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Clinical Assessment of Extra Pulmonary Manifestation of Coronavirus Disease -19 and its Relation to Severity of The Disease

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Abstract

COVID-19 not only affects the respiratory system but also causes multiple organ affection such as renal, hepatic, GIT and blood as an extrapulmonary manifestation of COVID-19, this manifestation ranging from mild and moderate to severe and critical patients who need ICU. But the severe and critical cases of covid 19 are more with extrapulmonary than cases of covid 19 without extrapulmonary manifestations. To assess the correlation between the rapidity of COVID-19 progression and extrapulmonary organ injuries, these extrapulmonary manifestations will guide us for proper treatment approaches to avoid decompensation. The current observational study included seventy patients *with extrapulmonary manifestation of covid19* compared to thirty covid 19 patients without extrapulmonary manifestations. Demographic, clinical and laboratory parameters including CBC, serum ALT, AST ALB, Creatinine, Urea and RT-PCR for covid 19 and CT chest were recorded. Seventy COVID-19 patients with extrapulmonary manifestations were included,34 were females and 36 were males. their age ranged from 42 to 69 years, together with thirty of covid 19 patients without extra pulmonary manifestations as 11 were females and 19 were males. their age ranged from 35 to 64 years, each Group were subdivided according to severity and rapidity of progression of disease into three groups: non-severe: patients with non-severe (Fever, respiratory symptoms, imaging findings of pneumonia), severe patients with any of the followings (Respiratory distress, RR ≥30 times/min, SpO_2 <93% at rest, $PaO_2/FiO_2 \leq 300$ mmHg, Patients showing a rapid progression (>50%) on CT imaging within 24- 48 hours) and critical patients with any of the followings (Respiratory failure, need mechanical assistance, Shock, multiple organ failure, intensive care unit is needed). The data demonstrated a significantly increased percentage of critical severity, increased percentage of ICU admission (65.7%), use of empirical anti-biotic, dexamethasone and Immune-modulatory drugs in covid 19 patients with extrapulmonary manifestations when compared with covid 19 patients without extrapulmonary manifestations. COVID-19 not only affects the respiratory system but also causes multiple organ affection such as renal, hepatic, GIT and blood. The clinician should be more understating about these extrapulmonary manifestations to avoid their complications.

Keywords: COVID-19, Clinical laboratory test, Extrapulmonary manifestation.

1. Introduction

The Corona virus appeared in Wuhan, China, in late 2019 and was called SARS 2, and at the beginning of 2020, the World Health Organization announced that it had become a global epidemic and called it Covid 19.[17].

At first, the symptoms of Covid 19 were expressed by upper or lower respiratory symptoms such as (fever, headache, runny nose, sore throat, cough and generalized fatigue up to ARDS), after extrapulmonary manifestation (as diarrhoea, vomiting, abdominal pain, oliguria and electrolyte disturbance) was reported and may be the first presentation of disease also [3].

COVID-19 lead to severe and acute pneumonia and multiple organ failure also up to death [1].

Pathogenesis

Viral invasion: covid 19 virus engaged with Angiotensin-converting enzyme 2 (ACE2) as an entry receptor of the host cell, then in the host cells, the virus replicates and survives within the target cells [13].

The invasion of covid 19 to endothelium cells results in infection-mediated endothelial injury which triggers the intravascular thrombus formation, dysregulation of the immune response and dysregulation of RAAS act as a pathophysiological mechanism of covid 19 infection–related, tissue damage [9].

We discuss in this review the extra pulmonary manifestation of covid 19.[9]

The hematological manifestation of covid 19: Lymphopenia occurs about 67–90% of cases and thrombocytopenia, occur in 5–36% of patients with COVID-19, leukocyte count may be normal or Leukopenia due to consumption of T calls as first defense of immune system [6]. These manifestations occurred by direct cytotoxic effect of the virus by ACE2-dependent entry into blood cells or apoptosis-mediated cell depletion which caused by a cytokine storm [2]. The GI manifestations have occurred in 11.4 61.1% of patients with COVID-19 **.**The most common GI symptoms as anorexia, diarrhea, nausea, vomiting and abdominal pain. This symptom may be the first presentation and most of GI cases were mild and self-limited [5]

Hepatic affection with COVID-19 varies from 14.8-53%. As elevated liver enzymes and decrease of albumin [11].

The renal manifestation of covid 19 is through expression of ACE2, TMPRSS2 in podocytes and tubule epithelial cells which facilitate the COVID 19 associated kidney injury [8]. Viral infection can induce tubular damage through the infiltration of $CD68^{+}$ macrophages in the tubule interstitium [3]. COVID-19 may be presented with oliguria, hematuria and proteinuria and metabolic acidosis in kidney affection [10]. affects >20% of patients with covid 19 with increase in level of serum creatinine, urea and electrolyte disturbance [3].

2. Patients and Methods

This study is a cross-sectional observational study conducted on 100 participants; they are divided into two groups. Group I: 70 patients of COVID-19 with extrapulmonary manifestation, group II: 30patients of covid 19 without extrapulmonary manifestation. Each Group was subdivided according to severity and rapidity of progression of disease into three groups:

1. Non-severe: patients with Fever, respiratory symptoms, some GIT symptoms, imaging findings of pneumonia).
2. Severe patients with any of the following (Respiratory distress, RR ≥30 times/min, SpO_2 <93% at rest, $PaO_2/FiO_2 \leq 300$ mmHg, Patients showing a rapid progression (>50%) on CT imaging within 24- 48 hours).
3. Critical patients with any of the following (Respiratory failure, need mechanical assistance, Shock, multiple organ failure, intensive care unit is needed).

All patients were recruited from the isolation department (Al-Zahraa University Hospital) after obtaining written consent to

participate in the study during the period from July 2021 to May 2022.
Inclusion criteria: Adult patients ≥ 18 years old confirmed diagnosis as covid 19 with hepatic renal and hematological manifestation.
Exclusion criteria: patient with hepatic renal and hematological manifestation but not diagnosed as covid 19.

2.1 Methods

All patients were subjected to the following: Full medical history and Clinical examination, CBC, serum urea, creatinine, AST, ALT, albumin, CRP, D.dimer, ferritin, blood gases, RT-PCR for covid 19 and CT chest as an investigation.

2.2 Statistical analysis

Data was analyzed using Statistical Program for Social Science (SPSS) version 24. Quantitative data were expressed as median and IQR. It was no expressed and mean ± SD as the data was abnormally distributed. Qualitative data were expressed as frequency and percentage.
IQR: it is the measure of statistical dispersion, being equal to the difference between 75^{th} and 25^{th} percentile

The following tests were done:

- Mann–Whitney U test (MW): was used when comparing between two means.
- Chi-square test (X^2): was used when comparing non-parametric data.
- Kruskal Willis test (KW): when comparing between more than two means.

2.2.1 Probability (P-value)

A P-value < 0.05 was considered significant. A P-value < 0.001 was considered highly significant. A P-value > 0.05 was considered insignificant.

2.3 Ethical Considerations

Written consent was attained from patients before enrollment into the study. The study protocol was approved by the institutional review board of the Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. Every patient can refuse participation or withdraw from the study at any time without any clarification of the reason and without troubling their rights of medical care. Moreover, data were nameless and coded to guarantee privacy of patients.

3. Results

As show in table 1, in our study demographic data revealed Seventy of covid 19 patients with extra pulmonary manifestation were included,34 were females and 36were males. their age ranged from 42 to 69 years, (44.3%) diabetic, (47%) hypertensive and (14.3%) with ischemic heart disease together with thirty of covid 19 patients without extra pulmonary manifestation as 11were females and 19 were males. Their age ranged from 35 to 64 years, (36.7%) diabetic, (33.3%) hypertensive and (14.3%) with IHD as regard to age and gender, and the presence of chronic diseases, no significant difference between studied groups. As show in table 3, in our study the most common symptoms in patients were fever, cough, dyspnea, and diarrhea, There was highly significant increased percentage of diarrhea in covid 19 patients with extrapulmonary manifestation (p-value =0.001), there was 2 cases in covid 19 patients without extra pulmonary manifestation (group II) this diarrhea was occurred once in course of disease so it not considerable as extra pulmonary manifestation .
As shown in table 4, there was no statistically significant difference (p-value > 0.05) between studied groups as regard vital signs (SBP, DBP, RR, temperature, pulse and O_2 saturation).
As shown in table 6 there was a significant increase ALT and AST and a decrease in

albumin and also highly significant increase in Create and urea in covid 19 patients with extra pulmonary manifestations when compared with covid 19 patients without extra pulmonary manifestations. (p-value = 0.01), (p-value = 0.002), (p-value = 0.004), (p-value = 0.001), respectively. There was no significant difference between studied groups as regards RBS (p-value > 0.05). Table (6) shows: There was significantly increased WBCs and neutrophil and d.dimer in covid 19 patients with extrapulmonary manifestations when compared with covid 19 patients without extra pulmonary manifestations. (p-value = 0.042), (p-value = 0.016), (p-value = 0.022) respectively.

As shown in Table .7 no significant difference between studied groups as regard symptoms of anti-viral drugs, hydroxychloroquine, anti-coagulant, supportive treatment and MV. (P-value > 0.05). There was significant increased percentage of ICU admission in in covid 19 patients with extrapulmonary manifestations (65.7%), significantly increased percentage of empirical anti-biotic, dexamethasone (65.1%) and highly significantly increased percentage of use of the immunomodulatory drug (52.9%) when compared with in covid 19 patients without extrapulmonary manifestations (p-value = 0.007), (p-value = 0.005), (p-value = 0.037), (p-value =0.001) respectively.

As shown in table 8 shows: There was a significantly increased percentage of critical severity in covid 19 patients with extrapulmonary manifestation (48.6%) when compared with covid 19 patients without extrapulmonary manifestation (10%). (p-value < 0.001).

As shown in Table .9, there was a highly significant increase of dyspnea in severe patients (63.2%) and critical patients (82.4%) when compared with non-severe patients (35.3%) (p-value =0.001).

As shown in table 10

- significant decreased SBP and DBP in critical patients when compared with severe patients and non-severe patients (p-value = 0.040, 0.041) respectively
- Highly significant increased RR in critical patients when compared with severe patients and non-severe patients (p-value = 0.001)
- Highly significant decreased O_2 saturation in critical patients when compared with severe patients and non-severe patients (p-value =0.001)

As shown in Table .11 there was a significant increase in ALT, AST and urea and decreased ALB in critical patients when compared with severe patients and moderate patients in group I. (p-value =0.001), (p-value = 0.002)

As in table (12): There was significant decreased PLTs and increased WBCs in critical patients when compared with severe patients and moderate patients in group I. (p-value = 0.013), (p-value = 0.002) respectively

There was highly significant decreased lymphocytes and increased neutrophils in critical patients when compared with severe patients and moderate patients in group I. (p-value < 0.001), (p-value < 0.001) respectively.

Table (1): Demographic data among group I and group II as regard age and sex.

		Group I (N = 70)		Group II (N = 30)		P-value	Significance
Age (years)	Median	58.5		55.5		0.174	NS
	IQR	42.3 – 69.3		35.5 – 64			
Sex	Male	36	51.4%	19	63.3%	0.273	NS
	Female	34	48.6%	11	36.7%		

Table (2): Comparison between studied groups as regards chronic diseases.

		Group I (N = 70)		Group II (N = 30)		P-value	Significance
DM	Yes	31	44.3%	11	36.7%	0.479	NS
	No	39	55.7%	19	63.3%		
HTN	Yes	33	47.1%	10	33.3%	0.201	NS
	No	37	52.9%	20	66.7%		
IHD	Yes	10	14.3%	2	6.7%	0.283	NS
	No	70	85.7%	28	93.3%		
	No	62	88.6%	28	93.3%		

Table (3): comparison between studied groups as regards symptoms.

		Group I (N = 70)		Group II (N = 30)		X^2	P-value
Fever	No	12	17.1%	7	23.3%	0.52	0.470 NS
	Yes	58	82.9%	23	76.7%		
Dyspnea	No	24	34.3%	11	36.7%	0.052	0.819 NS
	Yes	46	65.7%	19	63.3%		
Cough	No	9	12.9%	2	6.7%	0.82	0.365 NS
	Yes	61	87.1%	28	93.3%		
Diarrhea	No	34	48.6%	28	93.3%	17.8	< 0.001 HS
	Yes	36	51.4%	2	6.7%		
Sore throat	No	49	70.0%	24	80.0%	1.06	0.302 NS
	Yes	21	30.0%	6	20.0%		
Generalized fatigue	No	8	11.4%	3	10.0%	0.044	0.834 NS
	Yes	62	88.6%	27	90.0%		

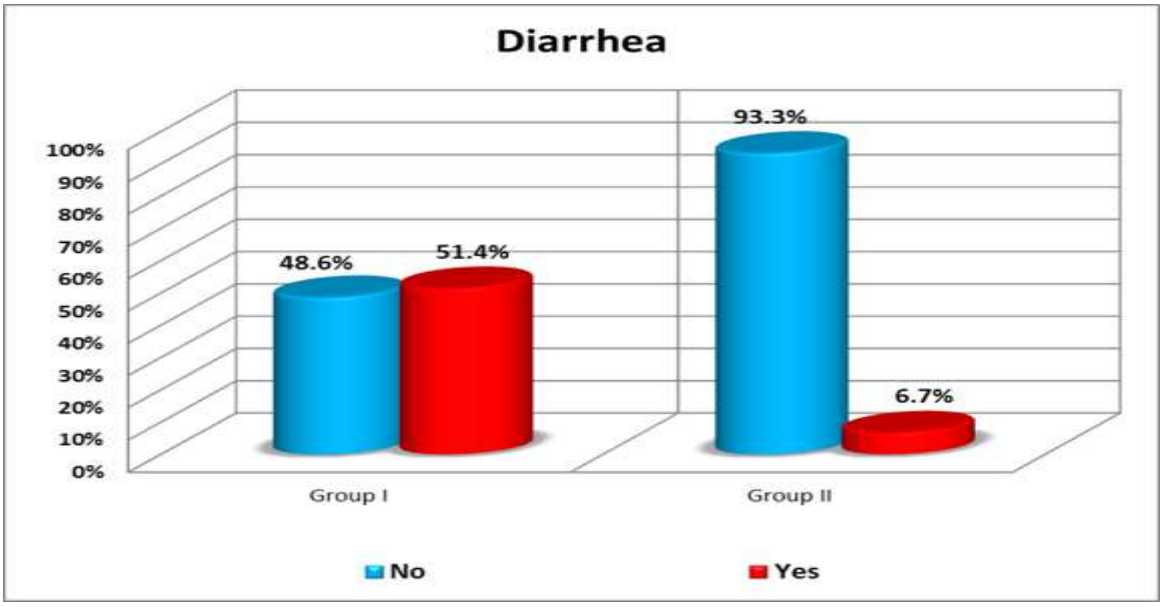

Figure (1): Comparison between studied groups as regards diarrhea.

Table (4): Comparison between studied groups as regards vital signs.

		Group I (N = 70)	Group II (N = 30)	MW	P-value
SBP (mmHg)	Median	120	120	1023	0.840 NS
	IQR	110 – 140	100 – 132		
DBP (mmHg)	Median	80	80	990.5	0.644 NS
	IQR	70 – 80	67.5 – 80		
R.R (cycle/min)	Median	27	26.5	920.5	0.329 NS
	IQR	22 – 33.8	22 – 32		
Temp (C^0)	Median	37.5	37.6	976	0.573 NS
	IQR	37 – 38	37 – 38		
Pulse (beat/min)	Median	100	105	975.5	0.574 NS
	IQR	90 – 112	99 – 113.5		
O_2 sat. (%)	Median	88	92.5	875.5	0.188 NS
	IQR	82.5 – 96	84.8 – 97.3		

Table (5): Comparison between studied groups as regards RBS and liver & kidney function tests.

		Group I (N = 70)	Group II (N = 30)	MW	P-value
RBS (mg/dl)	Median	178.5	164	958.5	0.491 NS
	IQR	134 – 223.5	117.5 – 240		
ALT (U/L)	Median	30	22	708	0.01 S
	IQR	18 – 81.3	14 – 31.3		
AST (U/L)	Median	39.5	22	636	0.002 S
	IQR	22 – 91.3	19 – 33.8		
ALB (g/dl)	Median	3.3	3.7	672.5	0.004 S
	IQR	2.6 – 3.9	3.4 – 4		
Create (mg/dl)	Median	1.35	0.75	498	< 0.001 HS
	IQR	0.8 – 2.9	0.6 – 1		
Urea (mg/dl)	Median	76.5	34.5	474	< 0.001 HS
	IQR	37 – 104	25.8 – 45		

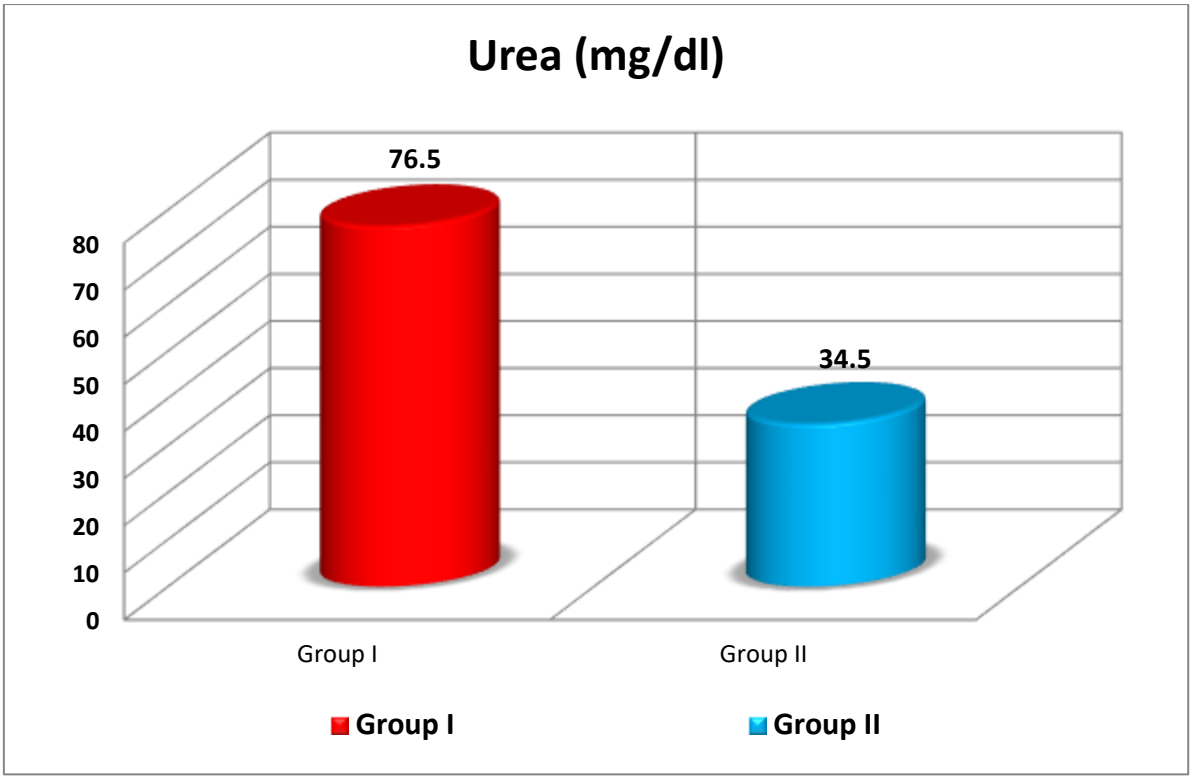

Figure (2): Comparison between studied groups as regard Urea.

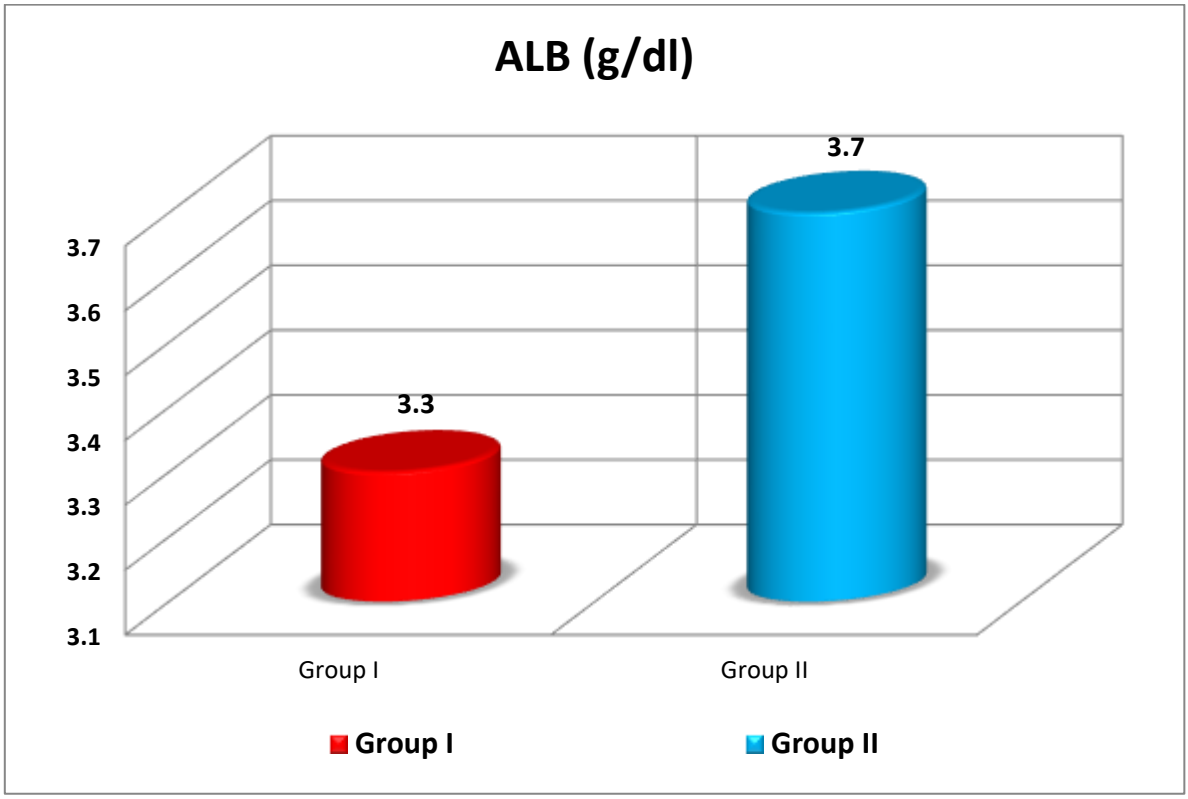

Figure (3): Comparison between studied groups as regards Albumin.

Table (6): Comparison between studied groups as regards RBS, CBC and D. Dimer.

		Group I (N = 70)	Group II (N = 30)	MW	P-value
RBCs (x10^6/ul)	Median	4.2	4.5	779.5	0.042 S
	IQR	3.7 – 4.7	4.1 – 4.9		
Hb (g/dl)	Median	11	11.3	972.5	0.560 NS
	IQR	9.9 – 12.7	10 – 12.8		
MCV (fl/cell)	Median	85	80.5	823	0.087 NS
	IQR	80 – 88	77.7 – 88		
MCH (pg/cell)	Median	27	26.3	1005.5	0.736 NS
	IQR	25 – 29	25 – 29.3		
PLTs (x10^3/ul)	Median	220	204	1048.5	0.991 NS
	IQR	152 – 276	171 – 246		
WBCs (x10^3/ul)	Median	8.05	6	730	0.016 S
	IQR	5.2 – 11	4.5 – 9.2		
Lymph (x10^3/ul)	Median	0.85	0.95	884	0.210 NS
	IQR	0.6 – 1.3	0.7 – 1.6		
Neut. (x10^3/ul)	Median	3.6	1.3	758	0.028 S
	IQR	1.17 – 8.2	0.8 – 4.8		
Eosino. (x10^3/ul)	Median	0	0.01	943	0.387 NS
	IQR	0 – 0.02	0 – 0.04		
Baso. (x10^3/ul)	Median	0	0	1020	0.883 NS
	IQR	0 - 0.004	0 – 0.003		
D-Dimer (mg/L)	Median	0.4	0.6	676.5	0.022 S
	IQR	0.3 - 0.49	0.3 - 0.9		

Table (7): Comparison between studied groups as regards admission site and treatment.

		Group I (N = 70)		Group II (N = 30)		X^2	P-value
Admission site	ICU	46	65.7%	11	36.7%	7.2	0.007 S
	Ward	24	34.3%	19	63.3%		
Anti-viral (remdesivir)	No	0	0%	0	0%	----	-----
	Yes	70	100%	30	100%		
Empirical antibiotic	No	23	32.9%	19	63.3%	8.0	0.005 S
	Yes	47	67.1%	11	36.7%		
Hydroxychloroquine	No	0	0%	0	0%	----	-----
	Yes	70	100%	30	100%		
Dexamethasone	No	24	34.3%	17	56.7%	4.3	0.037 S
	Yes	46	65.7%	13	43.3%		
Immune-modulatory drugs	No	33	47.1%	27	90%	16.1	< 0.001 HS
	Yes	37	52.9%	3	10%		
Anticoagulant	No	4	5.7%	4	13.3%	1.65	0.198 NS
	Yes	66	94.3%	26	86.7%		
	Yes	70	100%	30	100%		
Mechanical ventilation	No	58	82.9%	28	93.3%	1.91	0.166 NS
	Yes	12	17.1%	2	6.7%		

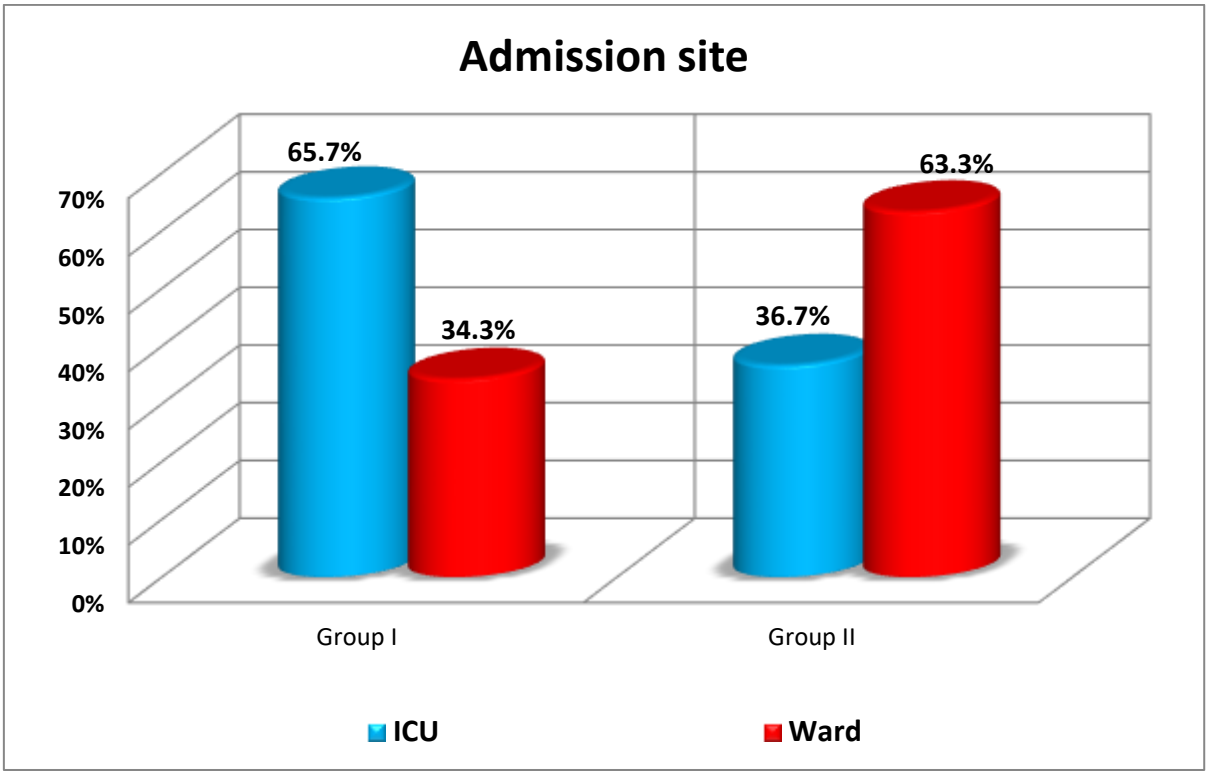

Figure (4): Comparison between studied groups as regard admission site.

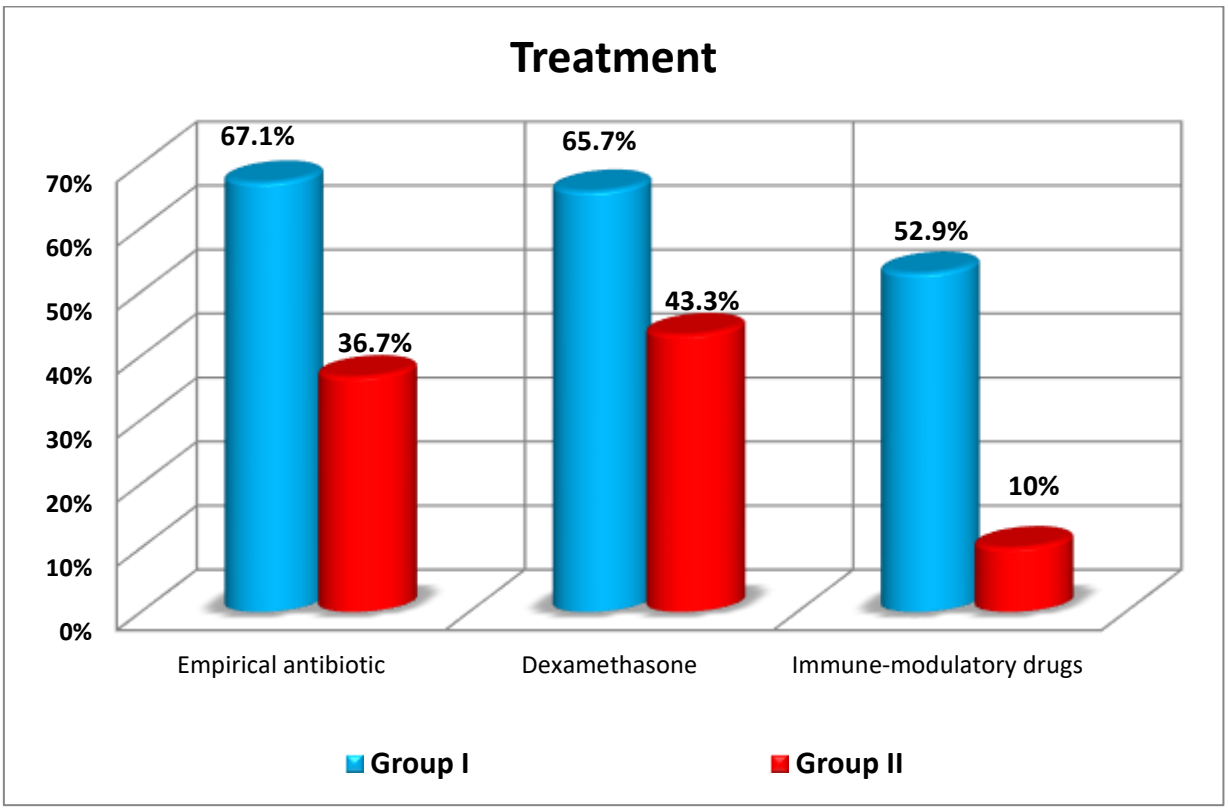

Figure (5): Comparison between studied groups as regards treatment.

Table (8): Comparison between studied groups as regards severity and outcome.

		Group I (N = 70)		Group II (N = 30)		X^2	P-value
Severity	Non-severe	17	24.3%	15	50%	12.9	0.001 S
	Severe	19	27.1%	12	40%		
	Critical	34	48.6%	3	10%		
Outcome	Died	7	10.0%	4	13.3%	0.23	0.625 NS
	Survived	63	90.0%	26	86.7%		

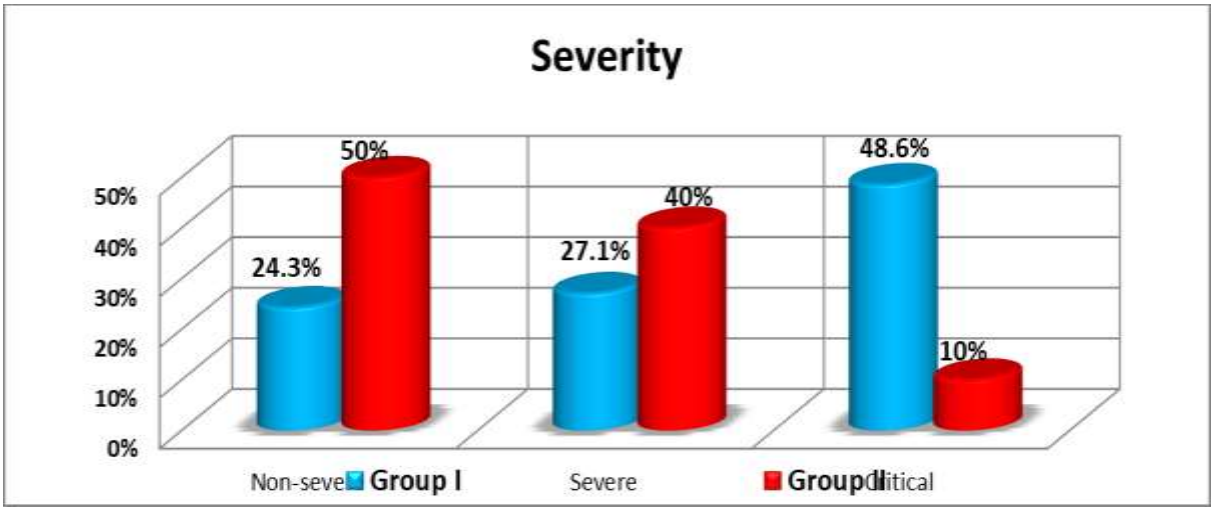

Figure (6): Comparison between studied groups as regards severity.

Table (9): relation between severity and symptoms in group I.

Group I		Severity						X2	P-value
		Non-severe (n = 17)		Severe (n = 19)		Critical (n = 34)			
Fever	No	0	0%	3	15.8%	9	26.5%	5.6	0.06 NS
	Yes	17	100%	16	84.2%	25	73.5%		
Dyspnea	No	11	64.7%	7	36.8%	6	17.6%	112.1	0.004 S
	Yes	6	35.3%	12	63.2%	28	82.4%		
Cough	No	4	23.5%	1	5.3%	4	11.8%	2.7	0.254 NS
	Yes	13	76.5%	18	94.7%	30	88.2%		
Diarrhea	No	8	47.1%	9	47.4%	17	50%	0.05	0.973 NS
	Yes	9	52.9%	10	52.6%	17	50%		
Sore throat	No	14	82.4%	15	78.9%	20	58.8%	3.9	0.137 NS
	Yes	3	17.6%	4	21.1%	14	41.2%		
Gen. fatigue	No	1	5.9%	0	0%	7	20.6%	5.7	0.055 NS
	Yes	16	94.1%	19	100%	27	79.4%		

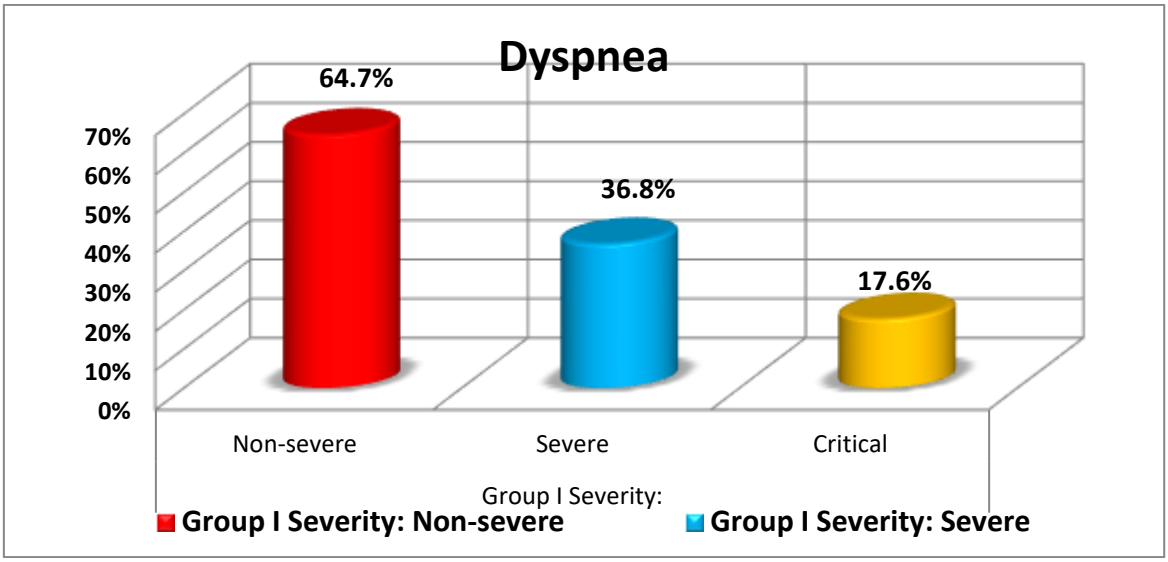

Table (10): Relation between severity and vital signs in group I.

Group I		Severity			KW	P-value
		Non-severe (n = 17)	Severe (n = 19)	Critical (n = 34)		
SBP (mmHg)	Median	120	130	110	6.4	0.040 S
	IQR	110 – 145	120 – 140	100 – 130		
DBP (mmHg)	Median	80	80	70	6.3	0.041 S
	IQR	75 – 90	70 – 80	60 – 80		
R.R (cycle/min)	Median	23	23	32	21.6	< 0.001 HS
	IQR	22 – 25.5	20 – 30	28 – 37		
Temp (C^0)	Median	37.8	37.1	37.5	1.28	0.525 NS
	IQR	37 – 38	37 – 38	37 – 38		
Pulse (beat/min)	Median	105	97	102	2.66	0.264 NS
	IQR	98 – 116.5	88 – 110	92 – 112		
O_2 sat. (%)	Median	97	91	85	37.8	< 0.001 HS
	IQR	95.5 - 98	85 – 96	75 – 88		

Table (11): Relation between severity and (liver, kidney functions and RBS) in group I.

Group I		Severity			KW	P-value
		Non-severe (n = 17)	Severe (n = 19)	Critical (n = 34)		
RBS (mg/dl)	Median	154	174	185	1.13	0.567 NS
	IQR	124 – 208	134 – 220	138 – 233		
ALT (U/L)	Median	18	33	67	15.2	< 0.001 HS
	IQR	13 – 23	20 – 62	23 – 135		
AST (U/L)	Median	22	42	73	16.3	< 0.001 HS
	IQR	16.5 – 29	26 – 73	29 – 145		
ALB (g/dl)	Median	3.9	3.6	2.8	18.2	< 0.001 HS
	IQR	3.4 – 4.2	3.1 – 4	2.4 – 3.3		
Creat (mg/dl)	Median	0.9	1.2	1.95	5.88	0.053 NS
	IQR	0.65 – 1.3	0.8 – 2.9	0.8 – 3.2		
Urea (mg/dl)	Median	37	60	96	12.5	0.002 S
	IQR	23 – 74.5	40 – 90	48 - 109		

Table (12): Relation between severity and CBC in group I.

Group I		Severity			KW	P-value
		Non-severe (n = 17)	Severe (n = 19)	Critical (n = 34)		
RBCs ($x10^6$/ul)	Median	4.2	4.5	4.1	2.73	0.255 NS
	IQR	4 – 4.6	3.9 – 4.8	3.4 – 4.6		
Hb (g/dl)	Median	11.5	11	10.6	2.67	0.263 NS
	IQR	10.6 – 12.3	9.5 – 13.2	9.6 – 12		
MCV (fl/cell)	Median	86	87	85	1.86	0.393 NS
	IQR	81 – 88	80 – 90	78 – 87		
MCH (pg/cell)	Median	27	29	27	0.46	0.794 NS
	IQR	24.5 – 28.5	25 – 29	25 – 29		
PLTs ($x10^3$/ul)	Median	256	208	176	8.6	0.013 S
	IQR	209 – 347	152 – 227	133 – 255		
WBCs ($x10^3$/ul)	Median	6	7	10.8	12.8	0.002 S
	IQR	4.1 – 9	5 – 9.9	6.9 – 14.8		
Lymph ($x10^3$/ul)	Median	1.4	1	0.6	18.6	< 0.001 HS
	IQR	0.85 – 2	0.7 – 1.6	0.5 – 0.9		
Neut. ($x10^3$/ul)	Median	1.3	1.4	7.6	28.4	< 0.001 HS
	IQR	0.65 – 2.2	0.9 – 5.4	5.2 – 10.2		
Eosino. ($x10^3$/ul)	Median	0.03	0.01	0	9.8	0.007 S
	IQR	0 – 0.06	0 – 0.02	0 – 0.01		
Baso. ($x10^3$/ul)	Median	0	0	0	4.4	0.109 NS
	IQR	0 - 0	0 – 0.003	0 – 0.01		

4. Discussion

In our study, we aimed to perform analysis of clinical and laboratory characteristics of 100 patients with COVID-19, admitted to Al-Zahraa Hospital, to evaluate the correlation between the extrapulmonary manifestations of coronavirus disease, progression of COVID-19, our study may be of considerable value to the early identification of patients with a high risk of progression to severe, critical cases of COVID-19, to guide us for proper treatment and avoid complications. The current observational study included seventy patients with extrapulmonary manifestation of COVID-19 compared to thirty covid 19 patients without extrapulmonary manifestation.

A retrospective, observational trial of patients with COVID-19 who were admitted in Al-Zahraa hospital between June 2021 and December 2021, was conducted. The patients were diagnosed with covid (RT-PCR) and resemble rapidity of progression of disease categorized as non-sever, severe and critical.

In our study there was no statically significant difference between covid 19 patients with and without extra-pulmonary manifestation according to their sex and age and this in agreement with [4].

In the current study showed that there is a statically significant increase in diarrhoea in group I when compared ton group II and this in agree with Finsterer, et al (2021), Wan Y, et al (2020), [4], [9] and [15] who

found that the most common extrapulmonary symptom of covid19 disease was diarrhea.

In our study the ICU admission was significantly higher in group I than group II and this in accordance with Martinot et al. (2021) and Yuhong Chen et al. (2020) found that most extrapulmonary complications occurred in ICU patients.

As also, in Shiqiang Xiong et al. (2020) and Elrobaa[4] and New (2021) found [4] severe cases were more liable to having one of extrapulmonary complications than non-severe cases.

Our study showed that there was a highly significant increase of dyspnea in severe and critical patients when compared with non-severe patients in covid 19 patients with or without extrapulmonary manifestation.

Our results were in agreement Tian et al. (2020) and in Kunhua Li et al. (2020), who found that Compared with the mild, moderate group, the severe, critical group had higher incidences of dyspnea.

Also, our results were Compatible with Li J.et al 2020 who performed meta-analysis included 12 cohort studies including 2,445 patients with COVID-19. Compared with non-sever patients, severe disease, dyspnea were found to be significantly associated with more severe COVID-19., Yuhong Chen et al 2020, Tian, et al 2020 and in Kunhua Li, et al 2020, they study on COVID-19 patients severe and critical cases and mild or moderate cases were ,found, the severe and critical group had higher incidences of dyspnea.

Our study showed that patients with critically, severe COVID-19 showed an increase in respiratory rate, hypotension and decrease oxygen saturation than those with or non-severe. respectively. No significant relation between severity and (temperature and pulse). in covid 19 patients. Our results were consistent with from (Long Brit, et al 2022), Omran D, et al. (2021) as there was an increase in respiratory rate, decrease in O2 saturation in critically ill patients, our results were in agreement with Qingming Chen et al. (2020) among 54 patients of covid 19, Hypotension was found in severe and critical cases during hospitalization. Our results were in agreement with Paolo Manunta2020, and colleagues studied 392 consecutive COVID-19 patients and found regardless of age, comorbid diseases, and COVID-19 severity, having mild hypotension as first presentation. Zayed et al (2022) agree with our result as severe group had more hypoxemia than non-severe group. While Omran D, et al. (2021) disagreed with our result according to hypotension.

Our result agrees with Abdur Rahman et al. (2020) results found fever and cough as insignificant risk factors for COVID-19 severity. But a meta-analysis published fever as a significant risk factor for the severity of COVID-19 in (Xu et al., 2020). This mismatch due to many patients in our study who came to hospital late after subsiding of fever.

Our results showed highly significant leukocytosis with lymphopenia and neutrophilia in critical when compared with severe patients and moderate patients in group (I, II).

Our study was compatible with (Aleksandra Barbachowska, et al 2022) they found that leukocytosis, lymphopenia, neutrophilia, and thrombocytopenia in critical case of covid

Also, Zayed et al (2022), (Long Brit, et al 2022) agree with us as severe group had more lymphopenia than non-severe group.

Ramadan et al, (2020) [16], Ghweil et al., (2020) and Elshazli et al., (2020) also agree with us as the mean lymphocytic count was at the lower limit of normal, but a significantly lower percent of lymphocytes was observed in the severe group relative to non-severe groups.

But Ghweil et al., (2020) in disagreement with us they found that there was significantly lower WBC count among severely infected than those had mild to moderate COVID-19. In our study there was statistically significant decreased PLTs

in critical patients when compared with severe patients and moderate patients

Our result was in agreement with Guan et al. (2020) lymphocytopenia, thrombocytopenia, were more prominent among severe vs non-severe cases.

Also, Weifeng Shang et al. (2020) found that platelet and lymphocyte counts were lower in the severe group than in the non-severe group

In our study there was a highly significant increase in ALT, AST and significant decreased ALB in critical patients of covid 19 when compared with severe patients and non-severe patients in group (I, and II).

Our results were compatible with those from, (Li, L.et al 2022) [10], (Long Brit, et al 2022) Ramadan et al.,[16] (2020) they found ALT and AST were significantly higher in the severe group compared to mild group. According to Ghweil et al., (2020) there were significantly higher mean serum values of both ALT and AST with significantly lower serum levels of albumin among severely infected COVID-19 patients verses who had mild to moderate infection.

Our results were in agreement with Omran D, et al. (2021) [14] as serum levels of ALT and AST were higher in critically ill patients. On the opposite side there was an increase in serum albumen in critically ill patients. Also Zayed et al. (2022) reveal higher ALT and AST in severe group when compared with non-severe group.

Our study shows that there was significantly increased creation of cure and urea in critical patients when compared with severe patients and non-severe patients in group (I, II). This result compatible with, (Li, L.et al 2022) [10], Ramadan et al., (2020) [16] who`s study included 260 COVID-19 patients found, Serum creatinine was significantly different among all groups, with the highest level in the severe group and Omran D, et al. (2021) [14] creatinine in critically ill patients. Also, Zayed et al (2022) reveal that severe COVID-19 patients had higher serum creatinine, than non-severe patients.

In our study, there was a significantly increased percentage of critical severity in covid 19 patients with extrapulmonary manifestations (48.6%) when compared with covid 19 patients without extrapulmonary manifestations (10%).

In our study compatible with (Paul Toluwatope, et al 2020) we found that covid 19 patients with extrapulmonary manifestation show an increased percentage of use of dexamethasone and immunomodulatory drugs to limit the inflammatory response on different organs.

Study Limitations

1. Several variants have emerged during our study. These variants have different disease severities, and vaccines might have different protective effects, affecting overall mortality.
2. Not all Mild cases admitted in hospital during our study
3. Some cases were neglected and too late to ask medical advice up to severely critical state.

5- Conclusion

1.We found that the covid 19 is not limited to symptoms of respiratory system. It can cause extrapulmonary complications too.

2. There is evidence that covid 19 has an initial clinical symptom and signs of extrapulmonary organs affected and the most frequent of extrapulmonary organs affected is gastrointestinal and hepatic.

3. Extrapulmonary complication presented in covid 19 patients ranging from stable to severely critical patients who need ICU.

Recommendations

1-Covid19 may start with extrapulmonary presentation so there is need to alert the attending physician about that.

3-Clinicians around the world need comprehensive understanding about the pathophysiology and clinical manifestation of extrapulmonary affection of covid 19.

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