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Serum Soluble Triggering Receptor Expressed on Myeloid Cells -1 as a Diagnostic and Prognostic Marker in Neonatal Ventilator-Associated Pneumonia

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Abstract

Background: Neonatal ventilator associated pneumonia (NVAP) is a major hospital-acquired infection in acute care settings, associated with high mortality and poor outcome. Myeloid cell trigger receptor-1 (TREM-1) is a member of the immunoglobulin super receptor family mainly expressed on the surface of myeloid cells such as neutrophils and monocytes/ macrophages. Soluble TREM- 1 (sTREM-1), is a TREM-1 subtype that has been reported as a novel and strong indicator of pneumonia.

Aim of Study: The Primary objective is to assess the value of sTREM- las a diagnostic and a prognostic marker in NVAP and the Secondary Objective is to compare between sTREM-1 and CRP specificity and sensitivity.

Subjects and Methods: This was a case-control study in the NICU at Children's Hospital, Ain Shams University, Cairo, Egypt (6 months duration). This study was carried out on 50 cases devided into two groups each included 25 cases: Group A: Ventilator associated pneumonia (VAP) in neonates (cases). Group **B:** Age and sex matched neonates diagnosed with respiratory distress syndrome other than pneumonia and not ventilated (controls). The randomization was based on odd or even numbers of patient files number.

Result: Regarding Day 1 sTREM-1, AUC was 0.942, Cutoff value was 112.55, Sensitivity was 92% and Specificity was 16%. Regarding Day 4 sTREM-1, AUC was 0.931, Cutoff value was 123.8, Sensitivity was 88% and Specificity was 80%. Regarding Day 1 CRP, AUC was 0.534, Cutoff value was 3.9, Sensitivity was 64% and Specificity was 44%. Regarding Day 4 CRP, AUC was 0.640, Cutoff value was 4.7, Sensitivity was 68% and Specificity was 40%.

Conclusion: sTREM-1 is as a diagnostic and prognostic indicator in ventilator-associated pneumonia for newborn. Comparison of sTREM-1 and C-reactive protein in terms of accuracy and sensitivity. STREM-1 has shown it to be more specific and sensitive than C-reactive protein (CRP).

Key Words: Serum Soluble Triggering Receptor Expressed — Myeloid Cells -1 — Neonatal Ventilator-Associated Pneumonia.

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Introduction

NEONATAL ventilator associated pneumonia (NVAP) is a major hospital-acquired infection in acute care settings, associated with high mortality and poor outcome [1]. It is defined as a nosocomial lower airway infection in intubated patients with an onset after 48 hours or more of invasive mechanical ventilation **[2].**

NVAP is a major source of increased length of hospitalization, illness, and death, with a mortality rate of 20-30%. The early diagnosis of NVAP remains a challenge because clinical signs and radiological manifestations are non-specific, and tissue culture as the gold standard of diagnosis is time consuming, invasive and easily contaminated [3].

The lack of a diagnostic gold standard has a negative impact on research for the prompt management of VAP in the direction of prevention and appropriate antibiotic use **[4].**

Myeloid cell trigger receptor-1 (TREM-1) is a member of the immunoglobulin super receptor family mainly expressed on the surface of myeloid cells such as neutrophils and monocytes/macrophages. Soluble TREM-1 (sTREM-1), is a TREM-1 subtype that has been reported as a novel and strong indicator of pneumonia [3].

It has been used as a marker for identifying infection and assessing inflammation severity in adult patients with ventilator-associated pneumonia (VAP) **[2].**

The serum sTREM-1 concentration was found to be a reliable biomarker for the prediction of NVAP [3].

Aim of the work:

Primary objective: To assess the value of sTREM- 1 as a diagnostic and a prognostic marker in NVAP.

Secondary objective: To compare between sTREM-1 and CRP specificity and sensitivity in NVAP.

Patients and Methods

This was a case control study that was performed during the period from December 2022 to march 2023 at NICU at Children's Hospital, Ain Shams University through 6 months.

Study population: This study was carried out on 50 cases devided into two groups each included 25 cases:

- Group A: Ventilator associated pneumonia (VAP) in neonates (cases).
- Group B: Age and sex matched neonates diagnosed with respiratory distress syndrome other than pneumonia and not ventilated (controls).

The randomization was based on odd or even numbers of patient files number.

Selection criteria for cases: Inclusion criteria: All newborns (including preterm and full-term) with mechanical ventilation initiation within 48 hours of birth meeting the following criteria were included:presence of respiratory distress syndrome (RDS), presence of congenital pneumonia, history of meconium aspiration and congenital heart diseases. Ventilator associated pneumonia (VAP) was diagnosed based on the presence of a new persistent infiltrate on chest radiograph and at least two of the following: Fever of -38°C, leucopenia (<4000 white blood cells (WBC)/mm^3) or leukocytosis (>_12,000 WBC/mm3) and worsening gas exchanged (Pa02/ Fi02 <240). Exclusion Criteria: Neonates with the following were excluded from the study: Surgical problem related to the respiratory system and chromosomal abnormalities such as down syndrome.

Sample size: Using PASS 11 program for sample size calculation, setting power at 80% and a error at 5%, it is estimated that 40 cases (20 cases of ventilatorassociated pneumonia (VAP) in neonates and 20 cases of controls) were required to detect an expected the area under the curve (AUC) = 0.902 for the predictive ability of STREM-1 at 72 hours for NVAP regarding Zhao et al. [3]. Assuming the dropout rate is 15%, the total needed sample size is at least 50 Case (25 case per group).

Methods: All the neonates at this study were subjected to: (1) Comprehensive history taking that include: Antenatal history: Maternal age, maternal gravidity and parity, maternal disease (diabetes and hypertension), maternal diabetic control, maternal infection, maternal medication during this pregnancy, last menstrual period. Obstetric history: In the form of problems during delivery and premature rupture of membrane. Natal history: Gestational age, neonatal sex and date of birth. Postnatal history: Respiratory distress and cyanosis, resuscitation data and Apgar score. Family history: congenital anomalies, previous abortion, sibling death and still birth. (2) Clinical examination for neonates: General examination including vital data (respiratory rate, blood pressure, heart rate & body temperature) and local examination including abdominal, chest, heart, and neurological examination. (3) Radiological study: X-rays, sonar (cranial or abdominal) and Echo were done according to the cases. (4) Laboratory investigations: All the following investigations were done to all neonates involved in the study: Complete blood count (CBC) at day 1 of suspected pneumonia and day 4 from initiation of treatment: For the measurement of haemoglobin, total leucocytic count (TLC) and platelets levels. 5m1 of venous blood were collected from the newborn and was analysed on XN-1000 SYSMEX (Sysmex Europe GmbH., Bornbarch 1,22848 Norderstedt, Germany)

Test principle for haemoglobin measurement on XN-1000 SYSMEX: Using cyanide-free sodium lauryl sulphate (SLS) detection method. SLS haemoglobin detection method uses cyanide-free sodium lauryl sulphate (SLS). By the reagent lyses red blood cells and white blood cells in the sample. The chemical reaction begins by altering the globin and then oxidising the haem group. Now the SLS' hydrophilic groups can bind to the haem group and form a stable, coloured complex (SLS-HGB), which is analysed using a photometric method and A LED sends out monochromatic light and by moving through the mixture light is absorbed by the SLS-HGB complexes. The absorbance is measured by a photo sensor and is proportional to the haemoglobin concentration of the sample.

Test principle for haematocrit (HCT), red blood cell count (RBC), mean corpuscular volume (MCV), platelets and white blood cell count (WBCs) measurement on XN-1000 SYSMEX:impedance technology, cells traversing an aperture through which an electric current is flowing create electric resistance, and are counted and measured as pulses. While number of pulses indicate particle count, their amplitude reflect cell size and that is called electric "impedance principle". In such instruments patient sample is divided between two channels, one for counting white blood cells and platelets, while the other channel is for determining the hemoglobin and red blood cell counts.

The RBC, HCT and MCV are all closely interrelated as they are derived from information obtained from the passage of cells through the aperture of the impedance channel of an automated haematologyanalyser. The impedance technology is based on the principle that an electrical field, created between two electrodes of opposite charge, can be used to count and determine the size of cells. Blood cells are poor conductors of electricity. The diluent in which they are suspended as they pass through the aperture during counting is an isotonic solution which is a good conductor of electricity.

Consequently, when the cells suspend in the diluent pass through the aperture between the electrodes, each individual cell will momentarily increase the impedance (resistance) of the electrical path between the electrodes. Each cell generates an electrical pulse, in proportion to its size.

WBCs were further examined by Leishman-stained smears for differential white blood cell (WBC) count.

Test principle for MCH on XN-1000 SYSMEX: MCH is calculated using the red blood cell analysis. MCH is calculated by dividing the amount of hemoglobin in a given volume of blood by the number of red blood cells present.

Test principle for MCHC on XN-1000 SYSMEX: It can be calculated by dividing the hemoglobin (in g/L) by the RBC count. MCHC measures the average concentration of hemoglobin in the RBCs, and is calculated by dividing the hemoglobin by the hematocrit. Like hemoglobin, the MCHC is reported in g/dL. MCHC (g / dL) = hemoglobin + hematocrit.

Test principle for RDWonXN-1000 SYSMEX: RBC distribution width is the variation in the size of the red blood cells RDW is usually calculated by dividing the standard deviation (SD) of the mean corpuscular volume (MCV) by the MCV and multiplying by 100 to yield a percentage value to be on behalf of the RBC size heterogeneity.

C-reactive protein (CRP) at day 1 of suspected pneumonia and day 4 from initiation of treatment:CRP was assayed by immunoturbidimetric method and was done using Roche/Hitachi Cobas il) c311 System (Roche Diagnostics International Ltd., Switzerland).

Test principle: Immunoturbidimetry is a simple method where direct interaction between an antigen and an antibody is measured by changing solution turbidity for CRP.

Blood culture and sensitivity at day 1 of diagnosis: For all neonates will be withdrawn on admission, before starting the antibiotic therapy or at the trough level, 30 minutes before the next dose. Two samples were withdrawn simultaneously from 2 different sites, 1-3m1 blood each on BACTEC-Peds automated blood culture bottles under complete aseptic conditions.

Test principle: Blood samples were collected for bacterial culture in blood culture bottles (BACTEC Peds P1usTM /F, Becton Dickinson, Europe, meylan, France) by vein puncture. The BACT/ALERT 3D instrument is an automated microbial detection system in which blood culture bottles are incubated. After incubation for 2-7 days at 37°C, samples with positive bacterial growth showed a positive signal. Samples with positive growth will be further cultivated on blood, Maconkey& chocolate agar plates (Oxoid, England) and identification of isolated organisms from blood specimens was done by macroscopical, microscopical and biochemical examination.

Serum soluble triggering receptor expressed on myeloid cell-1 (STREM-1) assay using a commercial ELISA kit: Serum samples were collected from all neonates involved in study at day 1 of suspected pneumonia and day 4 from initiation of treatment, and centrifugated for 20 minutes at speed of 2000-3000 R.P.M, then stored at —80°C till the time of analysis, using quantitative human Enzyme Linked Immunosorbent Assay (ELISA Kit, (Cat.No E0310Hu) (202 5/F 2 Bldg, 501 Changsheng S Rd, NanhuDist, Jiaxing, Zhejiang, China).

Samples were analyzed on Thermo Scientific Multiskan FC (Life Technologies Holdings Pte. Ltd, a part of Thermo Fisher Scientific Inc., 33, Marsiling Industrial Estate Road 3, #7-06, Singapore 739256).

Test principle for STERM-1 assay: This assay employs the quantitative double-antibody sandwich enzyme-linked immunoassay technique (ELISA) to assay STERM-1 marker in samples. Monoclonal antibodies specific for STERM-1 have been pre-coated onto a microplate. Standards and samples were pipetted into their corresponding wells, and the immobilized antibody bound any STERM-1 present. After removing any unbound substances, a biotin-conjugated antibody specific for STERM-1 was added to the wells. After washing, streptavidin conjugated Horseradish Peroxidase (HRP) was added to the wells. A substrate solution was added to the wells following a wash to remove any unbound streptavidin-HRP reagent. The color developed in proportion to the amount of STERM-1 bound in the initial step. The color development was stopped, and the intensity of the color was measured by spectrophotometry at wavelength 450nm. The concentrations of STERM- lin the samples were calculated by plotting the optical density of the samples on the standard curve (Table 1).

Table (1): Material provided in STERM-1 kit.

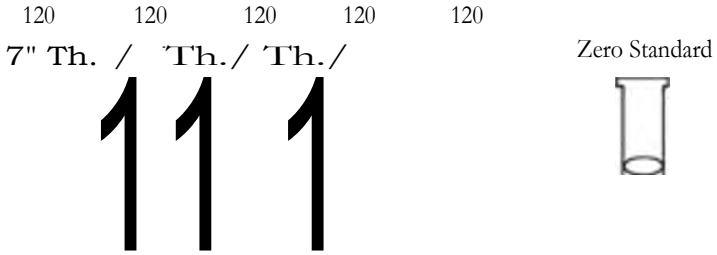
Components	Quantity (96T)	Quantity (48T)
Standard solution (240Ong/L)	0.5ml xl	0.5ml xl
Pre-coated ELISA plate	12 * 8 well strips xl	12 * 4 well strips xl
Standard diluent	3m1x1	3mlxl
Streptavidin-HRP	6m1x1	3mlxl
Stop solution	6m1x1	3mlxl
Substrate solution A	6m1x1	3mlxl
Substrate solution B	6m1x1	3mlxl
Wash buffer Concentrate (25x)	20m1 xl	20m1 xl
Biotinylated Human TREM1 antibody	1ml xl	1ml xl
User instruction	*1*	*1*
Plate sealer	2 pics	2 pics

Reagent preparation: All reagents were brought to room temperature at 25°C before use for 30min and standard dilution: The original standard reagent was diluted according to the instructions.

Standard dilution: The 120111 of the standard (2400pg/ml) with 120111 of standard diluent to generate a 1200ng/L standard stock solution. The standard was allowed to sit for 15mins with gentle agitation prior to making dilutions. Duplicate standard points were prepared by serially diluting the standard stock solution (1200ng/L) 1:2 with standard diluent to produce 600ng/L, 300ng/L, 15Ong/L and 75ng/L solutions. Standard diluent serves as the zero standard (Ong/L). Dilution of standard solutions suggested are as Table (2).

Table (2): Standard dilution of STREM-1.

1200pg/mL	Standard No.5	120u1 Original standard + 120u1 Standard diluent
600pg/mL	Standard No.4	120u1 Standard No.5 + 120u1 Standard diluent
300pg/mL	Standard No.3	120u1 Standard No.4 + 120u1 Standard diluent
150pg/mL	Standard No.2	120u1 Standard No.3 + 120u1 Standard diluent
75pg/mL	Standard No.1	120u1 Standard No.2 + 120u1 Standard diluent



Standard concentration	Standard No.5	Standard No.4	Standard No.3	Standard No.2	Standard No.1
2400pg/m1	1200pg/m1	600pg/m1	300pg/m1	150pg/m1	75pg/m1

Assay procedure: All samples were brought to room temperature before starting the assay.

Inject samples: a. Blank well: In which chromogen solutions A and B, and stop solutions are added. b. Standard wells: 50p1 of the standard and 50p1 Streptavidin-HRP are added (since the standard already has combined biotin antibody, it was not necessary to add antibody). c. Test wells: 40111 of each sample was added and then 10111 of progranulin-antibody and 50p1 of Streptavidin-HRP were added. The wells were then sealed by a sealing membrane, gently shaken and incubated for 60 minutes at 37°C.

Washing: The membrane was removed carefully and the liquid was drained and the remaining water was shaken-away.

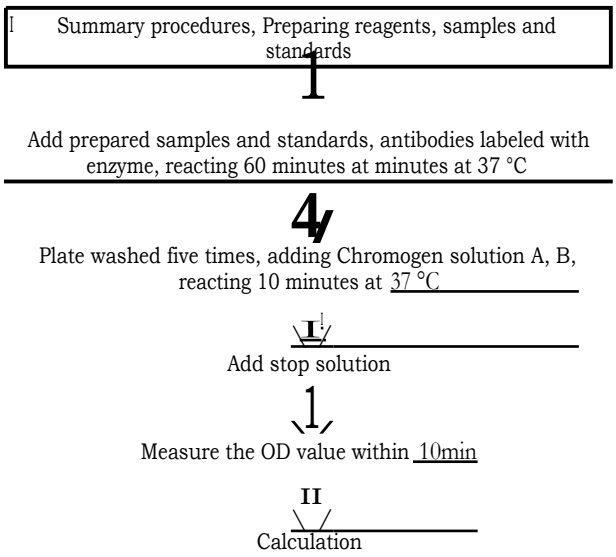
A 50p1 of chromagen A was added, then 50p1 of chromogen solution B was added to each well. Gently mixed and incubate for 10min at 37°C away from light.

50p1 of the stop solution was added into each well to stop the reaction (the blue color changed into yellow immediately).

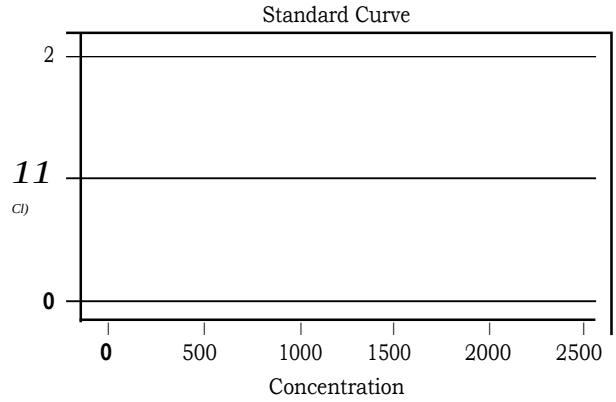
Final measurement: The blank well was taken as zero, the optical density (OD) under 450nm wavelength was measured within 15min after adding the stop solution.

According to standards' concentration and the corresponding OD values, the standard curve linear regression equation was calculated out, and the OD values of each sample were applied on the regression equation to calculate the corresponding sample's concentration. The detection ranges were from 5pg/mL to 2000pg/mL for STERM-1 assay.

Summary of the procedure:



Calculation of result:the standard density was taken as the horizontal and the OD value for the vertical then the standard curve was drawn on graph paper. The corresponding density was indicated according to the sample OD value by the Sample curve (the result is the sample density). The straight-line regression equation of the standard curve was calculated with the standard density and the OD value, with the sample OD value in the equation, the sample density was calculated.



Ethical consideration: The study was conducted after approval of the Research Ethics Committee of Ain Shams University Hospitals and informed consent was collected from patients' parents or caregivers approval to use the data.

Statistical analysis: The data were collected and statistically analyzed using statistical package for social science (SPSS 27), suitable statistical tests will be used according to the type of data and data were expressed as number and percentage for qualitative variables and mean ± standard deviation (SD) for quantitative one.

Level of significance: p-value of >0.05 indicates non-significant results and p-value of <0.05 indicates significant results.

Results

Table (1) showed Demographic data among the study groups. Regarding Gestational age (weeks), There was no statistical significant difference between the two studied groups (p=0.754). Regarding Sex, There was no statistical significant difference between the two studied groups (p=0.765).

Table (1): Demographic data among the study groups.

	Group A (n=25)	Group B (n=25)	Test of Sig.	*P*
Gestational age (weeks):				
Full term (37-41 weeks)	6 (24%)	5 (20%)	X^2 = 1.197	0.754
Late preterm (33-36 weeks)	9 (36%)	8 (32%)		
Preterm (28-32 weeks)	10 (40%)	11 (44%)		
Post term (42 weeks)	0 (0%)	1 (4%)		
Sex:				
Male	16 (64%)	17 (68%)	X^2 = 0.089	0.765
Female	9 (36%)	8 (32%)		

x2: Chi- Square test.
p : p-value for comparing between the studied groups.
p-value >0.05 : Non significant.
p-value <0.05 : Significant.
p-value <0.001: Highly significant.

Table (2) showed Clinical data among the study groups. Regarding Birth weight (gm), There was no statistical significant difference between the two studied groups (p=0.264). Regarding Maternal condition, There was no statistical significant difference between the two studied groups (p43.965). Regarding Type of delivery, There was no statistical significant difference between the two studied groups (p=0.637).

Table (3) showed vital data among the study groups. Regarding Temperature, There was a significant difference between the two studied groups (p43.017). Regarding RR, There was no statistical significant difference between the two studied groups (p=0.068). Regarding Heart rate, There was a significant difference between the two studied groups (p=0.001).

Table (4) showed Medication usage among the study groups. Regarding Surfactant, There was no statistical significant difference between the two studied groups (p43.684). Regarding TPN, There was no statistical significant difference between the two studied groups (p=0.684). Regarding Sedative use, There was no statistical significant difference between the two studied groups (*p*= 0.069).

Table (2): Clinical data among the study groups.

	Group A (n=25)	Group B (n=25)	Test of Sig.	p
Birth weight (gm):				
Normal	8 (32%)	7 (28%)	X^2=2.667	0.264
Low birth weight	10 (40%)	15 (60%)		
Very low birth weight	7 (28%)	3 (12%)		
Maternal condition:				
No Risk	12 (48%)	11 (44%)	X^2 1;1.586	0.965
PROM	5 (20%)	5 (20%)		
Gestational DM	2 (8%)	3 (12%)		
Pre-clampsia	3 (12%)	2 (8%)		
Multiple gestation	3 (12%)	4 (16%)		
Type of delivery:				
Vaginal	3 (12%)	2 (8%)	X^2 1:1.222	0.637
Caesarean section	22 (88%)	23 (92%)		

x2: Chi- Square test.
p : p-value for comparing between the studied groups.
p-value >0.05 : Non significant.
p-value <0.05 : Significant.
p-value <0.001: Highly significant.

Table (3): Vital data among the study groups.

	Group A (n=25)	Group B (n=25)	Test of Sig.	p
Temperature:				
Normal	4 (16%)	13 (52%)	X^2=8.193	0.017
Hypothermia	12 (48%)	9 (36%)		
Hyperthermia	9 (36%)	3 (12%)		
RR:				
Normal	1 (4%)	7 (28%)	X^2=5.369	0.068
Tachypnea	19 (76%)	14 (56%)		
Apnea	5 (20%)	4 (16%)		
Heart rate:				
Normal	5 (20%)	18 (72%)	X^2=15.183	0.001
Tachycardia	12 (48%)	2 (8%)		
Bradycardia	8 (32%)	5 (20%)		

x2: Chi- Square test.
p : p-value for comparing between the studied groups.
p-value >0.05 : Non significant.
p-value <0.05 : Significant.
p-value <0.001: Highly significant.

Table (4): Medication usage among the study groups.

	Group A (n=25)	Group B (n=25)	Test of Sig.	p
Surfactant	3 (12%)	4 (16%)	X^2 1;1.166	0.684
TPN	21 (84%)	22 (88%)	X^2 1;1.166	0.684
Sedative use	11 (44%)	5 (20%)	X^2=3.309	0.069

x2: Chi- Square test.
p : p-value for comparing between the studied groups.
p-value >0.05 : Non significant.
p-value <0.05 : Significant.
p-value <0.001: Highly significant.

Table (5) showed Outcome results among the study groups. Duration of ventilation (d) in Group A ranged from 20 to 31 with mean ± SD = 25.48±3.1 while in Group B the Duration of ventilation (d)ranged from 8 to 14 with mean ± SD = 10.92±1.44 with highly statistical significant difference (p=<.001) between the two groups. Duration of hospital stay (d) in Group A ranged from 28 to 49 with mean ± SD = 39.72±4.81 while in Group B the Duration of hospital stay (d) ranged from 17 to 26 with mean ± SD = 21.16±2.56 with highly statistical significant difference (p=<.001) between the two groups. Regarding Mortality rate, There was a significant difference between the two studied groups (p=0.004).

Table (5): Outcome results among the study groups.

	Group A (n=25)	Group B (n=25)	Test of Sig.	p
Duration of ventilation (d):				
Mean ± SD	25 .48±3 .1	10.92±1.44	*t*=	<0.001
Median (IQR)	25 (23-27)	11 (10-12)	21.311	
Range (Min-Max)	11 (20-31)	6 (8-14)		
Duration of hospital stay (d):				
Mean ± SD	39 .72±4.81	21.16±2.56	*t*=	<0.001
Median (IQR)	41 (36-43)	21 (19-22)	17.033	
Range (Min-Max)	21 (28-49)	9 (17-26)		
Mortality rate:				
Died	16 (64%)	6 (24%)	X^2=	0.004
Survived	9 (36%)	19 (76%)	8.117	

x2: Chi-Square test. SD : Standard deviation.
t: Independent t-test. IQR: Interquartile range.
p : p-value for comparing between the studied groups.
p-value >0.05 : Non significant.
p-value <0.05 : Significant.
p-value <0.001: Highly significant.

Table (6) showed Day 1 Lab results among the study groups. Day 1 CRP in Group A ranged from 1.2 to 157 with mean ± SD = 53.24±37.05 while in Group B the Day 1 CRP ranged from 0.3 to 189 with mean ± SD = 22.56±43.84 with statistical significant difference (p=0.01) between the two groups. Day 1 TLC in Group A ranged from 5.5 to 66 with mean ± SD = 17.47±15.49 while in Group B the Day 1 TLC ranged from 6.5 to 57 with mean ± SD = 14.27±10.55 with no statistical significant difference (p=0.398) between the two groups.

Table (7) showed Day 4 Lab results among the study groups. Day 4 CRP in Group A ranged from 2.4 to 192 with mean ± SD = 47.57±50.93 while in Group B the Day 4 CRP ranged from 0.5 to 148 with mean ± SD = 18.61±33.53 with statistical significant difference (p=0.022) between the two groups. Day 4 TLC in Group A ranged from 3 to 19.4 with mean ± SD = 10.18±4.97 while in Group

B the Day 4 TLC ranged from 1.4 to 66 with mean ± SD = 16.72±16.03 with no statistical significant difference (p43.061) between the two groups.

Table (8) showed sTREM-1 Elisa test results among the study groups. day 1 sTREM-1 in Group A ranged from 93.63 to 1380 with mean ± SD = 633.58±488.49 while in Group B the day 1 sTREM-lranged from 11.2 to 136.2 with mean ± SD = 86.53±30.81 with highly statistical significant difference (p=<.001) between the two groups. Day 4 sTREM-1 in Group A ranged from 84.3 to 1518 with mean ± SD = 648.27±505.08 while in Group B the Day 4 sTREM-lranged from 12.3 to 149.8 with mean ± SD = 87.14±32.73 with highly statistical significant difference (p=<.001) between the two groups.

Table (9) showed Logistic regression with odds ratios and 95% confidence intervals (CI) predicting mortality rate. Odds ratio of Gestational age (Preterm group) was 0.088, with a significant logistic regression relationship between the two variables (p43.001). Odds ratio of Duration of ventilation (days) was 1.193, with a highly significant logistic regression relationship between the two variables (p<0.001). Odds ratio of Duration of hospital stay (days) was 1.161, with a highly significant logistic regression relationship between the two variables (p<0.001).

Table (10) showed Sensitivity and Specificity of day 1 and day 4 sTREM-1 to predict NVAP. Regarding Day 1 sTREM-1, AUC was 0.942, Cutoff value was 112.55, Sensitivity was 92% and Specificity was 84%. Regarding Day 4 sTREM-1, AUC was 0.931, Cutoff value was 123.8, Sensitivity was 92% and Specificity was 80%.

Table (11) showed Sensitivity and Specificity of day 1 and day 4 CRP to predict NVAP. Regarding Day 1 CRP, AUC was 0.534, Cutoff value was 3.9, Sensitivity was 64% and Specificity was 56%. Regarding Day 4 CRP, AUC was 0.640, Cutoff value was 4.7, Sensitivity was 68% and Specificity was 60%.

Table (6): Day 1 lab results among the study groups.

	Group A (n=25)	Group B (n=25)	Test of Sig.	*p*
Day 1 Blood culture:				
Staph	1 (4%)	0 (0%)	X^2 = 2.083	0.353
Klebsiella	1 (4%)	0 (0%)		
No	23 (92%)	25 (100%)		
Day 1 CRP:				
Mean ± SD	5324±37.05	22.56±43.84	*t* = 2.672	0.01
Median (IQR)	66 (18-72)	3 (12-16.7)		
Range (Min-Max)	155.8 (1.2-157)	188.7 (0.3-189)		
Day 1 TLC:				
Mean ± SD	17 .47±15 .49	1427±10.55	*t* = 0.855	0.398
Median (IQR)	14 (10-17.6)	11.6 (8.7-14.2)		
Range (Min-Max)	60.5 (5.5-66)	50.5 (6.5-57)		

x2: Chi-Square test. SD: Standard deviation. IQR: Interquartile range. *t:* Independent t-test.
p : p-value for comparing between the studied groups.
p-value >0.05: Non significant. p-value <0.05: Significant. p-value <0.001: Highly significant.

Table (7): Day 4 lab results among the study groups.

	Group A (n=25)	Group B (n=25)	Test of Sig.	*p*
Day 1 Blood culture:				
Staph	1 (4%)	0 (0%)	X^2 = 2.083	0.353
Klebsiella	1 (4%)	0 (0%)		
No	23 (92%)	25 (100%)		
Day 1 CRP:				
Mean ± SD	47.57±50.93	18.61±33.53	*t* = 2375	0.022
Median (IQR)	24 (5.4-74)	3.5 (0.9-24)		
Range (Min-Max)	189.6 (2.4-192)	147.5 (0.5-148)		
Day 1 TLC:				
Mean ± SD	10.18±4.97	16.72±16.03	*t* = -1.947	0.061
Median (IQR)	8.9 (6.9-14)	10.9 (9.4-15.1)		
Range (Min-Max)	16.4 (3-19.4)	64.6 (1.4-66)		

t: Independent t-test. SD: Standard deviation. IQR: Interquartile range.
p : p-value for comparing between the studied groups.
p-value >0.05 : Non significant. p-value <0.05 : Significant. p-value <0.001: Highly significant.

Table (8): sTREM-1 Elisa test results among the study groups.

	Group A (n=25)	Group B (n=25)	Test of Sig.	*p*
Day 1 sTREM-1:				
Mean ± SD	633.58±488.49	86.53±30.81	*t=5.588*	<0.001
Median (IQR)	443.6 (166.8-1117)	84.09 (77.98-103.7)		
Range (Min-Max)	1286.37 (93.63-1380)	125 (112-1362)		
Day 4 sTREM-1:				
Mean ± SD	648.27±505.08	87.14±32.73	*t* = 5.543	<0.001
Median (IQR)	488 (150.1-1186.9)	89 (72.7-108.7)		
Range (Min-Max)	1433.7 (843-1518)	137.5 (12.3-149.8)		

t : Independent t-test. SD: Standard deviation. IQR: Interquartile range.
p: p-value for comparing between the studied groups.
p-value >0.05: Non significant. p-value <0.05: Significant. p-value <0.001: Highly significant.

Table (9): Logistic regression with odds ratios and 95% confidence intervals (CI) predicting mortality rate.

	Mortality rate			
	OR	95% CI		*p*
		Lower	Upper	
sTREM-1	1.001	0.999	1.002	0.251
Gestational age (Preterm group)	0.088	0.021	0371	0.001
Sex (Male group)	1.190	0.364	3.891	0.773
Duration of ventilation (d)	1.193	1.085	1312	<0.001
Duration of hospital stay (d)	1.161	1.074	1 254	<0.001

OR: Odds ratio. CI: Confidence Interval. *p:* p-value.

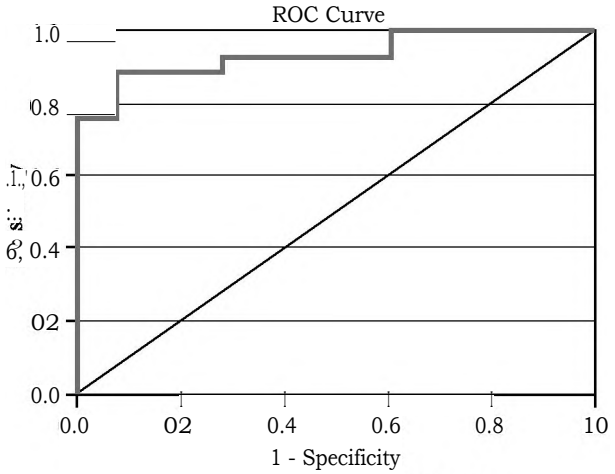


Fig. (2): ROC curve of Day 4 sTREM1-.

Table (10): Sensitivity and Specificity of day 1 and day 4 sTREM-1 to predict NVAP.

	Diagnostic parameters			
	AUC	Cutoff value	Sensitivity	Specificity
Day 1 sTREM-1	0.942	112.55	92%	84%
Day 4 sTREM-1	0.931	123.8	88%	92%

Table (11)• Sensitivity and Specificity of day 1 and day 4 CRP to predict NVAP.

	Diagnostic parameters			
	AUC	Cutoff value	Sensitivity	Specificity
Day 1 CRP	0.534	3.9	64%	56%
Day 4 CRP	0.640	4.7	68%	60%

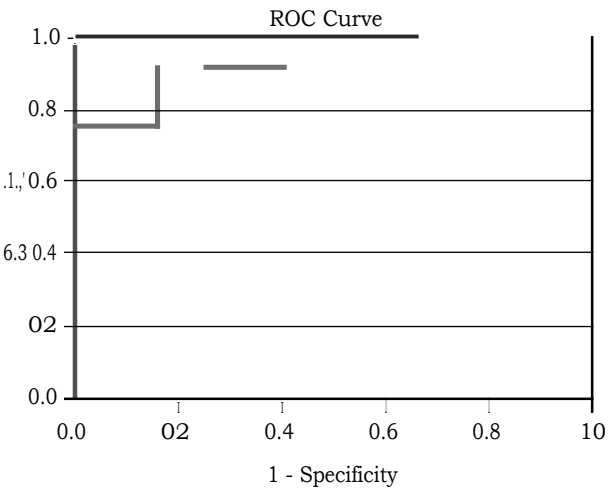


Fig. (1): ROC curve of Day 1 sTREM1-.

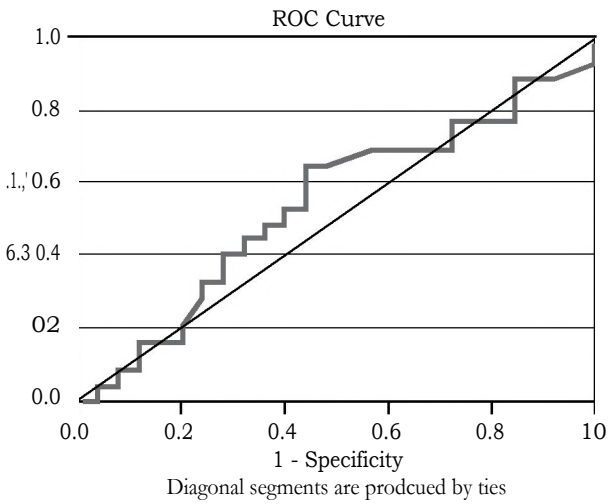


Fig. (3): ROC curve of Day 1 CRP.

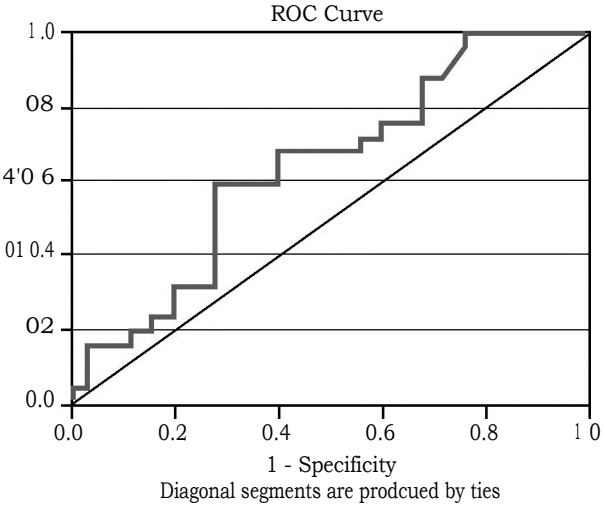


Fig. (4): ROC curve of Day 4 CRP.

Discussion

Neonatal ventilator-associated pneumonia (NVAP) is a common nosocomial infection as well as one of the main causes of mechanical ventilation failure. It is defined as a lower airway infection in intubated patients with an onset after '-48h of invasive mechanical ventilation. Goerens et al. **[5]** The NVAP infection rate in newborns can reach up to 6.8-32.2% **[6].**

Furthermore, in child patients, NVAP occurrence prolongs in hospitalization time and increases mortality and the generation of multiple-resistant strain Bouchon et al. **[7].** Triggering receptors expressed on myeloid cells-1 (TREM-1) are an important member of the immunoglobulin superfamily; they play a role in the immune response following exposure to microorganism. Soluble TREM-1 (sTREM-1) is a TREM-1 subtype that can be released into the blood or bodily fluids during an infection [8].

The sTREM-1 level has been used as a marker for identifying infection and assessing inflammation severity in adult patients with septicemia, ventilator-associated pneumonia (VAP), and severe pancreatitis **[2].**

Chao et al. [9] found that the C-reactive protein (CRP) and sTREM-1 can be used to forecast non-community-acquired pneumonia (non-CAP) in adult patients on the third day.

The different sTREM-1 and CRP trends in patients with non-CAP indicate that sTREM-1 is a kind of auxiliary forecasting biomarker in patients with CRP-relative CAP [2].

Zhong et al. [10] found that among 60 child patients with pneumonia, 25 had bacterial pneumonia, 17 had viral pneumonia, and 18 had mycoplasma pneumonia. Furthermore, CD64 and sTREM-1 expressions were obviously higher among patients with mycoplasma pneumonia than in patients with viral pneumonia, patients with mycoplasma pneumonia, and patients in the study's control groups ($p<0.05$) **[3].**

Li et al. [ill suggested that the detection of sTREM-1 in broncho alveolar lavage fluid (BALF) and exhaled ventilator condensate samples may be useful for VAP diagnosis in children after heart surgery. Yu et al. [12] reported that sTREM-1 in the BALF and exhaled ventilator condensate had good diagnostic performances in differentiating between YAP-positive and VAP negative patients with ischemia. However, Palazzo et al. **[13]** showed that sTREM-1 failed to categorize adult patients as VAP-positive or VAP-negative.

This study aimed at measurement (sTREM-1) as a diagnostic and prognostic indicator in ventilator-associated pneumonia for newborn. Comparison of sTREM-1 and C-reactive protein in terms of accuracy and sensitivity.

This study was conducted on Newborns with ventilator-associated pneumonia attending the neonatal care unit, Children's Hospital, Ain Shams University and Cairo, Egypt.

Our results showed that, there was no statistically significant difference between the two studied groups ($p=0.754$) regarding gestational age and sex ($p43.765$).

Our results in line with Gohr et al. [1] who found that There were no significant differences as regard to sex or mode of delivery.

Our results showed that there was no statistically significant difference between the two studied groups ($p43.264$). Regarding Maternal condition, there was no statistically significant difference between the two studied groups ($p=0.965$). Regarding Type of delivery, there was no statistically significant difference between the two studied groups ($p43.637$). Also, regarding Temperature, there was a significant difference between the two studied groups ($p=0.017$). Regarding RR, there was no statistically significant difference between the two studied groups ($p=0.068$). Regarding Heart rate, there was a significant difference between the two studied groups ($p=0.001$). Gohr et al. [1] found results similar to our results.

These results reported by Gohr et al. [1] who found that there were significant differences between VAP and non-VAP groups concerning the clinical findings. The most significant clinical findings with VAP were changes in temperature (either hypothermia or hyperthermia or fluctuation in temperature), heart rate tachycardia or bradycardia.

Our results showed that regarding Surfactant, there was no statistically significant difference between the two studied groups ($p=0.684$). Regarding TPN, there was no statistically significant differ-

ence between the two studied groups (p43.684). Regarding Sedative use, there was no statistically significant difference between the two studied groups (p=0.069).

In current study, Outcome results among the study groups. Duration of ventilation in cases group ranged from 20 to 31 with mean ± SD = 25.48±3.1 while in controls group the Duration of ventilation ranged from 8 to 14 with mean ± SD = 10.92±1.44 with highly statistically significant difference (p=<.001) between the two groups. Duration of hospital stay in cases group ranged from 28 to 49 with mean ± SD = 39.72±4.81 while in controls group the Duration of hospital stay ranged from 17 to 26 with mean ± SD = 21.16±2.56 with highly statistically significant difference (p=<.001) between the two groups. Regarding Mortality rate, there was a significant difference between the two studied groups (p= 0.004) so the results by Gohr et al. [1]; Li et al. [11]; Galal et al. **[14]** were in line with our results.

The outcomes compared between the VAP and non-VAP groups. There was significant longer duration of ventilation (26.0±11.5 days, p<0.001) and duration of hospital stay (40.3±14.9) with the VAP group, adding the in-hospital mortality rates in the VAP and non-VAP groups were 65% and 25.5% respectively (p<0.001) these results reported by Gohr et al. [1].

Also, our results were in line with Li et al. [11] who found that the duration of mechanical ventilation and hospital length of stay were significantly increased in the VAP group compared with that in the non-VAP control group (p<0.01).

Similarly, our results were in line with Galal et al. **[14]** who found thatoutcome the total duration of MV and that of ICU stay among patients with VAP (median=8, IQR=5-15 and median=11, IQR=7-18.5, respectively) was significantly shorter (p<0.001) compared to non-VAP patients (median=12, IQR=8-18 and median=17, IQR=1 respectively). Mortality rate among VAP patients was significantly higher compared to non-VAP patients (68.2% vs. 48.5%, P96 h) was significantly associated with higher mortality rate (77.6% vs. 58.5%, p=0.025) than early onset VAP (<96h).

VAP increases the duration of hospital stay and vice versa. the babies with VAP (VAP-positive) were hospitalized for a much longer period than the YAP-negative patients (mean duration of admission: 33.2±2.4 days vs. 22.4±17.8 days, respectively), similar to Apisarnthanarak's study in which the mean duration of hospitalization for the VAP positive babies was 138 days and for the VAP-negative patients 82 days **[15].**

Our results showed that Day 1 lab results among the study groups. Regarding Day 1 Blood culture, there was statistically significant difference between the two studied groups (p43.018). Day 1 CRP in Cases group ranged from 1.2 to 157 with mean ± SD = 53.24±37.05 while in Controls group the Day 1 CRP ranged from 0.3 to 189 with mean ± SD = 22.56±43.84 with statistically significant difference (p=0.01) between the two groups. Day 1 TLC in cases group ranged from 5.5 to 66 with mean ± SD = 17.47±15.49 while in controls group the Day 1 TLC ranged from 6.5 to 57 with mean ± SD = 14.27±10.55 with no statistically significant difference (*p*= 0.398) between the two groups so the results by El Nadyand collegues in line with our results. However, Khattab and collegues contrast to our results.

C-reactive protein (CRP) is a protein of an acute phase and it acts as a well-known biomarker of inflammation. The diagnostic value of CRP was investigated by many researchers. It was compared to many different markers to assess its sensitivity. Since it is an "indirect" marker of infection, the sensitivity and specificity is not 100% and vary. There was significant difference with CRP in the pneumonia cases than the control group p=0.002 this reported by El Nady et al. **[16].**

Our results were in contrast withKhattab et al. **[17]** who found thatof 85 neonates who needed mechanical ventilation, 55.2% developed YAP. Prematurity, low birth weight. Increased total leukocyte count, C-reactive protein, and hypo albuminuria were significantly present in the VAP group. There were significant differences between VAP and non-VAP groups regarding hypothermia. The microorganisms associated with bloodstream infection in the VAP-diagnosed group were Staphylococcus aureus (15%), Klebsiella spp. (8.5%), Candida spp. (6.5%), Pseudomonas spp. (4.2%), and Escherichia coli (4.2%).

Our results showed that 4 lab results among the study groups. Day 4 CRP in Cases group ranged from 2.4 to 192 with mean ± SD = 47.57±50.93 while in Controls group the Day 4 CRP ranged from 0.5 to 148 with mean ± SD = 18.61±33.53 with statistically significant difference (p=0.022) between the two groups. Day 4 TLC in cases group ranged from 3 to 19.4 with mean ± SD = 10.18±4.97 while in controls group the Day 4 TLC ranged from 1.4 to 66 with mean ± SD = 16.72±16.03 with no statistically significant difference (p=0.061) between the two groups, so the results by Povoa et al. **[18]** was in line with our results.

Povoa et al. **[18]** reported that there were significant differences between VAP and non-VAP groups regarding total leukocyte count and CRP titer. The CRP levels in infected patients with sepsis, severe sepsis and septic shock were 15.2±8.2, 20.3±10.9 and 23.3±8.7mg/dL, respectively (*p* 0.044). It was concluded that CRP was a better marker of infection. This in line with our results. However, CRP higher in our results.

C-reactive protein (CRP) is a well-known biochemical marker of inflammation, and has also been shown to be involved in several immunological functions. The usefulness of CRP measurements in the diagnosis of infection has been studied previously in several clinical settings, and various studies have suggested that the CRP cut-off level for infection diagnosis is between 5 and 10mg/dL **[19].**

Our results showed that day 1 sTREM-1 levels were highly statistically significant difference (p=<.001) between the two groups. There was highly statistically significant difference (p=<.001) between the two groups regarding Day 4 sTREM-1.

Day 1 sTREM-1 in cases group ranged from 93.63 to 1380 with mean ± SD = 633.58±488.49 while in controls group the day 1 sTREM-1 ranged from 11.2 to 136.2 with mean ± SD = 86.53±30.81 Day 4 sTREM-1 in Cases group ranged from 84.3 to 1518 with mean ± SD = 648.27±505.08 while in Controls group the Day 4 sTREM-1 ranged from 12.3 to 149.8 with mean ± SD = 87.14±32.73 with highly statistically significant difference (p=<.001) between the two groups.

Trigger receptors expressed on myeloid cells (sTREM-1) are considered innate inflammatory transmembrane receptors. STREM-1 is expressed on neutrophils, mature monocytes, and macrophages and is related to immunoglobulin superfamily receptors. STREM-1 amplifies inflammation after exposure to extracellular bacterial and fungal pathogen. Therefore, it was initially proposed as the early marker of infection. TREM-1 expression is increased in peritoneal neutrophils of septic shock patients **[20].**

STREM-1 has a significant diagnostic value when it comes to lung diseases as it has been studied in the diagnosis of ventilator-associated pneumonia (VAP) for ICU patients **[12].** STREM-1 had a good diagnostic performance to differentiate patients with and without VAP.This supports our findings because significant differences have been identified between ventilated cases and control groups and this can be explained by that the ventilation is an add on factor for rising sTREM-1 level with the bacterial infection.

This is in line with results of many recent studies which assessed the sTREM level either in bronchoalveolar lavage or serum in ICU patient. It was concluded that sTREM-1 is present at a high concentration in patients' lungs with bacterial infections, which can be used as a reliable early marker for VAP and can accurately discriminate VAP from non-pulmonary infection **[21].**

Our results in line with Zhao et al. **[3]** who found that Potential correlations between the measured biomarkers and VAP were analyzed at 0, 24, 72 and 120h of MN/. A positive correlation was observed between the serum sTREM-1 concentration at 72h and VAP (r=0.697,p<0.001). The serum concentrations of sTREM-1, CRP and after 120h of MV were not associated with the diagnosis of YAP. The Hosmer-Lemeshow test showed that the p-value for the correlation between sTREM-1 and VAP was greatest at 72h (p=0.759 >0.05), which implied a better degree of fitting.

Also, our results were in line with Yang et al. **[2]** who found that STREM-1 was positively correlated with the WBC count, neutrophil granulocyte absolute count, immature/total neutrophil granulocyte specific value, high sensitivity CRP (hs-CRP).

Our results showed that Sensitivity and Specificity of day 1 and day 4 sTREM-1 to predict NVAP. Regarding Day 1 sTREM-1, AUC was 0.942, Cutoff value was 112.55, Sensitivity was 92% and Specificity was 84%. Regarding Day 4 sTREM-1, AUC was 0.931, Cutoff value was 123.8, Sensitivity was 88% and Specificity was 92%. Sensitivity and Specificity of day 1 and day 4 CRP to predict NVAP. Regarding Day 1 CRP, AUC was 0.534, Cutoff value was 3.9, Sensitivity was 64% and Specificity was 56%. Regarding Day 4 CRP, AUC was 0.640, Cutoff value was 4.7, Sensitivity was 68% and Specificity was 60% so the results by El Nady et al. **[16]** and Zhao et al. **[3]** were in line with our results.

The diagnostic role of CRP and sTREM-1 as biomarkers was investigated in VAP and they found that sTREM-1 was more specific and sensitive than C-reactive protein (CRP). In our study there was no significant correlation between TREM-1 level and CRP level in the studied children. These results reported byEl Nady et al. **[16]** who in line with our results.

Similarly, Zhao et al. **[3]** who found that the area under the curve (AUC) values were obviously greater after 72h of MV, and at this time point, the optimal cutoff value for the serum sTREM-1 concentration was 165 .05pg/m1 with an AUC of 0.902. The predictive sensitivity of sTREM-1 for VAP was 90% and the specificity was 77% was in line with our results.

Conclusion:

sTREM-1 is as a diagnostic and prognostic indicator in ventilator-associated pneumonia for newborn. Comparison of sTREM-1 and C-reactive protein in terms of accuracy and sensitivity. STREM-1 has shown it to be more specific and sensitive than C-reactive protein (CRP).

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مستوى مستقبلات تنشيط الخلايا النخاعية -١ف المصل كعلامة تشخيصية وإنذارية فى الالتهاب الرئوى المرتبط بجهاز التنفس الصناعى لحديثى الولادة

الخلفية: تعد الالتهاب الرئوى المرتبط بجهاز التهوية للمواليد الجدد (NVAP) من العدوى الرئيسية المكتسبة فى المستشفى فى بيئات الرعاية الحادة، ومرتبطة بمعدل وفيات عالٍ ونتائج ضعيفة. مستقبل مفتاح الخلية النخاعى-١ (TREM-1) هو عضو فى عائلة مستقبلات الأجسام المناعية والذى يتم التعبير عنه بشكل رئيسى على سطح الخلايا النخاعية مثل العدلات والكريات البيض والخلايا العملاقة/الكريات المناعية. المستقبل المفتوح لـ sTREM-1 (TREM-1) هو نوع من مستقبلات TREM-1 وقد تم الإبلاغ عنه كمؤشر جديد وقوي للالتهاب الرئوى.

الهدف والأهداف: الهدف الأساسى هو تقييم قيمة sTREM-1 كعلامة تشخيصية وتوقعية فى NVAP والهدف الثانوى هو مقارنة الخصوصية والحساسية بين sTREM-1 وبروتين الاستجابة السيتولوجية.

المواضيع والأساليب: كانت هذه دراسة حالة – شاهد فى وحدة العناية المركزة الجديدة في مستشفى الأطفال بجامعة عين شمس، القاهرة، مصر (مدة ٦ أشهر). تمت الدراسة على ٥٠ حالة مقسمة إلى مجموعتين، تم تضمين ٢٥ حالة فى كل مجموعة: المجموعة أ: الالتهاب الرئوى المرتبط بجهاز التهوية للمواليد الجدد (VAP) (الحالات). المجموعة ب: مواليد جدد متطابقين من حيث العمر والجنس تم تشخيصهم بمتلازمة صعوبة التنفس بخلاف الالتهاب الرئوى ولم يتم توصيلهم بجهاز تهوية (السيطرة). تمت عملية العشوائية استنادًا إلى أرقام ملفات المرضى سواء كانت أرقام فردية أو زوجية.

النتيجة: بالنسبة ليوم ١ sTREM-1، كان مساحة أسفل المنحنى (AUC) تساوى ٠,٩٤٢، القيمة الحدية كانت ١١٢,٥٥، الحساسية كانت ٩٢٪ والخصوصية كانت ١٦٪. بالنسبة ليوم ٤ sTREM-1، كان AUC يساوى ٠,٩٣١، القيمة الحدية كانت ١٢٣,٨، الحساسية كانت ٨٨٪ والخصوصية كانت ٨٠٪. بالنسبة ليوم ١ CRP، كان AUC يساوى ٠,٥٣٤، القيمة الحدية كانت ٣,٩، الحساسية كانت ٦٤٪ والخصوصية كانت ٤٤٪. بالنسبة ليوم ٤ CRP، كان AUC يساوى ٠,٦٤٠، القيمة الحدية كانت ٤,٧، الحساسية كانت ٦٨٪ والخصوصية كانت ٤٠٪.

الاستنتاج: sTREM-1 هو مؤشر تشخيصى وتوقعى فى الالتهاب الرئوى المرتبط بجهاز التهوية للمواليد الجدد. مقارنة بين sTREM-1 وبروتين الاستجابة السيتولوجية من حيث الدقة والحساسية. أظهر sTREM-1 أنه أكثر دقة وحساسية من بروتين الاستجابة السيتولوجية (CRP).