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Serum Plasmin(ogen) Level as a Predictor for COVID-19 Severity: A Pilot Study from Egypt

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Abstract

Background: The pathogenesis of (COVID19), is still not totally delineated. COVID-19 is both a respiratory and systemic thrombotic disease. Given the dual function of plasmin(ogen) in promoting viral infection and regulating fibrinolysis, the dysregulation of which is the most severe consequence of COVID-19, our attention has been directed towards investigating this process.

Aim of Study: This study aimed to find a link between the level of plasmin in serum of patients with comorbidities as compared to those without and correlate it with the severity of Covid-19.

Results: Sixty-eight hospitalized patients having COVID-19 were included in this study. A total of twenty-six individuals who were matched in terms of age and sex to the non-Covid-19 ill group were selected as controls. Serum plasmin level was lower in patients than in control subjects (Median (Range):136.05pg/ml (7.10-1000pg/ml), 152.15pg/ml (8.90-988.60pg/ml), respectively), however it was not statistically significant (*p*-value: 0.062). Lower plasmin level, higher ferritin, higher creatinine, and older age were significantly associated with the presence of comorbidities. Serum plasmin level was substantially lower in hypertensive patients andother comorbidities but did not differ with diabetic patients. Plasmin level did not correlate with CT severity.

Conclusion: Serum plasmin level in covid patients was not correlated to disease severity. It was significantly lower in those with hypertension and other comorbidities (*p*-values 0.001,0.048 respectively), but not with diabetes. However, only diabetes was significantly associated with CT severity (*p*-value 0.006).

Key Words: *Covid 19 – Plasmin – Comorbidities – Severity..*

Introduction

THE clinicalpresentation of COVID-19 clinically can encompass variable medical conditions, including respiratory failure requiring artificial ventilation as well as intensive care unit (ICU) support, besides by systemic manifestations such as septicaemia, septic shock, as well as multiple organ dysfunction syndromes (MODS).Severe pneumonia and ARDS are pathological consequences that can arise from COVID-19. Mortality rates are impacted by various host-related characteristics, including age, male gender, immunological response, as well as comorbidities **[1].**

While SARS-CoV-2 always recognized as a predominant respiratory pathogen, it is more appropriate to classify COVID-19 as a disease that hits both the respiratory system and the systemic thrombotic processes **[2]**. The primary pathological characteristic of viral-induced ARDS is the presence of fibrin buildup in the microvasculature and alveoli. Several autopsy dependent studies have substantiated that the vast majority of individuals who suffer from COVID-19 exhibit widespread pulmonary microthrombi as a significant manifestation **[3].** The adverse effects of COVID-19 are further aggravated by the capacity of the SARS-CoV-2 virus to induce thrombosis in blood vessels **[4]**, resulting in disseminated intravascular coagulation (DIC) as well as massive release of cytokines, which is called a cytokine storm **[5].**

The presence of a condition of hyperfibrinolysis, marked by elevated levels products of fibrin breakdown, as D-dimer, and decreased platelet count, is notably observed in COVID-19 patients showing high mortality rate **[6]**. Fibrinolysis is a complex biological process in which a thrombus composed of fibrin is broken down and restructured by the protease plasmin. Plasmin is generated through the change of plasminogen, a zymogen, facilitated by plasminogen activators such as tissue-type (tPA) and urokinase-type (uPA), as well as plasminogen activator inhibitor-1 (PAI1) **[7]**. The existence of a

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furin site in the envelope proteins of several viruses, including SARS-CoV-2, has been proposed toplay an important role in increasing the virulence as well as pathogenicity of these viruses by its interaction with plasmin (ogen) **[8]**, Plasmin has the potential to break the S protein of the virus, which increases its affinity for angiotensin converting enzyme 2 receptors on host cells. This process facilitates the entry and fusion of the virus **[8]**. In recent studies, there has been a suggestion that tPA and PAI-1 could serve as potential biomarkers for COVID-19, as higher levels of both have been observed in patients who have been hospitalized due to the virus **[9].**

Consequently, in the current investigation, our objective was to find a link between these observations by measuring the level of plasmin in the serum of patients with comorbidities as contrastedwith those without comorbidity and correlate it with the severity of Covid-19 presentation, in a population of infected Egyptian patients.

Patients and Methods

Study done after obtaining Ethical approval committee letter.

IRB: N-184-2023.

Sixty-eight patientssuffering from COVID-19 diagnosed by swab SARS CoV2 using reverse transcription-polymerase chain reaction (RT-PCR) test were included in this investigation. Patients were admitted to the Chest Department of KasrAlainy-School of Medicine, Cairo University. Twenty-six age and sex-matched sicknon-covid subjects (*p*-values: 0.813, 0.621, respectively) were recruited as controls.

Inclusion criteria: Admitted patients proved to have Covid-19 by swab PCR testing of different severity of infection.

Exclusion criteria: Non covid patients or patients suspected to be Covid with no swab results.

All participants in the study provided written informed permission in accordance with the principles outlined in the Declaration of Helsinki..The patients underwent a comprehensive process of history taking, which encompassed gathering information about their medical history, including any existing comorbidities as COPD, IHD, hypertension, renal disease and diabetes, clinical examination, imaging (Chest X-ray and/or high-resolution computerized tomography of chest (HRCT-chest) when feasible). Laboratory analysis in the form of complete blood pictures (CBC), kidney function tests, liver function tests, as well as blood sugar was also done. Serum plasminogen level was measured uponpatient's admission using [(Human (PL/Fbn) ELISA kit, catalogue no.: 201-12-1137, Shanghai] according to manufacturer instructions. The samples were subjected to centrifugation at a force of 2000 × g for 15min at a temperature of 4°C and subsequently frozen at −80°C until analysis. Patients were classified into three classes: Mild, moderate, as well as severe based on CT findings.

In accordance with the Chinese guidelines for the management of COVID-19, the classification of Severe COVID-19 was determined by the observation of radiological indications of lung infiltration over 50%, coupled with the presence of either a respiratory rate equal to or greater than 30 breaths per minute, or an oxygen saturation level (SaO2) below 92%.

The data were gathered on the first day of admission for each subject.

Statistical analysis:

Data were coded then entered by using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Mean, standard deviation, median, minimum, and maximum were used to summarize quantitative data, while frequency (count) as well as relative frequency (percent) were used to represent categorical data. The non-parametric Mann-Whitney test was employed to conduct comparisons between quantitative variables. A Chi-square (χ^2) test was conducted to compare categorical data. The exact test was used in cases where the anticipated frequency is below 5. The Spearman correlation coefficient was utilized to examine the correlations between quantitative variables. Statistical significance was attributed to *p*-values that were less than 0.05.

Results

Demographic, clinical as well as laboratory findings are presented in Table (1). The level of serum plasmin was found to be significantly lower in patients compared to control individuals.]Median (Range): 136.05pg/ml (7.10-1000.00pg/ml), 152.15pg/ml (8.90-988.60pg/ml), respectively], however, it was not statistically significant (*p*-value: 0.062). Comparisons between patients having comorbidities and those without are shown in Table (2). Lower plasmin level, higher ferritin, higher creatinine, and older age were significantly associated with the presence of comorbidities. Serum plasmin level was significantly lower in hypertensive patients and those with other comorbidities but did not differ with diabetic patients Table (3). However, all diabetic patients had moderate or severe CT pictures

with none havinga mild picture Table (3). Someparameters correlated positively with the CT severity for covid patients, such as age, AST, ALT, ferritin, and CRP. Lymphocytes correlated negatively with severity. Others including plasmin level did not correlate with CT severity, as shown in Table (4).

Table (1): Demographic, clinical and laboratory data of the studied patients.

		Count	%
Sex	Male	43	63.2
	Female	25	36.8
Comorbidity	Present	40	58.8
	Absent	28	41.2
Diabetic	Present	23	33.8
	Absent	45	66.2
Hypertension	Present	30	44.1
	Absent	38	55.9
Another comorbidity	Present	20	29.4
	Absent	48	70.6
Other comorbidity details	Renal	2	2.9
	Parkinson	1	1.5
	Malignancy	1	1.5
	IHD	4	5.9
	Hypothyroidism	2	2.9
	Hepatic	3	4.4
	CKD	1	1.5
	Asthma	1	1.5
	AF	5	7.4
	Absent	48	70.6
CT severity	Mild	13	19.1
	Moderate	27	39.7
	Severe	28	41.2

	Mean	Standard Deviation	Median	Minimum	Maximum
Age (Years)	56.63	15.61	57.50	28.00	88.00
WBC (x 10^3 /mm^3)	8.34	4.10	7.50	1.70	27.50
Lymphocyte count (x 10^3 /mm^3)	1.26	1.29	0.92	0.10	10.00
Urea (mg/dl)	41.29	45.07	31.00	9.80	300.00
Creatinine (mg/dl)	1.30	2.24	0.90	0.20	17.00
AST (IU/L)	48.99	46.02	32.50	11.00	220.00
ALT (IU/L)	49.76	34.90	38.50	12.00	178.00
Ferritin (ng/ml)	656.47	653.75	480.00	11.00	3000.00
D dimer (µg/ml)	1.03	1.40	0.57	0.07	8.00
CRP (mg/L)	58.62	70.04	43.50	0.10	399.00
Plasmin level (pg/ml)	177.79	175.44	136.05	7.10	1000.00

Table (2): Comparison between patients with concomitant comorbidities and those without comorbidities.

		Comorbidity				p-value
		Present (N=40)		Absent (N=28)		
		Count	%	Count	%	
Sex	Male	25	62.5	18	64.3	0.881
	Female	15	37.5	10	35.7	
CT severity	Mild	4	10.0	9	32.1	0.069
	Moderate	17	42.5	10	35.7	
	Severe	19	47.5	9	32.1	

	Comorbidity										p-value
	Present					Absent					
	Mean	SD	Median	Mini-mum	Maxi-mum	Mean	SD	Median	Mini-mum	Maxi-mum	
Age (Years)	62.38	11.66	61.00	43.00	88.00	48.43	17.02	41.50	28.00	80.00	<0.001
WBC (x 10^3 /mm^3)	7.72	4.38	6.75	2.60	27.50	9.23	3.55	9.95	1.70	15.70	0.022
Lymph (x 10^3 /mm^3)	0.97	0.53	0.90	0.10	2.56	1.68	1.84	1.27	0.39	10.00	0.085
Urea (mg/dl)	49.01	57.06	37.00	9.80	300.00	30.25	11.16	30.00	13.00	71.00	0.112
Creatinine (mg/dl)	1.65	2.87	1.00	0.50	17.00	0.81	0.34	0.70	0.20	1.40	0.027
AST (IU/L)	43.75	22.80	37.00	13.00	129.00	56.46	66.38	30.50	11.00	220.00	0.058
ALT (IU/L)	47.35	30.39	38.50	12.00	178.00	53.21	40.84	38.50	16.00	160.00	0.891
Ferritin (ng/ml)	890.99	753.40	709.00	41.70	3000.00	321.43	206.78	257.50	11.00	749.00	<0.001
D dimer (µg/ml)	0.96	1.47	0.44	0.24	8.00	1.11	1.31	0.75	0.07	4.50	0.280
CRP (mg/L)	70.73	80.25	50.00	0.10	399.00	41.32	48.40	19.15	0.37	168.00	0.070
Plasmin level (pg/ml)	137.89	146.22	126.10	7.10	1000.00	234.79	199.42	168.55	7.70	851.70	<0.001

Table (3): Serumplasminogen level and CT severity in patients with comorbidities.

	Diabetic		Hypertension		Other comorbidities	
	Present	Absent	Present	Absent	Present	Absent
Plasmin level (pg/ml):						
Mean ± SD	160.72±186.42	186.52±171.07	142.56±167.28	205.61±178.9	123.82±33.31	200.28±204.14
Median (Range)	124.8 (11.3-1000)	144.7 (7.1-851.7)	123.55 (7.7-1000)	154.7 (7.1-851.7)	132.3 (7.1-187.4)	145.3 (7.7-1000)
p-value	0.104		0.001		0.048	

		Diabetic		Hypertension		Other comorbidities	
		Present	Absent	Present	Absent	Present	Absent
CT severity:							
Mild	Count (%)	0 (0%)	13 (28.9%)	4 (13.3%)	9 (23.7%)	4 (20 %)	9 (18.8%)
Moderate	Count (%)	10 (43.5%)	17 (37.8%)	13 (43.3%)	14 (36.8%)	11 (55%)	16 (33.3%)
Severe	Count (%)	13 (56.5%)	15 (33.3%)	13 (43.3%)	15 (39.5%)	5 (25%)	23 (47.9%)
p-value		0.006		0.555		0.183	

Table (4): Correlation between Covid severity and other variables.

	CT severity		
	Correlation Coefficient	*p*-value	N
Age	0.274	0.023	68
WBC	0.074	0.550	68
Lymphocytes count	-0.246-	0.043	68
Urea	0.189	0.123	68
Creatinine	0.187	0.127	68
AST	0.242	0.047	68
ALT	0.256	0.035	68
Ferritin	0.294	0.015	68
D dimer	0.174	0.157	68
CRP	0.376	0.002	68
Plasmin level	0.102	0.406	68

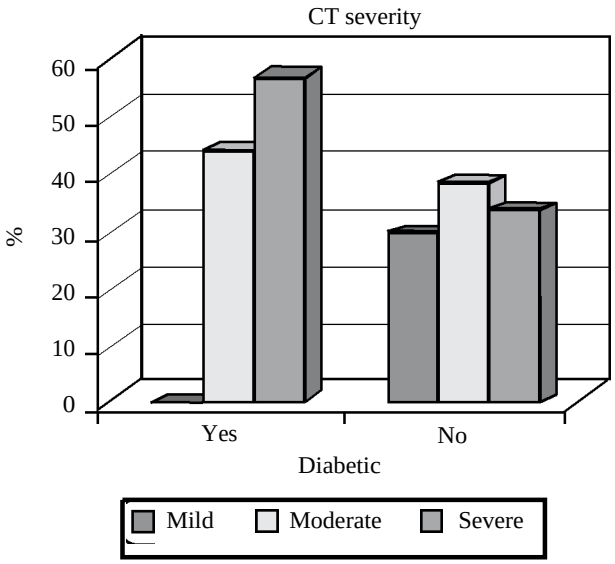

Fig. (1): The relation of the presence of diabetes to the CT severity state in the studied covid-19 patients.

Discussion

The observation of markedly elevated levels of fibrin degradation products (FDPs) as well as decreased platelet counts in individuals having severe COVID-19 is indicative of the occurrence of hyperfibrinolysis. Plasmin, an essential component in the fibrinolysis mechanism, contributes to the increased virulence as well as pathogenicity of viruses that contain a furin site within their envelope proteins, such as SARS-CoV-2 *[10]*.

The purpose of this study is to find a link between these observations by measuring the level of plasmin in serum of hospitalized covid 19 patients with comorbidities as contrasted with those without comorbidity and correlate it with the severity of Covid-19 presentation, in a population of infected Egyptian patients. This study represents a novel investigation, as it is the first known attempt to quantify serum plasmin levels in Egyptian individuals diagnosed with covid-19, while also considering the presence of concurrent comorbidities. The current study included 68 RT PCR confirmed Covid 19 hospitalized patients, in addition to 26 age and sex-matched non-covid19 sick control subjects. The mean age of the covid 19 patients was 56.6±15.6 with male predominance (63.2%). Although Covid -19 infection has the potential to impact individuals across all age groups, the mean age of patients who need hospital admission may be higher, especially in those with underlying comorbidities. Moreover, the observed male preponderance can be related to the phenomenon that females frequently showed decreases susceptibility to viral infections due to their development of more strong immune responses compared to males. This disparity in immune response strength can be attributed to the crucial involvement of sex hormones in both innate as well as adaptive immunity *[11]*. This was conforming to the previous reports of Jaiswal et al., 2022 *[12]*.

Nearly two-thirds of the studied patients had pre-existing comorbidities (58.8%), mostly hypertension [30 patients (44.1%)] followed by 23 patients (33.8%) with diabetes, 5 had AF, 4 had IHD, 3 were hepatic, 2 had hypothyroidism, 2 with renal disorders, 1 had Parkinson, 1 with chronic kidney disease (ckd), 1 had bronchial asthma and 1 had malignancy. Despite the relatively low death rate associated with SARS-CoV-2 infection, it possesses the potential to cause significant fatality, particularly among those with underlying health conditions who are considered high-risk. The literature has documented an incidence of SARS-CoV-2 infection accompanied by co-morbidities of up to 26%. A similar incidence rate of 30.8%, was also reported *[12]*. This finding is consistent with previous research conducted by Ramadan et al., which identified diabetes mellitus and hypertension as the most frequently reported comorbidities, accounting for 29.2% and 23.7% of cases, respectively *[11]*. Likewise, other studies have indicated that hypertension was the predominant comorbidity among the enrolled individuals, with diabetes mellitus coming second *[13]*. In the context of COVID-19 patients, it is often documented that the most prevalent comorbidities are hypertension, diabetes, chronic cardiovascular illnesses, cerebrovascular diseases, COPD, as well as chronic kidney dysfunction *[14]*.

In this work, the plasmin level in covid patients was less than that in sick non-covidcontrol subjects, however, it was statistically insignificant. This finding is consistent with the findings of Henry et al.'s study conducted in 2020, which indicated that

there was no frequent occurrence of significantly abnormal plasminogen levels among patients with COVID-19. The researchers were unable to detect elevated levels of plasminogen on admission in patients diagnosed with COVID-19 as compared to individuals in the control group who were also ill. Furthermore, it was shown that patients who had elevated levels of plasminogen upon admission did not show a tendency to develop more severe pictures of the disease [15].

The observed modest drop in plasmin levels can be attributed to multiple factors. The most probable hypothesis suggests that plasminogen is depleted through the process of clot breakdown, as well as the breakdown of hyaline membranes within the alveoli. Another potential explanation suggests that the activation of fibrinolysis may be initiated by a viral activator, leading to increased consumption of plasminogen and enhanced (tPA) levels [16]. Furthermore, the observed decline in disease severity may be attributed to the enhanced binding of plasminogen to receptors found on endothelial cells and inflammatory cells such as monocytes as well as macrophages [17]. Finally, viral-mediated inflammation with accompanying bradykinin elevation may increase vascular endothelial tPA release, leading to plasminogen consumption [18]. Furthermore, as ACE2 is involved in the metabolism of bradykinin, reduction of enzyme function due to viral binding as well as internalization may lead to elevated bradykinin, further boosting tPA release [19].

Out of the studied 68 Covid-19 patients, the CT severity was mild in 13 patients (19%), moderate in 27 patients (40%), and severe in 28 patients (41%). This findingmatched with the results of a study conducted in China, which revealed that a majority of the patients had severe symptoms (47.5%), while 37.8% presented with a moderate form of the disease. Additionally, 14.2% of the patients were classified as having a critical condition, and a small proportion (0.5%) experienced mild infection [20]. In contrast, an alternative investigation revealed that a significant proportion of patients exhibited mild severity (59.79%), while 21.13% were classified as moderate, 12.89% as severe, and 6.19% as critically ill [21]. Meanwhile, in Ramadan'sstudy [11], a significant proportion of patients exhibited a moderate level of severity in their COVID-19 symptoms, consistent with the findings of a meta-analysis which indicated that 25.6% of patients experienced severe illness [22]. The observed differences in disease severity between studies may be explained by variations in the criteria used to classify disease severity, the exact time of patient presentation to the hospital, individual patient characteristics, as well as geographical distribution. In addition, the hospitalization of patients who arrive late increases the likelihood of presenting with a severe or critical stage upon admission. Conversely, an early medical evaluation has the effect of reducing the severity of the condition [11].

In this work, on comparing Covid-19 patients having concomitant comorbidities to those without, Covid patients with comorbidities were older in age, had significantly higher creatinine and ferritin levels, and had lower WBCs counts and lower serum plasmin levels than those without comorbidities. No significant associations were observed between the existence of comorbidities and covid severity except for diabetes which was exclusively and significantly associated with moderate and severe cases with complete absence of mild cases. Regarding the high ferritin levels,in the study of Cheng et al., 2020 [23], COVID-19 persons with comorbidities as diabetes, thrombotic complications, and cancer had elevated levels of ferritin compared to COVID-19 patients lacking these comorbidities [23]. Similarly, in the study of Daef et al., comorbidities were associated with higher ferritin levels as well as older age [24]. There exists an independent association between an elevated level of ferritin and the prevalence of several health conditions, including diabetes, hypertension, CKD, COPD, and exacerbated asthma symptoms. This association can be attributed to a robust correlation between elevated ferritin levels and systemic inflammation [25]. In the current study,creatinine level was higher in those with comorbidities than those without due to the presence of diabetic and renal patients. Many previous studies as that done by Puri et al., [26] demonstrated a statistically substantial link between pre-existing comorbidities and the occurrence of severe cases of COVID-19. Regarding the leukocytic count, contrary to our results, Zhao et al., revealed a significant occurrence of leukocytosis among older patients who had co-morbidities [27].

Della Morte et al., conducted a study involving older patient population diagnosed with COVID-19 and presenting a high prevalence of comorbidities. Their findings revealed a significant correlation between reduced levels of plasminogen and various prognostic indicators of complications, including inflammatory markers (CRP, PCT, and IL-6), coagulation markers (D-dimer, INR, and APTT), as well as markers of organ dysfunction (FBG and GFR) [28]. However, in contrary to our findings, Ji et al., It has been shown that individuals who are prone to SARS-CoV-2 infection, including those with hypertension, diabetes, cardiovascular illness, and cerebrovascular diseases, commonly exhibit

higher levels of plasmin(ogen), which serves as a biomarker *[29]*. Gacche et al.,revealed that an increased concentration of plasminogen is a prevalent clinical characteristic observed in chronic diseases linked with the severity of COVID-19, such as hypertension, cardiovascular disease, diabetes, as well as chronic renal disorders *[30]*.

In the current study, severity was significantly correlated to older age, higher AST, ALT, CRP, ferritin and lower lymphocytes count, however, neither gender norplasmin levelor D dimer values was correlated with severity. Also, the presence of comorbidities did not statistically correlate with severity, with the exception of diabetes, which exhibited a statistically significant association with the severity of CT findings (*p*-value 0.006).

It was initially unclear if the difference among age groups reflected the lower risk of severe disease or a reduced vulnerability to infection, but recent reports showed that younger individuals had similar vulnerability to older age groups, indicating that the difference among age groups is one of infection resistance *[31]*. The critical disease observed in elderly people can be attributed to various pathogenic causes, one of which is the reduced expression of angiotensin-converting enzyme 2 (ACE2) in older individuals *[32]*, age-related impairment in the ability to clear particles from the airways, elevated levels of inflammatory mediators in “inflammation” among the aged, a deficient immunological response, as well as a high prevalence of co-morbidities among the elderly *[33]*. According to recent retrospective research in Egypt COVID-19 is more dangerous and lethal for people of advanced age *[34]*.

Consistent with present findings in our study, the study conducted by Omran et al. *[35]* revealed that several characteristics are correlated with the severity of COVID-19, such as advanced age, preexisting diabetes, as well as other comorbidities.In addition, it has been observed that increased levels of (ALT), (AST), as well as ferritin in the blood are linked to unfavourable outcomes. Furthermore, advanced age as well as elevated serum ferritin have been detected as important risk factors for the having severe COVID-19. The findings of their research agree with our own, indicating that there is no of statistically significant difference among both sexes in relation to the severity of COVID-19. Likewise, Nasiri et al., found no gender differences in ICU admissions reflecting severity *[36]*. A further study conducted in Egypt, with a 260 individuals diagnosed with COVID-19, revealed that there existed no statistically significant correlation between male gender as well as the likelihood of developing critical illness *[37]*. Ciceri et al. *[38]* conducted a study in Italy and found no statistically significant correlation between being female and the likelihood of developing severe illness. On the contrary, current surveillance data has indicated that male patients have a higher vulnerability to severe illness and fatality rates associated with COVID-19 *[39]*, furthermore, past epidemics of SARS have also documented the presence of this gender-specific difference. *[40]*. Lagadinou et al., study showed that males are more susceptible in developing severe disease *[12]*. Ramadan et alstated that older males (>50 years), particularly those with underlying co-morbidities, may be at greater risk for severe SARS-CoV 2 infection *[11]*.

In Omran’s research, a statistically significant association was observed between diabetes mellitus, along with cardiovascular illnesses, chronic renal disease, as well as cancer, in addition to an elevated risk of critical illness *[35]*. Furthermore, some investigations performed in China and Italy have demonstrated a heightened severity of SARSCoV-2 infection, necessitating the transfer of patients with diabetes to the ICU as well as the utilization of mechanical ventilation *[41]*. In a longitudinal study conducted in China, a sample of 7300 patients was examined to assess the effect of (T2D) on mortality rates associated with COVID-19. The findings revealed a statistically significant rise in mortality among individuals with T2D, with almost three times higher mortality rates compared to nondiabetic individuals *[42]*. The occurrence of respiratory tract infections is often associated by the transient development of insulin resistance, particularly among those who are overweight. The complexity of this scenario arises from the necessity of administering glucocorticoids, resulting in a subsequent increase in the dosage of medications for reducing blood sugar. Diabetes is characterized by a maladaptive inflammatory response, which contributes to the exacerbation of viral infection progression and the potential occurrence of secondary bacterial complications *[43]*.

Individuals diagnosed with COVID-19 typically exhibit a haematological profile that is distinguished by either a normal or reduced white blood cell count, as well as a diminished amount of lymphocytes *[44]*. A substantial correlation between total leukocytic counts and CT severity of the individuals under study was not observed, contrarily, inOmran’s study, *[35]*. Significant leucocytosis was observed among the critically ill patients. Significant leucocytosis was also discovered by Zhao et al., in older adults with many medical conditions *[45]*.

In a study conducted by Ramadan et al., findings were consistent with our own research, revealing a negative correlation between lymphocyte count as well as disease severity. Additionally, severe and extremely severe patients exhibited elevated levels of ferritin and D-dimer [11]. The prevalence of reduced lymphocyte count in individuals with COVID-19 indicates that the virus may impact lymphocytes, specifically T cells, leading to a decrease in CD4 levels [46]. The occurrence of lymphocytopenia has been thoroughly documented in a retrospective review conducted on patients from Hong Kong and Singapore who were affected by the SARS in 2003. This condition was found to be associated with adverse effects and the need for ICU admission [47]. In the study conducted by Lagadinou et al. (2020), no statistically significant differences were seen among the groups of patients classified as severe and moderate [12].

Most ofthe patients with COVID-19 also had elevated CRP levels. Furthermore, it is widely recognized that COVID-19 patients exhibit elevated levels of CRP and other inflammatory biomarkers, which are regarded as key distinguishing features [48]. According to the findings, there exists a strong association between early rise of CRP levels and the occurrence of mechanical ventilation or mortality [49].

In accordance with the results of our study, Omran et al. [35] demonstrated that ALT, AST, as well as serum ferritin levels can serve as valuable indicators for predicting the severity of COVID-19. Among the COVID-19 infected individuals, liver abnormalities were also a prominent observation. In COVID-19, liver damage is a possibility. Patients with COVID-19 were found to have elevated liver enzymes as well as bilirubin in a reported range of 14.8% to 53.1%. Moreover, the severity of COVID-19 is correlated with the extent of liver damage [50]. Patients with COVID-19 had considerably higher serum ferritin levels than healthy controls in the ICU. Serum ferritin levels were also shown to rise as the case deteriorated and to be considerably higher in non-survivors than in survivors [51]. Shoenfeld et al.,reported that the ferritin H-chain induced higher levels of inflammatory cytokine production in macrophages. Understanding the pathogenesis of hyperferritinemia syndrome, which includes COVID-19 infection, became a priority [52]. Moreover, Ramadan et al. [11] showed that age >53 years,diabetes mellitus, ischemic heart disease, CT involvement of two or more lung lobes, bilateral lung lesion, lymphopenia, high CRP, elevated ferritin, elevated liver enzymes (ALT & AST), urea, creatinine as well as presence of co-infection weresignificantly contributed to the development of serious disease. Notably, our research findings also indicated a lack of statistically significant correlation between the level of D-dimer as well as the severity of COVID-19 [11].

The biomarker D-dimer has been previously recognized as a significant indicator for the evaluation of risk in patients with COVID-19. It holds predictive significance for various critical clinical outcomes, including mortality,ICU treatment as well as thromboembolic disease [53]. In the study of Niklas et al., 2022, Non-survivors had more than double the median levels of D-dimer of survivors among COVID-19 patients. The researchers also reached the conclusion that diminished plasmin activity, which can occur due to either reduced release of tPA caused by direct viral damage to the endothelium or depletion of plasminogen levels, may result in the inability of the fibrinolytic system to effectively break down fibrin polymers that are liberated into the bloodstream during advanced COVID-19 infection. This can lead to lowered levels of fibrinolytic end products in the blood of affected patients, even when high levels of D-dimer are present. Therefore, our data enhance the justification for the ongoing assessment of therapies that enhance fibrinolytic activity in hospitalized individuals with COVID-19 [54].

Also, Lagadinou et al., in 2020 observed significant variations in D-dimers as well as inflammatory markers such as CRP, ferritin, and others between severe as well as non-severe cases. The statistically significant elevation that was found in more severe cases, may be related to the activated and accelerated response to infection. Coagulationis also believed to have an immune function which can be hence considered another line of defence against severe infection [12]. Also, a series of studies [14,15] have shown the prevalence of high D-dimer values in patients having severe COVID-19.

In addition, regarding plasmin levels,Della Morte et al., [28] said that low plasminogen levels were an independent predictor of bad outcomes in people with COVID-19, and that this association was as large as a 12-fold increase in risk of mortality. They showed that plasminogen consumption is linked to elevated levels of inflammatory and coagulation indicators as well as organ dysfunctions. In line with these data, Henry et al., in 2020,showed that patients with COVID-19 who had low plasminogen levels were more prone to be admitted to the ICU [15]. They explained that this may be due to hospital admission of patients sometime after disease progression and plasmin consumption. They found a small but statistically significant decline

in plasminogen concentration in proportion to the progression of disease. This association may be attributed to the shift in the procoagulant pathways has been noticed in the later stages of COVID-19 additionally, the activation of plasmin(ogen) can facilitate the progression of infection, in addition to disseminated intravascular coagulation, by enzymatically cleaving proteins that facilitate cellular infection **[55].**

Based on the available literature, this investigation appears to be the first of its kind addressing level of plasmin in the serum of patients with comorbidities in Covid-19 patients in comparison to those without, however we faced some limitations in our study. Among these limitations faced in our work was the small number of patients being a single center study in addition to the absence of an established reference range for serum plasmin level which was compensated for by recruiting control subjects. Another limitation was failure to have a baseline measurement of plasmin at the disease onset,before hospitalization, especially in patients with comorbidities.

Conclusions:

Given the nonsignificant difference in plasmin level between cases and controls, the useantiproteases for treating COVID-19 should be limited. Serum Plasmin level in covid patients was not correlated to disease severity. It was significantly lower in those with hypertension and other comorbidities, but not with diabetes. However, only diabetes was significantly associated with CT severity. More exploration together with serial measurement of serum plasmin levels may give us insights fortailoring novel treatment approaches and designing target oriented therapeutic agents against COVID-19 especially in those with pre-existing comorbidities, as hypertensive patients may be candidates for plasmin therapy in future experimental studies.

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مستوى البلازمين (اوجين) فى الدم كمؤشر لشدة مرض COVID-19: دراسة تجريبية من مصر

مقدمه: لايزال الكثير غير واضح فيما يخص كيفية حدوث الية مرض كوفيد-١٩ و الذى له اثار على الجهاز التنفسى واثار عى اجهزة الجسم كافه بالاضافه إلى ظاهرة التجلطات، نظرا للوظيفة المزدوجة للبلازمين (الجين) فى تعزيز العدوى الفيروسية وتنظيم انحلال الفيبرين المتكون داخل الجلطات، والذى يعد عدم تنظيمه هو أخطر عواقب COVID-19، فقد تم توجيه انتباهنا نحو التحقيق فى هذه العملية.

كنا نهدف إلى إيجاد صلة بين مستوى البلازمين فى مصل المرضى الذين يعانون من أمراض مصاحبة مقارنة بأولئك الذين لا يعانون منها وربطه بشدة COVID-19.

النتائج: تم تضمين ثمانية وستين مريضاً فى المستشفى مصابين ب COVID-19 فى هذه الدراسة. تم اختيار ما مجموعه ستة وعشرون فرداً تمت مطابقتهم من حيث العمر والجنس مع المجموعة المريضة غير COVID-19 كمجموعه ضابطه. كان مستوى بلازمين في الدم أقل فى المرضى منه فى الأشخاص الضابطين (المتوسط (المدى): ١٣٦,٠٥ بيكوغرام / مل (٧,١٠-١٠٠٠ بيكوغرام / مل) ، ١٥٢,١٥ بيكوغرام / مل (٨,٩٠- ٩٨٨,٦٠ بيكوغرام / مل) ، على التوالى) ، ومع ذلك لم يكن ذا دلالة إحصائية (قيمة p: ٠,٠٦٢). ارتبط انخفاض مستوى البلازمين، وارتفاع الفيريتين، وارتفاع الكرياتينين، وكبار السن بشكل كبير مع وجود الأمراض المصاحبة. كان مستوى البلازمين فى الدم أقل بكثير فى مرضى ارتفاع ضغط الدم والأمراض المصاحبة الأخرى ولكنه لم يختلف مع مرضى السكرى. لم يرتبط مستوى البلازمين بشدة الاصابه فى الاشعه المقطعيه.

الاستنتاج: لم يكن مستوى البلازمين فى الدم لدى مرضى كوفيد مرتبطاً بشدة المرض. كان أقل بكثير فى أولئك الذين يعانون من ارتفاع ضغط الدم بدرجه ذات دلاله احصائيه و(قيم p ٠,٠٤٨، ٠,٠٠١ على التوالى) ، ولكن ليس مع مرض السكرى. ومع ذلك، ارتبط مرض السكرى فقط بشكل كبير مع شدة الاصابه فى الاشعه المقطعيه (قيمة p ٠,٠٠٦).