International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2023; 6(3): 80-87
Received: 08-05-2023
Accepted: 15-06-2023

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Thrombotic complications of COVID-19 and its relation with NADPH oxidase and tissue factor

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DOI: https://doi.org/10.33545/pathol.2023.v6.i3b.538

Abstract
Background: The severe acute respiratory syndrome corona-virus 2 (SARS CoV-2) is the virus responsible for the corona-virus disease 19 (COVID-19), a highly contagious and pathogenic viral illness. Individuals with severe illnesses may develop acute respiratory distress syndrome (ARDS) and have altered coagulation functioning, which puts them at risk for developing thromboembolic consequences. This work aimed to evaluate the relation between NADPH oxidase 2 (NOX2), tissue factor (TF) and the thrombotic complications in COVID-19 infection.
Subjects: This case-control work was performed on 180 subjects. Individuals with COVID-19 group included 100 patients proved to be COVID-19 positive. Control group included 80 apparently healthy age and sex matched subjects.
Methods: Blood levels of NOX2, TF and Interleukin-6 (IL-6) had been assessed by sandwich enzyme-linked immune-sorbent assay (ELISA) method.
Results: a substantial increase was existed in NOX2, TF and IL-6 in COVID-19 patients and patients with thromboembolic events (TEEs) when compared with control subjects and patients without TEEs. ROC curve for serum NOX2 to predict thromboembolic events showed sensitivity 96.55, specificity 94.37 and positive predictive value 87.5. ROC curve for plasma TF to predict thromboembolic events had sensitivity 93.10, specificity 92.96, and positive predictive value 84.4.
Conclusions: High levels of NADPH oxidase2, tissue factor and IL-6 are associated with increased incidences of the thromboembolic complications, mortality rates and admission at ICU in individuals with COVID-19.

Keywords: NADPH oxidase2, tissue factor, thromboembolic complications, COVID-19

Introduction
A series of acute respiratory infections, vary from mild to critical clinical presentations established by the novel coronavirus named SARS-CoV-2, belonging to the family Coronaviridae. Globally, COVID-19's worldwide pandemic produced tremendous losses of lives [1].

A cytokines storm profile, characterized by elevated amounts of Proinflammatory cytokines and chemokines, including interleukins (IL), especially IL-1 and IL-6, tumor necrosis factor-α (TNF-α), may be detected in a subset of individuals who are most severely impacted by COVID-19. Mononuclear cells may express tissue factors when exposed to IL-6, which causes the coagulation system to become activated and thrombin to be produced [2].

One of the important processes that are related to respiratory infection with viruses and associated to inflammatory processes and subsequently damage to tissues involves alterations in the homeostasis of redox in infected cells. Infections with viruses promote cell death and NOX2-mediated oxidative stresses [3]. Additionally, NOX2 is linked to thrombosis because it causes aggregation of platelets by excessive hydrogen peroxide generation or suppression of nitric oxide [4].

It has been demonstrated that a number of Proinflammatory agents, such as antiphospholipid antibodies, tumor necrosis factor-α (TNF-α), and homocysteine, cause TF in endothelial cells by activating NADPH oxidase complexes in a necessary manner [5].

If the infection with SARS-CoV-2 of endothelial cells produces luminal expression of tissue factors through the NADPH-oxidase signaling systems that may then interact with circulatory coagulant factor VII triggering a proteolytic cascade ultimately leading to the production of thrombin and fibrin, then the thrombotic negative consequences of infection with COVID-19 could be readily comprehended [6].

This work aimed to find out the relation among NADPH oxidase, tissue factor and the thrombotic consequences in infection with COVID-19 and their role in the COVID-19 pathogenesis and to study the relationship between these markers and the disease severity and progression.

Subjects and methods

This case-control work was performed throughout the course of an 18-month period from January 2021 to June 2022, at Tanta University Hospitals.

The Tanta University ethics committee gave the research its approval. The Tanta University Faculty of Medicine's Research Ethical Committee assigned the authorization code, which was 34336/12/20. All participants completed written informed approval forms. A secret code number was used to maintain the secrecy of the information and the privacy of the study participants.

We prospectively studied 147 subjects potentially eligible for our study who were proved by clinical correlation and CT chest findings with rapid antigen detecting test or positive PCR to be COVID-19 positive patients. A flowchart of study subjects is provided in figure (1). 100 hospital admitted patients' positive for COVID-19 were included for final analysis. They were 54 males and 46 females and their ages ranging between 34 and 81 years old with mean 60.72 ± 8.78.

A control group of 80 volunteer subjects who agreed to share in the work. They had been apparently healthy age- and sex-matched subjects from outpatient clinics. Control subjects had been 46 males and 34 females and their ages ranging between 30 and 75 years old with mean 56.40 ± 7.98.

Exclusion criteria were coexistence of autoimmune diseases, pregnancy or lactation, coexistence of chronic infections that include hepatitis C or B infections, infection with Immuno-deficiency virus (HIV), cancers, coexistence of any other chest diseases (e.g. Tuberculosis) and patients aged less than 18 years old.

The studied Covid-19 individuals had been classified into 2 groups: individuals with thromboembolic events (TEEs) and individuals without thromboembolic events. The thromboembolic events included any of the following: pulmonary-embolism, myocardial infarction, stroke or deep vein thrombosis.

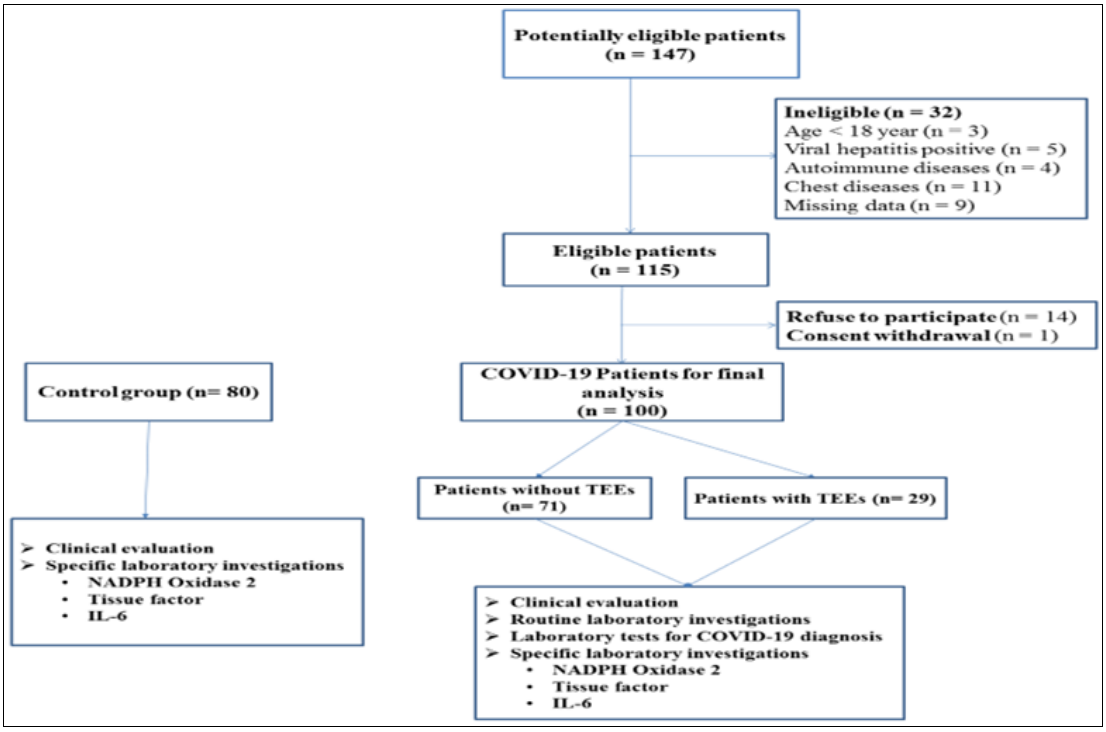

Fig 1: Flowchart of study subjects, (N= number)

Routine laboratory investigations:

- CBC using Erma Inc. Apparatus, fully automatic blood cell counter, with examination of giemsa-stained peripheral blood (pb) smears for differential leucocytic count.
- Serum ferritin, d-dimer, and procalcitonin using tosoh 1800 apparatus.
- INR and activated partial thromboplastin time (aptt) using stago apparatus.
- Liver function tests & kidney function tests, ldh and crp using automated indiko plus apparatus.

Specific laboratory investigations:

- Measurement of serum nadph oxidase 2 level using sandwich elisa kit for the quantitative determining of human nadph oxidase 2 (nox2) provided by sunlong biotech company, (catalogue no: sl2428hu).
- Measurement of plasma tissue factor level using sandwich elisa kit for the quantitative determining of human coagulation factor iii, human tissue factor (tf) in plasma samples, provided by r&d systems, inc., (catalogue no: dcf300).
- Measurement of serum interleukin-6 level using sandwich elisa approach for the quantitative

determining of human interleukin-6 (il-6) in serum samples, provided by r & d systems, Inc. (catalogue no: d6050).

Statistical analysis

With the use of the IBM SPSS software programme version 20.0 (IBM CORP, Armonk, NY), data had been input into the computer and analysed. The range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR) have been utilized for describing quantitative data. Utilizing the Pearson coefficient, the correlations among two quantitative parameters were evaluated. The outcomes obtained were considered significant at the 5% level.

The used tests were student t-test, chi-square test, Mann-Whitney test, correlation coefficient (r), receiver operating characteristic curve (ROC).

Results

COVID-19 patients were classified according to the occurrence of thromboembolic events (TEEs) to two groups: patients with TEEs 29% and patients without TEEs 71%. Pulmonary embolism (PE) represented the highest incidence among patients with TEEs by 41.4%, 12 patients. Stroke incidence was 27.6%, 8 patients. Patients with myocardial infarction (MI) were 17.2%, 5 patients. DVT was the least incidence among patients with TEEs by 13.8%, just 4 patients.

There was a significant increase of TEEs among COVID-19 patients with critically ill ministry of health (MOH) class of disease severity (P = 0.006) table (1).

Table 1: Distribution of TEEs among COVID-19 patients with different MOH class illness severity

Distribution of TEEs	Moderate (n= 40)		Severe (n= 33)		Critical (n= 27)		p
	No.	%	No.	%	No.	%	
Patients without TEEs	35	87.5	22	66.7	14	51.9	0.006*
Patients with TEEs	5	12.5	11	33.3	13	48.1	

Statistically significant at $p \leq 0.05$

A significant increase was existed in NOX2, TF, IL-6 in individuals COVID-19 when contrasted to control group table (2).

Table 2: Comparison between controls group and COVID-19 patients group according to TF (pg/mL), NOX2 (pg/mL) and IL-6 (pg/mL).

	Controls (n = 80)	COVID-19 patients (n= 100)	P
NOX2 (pg/mL)			
Min. – Max.	10.0 – 27.0	11.0 – 56.20	<0.001*
Mean ± SD.	16.04 ± 7.15	30.88 ± 11.35	
TF (pg/mL)			
Min. – Max.	149.0 – 172.0	153.0 – 221.0	<0.001*
Mean ± SD.	157.2 ± 6.14	173.62 ± 19.78	
IL-6 (pg/mL)			
Min. – Max.	0.50 – 7.0	2.60 – 133.90	<0.001*
Median (IQR)	2.4 (0.9 – 5.0)	24.15 (6.35 – 85.0)	

Table (3) showed significant higher levels of WBCs count, neutrophil, ALT, AST, urea, creatinine, LDH, CRP, ferritin, procalcitonin, INR, APTT, D-dimer, NOX2, TF, IL-6 in patients with TEEs than patients without TEEs.

Table 3: Comparison between the two studied groups according to laboratory parameters

	Patients without TEEs (n= 71)	Patients with TEEs (n= 29)	P
Hemoglobin (g/ dl)			
Min. – Max.	7.40 – 14.50	8.0 – 14.0	0.364
Mean ± SD.	11.15 ± 1.65	11.49 ± 1.68	
WBCs ($\times 10^9$ /L)			
Min. – Max.	4.30 – 22.0	6.30 – 25.30	0.033*
Median (IQR)	10.30 (7.90 – 12.60)	12.10 (9.30 – 15.30)	
Neutrophil ($\times 10^9$ /L)			
Min. – Max.	2.50 – 19.80	5.0 – 21.40	0.021*
Median (IQR)	7.0 (5.45 – 10.0)	10.0 (5.90 – 12.80)	
Lymphocyte ($\times 10^9$ /L)			
Min. – Max.	0.60 – 3.50	0.60 – 2.70	0.882
Median (IQR)	1.50 (1.15 – 2.0)	1.50 (1.30 – 2.0)	
Platelet ($\times 10^9$ /L)			
Min. – Max.	47.0 – 423.0	48.0 – 423.0	0.473
Median (IQR)	215.0 (157.0 – 296.0)	186.0 (129.0 – 289.0)	
Albumin (g/dl)			
Min. – Max.	1.90 – 4.20	2.0 – 3.90	0.002*
Median (IQR)	3.50 (3.10 – 3.70)	3.0 (2.50 – 3.40)	
ALT (U/L)			
Min. – Max.	15.0 – 186.0	45.0 – 245.0	0.004*
Mean ± SD.	90.63 ± 49.52	121.34 ± 41.04	
AST (U/L)			
Min. – Max.	19.0 – 220.0	40.0 – 231.0	0.002*
Mean ± SD.	97.03 ± 48.72	131.24 ± 48.0	

Urea (mg/dl)			
Min. – Max.	22.0 – 259.0	25.0 – 263.0	0.041*
Median (IQR)	63.0 (38.50 – 116.50)	94.0 (55.0 – 145.0)	
Creatinine (mg/dl)			
Min. – Max.	0.70 – 7.0	0.80 – 7.90	0.027*
Median (IQR)	1.60 (1.10 – 2.60)	2.80 (1.50 – 3.60)	
LDH (U/L)			
Min. – Max.	61.0 – 964.0	259.0 – 966.0	0.002*
Median (IQR)	338.50 (264.0 – 739.0)	729.0 (420.0 – 839.0)	
CRP (mg/L)			
Min. – Max.	2.70 – 105.0	5.20 – 120.0	<0.001*
Median (IQR)	15.0 (8.0 – 57.70)	57.0 (27.80 – 86.20)	
Ferritin (ng/mL)			
Min. – Max.	79.0 – 1378.0	50.0 – 1446.0	0.004*
Median (IQR)	743.0(273.5 –1055.5)	1048.0(767.0–1245.0)	
Procalcitonin (ng/mL)			
Min. – Max.	0.0 – 3.75	0.17 – 4.0	0.006*
Median (IQR)	0.53 (0.27 – 0.75)	0.80 (0.53 – 2.64)	
INR			
Min. – Max.	0.80 – 1.95	0.88 – 1.97	0.003*
Median (IQR)	1.13 (0.98 – 1.48)	1.40 (1.20 – 1.70)	
APTT (sec)			
Min. – Max.	25.0 – 57.0	29.0 – 57.0	<0.001*
Median (IQR)	39.0 (32.0 – 48.0)	49.0 (47.0 – 51.0)	
D-dimer (µg/L)			
Min. – Max.	0.10 – 8.4	0.70 – 12.7	*0.001
Median (IQR)	1.80 (0.60 – 5.90)	4.60 (2.40 – 8.7)	
NOX2 (pg/mL)			
Min. – Max.	11.0 – 37.40	32.90 – 56.20	<0.001*
Mean ± SD.	25.17 ± 7.31	44.87 ± 6.02	
TF (pg/mL)			
Min. – Max.	153.0 – 184.0	175.0 – 221.0	<0.001*
Mean ± SD.	163.93 ± 12.14	197.34 ± 13.92	
IL-6 (pg/mL)			
Min. – Max.	2.60 – 132.0	4.40 – 133.9	0.001*
Median (IQR)	8.60 (5.45 – 66.0)	63.60 (14.70 – 107.0)	

There were significant positive correlations between NOX2 and all of TF, IL-6, APTT and D-dimer. NOX2 was significantly negatively correlated with platelet count. TF had significant positive correlations with and all of NOX2, IL-6, APTT and D-dimer. NOX2 and TF were significantly negatively correlated with platelet count table (4).

Table 4: Correlation between NOX2, TF, IL-6 and different parameters

	NOX2 (pg/mL)		**TF (pg/mL)**		**IL-6 (pg/mL)**	
	R	**P**	**r**	**p**	**r**	**P**
TF (pg/mL)	0.854	<0.001*			0.542	<0.001*
IL-6 (pg/mL)	0.596	<0.001*	0.542	<0.001*		
Platelet ($\times 10^9$ /L)	-0.546	<0.001*	-0.309	0.002*	0.152	0.245
APTT (sec)	0.787	<0.001*	0.590	<0.001*	0.392	0.002*
D-dimer (µg/L)	0.457	<0.001*	0.242	0.015*	0.418	<0.001*

ICU admitted COVID-19 patients had significant higher serum level of NOX2, plasma level of TF and serum IL-6 than non ICU-admitted patients table (5).

Table 5: Relation between ICU admitted and different parameters.

	ICU admitted COVID-19 patients		P
	No (n= 40)	**Yes (n= 60)**	
NOX2 (pg/mL)			
Min. – Max.	11.0 – 49.60	25.30 – 52.5	<0.001*
Mean ± SD.	22.03 ± 9.19	36.79 ± 8.47	
TF (pg/mL)			
Min. – Max.	125.0 – 221.0	145.0 – 220.0	<0.001*
Mean ± SD.	161.63 ± 16.76	181.62 ± 17.56	
IL-6 (pg/mL)			
Min. – Max.	2.60 – 9.70	7.30 – 133.90	<0.001*
Median (IQR)	5.75 (3.2 – 8.18)	74.25 (44. 5 – 102.4)	

Non-survived COVID-19 patients had significant higher serum level of NOX2, plasma level of TF and serum IL-6 than survived patients table (6).

Table 6: Relation between Survival outcome of COVID-19 patients and different parameters

Survival outcome of COVID-19 patients			P
	Died (n= 39)	**Survived (n= 61)**	
NOX2 (pg/mL)			
Min. – Max.	25.30 – 56.20	11.0 – 45.70	<0.001*
Mean ± SD.	40.21 ± 8.76	24.92 ± 8.44	
TF (pg/mL)			
Min. – Max.	148.0 – 221.0	125.0 – 193.0	<0.001*
Mean ± SD.	187.67 ± 19.31	164.64 ± 14.11	
IL-6 (pg/mL)			
Min. – Max.	8.40 – 133.90	2.60 – 92.60	<0.001*
Median (IQR)	94.60 (50.2 – 112.38)	7.40 (6.5 – 34.7)	

Using ROC curve to predict thromboembolic events showed that serum NOX2 cut off was > 35.2 pg/mL, sensitivity 96.55, specificity 94.37, positive predictive value 87.5, negative predictive value 98.5 and area under a curve 0.991. As regard plasma TF, cut off was > 179 pg/mL, sensitivity 93.10, and specificity 92.96, and positive predictive value 84.4, negative predictive value 97.1and area under a curve 0.987 figure (2).

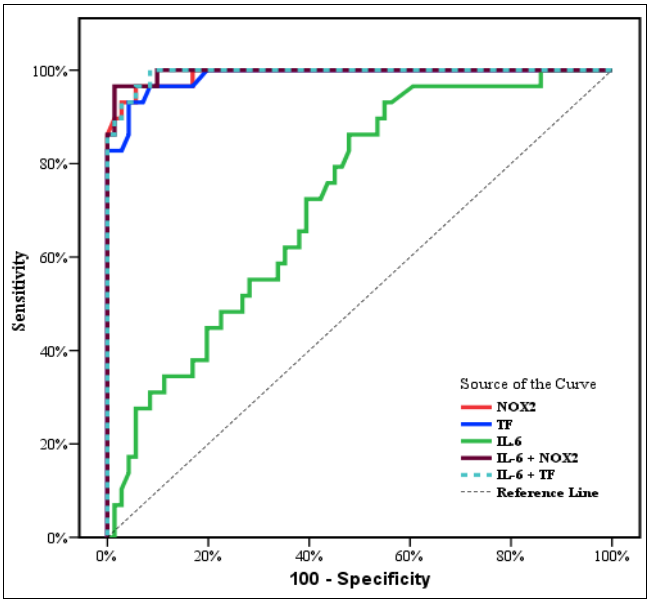

Fig 2: ROC curve for different parameters to predict thromboembolic events

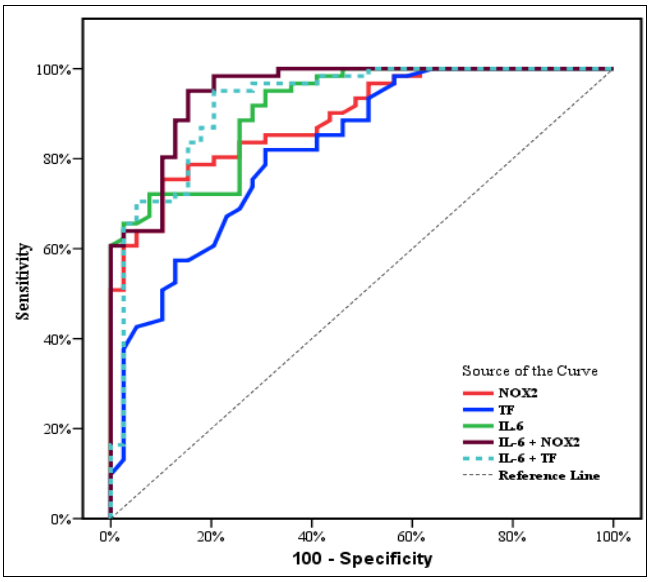

Fig 3: ROC curve for different parameters to predict mortality

Using ROC curve to predict mortality showed that serum NOX2 cut off was > 29.4 pg/mL, sensitivity 89.74, specificity 75.41, positive predictive value 70.0, negative predictive value 92.0 and area under a curve 0.889. As regard plasma TF, cut off was > 172 pg/mL, sensitivity 74.36, specificity 68.85, positive predictive value 60.4, negative predictive value 80.8 and area under a curve 0.823 figure (3).

Discussion

In the present study, from overall included patients, male patients were more than female. This was in concordance with a study done by Goyal *et al*., (2020) [7] who stated that, the incidence of COVID-19 is greater in males compared to females. The gender difference potentially related to greater prevalence of smoking of cigarettes in men (Youn *et al*., 2021) [8].

In the current study, the occurrence of TEEs among hospital admitted COVID-19 patients was 29% which was slightly lower than that reported by Klok *et al*., (2020) [9] which was 31%. This wasn't coincided with the study of Violi *et al*., (2021) [10] that revealed that Covid-19 is complicated by thrombosis in roughly 20% of participants. These differences might be due to differences in selection of studied population.

When the sites of TEEs were studied, PE was the highest incidence. This was in concordance with Kurata *et al*., (2023) [11] who reported that the frequency of PE had the greatest incidence in the Middle East.

The incidence of TEEs significantly higher with increased COVID-19 illness severity. This agreed with Helms *et al*., (2020) [12] who reported that severe SARS-COV2 infections associated with development of life-threatening thrombotic complications.

As regard Hematological profile, this study showed that WBCs and neutrophil counts were substantially greater in individuals with TEEs. These was in line with the work of Xiong *et al*., (2021) [13] who reported that following SARS-Cov-2 infection, individuals with thrombotic problems had greater WBC counts than those without thrombosis. Hojker *et al*., (2023) [14] reported in their study significant higher Neutrophils count in patients with COVID-19 with venous thromboembolism (VTE) than non-VTE ones.

Regarding platelet count, this study showed no significant differences between studied groups, which was consistent with Czupryna *et al*., (2022) [15] study that demonstrated no substantial variation among COVID-19 individuals with and without PE as regard platelet count. In contrast Srihirun *et al*., (2023) [16] who stated that significant lower platelet count was demonstrated in patients with COVID-19 with thrombotic complication and severe pneumonia.

This may be attributed to the existence of pulmonary inflammation in COVID-19 patients, which causes the release of thrombopoietin in addition to the activation of megakaryopoiesis and/or thrombopoiesis, which accelerates platelet synthesis [17].

When observing the differences in coagulation profile between studied groups, patients with TEEs had significant higher D-dimer levels. This results was in agreement with the results of Hojker *et al*., (2023) [14], Czupryna *et al*., (2022) [15], and Fu *et al*., (2022) [18] which confirmed the association between elevated D-dimer and incidence of thrombotic complications in COVID-19 patients.

Also, in this study D-dimer had a positive significant correlation with NOX2. This agreed with Violi *et al*., (2020) [19] who stated that if NOX2 and D-dimer increase are associated among individuals with vascular problems, Covid-19-related ischemic incidents may be connected to clotting/platelet activation.

The study results demonstrated significant positive correlation between D-dimer and TF. This was in line with Rosell *et al*., (2021) [20] who stated that concertations of circulating TF-positive extracellular vesicles (EV-TF) associated with multiple plasma markers, that includes D-dimer, that associated with thrombosis in COVID-19 patients.

Rosell *et al*., (2021) [20] stated revealed as contrasted with controls, EV-TF levels of activity were considerably greater in COVID-19 patients. Furthermore, EV-TF levels of activity were linked to illness severity and death. Also Srihirun *et al*., (2023) [16] stated that TF and platelet activation with life-threatening thrombosis was substantially greater among individuals with severe pneumonia when contrasted with mild-to-moderate pneumonia in COVID-19 patients.

In the present work, tissue factor in individuals with TEEs and ICU admitted patients was significantly higher when compared with patients without TEEs and non- ICU admitted patients respectively. This was in line with Guervilly *et al*., (2021) [21] who demonstrated significant greater levels of EV-TF in patients with covid-19 with TEEs against patients without TEEs and greater levels in severely-ill patients when contrasted with moderately ill patients.

Elevated concentrations of TF, IL-6, IL-8, complement anaphylatoxin C5a, and TNF-α were shown to be positively correlated with death in COVID-19 patients receiving intensive care [22].

As regard IL-6, significant higher level found in patients with TEEs. This was in concordance with Czupryna *et al*., (2022) [15] study which showed significant higher IL-6 in patients with PE when compared with free ones. Moreover, McConnell *et al*., (2021) [23] showed that elevated IL-6 levels in liver tissue of COVID-19 patients and its signalling pathways could promote liver injury with portal vein and periportal sinusoids occlusive thrombosis.

In this study Il-6 was significantly correlated positively with NOX2. This correlation could be explained by IL-6 induction of reactive oxygen species generation that is dependent on NOX2, increasing the endothelial oxidative stress that maintains endothelial dysfunction and vascular inflammation [8].

The study results showed that IL-6 also, correlated in a significant positive manner with TF. In line with this, Subramaniam *et al*., (2022) [24] reported that In COVID-19 patients, targeted suppression of IL-6 had been demonstrated to lower biomarkers of inflammation and thrombosis and modestly increase the rate of survival.

As regard NOX2 levels, this study showed significant higher levels in COVD-19 patients than control subjects. In line with this, Violi *et al*., (2020) [19] reported significant higher levels of NOX2 activation in COVID-19 patients versus controls.

The study showed significant greater levels of NOX2 in individuals with TEEs, ICU-admitted patients and patients with mortality outcome. This was in line with Violi *et al*., (2020) [19] who noted increased NOX2 activation levels in those suffering from severe illness, or those who required ICU hospitalisation, which may suggest a function for NOX2 as a factor promoting the worsening of COVID-19 infection. Additionally, NOX2 activation was greater in

COVID-19 individuals with thrombotic problems in contrast to those without events.

The upregulation of Toll-like receptor 7 caused by RNA viruses may cause COVID-19 to activate NOX2; this has an adverse impact on the body's defence system against viruses since they employed NOX2 activation to spread the infection and impair the immune response [25].

ROC curves analysis showed significant ability of NOX2 and TF to predict thromboembolic events and mortality occurrence among COVID-19 patients and their sensitivity and specificity increased when combined with IL-6.

So, all these results suggested that NADPH oxidase 2 could play a role in COVID-19 related coagulopathy and disease outcome through enhancing endothelial injury with increased expression and release of tissue factor. This could be occurred under umbrella of cytokines storm.

Conclusions

The current study showed high levels of NADPH oxidase2, tissue factor and IL-6 are associated with increased incidences of the thromboembolic complications, ICU admission and mortality rates in COVID-19 patients. Therefore, they should be regularly investigated as predictor biomarkers of COVID-19 bad outcome. Usage of targeted antioxidant and anti-inflammatory medication could reduce thrombotic complications associated with COVID-19 and improve disease outcome.

Recommendations

Additional research on more patients is required for more thorough statistical analysis and more favourable conclusions and to fully understand this association between high serum levels of NOX2, IL-6 and high plasma level of TF and bad outcome in COVID-19. Further studies on the pathogenesis of NOX2, TF and IL-6 to understand their roles in intracellular signaling and pathophysiology of COVID-19 related coagulopathy. These help in the search for successful thromboprophylaxis in microbial infections generally and COVID-19 specially.

Acknowledgement

Not available

Author's Contribution

Not available

Conflict of Interest

Nil

Financial Support

Nil

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How to Cite This Article
Abdelghany SSM, Sharshar RS, Ahmed AY, Mabrouk MM, Elzamarany EA. Thrombotic complications of COVID-19 and its relation with NADPH oxidase and tissue factor. International Journal of Clinical and Diagnostic Pathology. 2023; 6(3): 80-87.