value in critical group relative to severe group.

Table (5)
System manifestation of the studied groups according to clinical severity

System manifestation	Clinical severity Moderate (n=138)	Severe(n=154)	Critical (n=112)	P1	P2	P3
General						
Fever	120 (87%)	134 (87%)	100 (89.3%)	1.000	0.718	0.705
Chills	9 (6.5%)	12 (7.8%)	10 (8.9%)	0.840	0.636	0.923
Body aches	26 (18.8%)	28 (18.1%)	24 (21.4%)	0.998	0.725	0.607
Fatigue	4 (2.8%)	27(17.5%)	37 (33%)	<0.001**	<0.001**	0.006*

System manifestation	Clinical severity					
	Moderate (n=138)	Severe(n=154)	Critical (n=112)	P1	P2	P3
Respiratory symptoms						
Sore throat	47 (32%)	50 (32.4%)	37 (33%)	0.958	0.974	0.977
Runny nose	12 (8.7%)	12 (7.7%)	8 (7.1%)	0.922	0.818	0.958
Dry cough	113 (81.9%)	120 (77.9%)	90 (80.3%)	0.482	0.874	0.748
Dyspnea	25 (18.1%)	103 (66.9%)	96 (85.7%)	<0.001**	<0.001**	<0.001**
Sputum production	6 (4.3%)	34 (22%)	41 (36.6%)	<0.001**	<0.001**	0.013*
Chest pain	2 (1.4%)	18 (11.7%)	49 (43.7%)	<0.001**	<0.001**	<0.001**
ARDS	0	39 (25.3%)	57 (50.9%)	<0.001**	<0.001**	<0.001**
GIT symptoms						
Abdominal pain	1 (0.72%)	10 (6.4%)	13 (11.6%)	0.024*	<0.001**	0.203
Anorexia	15 (10.8%)	55 (35.7%)	52 (46.4%)	<0.001**	<0.001**	0.103
Nausea	12(8.6%)	15(9.7%)	12 (10.7%)	0.903	0.730	0.951
Vomiting	12(8.6%)	15(9.7%)	12 (10.7%)	0.903	0.730	0.951
Diarrhea	8 (5.2%)	16 (14.3%)	24 (17.4%)	0.017*	0.004*	0.605
CNS symptoms						
New loss of smell	36 (26%)	38 (24.7%)	26 (23.2%)	0.904	0.717	0.891
New loss of taste	36 (26%)	38 (24.7%)	26 (23.2%)	0.904	0.717	0.891
Headache	24 (17.4%)	30 (19.4%)	23 (20.5%)	0.773	0.645	0.947
Dizziness	22 (15.9%)	26 (16.9%)	20 (17.9%)	0.943	0.802	0.962
Altered mental state	1 (0.72%)	10(6.4%)	11 (9.8%)	0.024*	0.007*	0.431
Stroke	1(0.72%)	9 (5.8%)	7 (6.2%)	0.039*	0.036*	0.899
Eye symptoms						
Conjunctivitis	8 (5.7%)	22 (14.3%)	28 (25.0%)	0.026*	<0.001**	0.041*
Foreign body sensation	8 (5.7%)	10 (6.4%)	8(7.1%)	0.996	0.849	0.982
Dry eye	8 (5.7%)	10 (6.4%)	8(7.1%)	0.996	0.849	0.982

System manifestation	Clinical severity					
	Moderate (n=138)	Severe(n=154)	Critical (n=112)	P1	P2	P3
Epiphora	1 (0.72%)	10 (6.4%)	8 (7.1%)	0.024*	0.048*	0.982
Conjunctival discharge	1 (0.72%)	10 (6.4%)	10 (8.9%)	0.024*	0.014*	0.596
Skin symptoms						
Morbilliformrash	8 (5.7%)	28 (18.1%)	24 (21.4%)	0.002*	<0.001**	0.607
Acral pernio-like lesions	25(18.1)	16 (10.3)	11 (9.8)	0.008*	0.009*	0.942
Urticaria	19 (13.7%)	20(12.9%)	15 (13.3%)	0.973	0.925	0.929
Vesicular eruptions	12 (8.6%)	15 (9.7%)	12 (10.7%)	0.903	0.730	0.951
CVS symptoms						
Heart failure	3 (2.1%)	15 (9.7%)	22 (19.6%)	0.014*	<0.001**	0.034*
Arrhythmias	4 (2.8%)	21 (13.6%)	28 (25.0%)	0.002*	<0.001**	0.028*
Acute cardic injury /Myocarditis	4 (2.8%)	26 (16.8%)	32 (28.6%)	<0.001**	<0.001**	0.033*
ACS/ MI	0 (0%)	7 (4.5%)	14 (12.5%)	0.033*	<0.001**	0.031*
Pulmonary embolism	2 (1.44%)	15 (9.7%)	22 (19.6%)	0.006*	<0.001**	0.034*
Renal manifestations						
AKI	2 (1.44%)	20 (12.9%)	24 (23.2%)	<0.001**	<0.001**	0.042*

Using: Chi-square test
* P < 0.05 is considered significant
P1: P-value in severe group relative to moderate group.
P2: P-value in critical group relative to moderate group.
P3: P-value in critical group relative to severe group.
ARD: Acute Respiratory Distress Syndrome, ACS: acute coronary syndrome, MI: Myocardial infarction, AKI: acute kidney injury.

Discussion

Males comprised 54.9 percent of the patients in our research, while females comprised 44.1 percent. The average age of the patients was 61.7 years old, with a standard deviation of 12.5. On a scale of clinical seriousness, we found that 34.2% of patients had a moderate degree of illness; 38.1% had severe illness; and 27.7% had critical illness. Older people were more likely to suffer from severe and critical illness, which was statistically significant (p 0.05).

41.1 percent of our patients had a serious disease, and 58.9 percent of our patients had non-severe infection. Patients with severe infection were much older (mean [SD] age, 58.2 [15.0] vs 48.9 [14.7] years; P.001) **(9)**. In a study by **Ghweil et al., (10)** in Egypt, severe infection (62.6 years old 10.1SD) was significantly older than mild to moderate infection (55.5 10.1) (p0.05). In terms of gender, male patients were more likely to suffer from serious illness (p 0.05).

Men have greater plasma ACE2 levels than women, which may be due to ACE2 expression in the testes. COVID-19 was shown to be more often found in males than in women who were also more likely to smoke or drink **(3)**. There was no significant difference in gender between critical and non-critical groups ($p=0.655$) according to **Omran et al. (11)** Diabetes Mellitus (DM) was more prevalent in severe patients (p 0.05) according to our findings.

Patients with severe forms of COVID-19 illness had a considerably higher incidence of diabetes than those with less severe forms of the condition, as discovered by Guan et al (34.6 percent versus 14.3 percent). A statistically significant difference was found between the prevalence of hypertension (HTN) in severe and critical situations (p0.05). According to **Mubarik et al., (12)** those with high blood pressure were more likely to have severe COVID-19 illness. In contrast to our findings, an Italian cross-sectional study failed to detect hypertension as a factor influencing the outcome of the COVID-19 trial **(13)**. When it comes to general symptoms like tiredness, the severe and critical groups had a statistically significant difference above the moderate group (2.8 percent) (p0.05).

When it came to symptoms like fever, chills, and generalised discomfort, there was no statistically significant difference between groups ($p>0.05$). For patients with severe COVID-19 pneumonia, signs like anorexia (p 0.001) and exhaustion were significantly more prevalent than those with milder cases (p 0.01), but symptoms like headache ($p > 0.05$) and myalgia were not significantly different between the two groups ($p > 0.05$). **(14)** In the severe (66.9%), as well as the critical (85.7%), as well as the moderate groups (36.6%), as well as the acute respiratory distress syndrome (ARDS), there were more cases of dyspnea, expectoration, chest discomfort, and acute respiratory distress syndrome (ARDS) (18.1 percent, 4.3 percent, 1.4 percent, 0 percent).

There was a statistically significant difference in the prevalence of dyspnea, expectoration, chest pain, and ARDS between the critical and severe groups (85.7%, 36.6 percent, 43.7 percent, and 50.9 percent) (p0.05). Sore throat, rhinorrhea, and dry cough were not significantly different across groups ($p>0.05$). His team found that patients with severe COVID-19 pneumonia had more dyspnea (p 0.001) and expectoration (p 0.01) than those with moderate cases, but no chest tightness ($p > 0.05$) or pharyngalgia ($p > 0.05$) in patients with mild cases **(14)**. According to our findings, which corroborate those of the Xu et al. study (odds ratio [OR], 13.206; 95% confidence interval [CI], 8.550–20.397; P 0.001), the severity assessment at admission was significantly associated with ARDS. **(15)**

This study found a statistically significant difference between the severe (6.4%) and critical (11.6%) groups when it came to abdominal pain and anorexia and

diarrhoea (0.072%) in comparison to the moderate (0.72%) group (p0.05). When it came to nausea and vomiting, there was no statistically significant difference between the groups (p>0.05). Our findings are consistent with **Zeng et al., (16)** meta-analysis's which found a strong correlation between COVID-19 severity and gastrointestinal symptoms. They found a link between stomach pain and COVID-19 intensity.

There was a statistically significant difference (p 0.05) between the severe and critical groups in the prevalence of altered mental state and stroke (both 6.4% and 5.8%), as well as the critical group (both 9.8% and 6.2%) in terms of neurological symptoms. New loss of smell/taste, headache, and dizziness were not significantly different across groups (p>0.05). **Mao et al.**, **(17)** showed that patients with more severe infections exhibited neurological symptoms such altered awareness (13 [14.8 percent] vs 3 [2.4 percent]; P.001). Our results are in line with that.

Retrospective cohort studies from two New York City academic hospitals indicated that 31 of the 1683 COVID-19 hospitalised patients experienced an acute ischemic stroke (1.8 percent; 95 percent CI, 1.3% to 2.6%). Those who had had an ischemic stroke had greater blood levels of inflammatory markers and were in poorer health than those who had not. **(18)**

A statistically significant difference (p 0.05) was seen between the severe and critical groups when it came to the ocular symptoms of conjunctivitis and conjunctival discharge, respectively, as compared to the moderate group. A statistically significant difference (p 0.05) showed that conjunctivitis was more prevalent in the critical group (25 percent) than the severe group (14.3 percent). When comparing the two groups, there was no statistical difference in terms of foreign body feeling or dry eye.

Ocular involvement increased in direct proportion to the severity of COVID-19: mild (5.3%), moderate (24.6%), and severe (58.8%) (p=0.0006) **(19)**. Patients with severe COVID-19 were more likely to have conjunctivitis, tears, or epiphora **(20)** in a Chinese study of 38 patients, with 31.6% reporting it as their predominant clinical complaint.

Morbiliform rash was more common in the severe and critical groups than in the moderate group, with a statistically significant difference (p0.05). Acral pernio-like lesions were more common in the intermediate group (18.1%) than in the severe (10.3%) or critical (9.8%) groups, and this difference was statistically significant (p0.05). Urtecria and vesicular eruptions were not significantly different across groups (p>0.05).

A substantial (p=0.03) relationship between sickness severity and certain skin lesions 24 was discovered by **Muhammad et al., (21)** and our findings are in line with those of **Muhammad et al., (21)** A previous study by Méndez Maestro et al. revealed no correlation between severity of COVID-19 sickness and different skin patterns. **(22)**

Acute cardiac injury/myocarditis, ACS/MI, and pulmonary emboli were more common in the severe group (9.7 percent, 13.6 percent, 16.8 percent, 4.5 percent, 9.7 percent) and critical group (19.6 percent, 25 percent, 28.5 percent, 12.5, 19.6 percent) than in the moderate group (2.1 percent, 2.8 percent, 2.8 percentage points) There was a statistically significant difference between the critical group and the severe group in terms of heart failure, arrhythmias, ACS/MI/pulmonary embolism (p 0.05) in terms of the prevalence of these four conditions in the critical group.

According to Zhou F et al., a Chinese retrospective cohort research, heart failure was documented in 44/191 (23 percent) of patients, with a large number of non-survivors suffering heart failure (52 percent vs 21 percent; p0.001). **(23)** According to Shi et al., out of 416 hospitalised patients, 82 patients (19.7 percent) had cardiac damage, and those patients had more severe acute illness than those who didn't have cardiac injury. Our data support theirs **(24)**. For patients who needed ICU admission, the arrhythmia rate was 44.4%, whereas only 6.9% of those who did not need ICU admission had any arrhythmia at all, according to **Ferguson et al., (25)**

Among the 100 COVID-19 patients who had contrast-enhanced CT, **Grillet et al., (26)** discovered pulmonary thrombosis in 23% of those who required mechanical ventilation and critical care hospitalisation. More patients in the critical and severe groups had acute kidney disease (AKI) compared to those in the moderate group (1.44%), with a statistically significant difference (p 0.01). There was a statistically significant difference (p 0.05) in AKI prevalence in the Critical group and the severe group (22.2% vs. 12.9%).

Similar to our results, **Yildirim et al., (27)** found that the frequency of AKI in mild, moderate, and severe COVID-19 patients was 1.3 percent, 9.0 percent, and 76.7 percent, respectively.

Acknowledgments

Disclosure

The author reports no conflicts of interest in this work.

Ethical Considerations:

Ethical approval was obtained from the Research ethical Committee at Faculty of Medicine, Beni-Suef University (The FM – BSU).
Ethical approval number: FMBSUREC/03052020/Ahmed.

Abbreviations:

ALT: alanine aminotransferase
AST: aspartate aminotransferase
CRP: C-reactive protein
CSF: cerebrospinal fluid
CT: computerized tomography
ESR: erythrocyte sedimentation rate
GGT: gama-glutamyltransferase
INR: international normalized ratio
MRI: magnetic resonance imaging

PT: Prothrombin time
PTT: partial thromboplastin time

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