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# Study of Plasminogen Activator Inhibitor-1 (PAI-1) as Prognostic Marker in Sepsis

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Sepsis is an unorganized host response to infection that is manifested by the failure of organs and DIC and systemic coagulation due to failure of Plasmin as an important fibrin lytic protein that is regulated by plasminogen activators and inhibitors. Our theory is that elevated PAI-1 may have a role in multi-system organ failure in patients with septicemia and systemic coagulopathy.
**Aim:** to evaluate plasminogen activator inhibitor-1 as a prognostic factor in patients with septicemia and DIC.
**Patients and Methods:** 60 cases with septicemia and in shock, in addition to 20 healthy individuals. Cases were selected from surgical ICU, Tanta University hospitals. Normal healthy subjects were matched by age and gender with the patients' group.
**Results:** Respiratory system and urinary tract infections, were the most common infections and high SOFA and APACHE scores in the selected cases. The hematological findings in septic patients are anemia, thrombocytopenia, and leukocytosis. There was a significant increase in urea, creatinine, SGOT, SGPT levels, and CRP in patient groups. Higher levels of PAI-1 in cases suffering sepsis. An increased mortality rate after 28 days of follow-up was noticeable in cases with

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established septic shock compared to other patient groups in Tanta university surgical intensive care. We found a direct correlation between PAI-1and SOFA, APACHE, bilirubin, creatinine, PT, APTT, and Procalcitonin.
**Conclusions:** PAI-1 level has a prognostic value in cases with infections or septicemia presented to our emergency center.

*Keywords: Plasminogen activator inhibitor-1; Sepsis.*

## 1. INTRODUCTION

In ancient Greek, "Sepsis" means to break apart and this expression appeared in very ancient Greek poetry [1].

Sepsis is a clinical syndrome of bacteremia. When micro-organisms break into the natural body barriers and get over the immune system, they can cause generalized systemic infection to more than one body organ or what is known as septicemia or may affect vital systems like pneumonia or encephalitis [2].

Bacteria are the main cause of infection that causes sepsis, only a small portion of septicemia is caused by viruses, fungi, and parasites. Which could be the infectious agent when a certain bacteria species could not be found, despite septicemia [3].

The Morbidity and Mortality rates in cases of Sepsis despite intensive medical care and the use of proper wide-spectrum antibiotics have become a major health problem. Physicians need to have more specific and sensitive tools to identify patients who require early broad antibiotic coverage and intensive supportive care and we also need to collect more information about the immune–pathogenesis of septicemia and sepsis to generate appropriate treatment modalities and preventive measures [4].

Initial appropriate antibiotic therapy reduces morbidity and mortality in septic patients as empiric inappropriate use of antibiotics develops multidrug resistance organisms that are difficult to manage [5].

More than 178 sepsis markers have been found, most of which are intermediate inflammatory products and pro-inflammatory cytokines as (CRP, procalcitonin, interleukin-6, etc.) [6].

Multiple organ failure (MOF) is the result of Sepsis as an example: Cardiovascular dysfunction or acute respiratory failure [7].

septic shock is manifested by cardiovascular failure, requiring inotropes and vasopressors. Due to the rising importance of blood biomarkers, much research has been done to find biomarkers that would predict sepsis [8].

Plasminogen activator inhibitor-1 inhibits fibrinolysis by inhibiting plasminogen activator which activates plasmin that breaks down fibrin a main component of coagulation, the abnormal increase in PAI-1 activity in case of sepsis will lead to coagulation in many body organs DIC and MOF multi-organ failure [9].

This study aimed to evaluate plasminogen activator inhibitor-1 as a prognostic factor in patients with septicemia and DIC.

## 2. SUBJECTS AND METHODS

This study was done on 60 cases of septicemia and cardiovascular shock, in addition to 20 normal individuals as reference. Patients were selected from surgical ICU, Tanta University hospitals from June 2019 to Feb 2020 in the clinical pathology department, Tanta University Hospitals. Normal healthy subjects were matched by age and gender with the patients' group. The studied subjects were put into three groups:

**Group (1):** Thirty cases with sepsis. They were 17 males and 13 females with ages ranging from 21-62 years.

**Group (2):** Thirty patients with septic shock. They were 19 male cases and 11 female cases with ages from 23 to 71 years.

**Group (3):** Twenty healthy individuals were 12 males and 8 females with ages ranging from 20-61 years.

### 2.1 Inclusion Criteria

- Cases that were admitted to the ICU due to one or more than one organ damage with sepsis include one or more organ failures including cardiovascular system failure or disturbed conscious level.
- All control subjects were non-medicated, apparently healthy, and showed no evidence of any pathological conditions.

## 2.2 Exclusion criteria

- **The following cases were excluded from the study:**
  - Younger than 18 years.
  - Presence of blood malignancy, chronic liver damage, Diabetes mellitus, and cardiac arrest on admission.
  - Occurrence of death within 24 hours of ICU admission.
- **All cases and controls were subjected to the following:**
  - Complete clinical examination.
  - Routine laboratory investigations (complete blood cell count, liver function test, renal function test, blood glucose level, arterial blood gases, CRP level, procalcitonin level, prothrombin time and activated partial thromboplastin level.
  - Specific laboratory investigations: measurement of plasminogen activator inhibitor-1 level by ELISA technique.
  - Sequential Organ Failure Assessment (SOFASCORE) [10]: Respiratory system assessment by PaO2/FiO2 (ABG), Nervous system evaluation by Glasgow coma scale, Cardiovascular system assessment by mean arterial pressure OR administration of vasopressors, bilirubin level to ***assess*** liver function, creatinine level for renal function evaluation and platelet count for coagulation system).

## 2.3 Statistical Analysis

Statistical presentation and analysis of the present study were conducted, using the mean value ± standard deviation using ANOVA test and chi-square test by SPSS V.22. The p-value is a measure of the probability that an observed difference could have occurred just by random chance. The lower the p-value, the greater the statistical significance of the observed difference.

The Acute Physiology and Chronic Health Evaluation (APACHE) score is an illness severity score that was used in predicting the mortality of sepsis and septic shock upon admission to intensive care.

## 3. RESULTS

Table 1 showed that the mean value of the SOFA score inpatient group ranged between (7.13 ±2.05 and 16.60±3.94) in sepsis and septic shock respectively.

Regarding APACHE score the mean value of the patient group ranged between (11.17 ± 4.14 and 20.93± 5.11) in sepsis and septic shock respectively.

There was a significant difference in SOFA and APACHE scores in patient groups as their levels increased with the severity of sepsis.

Table 2 showed that serum C - reactive protein (CRP) levels in the studied groups ranged between (4-150, 40- 210, and 2–6 mg/l) in sepsis, septic shock, and control groups respectively with a mean value of (44.10±36.14,119.43±65.11and 4.95 ± 1.28) in sepsis, septic shock, and control groups respectively.

There was a significant difference in CRP levels in patient groups as their levels increased with severity of sepsis (p-value) = 0.001). p1 between sepsis and septic shock group (0.001), p2 between sepsis and control group (0.004), and p3 between septic shock and control group (0.001).

Table 3 showed that procalcitonin levels in the studied groups ranged between (2–10, 15–28and 1-5 ng/ml) in sepsis, septic shock, and control groups respectively with a mean value of (5.87 ±2.46, 21.70±3.74 and2.75±1.33) in sepsis, septic shock, and control groups respectively.

**Table 1. Clinical scoring system of patients groups**

| | | Range | | | Mean | ± S. D | T. test | P. value |
|---|---|---|---|---|---|---|---|---|
| SOFA SCORE | Sepsis | 3 | – | 11 | 7.13 | ± 2.05 | 11.668 | 0.001* |
| | Septic Shock | 9 | – | 28 | 16.60 | ± 3.94 | | |
| APACHE SCORE | Sepsis | 5 | – | 20 | 11.17 | ± 4.14 | 8.128 | 0.001* |
| | Septic Shock | 11 | – | 30 | 20.93 | ± 5.11 | | |

There was also a significant increase in procalcitonin levels in patient groups as their levels increased with the severity of sepsis (p-value = 0.001). p1 between sepsis and septic shock group (0.001), p2 between sepsis and control group (0.004), and p3 between septic shock and control group (0.001).

Table 4 showed that PAI-1 levels in the studied groups ranged between (7.7-63.2, 18.5–65and 2.5-5 ng/ml) in sepsis, septic shock, and control groups respectively with a mean value of (19.20±9.82, 42.71±9.04 and3.91±0.75) in sepsis, septic shock, and control groups respectively.

There was also a significant increase in PAI-1 levels in patient groups as their levels increased with the severity of sepsis (p-value =0.001).

## 4. DISCUSSION

In the present work, there was a significant difference in CRP levels in patient groups as their levels increased with the severity of sepsis.

CRP levels in septic shock were significantly higher than cases in sepsis and the control group (p = 0.001).

This was in accordance with Seki et al. [11] and Koyama et al. [12] as they found much increased levels of CRP in cases with sepsis with increased morbidity and mortality.

CRP is a well-known marker of infection and inflammation because the levels of CRP rise rapidly in the early phases of inflammation and reach higher levels more than any other biomarkers so it is a sensitive indicator for systemic inflammation [13].

In the present work, there was a significant difference in procalcitonin levels in patient groups as their levels increased with the severity of sepsis (p=0.001).

This copes with Liu et al. [14] and Samsudin and Vasikaran [15] as they found that septic patients had significantly higher levels of procalcitonin.

The primary pathophysiological trigger for an elevated level of PCT is infection. Investigations identified PCT as part of the complex proinflammatory response of the innate immune system. A marked increase in serum PCT often indicates an exacerbation of the disease, and a decreasing level is a sign of improvement [16].

In the present study, the results showed that there is no significant correlation between serum PAI-1in the studied groups and their age and gender.

This was in agreement with Hoshino et al. [17] who didn't find a significant correlation between serum PAI-1 levels and age. Unlike, Lorente et al. [18] who found significantly higher levels of serum PAI-1 in elderly patients, and Koyama et al. [11] who found that PAI-1 was slightly higher in men compared with women.

**Table 2. Serum C-Reactive protein levels in patient and control groups**

| | | Range | | | Mean | ± | S. D | F. test | P.value | |
|---|---|---|---|---|---|---|---|---|---|---|
| CRP | Sepsis | 4 | – | 150 | 44.10 | ± | 36.14 | 41.563 | 0.001* | P1 0.001 |
| (mg/l) | Septic Shock | 45 | – | 210 | 119.43 | ± | 65.11 | | | P2 0.004 |
| | Control | 2 | – | 6 | 4.95 | ± | 1.28 | | | P3 0.001 |

**Table 3. Procalcitonin (ng/mL) levels in the studied groups**

| | | Range | | | Mean | ± | S. D | F. test | P.value | |
|---|---|---|---|---|---|---|---|---|---|---|
| Procalcitonin | Sepsis | 2 | – | 10 | 5.87 | ± | 2.46 | 149.429 | 0.001* | P1 0.001 |
| (ng/mL) | Septic Shock | 15 | – | 28 | 21.70 | ± | 3.74 | | | P2 0.004 |
| | Control | 1 | – | 5 | 2.75 | ± | 1.33 | | | P3 0.001 |

**Table 4. PAI-1 (ng/mL) levels in the studied groups**

| | | Range | | | Mean | ± | S. D | F. test | P.value | |
|---|---|---|---|---|---|---|---|---|---|---|
| PAI-1 | Sepsis | 7.7 | – | 63.2 | 19.20 | ± | 9.82 | 138.933 | 0.001* | P1 0.001 |
| (ng/mL) | Septic Shock | 18.5 | – | 65 | 42.17 | ± | 9.04 | | | P2 0.001 |
| | Control | 2.5 | – | 5 | 3.91 | ± | 0.75 | | | P3 0.001 |

In the present study, the 28-day mortality rate is significantly higher in patients with a high level of PAI-1.

This is in accordance with Okabayashi et al. [19] who found that high PAI-1 levels predicted increased mortality, PAI-1 is a strong marker of mortality risk.

Peres et al. [20] also found that high levels of PAI-1had been widely demonstrated to correlate with morbidity and outcome, supporting its value as a prognostic biomarker in infected patients.

Despite the relatively small number of patients included in the study, there were significantly higher levels of plasma PAI-1 in patients with severe sepsis compared to less severe septic patients upon admission to the ICU. The results suggest that PAI-1 is a marker of inflammation in patients with sepsis. The difference between severe sepsis and less severe septic patients prompted the power of PAI-1 to assess the severity of sepsis.

This was in agreement with Shapiro et al. [21] and Seki et al. [22] as they found that Plasma levels were significantly higher in patients with severe sepsis than in the less severe group. Their study suggested that PAI-1is a powerful marker of coagulation-fibrinolytic disorders in patients with sepsis.

## 5. CONCLUSION

Based on our present study's findings, the PAI-1 level has been shown to represent a crucial prognostic value in the cases of patients suffering infections or septicemia. It's also evident that there is a direct correlation between PAI-1and SOFA, APACHE, bilirubin, creatinine, PT, APTT, and procalcitonin.

## 6. RECOMMENDATIONS

Given the findings of the present study, we recommended the following:

i. The need for further studies on a larger number of patients for more comprehensive statistical analysis.

ii. Future follow-up studies may be needed to clarify the clinical usefulness of the combination of PAI-1 with other biomarkers like CRP in critically ill patients and combination with clinical scores like SOFA and APACHE.

iii. PAI-1 can be incorporated as a predictor for ICU and overall survival in septic patients.

## CONSENT AND ETHICAL APPROVAL

The study was approved by the Ethical Committee of the Faculty of Medicine at Tanta University and written informed consents were obtained from all participants.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Medicine. 2019;7:20503121198350 43.
2. Paolucci M, Landini MP, Sambri V. How can the microbiologist help in diagnosing neonatal sepsis? International journal of pediatrics. 2012;2012.
3. Lin G-L, McGinley JP, Drysdale SB, Pollard AJ. Epidemiology and immune pathogenesis of viral sepsis. Frontiers in immunology. 2018;9:2147.
4. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama. 2016;315:801-10.
5. Rello J, Valenzuela-Sánchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: a review of advances in management. Advances in therapy. 2017;34:2393-411.
6. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority—a WHO resolution. New England Journal of Medicine. 2017;377:414-7.
7. Pierrakos C, Vincent J-L. Sepsis biomarkers: a review. Critical Care. 2010; 14:1-18.
8. Coopersmith CM, De Backer D, Deutschman CS, Ferrer R, Lat I, Machado FR, et al. Surviving sepsis campaign: research priorities for sepsis and septic shock. Intensive Care Medicine. 2018;44: 1400-26.
9. Tipoe TL, Wu WK, Chung L, Gong M, Dong M, Liu T, et al. Plasminogen activator

inhibitor 1 for predicting sepsis severity and mortality outcomes: a systematic review and meta-analysis. Frontiers in immunology. 2018;9:1218.

10. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. Critical Care. 2019;23:1-9.
11. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. Journal of Intensive Care. 2014;2:1-8.
12. Koyama K, Madoiwa S, Nunomiya S, Koinuma T, Wada M, Sakata A, et al. Combination of thrombin-antithrombin complex, plasminogen activator inhibitor-1, and protein C activity for early identification of severe coagulopathy in initial phase of sepsis: a prospective observational study. Critical care. 2014;18:1-11.
13. Faix JD. Biomarkers of sepsis. Critical reviews in Clinical Laboratory Sciences. 2013;50:23-36.
14. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, et al. The timing of early antibiotics and hospital mortality in sepsis. American journal of respiratory and critical care medicine. 2017;196:856-63.
15. Samsudin I, Vasikaran SD. Clinical utility and measurement of procalcitonin. The Clinical Biochemist Reviews. 2017;38:59.
16. Gilbert DN. Procalcitonin as a biomarker in respiratory tract infection. Clinical Infectious Diseases. 2011;52:S346-S50.
17. Hoshino K, Kitamura T, Nakamura Y, Irie Y, Matsumoto N, Kawano Y, et al. Usefulness of plasminogen activator inhibitor-1 as a predictive marker of mortality in sepsis. Journal of Intensive Care. 2017;5:1-8.
18. Lorente L, Martín MM, Borreguero-León JM, Solé-Violán J, Ferreres J, Labarta L, et al. Sustained high plasma plasminogen activator inhibitor-1 levels are associated with severity and mortality in septic patients. Thrombosis Research. 2014;134: 182-6.
19. Okabayashi K, Wada H, Ohta S, Shiku H, Nobori T, Maruyama K. Hemostatic markers and the sepsis-related organ failure assessment score in patients with disseminated intravascular coagulation in an intensive care unit. American Journal of Hematology. 2004;76:225-9.
20. Wingeyer SDAP, Cunto ER, Nogueras CM, San Juan JA, Gomez N, de Larrañaga GF. Biomarkers in sepsis at time zero: intensive care unit scores, plasma measurements and polymorphisms in Argentina. The Journal of Infection in Developing Countries. 2012;6:555-62.
21. Shapiro NI, Schuetz P, Yano K, Sorasaki M, Parikh SM, Jones AE, et al. The association of endothelial cell signaling, severity of illness, and organ dysfunction in sepsis. Critical Care. 2010;14:1-12.
22. Seki Y, Wada H, Kawasugi K, Okamoto K, Uchiyama T, Kushimoto S, et al. A prospective analysis of disseminated intravascular coagulation in patients with infections. Internal Medicine. 2013;52: 1893-8.



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