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LABORATORY PARAMETERS INTERPRETATION WITH CARDIAC MANIFESTATIONS IN COVID-19 PATIENTS

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has emerged as a major cause of morbidity and mortality. Both COVID-19 and other pneumonias may present with elevated levels of T/I troponins suggesting injured myocardium.

Aim and objectives:to improve our understanding of the cardiac manifestations of COVID-19 without pre-existing cardiovascular disease, and to provide insights into the characteristics of patients more susceptible to cardiovascular disease.

Subjects and Methods: At isolation hospital in Zagazig, and the isolation hospital in Tripoli, Libya, 42 COVID-19 positive subjects were studied for their echocardiographic parameters, the study was carried out from March 5th 2021 to September 4th 2021.

Results: There was statistically significant difference in age but there was no statistically significant difference in sex in relation to severity of disease where 69.2% of male were severe status vs 56.3% of female patients, patients with mild disease were statistically younger than patient with severe disease where age of the studied patients in mild cases ranging from 27-57 years old with mean 45.2 ± 11.9 years old while age of the studied patients in severe COVID-19 disease ranging from 34-65 years old with mean 56.37 ± 7.4 years old. There was statistically significant difference in D.dimer , o2 saturation and CT findings in relation to COVID-19 severity where d.dimer was statistically higher in severe disease patients than moderate > mild cases (figure8), and O2 saturation was statistically lower in severe disease patients than moderate > mild cases, there was no statistically significant difference regrading other laboratory investigation.

Conclusion: Our findings support findings of abnormalities in laboratory findings of COVID-19 patients correlated with disease severity as well asD.dimer was statistically higher in patients with pulmonary hypertension , the cardiac monitoring can provide us with important information which can help in management of covid-19 patients but we must consider risk of contamination and transmission of disease.

Keywords: Coronavirus Disease, Laboratory findings, Pulmonary hypertension.

Introduction

Coronavirus disease 2019 (COVID-19) has emerged as a major cause of morbidity and mortality that is placing unprecedented pressure on healthcare services across the world **(1).**

COVID-19 usually enters the human body from the respiratory tract and gradually causes systemic disease. The virus result in multi-organ dysfunction and failure and the most affected organ is the lungs, and the cardiovascular system follows it closely. **(2).**

Whilst the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for COVID-19 predominantly affects the respiratory tract, patients with cardiovascular risk factors or established disease and those with elevated cardiac biomarkers appear to be more susceptible and to have a worse prognosis **(3).**

The mechanisms underlying these initial observations remain unclear. Early case reports suggest that COVID-19 can cause a wide range of cardiac conditions that include acute myocardial infarction, (**4)** myocarditis, **(5)** and takotsubo cardiomyopathy. Acute left and right ventricular failure may be a direct consequence of cardiac pathology, with the latter also arising secondary to elevations in right ventricular afterload due to pulmonary embolism or pneumonia **(6).**

Chen et al. (7) and Varga et al. (8) reported that the proposed pathophysiological mechanisms of cardiac injury include inflammatory plaque rupture, stent thrombosis, cardiac stress due to high cardiac output, and infection via the angiotensin-converting enzyme 2 receptors causing systemic endothelitis.

Both COVID-19 and other pneumonias may present with elevated levels of T/I troponins suggesting injured myocardium or raised concentrations of natriuretic peptides as an index of hemodynamic overload **(9).**

A small number of autopsy cases suggest infiltration by interstitial mononuclear inflammatory cells, suggesting myocardial inflammation as the underlying mechanism **(10).**

Virus particles have been observed in the myocardium and vascular endothelium in patients with COVID-19 and cardiogenic shock **(11).**

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

However, the incidence of these cardiac complications and the subsequent implications for treatment and resource allocation are unknown. Consequently, there is an urgent need to better understand the interactions between COVID-19 and the heart **(11).**

This study aimed to improve our understanding of the cardiac manifestations of COVID-19 without pre-existing cardiovascular disease, and to provide insights into the characteristics of patients more susceptible to cardiovascular disease.

Patients and Methods

At isolation hospital in Zagazig, and the isolation hospital in Tripoli, Libya, 42 COVID-19 positive subjects were studied for their echocardiographic parameters, the study was carried out from March 5th 2021 to September 4th 2021. As long as all participants signed informed consent forms and submitted them to Zagazig University's research ethics committee, the study was allowed (ZU-IRB#6693). We followed the World Medical Association's ethical code for human experimentation, the Helsinki Declaration.

Inclusion criteria:

- Non-Cardiac patients.
- Having suffered COVID-19 illness confirmed by RT-PCR on nasopharyngeal swab or imaging findings (Chest CT scan).
- Men or women.
- Age from18 years to 65 years.
- No history of lung disease.
- No ongoing or previous cardio or vasoactive treatment.
- Able to give informed consent
- DM (new diagnosed without treatment).

Exclusion criteria:

- Patients with recent non COVID -19 infection.
- Patient in atrial fibrillation or known coronary artery disease.
- Pregnancy.
- Patients with malignancies or inflammatory diseases.
- Inability to provide consent.
- chronic hepatic or renal disease.
- Diabetes mellitus
- Dyslipidemia:

42 COVID-19 positive patient with echocardiography. COVID-19 infection was confirmed by real-time reverse transcription polymerase chain reaction (rRT-PCR) from nasopharyngeal swabs and by chest CT scan, patient with CORAD scoring equal or more than 4 were included in the study. CORAD1 (no suspicious of COVID-19), CORAD2 (low suspicious of COVID-19), CORAD3 (intermediate suspicious of COVID-19), CORAD4 (high suspicious of COVID-19), CORAD 5 (very high suspicious of COVID-19).

All patients were submitted to full history taking, clinical examination and:

In general, the prevalence of the range of illness severity according to WHO as follows:

(1) Mild covid-19: defined as respiratory symptoms without evidence of pneumonia or hypxia .

(2) Moderate covid-19: presence of clinical and radiological evidence of pneumonia, oxygen saturation (Spo2) equal or more than 90% on room air.

(3) Severe covid-10: presence of clinical and radiological evidence of pneumonia, oxygen saturation (SPO2) less than 90% on room air at sea level, or respiratory rate more than 30 breath /min, or lung infiltration more than 50%.**(10).**

- **ECG**

12 ead electrocardiography. It was recorded in each patient on admission and after improvement of symptoms. ECG was performed with ECG Comen CM 100 and with ECG Schiller AT 102 at a paper speed of 25mm/s and amplification of 10mm/mv.

- **Following laboratory tests**: sample was collected from each patient for:

- CBC: WBC (Neutrophils, Lymphocytes), Hemoglobin, Platelet count.
- Fasting plasma glucose (FPG).
- Liver function test.
- Kidney function test.
- D-dimer.
- Troponin.
- C.reactive protein.

Statistical analysis: The data was coded, entered, and analyzed using Microsoft Excel software throughout the history, clinical examination, laboratory investigations, and outcome measures. The data was tabulated and analyzed using SPSS (statistical package for social science). Independent samples Student's t-test was used to compare between two groups of normally distributed variables while Mann-Whitney U Test is a statistical test for comparing two groups with quantitative variables that do not have a normal distribution. The Chi-square test (X2) or fisher were performed to compare and correlate

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

two qualitative variables. The results were considered statistically significant and highly statistically significant when the significant probability (P value)was < 0.05* and <0.001** respectively.

Results

age of the studied group ranging from 27-65 years old with mean 54.98 ± 8.53 years old and about 2\3 of them were male (61.9 %). **Figure (1)** As regard clinical data among the studied patients , mean of systolic and diastolic pressure were 119.24 ± 17.38 and 70.12 ± 9.39 respectively, mean of heart rate was 95.21 ± 18.4 beat \min and it ranged from 55-123 beat\min.

laboratory finding as regard WBCs, lymphocytes, RBS, CRP , urea and Serum creatinine among the studied group, where mean of WBCs was 17.11 ± 9.38, lymphocytes were low among 11.9% of the studied patients, CRP finding was high as it was 127.82 ± 84.37 ranged from 6.6 to 350, D.dimer ranged from 0-9 mg/l while troponin ranged from 0-6 ng/ml. Regarding serum electrolyte as Na, Cl, K and liver function tests among the studied group, mean of Na was 137.23± 4.21, liver function tests were within normal ranges. **Table (1)**

PR-interval was ranged from 0.12-0.28 (Sec) among the studied group, QRS duration was ranged from 0.08-0.24, QTc Bazzet's formula was ranged from 0.13-0.72, as regard ECG findings APCs, VPCS, LBBB, RBBB, and S. TACY were positive among (9.5%, 9.5%, 4.8%, 4.8% & 45.2%) respectivel. **Table (2)**

There was statistically significant difference in age but there was no statistically significant difference in sex in relation to severity of disease where 69.2% of male were severe status vs 56.3% of female patients, patients with mild disease were statistically younger than patient with severe disease where age of the studied patients in mild cases ranging from 27-57 years old with mean 45.2 ± 11.9 years old while age of the studied patients in severe COVID-19 disease ranging from 34-65 years old with mean 56.37 ± 7.4 years old.There was statistically significant difference in D.dimer , o2 saturation and CT findings in relation to COVID-19 severity where d.dimer was statistically higher in severe disease patients than moderate > mild cases (figure8), and O2 saturation was statistically lower in severe disease patients than moderate > mild cases, there was no statistically significant difference regrading other laboratory investigation. **Table (3)**

there was statistically significant difference in Age in relation to pulmonary hypertension among the studied patients, patients with pulmonary hypertension were statistically older than patients with no pulmonary hypertension. There was no statistically significant difference in sex in relation to pulmonary hypertension. There was statistically significant difference in D.dimer in relation to pulmonary hypertension among the studied patients where D.dimer was statistically higher in patients with pulmonary hypertension, there was no statistically significant difference regarding other laboratory investigations. **Table (4).**

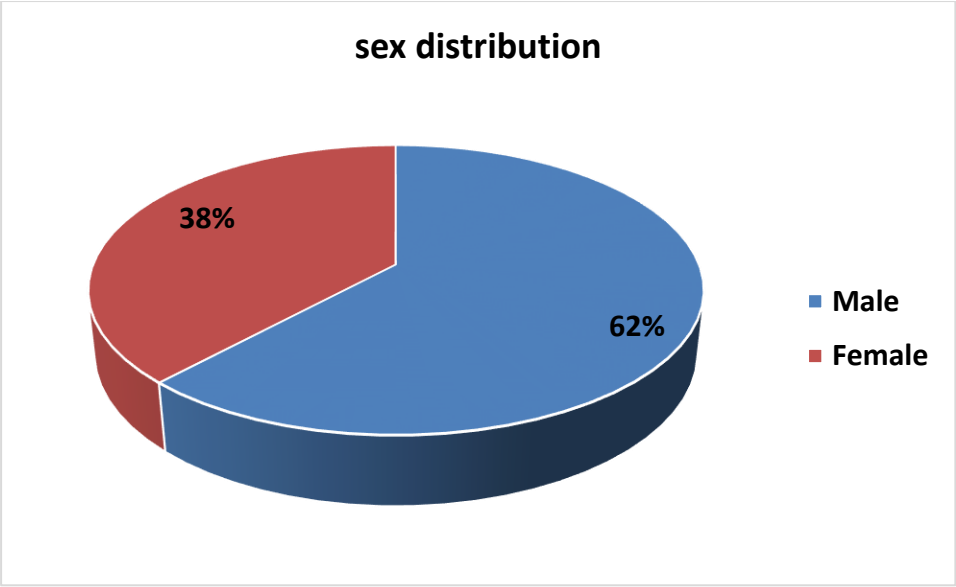

Figure (1):Sex distribution among the studied group

Table (1) Laboratory data among the studied patients:

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

Item		Studied group (N= 42)
WBCs	Mean ± SD	17.11 ± 9.38
	Median (Range)	15.11(6.8-64.55)
Lymphocytes	Mean ± SD	1.31 ± 0.81
	Median (Range)	1.06(0.32-4.2)
	Low *	5(11.9%)
RBS	Mean ± SD	116.71 ± 30.1
	Median (Range)	108(71-180)
CRP	Mean ± SD	127.82 ± 84.37
	Median (Range)	116.7(6.6-350)
Urea	Mean ± SD	40.15 ± 14.58
	Median (Range)	37.5(15-80)
S. creatinine	Mean ± SD	0.94 ± 0.34
	Median (Range)	0.9(0.4-2.2)
D.dimer	Mean ± SD	2.97 ± 2.86
	Median (Range)	1.37(0-9)
Troponin	Mean ± SD	2.28 ± 2.03
	Median (Range)	2.5(0-6)
	> 0.1*	18(42.9%)
NA	Mean ± SD	137.23± 4.21
	Median (Range)	137(127-147)
K	Mean ± SD	4.14 ± 0.53
	Median (Range)	4.25(3.3-5.6)
CL	Mean ± SD	101.49 ± 4.2
	Median (Range)	100.5(95.2-113)
S.GOT	Mean ± SD	28.57 ± 10.95
	Median (Range)	30.15(12-63)
S.GPT	Mean ± SD	24.96 ± 14.48
	Median (Range)	21.65(10-70)
Total bilirubin	Mean ± SD	0.49 ± 0.24
	Median (Range)	0.41 (0.07-1.3)
Direct bilirubin	Mean ± SD	0.22 ± 0.11
	Median (Range)	0.2(0.09-0.6)

Table (2) ECG reading among the studied patients:

Item		Studied group N= 42	
PR-interval (Sec)	Mean ± SD	0.17 ± 0.03	
	Median (Range)	0.16(0.12-0.28)	
QRS duration (Sec)	Mean ± SD	0.11 ± 0.02	
	Median (Range)	0.12(0.08-0.24)	
QT"bazzet's formula"(Sec)	Mean ± SD	0.43 ± 0.09	
	Median (Range)	0.44(0.13-0.72)	
Arrhythmias		**N**	**%**
▪ **APCs**	Positive	4	9.5 %
	Negative	38	90.5%
▪ **VPCS**	Positive	4	9.5%
	Negative	38	90.5%
▪ **S.TACY**	Positive	19	45.2%
	Negative	23	54.8%
▪ **BBB**	Negative	38	90.5%
	RBBB	2	4.8%
	LBBB	2	4.8%

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

Myocardial infarction	NSTEMI	4	9.5%
	STEMI	2	4.8%
	NONE	36	85.7%

Table (3) Relation between(Demographic and clinical and laboratory data) and COVID-19 severity among the studied patients:

Variable		**COVID-19 severity**						**Test**	**p-value**
		Mild (N=5)		**Moderate (N=10)**		**Severe (N=27)**			
		No	**%**	**No**	**%**	**No**	**%**		
Age (years)	Mean ± SD	45.2 ± 11.9		56.1 ± 6.9		56.37 ± 7.4		4.32 [a]	0.020* (S)
	(Range)	27-57		45-65		34-65			
Sex	Male (n= 26)	1	3.6	7	26.9	18	69.2	4.26[b]	0.119 (NS)
	Female (n=16)	4	25.0	3	18.8	9	56.3		
CT findings	negative	5	100.0	0	0.0	0	0.0	42.00	0.000* (HS)
	Positive	0	0.0	10	100.0	27	100.0		
HR	Mean ± SD	92.2 ± 17.93		97.2 ± 17.7		95.04 ± 19.2		0.121	0.886 (NS)
	(Range)	71-120		60-120		55- 123			
O2 saturation	Mean ± SD	98.6 ± 0.54		97.4 ± 0.51		75.51 ± 7.14		70.13	0.000* (HS)
	(Range)	98-99		97-98		65-88			
TLC	Mean ± SD	13.56 ± 2.01		15.05 ± 4.5		18.5 ± 11.17		0.881	0.423 (NS)
	(Range)	11.1-16.5		6.8-22.25		10.32-64.55			
S.Creatinine	Mean ± SD	0.72 ± 0.23		1.0 ± 0.47		0.97 ± 0.29		1.31	0.282 (NS)
	(Range)	0.4-1.0		0.5-2.2		0.5-1.8			
Treponin	Mean ± SD	1.33 ± 1.69		0.07		2.56 ± 2.06		2.82	0.071 (NS)
	(Range)	0-3		0		0-6			
D.dimer	Mean ± SD	0.84 ± 0.39		2.27 ± 3.01		3.87 ± 2.85		4.061	0.025* [c]0.034*
	(Range)	0-1		0-9		0-9			
CRP	Mean ± SD	103.17 ± 51.7		122.3 ± 102.7		134.4 ± 83.6		0.305	0.739 (NS)
	(Range)	45.6-186		8.97-350		6.61-350			

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

Table (4) demographic and clinical data in relation to pulmonary hypertension among the studied patients:

Variable		pulmonary hypertension		p-value
		No (N=26)	Yes (N=16)	
Age (years)	Mean ± SD	45.1± 10.8	56.3 ± 6.8	0.030*
	(Range)	27-56	46-65	(S)
#Sex	Male	15(57.7%)	11(68.8%)	0.651
	female	11(42.3%)	5(31.2%)	(NS)
#CT findings	Negative	4 (15.3%)	1(6.2%)	0.431
	positive	22(84.7%)	15(93.8%)	(NS)
HR	Mean ± SD	95.66 ± 16.82	94.6 ± 18.24	0.532
	(Range)	55-118	55-123	(NS)
O2 saturation	Mean ± SD	85.7 ± 11.43	83.23 ± 10.67	0.546
	(Range)	67-99	66-98	(NS)
TLC	Mean ± SD	15.38 ± 10.7	18.3 ± 7.14	0.368
	(Range)	6.5-65.43	11.2-33.14	(NS)
S.Creatinine	Mean ± SD	0.8 ± 0.46	0.96 ± 0.24	0.362
	(Range)	0.50-2.3	0.4-1.7	(NS)
Troponin	Mean ± SD	1.68 ± 1.45	2.51 ± 2.19	0.323
	(Range)	0-4	0-6	(NS)
D.dimer	Mean ± SD	1.54 ± 1.69	3.81 ± 3.07	0.020*
	(Range)	0-5	0-9	(S)
CRP	Mean ± SD	134.23 ± 86.51	114.6 ± 75.19	0.261
	(Range)	6.22-350	7.26-350	(NS)

Discussion

Corona virus disease 2019 (covid-19) is global pandemic disease caused by severe acute respiratory syndrome Corona virus 2, which invades cells through the angiotensin –converting enzyme 2 receptor. among patients with covid-19, there is a high prevalence of cardiovascular disease. **Clerkinet al., (12).**

Acute cardiac injury, defined as significant elevation of cardiac troponins, is the most commonly reported cardiac abnormality in covid-19. Direct myocardial injury due to involvement of cardiomyocytes and the effect of systematic inflammation appear to be the most common mechanisms responsible for cardiac injury. **Bansal et al., (13).**

In our study, age was distributed as 54.98 ± 8.53 with minimum 27 and maximum 65 years old, and there was statistically significant difference (P=0.020) between the studied groups were patients with mild disease statistically younger than patients with severe disease, age of studied group in mild cases ranging from 27-57 years old , while the age of studied group in moderate cases from 45-65 years old and in severe cases ranging from 34-65 years old.

Also, came in agreement with **Xing et al., (14)** that enrolled in there study 32 patients, 13 patient were under 60 years old, and 19 patients were above 60 years old, they demonstrated that a high proportion of critically ill patients were 60 or older and rapidly disease progression was noted in elderly patients (P=0.01).

Age related changes influence the host immune response and therefore not only weaken the ability to fight respiratory infections but also to mount effective response to vaccines. Immunosenescence and inflamm-aging are considered key features of the aging immune system wherein accumulation of senescent immune cells contribute to its decline and simultaneously increased inflammatory phenotypes cause immune dysfunction. **Bajaj et al., (15).**

In this study, mean of heart rate was 95.21 ± 18.4 beat/min and it ranged from 55-123 beat/min, and there was no statistically significant difference between studied groups (P=0.886) were in mild cases ranged from 71-120 beat/min and in moderate cases ranged from 60-120 beat /min, and in severe cases ranged from 55-128 beat /min.

These findings came in agreement with study by **Zhang et al., (16)** who enrolled 112 covid-19 patients and revealed that mean of HR (92.8 ± 23.6), and there was no statistically significant difference in relation to severity (P=0.66).

This could be due to the vast majority of patients presenting with a systemic illness consistent with covid-19 had no symptoms and signs of arrythemias or conduction system disease. Patients may be tachycardic in setting of other illness – related symptoms e.g fever , shortness of breath, pain, etc .**Prutkin et al.,(17).**

In our study, there was statistically significant difference in D.dimer in relation to covid-19 severity (P=0.025), were D.dimer is statistically higher in severe cases than moderate and mild cases.

These findings came in agreement with **Zhang et al., (16)** that reported, D.dimer level was higher in severe cases and there was statistically significant difference in D.dimer level in relation to severity (P<0.01).

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

This could be due to that D.dimer is a fibrin degradation product, it is a biomarker for thrombotic disorder, increase with increasing age. The level of, D.dimer rise with increased severity of pneumonia, and identified as a potential indicator for prognosis in covid-19. **Poudel et al. (18).**

In this study, D.dimer level was statistically higher in covid-19 patients complicated by myocardial infarction (P=0.022).

These findings came in agreement with **Yang et al., (19)** that demonstrated,D.dimer was statistically higher in patients with covid-19 and myocardial injury compared with patients with covid-19 with no myocardial injury (P<0.001). this could be due to Coagulopathy is one of the major complications of covid-19, both venous and arterial thrombosis are observed in covid-19. D.dimer and fibrin degradation products are the characteristic change seen in covid-19 associated coagulopathy (CAC) including myocardial infarction.**Rajendran et al., (20).**

In this study, troponin level was higher in severe cases (range 0-6 ng/ml) compared to mild cases (range 0-3 ng/ml) but there was no statistically significant difference in troponin level in relation to covid-19 severity (P=0.071).

These findings came in different with **Barman et al., (21)** that revealed, there was statistically significant difference in troponin level in relation to severity of covid-19 (P=0.004).

This difference could be due to that we excluded all risk factors of CVD and pre-existing cardiovascular disease in our study while these studies didn't exclude risk factors and CVD as smoking, dyslipidemia, DM , hypertension, IHD which can lead to more cardiovascular events in covid-19 patients therefore more high troponin levels.

In current study, C – reactive protein (CRP) in mild cases ranged from 45.6-186 mg/l and in moderate cases ranged from 8.97—350 mg/l and in severe cases ranged from 6.61-350 mg/l, and there was no statistically signficant difference in CRP level between studied group (P=0.739).

These came in different with **Zhang et al., (16)** that enrolled 112 covid-19 patients, revealed that the levels of CRP in the severe group were higher than those in non-severe group with statistically significant difference (P<0.01). This could be due to **Zhang et al., (16)** didn't exclude patients with COPD and other inflammatory diseases which may affect on CRP levels.

In the current study, there was no statistically significant difference in arrhythmia or myocardial infraction (P=0.421) in relation to covid-19 severity.

These came in different from **Wen et al.,(22)** meta-analysis included five articles (1553 covid-19 patients), showed that incidence of arrhythmia in patient with severe covid-19 was greater than that of those with non-severe covid-19.

this difference could be due to the sample is large compared with our sample and these studies not exclude risk factors that may increase incidence of arrhythmia.

In our study, there was statistically significant difference in D.dimer level (P=0.020) between patients with pulmonary hypertension (PH) and patients with no pulmonary hypertension (PH).

these findings came in agreement with **Pagnesi et al., (23),** demonstrated that D.dimer level was higher in patients with pulmonary hypertension and there was statistically significant difference in D.dimer level between patients with pulmonary hypertension (PH) and patients with no pulmonary hypertension (P=0.013).

This could be due to in covid-19 pulmonary involvement is bilateral, consisting of extensive interstitial and alveolar inflammatory infiltrates, thickining of alveolar Sept, vascular congestion, and lung edema, which could be responsible, in some patients, for the development of pulmonary fibrosis. As consequence of lung parenchymal damage and of altered pulmonary circulation, pulmonary hypertension may develop. The pathophysiology of this type of PH is complex and multifactorial and mechanisms such as oxidative stress, mitochondrial dysfunction,and DNA damage,inflammation, hypoxia, associated with endothelial dysfunction, and pulmonary micro-embolism have been considered potential factors for the alternations of pulmonary circulation. **Tudoran et al., (24).**

Our findings came in different with**Noderfeldt et al., (25),** that enrolled 67 covid-19 patients ,26 of them had PH and 41 of them non-PH reported that there was no statistically significant difference in D.dimer level between patients with PH and patients with no PH.

This lack of difference could be due to the following finding: both groups had a similar thromboembolism burden, but the blood clots in the non-aPH group were fixed in the peripheral veins, whereas a certain amount of blood clots had detached and embolized the pulmonary circulation in the aPH group, thereby producing increased sPAP. Alternatively, perhaps the aPH patients had more severe endothelitis of the pulmonary micro-vessels, thereby creating a more pronounced spastic component of pulmonary vascular resistance than the non-aPH group.**Noderfeldt et al., (25).**

Conclusion

From all the mentioned data we can conclude that abnormalities in laboratory findings of COVID-19 patients correlated with disease severity as well as D.dimer was statistically higher in patients with pulmonary hypertension , the cardiac monitoring can provide us with important information which can help in management of covid-19 patients but we must consider risk of contamination and transmission of disease.

Conflicts of interest: None.

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ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 05, 2021

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