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ASSOCIATION BETWEEN INFLAMMATORY BIOMARKERS AND ANTIBIOTIC ESCALATION PATTERNS IN HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED INFECTIONS: A PROSPECTIVE STUDY

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ABSTRACT

Background: Community-acquired infections frequently require empirical antibiotics, but delayed treatment modification and unnecessary broad-spectrum escalation may adversely affect outcomes and antimicrobial stewardship. Objective: To evaluate associations between inflammatory biomarkers and antibiotic escalation among hospitalized patients with community-acquired infections.

Methods: A prospective observational study was designed using records of 345 adult inpatients. Demographic variables, comorbidities, infection site, empirical antibiotics, cultures, CRP, procalcitonin, TLC, NLR, ESR, escalation patterns and clinical outcomes were evaluated. Descriptive statistics, chi-square tests, group comparisons and logistic regression were applied.

Results: Antibiotic escalation occurred in 156 patients (45.2%). Escalation was more frequent among older patients and those with diabetes, chronic kidney disease or COPD. Mean CRP, procalcitonin, TLC, NLR and ESR were significantly higher in the escalation group. Culture positivity increased escalation odds. CRP above 100 mg/L, procalcitonin above 2 ng/mL, TLC above $15\times10^3/\mu L$ and NLR above 6 showed strong graded associations. Multivariable analysis identified CRP, procalcitonin, TLC, NLR, diabetes, chronic kidney disease, positive culture and hospital stay as independent predictors. Escalation was associated with ICU admission, mechanical ventilation and mortality, while clinical cure was lower.

Conclusion: Inflammatory biomarkers, particularly procalcitonin and CRP, may assist early risk stratification and stewardship-guided antibiotic reassessment. Prospective validation is required before implementation.

Keywords: Inflammatory biomarkers; Antibiotic escalation; Community-acquired infections.

INTRODUCTION

BACKGROUND OF THE STUDY

Community-acquired infections (CAIs) remain one of the leading causes of morbidity, hospitalization, antimicrobial consumption, and infection-related mortality worldwide. These infections are acquired outside healthcare facilities or become clinically evident within 48 hours of hospital admission in individuals who have not recently been exposed to healthcare-associated settings. Despite remarkable advances in vaccination, diagnostic microbiology, infection prevention, and antimicrobial therapy, CAIs continue to place a substantial burden on healthcare systems because of increasing antimicrobial resistance, aging populations, urbanization, environmental pollution, and the growing prevalence of chronic diseases such as diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, and cardiovascular disorders.

COMMUNITY-ACQUIRED INFECTIONS (CAIs)

Community-acquired infections are infectious diseases that develop in individuals outside hospitals or healthcare institutions and are present at the time of hospital admission or become clinically evident within the first 48 hours of hospitalization. These infections are caused by microorganisms acquired from the community rather than healthcare-associated environments.

The development of community-acquired infections depends upon the interaction between pathogenic microorganisms, host immune defenses, environmental factors, and underlying medical conditions. When pathogenic bacteria overcome normal host defense mechanisms, they invade tissues, multiply rapidly, and trigger an inflammatory response that produces the clinical manifestations of infection.

Patients commonly present with fever, chills, localized pain, cough, dysuria, purulent discharge, abdominal pain, erythema, hypotension, leukocytosis, elevated inflammatory biomarkers, and varying degrees of organ dysfunction depending upon the site and severity of infection.

Early recognition and timely antimicrobial therapy remain essential because delayed treatment may result in sepsis, septic shock, multiple organ dysfunction syndrome, prolonged hospitalization, and increased mortality.

BIOMARKERS USED IN THE PRESENT STUDY

- C-Reactive Protein (CRP)
- Procalcitonin (PCT)
- Total Leukocyte Count (TLC)
- Neutrophil-to-Lymphocyte Ratio (NLR)
- Erythrocyte Sedimentation Rate (ESR)

ROLE OF BIOMARKERS IN DIAGNOSIS

Inflammatory biomarkers complement clinical examination and microbiological investigations by providing rapid and objective evidence of infection severity. They assist clinicians in differentiating bacterial from non-bacterial infections, assessing disease progression, monitoring therapeutic response, identifying patients at increased risk of complications, and determining the need for antibiotic escalation.

MATERIALS AND METHODOLOGY

5.1 Study Design

The present study was designed as a hospital-based, prospective observational study. Medical records of hospitalized patients diagnosed with community-acquired infections were reviewed to evaluate the association between inflammatory biomarker levels and antibiotic escalation patterns.

The study did not involve any direct intervention or modification of treatment. All demographic, clinical, laboratory, microbiological, pharmacotherapeutic, and outcome-related information was obtained from existing patient case records.

5.2 Study Site

The study was conducted in the Shadan Hospital And Research Centre, Peerancheru, Hyderabad and associated outpatient clinics of the selected study center. Patients receiving conventional medical treatment as well as those utilizing complementary healthcare approaches were included after obtaining informed consent.

5.3 Study Population

The study population consisted of adult patients admitted to the hospital with a diagnosis of community-acquired infection. Patients with community-acquired pneumonia, urinary tract infection, skin and soft-tissue infection, intra-abdominal infection, bloodstream infection, and other eligible community-acquired bacterial infections were considered.

5.4 Sample Size

A total of **345 patient case records** satisfying the predefined eligibility criteria were included in the study.

Sample Size Calculation (Infinite Population)

For an infinite population, assuming a standard **95% confidence level**, the sample size is calculated using the following formula:

Formula

$$n = \frac{Z^2 \times p \times (1-p)}{E^2}$$

Required Values

- **Z-score (Z)** = **1.96** (for 95% confidence level)
- **Population proportion (p)** = **0.5**
- **Margin of error (E)** = **0.05276** (5.28%)

Calculation

1. Square the Z-score:

$$1.96^2 = 3.8416$$

2. Multiply by the population proportion:

$$3.8416 \times 0.5 \times 0.5 = 0.9604$$

3. Square the margin of error:

$$0.05276^2 = 0.0027837$$

4. Divide the values:

$$n = \frac{0.9604}{0.0027837} = 345.009$$

5. Round to the nearest whole number:

$$\boxed{n = 345}$$

Final Sample Size

The required sample size is 345 participants.

5.5 Sampling Method

A consecutive sampling method was used. All eligible medical records available during the selected study period were screened, and records satisfying the inclusion and exclusion criteria were included until the required sample size of 345 patients was achieved.

Inclusion Criteria

Patients were included when they fulfilled the following criteria:

1. Patients aged 18 years or above.
2. Patients of either gender.
3. Patients admitted with a community-acquired infection.
4. Patients diagnosed with community-acquired bacterial infections that were present at the time of hospital admission or identified within 48 hours of hospitalization, including community-acquired pneumonia, urinary tract infection, skin and soft tissue infection, intra-abdominal infection, bloodstream infection, and other documented community-acquired bacterial infections.

5. Patients who received at least one systemic empirical antibiotic after hospital admission with documented details of the initial empirical antibiotic therapy.
6. Patients with at least one available inflammatory biomarker result, including CRP, procalcitonin, TLC, NLR, or ESR.
7. Patients with adequate information regarding antibiotic continuation, modification, or escalation.
8. Patients whose clinical outcomes were available at discharge, transfer, or death.

Exclusion Criteria

The following patients were excluded:

1. Patients with infections developing more than 48 hours after hospital admission.
2. Patients admitted only for elective surgical procedures without an active community-acquired infection.
3. Patients receiving antibiotics solely for surgical or procedural prophylaxis.
4. Patients with incomplete medical or medication records.
5. Patients without documented inflammatory biomarker findings.

5.6 Study Duration

The study was designed for a duration of 6 months which includes a defined prospective data-collection period followed by data entry, statistical analysis, interpretation, and preparation of the final report.

5.7 Source of Data

Data for the present retrospective study were collected from multiple hospital records to ensure complete and accurate patient information. The primary sources included **inpatient medical records, medication and treatment charts, physician progress notes, nursing records, laboratory investigation reports, microbiological culture and sensitivity reports, pharmacy dispensing records, and intensive care unit (ICU) and discharge records**. Information obtained from these sources was used to collect demographic details, clinical characteristics, inflammatory biomarker values, microbiological findings, antibiotic therapy, and patient outcomes for subsequent statistical analysis.

RESULTS

Table 1. Age Group and Antibiotic Escalation

Age Group	*Total*	*Escalation n (%)*	*No Escalation n (%)*	*Coefficient*	*OR*	*95% CI*	*p-value*
18–30	42	12 (28.6)	30 (71.4)	Reference	1.00	-	-
31–45	95	35 (36.8)	60 (63.2)	0.38	1.46	0.66–3.24	0.348

46–60	128	63 (49.2)	65 (50.8)	0.88	2.42	1.13–5.18	0.022
>60	80	46 (57.5)	34 (42.5)	1.22	3.38	1.50–7.62	0.003

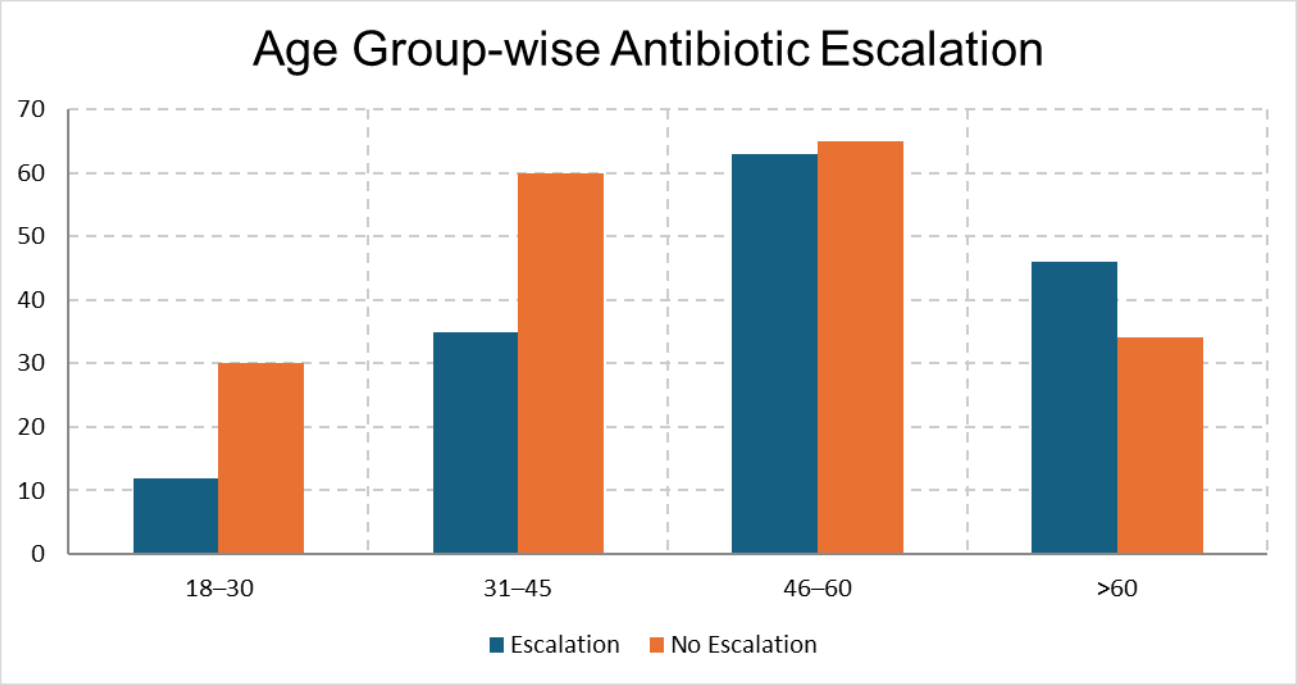

Fig. 1 Age Group and Antibiotic Escalation

The above Table no.1: Represents the distribution of antibiotic escalation across different age groups, showing that escalation increased significantly with advancing age.

Table 2. Gender and Antibiotic Escalation

Gender	*Total*	*Escalation n (%)*	*No Escalation n (%)*	*Coefficient*	*OR*	*95% CI*	*p-value*
Female	147	58 (39.5)	89 (60.5)	Reference	1.00	-	-
Male	198	98 (49.5)	100 (50.5)	0.40	1.50	0.97–2.31	0.068

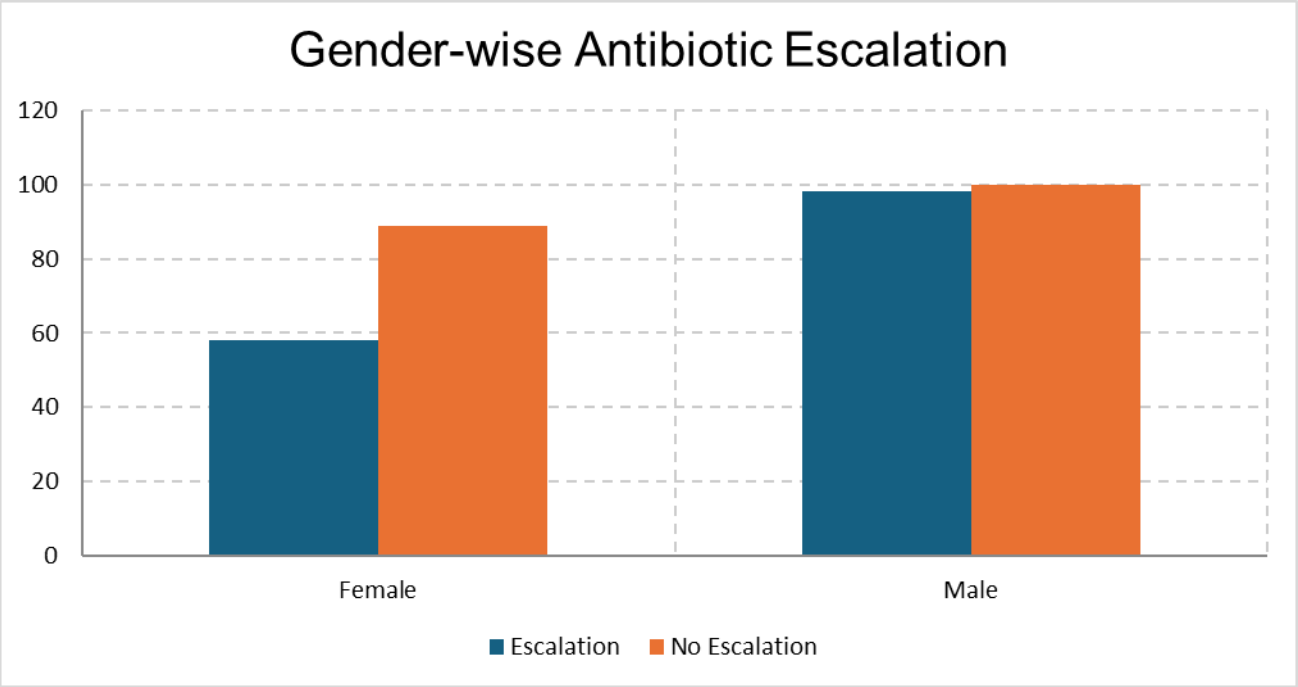

Fig. 2 Gender and Antibiotic Escalation

The above Table no.2 represents the association between gender and antibiotic escalation, indicating a higher frequency among males than females.

Table 3. Co- and Antibiotic morbidities Escalation

Co-morbidity	*Present n*	*Escalation n (%)*	*Coefficient*	*OR*	*95% CI*	*p-value*
Diabetes Mellitus	118	65 (55.1)	0.56	1.75	1.12–2.74	0.014
Hypertension	154	78 (50.6)	0.33	1.39	0.91–2.12	0.127
CKD	39	27 (69.2)	1.13	3.10	1.48–6.49	0.003
COPD	57	34 (59.6)	0.73	2.08	1.16–3.72	0.014
IHD	43	25 (58.1)	0.61	1.84	0.96–3.52	0.066

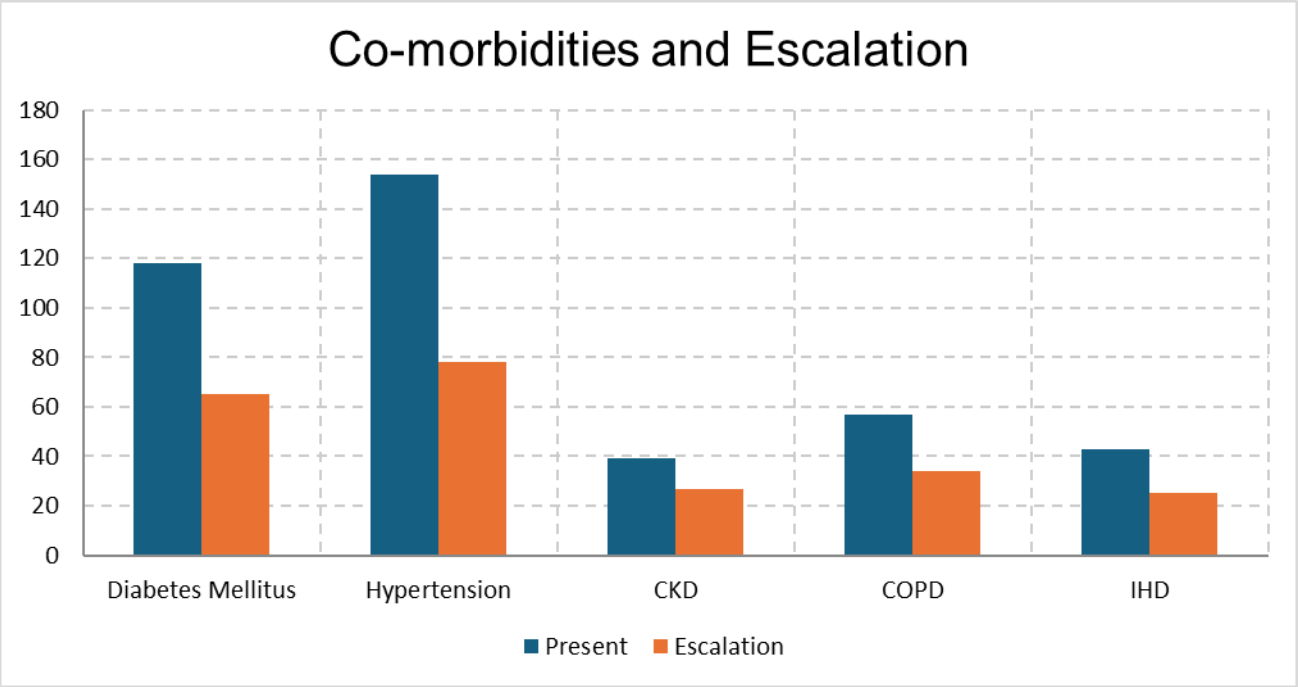

Fig. 3 Co- and Antibiotic morbidities Escalation

The above Table 3 represents the relationship between major co-morbidities and antibiotic escalation, demonstrating increased escalation among patients with diabetes mellitus, chronic kidney disease, and COPD.

Table 4. Site of Infection and Antibiotic Escalation

Infection Site	*Total*	*Escalation n (%)*	*Coefficient*	*OR*	*95% CI*	*p-value*
UTI	82	28 (34.1)	Reference	1.00	-	-
Pneumonia	128	68 (53.1)	0.78	2.18	1.23–3.86	0.008
Skin & Soft Tissue	46	17 (37.0)	0.13	1.14	0.54–2.41	0.731
Intra-abdominal	41	22 (53.7)	0.80	2.22	1.02–4.83	0.044
Bloodstream Infection	24	16 (66.7)	1.36	3.89	1.43–10.60	0.008
Others	24	5 (20.8)	-0.68	0.51	0.17–1.49	0.218

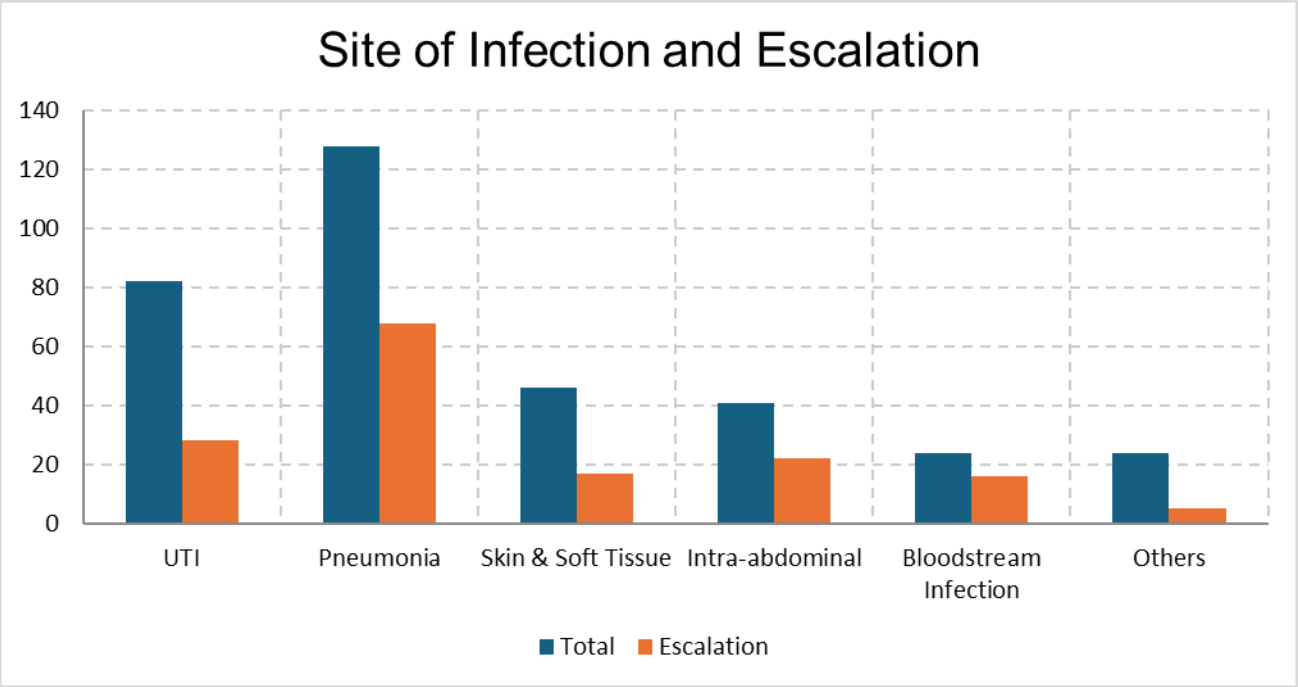

Fig. 4 Site of Infection and Antibiotic Escalation

The above Table 4 represents the association between infection site and antibiotic escalation, with bloodstream infection and pneumonia showing the highest escalation rates.

Table 5. Baseline Biomarkers

Biomarker	***Mean ± SD***	***Escalation Mean ± SD***	***No Escalation Mean ± SD***	***Coefficient***	***OR***	***p-value***
C-Reactive Protein	84.2 ± 42.8	112.4 ± 44.2	61.6 ± 28.5	0.030	1.03	<0.001
Procalcitonin	2.94 ± 1.83	4.11 ± 1.89	1.73 ± 0.92	0.476	1.61	<0.001
Total Leukocyte Count	13.4 ± 4.6	15.2 ± 4.8	11.7 ± 3.2	0.077	1.08	0.002
Neutrophil-to-Lymphocyte Ratio	6.9 ± 2.7	8.3 ± 2.8	5.4 ± 1.9	0.166	1.18	<0.001
Erythrocyte Sedimentation Rate	48.6 ± 21.8	58.2 ± 22.4	40.7 ± 17.5	0.018	1.02	0.006

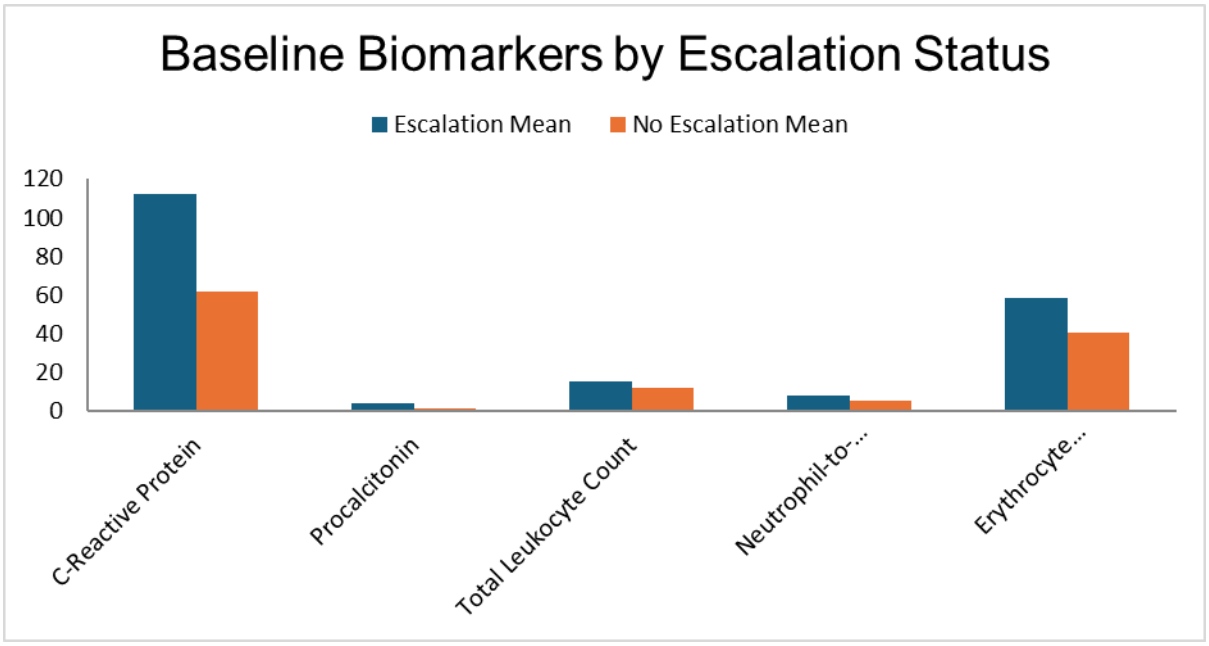

Fig. 5 Baseline Biomarkers

The above Table 5 represents the comparison of baseline inflammatory biomarker levels between escalation and non-escalation groups, showing significantly higher biomarker values in patients requiring antibiotic escalation.

Table 6. Culture Positivity and Escalation

Culture Result	*Total*	*Escalation n (%)*	*No Escalation n (%)*	*Coefficient*	*OR*	*95% CI*	*p-value*
Negative	141	42 (29.8)	99 (70.2)	Reference	1.00	-	-
Positive	204	114 (55.9)	90 (44.1)	1.09	2.99	1.90–4.70	<0.001

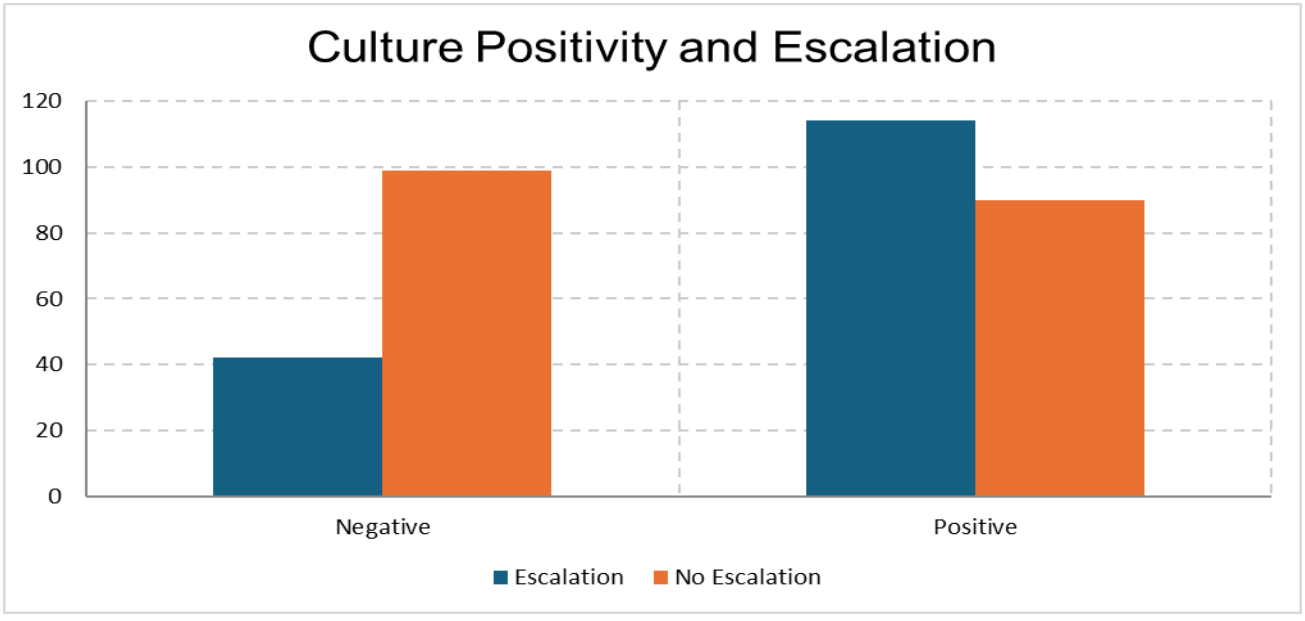

Fig. 6 Culture Positivity and Escalation

The above Table 6 represents the association between microbiological culture positivity and antibiotic escalation, demonstrating significantly greater escalation among culture-positive patients.

Table 7. Organism Isolated and Escalation

Organism	*Total*	*Escalation n (%)*	*Coefficient*	*OR*	*95% CI*	*p-value*
Streptococcus pneumoniae	37	15 (40.5)	Reference	1.00	-	-
Escherichia coli	72	39 (54.2)	0.55	1.74	0.77–3.93	0.181
Klebsiella pneumoniae	48	31 (64.6)	0.99	2.69	1.08–6.72	0.034
Staphylococcus aureus	29	16 (55.2)	0.60	1.82	0.64–5.17	0.261
Pseudomonas aeruginosa	18	13 (72.2)	1.31	3.70	1.06–12.90	0.040
Others	20	10 (50.0)	0.38	1.46	0.47–4.50	0.512

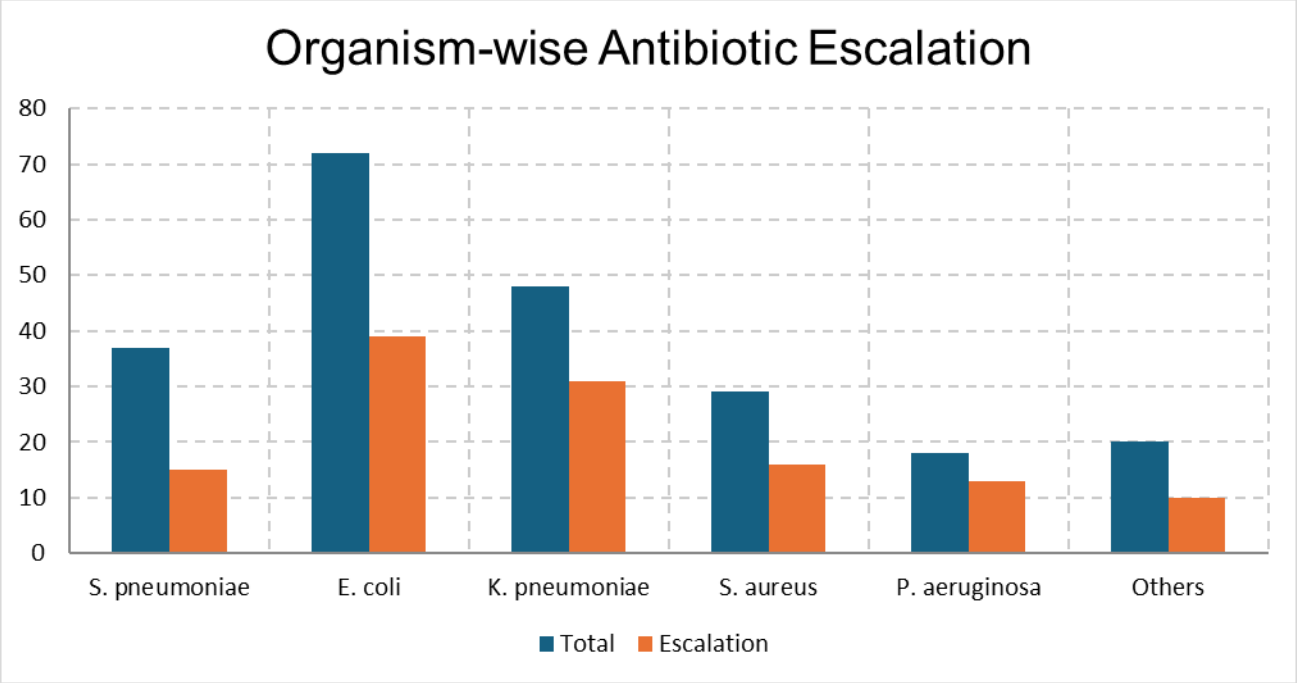

Fig. 7 Organism Isolated and Escalation

The above Table 7 represents the distribution of antibiotic escalation according to isolated microorganisms, with Pseudomonas aeruginosa and Klebsiella pneumoniae showing higher escalation rates.

Table 8. Initial Empirical Antibiotic and Escalation

Initial Antibiotic	*Total*	*Escalation n (%)*	*Coefficient*	*OR*	*95% CI*	*p-value*
Amoxicillin-Clavulanate	46	14 (30.4)	Reference	1.00	-	-
Ceftriaxone	122	48 (39.3)	0.40	1.49	0.72–3.07	0.283
Piperacillin/Tazobactam	87	45 (51.7)	0.88	2.40	1.11–5.20	0.026
Cefoperazone-Sulbactam	39	20 (51.3)	0.86	2.36	0.96–5.82	0.061
Meropenem	31	22 (71.0)	1.70	5.47	1.97–15.20	0.001
Others	20	7 (35.0)	0.20	1.23	0.40–3.79	0.720

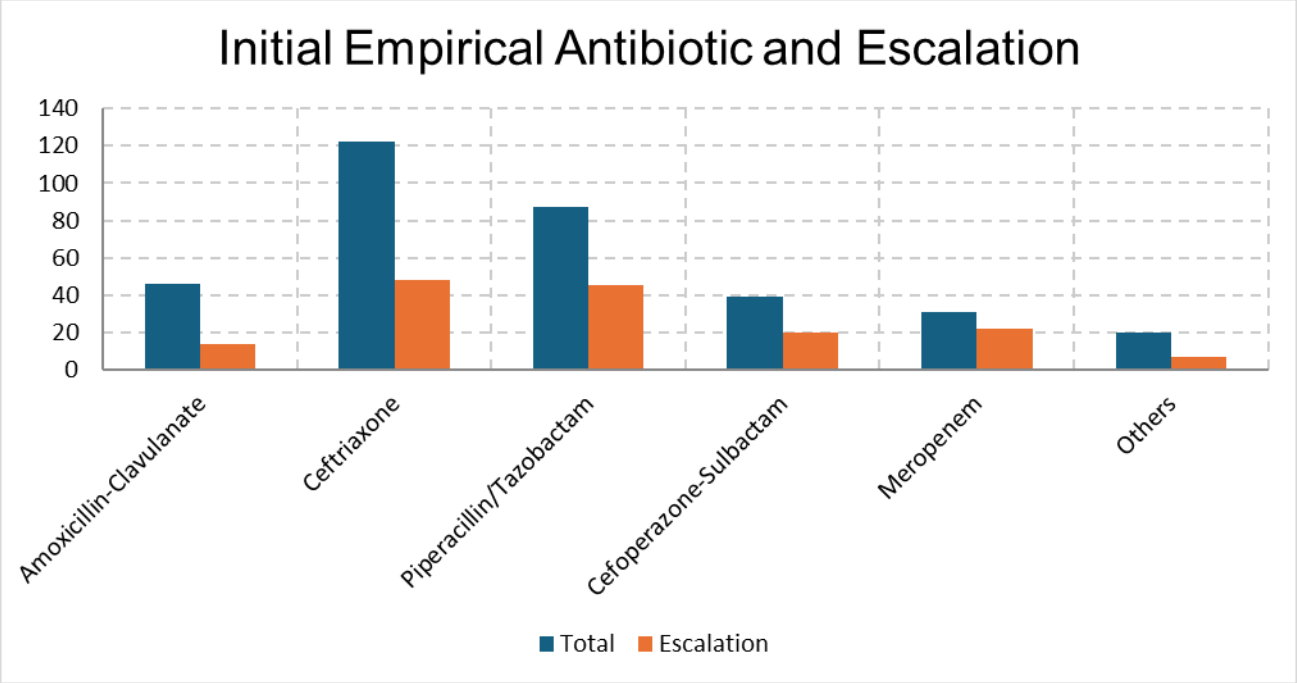

Fig. 8 Initial Empirical Antibiotic and Escalation

The above Table 8 represents the relationship between initial empirical antibiotic therapy and subsequent antibiotic escalation, with meropenem-treated patients showing the highest escalation frequency.

Table 9. Antibiotic Escalation Frequency

Escalation Pattern	*n*	*%*	*Coefficient*	*OR*	*p-value*
No Escalation	189	54.8	Reference	1.00	-
Escalated Once	103	29.9	1.00	2.72	<0.001
Escalated Twice	41	11.9	1.64	5.16	<0.001

Escalated ≥3 Times	12	3.5	2.08	8.00	<0.001

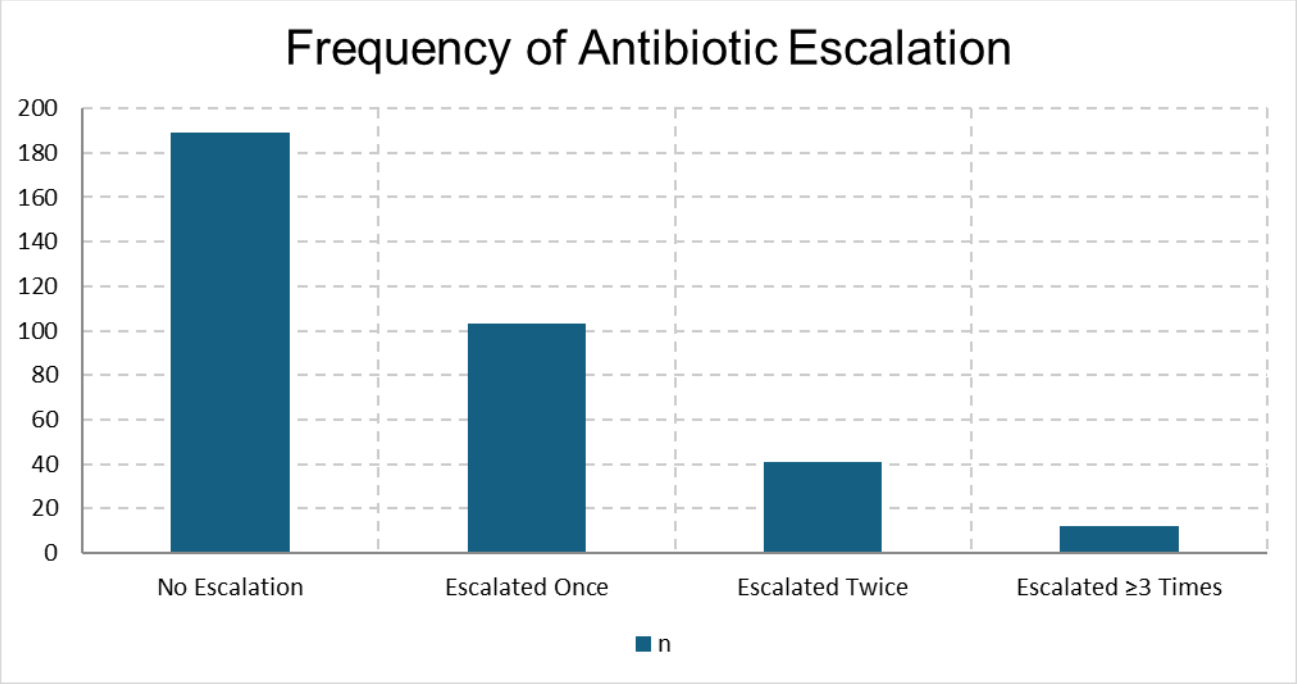

Fig. 9 Antibiotic Escalation Frequency

The above Table 9 represents the frequency distribution of antibiotic escalation patterns, indicating that most patients required no escalation while a smaller proportion underwent repeated escalation.

Table 10. C-Reactive Protein Category and Escalation

C-Reactive Protein Level	*Total*	*Escalation*	*No Escalation*	*Coefficient*	*OR*	*p-value*
<50 mg/L	114	21	93	Reference	1.00	-
50–100 mg/L	136	64	72	1.37	3.94	<0.001
>100 mg/L	95	71	24	2.57	13.10	<0.001

Chi-square = 74.6, $p < 0.001$

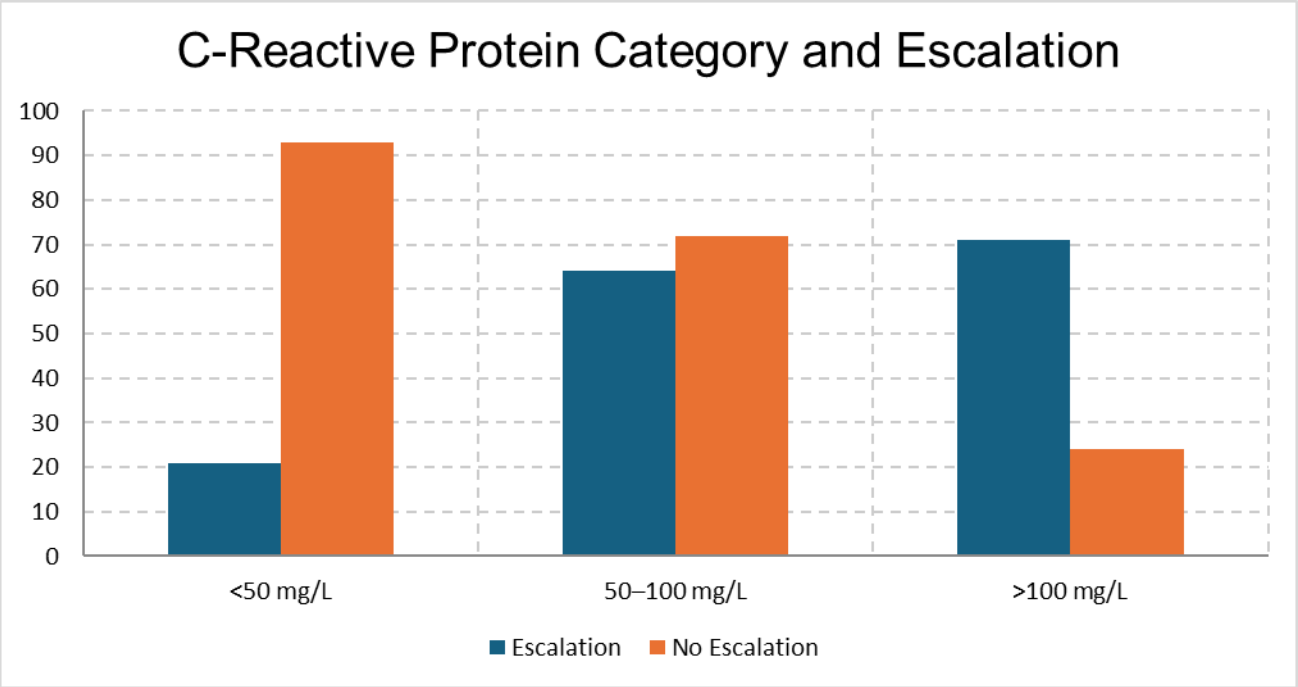

Fig. 10 C-Reactive Protein Category and Escalation

The above Table 10 represents the association between C-reactive protein categories and antibiotic escalation, demonstrating progressively higher escalation rates with increasing CRP levels.

Table 11. Procalcitonin Category and Escalation

Procalcitonin Level	*Total*	*Escalation*	*No Escalation*	*Coefficient*	*OR*	*p-value*
<0.5 ng/mL	93	12	81	Reference	1.00	-
0.5–2 ng/mL	126	54	72	1.62	5.06	<0.001
>2 ng/mL	126	90	36	2.83	16.88	<0.001

Chi-square = 85.3, $p < 0.001$

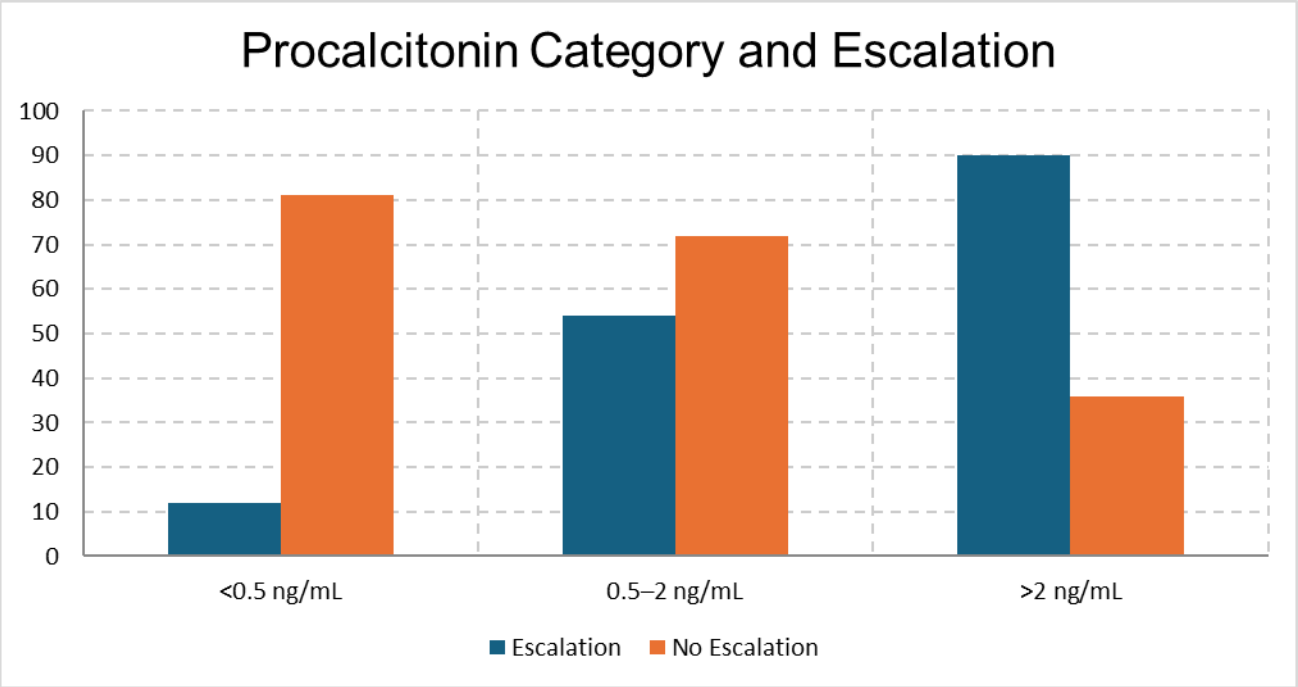

Fig. 11 Procalcitonin Category and Escalation

The above Table 11 represents the association between procalcitonin categories and antibiotic escalation, showing that higher procalcitonin levels were strongly associated with increased escalation.

Table 12. Total Leukocyte Count Category and Escalation

Total Leukocyte Count Level	*Total*	*Escalation*	*No Escalation*	*Coefficient*	*OR*	*p-value*
<10 ×10³/μL	91	22	69	Reference	1.00	-
10–15 ×10³/μL	158	69	89	0.89	2.43	0.003
>15 ×10³/μL	96	65	31	1.88	6.58	<0.001

Chi-square = 46.2, $p < 0.001$

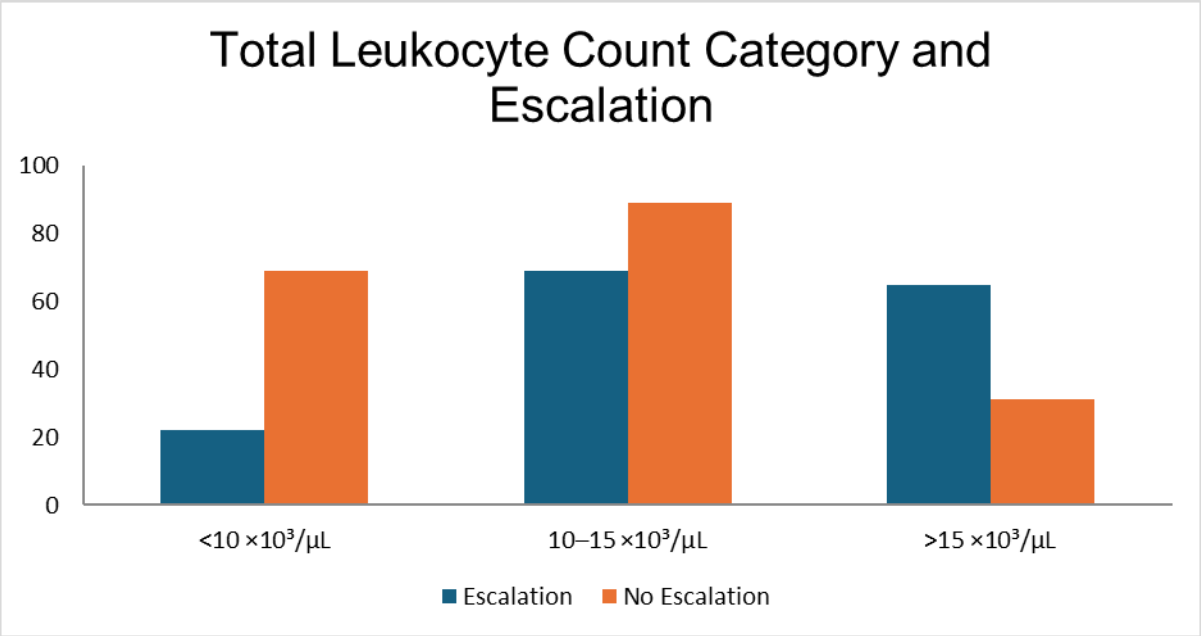

Fig. 12 Total Leukocyte Count Category and Escalation

The above Table 12 represents the relationship between total leukocyte count categories and antibiotic escalation, indicating that higher leukocyte counts were associated with greater escalation rates.

Table 13. Neutrophil-to-Lymphocyte Ratio Category and Escalation

Neutrophil-to-Lymphocyte Ratio Level	*Total*	*Escalation*	*No Escalation*	*Coefficient*	*OR*	*p-value*
<3	58	10	48	Reference	1.00	-
3–6	142	53	89	1.05	2.86	0.004
>6	145	93	52	2.19	8.59	<0.001

Chi-square = 57.8, $p < 0.001$

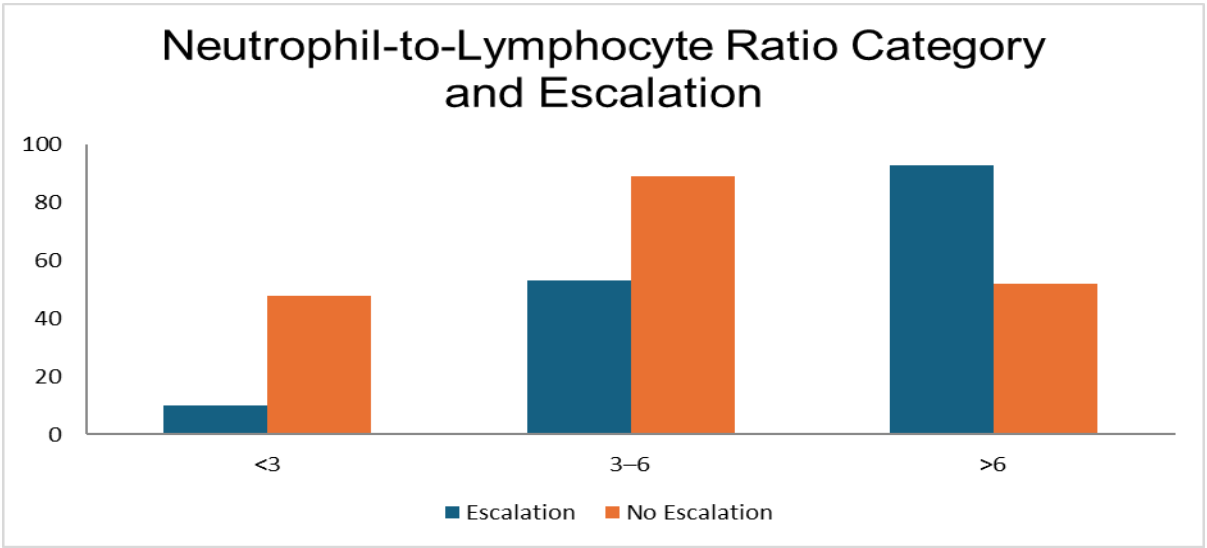

Fig. 13 Neutrophil-to-Lymphocyte Ratio Category and Escalation

The above Table 13 represents the association between neutrophil-to-lymphocyte ratio categories and antibiotic escalation, demonstrating that increasing NLR was associated with higher escalation frequency.

Table 14. Clinical Outcomes According to Escalation

Outcome	*Escalation n (%)*	*No Escalation n (%)*	*Coefficient*	*OR*	*95% CI*	*p-value*
ICU Admission	39 (25.0)	12 (6.3)	1.59	4.90	2.45–9.80	<0.001
Mechanical Ventilation	22 (14.1)	5 (2.6)	1.79	5.98	2.20–16.20	<0.001
Mortality	15 (9.6)	4 (2.1)	1.57	4.80	1.55–14.90	0.007
Clinical Cure	123 (78.8)	177 (93.7)	-1.33	0.26	0.13–0.52	<0.001

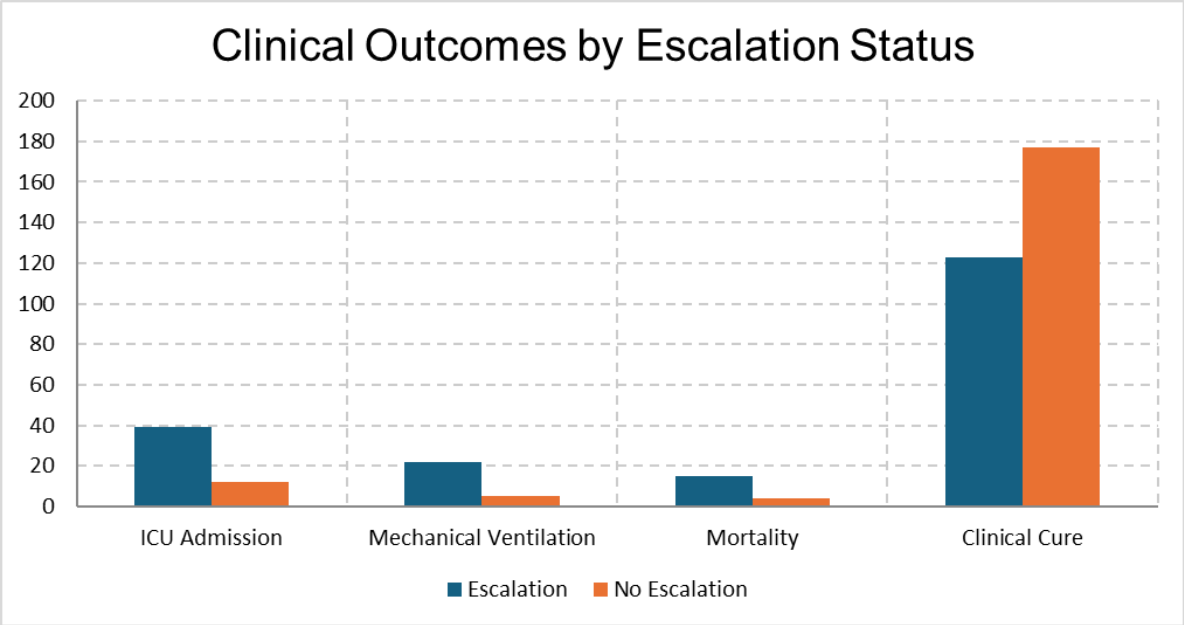

Fig. 14 Clinical Outcomes According to Escalation

The above Table 14 represents the comparison of clinical outcomes according to antibiotic escalation status, showing higher ICU admission, mechanical ventilation, and mortality, with lower clinical cure in the escalation group.

Table 15. Multivariate Logistic Regression for Predicting Antibiotic Escalation

Predictor	*Coefficient*	*SE*	*Wald*	*Adjusted OR*	*95% CI*	*p-value*
C-Reactive Protein	0.025	0.006	17.36	1.03	1.01–1.04	<0.001
Procalcitonin	0.419	0.091	21.18	1.52	1.27–1.82	<0.001

Total Leukocyte Count	0.061	0.023	7.03	1.06	1.02–1.11	0.008
Neutrophil-to-Lymphocyte Ratio	0.132	0.047	7.90	1.14	1.04–1.25	0.005
Diabetes Mellitus	0.351	0.176	3.97	1.42	1.01–2.01	0.046
Chronic kidney disease	0.642	0.288	4.97	1.90	1.08–3.35	0.026
Culture Positive	0.718	0.214	11.25	2.05	1.35–3.12	0.001
Hospital Stay	0.146	0.039	14.02	1.16	1.07–1.25	<0.001

Model χ^2 = 118.6, p < 0.001
Nagelkerke R^2 = 0.41
Classification accuracy = 78.3%

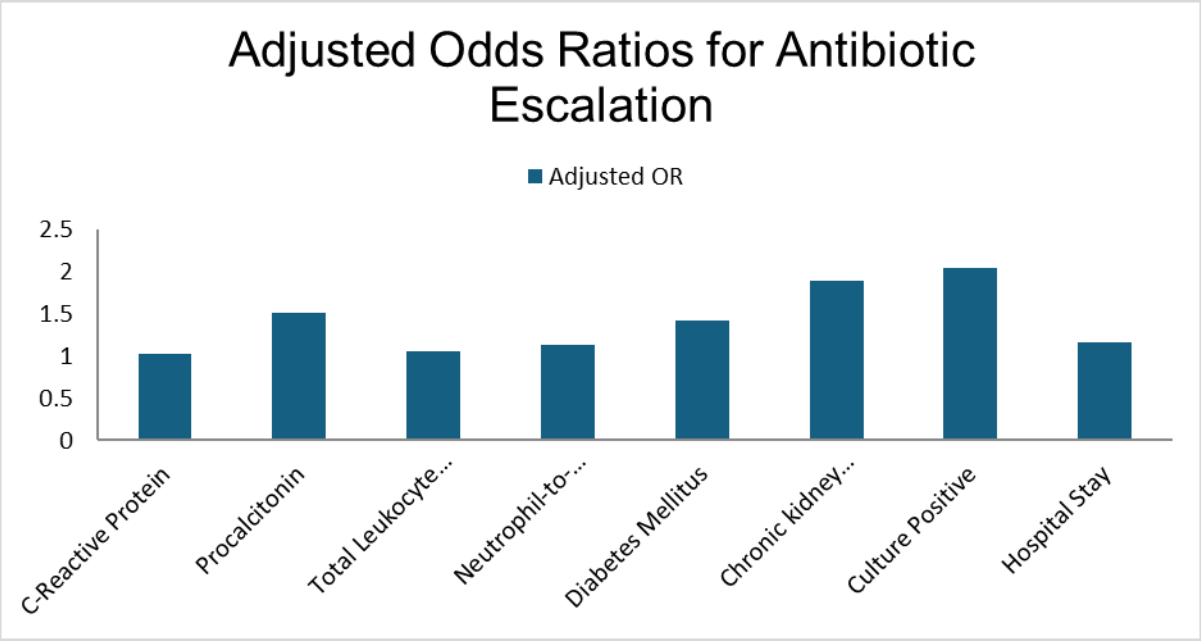

Fig. 15 Multivariate Logistic Regression for Predicting Antibiotic Escalation

The above Table 15 represents the multivariate logistic regression analysis identifying CRP, procalcitonin, total leukocyte count, neutrophil-to-lymphocyte ratio, diabetes mellitus, chronic kidney disease, culture positivity, and hospital stay as independent predictors of antibiotic escalation.

DISCUSSION

The present prospective study evaluated the association between inflammatory biomarkers and antibiotic escalation patterns among 345 hospitalized patients with community-acquired infections. The findings demonstrated that antibiotic escalation was related to patient age, selected comorbidities, infection site, inflammatory biomarker levels, culture positivity, isolated organisms, initial empirical antibiotic selection, and adverse clinical outcomes. Multivariate logistic regression further identified CRP, procalcitonin, TLC, NLR, diabetes mellitus, chronic kidney disease, positive culture, and hospital stay as independent predictors of antibiotic escalation.

Outcomes

Escalated patients had higher rates of ICU admission, mechanical ventilation, and mortality. Escalation was associated with 4.90 times greater odds of ICU admission, 5.98 times greater odds of mechanical ventilation, and 4.80 times greater odds of death. Clinical cure was lower, with an odds ratio of 0.26.

These findings indicate that escalation was a marker of a more complicated clinical course. They do not prove that antibiotic escalation caused poor outcomes. Patients who are severely ill, have resistant organisms, show persistent inflammation, or develop organ dysfunction are inherently more likely both to receive escalation and to experience adverse outcomes.

This phenomenon is known as confounding by indication. Therefore, the findings should be expressed as associations between escalation and outcomes, not as evidence that escalation independently worsened prognosis.

Culture positivity doubled the adjusted odds of escalation, while CKD increased the odds by 90%. Each unit increase in procalcitonin increased adjusted odds by 52%. The positive biomarker coefficients indicate that higher inflammatory values were independently associated with escalation after adjustment for other model variables.

Hospital stay was also associated with escalation. However, temporality requires caution. A prolonged stay may contribute to greater opportunity for treatment modification, while escalation and severe infection may themselves prolong hospitalization. For prediction of escalation, only hospital stay accumulated before escalation should ideally be used. Total hospital stay is more appropriately treated as an outcome unless time-dependent analysis is performed.

Implications

The study supports a combined assessment model in which biomarker trends, culture findings, infection site, comorbidity burden, clinical deterioration, and response to empirical therapy are reviewed together. Biomarker-guided algorithms have been shown to reduce antibiotic exposure in hospitalized community-acquired pneumonia, but their implementation requires active clinical feedback and predefined stewardship rules.

CONCLUSION

The present study concluded that inflammatory biomarkers were significantly associated with antibiotic escalation among hospitalized patients with community-acquired infections.

Higher CRP, procalcitonin, TLC, NLR, and ESR values were observed in patients requiring escalation. Procalcitonin and CRP showed particularly strong graded associations, indicating that increasing biomarker levels may help identify patients at greater risk of inadequate response to empirical treatment.

Older age, diabetes mellitus, chronic kidney disease, COPD, bloodstream infection, pneumonia, culture positivity, and isolation of resistant-prone organisms were also associated with escalation.

The multivariate analysis demonstrated that CRP, procalcitonin, TLC, NLR, diabetes mellitus, chronic kidney disease, culture positivity, and hospital stay independently predicted escalation. These variables may therefore contribute to hospital-based risk-assessment and antimicrobial stewardship strategies.

Antibiotic escalation was associated with ICU admission, mechanical ventilation, mortality, and reduced clinical cure. However, these findings should not be interpreted as evidence that escalation caused adverse outcomes. Escalation was more likely to occur in patients with severe infection, resistant pathogens, treatment failure, or clinical deterioration.

Inflammatory biomarkers should not be used as isolated triggers for broad-spectrum antibiotic administration. Their greatest value lies in structured interpretation alongside clinical examination, serial response, microbiological cultures, susceptibility results, infection source, organ function, and local antibiotic policies.

The study supports active participation of Pharm.D professionals and clinical pharmacists in biomarker monitoring, culture review, dose optimization, antibiotic reassessment, and antimicrobial stewardship. Prospective multicenter studies with serial biomarker monitoring are recommended to validate the proposed predictors and develop reliable escalation and de-escalation algorithms.

Conflict of Interest: The Authors declares no conflict of interest.

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