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# Evaluation of von Willebrand factor as a marker for early diagnosis of Acute Respiratory Distress Syndrome in comparison to Interleukin-6

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## Abstract

**Background:** Acute respiratory distress syndrome (ARDS) constitutes a clinical phenotype of severe lung injury associated with many causes. Endothelial activation and injury is a component of ARDS. The release of von Willebrand factor (vWF) indicates direct endothelial cell damage has occurred, and this can be used as a marker of endothelium injury. The aim of the study was to investigate the diagnostic value of vWF antigen as a determinant of early detection of ARDS in comparison to interleukin-6 (IL-6) as a control biomarker. vWF antigen and IL-6 were measured in 60 patients who were at risk of developing ARDS on T0 (at the start of the study), T48 (after 48 h), and T72 (after 72 h).

**Results:** Higher vWF Ag levels were seen in patients at risk of developing ARDS with direct cause of lung injury than those with indirect causes. Include groups I and II. There was a highly significant increase between the "at risk of developing ARDS" patients, vWF Ag, and IL-6 levels. The results were recorded at T0 (i.e., at start of the study baseline reading), T48 (after 48 h), and T72 (after 72 h),  $p$  0.001 and  $p$  0.05, respectively. A value of vWF Ag of 447% on the 3rd day of ARDS showed a sensitivity of 94.9% and specificity 56.7% compared to IL-6 at 246 pg/ml with 79.5% sensitivity and 52.4% specificity. As a comparison between vWF and IL6 levels among ARDS patients, they both show statistical correlation together.

**Conclusion:** The results of our study point out to vWF as a sensitive and good diagnostic marker for ARDS diagnosis.

**Keywords:** Acute respiratory distress syndrome, Endothelial injury, von Willebrand factor, Interleukin-6

## Background

Acute respiratory distress syndrome (ARDS) constitutes a clinical phenotype of severe lung injury associated that can result from direct lung injury or as an indirect result of injury in other organs. The clinical appearance of the specific histopathological lesion is diffuse alveolar damage (DAD).

ARDS is associated with an intense pulmonary inflammatory response that can be described in three stages: (a) accumulation of pro-inflammatory mediators, (b) endothelial cell activation, and (c) release of inflammatory mediators followed by functional and structural endothelial injury, so the detection of these three processes helps to detect ARDS and even its prognosis (Rocco and Santos 2009).

IL-6 shares both pro- and inflammatory properties and could be considered as acute phase response regulator involved in the ARDS pathogenesis. The concentration

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of IL-6 among other ARDS biomarkers is shown to have a significant impact in relation to the course of ARDS (Peter et al. 2003). Endothelial activation and injury is an essential ARDS mechanism. Biomarkers that reflect this process are promising in identifying the “at risk” patients for ARDS development. The injured endothelium releases proteins such as von Willebrand factor (VWF) (Ley et al. 2007). VWF release is reasonable to assume that direct endothelial cell damage has occurred. This has facilitated its possible use as a marker of endothelial injury (Franchini and Lippi 2006). VWF is also known to be an acute phase reactant affected by inflammatory cytokines and may be elevated even in the absence of endothelial damage (Horvath et al. 2004). These facts were studied by many authors, and they all approved that VWF has potential significance in predicting ARDS development and even they found a significant correlation of elevated VWF plasma levels with adverse ARDS outcomes, including mortality, duration of mechanical ventilation, and organ failure (Agrawal et al. 2012).

The primary objective of this study is to test the hypothesis that von Willebrand factor is more specific and sensitive as a determinant of acute respiratory distress syndrome in comparison to interleukin-6.

## Methods

This observational study was conducted on sixty (60) patients, admitted to a University hospital's intensive care units (ICUs) for more than 24 h, from September 2015 to December 2017. Approval of research ethical committee of Faculty of Medicine, Ain-Shams University was obtained (code number: FMASU 806/2010) and written informed consent was obtained from patients' legal guardian(s) after a description of the procedure and its potential complications. Patients between 18 and 80 years old of both sexes who were admitted to the ICUs were included in this study and were diagnosed according to the criteria of Berlin definition of ARDS (Ferguson et al. 2012) and Murray score of acute lung injury.

These patients included were at risk of developing ARDS either by direct lung injury including severe pneumonia (infection), aspiration of stomach contents, breathing harmful fumes or smoke, severe trauma to the chest, or other direct causes of mechanical lung injury. Causes of indirect lung injury included sepsis, severe injury or trauma with shock, blood transfusions, drug overdose, acute pancreatitis, fracture of the long bones, near drowning, anaphylaxis, uremia, fat embolus, and intracranial insult.

Patients were excluded if they had a preexisting medical condition with a life expectancy less than 3 months, evidence of cardiogenic pulmonary edema, age under 18 years old or above 80 years old, late stages of liver cell

failure, renal failure, severe myocardial infarction, deep coma, and pregnant females.

Written informed consents were taken and validated by the patients or their relatives in charge before history taking, physical examination, and blood sample withdrawal. The procedures applied in this study were approved by The Ethical Committee of Human Experimentation of the University, number FMASU 806/2010, and are in accordance with the Helsinki Declaration. The consent included the aim of the sampling method and number of samples withdrawn and the amount of blood which was withdrawn.

On admission, the demographic data was recorded, full medical history was taken to select patients included in the study, and patients were monitored.

Plasma levels of both VWF and IL-6 were measured at T0 (i.e., at the start of the study once the patient considered to be at risk of developing ARDS to obtain their baseline levels), T48 (after 48 h), and T72 (after 72 h). Sixty (60) patients who were at risk of developing ARDS were included in this study, progressed into ARDS (group I) and not progressed into ARDS (group II)

All study patients were subjected to daily routine ICU assessments including scoring systems, clinical parameter, laboratory parameters, chest X-ray with calculation of lung injury score, ECG, and echocardiography for some patients according to the clinical condition. Also, measurements of the respiratory parameter (respiratory rate, arterial blood gas analysis ABG, FIO<sub>2</sub>), the need for mechanical ventilation, ventilatory parameters, lung injury score, duration of mechanical ventilation, length of ICU stay, and outcomes were also assessed.

Under complete aseptic conditions, arterial blood sample was withdrawn on heparin and immediately assayed for ABG. Then 10 mL of venous blood were obtained by a clean from central line, 2 ml were placed in EDTA tube and properly mixed for immediate assay of CBC. Two milliliters placed on citrate tube and mixed following which plasma was collected in two aliquots by centrifugation (1500×g for 15 min) at room temperature. One aliquot was assayed immediately for partial thromboplastin time (PTT), prothrombin time (PT), and INR. The second aliquot was assayed for VWF Ag levels in plasma by immunoturbidimetry. At the same time, the remaining whole blood was evacuated in two plain test tubes. The serum of both tubes was separated by centrifugation (1000×g for 15 min). Serum of one tube was immediately assayed for serum creatinine, blood urea nitrogen (BUN), AST, and ALT, while the serum collected in the other tube was stored in pyrogen/endoxin-free tubes at - 20 °C for subsequent assay of serum IL-6 by ELISA. Hemolyzed samples were discarded.

VWF Ag is measured in plasma using Sysmex CA-5100 autoanalyzer (Siemens, Erlangen, Germany) for the

quantitative determination of VWF Ag level in plasma by detecting Ag-Ab aggregation with immunoturbidimetric technique using reagents supplied by the company. The VWF is expressed in percentage of the normal that obtained by multiplying the titer of the specimen with the limit of detection which is stated on the vial label. The expected value of plasma VWF level in the adult population is of 50–160% of the normal.

Serum IL-6 was assayed by commercially available ELISA kit supplied by Bioassay Technology Laboratory (1008 Junjiang Inter. Bldg., 228 Ningguo Rd., Yangpu-Dist, Shanghai, China). The standard curve is generated by multiple dilution of standard. The optical density of each sample is plotted on curve to determine the concentration of IL-6 in pg/mL in sample.

Using PASS11 based on the previous study (Flori et al., 2007) for sample size calculation, it was calculated that a sample size 25 per group will achieve 87% power to detect a difference of 146 between the level of vWF with group means of 316 and 191 and estimated group standard deviation of 173 and 89, respectively, with an alpha level of 0.05 aiding a two-sided sample *t* test

Statistical analysis was done on a personal computer using the Statistical Package for Social Sciences version 17.0 (SPSS© v. 16.0, SPSS Inc., Chicago, IL, USA). Data were expressed descriptively as Mean ( $\bar{x}$ )  $\pm$  standard deviation (SD) for quantitative parametric data, interquartile range (IQR) for quantitative non-parametric values, and as a percent for qualitative data. Comparative statistics were done using independent (Student) *t* test for parametric data. Pearson chi-square test was used for comparison between two independent groups as regards

the categorized data. Correlation analysis was performed using Pearson's correlation coefficient (*R*) for parametric data. Receiver operator characteristic (ROC) curves were constructed and optimal cutoff values for plasma VWF level and serum IL6 were established by the best sensitivity and specificity where the right angle at the upper left corner is the best diagnostic threshold (cutoff) of the parameter being varied. In all statistical analyses, *p* value  $> 0.05$ : non significant; *p* value  $< 0.05$ : significant; and *p* value  $< 0.001$ : highly significant.

## Results

Sixty (60) patients who were at risk of developing ARDS were included in this study. Thirty-nine patients of them progressed into ARDS (group I) and twenty-one not progressed into ARDS (group II)

ARDS patients' group was diagnosed according to the criteria of Berlin definition of ARDS and Murray score of acute lung injury.

Results of the present study showed no statistically significant difference between studied demographic data (age and sex) and ARDS development ( $p > 0.05$ ) (Table 1). There was no statistically significant difference between different risk factors (burn, pancreatitis, sepsis, DIC, hepatic coma, trauma, pneumonia, status asthmatics, lung inhalation injury, respiratory failure, and pneumonia) and ARDS development ( $p > 0.05$ ) (Table 1). Higher VWF Ag levels are seen in patients at risk of developing ARDS due to direct cause of lung injury than those with indirect cause (Table 2). Among the group of ARDS patients with indirect causes of lung injury, the highest levels of VWF Ag has been recorded in burn and sepsis, while the lowest level has

**Table 1** Patients characteristics and ARDS risk factors at the day of enrollment

	Group I (n = 39), mean $\pm$ S.D.	Group II (n = 21), mean $\pm$ S.D.	P value
Age ( years)	47.7 $\pm$ 12.2	50.3 $\pm$ 12.4	0.42
Sex (M/F) (male/female)	21/18	14/7	0.6
APACHEII score (mean $\pm$ SD)	5.02 $\pm$ 23.71	2.67 $\pm$ 14.86	0.14
Weight in kg (mean $\pm$ SD)	82 $\pm$ 2.5	87 $\pm$ 2.4	0.63
<b>ARDS risk factors:</b>			
Pneumonia	7 (17.9%)	4 (19%)	0.961
Trauma	6 (15.3%)	3 (14.2%)	
Respiratory failure	5(12.8%)	3 (14.2%)	
Sepsis	4 (10.2%)	2 (9.5%)	
Septic bronchiolitis	4 (10.2%)	2 (9.5%)	
Burn	4 (10.2%)	2 (9.5%)	
Inhalation lung injury	3 (7.6%)	1(4.7%)	
Hepatic coma	2 (5.1%)	1(4.7%)	
Pancreatitis	2 (5.1%)	1(4.7%)	
DIC	1(2.5%)	1(4.7%)	
Uremia	1(2.5%)	1(4.7%)	

**Table 2** Levels of vWF in Group I patients with direct and indirect causes of ARDS

	ARDS patients (group I) with indirect cause of lung injury, n = 20	ARDS patients (group I) with direct cause of lung injury, n = 19	P value
VWF level in T0	403.6 ± 80	422 ± 89.3	< 0.005
VWF level in T48	464.58 ± 80.3	489.3 ± 77	< 0.005
VWF level in T72	531.3 ± 70	552.85 ± 65	< 0.005

been recorded in trauma as seen in Fig. 1. However, IL-6 levels showed no variation among different causes of indirect lung injury

As seen in Table 3, there was a highly significant increase between the “at risk of developing ARDS” patients, VWF Ag, and IL-6 levels, and the results were recorded at T0 (i.e., at start of the study baseline reading), T48 (after 48 h), and T72 (after 72 h),  $p < 0.001$  and  $p < 0.05$ , respectively.

Regarding the comparison between VWF and IL-6 levels among ARDS patients, they both show statistical correlation together (Fig. 2).

Finally, in our study plasma level of vWF Ag at cutoff level of 447% on the 3rd day of ARDS development, prediction period showed a sensitivity of 94.9% and

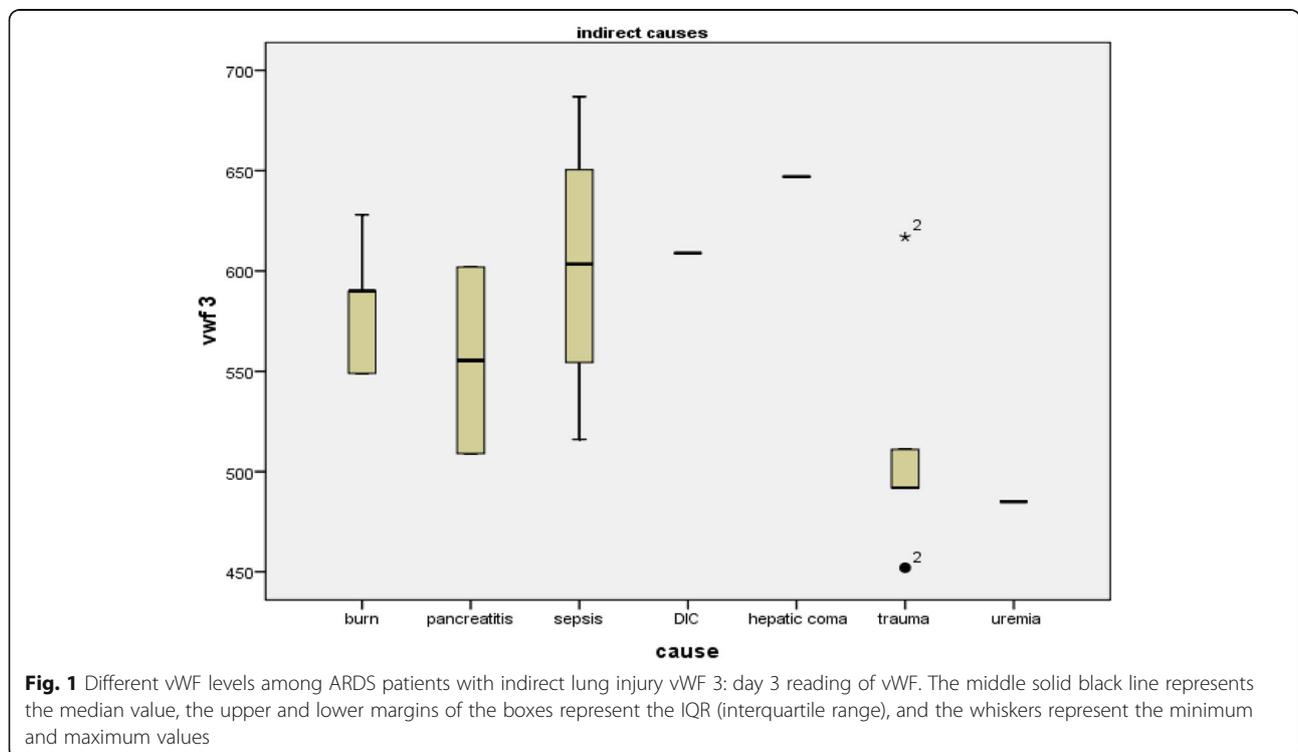
specificity 56.7% compared to IL6 at cutoff level 246 pg/ml which provided, 79.5% sensitivity and 52.4% specificity (Table 4).

**Discussion**

The results of the current study revealed that there were no statistically significant differences of age and sex, on different VWF levels. This is in agreement with Al-Awadhi et al. (2014).

Statistically significant difference was detected between VWF levels and ARDS developments. Our results together with several previous reports confirmed a documented high VWF levels in patients at risk for ARDS especially if they progressed to ARDS (Agrawal et al. 2012; Ware et al. 2004; Ware and Conner 2001; Rubin et al. 1990; Kayal et al. 1998; Carvalho et al. 1982; Flori et al. 2007).

In this study, it was found that VWF has a higher sensitivity of ARDS development and nearly similar specificity compared to IL-6. The high sensitivity and low specificity for VWF could be explained as VWF is an endothelial cell injury biomarker and could be increased at any endothelial injury rather than pulmonary endothelium (Mannuccio 1998); however, it increased at a higher level in pulmonary endothelium injury rather than anywhere else due to its large surface area. This theory could also explain why VWF is increased in the direct causes of ARDS rather than the



**Table 3** Comparison between vWF and IL-6 different levels in ARDS and non ARDS patients  $p < 0.05$  is considered statistically significant

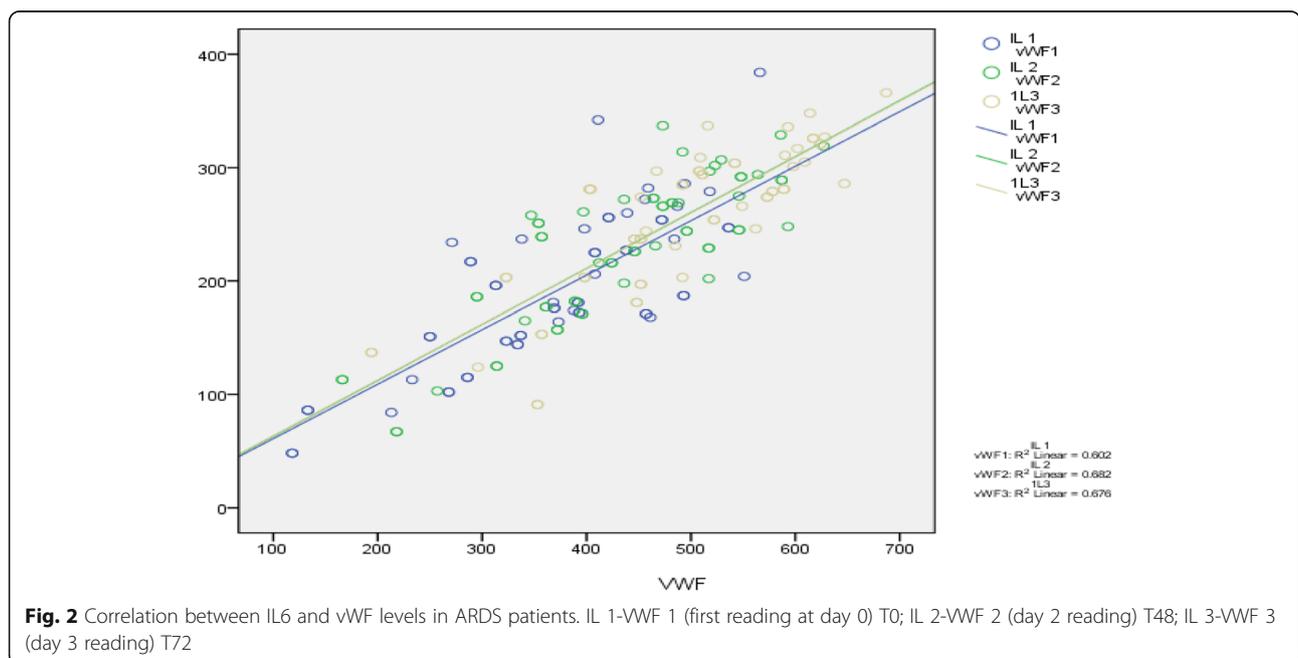
Parameter	Group I (n = 39), mean ± S.D.	Group II (n = 21), mean ± S.D.	P value
vWF T0	420.5 ± 80.48	284.57 ± 98.99	< 0.001
vWF T48	483.26 ± 77.86	338.62 ± 92.68	< 0.001
vWF T72	548.03 ± 69.59	388 ± 88.34	< 0.001
IL-6 T0	209.46 ± 60.49	160 ± 68.6	< 0.05
IL-6 T48	249.15 ± 49.7	186.38 ± 70.1	< 0.001
IL-6 T72	281.2 ± 45.96	210.1 ± 70	< 0.001

indirect lung injury (Ware et al. 2004; Ware and Conner 2001).

As regard to IL-6 as a biomarker for ARDS development, Bourros et al. (2004) and Takala et al. (2002) showed that there is a persistent elevation of inflammatory markers including IL-6 in patients with acute lung injury and that precedes its clinical diagnosis. Bauer et al. (2000) showed that serum levels of IL-6 is associated with the degree of lung injury rather than clarifies its specific etiology. Meduri et al. (1995) approved superiority of IL-1β and IL-6 plasma levels in monitoring ARDS development over commonly applied clinic-physiologic parameters. Schutte et al. (1998) found that consistently elevated serum levels of IL-6 and IL-8 in acute lung injury patients, discriminate ARDS patients from cardiogenic pulmonary edema.

The comparison between different risk factors and ARDS development showed no statistically significant difference that was agreed with Papaioannou and Pneumatikos (2009), although they did not show a

correlation to each other, but when they were classified into direct and indirect ARDS risk factors, they showed correlation with VWF levels among ARDS patient and even they showed high VWF levels among ARDS patient with direct causes of lung injury than those with indirect causes, that agreed with Ware et al. who conformed higher VWF levels among ARDS patient with direct causes of lung injury than those with indirect causes (Ware et al. 2004; Ware and Conner 2001). It was observed that trauma as a cause of ARDS recorded low VWF levels than other causes, that may be due to its association with less endothelial activation and injury, this result agrees with Ware et al. (2004) and Moss et al. (1996) results (Moss et al. 1996). However, it disagrees with Treggiari et al. (2004). Higher VWF levels were recorded in sepsis and burn rather than other indirect lung injury risk factors due to more endothelium damage (Ware et al. 2004). But unlike VWF, in this study, IL-6 had no correlation between its levels and direct and indirect causes of ARDS (Bauer et al. 2000).



**Fig. 2** Correlation between IL6 and vWF levels in ARDS patients. IL 1-VWF 1 (first reading at day 0) T0; IL 2-VWF 2 (day 2 reading) T48; IL 3-VWF 3 (day 3 reading) T72

**Table 4** Different cutoffs of vWF (% of normal) and IL6 (pg/ml) with their sensitivity and specificity for ARDS prediction during the study period

	Cutoff value	Sensitivity %	Specificity %
VWF T0	328.5	84.1	42.9
VWF T48	366.5	87.2	48.3
VWF T72	447	94.9	56.7
IL 6 T0	158	82	44.6
IL6 T48	192	85.7	45.3
IL6 T72	246	79.5%	52.4

**Conclusion**

Our study gives support to previous observations which demonstrated the increasing plasma levels of VWF in ARDS risky patients; also, its higher levels facilitate the diagnosis of ARDS. Their increased levels were associated with bad outcome (including mortality and length of mechanical ventilation). Lastly, the results of our study pointed out to VWF as a sensitive and good diagnostic marker for ARDS diagnosis.

**Limitation of the study**

The results of this study may be affected by the primary condition of the patients (the predisposing risk factor) rather than the progress to ARDS.

It was difficult to demonstrate the precise source of VWF as it is released from endothelium injury that may be the result of the primary condition of the patients' illness.

The study although properly powered, the authors have conservations upon generalizing the results without the presence of a large multicenter cross-sectional trial nor without a confirmatory comprehensive meta-analysis.

**Recommendation**

Performing the study on a larger number of patients for more comprehensive statistical analysis and better conclusions aiming for increase the power of the proposed study. Further clinical study is needed for analysis of plasma VWF in ARDS risky patients and its relation to syndrome progression and complication. Follow-up of the patients' longer duration is needed to confirm the prognostic value of VWF in ARDS. More work is needed to detect the effect of the different ARDS therapeutic agents on the plasma level of VWF addition of VWF to the clinical routine follow-up after ARDS therapy to give a good view for discharging the patient or not.

**Abbreviations**

VWF: Von Willebrand factor; IL-6: Interleukin-6; ARDS: Acute respiratory distress

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**Authors' contributions**

DF designed the study, revised literature, performed the analysis, followed the patients, and wrote the manuscript. MA designed the study, performed the analysis, and wrote and critically revised the manuscript. EH and SI revised literature, performed the analysis, and critically reviewed the manuscript. DE revised literature, collected samples, and performed analysis. WA revised literature, followed the patients, collected the data, performed the analysis, and critically reviewed the manuscript. All authors have read and approved the manuscript.

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None.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

Written informed consents were taken and validated by the patients or their relatives in charge before history taking, physical examination and blood sample withdrawal. The procedures applied in this study were approved by the Research Ethical Committee of Human Experimentation of Faculty of Medicine, Ain-Shams University, code number FMASU 806/2010 and are in accordance with the Helsinki Declaration. The consent included the aim of the sampling method and number of samples withdrawn and the amount of blood which was withdrawn.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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