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# Dehydroepiandrosterone sulfate to cortisol ratio as a prognostic factor in cirrhotic patients with spontaneous bacterial peritonitis

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## Abstract

**Background** Chronic liver disease and decompensated cirrhosis are associated with serious complications; spontaneous bacterial peritonitis is considered one of them that may lead to sepsis and adrenal insufficiency. This trial aimed to study the role of dehydroepiandrosterone sulfate (DHEAS) and DHEAS/cortisol ratio for assessing cirrhotic patients' adrenal function and as a possible prognostic factor in cirrhotic cases with spontaneous bacterial peritonitis (SBP).

**Patients and methods** It was a prospective cohort trial carried out on 100 patients in the Internal Medicine Department, Tanta University Hospital, from June 2021 to July 2022 divided into 2 studied patient groups: group I, 50 cases with liver cirrhosis and sterile ascites; and group II, 50 cases with liver cirrhosis and SBP. Adrenal function was evaluated using serum cortisol levels (9 A.M, 9 P.M, and post synacthen stimulation test), DHEAS level, and DHEAS/cortisol ratio.

**Results** The cirrhotic patients with SBP have significantly decreased DHEAS, decreased DHEAS/cortisol ratio, and high cortisol level post stimulation compared with patients with sterile ascites, cirrhotic cases with decreased DHEAS/cortisol ratio ( $<0.65$ ) had elevated C-reactive protein (CRP) levels, a higher model for end-stage liver disease (MELD) score and Child–Pugh score had higher hospital mortality. Both DHEAS and the DHEAS/cortisol ratio were significant predictors of hospital mortality (area under the receiver operating characteristic curve 0.267 and 0.298, respectively). The cirrhotic patients with SBP had decreased DHEAS and DHEAS/cortisol ratio but higher hospital mortality, compared to the cirrhotic patients with sterile ascites.

**Conclusions** It was found that a significant increase in cortisol level was after synacthen stimulation, decreased DHEAS, and low DHEAS to cortisol ratio in the cirrhotic patients with spontaneous bacterial peritonitis and was associated with high mortality compared to cirrhotic patients without spontaneous bacterial peritonitis.

**Keywords** Adrenal androgen, Dehydroepiandrosterone sulfate, Cortisol, Cirrhosis, Spontaneous bacterial peritonitis

## Introduction

Chronic liver disease and decompensated cirrhosis are the world's leading causes of death and morbidity, with mortality caused by liver cirrhosis accounting for 2.4% of the total deaths globally [1].

The most frequent complications include ascites, liver cirrhosis, spontaneous bacterial peritonitis (SBP) infection, gastrointestinal variceal hemorrhage, hepatorenal syndrome, hepatic encephalopathy, and hepatocellular

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carcinoma [2]. Due to its link with refractory shock and higher mortality, relative adrenal insufficiency (RAI), which is a condition characterized by insufficient cortisol production by the adrenal cortex, is increasingly identified in cirrhosis, specifically in critically ill cases [3, 4].

During critical illness, Androgen and glucocorticoid responses show a considerable variation with declining adrenal androgen levels and elevation in glucocorticoid levels, this is more prevalent among critically ill cases and non-survivors, stating that adrenal steroidogenesis' functional adaptation may deplete the counter-regulatory mechanisms between glucocorticoid and adrenal androgen, thus lead to the negative effect on the critical disease' prognosis. Elevated cortisol to DHEAS ratio was found in non-survivors [5, 6].

Cirrhosis and septic shock share several hemodynamic disturbances which include elevated pro-inflammatory cytokines levels including tumor necrosis factor alpha (TNF $\alpha$ ) and interleukin-1 [7, 8], which has a detrimental effect on the Hypothalamic pituitary adrenal axis. Other involved mechanisms are (1) TNF $\alpha$  lowers adrenocorticotrophic hormone (ACTH) secretion from the pituitary by competing with corticotropin-releasing hormone, (2) cytokines are responsible for lower high-density lipoprotein levels by inhibiting apo lipo I protein A1 synthesis causing a decreased substrate delivery to adrenal glands, and (3) coagulopathy due to cirrhosis could cause adrenal insufficiency due to adrenal hemorrhage [9, 10]. In the fast-evolving area of clinical hepatology, adrenal insufficiency is a relatively recent condition [11]. This trial aimed to study the role of dehydroepiandrosterone sulfate (DHEAS) and DHEAS/cortisol ratio for assessing adrenal function in cirrhotic cases and as a possible prognostic factor in cirrhotic cases suffering from SBP.

#### Patients and methods

This trial was a prospective cohort trial performed on 100 subjects; it was found that the age ranged between 40 and 80 years old and was classified into 2 groups: group I, 50 cases with liver cirrhosis and sterile ascites; and group II, 50 cases with liver cirrhosis and SBP at the Internal Medicine Department, Tanta University Hospitals, from June 2021 to July 2022.

The subjects were classified according to ascitic fluid analysis using a sample of 10 ml of ascitic fluid that was obtained and sent for clinical pathology assessment. SBP was diagnosed by the presence of polymorphonuclear leukocytes in ascitic fluid with more than 250 cells/C.C [12].

The patient's informed written permission was obtained. The trial was conducted after the Ethical Committee approval of Tanta University Hospitals in June 2021 (approval code: 34,727/6/21).

Exclusion criteria were a history of corticosteroid therapy, receiving steroidogenesis inhibiting agents (e.g., mitotane, etomidate, and metyrapone) during the preceding 6 months, hematemesis, melena, hepatorenal syndrome, hepatic encephalopathy or any cause of sepsis other than SBP (e.g., chest infection and urinary tract infection).

All cases underwent thorough history taking, complete clinical examination (vital signs and general signs of hepatic decompensation), abdominal examination, laboratory examination such as complete blood count (CBC), complete liver functions such as aspartate aminotransaminase (AST), alanine aminotransferase (ALT), international normalized ratio (INR) and prothrombin time (PT), serum albumin, total and indirect bilirubin, serum creatinine and urea, potassium, and sodium levels, and blood glucose level.

Liver disease severity was graded by the model for end-stage liver disease (MELD) [13] and the Child–Pugh system [14]. ICU patients' illness severity was evaluated by the Sequential Organ Failure Assessment (SOFA) [15] score and the quick Sequential Organ Failure Assessment (q SOFA) score [16, 17].

Specific investigations such as serum cortisol levels [9 A.M, 9 P.M, post synacthen stimulation test (a short corticotropin stimulation test was done within 24 h of admission synthetic ACTH (synacthen was given intravenously)], DHEAS level, and DHEAS/cortisol ratio were performed. Three blood samples were drawn from the patient on the day of admission.

The first blood sample was obtained at 9:00 A.M.; 7 ml of venous blood was investigated for routine lab, and serum cortisol level was measured at 9 A.M. by a competitive immunoassay that uses direct chemiluminescent technology (COBAS, Roche Diagnostics, Mannheim, Germany), while DHEAS was measured by (COBAS, Roche Diagnostics, Mannheim, Germany).

The second blood sample was obtained at 9:00 P.M.; 2 ml of venous blood was investigated for serum cortisol by a competitive immunoassay that uses direct chemiluminescent technology (COBAS, Roche Diagnostics, Mannheim, Germany) at 9:00 P.M. The third blood sample was obtained 30 min after post synacthen stimulation test.

In the first 24 h of admission, synacthen stimulation test was conducted. Synthetic ACTH (250  $\mu$ g, Synacthen; Novartis Pharma AG, Basel, Switzerland) was administered via the intravenous route. Blood samples were drawn immediately 30 min after injection. Post synacthen stimulation cortisol levels were measured by a competitive immunoassay that uses direct chemiluminescent technology (COBAS, Roche Diagnostics, Mannheim, Germany).

Routine imaging including chest X-ray and pelviabdominal ultrasound was performed.

**Statistical analysis**

IBM, IL, Chicago, USA, developed SPSS version 19 (Statistical Package for Social Studies) was utilized to evaluate the gathered data. The mean and standard deviation were determined for numerical variables. Using an unpaired Student’s *t*-test, the differences between the two mean values were employed. For categorical data, the number and percentage were determined, and the chi-square and Monte Carlo exact tests were used to examine differences across subcategories. Using Pearson’s correlation coefficient, the correlation between the two variables was obtained. Recipient – observe characteristic curve was utilized to determine the differential effect of DHEAS and DHEAS/Cortisol on hospitalization. The selected significance threshold was *p* < 0.05.

**Results**

Significant variation was found between the studied groups with their correlation with Child–Pugh score (*P* < 0.001). No significant variation was found between the studied groups regarding age, sex, MELD score, and morning and evening cortisol (Table 1).

No significant variation between the studied groups was found regarding hemoglobin, Total leucocytic count (TLC), platelets, ALT, AST, serum albumin, total bilirubin, direct bilirubin, serum creatinine, serum urea, and also no significant variation regarding serum potassium and serum sodium between studied groups. Group I had significantly lower INR, cortisol post-stimulation, and CRP compared to group II while having significantly elevated levels of DHEAS and DHEAS/cortisol ratio compared to group II (*P* < 0.05) (Table 2).

**Table 1** Age, sex distribution, and baseline data of studied groups (*n* = 100)

| Variables        |         | Group I (non-SBP) | Group II (SBP) | <i>P</i> -value |
|------------------|---------|-------------------|----------------|-----------------|
| Age (years)      |         | 61.54 ± 8.96      | 60.96 ± 9.89   | 0.938           |
| Sex              | Males   | 30 (60%)          | 26 (52%)       | 0.420           |
|                  | Females | 20 (40%)          | 24 (48%)       |                 |
| Child-Paugh      | A       | 2 (4%)            | 0 (0%)         | < 0.001*        |
|                  | B       | 33 (66%)          | 17 (34%)       |                 |
|                  | C       | 15 (30%)          | 33 (66%)       |                 |
|                  |         |                   |                |                 |
| MELD score       |         | 18.24 ± 4.8       | 20.30 ± 6.62   | 0.148           |
| Morning cortisol |         | 26.67 ± 9.41      | 22.65 ± 11.65  | 0.067           |
| Evening cortisol |         | 21.52 ± 9.29      | 19.53 ± 11.30  | 0.396           |

Data are presented as mean ± SD or frequency (%), \*: significant as *P* < 0.05. SBP spontaneous bacterial peritonitis, non-SBP non-spontaneous bacterial peritonitis, MELD a model for end-stage liver disease score

**Table 2** Comparison of laboratory findings among studied groups

| Variables  | Group I (non-SBP) | Group II (SBP) | <i>P</i> -value |
|--|-------------------|----------------|-----------------|
| Hemoglobin (g/dl)                                | 9.94 ± 1.99       | 9.24 ± 1.53    | 0.051           |
| TLC (c/mm <sup>3</sup> × 10 <sup>3</sup> )       | 11.20 ± 13.41     | 9.08 ± 4.54    | 0.293           |
| Platelets (c/mm <sup>3</sup> × 10 <sup>3</sup> ) | 148.44 ± 80.62    | 133.66 ± 59.68 | 0.300           |
| ALT (U/L)  | 49.20 ± 45.43     | 57.42 ± 98.46  | 0.593           |
| AST (U/L)  | 65.62 ± 50.87     | 84.80 ± 79.51  | 0.154           |
| Serum albumin (gm/dl)                            | 2.80 ± 0.52       | 2.73 ± 0.55    | 0.479           |
| INR  | 1.50 ± 0.38       | 1.74 ± 0.54    | 0.014*          |
| Total bilirubin (mg/dl)                          | 3.16 ± 5.61       | 3.76 ± 5.95    | 0.610           |
| Direct bilirubin (mg/dl)                         | 1.63 ± 4.00       | 1.91 ± 3.28    | 0.681           |
| Serum urea (mg/dl)                               | 87.24 ± 65.70     | 93.54 ± 59.29  | 0.616           |
| Serum creatinine (mg/dl)                         | 2.01 ± 1.30       | 2.10 ± 1.40    | 0.734           |
| Serum sodium                                     | 132.96 ± 7.73     | 133.30 ± 7.38  | 0.823           |
| Serum potassium                                  | 4.11 ± 0.92       | 3.81 ± 0.91    | 0.108           |
| Cortisol post stimulation                        | 28.03 ± 9.98      | 37.08 ± 12.65  | < 0.001*        |
| DHEAS  | 41.41 ± 17.64     | 23.10 ± 11.43  | < 0.001*        |
| DHEAS/cortisol                                   | 1.57 ± 0.64       | 0.64 ± 0.29    | < 0.001*        |
| CRP  | 12.56 ± 13.63     | 56.84 ± 36.29  | < 0.001*        |

Data are presented as mean ± SD

\*: significant as *P* < 0.05. SBP spontaneous bacterial peritonitis, non-SBP non-spontaneous bacterial peritonitis, TLC total leucocytic count, ALT alanine transaminase, AST aspartate transaminase, INR international normalized time, DHEAS dehydroepiandrosterone sulfate, CRP C-reactive protein

qSOFA score varied significantly between the studied groups (*P* < 0.001\*). Group II had significantly higher mortality compared to group I (*P* = 0.001) (Table 3).

DHEAS and DHEAS/cortisol ratio were significant predictors of hospital mortality. Both tests were found to be discriminatory as the area under the curve was significantly small (0.267 and 0.298, respectively) (*p* < 0.001 and 0.002, respectively). For DHEAS, the suggested cut-off

**Table 3** Comparison of quick SOFA score and hospital mortality among studied groups

| Variables     |       | Group I (non-SBP) | Group II (SBP) | <i>P</i> |
|---------------|-------|-------------------|----------------|----------|
| qSOFA score   | 0     | 11 (22%)          | 1 (2%)         | < 0.001* |
|               | 1     | 27 (54%)          | 11 (22%)       |          |
|               | 2     | 11 (22%)          | 15 (30%)       |          |
|               | 3     | 1 (2%)            | 23 (46%)       |          |
| ICU admission |       | 12 (24%)          | 38 (76%)       | 0.001*   |
| Fate          | Died  | 6 (12%)           | 21 (42%)       | 0.001*   |
|               | Alive | 44 (88%)          | 29 (58%)       |          |

Data are presented as frequency (%)

\*: significant as *P* < 0.05. SOFA Sequential Organ Failure Assessment score, SBP spontaneous bacterial peritonitis, non-SBP non-spontaneous bacterial peritonitis

value was 18.54 with a sensitivity of 63% and specificity of 22%. For the DHEAS/cortisol ratio, the suggested cut-off value was at 0.65 with a sensitivity of 63% and specificity of 25% (Table 4, Fig. 1).

Both SOFA and CRP showed a good negative significant correlation with the DHEAS/cortisol ratio (−0.432 and −0.472, respectively ( $P < 0.001$ )) (Table 5).

### Discussion

Chronic liver disease and decompensated cirrhosis are associated with serious complications like spontaneous bacterial peritonitis (SBP) infection, gastrointestinal variceal hemorrhage, hepatorenal syndrome, and hepatic encephalopathy [2], and these may lead to refractory shock and higher mortality and relative adrenal insufficiency (RAI). During critical illness [3, 4], Androgen and glucocorticoid responses show a decrease in adrenal androgen levels and an increase in glucocorticoid levels [5]. In this study, we assessed the role of dehydroepiandrosterone sulfate (DHEAS) and DHEAS/cortisol ratio in cirrhotic patients and as a possible prognostic factor in cirrhotic cases suffering from SBP.

In our study, a significant variation was found between the studied groups regarding DHEAS levels as the patients with sterile ascites showed the mean value of DHEAS was  $41.41 \pm 17.64$ , while in patients with SBP, the mean value was  $23.1 \pm 11.43$ .

This agreed with Wiebke A, Djillali A, et al. [7] with the healthy individuals having a mean value of DHEAS of  $57 \pm 11.7$ , while in patients with sepsis, the mean values were  $28 \pm 6.6$ .

We found that no significant variations were found between both studied groups regarding sociodemographic data (age and sex) as in our study the (group 1) cases with sterile ascites the mean value of the age was  $61.5 \pm 8.9$  and 60% were male, while in group 2, the mean age was  $60.9 \pm 9.89$  and 52% were male.

This was with Roxana E, Andra L, et al. [18] who showed that the patients without SBP had a mean value of the age of  $62.2 \pm 5.6$  and 65% were male while the patients with SBP had a mean value of age of  $59.2 \pm 9.8$  and 66% were male.

**Table 4** Recipient – observe characteristic curve (ROC) for DHEAS and DHEAS/cortisol as predictors for hospital mortality

| Variable                 | DHEAS   | DHEAS/cortisol |
|--------------------------|---------|----------------|
| The area under the curve | 0.267   | 0.298          |
| <i>P</i>                 | <0.001* | 0.002*         |
| Cut of value             | 18.54   | 0.65           |
| Sensitivity              | 63.0%   | 63.0%          |
| Specificity              | 22%     | 25.0%          |

\* : significant as  $P < 0.05$ , DHEAS dehydroepiandrosterone sulfate

**Table 5** Correlation between DHEAS/cortisol, SOFA, and CRP

| Variables  | DHEAS/Cortisol |          |
|------------|----------------|----------|
|            | r/rho          | <i>P</i> |
| SOFA score | −0.432         | <0.001*  |
| CRP        | −0.472         | <0.001*  |

CRP C-reactive protein, SOFA Sequential Organ Failure Assessment score

\* : significant as  $P < 0.05$

In this study, the Child–Pugh score of patients with sterile ascites was as follows, score B was 66% and score C was 30% while in patients with SBP, there were 34% and 66% for score B and score C, respectively.

This was in argument with Thomas E et al. [19] who showed that the patient with SBP was 26% and 72% for scores B and C, respectively.

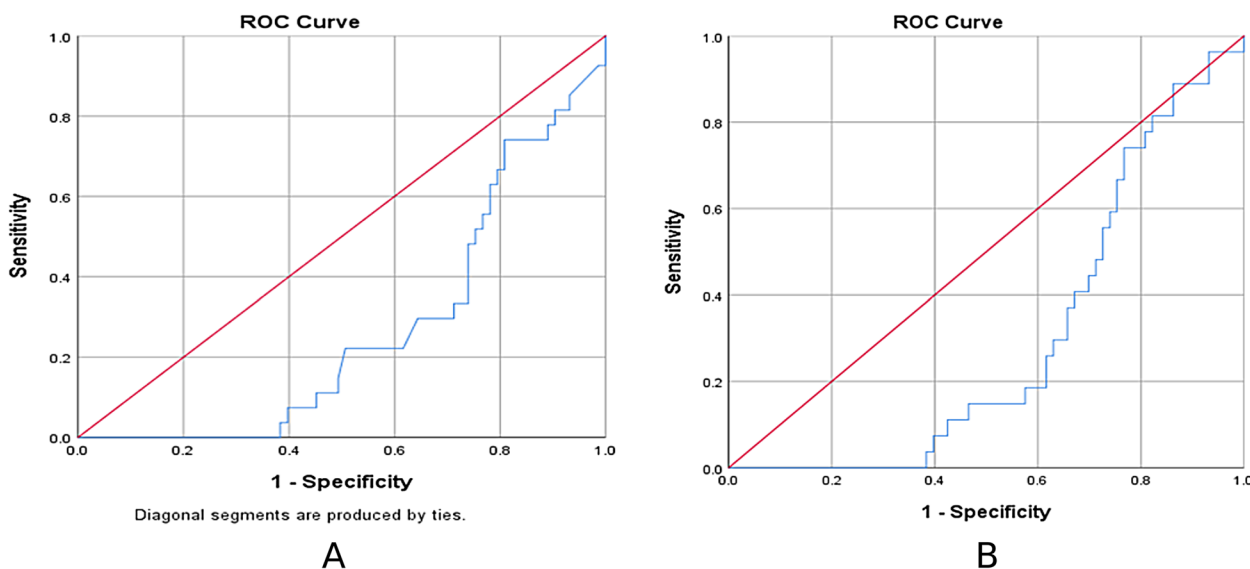
We found that no significant variation was found between the studied groups regarding MELD score as the patients with sterile ascites showed a mean value of MELD score of  $18.2 \pm 7.48$ , while in patients with SBP, there was  $22.65 \pm 11.65$ .

This agreed with Keith L et al. [20] who reported that sterile ascites cases had a mean value of MELD score of 18 while in SBP cases it was 24.1.

In our study, the liver enzymes of the patients with sterile ascites showing mean values of AST and ALT were  $65.6 \pm 50.87$  and  $49.2 \pm 45.43$ , respectively, while in patients with SBP, there were  $84.8 \pm 79.51$  and  $57.4 \pm 89.46$ , respectively, and there were insignificant.

This was with Roxana E, Andra L, et al. [18] who showed that the mean values of AST and ALT in patients with sterile ascites were  $77.03 \pm 50.9$  and  $44.7 \pm 30.7$ , respectively, while in patients with SBP, there were  $78.32 \pm 50.7$  and  $46.9 \pm 20.7$ , respectively, but against Khaled M, Tamer F et al. [21] who showed that the patients with sterile ascites were with the mean values of AST and ALT was 62.5 and 63.8, respectively, while in patients with SBP, there were 153.7 and 85.4.

We showed that relative adrenal insufficiency is associated with significantly elevated inflammatory markers and significantly decreased DHEAS/cortisol ratio levels, disease severity assessed by MELD score and Child–Pugh score, and hospital mortality. Also, the DHEAS/cortisol ratio had significant hospital survival predictability in cirrhotic cases with a sepsis-like SBP, suggesting that these two hormones (cortisol and DHEAS) should be measured to reflect adrenal dysfunction. Even though low doses administration of glucocorticoid in septic cases can reverse the shock status and restore vascular hyperreactivity [22], its influence on survival remains questionable [23]. In fact, higher rates of infections and severe hyperglycemia are linked to glucocorticoid administration [24,



**Fig. 1** **A** ROC curve for DHEAS as a predictor for hospital mortality. **B** ROC curve for DHEAS/cortisol as a predictor for hospital mortality

25]. DHEAS has been reported to boost immunity and aid to escape glucocorticoid’s catabolic effects [26].

In our trial, there was significant variation between the study groups regarding CRP levels as the patients with sterile ascites showed a mean value of CRP was  $12.56 \pm 13.63$ , while in patients with SBP, the mean value was  $56.84 \pm 36.2$ .

This was concurrent with Radwan A, Mostafa I [27] who reported that the mean value of CRP in cirrhotic cases with sterile ascites was  $12.32 \pm 11.8$ , while in cirrhotic patients with SBP, the mean value was  $65.69 \pm 30.7$ .

In our study, it showed significant variation between the studied groups regarding the mortality rate in cases with sterile ascites showing that the mortality rate was 12% while in patients with SBP, there was 42%.

This was in argument with Tsung H, Chen T, et al. [28] who showed that the patients with sterile ascites with a mortality rate of 14% on the other hand in patients with SBP there was 24% also our result was against Raim Iliaz et al. [29] that shows the mortality rate 26.1% in patient with SBP.

The leading causes of death were the development of hepatorenal syndrome type 1, severe sepsis due to spontaneous bacterial peritonitis, respiratory failure, and anemic heart failure due to chronic anemia.

A dissociation was found between post stimulation cortisol (increased) and DHEAS (reduced) upon ICU admission, especially in non-survivors of the cirrhotic group with SBP, suggesting a functional adrenal steroidogenesis adaptation in this subgroup due to SBP.

Finally, upon ICU admission, a low DHEAS/cortisol ratio is linked with critical illness and hospital mortality. In this clinical situation, the DHEAS/cortisol ratio can be utilized as a prognostic indicator [30].

**Conclusions**

We finally concluded that there was a significant increase in post stimulation cortisol levels, decreased DHEAS, and low DHEAS to cortisol ratio in the cirrhotic patients with spontaneous bacterial peritonitis that was associated with high mortality compared to cirrhotic patients without spontaneous bacterial peritonitis.

**Abbreviations**

|              |   |
|--------------|---|
| SBP          | Spontaneous bacterial peritonitis           |
| RAI          | Relative adrenal insufficiency              |
| DHEAS        | Dehydroepiandrosterone sulfate              |
| TNF $\alpha$ | Tumor necrosis factor alpha                 |
| ACTH         | Adrenocorticotrophic hormone                |
| CBC          | Complete blood count                        |
| AST          | Aspartate aminotransaminase                 |
| ALT          | Alanine aminotransferase                    |
| INR          | International normalized ratio              |
| PT           | Prothrombin time                            |
| MELD         | Model for end-stage liver disease           |
| ICU          | Intensive care unit                         |
| SOFA         | Sequential Organ Failure Assessment         |
| q SOFA       | Quick Sequential Organ Failure Assessment   |
| SPSS         | Statistical Package for the Social Sciences |
| TLC          | Total leucocytic count                      |
| CRP          | C-reactive protein                          |
| ROC          | Recipient – observe characteristic curve    |

**Acknowledgements**

None.



**Protocol registration**

The patient's informed written permission was obtained. The trial was conducted after the Ethical Committee approval of Tanta University Hospitals in June 2021 (approval code: 34,727/6/21).

**Authors' contributions**

Each author took part in the idea and design of the research. Preparation of materials and gathering and analysis of data were carried out by Mohamed Ramadan Asker, Loai Mohamed Elahwal, and Sahar Mohy-Eldin Hazzaa. The initial draught of the manuscript was written by Shireen Ali Elhoseeny and Mohamed Elsayed Sarhan. All authors provided feedback on earlier versions of the manuscript. The final manuscript was reviewed and approved by all authors.

**Funding**

No funding was received for this research.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available as MS Excel files from the corresponding author upon reasonable request.

**Declarations****Ethics approval and consent to participate**

The patient's informed written permission was obtained. The trial was conducted after the Ethical Committee approval of Tanta University Hospitals in June 2021 (approval code: 34727/6/21).

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

Received: 26 May 2023 Accepted: 9 October 2023

Published online: 16 October 2023

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