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ORIGINAL ARTICLE

The utility of presepsin as a biomarker in hospital acquired septicemia in PICUS and NICUS

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ABSTRACT

Keywords: Pediatric Sepsis; biomarkers, presepsin.

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Background: Pediatric Around the world, sepsis is a major caus illness and mortality for newborns and young children. Pediatric sepsi become more common in the last 20 years, and an increasing numb these patients have co-morbid illnesses. **Objectives:** To assess utilization of presepsin as a biomarker for early septicemia identific and its prognosis in order to direct antibiotic treatment. **Patient methods:** This is a case-control study including 20 patients with susp hospital-acquired septicemia and 20 non-septic patients who served a control group in the pediatric and neonatal intensive care units at A University Hospital**. Results:** Compared to the control group, the s group's mean presepsin levels were considerably higher., and decreased steadily over time in accordance with treatment, reflectin strong power of presepsin in sepsis predection. **Conclusion:** Presepsi promising biomarker for diagnosing nosocomial sepsis and predi outcomes**.**

INTRODUCTION

Sepsis is a potentially fatal condition that occurs as a result of an infection that damages tissues and organs.Sepsis can lead to shock, multiple organ failure, and death, especially if not diagnosed and treated quickly.[(1)]

More than 80% of infant and young child deaths in Egypt occur during the first year of life, with more than half occurring during the first month. The newborn mortality rate was observed at 14 deaths for every 1,000 births.[(2)]

Early comprehensive treatment can reduce sepsis-related morbidity and mortality by allowing for early diagnosis and severity assessment. A validated biomarker should be affordable, widely available, and easy to use, and results should be available quickly. There is no perfect test to identify sepsis, although a variety of biomarkers can help in the clinical setting to reach a reasonable decision. [(3)]

Biomarkers can improve the management of sepsis by providing important information about diagnosis, prognosis and response to therapy. **(4)**

Presepsin has good sensitivity and specificity in sepsis diagnosis and may be a useful and important biomarker in the early detection of sepsis. **(5)**

Presepsin is also a useful marker to monitor the effectiveness of antibiotic therapy in terms of improved prognosis and survival. **(6)**

PATIENTS AND METHODS

This case-control study at Aswan University Hospital's pediatric critical care unit and newborn intensive care unit included 20 suspected hospital-acquired septicemia patients and 20 non-septic patients as a control group. The study obtained approval from the Ethical and Research committees of Aswan University Hospital.

All patients were submitted to:

- Complete history
- Complete clinical examinations.
- Laboratory investigations:

- CBC with differential on day 1.
- Blood cultures on day 1 and day 4 (For negative cultures on day 1).
- Presepsinon day 1, day 4 and day 7.

- Blood sampling:

On days 1, 4, and 7 after the onset of septicemiaBlood samples were obtained for checking the presence of presepsin as well as for culture and sensitivity testing. The first day is defined as the clinical suspicion of hospital-acquired septicemia or the onset of clinical signs after 48 hours of admission.8 ml of blood was collected from every suspected case on the first, fourth, and seventh days as:

-Blood culture: 2–5 ml aseptically collected for blood culture: The sample was incubated at the BD BACTEC 9050 system (Becton Dickinson). Positive samples were promptly incubated and monitored in accordance with established protocols.**(5)**

- After being gram-stained, positive samples were subcultured on blood, MacConkey, and chocolate agar plates, which were then incubated at the proper temperatures. Using the Vitek 2 Compact (bioM'erieux), all of the organisms were fully identified.

- **Presepsin**:2 ml for presepsin: The sample was tested on PATHFAST (Mitsubishi Chemical Medience Corporation) according to the manufacture.

Plasma samples (100 µL) were stored at −80°C until analysis. Presepsin was evaluated using the PATHFAST immunoanalyzer (PATHFAST®, Mitsubishi Chemical Medience Corp., Tokyo, Japan), a small automated immunological analyzer based on a noncompetitive chemiluminescent enzyme immunoassay (CLEIA) with Magtration technology.

- **Complete blood count (CBC):**The differential count was performed using a Coulter LH750 Analyzer (Beckman Coulter Inc., USA), as well as peripheral blood smears.

Patient selection:

Inclusion criteria:

Any patient admitted to NICU or PICU with any diagnosis other than septicemia aged less than 12 years for a period of one year.

Sepsis Identification:

Any patient admitted to NICU or PICU with any diagnosis other than sepsis who develop within 48 hours at least 3 of the following signs:

- Fever: Temperature >38.0°c
- Bradycardia: Heart rate < 100 beats/min in infants <1year old.
- Oliguria: Low output of urine less than (0.5 ml/kg/h).
- Apnea: Transient cessation of breathing.

Exclusion criteria:

- Any patient who is admitted to the NICU or the PICU with a sepsis diagnosis.

Statistical analysis

Researcher verified, coded, and analyzed data using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Statistics by type: Calculated mean, SD, median, range, frequency, and percentages. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine continuous variable normality. A chi-square or Fisher's exact test was used to compare group frequency distributions. Student/Mann Whitney t-test Comparisons of dichotomous means and medians were done using U analysis. RM-ANOVA measured mean differences for continuous variables with more than two categories and repeated assessments. Bonferroni adjustments were used for post-hoc tests. The ROC curve with AUC, SE, and 95% CI was used to compare how well different markers and combinations of markers can diagnose and predict disease. The p-value was considered significant at <0.05.

RESULTS:

A total of 40 participants were included in the current study (20 cases diagnosed with sepsis and were eligible for inclusion, along with 20 control).

Table 1 showed CBC parameters, cases with sepsis had higher mean WBCs count (11.19± 1.7) compared with control (9.11 ± 2.4) and this association was statisticallyinsignificantly (p=0.241).

For the level of hemoglobin, it was less in sepsis cases (11.6 ± 2.9 g/dl) in comparison with controls (14.1 ± 2.3 g/dl) and this association was statistically significant (p=0.004). Likewise, the platelet count was less in sepsis cases (206.2 ± 30.1) in comparison with controls (289.9 ± 20.1) and this association was statistically significant (p=0.027). (Figure 1)

Regarding the validity of theCBC parameters as a tool for prediction of sepsis among the study cohort. For WBCs, the predictive power was fair i.e., AUC=0.536, p=0.695; 95% CI: 0.34-0.73. Moreover, using $9*10^3$ as a cutoff, the validity criteria were all 60%. (Table 2)

On the other hand, the predictive power of Hb was good i.e., AUC=0.249, p=0.007; 95% CI: 0.10-0.40. Moreover, using 10 g/dlas a cutoff, the validity criteria were as follows; 95% sensitivity, 55% specificity, 68% PPV, 91.5% NPV and overall, the test had 75% accuracy.

Similarly, the predictive power of platelet count was good i.e., AUC=0.249, p=0.011; 95% CI: 0.10-0.43. Moreover, using $160*10^3$ as a cutoff, the validity criteria were as follows; 95% sensitivity, 60% specificity, 70% PPV, 92% NPV and overall, the test had 77.5% accuracy.

For comparison between cases and controls, the mean presepsin level was significantly higher in the sepsis group than the control group from the 1st day till the 7th day (1st day (p<0.001), 4th day (p<0.001) and at 7th day (p<0.001). (Table 3, Figure 2)

The difference in the presepsin level between cases and control. In the sepsis group, the mean presepsin level showed significant (p = 0.007) decrease over time i.e., the mean presepsin at 1st day was 827.2 ± 62.1, at 4th day was 630.5 ± 64.1 and at 7th day was 554.9 ± 78.6. Likewise, the mean presepsin level showed significantly (p = 0.001) steady reduction in the control group over time i.e., the mean presepsin at 1st day was 145.4 ± 13.8, at 4th day was 129.3 ± 12.1 and at 7th day was 113.5 ± 9.3.

Also, there is a difference in the presepsin level between survivors and non-survivors; the presepsin level showed a significant increase over time (p = 0.037), while it showed a steady decrease in the survivors (p = <0.001).(Table 4, Figure 3)

The study evaluated the validity of presepsin as a tool for sepsis prediction. Presepsin showed almost perfect predictive power at the first day, with 95% accuracy. It also showed good predictive power at the 4th day, with 67.5% accuracy. However, on the 7th day, it had the lowest predictive power, with 82.5% accuracy. The Youden index confirmed the predictive power, with a higher value for the 1st and 4th days.(Table 5, Figure 4)

According to the validity of presepsin as a tool for prediction of mortality among the study cohort, the predictive power was almost perfect i.e., AUC=0.992, p=0.023; 95% CI: 0.80-1.00. Moreover, using 888 pg/ml as a cutoff, the validity criteria were as follows; 100% sensitivity, 91% specificity, 92% PPV, 100% NPV and overall, the test had 95.5% accuracy. (Table 6)

Respecting the distribution of the predominant causative organism of nosocomial septicemia. The most common organism was Klebsiella pneumoniae representing 17.5% (n=7), followed by Staphylococcus aureus representing 12.5% (n=5), then Enterobacter encompassing 5% (n=2). The least common organisms that were isolated in only one case each (2.5%) were E. coli, Enterococcus faecium, Pseudomonas aeruginosa, Streptococcus agalactiae, Serratiamarcescens, and Coagulase-negative staphylococci. (Table 7. Figure 5)

DISCUSSION

Sepsis is a life-threatening illness that affects many children, regardless of underlying medical conditions. According to statistics, sepsis is one of the leading causes of death among children worldwide, especially in wealthy countries. [7]

Regarding CBC parameters, cases with sepsis had an insignificantly higher mean WBCs count compared with controls (p = 0.241). For the level of hemoglobin, there was a statistically significant association (p = 0.004) between sepsis cases (11.6 ± 2.9 g/dl) and controls (14.1 ± 2.3

g/dl). Likewise, the platelet count was lower in sepsis cases (206.2 ± 30.1) in comparison with controls (289.9 ± 20.1), and this association was statistically significant (p = 0.027).

Concerning the validity of CBC parameters as a tool for prediction of sepsis among the study cohort, for WBCs, the predictive power was fair. Regarding Hb and platelets, the predictive power was was good.

Also **Singer et al.**[8]Discovered that the WBC count may appear normal or even reduced in certain instances of sepsis. Therefore, the overall WBC count has a low level of specificity, which restricts its effectiveness as a diagnostic for sepsis.

Similarly**Farkas.**[9]detected that the WBCs count is the parameter that is most frequently used to assess infection, but it is also the least effective. Leukocytosis or leukopenia may result from septic shock. There are a lot of sick people having a WBCs between these two extremes, with a normal range (these patients frequently experience leukocytosis that manifests slowly).

In contrast to our findings **Sakyi et al.**[10]observed a statistically significant increase in WBC count (WBC) in the sepsis group compared to the control group ($P < 0.05$).

Concerning Hb level **Docherty et al.**[11]It has been estimated that Approximately 66% of patients admitted to the intensive care unit (ICU) have hemoglobin (Hb) levels below 120 g/L, and around 40% have Hb levels below 100 g/L. Anemia develops in 97% of patients by day 8 and in 100% of patients by day 13 of their stay in the ICU.

Concerning platelet level and in accordance with our results **Vardon-Bounes et al.**[12]found that thrombocytopenia is a common finding in sepsis due to platelet consumption via thrombin-mediated platelet activation which is the most common mechanism and disseminated intravascular coagulation (DIC) insevere forms of sepsis.

For comparison between cases and controls, The average presepsin level was markedly elevated in the sepsis group compared to the control group, as well as in non-survivors compared to survivors, from the 1st day until the 7th day.

The validity of presepsin as a tool for prediction of sepsis among the study cohort, for presepsin at 1 st day, the predictive power was almost perfect. In our study for prespesin at 4 th day, the predictive power was good.While presepsin on the 7th day had the lowest predictive power, the predictive power was poor.

In our study, sepsis patients exhibited high presepsin levels at baseline. Later, however, monitoring showed a significant and rapid reduction in presepsin, which was consistent with the clinical improvement of the patients. On the other hand, non-survivors had increasing levels throughout the study days. Therefore, rather than being a marker of sepsis severity, presepsin might be thought of as a useful monitoring and mortality predictor.

Masson et al. [13]observed that presepsin values can serve as a suitable indicator for evaluating the effectiveness of antibiotic therapy. Specifically, on day 7, these values tended to decrease in patients with positive blood cultures who received adequate antibiotic medication, while they increased in patients who received incorrect antibiotic therapy.

In accordance with our results, **Abdallah Abdelmoaty et al.**[14]In prospective case-control research, a statistically significant disparity was seen between septic patients and controls. Additionally, a statistically significant disparity in presepsin levels was observed between the groups of those who survived and those who did not survive when comparing their respective levels.

In line with our study, **Ghazy et al.**[15]conducted a prospective study using a sample size of 30 patients admitted to the PICU at the Mansoura University Children's Hospital and measured presepsin on days 1 and 3. They found that patients with sepsis had a greater presepsin level compared to the control group. Also concerning the 30 day mortality, they found predictive values for presepsin on day 3 as follows: on day 3 with an AUC of 0.82, they had 73%, specificity and 86% sensitivity that were higher in non-survivors than predictive values on day 1, which were AUC = 0.58, had 57% specificity and 71% sensitivity, and this may explain the decrease in the predictive values in our study with successful initiation of antimicrobial therapy and improvements in clinical cases .

As regard Distribution of the predominant causative organism of nosocomial septicemia in cases and in line with our results **Fahmey**.[16]Reported thatKlebsiella pneumoniae was the most common pathogen from Gram-negative organisms (42.8%) while Staphylococcus aureus was the most common pathogen from Gram-positive organisms (8.7%).

Unlikely to our study**, Sakyi et al.**[9]reported that the most frequently identified bacteria were Coagulase-negative Staphylococcus (CNS) (28.7%), followed by Coagulase-positive Staphylococcus (CPS) (21.4%), and Klebsiella spp. (21.4%). The prevalence of E. coli is 14.3%, that of Methicillin-resistant Staphylococcus aureus (MRSA) is 7.1%, and that of Pseudo. Aeruginosa is also 7.1%.

CONCLUSION:

Sepsis results are improved by timely therapy; mortality rates are increased when treatment and identification are delayed. Presepsin may be a reliable biomarker to identify and assess the prognosis of nosocomial sepsis. Early detection of pediatric sepsis was made easier by the inclusion of the combination of this biomarker in conventional diagnostic tests for nosocomial sepsis.

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Table (1): Mean WBCs/ HGB/Platelet level Difference between Groups over Time

	Control (n = 20)	Sepsis (n = 20)	P-value
Other Laboratory Parameters			
• **WBCs*10^3**	9.11 ± 2.4	11.19 ± 1.7	= 0.241*
• **HGB (gm/dl)**	14.13 ± 2.3	11.61 ± 2.9	**= 0.004***
• **Platelet*10^3**	289.85 ± 20.1	206.20 ± 30.1	**= 0.027***

***Independent t-test was used to compare the mean differences between groups**

**** Means within groups were compared using a repeated measures one-way ANOVA test.**

Table (2): Diagnostic criteria of CBC Parameters for Sepsis Prediction

Criteria	WBCs	HGB	Platelet
• **AUC ***	**0.536**	**0.249**	**0.266**
• **95% CI****	**0.339 - 0.734**	**0.096 - 0.402**	**0.101 - 0.432**
• **SE*****	**0.101**	**0.078**	**0.084**
• **P-value********	= 0.695	**= 0.007**	**= 0.011**
• **Cut-off**	**9*10^3**	**10 g/dl**	**160*10^3**
• **Accuracy**	**60%**	**75%**	**77.5%**
• **Sensitivity%**	**60%**	**95%**	**95%**
• **Specificity%**	**60%**	**55%**	**60%**
• **PPV%**	**60%**	**68%**	**70%**
• **NPV%**	**60%**	**91.5%**	**92%**
• **Youden's J**	**0.2**	**0.5**	**0.55**

***AUC=Area Under the Curve**

****CI=Confidence Interval**

*****SE=Standard Error**

******Null hypothesis: true area=0.5**

----Sensitivity (true positives/all diseased); specificity (true negatives/all non-diseased); PPV (true positives/all test positives); NPV (true negatives/all test negatives).

Table (3): Mean Presepsin level Difference between Groups over Time

	Control (n = 20)	Sepsis (n = 20)	P-value
Presepsin			
• **1st day**	145.39 ± 13.8	827.20 ± 62.1	**< 0.001***
• **4th day**	129.30 ± 12.1	630.49 ± 64.1	**< 0.001***
• **7th day**	113.46 ± 9.3	554.88 ± 78.6	**< 0.001***
P-value**	**= 0.001**	**= 0.007**	

***Independent t-test was used to compare the mean differences between groups**

****Means within groups were compared using a repeated measures one-way ANOVA test.**

Table (4): Differences in Presepsin according to Mortality

Median & Range	Alive(n = 17)	Dead (n = 3)	P-value
Presepsin			
• **1st day**	520 (265 – 926)	2274 (1360 – 3257)	**= 0.001***
• **4th day**	148 (77 – 370)	2634 (2468 – 4560)	**< 0.001***
• **7th day**	59 (21 – 149)	2819 (2591 – 4571)	**< 0.001***
P-value**	**< 0.001**	**= 0.037**	

***Mann Whitney U-test was used to compare the differences in median between groups**

****Friedman's test was used to compare the median within group**

Table (5): Diagnostic criteria of Presepsin for Sepsis Prediction

Diagnostic criteria	Presepsin -1	Presepsin -4	Presepsin -7
• **AUC ***	**0.998**	**0.703**	**0.318**
• **95% CI****	**0.989 - 1.000**	**0.541 - 0.864**	**0.143 - 0.792**
• **SE*****	**0.004**	**0.082**	**0.089**
• **P-value********	**< 0.001**	**= 0.028**	**= 0.048**
• **Cut-off**	**255 pg/ml**	**110 pg/ml**	**45 pg/ml**
• **Accuracy**	**97.5%**	**67.5%**	**82.5%**
• **Sensitivity%**	**100%**	**75%**	**65%**
• **Specificity%**	**95%**	**60%**	**100%**
• **PPV%**	**95%**	**65%**	**100%**
• **NPV%**	**100%**	**70.5%**	**74%**
• **Youden's J**	**0.95**	**0.65**	**0.35**

***AUC=Area under the Curve**

****CI=Confidence Interval**

*****SE=Standard Error**

*****Null hypothesis: true area=0.5**

----Sensitivity (true positives/all diseased); specificity (true negatives/all non-diseased); PPV (true positives/all test positives); NPV (true negatives/all test negatives).

Table 6: Diagnostic criteria of Presepsin for Mortality Prediction among Cases

Diagnostic criteria	Presepsin
• AUC*	0.922
• 95% CI**	0.795 - 1.000
• P-value***	= 0.023
• Cut-off	888 pg/dl
• Accuracy	95.5%
• Sensitivity%	100%
• Specificity%	91%
• PPV%	92%
• NPV%	100%
• Youden's J	0.91

***AUC=Area under the Curve ** CI=Confidence Interval ***Null hypothesis: true area=0.5 ----Sensitivity (true positives/all diseased); specificity (true negatives/all non-diseased); PPV (true positives/all test positives); NPV (true negatives/all test negatives).**

Table (7): Predominant Causative Organism of Nosocomial Septicemia

Organism	n = 20
• **Klebsiellapneumoniae**	7 (17.5%)
• **Staphylococcus aureus**	5 (12.5%)
• **Enterobacter**	2 (5%)
• **E. Coli**	1 (2.5%)
• **Enterococcus faecium**	1 (2.5%)
• **Pseudomonas aeruginosa**	1 (2.5%)
• **Streptococcus agalactiae**	1 (2.5%)
• **Serratiamarcescens**	1 (2.5%)
• **Coagulase-negative staphylococci (CoNS)**	1 (2.5%)

Fig. (1): Mean Hgb/Platelet count level Difference between Groups over Time

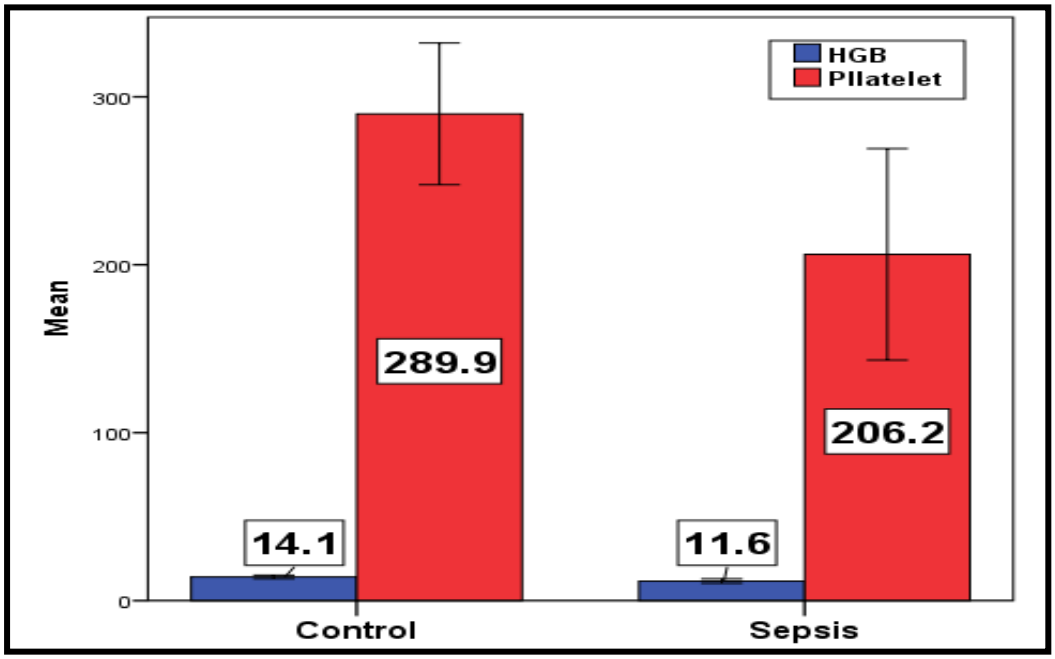

Fig. (2): Mean Presepsin level Difference between Groups over Time

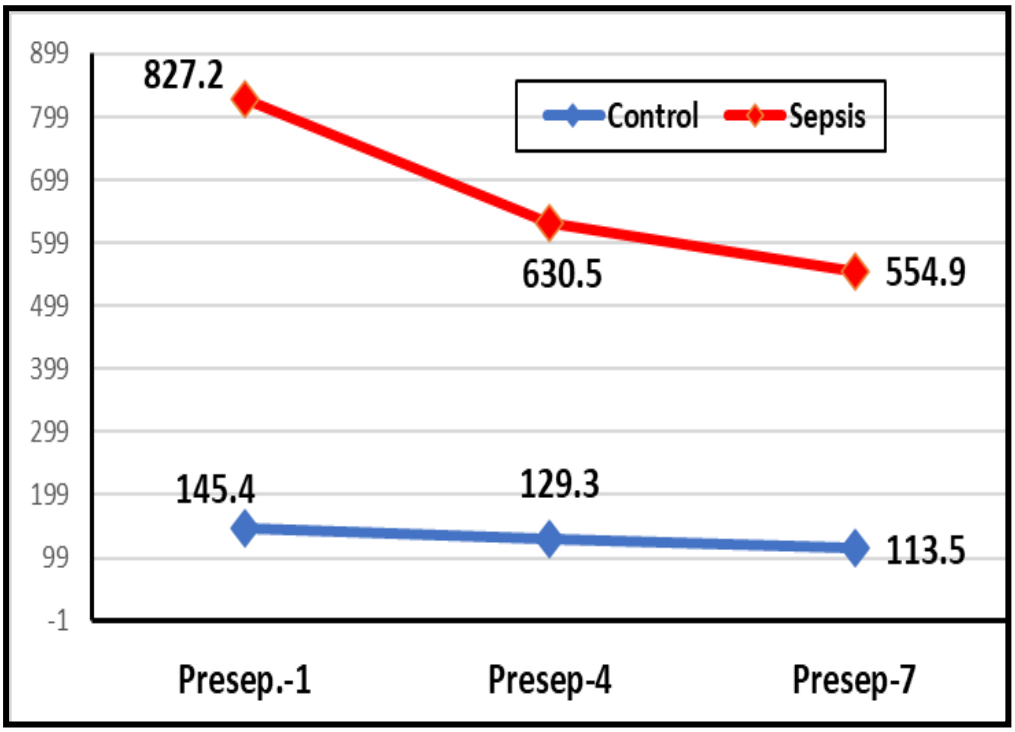

Fig.(3): Mean Presepsin level Difference between urvivors and non-survivors over Time

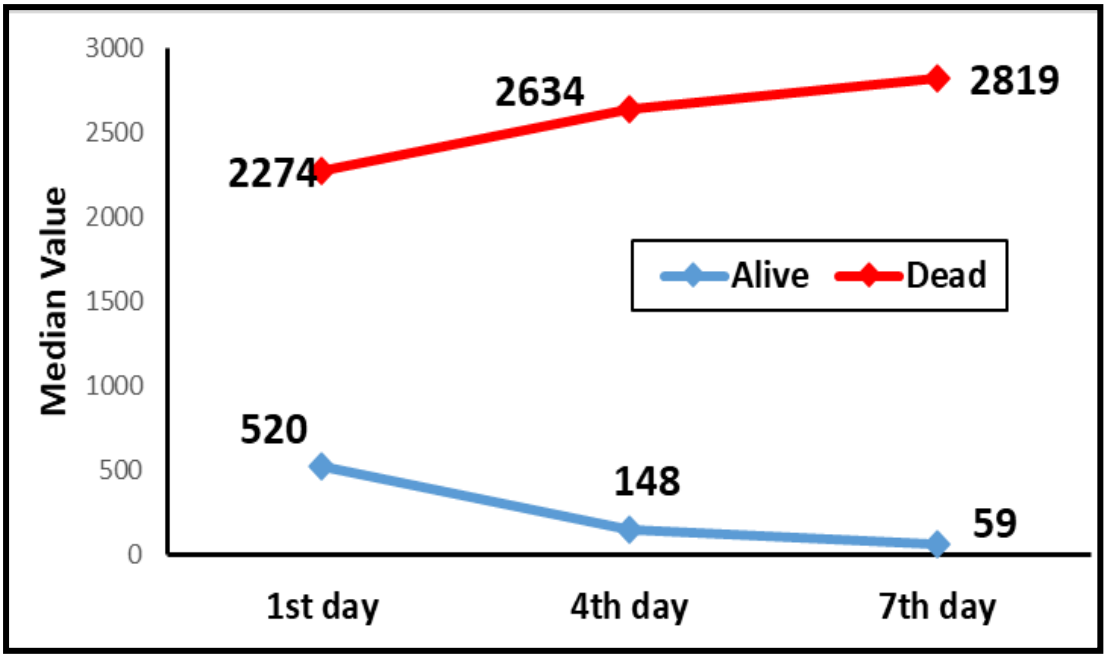

Fig. (4): ROC curve for Presepsin for Sepsis Prediction

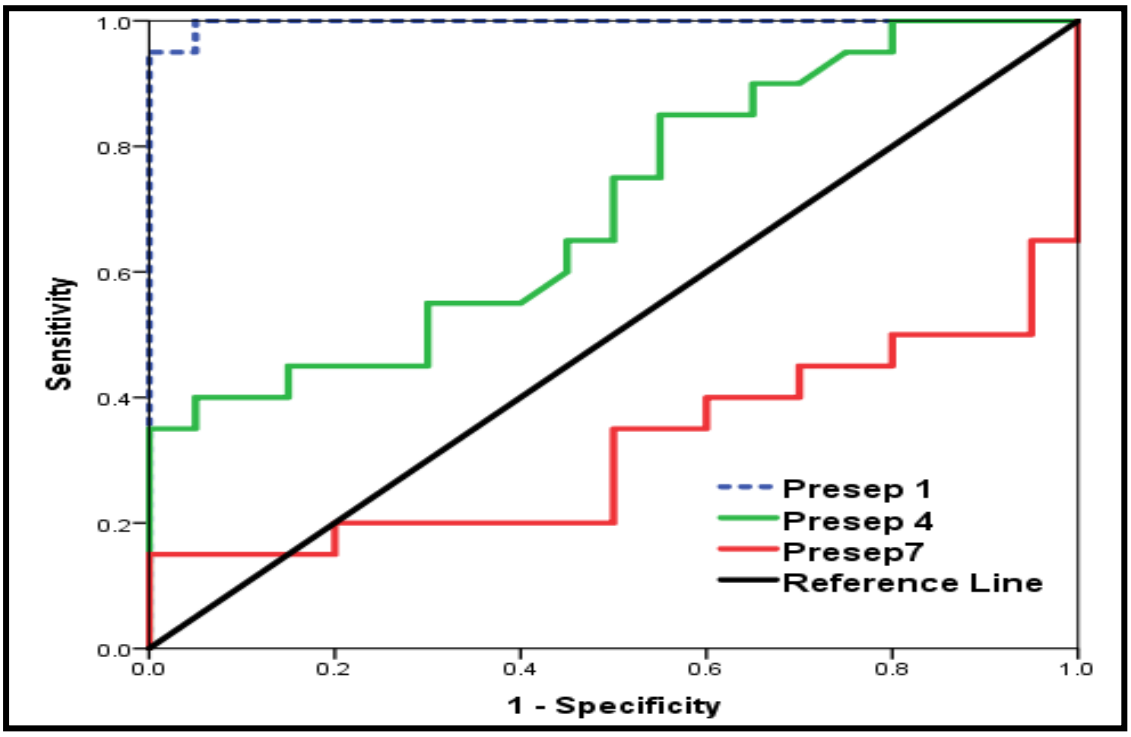

Fig. (5): Predominant Causative Organism of Nosocomial Septicemia