

The Extrapulmonary Clinical Manifestations among Patients with Different Grades of COVID-19 Severity

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Abstract: Background: Several epidemiological studies show that COVID-19 has a multisystem disease presentation, as well as a respiratory condition. The correlation between the extrapulmonary manifestations and the severity of the disease addressed in few retrospective studies and did not involve multiple systems. This study aims to identify the extrapulmonary clinical manifestations of SARS-CoV-2 cases in different grades of SARS-CoV-2 severity. Methods: It is a prospective observational study that has been conducted at Assiut University hospitals. It included 445 participants were diagnosed positive with COVID-19 based on PCR test (208 females and 237 males). They were categorized into four groups according to severity of illness; mild group (n=255), moderate group (n=60), severe group (n= 58), and critical group (n=29). Results: The highest COVID infection rates were found in the age group of 70 to 80 years (19.6%). Most critical cases of the COVID- 19 infection observed in the age range of 80 to 89 years (48.3%). Moreover, the higher COVID-19 infection was seen in males (53.3%). Smokers were (32.8%) in COVID-19 patients, the critical and severe cases had higher smoking rates (65.5% and 60.3%, respectively). The most encountered comorbid conditions among COVID-19 patients were diabetes (23.8%), followed by hypertension (14.4%), and ischemic heart disease (12.8%). The most common extrapulmonary manifestations of COVID-19 in this study were heart failure (14.8%), headache (57.3), smell impairment (41.3%), impaired consciousness (17.8), abdominal pain (31.3 %), nausea/vomiting (9.5%), hematuria (18.7%), albuminuria (15.7%), acute kidney injury (increase creatinine) (8.5%), leukocytosis (26.7%), thrombocytopenia (17.3%), lymphocytosis (25.7 %), raised C-Reactive Protein (53.9%), anemia (36%), lymphopenia (36%), ketoacidosis (8.8%) and thyrotoxicosis (2.7%). Conclusion: The incidence of extrapulmonary manifestations showed statistically significant difference among different grades of COVID-19 severity.

Keywords: SARS-CoV-2, COVID-19, extrapulmonary manifestations

1. Introduction

Several epidemiological studies show that COVID-19 has a multisystem disease presentation, as well as a respiratory condition¹. We had performed an extensive recording of extrapulmonary manifestations in adult patients aged \geq 18 years old with confirmed SARS-CoV-2 infection in different grades of disease severity.

Patients and methods

The study was conducted at Assiut University hospitals on a series of COVID-19 patients who were treated from April 1st, 2021, to June 5th, 2022. The study approved by the Medical Ethical Committee Institutional Review Board of Assiut University with approval number: 17101489 and registered at ClinicalTrials.gov. (NCT05046509). The study participants were recruited after written consent by patients or their relatives.

Inclusion criteria

Patients who were confirmed with SARS-CoV-2 infection based on PCR test aging \geq 18 years old

Exclusion criteria

- Patients Age <18 years
- Patient refused to participate.

All patients were subjected to full medical history including patients' demographic data, comorbidities and extrapulmonary manifestations. Complete blood picture (CBC), C-reactive protein, Ferritin, D dimer, lactate dehydrogenase, coagulation times, liver functions tests, kidney function test and PCR and Computed Tomography (CT) of the chest were done for all cases. In addition to any investigations were reported; according to each case when needed.

Sample Size Calculation:

Depending on the average monthly (40-50 cases) and type of the study we were used Steven K. Thompson equation 13 to calculate the size of the sample.

Statistical analysis:

Data was collected and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in

form of mean ± SD or median (range) while nominal data was expressed in form of frequency (percentage). The statistical analysis was made using the Chi2-test to study the significance of the severity of COVID among different demographic characteristics of the patients. A p-value of <0.05 was considered statistically significant.

2. Results

This prospective observational study includes 445 COVID-19 patients. They were classified into four grades 1; mild grade, with 225 (50.60%), followed by moderate grade, with 133 (29.90%), while the lowest grades were severe grade, with 58 (13%) and critical grade, with 29. (6.50 %) as illustrated in figure 1.

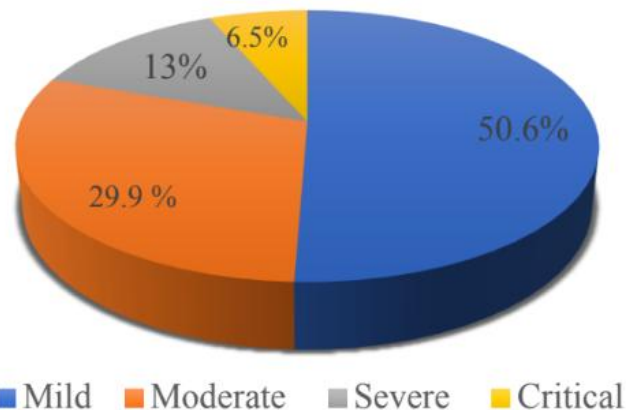


Figure 1: COVID-19 infection severity grades among examined patients

The demographic data and comorbidities among the studied patients:

The highest COVID infection rates were found in the age group of 70 to 80 years, where they reached 19.6%. There were 146 smokers in this study (32.8 %). Critical and severe cases have great numbers of smokers (65.6 % and 60.3%) respectively. As shown in table 1, The most encountered comorbidities in this study were diabetes (23.8%), hypertension (14.4%), and coronary artery disease (12.80%). In addition, this data showed a significant association between comorbidities and COVID-19 severity grades of the studied groups.

Table 1: The demographic data and comorbidities of the studied patients

Demographic data	Total N=445		COVID severity grades								Chi-square	
			Mild N=255		Moderate N=133		Severe N=58		Critical N=29		X2	P-value
			N	%	N	%	N	%	N	%		
Age (Years)	59.12±18.2		50.20±17.4		65.91±16.4		69.16±18.2		77.10±11.5		7.761	<0.001*
Age (groups)	N	%	N	%	N	%	N	%	N	%	174.618	<0.001*
18-30	36	8.1	30	13.3	3	2.3	3	5.2	0	0.0		
30-40	43	9.7	33	14.7	9	6.8	1	1.7	0	0.0		
40-50	60	13.5	43	19.1	15	11.3	2	3.4	0	0.0		
50-60	72	16.2	64	28.4	6	4.5	1	1.7	1	3.4		
60-70	81	18.2	22	9.8	35	26.3	18	31.0	6	20.7		
70-80	87	19.6	26	11.6	33	24.8	20	34.5	8	27.6		
80-89	66	14.8	7	3.1	32	24.1	13	22.4	14	48.3		
Sex												
Female	208	46.7	86	38.2	88	66.2	26	44.8	8	27.6	31.077	<0.001*
Male	237	53.3	139	61.8	45	33.8	32	55.2	21	72.4		
Smoking	146	32.8	51	22.7	41	30.8	35	60.3	19	65.5	44.759	<0.001*
Comorbid conditions												
Ischemic heart diseases	57	12.8	22	9.8	12	9.0	10	17.2	13	44.8	31.199	<0.001*
Heart failure	34	7.6	11	4.9	8	6.0	6	10.3	9	31.0	26.004	<0.001*
Hypertension	64	14.4	25	11.1	14	10.5	15	25.9	10	34.5	19.284	<0.001*
Diabetes	106	23.8	46	20.4	26	19.5	11	19.0	23	79.3	52.712	<0.001*
Asthma	48	10.8	17	7.6	12	9.0	7	12.1	12	41.4	31.175	<0.001*
COPD	35	7.9	14	6.2	8	6.0	8	13.8	5	17.2	7.797	0.050*
Tuberculosis (TB)	18	4.0	4	1.8	4	3.0	4	6.9	6	20.7	25.264	<0.001*
Chronic kidney diseases	13	2.9	4	1.8	4	3.0	1	1.7	4	13.8	13.420	0.004*

* Significant at (P ≤ 0.05)

The reported cardiovascular manifestations were unstable angina, myocardial infarction, pericarditis, arrhythmia, and cardiogenic shock, and there was no statistically significant difference (P > 0.05) among different severity grades. Only heart failure (14.8%) was statistically significant (P ≤ 0.05) among the patients who were examined as shown in table 2.

Table 2: Cardiovascular symptoms in different grades of COVID-19 severity

CVS symptoms	Total		COVID severity grades									
			Mild		Moderate		Severe		critical		Chi-square	
	N	%	N	%	N	%	N	%	N	%	X2	P-value
Unstable angina	58	13	28	12.4	15	11.3	7	12.1	8	27.6	5.896	0.117
Myocardial Infarction	35	7.9	19	8.4	9	6.8	4	6.9	3	10.3	0.647	0.886
Pericarditis	13	2.9	14	6.2	10	7.5	5	8.6	4	13.8	2.309	0.511
Arrhythmia	65	14.6	26	11.6	20	15	14	24.1	5	17.2	6.085	0.108
Cardiogenic shock	52	11.7	22	9.8	18	13.5	6	10.3	6	20.7	3.613	0.306
Heart Failure	66	14.8	27	12	23	17.3	7	12.1	9	31	8.444	0.038*

* Significant at (P ≤ 0.05)

The hematological laboratory findings in this study reported increased levels of C-Reactive Protein (CRP) (53.9%), leukocytosis (26.7%), lymphopenia (36%) anemia (36%), and thrombocytopenia (17.3%). All these hematological laboratory findings had statistically significant difference in different grades of COVID-19 severity (P ≤ 0.05).

Table 3: Hematological and laboratory findings in different grades COVID-19 severity.

Hematological laboratory findings	Total		COVID severity grades									
			Mild		moderate		Severe		critical		Chi-square	
	N	%	N	%	N	%	N	%	N	%	X2	P-value
Leukocytosis	119	26.7	62	27.6	39	29.3	3	5.2	15	51.7	23.541	<0.001*
Leukopenia	45	10.1	24	10.7	15	11.3	3	5.2	3	10.3	1.834	0.608
Thrombocytopenia	77	17.3	44	19.6	27	20.3	0	0.0	6	20.7	14.001	0.003*
Anemia	160	36.0	93	41.3	52	39.1	4	6.9	11	37.9	24.714	<0.001*
Lymphocytosis	115	25.8	42	18.7	27	20.3	30	51.7	16	55.2	41.467	<0.001*
D-dimer	222	49.9	120	53.3	64	48.1	23	39.7	15	51.7	3.703	0.295
Lactate dehydrogenase	276	62.0	139	61.8	77	57.9	39	67.2	21	72.4	2.968	0.397
High Ferritin	212	47.6	103	45.8	62	46.6	29	50.0	18	62.1	2.919	0.404
Lymphopenia	160	36.0	29	18.1	84	52.5	34	21.3	13	8.1	108.657	<0.001*
C-Reactive Protein (CRP)	240	53.9	75	31.3	100	41.7	44	18.3	21	8.8	77.825	<0.001*

* Significant at (P ≤ 0.05)

Gastrointestinal manifestations showed that the most common GIT symptoms were anorexia (42.50%) followed by abdominal pain (31.3%) and diarrhea (19.80%). Anorexia had greater incidence in the severe cases (51.7%), while diarrhea, had a higher incidence in the critical cases (24.1%) as showed in table (4).

Table 4: Gastrointestinal manifestations in different grades of COVID-19 severity.

GIT symptoms	COVID severity grades											
	Total		Mild		Moderate		Severe		Critical		Chi-square	
	N	%	N	%	N	%	N	%	N	%	X2	P-value
Anorexia	189	42.5	84	37.3	62	46.6	30	51.7	13	44.8	5.465	0.141
Diarrhea	88	19.8	41	18.2	28	21.1	12	20.7	7	24.1	0.857	0.836
Nausea/Vomiting	40	9.0	11	4.9	10	7.5	7	12.1	12	41.4	42.838	<0.001*
Abdominal Pain	61	13.7	19	8.4	18	13.5	10	17.2	14	48.3	35.181	<0.001*
Rectal Bleeding	22	4.9	7	3.1	9	6.8	2	3.4	4	13.8	7.657	0.054

* Significant at (P ≤ 0.05)

The most frequent neurological and psychological manifestations were headache (57.3%), taste impairment (44.5%), smell impairment (41.3%) and depression (30.8%). There were statistically significant differences ($P < 0.05$) among different grades of COVID-19 in headache, impaired consciousness, smell and vision impairment as showed in table (5).

Table 5: Neurological and psychiatric manifestations in different grades COVID-19 severity.

Neurological & Psychiatric symptoms	COVID severity grades											
	Total		Mild		moderate		severe		critical		Chi-square	
	N	%	N	%	N	%	N	%	N	%	X2	P-value
Dizziness	80	18.0	38	16.9	29	21.8	9	15.5	4	13.8	2.084	0.555
Headache	255	57.3	126	56.0	66	49.6	41	70.7	22	75.9	11.692	0.009*
Impaired consciousness	79	17.8	34	15.1	20	15.0	16	27.6	9	31.0	9.092	0.028*
Acute ischemic stroke	8	1.8	2	0.9	4	3.0	1	1.7	1	3.4	2.605	0.457
Seizure	6	1.3	2	0.9	1	0.8	1	1.7	2	6.9	7.486	0.058
Depression	137	30.8	73	32.4	43	32.3	18	31.0	3	10.3	6.128	0.106
Taste impairment	198	44.5	92	40.9	57	42.9	31	53.4	18	62.1	6.838	0.077
Smell impairment	184	41.3	79	35.1	48	36.1	36	62.1	21	72.4	26.934	<0.001*
Vision impairment	17	3.8	8	3.6	2	1.5	3	5.2	4	13.8	10.124	0.018*

* Significant at ($P \leq 0.05$)

The most reported renal symptoms caused by COVID-19 were hematuria (18.7%), albuminuria (15.7%), and proteinuria (14.4%). Depending on the severity of COVID-19, albuminuria, proteinuria and haematuria, vary significantly ($P \leq 0.05$) as illustrated in table (6).

Table 6: Renal manifestations in different grades COVID-19 severity

Renal manifestations	COVID severity grades											
	Total		Mild		Moderate		Severe		Critical		Chi-square	
	N	%	N	%	N	%	N	%	N	%	X2	P-value
Acute Kidney injury (increase of creatinine)	38	8.5	11	4.9	12	9.0	6	10.3	9	31.0	22.910	<0.001*
Albuminuria	70	15.7	26	11.6	24	18.0	8	13.8	12	41.4	18.052	<0.001*
Proteinuria	64	14.4	23	10.2	23	17.3	12	20.7	6	20.7	6.888	0.076
Hematuria	83	18.7	33	14.7	17	12.8	19	32.8	14	48.3	29.756	<0.001*

* Significant at ($P \leq 0.05$)

The most encountered endocrinal manifestations in this study were hypoglycemia (39.3%) followed by hyperglycemia (10.8%) and ketoacidosis (8.8%). There were statistically significant difference ($P \leq 0.05$) in ketoacidosis and thyrotoxicosis among different grades COVID-19 severity as illustrated in table (7).

Table 7: Endocrinal manifestations in different grades COVID-19 severity.

Endocrinal manifestations	COVID severity grades											
	Total		Mild		moderate		Severe		Critical		Chi-square	
	N	%	N	%	N	%	N	%	N	%	X2	P-value
Hypoglycemia	175	39.3	83	36.9	50	37.6	24	41.4	18	62.1	7.116	0.068
Ketoacidosis	39	8.8	14	6.2	7	5.3	6	10.3	12	41.4	42.619	<0.001*
Hyperglycemia	48	10.8	24	10.7	14	10.5	4	6.9	6	20.7	3.880	0.275
Thyrotoxicosis	12	2.7	7	3.1	1	0.8	1	1.7	3	10.3	8.738	0.033*

* Significant at ($P \leq 0.05$)

Musculoskeletal, ocular, and dermatological symptoms were uncommon and unrelated to COVID-19 severity ($P > 0.05$) as showed in table (8).

Table 8: Musculoskeletal, Dermatological and Ocular manifestations in different grades of COVID-19 severity

Musculoskeletal symptoms	COVID severity grades											
	Total		Mild		moderate		severe		critical		Chi-square	
	N	%	N	%	N	%	N	%	N	%	X2	P-value
Myalgia	102	22.9	49	21.8	34	25.6	12	20.7	7	24.1	0.880	0.830
Ocular manifestations												
Conjunctivitis	18	4.4	4	0.02	7	0.05	5	0.09	2	0.07	5.415	0.144
Dermatological manifestations												
Papulovesicular rash	24	5.4	14	6.2	5	3.8	2	3.4	3	10.3	2.822	0.420
Dryness	16	3.6	9	4	5	3.8	1	1.7	1	3.4	0.704	0.872
Urticaria	29	6.5	20	8.9	7	5.3	0	0	2	6.9	6.471	0.091

Significant at ($P \leq 0.05$)

3. Discussion

Regarding demographic, in this study the mild group had the lowest mean age (50.20 ± 17.4 years) compared to other groups. The highest incidence of COVID-19 infection was found in the age group of 70 to 80 years, while the critical cases were seen in the age group range between 80 to 89 years. This result matched with the results of **Romero S. et al. (2, 3)**. In contrast to this finding, **Wang et. al.**, affirmed that the severity of COVID-19 occurred in patients who were 52 years of age or older (4).

Moreover, we found that higher number COVID-19 infection was seen in males. The data also revealed that the disease was worse in men, and the number of critical cases in men were higher than in women. This result was consistent with that of **Bwire GM**, who found that males were more likely than females to experience COVID-19 (5). Contrarily, **Eid RA et al.**, discovered that women were more at risk than men (6).

This study demonstrates that smokers had a higher likelihood of developing COVID-19, and that smokers were more prevalent in severe and critical grades of illness. This finding is consistent with the research conducted by **D. Simon et al.**, in 2021 (7). In contrast, smoking, according to **Van Westen-Lagerweij NA et al.**, did not increase the severity of COVID-19 (8).

Regarding of cardiovascular system manifestations, heart failure, arrhythmia, and unstable angina were the most frequently seen cardiac symptoms of COVID-19 in this study, and that all three manifestations were statistically significant difference among different grades COVID-19 severity. These results were comparable to those of **Zheng et al.** It has been observed that 11.8 percent of COVID-19 patients without a history of cardiovascular disease present heart damage with raised troponin levels or cardiac arrest during hospitalization (9).

In this study, hematological laboratory findings show increased levels of lactate dehydrogenase, C-Reactive Protein (CRP), D-dimer and ferritin. Anemia, and lymphopenia were reported. The results correspond to the study done by **Yuan X et al.**, who concluded that; in COVID-19 patients, elevated levels of lactic dehydrogenase, the D-dimer, bilirubin, decreased platelets (PLTs), and mild anemia, may be influenced by excessive complement system activation, according to studies on SARS and Middle East respiratory syndrome (MERS) (10). Moreover, in this study, data showed higher rates of Lactate dehydrogenase in all severity grades. However, most of other researchers showed that LDH is mainly linked to more severe infections' grades (11).

In this study, the most common GIT symptoms were anorexia (42.5%), abdominal pain (31.3%), and diarrhea (19.8%). This is supported by data gathered from COVID-19 individuals with or without GI symptoms has shown that GI symptoms frequently manifest as the disease progresses (12). Conflicting findings from a substantial study done by **T. Menon et al.**, with 1, 099 participants found no difference in the percentage of GI symptoms between severe

and non-severe cases of COVID-19 (13).

Headache was the most observed neurological manifestation in this study (57.3%) and was more common in critical group (75.90%). These findings revealed a higher prevalence of headache than that of **Azhideh et al**, study which found that COVID-19 patients had headache prevalence rates ranging from 6.5% to 23% (14). In contrast to these findings, COVID-19 severity manifestations of neurological manifestations were more prevalent in severe patients, except for headache, which was more prevalent in non-severe patients (15).

In this study, hematuria, albuminuria, and AKI were the most prevalent urological symptoms of COVID-19 and they had statistical significant difference in different grades of COVID-19 severity. These findings are corroborated by **Kunutsor et al.**, who demonstrated that hospitalized COVID-19 patients frequently have AKI and chronic renal illness. (16). On the other hand, in another study showed that patients who survived COVID-19 exhibited an increased risk of kidney outcomes in the post-acute phase of the disease (17).

In this study, the most common endocrinal manifestations were hypoglycemia, hyperglycemia, and ketoacidosis. However, hyperglycemia was prevalent and unrelated to severity of illness. Another, research demonstrating a high percentage of hyperglycemia similar to that seen with other viral infections like SARS and MERS, not just COVID-19, supports this (18). In this study, thyrotoxicosis displayed a less severe endocrine manifestation. In contrast to these findings many studies showed that thyrotoxicosis was associated with severe COVID-19 cases (19, 20).

In this study, myalgia was diverse in occurrence and unrelated to COVID severity grades. In contrast to the findings of earlier clinical investigations, COVID-19 patients were shown to have a variety of musculoskeletal conditions, depending on the disease's severity (21, 22).

In this study, papulovesicular rash, dryness and urticaria were the main dermatological manifestations but not linked with COVID-19 severity grades. A study conducted on 88 COVID-19 patients in Italy found that 20.4% of individuals experienced cutaneous symptoms (23). Moreover, it is believed that medication reactions and viral rashes share clinical and histological similarities, making it challenging to distinguish whether or not these manifestations are caused by COVID-19, medication, or from other viral infection (24).

In this study, ocular symptoms including conjunctivitis was not increase with the disease's severity. These results were similar to data showing that conjunctivitis in certain studies is a primary symptom of COVID-19 (25). Moreover, conjunctivitis was reported in 3 percent in severe cases, and 0.7 percent in non-severe cases, according to a meta-analysis by **Loffredo et al.** (26).

4. Conclusion

In this study we found that the most frequent

extrapulmonary manifestations were neurological (Headache and smell impairment), followed by gastrointestinal (Nausea/vomiting and abdominal pain), hematological finding (Lymphopenia and anemia), urinary: (Hematuria and albuminuria), Cardiovascular (Heart failure) and endocrinal: (Ketoacidosis and thyrotoxicosis). All these manifestations had showed statistically significant difference among different grades of COVID-19 severity.

5. Limitations

The impact of COVID-19 vaccination on patient outcomes whether they were better or worse was not examined.

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