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Original Research Article

Assessment of Biomarker Dynamics in Neonates with Klebsiella Sp. and E. Coli

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Abstract:

Background: Neonatal sepsis, particularly from Klebsiella species and E. coli, is a major concern in NICUs due to its nonspecific symptoms and diagnostic challenges. Early and effective treatment is crucial but complicated by the immature neonatal immune system and the potential for antibiotic resistance. Current biomarkers like CBC, CRP, and IL-6 are used but are not fully reliable. Improved diagnostic tools and biomarkers are needed to enhance early detection and treatment of this critical condition.

Aim: To investigate the dynamics of biomarkers—Total Leukocyte Count (TLC), Neutrophil-to-Lymphocyte Ratio (NLR), Platelet Count, and C-reactive Protein (CRP)—in neonates with sepsis from Klebsiella species and E. coli, and to evaluate their potential for improving early diagnosis and management.

Objectives: Track and compare biomarker trends. Identify diagnostic markers for each pathogen. Assess immune response and systemic inflammation indicators.

Methods: This observational study involved 56 neonates with sepsis (35 Klebsiella, 21 E. coli). Biomarkers were monitored on Days 0, 1, 3, and 5, with data analyzed using chi-square and ANOVA.

Results: Klebsiella sepsis showed higher initial TLC and CRP with notable fluctuations, while E. coli sepsis exhibited more variable NLR and less fluctuation in TLC. Platelet counts declined in both groups. Statistical analysis revealed significant differences in biomarker levels between the two pathogens ($p < 0.05$).

Conclusion: Distinct biomarker patterns for Klebsiella and E. coli sepsis suggest different immune responses. Understanding these dynamics can enhance diagnosis and treatment, highlighting the need for personalized approaches in neonatal sepsis management.

Keywords: Neonates, Sepsis, C-reactive Protein, Klebsiella species, Escherichia coli.

Introduction

Neonatal sepsis remains a significant cause of morbidity and mortality in neonatal intensive care units (NICUs) worldwide, with *Klebsiella species* and *E. coli* being common causative pathogens. Despite advances in medical care, the diagnosis and management of neonatal sepsis, particularly those caused by *Klebsiella species* and *E. coli*, present ongoing challenges due to nonspecific clinical presentations and the limitations of current diagnostic methods. Consequently, there is a critical need for reliable biomarkers to aid in the early detection, monitoring, and management of sepsis in neonates. Neonatal sepsis remains a significant cause of morbidity and mortality in neonatal intensive care units (NICUs). This condition, characterized by a systemic inflammatory response to infection, presents diagnostic and therapeutic challenges due to its variable and non-specific symptoms. Early diagnosis and effective treatment are crucial for improving outcomes in affected neonates, yet the use of broad-spectrum antibiotics in high-risk infants can lead to adverse effects and the development of antibiotic resistant strains.[1]

Neonatal sepsis is classified into early-onset sepsis (EOS) and late-onset sepsis (LOS) based on the timing of onset relative to birth. EOS occurs within the first 72 hours of life and is often due to vertical transmission of pathogens from the mother, such as Escherichia coli and Group B Streptococcus (GBS). LOS, occurring after 72 hours, is frequently associated with nosocomial infections, particularly in preterm infants and those requiring invasive procedures or prolonged hospitalization. [2] The incidence of EOS in the United States is estimated at 0.77-1 per 1000 live births, with higher rates in very low birth weight (VLBW) infants.[3] The diagnosis of neonatal sepsis is complicated by the immature immune system of neonates, which results in a limited and non-specific response to infection. Clinical signs of sepsis, such as respiratory distress, temperature instability, and bradycardia, are common in many neonatal conditions, making clinical diagnosis challenging. Biomarkers such as complete blood count (CBC) components, C-reactive protein (CRP), and interleukin-6 (IL-6) are used to aid in the diagnosis, but their sensitivity and specificity can be influenced by various factors, including gestational age and the presence of non-infectious conditions. [4];[5] Biomarker Assessment in Neonatal Sepsis Studies on the use of CBC in neonatal sepsis diagnosis have focused on parameters such as white blood cell count (WBC), absolute neutrophil count, and the immature-to-total neutrophil ratio (I/T ratio). Although leucocytosis is a common finding, it is not present in all cases of sepsis, and WBC values can be influenced by factors other than infection, such as preeclampsia and perinatal asphyxia. Neutropenia, rather than neutrophilia, is considered more indicative of sepsis, particularly within the first 48 hours after birth.[6] CRP is another widely used biomarker for neonatal sepsis. Synthesized by hepatocytes in response to cytokines like IL-6, CRP levels rise significantly in the presence of infection. However, CRP levels can also be elevated due to non-infectious causes, reducing its specificity for sepsis diagnosis. Serial CRP measurements can improve diagnostic accuracy and help monitor the response to antibiotic therapy. [1] The search for reliable biomarkers in neonatal sepsis continues, with ongoing research into other inflammatory markers and their potential utility in early and accurate diagnosis. [3] Given the high stakes of both over-treatment and under-treatment, identifying effective diagnostic tools remains a priority in neonatal care. [7] *Klebsiella species* and *E. coli* in Neonatal Sepsis *Klebsiella species* and *E. coli* are significant pathogens in neonatal sepsis, particularly in cases of EOS. These gram-negative bacteria can lead to severe infections and are associated with high mortality rates. [8]

The dynamics of biomarkers in response to these infections are critical for understanding their pathophysiology and improving diagnostic strategies. *Klebsiella species* infections are often associated with hospital environments and invasive procedures, while *E. coli* infections are commonly linked to maternal transmission during birth. [1]; [9] Neonatal sepsis, particularly involving *Klebsiella species* and *E. coli*, requires a nuanced approach to diagnosis and treatment. Biomarker dynamics offer a promising avenue for improving clinical outcomes, though further research is necessary to refine these diagnostic tools and reduce the burden of this life-threatening condition. [10]

Aim

To investigate the dynamics of specific biomarkers—Total Leukocyte Count (TLC), Neutrophil-to-Lymphocyte Ratio (NLR), Platelet Count, and C-reactive Protein (CRP)—in neonates with sepsis caused by Klebsiella species and Escherichia coli (E. coli).

To assess their potential for improving early diagnosis and management of neonatal sepsis.

Objectives:

1. To Track Biomarker Trends.
2. To Compare Biomarker Dynamics.
3. To Identify Diagnostic Markers.
4. To Assess Immune Response Patterns.
5. To Highlight Systemic Inflammation Indicators.
6. To Propose Recommendations for Monitoring and Treatment.
7. To Suggest Future Research Directions.

Materials and Methods

This observational study aimed to assess the dynamics of biomarkers in neonates with sepsis caused by *Klebsiella* species and *E. coli*. The inclusion criteria for the study were all neonates diagnosed with sepsis due to *Klebsiella* species and *E. coli*. The exclusion criteria included neonates with incomplete medical records, neonates with polymicrobial sepsis, and neonates with known immunodeficiency. The target population comprised all neonates diagnosed with sepsis caused by *Klebsiella* species and *E. coli* who were admitted to the NICU in the paediatric department of a tertiary care teaching hospital in Gujarat. The sample size for this study was 56 neonates. Non-probability sampling, specifically convenience sampling, was used to select the study participants. Data were collected through medical records review. The data collection was carried out within the setting of the NICU. The biomarkers monitored included Total Leukocyte Count (TLC), Neutrophil Count, Lymphocyte Count, Neutrophil-to-Lymphocyte Ratio (NLR), Platelet Count, and C-

reactive Protein (CRP). Data for each biomarker were collected on Day 0, Day 1, Day 3, and Day 5 to assess their temporal dynamics. Comparative analysis was conducted between the biomarker levels in neonates with sepsis caused by *Klebsiella* species and those with sepsis caused by *E. coli*. The variations in biomarker levels were compared over the specified time points to identify distinct patterns and trends associated with each pathogen. Statistical analysis was performed to evaluate the significance of changes in biomarker levels over time and between the two groups. The chi-square test was used to assess the distribution of biomarkers between the *Klebsiella* and *E. coli* groups at various time points. Analysis of Variance (ANOVA) was employed to determine significant differences in the

mean values of TLC, Neutrophil count, Lymphocyte count, NLR, Platelet count, and CRP across different time points within both groups. A p-value of <0.05 was considered statistically significant for all comparisons.

Results

The study involved 56 neonates diagnosed with sepsis, with 35 cases caused by *Klebsiella* species and 21 cases by *E. coli*. The neonates were monitored for biomarkers including Total Leukocyte Count (TLC), Neutrophil, Lymphocyte, Neutrophil-to-Lymphocyte Ratio (NLR), Platelet Count, and C-reactive Protein (CRP) over a period of 5 days. Data for each biomarker were collected on Day 0, Day 1, Day 3, and Day 5.

Total Leukocyte Count (TLC):

In neonates with *Klebsiella* species sepsis, the TLC ranged from 3700 to 24310 on Day 0, showing variability over the subsequent days. Notably, on Day 3, a significant increase in TLC was observed in some patients, reaching values as high as 30690. Conversely, in *E. coli* sepsis cases, the TLC values showed a less pronounced fluctuation, with initial counts ranging from 1500 to 24200.

Neutrophil and Lymphocyte Counts:

The neutrophil count in *Klebsiella* species sepsis cases showed considerable variation, with values ranging from 1562 to 22140 on Day 0. The counts generally decreased by Day 5. Lymphocyte counts displayed similar variability, with a range from 950 to 12375 on Day 0, often increasing by Day 3 and stabilizing by Day 5. For *E. coli* sepsis, neutrophil counts ranged from 975 to 13859 on Day 0, generally increasing over time. Lymphocyte counts were observed to range from 525 to 13846 on Day 0, with notable increases by Day 3.

Neutrophil-to-Lymphocyte Ratio (NLR):

The NLR was calculated to assess the balance between neutrophils and lymphocytes. In *Klebsiella* species sepsis, the NLR values varied widely, with Day 0 values ranging from 0.316 to 6.143. By Day 3, the ratios showed fluctuations, often decreasing by Day 5. In *E. coli* sepsis, the NLR also exhibited significant variability. Initial values ranged from 0.292 to 15.0, with the highest ratios observed on Day 1 and subsequent decreases by Day 5.

Platelet Count:

Platelet counts in *Klebsiella* species sepsis cases ranged from 27000 to 667000 on Day 0. Over the course of 5 days, platelet counts showed a tendency to decrease, with significant drops observed in some cases by Day 3 and partial recovery by Day 5. *E. coli* sepsis cases displayed initial platelet counts ranging from 51000 to 387000. The counts generally showed a declining trend over the days, with some cases experiencing significant reductions by Day 5.

C-reactive Protein (CRP):

CRP levels in *Klebsiella* species sepsis varied widely, with values from 0.79 to 148.29 on Day 0. Notably, CRP levels often peaked on Day 1 or Day 3, with values such as 263.22 observed, before showing a decline by Day 5. In *E. coli* sepsis, CRP levels ranged from 0.15 to 113.92 on Day 0, with peaks typically occurring on Day 1 or Day 3. Values often showed a declining trend by Day 5, similar to the pattern observed in *Klebsiella* species sepsis cases.

Comparative Analysis:

Comparative analysis between *Klebsiella* species and *E. coli* sepsis cases revealed that both infections lead to significant changes in biomarker levels over time. However, certain trends were more pronounced in one infection over the other. For instance, NLR values showed more extreme fluctuations in *E. coli* sepsis, while TLC and CRP levels tended to be higher in *Klebsiella* species sepsis cases. The chi-square test indicated significant differences in the distribution of all the biomarkers between the *Klebsiella* species and *E. coli* groups at various time points ($p < 0.05$ for all comparisons). The ANOVA results showed significant differences in the mean values of TLC, neutrophil count, lymphocyte count, NLR, platelet count, and CRP across the different time points within both *Klebsiella* species and *E. coli* groups ($p < 0.05$ for all biomarkers).

The results indicate that there are significant temporal changes in the biomarker levels in neonates with sepsis caused by *Klebsiella* species and *E. coli*. These changes are statistically significant and suggest different patterns of immune response and disease progression between the two bacterial infections. Overall, the study highlights the dynamic nature of biomarker levels in neonatal sepsis, and this information can be crucial for clinicians to

tailor treatment strategies based on the specific dynamics of these biomarkers in neonatal sepsis.

Mean Biomarkers for E. coli and Klebsiella Species in Neonatal Sepsis

Biomarker	Day 0	Day 1	Day 3	Day 5
E. coli				
TLC (Mean ± SD)	13811.71 ± 6160.65	12556.48 ± 11450.28	9657.05 ± 4300.99	15200.00 ± 8063.68
Neutrophil (Mean ± SD)	6191.78 ± 3891.54	7491.34 ± 7387.61	4780.49 ± 3143.77	7115.21 ± 5254.53
Lymphocyte (Mean ± SD)	7321.18 ± 3358.53	4929.89 ± 6763.61	4744.62 ± 2744.17	7929.07 ± 4352.08
NLR (Mean ± SD)	0.95 ± 0.55	3.34 ± 4.28	1.97 ± 3.60	0.91 ± 0.65
Platelet Count (Mean ± SD)	202761.90 ± 101674.93	138857.14 ± 89933.47	132095.24 ± 101347.38	212238.10 ± 205387.90
CRP (Mean ± SD)	26.76 ± 34.80	56.18 ± 63.58	48.76 ± 54.48	34.76 ± 64.07
Klebsiella Species				
TLC (Mean ± SD)	13505.00 ± 5611.81	12265.03 ± 7862.15	11756.83 ± 7535.33	10404.57 ± 4534.95
Neutrophil (Mean ± SD)	6920.24 ± 3754.60	7952.82 ± 6411.85	6779.42 ± 4808.05	5505.90 ± 2708.92
Lymphocyte (Mean ± SD)	6300.94 ± 3529.88	4063.27 ± 2979.69	4622.79 ± 3159.79	4816.79 ± 2723.15
NLR (Mean ± SD)	1.60 ± 1.48	2.65 ± 2.02	1.76 ± 1.23	1.64 ± 1.48
Platelet Count (Mean ± SD)	220714.29 ± 109465.70	159542.86 ± 110680.34	109142.86 ± 105661.54	124031.43 ± 120464.34
CRP (Mean ± SD)	32.18 ± 35.03	72.04 ± 65.80	78.28 ± 65.43	86.95 ± 83.59

Table summarizes the mean values and standard deviations (SD) of biomarkers monitored in neonates diagnosed with sepsis caused by E. coli and Klebsiella species over a period of 5 days.

Comparative Analysis

Comparative analysis between E. coli and Klebsiella species sepsis cases revealed significant differences in biomarker levels over time. Both infections showed distinct patterns in biomarker responses:

- **Total Leukocyte Count (TLC)**: E. coli sepsis exhibited less fluctuation compared to Klebsiella species sepsis, with higher variability observed in the latter.
- **Neutrophil and Lymphocyte Counts**: Neutrophil counts generally increased over time in E. coli sepsis, whereas Klebsiella species sepsis showed more variable trends.
- **Neutrophil-to-Lymphocyte Ratio (NLR)**: E. coli sepsis displayed more extreme fluctuations in NLR values compared to Klebsiella species sepsis.
- **Platelet Count**: Both infections led to declines in platelet counts over the observation period, with varying degrees of recovery.
- **C-reactive Protein (CRP)**: CRP levels peaked earlier in Klebsiella species sepsis cases compared to E. coli sepsis, with subsequent declines noted by Day 5 in both groups.

Statistical Analysis

Statistical tests including chi-square and ANOVA indicated significant differences ($p < 0.05$) in biomarker distributions and mean values across different time points within each infection group, highlighting the dynamic nature of biomarker responses in neonatal sepsis caused by E. coli and Klebsiella species.

Table.1

Table 1: Mean Biomarker Levels in Neonatal Sepsis Caused by E. coli and Klebsiella Species

Mean Biomarkers for *Klebsiella species*	Day 0		Day 1		Day 3		Day 5	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
TLC	13505.00	5611.81	12265.03	7862.15	11756.83	7535.33	10404.57	4534.95
NEUTROPHIL	6920.24	3754.60	7952.82	6411.85	6779.42	4808.05	5505.90	2708.92
LYMPHOCYTE	6300.94	3529.88	4063.27	2979.69	4622.79	3159.79	4816.79	2723.15
NLR	1.60	1.48	2.65	2.02	1.76	1.23	1.64	1.48

PLATELET COUNT	220714.29	109465.70	159542.86	110680.34	109142.86	105661.54	124031.43	120464.34
CRP	32.18	35.03	72.04	65.80	78.28	65.43	86.95	83.59

Table 2: Mean Biomarker Levels in Neonatal Sepsis Caused by E. coli and Klebsiella Species

Mean Biomarkers for E. coli	Day 0		Day 1		Day 3		Day 5	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
TLC	13811.71	6160.65	12556.48	11450.28	9657.05	4300.99	15200.00	8063.68
Neutrophil	6191.78	3891.54	7491.34	7387.61	4780.49	3143.77	7115.21	5254.53
Lymphocyte	7321.18	3358.53	4929.89	6763.61	4744.62	2744.17	7929.07	4352.08
NLR	0.95	0.55	3.34	4.28	1.97	3.60	0.91	0.65
Platelet Count	202761.9	101674.93	138857.14	89933.47	132095.24	101347.38	212238.1	205387.9
CRP	26.76	34.80	56.18	63.58	48.76	54.48	34.76	64.07

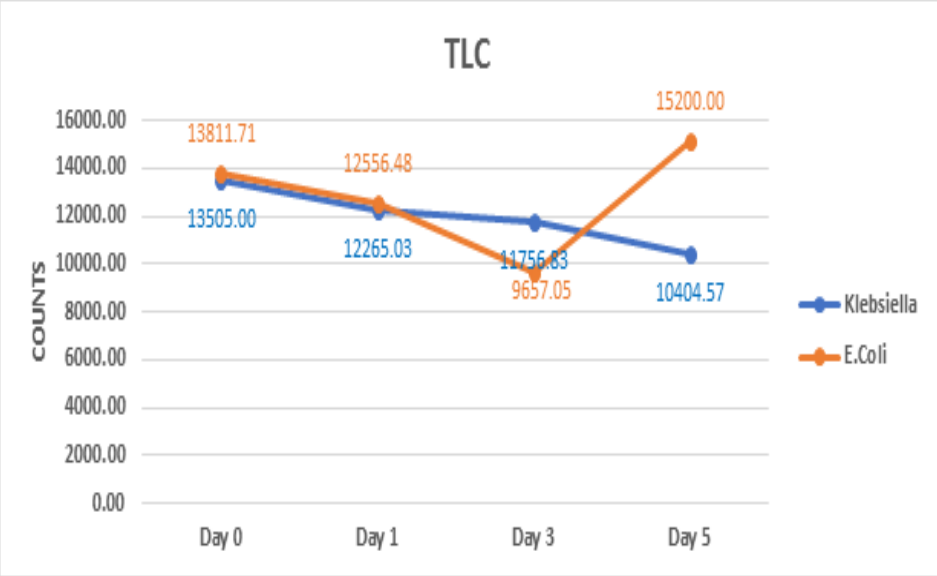

Figure 1: Total Leucocyte Count pattern in neonatal sepsis caused by Klebsiella species and E. coli

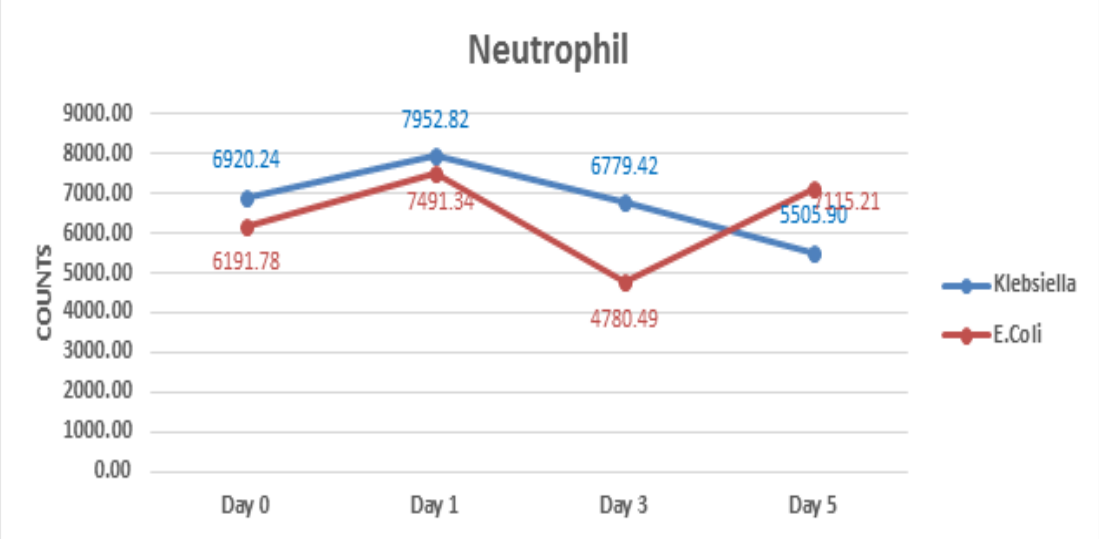

Figure 2: Neutrophil pattern in neonatal sepsis caused by *Klebsiella species* and *E. coli*

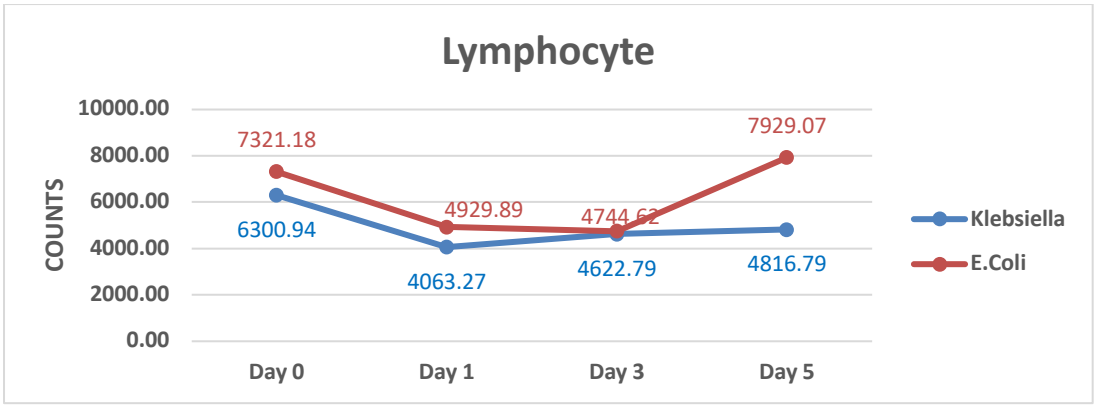

Figure 3: Platelet count pattern in neonatal sepsis caused by *Klebsiella species* and *E. coli*

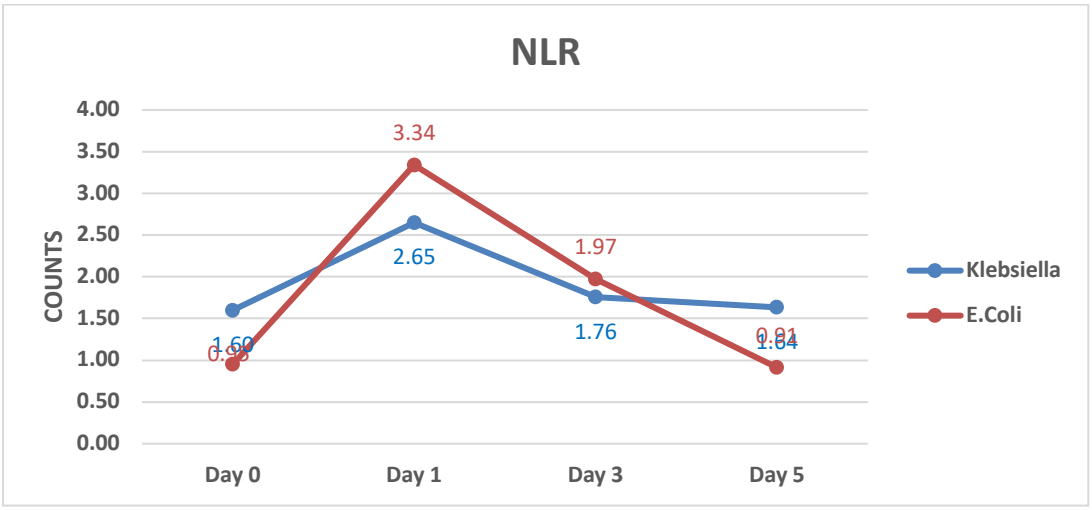

Figure 4: Neutrophil to Lymphocyte Ratio in neonatal sepsis caused by *Klebsiella species* and *E. coli*

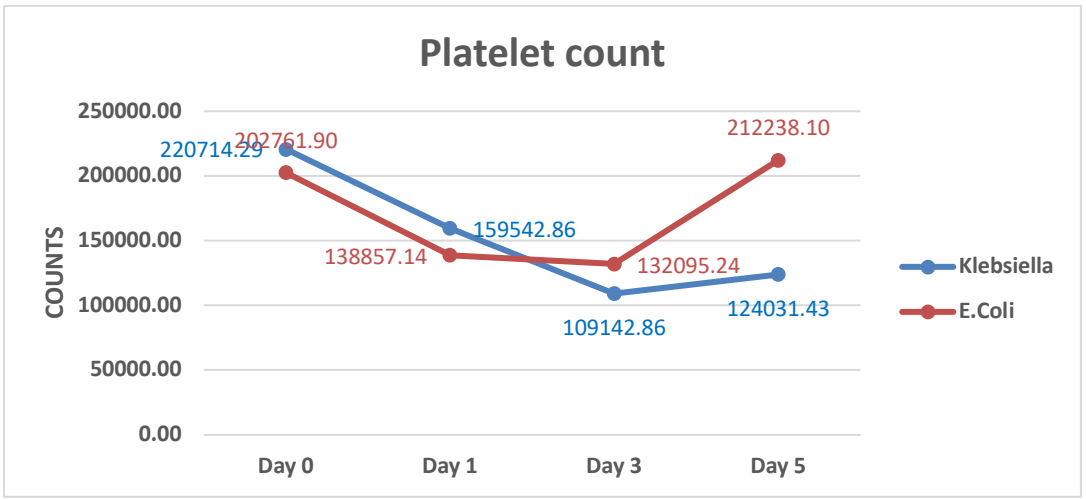

Figure 5: Platelet count pattern in neonatal sepsis caused by *Klebsiella species* and *E. coli*

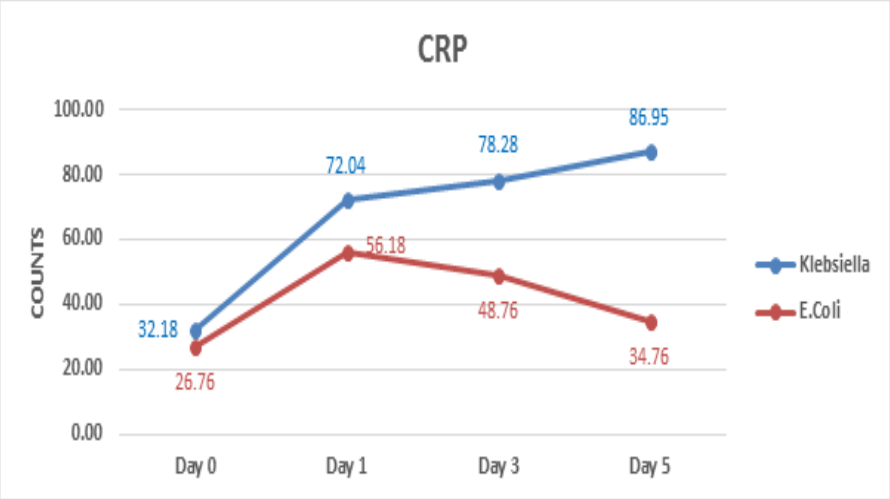

Figure 6: CRP pattern in neonatal sepsis caused by *Klebsiella species* and *E. coli*

Discussion

Neonatal sepsis, a critical condition in neonatal intensive care units (NICUs), remains a significant challenge due to its diverse etiology and nonspecific clinical presentation. This study focused on assessing biomarker dynamics in neonates with sepsis caused by Klebsiella species and E. coli, highlighting distinct patterns in biomarker responses between these two pathogens. The diagnostic landscape for neonatal sepsis relies heavily on biomarkers such as Total Leukocyte Count (TLC), Neutrophil-to-Lymphocyte Ratio (NLR), Platelet Count, and C-reactive Protein (CRP). These biomarkers play crucial roles in early detection, monitoring, and guiding therapeutic decisions. Our findings underscore significant temporal variations in these biomarkers, reflecting the evolving immune response during the course of infection. In both Klebsiella species and E. coli sepsis cases, TLC exhibited notable fluctuations, with Klebsiella species sepsis often showing higher initial counts [11]. Neutrophil counts generally trended downwards over time in Klebsiella species sepsis, contrasting with the fluctuating patterns observed in E. coli sepsis [12]. Lymphocyte counts also showed variable responses, indicative of the complex immune interactions in septic neonates [13]. The NLR proved to be a sensitive indicator of infection severity, with both pathogens displaying distinct fluctuations [14]. E. coli sepsis exhibited more pronounced NLR variability, suggesting a potentially more dynamic immune response compared to Klebsiella species sepsis [15]. Platelet counts declined consistently over time in both groups, reflecting the systemic impact of sepsis on haematological parameters [16]. CRP levels peaked early in Klebsiella species sepsis cases, followed by a decline, whereas E. coli sepsis showed more variable CRP dynamics [17]. These observations highlight the heterogeneous nature of bacterial sepsis in neonates and emphasize the need for tailored biomarker panels to optimize diagnostic accuracy and therapeutic efficacy [18]. Our study contributes to the growing body of evidence supporting the utility of biomarkers in neonatal sepsis management. By elucidating distinct biomarker profiles associated with Klebsiella species and E. coli infections, our findings underscore the potential for personalized treatment strategies based on pathogen-specific immune responses [19,20].

Conclusion

This study involved 56 neonates diagnosed with sepsis, comprising 35 cases caused by *Klebsiella* species and 21 by *E. coli*. Over five days, we monitored biomarkers such as Total Leukocyte Count (TLC), Neutrophil Count, Lymphocyte Count, Neutrophil-to-Lymphocyte Ratio (NLR), Platelet Count, and C-reactive Protein (CRP). The findings revealed distinct patterns of biomarker dynamics in response to the two pathogens. *Klebsiella* species sepsis was characterized by higher initial TLC and CRP levels, with significant fluctuations over time. In contrast, *E. coli* sepsis displayed more pronounced variability in NLR values and less fluctuation in TLC levels. Platelet counts declined consistently in both infections, while lymphocyte counts showed variable responses. These temporal changes in biomarkers were statistically significant, indicating different immune response patterns and disease progression between *Klebsiella* species and *E. coli* sepsis in neonates.

Overall, the study highlights the importance of monitoring biomarker dynamics in neonatal sepsis to tailor treatment strategies. Understanding the specific patterns associated with different pathogens can enhance diagnostic accuracy and

therapeutic efficacy, ultimately improving neonatal care.

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