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Is either arterial or venous antithrombin III level linked to outcome in elderly males versus females with severe sepsis?

Nermien N. Adly[1], Rania M. Abou-Hashem[1]

[1]*Lecturer of Geriatric Medicine, Geriatrics and Gerontology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt*

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ABSTRACT

Objectives: We aimed to study arterial and venous ATIII levels, in elderly males and females with severe sepsis, and their impact upon the patients' outcomes. **Patients and Methods:** A cohort study was performed in thirty-nine elderly patients with severe sepsis. Arterial and venous ATIII levels were measured. Sequential Organ Failure Assessment (SOFA) score was calculated. **Results:** Both arterial and venous ATIII levels were negatively correlated with age in the whole sample (P = 0.004 and .05 consecutively) (r = −0.45 and −0.32 consecutively). There was a significant difference between the arterial and venous ATIII levels in males (P = 0.04). In males, SOFA score was positively correlated with arterial ATIII and the difference between arterial and venous ATIII levels (P = 0.04 and .05 consecutively). Arterial and venous ATIII were the significant predictors of SOFA score, only in males (P < 0.001 and 0.003 consecutively). **Conclusion:** ATIII level decreased with increasing age. In males, both higher arterial and lower venous ATIII levels were significant predictors of worse organ dysfunction.

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Key words: Severe sepsis, Gender, Antithrombin III, Outcome, SOFA, Elderly, Egypt

INTRODUCTION

Sepsis is one of the most common causes of admission to the Intensive Care Unit (ICU).[1] Sepsis is much increasing among elderly population either in incidence or prevalence.[2]

Mortality can reach up to 30-50% in those with severe sepsis and septic shock[3] and this percentage is expected to be more in the elderly population.[4]

Many mortality prediction models are widely used in sepsis, Sequential Organ Failure Assessment (SOFA) score was developed in order to describe organ failure in septic patients.[5]

Activation of coagulation is inhibited by three major anticoagulant pathways. Antithrombin III (ATIII) is one of the major anticoagulant pathways.[6] Changes in this parameter precede the development of organ dysfunction.[7]

It is well known that stimulation of the coagulation system along with activation of the inflammatory pathways can contribute to micro-vascular thrombosis leading to multiple organ failure in patients with severe infection.[8]

Although there is a link between ATIII and pathogenesis of sepsis,[7] there is a difference in the association between ATIII level and different sepsis outcomes.[9,10]

In addition, a study conducted elsewhere found a difference between arterial and venous samples of some coagulation parameters in different conditions. Therefore, the accurate measurement of coagulation parameters plays an important role in the evaluation of patients especially during critical illness.[11]

Earlier studies have reported that the factors that help ATIII in its functions are defective in females.[12-14]

Address for Correspondence:
Dr. Nermien Naim Adly, Geriatrics and Gerontology Department, Faculty of Medicine, Ain Shams University, Abbassia, Cairo, Egypt.
E-mail: drnermienadly@yahoo.com; **Telephone:** +201114101969

To our knowledge, the differential link between severe sepsis outcome and both arterial and venous ATIII levels in each gender is lacking. Therefore, the aim of the present study was to study the arterial and venous ATIII levels, in elderly males and females with severe sepsis, and their impact upon the patients' outcomes (septic shock, organ dysfunction as assessed by SOFA score and ICU mortality).

PATIENTS AND METHODS

Study design, Setting and population

A prospective cohort study was performed in thirty-nine Egyptian elderly patients (aged ≥60 years) admitted with severe sepsis to the Geriatric ICU. Patients were recruited from August 2011 to March 2012. Forty three patients were recruited; however four were excluded because of some missing data. Each subject gave informed consent and patient anonymity was preserved. The study was approved by the ethical committees of our department.

Elderly patients using anticoagulants or estrogens or known to have ATIII deficiency or nephrotic syndrome were excluded from the study.

STUDY PROTOCOL

Data collection

Data were collected within 24 hours of patients' presentation with severe sepsis including demographic data, past medical history, the source of sepsis and clinical assessment. Patients were followed up daily until death or discharge from the ICU.

Systemic inflammatory response syndrome (SIRS) is recognized clinically by the presence of 2 or more of the followings: temperature >38°C or <36°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or a $PaCO_2$ in arterial gas <32 mm Hg; and white blood cells count >12,000 cells/μl, <4000 cells/μl or >10% band forms.[15]

The combination of SIRS with a confirmed infectious process was then called sepsis. Severe sepsis was defined as sepsis associated with organ dysfunction, hypo-perfusion abnormality or sepsis-induced hypotension. Septic shock was defined as severe sepsis with sepsis-induced hypotension persisting despite adequate fluid resuscitation.[15]

An example of typical threshold identification of severe sepsis is (the presence of any of the following that is thought to be due to the infection): sepsis-induced hypotension; lactate greater than the upper limits of normal laboratory results; urine output <0.5 mL/kg/ hr for >2 hrs, despite adequate fluid resuscitation; acute lung injury with PaO_2/FIO_2 <250 in the absence of pneumonia as infection source; acute lung injury with PaO_2/FIO_2 <200 in the presence of pneumonia as infection source; creatinine >2.0 mg/dl; bilirubin >2 mg/dl; platelet count <100,000 per microliter; or coagulopathy (INR>1.5).[16]

In addition, SOFA scoring system was used in order to describe organ failure in septic patients. Scoring was calculated from 0-4 points for each organ (respiratory, cardiovascular, neurological, hepatic, renal and coagulation) according to the degree of the dysfunction and then the worst scores for each of the organ systems were summed to give the final score.[5] Initial SOFA score was calculated.

LABORATORY INVESTIGATIONS

Two blood samples were collected: arterial blood sample for measurement of arterial blood gases and venous sample for complete blood count, coagulation profile, kidney functions, total bilirubin and random blood sugar.

In both arterial and venous samples, ATIII levels were measured using Diffuplate radial immunodiffusion. Five ml of the serum was introduced in the plate and was incubated in room temperature; the diameter was measured within 0.1 mm. Then the results were obtained using the reference table.

Outcomes

Patient outcomes were recorded regarding septic shock, organ dysfunction (as assessed by SOFA score) and ICU mortality.

Data analysis

Data were collected and introduced into personal computer for statistical analysis. Qualitative data were presented in the form of frequency tables (number and percent). Quantitative data were presented in the form of means and SD (for parametric data) or median values (for non parametric data).

Normality distribution of the variables was tested using one sample Kolmogorov Smirnov test. Regarding Quantitative data, differences between two groups were assessed using the Student's t test for parametric data or Mann Whitney U test for non-parametric data. Regarding qualitative data, the Chi-square test or Fisher's Exact test was used to compare between the two groups.

Pearson correlation coefficient was used for parametric data and Spearman correlation coefficient was used for non-parametric data. Wilcoxon test was used to test for the difference between arterial and venous ATIII levels. Linear regression analysis was used to determine the most significant predictors of SOFA score, in each gender, including arterial and venous ATIII levels and the difference between both levels, after adjusting for the age.

Statistical Package for Social Science (SPSS) statistical software version 16 was used in data analysis.

RESULTS

Current study included thirty-nine patients with median age of 70 years and 56.4% were males. Median of SOFA score was 6 and 74.4% died in the ICU (Table 1).

There was a significant difference between arterial and venous ATIII only in males (P=0.04) (Table 2).

There was no significant difference between males and females as regard age, arterial or venous ATIII level, SOFA score or ICU mortality (P = 0.21, 0.12, 0.43, 0.36 and 0.64 consecutively). However, males had higher incidence of septic shock than females (P = 0.03) (Table 3). There was no difference in other laboratory data including sodium, potassium, random blood sugar, PT, PTT, renal functions or complete blood count.

Both arterial and venous ATIII levels were negatively correlated with age in the whole sample (P = 0.004 and 0.05 consecutively) (r = −0.45 and -0.32 consecutively). SOFA score was positively correlated with both arterial ATIII and the difference between arterial and venous ATIII only in males (P = 0.04 and 0.05 consecutively) (r= 0.45 and 0.43 consecutively) (data were not presented in tables).

Linear regression analysis revealed that arterial and venous ATIII were the significant predictors of SOFA score only in males (P < 0.001 and .003 consecutively) (B = 0.46 and −0.26 consecutively) (OR = 1.6 and .78 consecutively) (CI= 1.5-1.7 and 0.7-0.9 consecutively) (data were not presented in tables).

Neither arterial nor venous ATIII level had significant difference between survived and non survived cases (P = 0.93 and 1 consecutively), septic shock versus severe sepsis without septic shock (P = 0.43 and 0.28 consecutively). In the non-survived group, there was a higher SOFA score than the survived group (P = 0.003) (data were not presented in tables).

Table 1: Description of demographic data, clinical assessment, laboratory results and outcomes of the studied group

Variables	Values
Demographic data & past history	
Age (years) (median)	70
Male gender number, n (%)	22 (56.4%)
HTN, n (%)	18 (46.2%)
DM, n (%)	22 (56.4%)
Stroke, n (%)	11 (28.2%)
CLD, n (%)	5 (12.8%)
Source of infection	
Pneumonia, n (%)	14 (35.9%)
COPD exacerbation, n (%)	20 (51.2%)
Urinary Tract infections, n (%)	3 (7.7%)
Cellulitis, n (%)	1 (2.6%)
Infected pressure ulcers, n (%)	4 (10.25%)
Clinical assessment	
GCS (median)	11
HR (beat/min) (median)	100
RR (breath/min) (median)	27
Temperature(°C) (median)	37.5
SystolicBP (mmHg), mean±SD	113.00±33.19
DiastolicBP (mmHg), mean±SD	66.15±17.86
Urine output (ml/day), median	1000
Laboratory results	
ATIII arterial level (mg/dl), mean±SD	19.88±6.32
ATIII venous level (mg/dl) (median)	19.80
Arterial Blood Gas (ABG)	
PH (median)	7.45
PO_2 (mmHg), mean±SD	71.90±22.96
PCO_2 (mmHg), median	30
HCO_3 (mEq/L), mean±SD	22.03±10.14
O_2SAT (%) (median)	95
PO_2/FIO_2 (mmHg) (median)	247.6
FIO_2 (median)	0.21
Outcomes variables	
Septic shock, n (%)	9 (23.1%)
SOFA score (median)	6
ICU mortality, n (%)	29 (74.4%)

Values were expressed in form of mean ± SD or mediam for quantitative data and number (%) for qualitative data. ATIII: Antithrombin III, BP: Blood pressure, CLD: Chronic liver disease, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, GCS: Glascow coma scale, HTN: Hypertension, HR: Heart rate, ICU: Intensive care unit, RR: Respiratory rate, SOFA: Sequential organ failure assessment

DISCUSSION

Current data revealed a significant negative correlation between age and ATIII level. This agrees with Amin et al.[17] who found that lower ATIII activity was observed in the older group, whereas the younger group demonstrated significantly higher ATIII activity (P = 0.001). This could be explained by the age related changes in the coagulation and fibrinolytic systems, as natural anticoagulants are decreasing while levels of coagulation factors are highly increasing which are exposing elderly people to a higher risk of thrombosis.[18]

The present study revealed statistically significant difference between the arterial and venous ATIII levels only in males.

Table 2: The difference between both genders in the arterial and venous ATIII levels

All patients		P	Males		P	Females		P
Arterial ATIII	Venous ATIII		Arterial ATIII	Venous ATIII		Arterial ATIII	Venous ATIII	
19.9±6.3 (mg/dl)	19.80 (mg/dl)	0.179	21.3±6.1 (mg/dl)	19.80 (mg/dl)	0.04	18.1±6.3 (mg/dl)	17.6 (mg/dl)	0.96

Wilcoxon test was used. Values were expressed in form of mean ± SD or median for quantitative data. ATIII: Antithrombin III

Table 3: Comparing between males and females regarding demographic data, clinical assessment, laboratory results, and outcomes

Variables	Males number = 22	Females number = 17	P value
Demographic data & past history			
Age (years)*	64.50	70.00	0.21
HTN, n (%)	7 (31.8%)	11 (64.7%)	0.04
DM, n (%)	12 (54.5%)	10 (58.8%)	0.79
Stroke, n (%)	3 (13.6%)	8 (47.1%)	0.02
CLD, n (%)	4 (18.2%)	1 (5.9%)	0.36
Source of infection			
Pneumonia, n (%)	7 (31.8%)	7 (41.2%)	0.55
COP dexacerbation, n (%)	13 (59.1%)	7 (41.2%)	0.27
Urinary tract infections, n (%)	2 (9.1%)	1 (5.9%)	1.00
Cellulitis, n (%)	1 (4.5%)	0 (0%)	1.00
Infected pressure ulcers, n (%)	1 (4.5%)	3 (17.6%)	0.30
Clinical assessment			
GCS*	13.50	10.00	0.55
HR (beat/min)*	100.0	100.0	0.26
RR (breath/min)*	27	22	0.66
Temperature (°C)*	37.40	37.50	0.71
Systolic BP (mmHg)	112.73±38.57	114.12±25.75	0.89
Diastolic BP (mmHg)	64.55±19.69	68.23±15.51	0.52
Mean arterial blood pressure	80.61±25.65	83.53±18.58	0.68
Urine output (ml/day)*	1200	800	0.21
laboratory results			
ATIII arterial level (mg/dl)	21.29±6.05	18.07±6.39	0.12
ATIII venous level (mg/dl)*	19.80	17.60	0.43
Arterial blood gases			
PH*	7.43	7.45	0.92
PO_2 (mmHg)	76.38±23.63	66.11±21.36	0.16
PCO_2 (mmHg)*	26.5	38	0.02
HCO_3 (mEq/L)	18.86±8.48	26.14±10.87	0.03
O_2SAT (%)*	95.00	95.00	0.39
PO_2/FIO_2 (mmHg)*	248.3	265.1	0.75
FIO_2*	0.21	0.21	0.67
Outcomes variables			
Septic shock, n (%)	8 (36.4%)	1 (5.9%)	0.03
SOFA score*	7.50	6.00	0.36
ICU mortality, n (%)	17 (77.3%)	12 (70.6%)	0.64

Values were expressed in form of mean ± SD or mediam for quantitative data and number (%) for qualitative data. *Mann-whitney U was used where median values were expressed. ATIII: Antithrombin III, BP: Blood pressure, CLD: Chronic liver disease, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, GCS: Glascow coma scale, HTN: Hypertension, HR: Heart rate, ICU: Intensive care unit, RR: Respiratory rate, SOFA: Sequential organ failure assessment

This is similar to Durila et al[11] who reported a significant difference between arterial and venous ATIII activity in the septic patients. This significant difference could be attributed to the higher presence of males rather than females in their sample of patients (n = 28 vs. 16 respectively).

The current study found that there was a significant difference between males and females in the incidence of septic shock, as males had higher progression from severe sepsis to septic shock. However, there was no difference in mortality.

This could be supported by Angus et al[2] who found that sepsis had better course in females rather than males.

In the current work, there was a positive correlation between SOFA score in males and both arterial ATIII level and the difference between arterial and venous ATIII levels. This indicates that the higher the arterial ATIII was, the worse the organ dysfunction was, in males. Furthermore, ATIII was consumed in venous side which was correlated with organ dysfunction only in males. This is in accordance with LaRosa et al[10] who found that patients with lower

venous AT levels were more exposed to higher degrees of organ dysfunction than other patients. They included more males than females (19 vs. 11).

This is further supported by our linear regression analysis which revealed that higher arterial and lower venous ATIII levels were the significant predictors of SOFA score, only in males.

The attenuation of the role of the ATIII in females rather than males could be explained by lower heparan sulfate[12] and glycosaminoglycans levels in healthy females as a part of normal aging.[13] Heparan sulfate is responsible for optimizing the action of ATIII[19] and glycosaminoglycans enhance the transformation of the ATIII molecule from a slow protease inhibitor to a very efficient inhibitor of thrombin.[20] In addition, animal studies revealed decreased glycocalyx volume in females[14] which in turn decreases ATIII expression.[21]

This could predict an optimal function of ATIII in males rather than females. Therefore, its level is a significant predictor of sepsis outcome in males. This might partially explain the controversies about ATIII treatment outcomes in various studies,[22,23] even if ATIII therapy was activity guided.

It is known that elderly females had higher ATIII level than elderly males.[24] The absence of significant difference between both genders in ATIII level could be explained by Reade et al[25] who found that males express more ATIII with pneumonia infection rather than females. The absence of worse SOFA in females, along with the suspected defective role of ATIII, might be attributed to other protective mechanisms in females as lower pro-inflammatory markers expression with infection, comparing with males,[25] and the number of resting resident leukocytes in the peritoneal and pleural cavities is much more in female than male rats.[26]

There was no significant difference between survivors and non-survivors patients in either arterial or venous ATIII level. This agrees with Sakr et al[9] who found that ATIII level, in patients with severe sepsis, was not associated with increased ICU mortality, although it was associated with organ dysfunction. Moubarak et al[23] explained that by the possibility of the role of organ function as a precedent, but not a sufficient condition for a better survival rate. Additional factors such as specific time impact, as temporary versus persistent, or unknown variables which are impossible to be controlled may be important.

Current results of the link between worse outcome and higher arterial ATIII level could be explained by the multiple reports about high ATIII in patients with higher thrombus risk. In patients with ischemic heart disease, ATIII value was highest in patients with acute myocardial infarction.[27] In the Northwick park heart study, upon males, higher mortality of ischemic heart disease was present in the highest and lowest tertiles of ATIII.[28]

Lee et al[29] found increased ATIII levels in patients with diabetes mellitus with evidence of renal damage. Similarly, Fuller et al[30] showed that ATIII values were high in diabetics with microvascular disease, males were 59% of the sample.

A possible explanation of the data of the current work and similar studies in thrombosis is that patients with active atherosclerosis have increased levels of ATIII levels as a protective mechanism against pro-coagulatory effects combined with an increased consumption. Therefore, increased (as a compensatory mechanism) as well as decreased levels (as a direct cause) of ATIII may accompany an increased risk of vascular damage.[24,28]

Limitations of the current study could be focused upon the absence of results regarding the impact of ATIII treatment upon outcomes in both genders.

CONCLUSION

ATIII levels were inversely proportional to aging process. The higher the arterial and the lower the venous ATIII levels were, the worse the organ dysfunction was, in males. Although there was a difference between arterial and venous ATIII levels in males, both higher arterial and lower venous ATIII levels were significant predictors of worse organ dysfunction in males. Therefore, it is better to measure both the arterial and the venous ATIII levels in elderly males with severe sepsis. There was no effect of ATIII level upon ICU mortality in either elderly males or females with sever sepsis.

Recommendations

We would like to suggest studying the impact of ATIII treatment, separately in both genders, upon outcomes in patients with severe sepsis, in future researches.

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Authors Contribution:
NN – designed the study, collected the data, analyzed the data, drafted the manuscript & reviewed the manuscript**; RM** – designed the study, collected the data, drafted the manuscript & reviewed the manuscript**.**

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