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Comparison of Polymyxin B with Minocycline versus Polymyxin B with High-Dose Sulbactam in Carbapenem-Resistant Acinetobacter baumannii Ventilator-Associated Pneumonia: A Randomized Double-Blind Non-Inferiority Trial

Parimal Chintala
All India Institute of Medical Sciences
Ashwini A Kundar
All India Institute of Medical Sciences
Bharat Yalla
Yashoda Hospitals
Ganga Prasad
drgpd@yahoo.com

All India Institute of Medical Sciences
Souvik Maitra
All India Institute of Medical Sciences
Rahul Kumar Anand
All India Institute of Medical Sciences
Babita Gupta
All India Institute of Medical Sciences
Kapil Dev Soni
All India Institute of Medical Sciences
Richa Agarwal
All India Institute of Medical Sciences
Purva Mathur
All India Institute of Medical Sciences

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Abstract

Background:
Ventilator-associated pneumonia (VAP) remains a frequent and clinically important complication of mechanical ventilation, and its diagnosis is inherently challenging in critically ill adults. In many Asian ICUs, Acinetobacter baumannii is a leading VAP pathogen, with high rates of multidrug resistance and carbapenem resistance. Therapeutic options are constrained by resistance and the toxicity/pharmacokinetic limitations of polymyxins and sulbactam. Given the uncertainty regarding the optimal companion agent to polymyxin B, this study aimed to test whether polymyxin B plus minocycline is non-inferior to polymyxin B plus high-dose sulbactam for carbapenem-resistant A. baumannii CRAB VAP.

Materials and methods:

We conducted a prospective randomized double-blind non-inferiority trial in medical and surgical ICUs at AIIMS, New Delhi, enrolling adults (≥18 years) with microbiologically confirmed CRAB VAP, whose isolates were intermediate to polymyxins and susceptible to minocycline; patients with short ventilation (<48 h), prior exposure to study drugs, polymicrobial/culture-negative VAP, allergy, or pregnancy were excluded. Participants were randomized (74/group) to polymyxin B (25,000 U/kg loading, then 12,500 U/kg q12h) plus minocycline 200 mg IV q12h, or the same polymyxin B plus sulbactam 9 g/day (as plain sulbactam or cefoperazone–sulbactam by prolonged infusion), planned for 14 days with blinded clinical management and independent microbiological review.

Results:

148 patients were included in the final analysis (74 per group). By day 14, clinical cure occurred in 77.03% of the minocycline group versus 67.57% in the sulbactam group (risk difference +9.46%); the lower bound of the 90% confidence interval for the difference (−2.57%) exceeded the prespecified −20% margin, confirming non-inferiority. Microbiological eradication, ventilator-free days, ICU length of stay, VAP-related mortality, 28-day mortality, and new-onset AKI did not differ significantly between the groups.

Multivariable analysis identified baseline SOFA (adjusted OR, 0.79 per point) and early clinical progress days (adjusted OR, 1.68 per day) as independent predictors of cure, with no interaction by ICU type or severity.

Conclusion:

Polymyxin B plus minocycline, therefore, provides randomized evidence of non-inferior clinical efficacy to polymyxin B plus high-dose sulbactam for CRAB VAP, supporting minocycline as a pragmatic companion agent in settings with prevalent sulbactam resistance and limited access to newer therapies, while underscoring the dominant influence of baseline organ failure on outcomes.

Trial Registration: CTRI/2024/08/071797. (Registered on 1-08-2024)

Background

Ventilator-associated pneumonia (VAP) is a common complication of mechanical ventilation, with a global prevalence of 15%–20% [1]. Incidence is higher in low-income countries and in patients with impaired consciousness, trauma, prolonged ventilation, and prior antibiotic exposure.[2] Diagnosis remains difficult as hypoxemia and radiographic infiltrates lack specificity, with no single strategy consistently improving outcomes.[3,4]

Gram-negative bacilli predominate in VAP, with Acinetobacter species being the leading pathogens in Asia[2]. Indian studies have shown gram-negative organisms in 96% of VAP cases, with Acinetobacter causing one-third, and regional reviews have identified A. baumannii as the most frequent pathogen at 26% [5]. A. baumannii is a major ICU threat due to environmental persistence and resistance, with mortality of 35%–70% and increasing multidrug-resistant strains[6–8].

Therapeutic options for carbapenem-resistant A. baumannii pneumonia remain limited. Polymyxins retain activity against most carbapenem-resistant A. baumannii (CRAB) isolates (> 80%), but are limited by nephrotoxicity, poor pulmonary penetration, and variable colistin conversion[9,10]. Polymyxin B reaches steady state faster and shows consistent exposure across renal function, making it preferred when polymyxins are used. Sulbactam has intrinsic activity against Acinetobacter through PBP binding; however, multiple β-lactamases compromise this activity. Pharmacokinetic modelling shows declining target attainment with increasing MICs[11,12]. Sulbactam can be degraded by class A, C, D, and B metallo β-lactamases, with OXA enzymes driving rising resistance. Standard sulbactam dosing covers susceptible isolates, whereas prolonged infusion regimens extend coverage to MIC 8 mg/L; however, it is ineffective as monotherapy at MIC ≥ 16 mg/L [13,14]. Tetracycline derivatives, particularly minocycline, show activity against CRAB isolates, with favourable pulmonary penetration and synergy with polymyxins[15–17]. Clinical series document its use in nosocomial pneumonia, though target attainment may be challenging at higher MICs[18]. Most data supporting minocycline combinations come from observational studies, limiting definitive conclusions.

Liu et al.[19] reported that high dose ampicillin-sulbactam with a second agent showed greatest mortality reduction in critically ill patients with MDR/XDR A. baumannii. Combination therapy is used due to limited single-agent efficacy, toxicity, and pharmacokinetic limitations. The IDSA[20] and ESCMID[21] guidelines recommend the use of two in vitro active agents. In trials of polymyxin regimens, survival benefits were inconsistent with common toxicity, and no trials have evaluated polymyxin B[22–24]. IDSA has positioned polymyxins as combination therapy adjuncts with sulbactam agents. The IDSA recommendation for high dose sulbactam relies on Makris et al[25], who showed better clinical response with colistin plus high dose ampicillin sulbactam versus colistin alone. However, this trial had limitations: small sample size, susceptible isolates, unblinded design, and permitted antibiotic changes. Minocycline

shows promise as an alternative partner given its activity against CRAB, pulmonary penetration, and synergy with polymyxins, but comparative efficacy versus sulbactam remains uncertain. Given that CRAB ventilator-associated pneumonia has high mortality and a lack of evidence for superior companion agents, testing whether polymyxin B plus minocycline is non-inferior to polymyxin B plus high-dose sulbactam is important. We proposed a randomized double-blind trial comparing these combinations for CRAB ventilator-associated pneumonia.

Materials and Methods

This prospective randomized double-blind non-inferiority trial was conducted in medical and surgical ICUs under the Department of Anaesthesiology, Pain Medicine & Critical Care at AIIMS, New Delhi, India, after obtaining approval from the Institutional Ethics Committee [IECPG-POLMIN] and written informed consent from the patient's legally acceptable representative and CTRI [CTRI/2024/08/071797] registered on 1-08-2024. The current trial is reported according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines[26]. **(CONSORT Checklist-supplementary file).** Hospitalized adults, aged ≥ 18 years, with microbiologically confirmed VAP caused by carbapenem-resistant Acinetobacter baumannii, with isolates demonstrating intermediate susceptibility to polymyxin and preserved susceptibility to minocycline, were included. The exclusion criteria included patients who refused to participate in the study; those receiving short-term mechanical ventilation for less than 48 hours; patients receiving empirical antimicrobial therapy with colistin, polymyxin B, tigecycline, minocycline, or sulbactam-based regimens; patients with a clinical diagnosis of ventilator-associated pneumonia (VAP) without microbiological confirmation or with polymicrobial VAP; patients with known allergies to polymyxin, sulbactam, or minocycline; and pregnant patients.

Patients were randomly allocated to **Group 1 or Group 2** using computer-generated random sequences. **Group 1** received polymyxin B + minocycline, an intravenous loading dose of polymyxin B 25,000 U/kg actual body weight, followed by 12,500 U/kg every 12 hours as maintenance. Minocycline 200 mg IV every 12 hours was co-administered, and **Group 2** received polymyxin B + high-dose sulbactam, the same polymyxin B dosing as above. Sulbactam was given as plain sulbactam or as cefoperazone-sulbactam (2:1), depending upon the availability, to deliver sulbactam (high dose) of 9 g/day; cefoperazone-sulbactam 4.5 g was infused every 4 hours as a 3-hour continuous infusion. Allocation concealment was ensured using sequentially numbered, sealed, and opaque envelopes. Both groups received 14 days of antibiotic therapy.

Clinical management was performed by the treating ICU physician, who was blinded to treatment allocation and responsible for all bedside management decisions. Clinical improvement or failure was determined using predefined study criteria. In cases of uncertainty, the final assessment was made by consensus among the ICU physicians. Antibiotics were de-escalated or discontinued at the clinician's discretion in accordance with antimicrobial stewardship principles when clear clinical improvement was observed. Bronchoalveolar lavage or endotracheal aspirate sampling was performed after antibiotic therapy on day 14 or at the time of extubation, if extubation occurred earlier.

All microbiological data, including culture results and antimicrobial susceptibility profiles, were reviewed by an independent ICU physician who was not involved in patient care, treatment decisions, or the assessment of clinical outcomes.

We recorded baseline demographics, comorbidities, type of ICU, provisional diagnosis, vital signs, APACHE II and SOFA scores, and the presence of septic shock. APACHE II was calculated from the worst values in the first 24 h after VAP diagnosis. SOFA was recorded at the time of CRAB VAP diagnosis.

The primary outcome was to compare clinical response (clinical cure and clinical failure) in patients after 14 days of treatment between the two groups.

Patients were considered clinically cured of CRAB VAP when there was an improvement in signs and symptoms (i.e., fever resolution, infiltrate resolution on imaging, improvement in vital signs/TLC/FiO2/purulent secretions) for at least 48 h after the initiation of antibiotics, and clinical failure was considered when there was only partial improvement, persistence, or worsening of VAP signs and symptoms. Treatment was also considered a failure if the patient died during the deterioration of clinical findings of VAP or septic shock or if the physician in charge of the patient changed therapy after deterioration; however, if the death occurred within 48 h of the initiation of therapy, the case was not considered a true antibiotic failure and was not included in the study.

The secondary outcomes included microbiological clearance of *Acinetobacter baumannii*, which will be evaluated using tracheal aspirate sampling at the end of therapy on day 14 or earlier in patients undergoing extubation before day 14 of antibiotic therapy. The median number of days from the initiation of antibiotics to clinical improvement will be compared between the two groups among patients who achieved clinical cure. A comparison of Sequential Organ Failure Assessment (SOFA) scores on day 5 between the two treatment groups will also be performed. Additional outcomes included the number of patients extubated by day 14 of antibiotic therapy, ventilator-free days by day 28 (considering day 1 as the start of antibiotic therapy), and the total number of ICU days between the groups. VAP-related mortality between groups during the first 14 days will be assessed; VAP-related mortality is defined as death occurring during the treatment period when signs of pneumonia persist, or death due to septic shock not attributable to causes other than VAP. Early VAP-related mortality was defined as death occurring from day 3 to day 5, and late VAP-related mortality from day 6 to day 14, with only the first episode of VAP considered for analysis in each patient. Additionally, 28-day crude mortality between the groups will be compared. New-onset acute kidney injury (AKI) after initiation of treatment will also be evaluated. In patients with normal baseline renal function, nephrotoxicity will be defined as a serum creatinine value > 2 mg/dL, or a reduction in calculated creatinine clearance by 50% compared with baseline, or a decline in renal function necessitating renal replacement therapy. In patients with pre-existing renal dysfunction, nephrotoxicity will be defined as an increase of > 50% in baseline serum creatinine or a reduction in calculated creatinine clearance by 50% relative to the value at therapy initiation

Statistical analyses:

Categorical variables were summarized as frequencies and percentages. Continuous variables are presented as mean ± standard deviation for normally distributed data and as median with interquartile range for non-normally distributed data. Normality of distribution was assessed using the Shapiro–Wilk test.

Comparisons between the two independent groups were performed using the independent-samples t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed variables. Paired continuous variables were analyzed using the paired t-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. For comparisons involving more than two repeated measurements, repeated-measures analysis of variance was used for normally distributed data, and the Friedman test was applied for non-normally distributed data.

Categorical variables were compared using the Chi-square test. Fisher's exact test was used when more than 20% of the cells in a contingency table had an expected frequency of less than 5. Correlations between two continuous variables were assessed using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-normally distributed data. Outcome measures were reported as mean differences or risk ratios with 95% confidence intervals. A two-sided p value of less than 0.05 was considered statistically significant. Associations between treatment exposure and response or survival outcomes were evaluated using univariate and multivariate logistic regression analyses, and results were expressed as unadjusted and adjusted odds ratios with 95% confidence intervals. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (IBM Corp., Chicago, USA), version 23.0.

Results

A total of 269 patients were initially recruited for this study between 2024 and 2026. Of these, 121 patients were subsequently excluded based on the predefined exclusion criteria. Consequently, 148 patients were included in the study, with 74 allocated to each treatment group. Figure 1

Baseline characteristics are presented in Table 1. Most patients were admitted to medical intensive care units with sepsis or septic shock, and acute respiratory distress syndrome (ARDS) was not the primary cause. Patterns of empiric antibiotic therapy and the time to availability of culture reports were comparable between the two groups.

Table 1

Demographic characteristics distribution. (BMI- Body Mass Index, ICU- Intensive Care Unit, ARDS- Acute Respiratory Distress Syndrome, VAP- Ventilator Associated Pneumonia, CT- Computed Tomography, TLC- Total Leucocyte Count, Fio2- Fraction inspired oxygen, SOFA- Sequential Organ Failure Assessment, APACHE- Acute Physiology and Chronic Health Evaluation)

Parameters	**Group**	
	Polymyxin B with Sulbactam **(n = 74)**	**Polymyxin B with Minocycline** **(n = 74)**
Age (Years)	44.91 ± 18.24	44.12 ± 19.64
Gender		
Male	42 (56.8%)	43 (58.1%)
Female	32 (43.2%)	31 (41.9%)
BMI (kg/m²)	24.43 ± 4.31	23.95 ± 3.72
Chronic Lung Disease (Present)	13 (17.6%)	11 (14.9%)
Diabetes Mellitus (Present)	8 (10.8%)	6 (8.1%)
ICU Type		
Medical ICU	42 (56.8%)	36 (48.6%)
Surgical ICU	32 (43.2%)	38 (51.4%)
Diagnosis		
Others	8 (10.8%)	2 (2.7%)
ARDS/Respiratory Failure	5 (6.8%)	6 (8.1%)
Sepsis/Septic Shock (Excluding ARDS as Cause)	32 (43.2%)	32 (43.2%)
Trauma	7 (9.5%)	12 (16.2%)
Surgery	20 (27.0%)	19 (25.7%)
Poisoning	2 (2.7%)	3 (4.1%)
Days From Hospital to ICU Admission	3.91 ± 13.03	3.12 ± 7.37
Days From Intubation to VAP Suspicion	5.23 ± 2.74	6.14 ± 4.41
Chest X-Ray/CT		
None	0 (0.0%)	0 (0.0%)
Right	31 (41.9%)	30 (40.5%)

Parameters	Group	
	Polymyxin B with Sulbactam **(n = 74)**	**Polymyxin B with Minocycline** **(n = 74)**
Left	20 (27.0%)	20 (27.0%)
Bilateral	23 (31.1%)	24 (32.4%)
Temperature		
Afebrile	23 (31.1%)	26 (35.1%)
Hyperthermia	50 (67.6%)	45 (60.8%)
Hypothermia	1 (1.4%)	3 (4.1%)
TLC		
Normal Range	37 (50.0%)	33 (44.6%)
Leukocytosis	33 (44.6%)	39 (52.7%)
Leukopenia	4 (5.4%)	2 (2.7%)
Increase In FiO_2 (Present)	62 (83.8%)	69 (93.2%)
Increase In Purulent Secretions (Present)	34 (45.9%)	29 (39.2%)
Vasopressor Use		
None	48 (64.9%)	52 (70.3%)
Single Vasopressor	14 (18.9%)	10 (13.5%)
Double Vasopressor	12 (16.2%)	12 (16.2%)
SOFA Score	10.92 ± 3.80	10.69 ± 3.50
APACHE Score	20.70 ± 6.18	21.12 ± 6.14
Empiric Antibiotic Therapy for VAP		
None	1 (1.4%)	1 (1.4%)
Betalactam	4 (5.4%)	3 (4.1%)
Betalactam - Betalactamase Inhibitor	21 (28.4%)	26 (35.1%)

Clinical response in patients after 14 days of treatment between the two groups

By day 14, clinical cure was observed in 77.03% of patients receiving the combination of polymyxin B and minocycline, compared to 67.57% of those treated with polymyxin B and sulbactam. This corresponds to an absolute risk difference of + 9.46%, favouring the minocycline combination. Utilizing a prespecified noninferiority margin of − 20%, the lower bound of the 90% confidence interval for the risk difference (− 2.57%) remained above the noninferiority threshold, thereby meeting the criterion for noninferiority. This result was further corroborated by the Farrington–Manning score test ($Z = 4.004$, $p < 0.0001$). Although the point estimate favoured the minocycline group, the confidence interval included 0, and the study was not designed to evaluate superiority. Figure 2

In a univariable logistic regression analysis, the treatment arm did not exhibit a statistically significant association with clinical cure by day 14 (OR 1.61, 95% CI 0.78–3.37, $p = 0.200$). In contrast, higher baseline severity was inversely correlated with the likelihood of cure, as indicated by the SOFA score (OR, 0.78; 95% CI, 0.69–0.87; $p < 0.001$) and the APACHE II score (OR, 0.89; 95% CI, 0.83–0.95; $p < 0.001$). The number of clinical progress days showed a strong positive association with cure (OR, 1.74; 95% CI, 1.47–2.12; $p < 0.001$). Age and the duration from intubation to the suspicion of VAP did not demonstrate a significant association with clinical cure. Figure 3

In a multivariable logistic regression analysis, five candidate predictors were evaluated for Day-14 cure. Clinical progress days were the only significant predictor, with an adjusted odds ratio (OR) of 1.69 (95% CI 1.42–2.07, $p < 0.001$) for cure per additional day. A bidirectional stepwise selection process retained the SOFA score and the number of clinical progress days as significant predictors. In the final model, both variables independently predicted cure: baseline SOFA score (adjusted OR 0.79 per point increase, 95% CI 0.69–0.91, $p = 0.001$) and clinical progress days (adjusted OR 1.68 per day, 95% CI 1.39–2.01, $p < 0.001$). The stepwise selection process in this study confirmed that the severity of illness, as measured by the Sequential Organ Failure Assessment (SOFA) score, and early clinical response are the primary determinants of treatment success. There was no evidence of a significant interaction between treatment assignment and ICU type or baseline severity (all interaction p-values > 0.10), indicating the consistent effectiveness of polymyxin B + minocycline versus polymyxin B + sulbactam across patient subgroups. No other covariate interactions were significant. Figure 4

Microbiological eradication

There was no significant association between the treatment group and microbiological eradication ($\chi^2 = 1.834$, $p = 0.176$). In the polymyxin B with sulbactam group, microbiological eradication was achieved in 71.6% of patients compared to 81.1% in the polymyxin B with minocycline group. Table 2

Table 2
Secondary outcomes

Outcomes	Polymyxin B with Sulbactam (n = 74)	Polymyxin B with Minocycline (n = 74)	P Value
Microbiological eradication	71.6%	81.1%	0.176
Clinical Progress (days)	5 (4–8)	6 (5–7)	0.833
Day 5 SOFA Score	8 (4.25–13.5)	6 (5–9)	0.106
Extubated By Day 14	64.9%	70.3%	0.482
Ventilator Free Days By Day 28	17 (0–20)	18.5 (8.25-21)	0.089
Duration of ICU Stay (Days)	14.5 (10–18)	16 (12.25-19)	0.153
VAP Mortality	12.2%	17.6%	0.355
Early VAP	6.8%	4.1%	0.646
Late VAP	10.8%	8.1%	0.646
Crude 28 Day Mortality	27.0%	20.3%	0.333
New Onset AKI After Start of Treatment	33.8%	29.7%	0.596

(SOFA- Sequential Organ Failure Assessment, ICU- Intensive Care Unit, VAP- Ventilator Associated Pneumonia, AKI- Acute Kidney Injury)

Clinical progress days

The median (IQR) number of clinical progress days was 5 (4–8) in the polymyxin B plus minocycline group and 6 (5–7) in the polymyxin B plus sulbactam group. No significant difference was observed between the groups (W = 1391, p = 0.833). Table 2

Day 5 SOFA Score

The polymyxin B and sulbactam group exhibited a median (IQR) day 5 SOFA score of 8 (4.25–13.5), compared to a score of 6 (5–9) in the group treated with polymyxin B and minocycline. The difference between the groups was not statistically significant (W = 3158.0, p = 0.106). Table 2

Extubation by Day 14

There was no significant difference in Day 14 extubation status between the two groups ($\chi^2 = 0.493$, p = 0.482). In the polymyxin B with sulbactam group, 64.9% were extubated by Day 14, compared to 70.3% in the polymyxin B with minocycline group. Table 2

Ventilator-free days by day 28

There was no statistically significant difference between groups for ventilator-free days by day 28 (W = 2300.500, p = 0.089). The polymyxin B-with-sulbactam group had a median (IQR) of 17 (0–20) versus 18.5 (8.25–21) days in the polymyxin B-with-minocycline group. Table 2

Duration of ICU stay (Days)

The median ICU stay was 15 days (IQR, 10–18) in the polymyxin B plus sulbactam group and 16 days (IQR, 12–19) in the polymyxin B plus minocycline group, with no statistically significant difference between groups (W = 2365.5, p = 0.153). The slightly lower median ICU stay observed in the sulbactam group reflects the inclusion of patients who died earlier during ICU admission, for whom the length of stay was calculated until death. Table 2

VAP mortality

In the polymyxin B plus minocycline group, 12.2% died, compared with 17.6% in the polymyxin B plus sulbactam group, with no significant difference between groups ($\chi^2 = 0.854$, p = 0.355).

Early VAP is defined as when mortality occurs from day 3 to day 5, and late VAP from day 6 to day 14. The distribution of VAP mortality did not differ significantly between the groups ($\chi^2 = 0.913$, p = 0.646). Table 2

Crude 28-day mortality

In the polymyxin B with sulbactam group, 27% died by day 28, whereas in the polymyxin B with minocycline group, 20% died; no significant difference was observed in mortality distribution between the groups ($\chi^2 = 0.94$, p = 0.33). Table 2

New onset AKI after start of treatment

No significant difference was observed in the distribution of new-onset AKI between the groups ($\chi^2 = 0.28$, p = 0.60). New-onset AKI occurred in 34% of patients in the polymyxin B with sulbactam group versus 30% in the polymyxin B with minocycline group. Table 2

Discussion

In this randomized double-blind non-inferiority trial involving critically ill patients with ventilator-associated pneumonia due to carbapenem-resistant Acinetobacter baumannii, the combination of polymyxin-B with minocycline achieved clinical cure rates that were non-inferior to polymyxin-B with high-dose sulbactam. The observed clinical cure rates in our study are consistent with prior reports of combination therapy in CRAB pneumonia, where success rates typically range between 60% and 75% despite aggressive antimicrobial strategies. Microbiological eradication rates were higher in the minocycline group (81% compared to 72%); however, this difference did not reach statistical

significance[27]. A significant factor contributing to this observation is the limitation of endotracheal sampling in cases of ventilator-associated pneumonia. Patients who exhibited earlier clinical improvement were frequently extubated before day 14, resulting in endotracheal cultures being obtained at the time of extubation rather than at a predetermined day-14 time point. This methodology may have captured residual colonization or non-viable organisms despite clinical resolution, potentially leading to an underestimation of true microbiological eradication. Similar methodological limitations were also identified in the study by Makris et al[25]. Despite these constraints, the observed directionality toward higher eradication with minocycline is biologically coherent and consistent with in-vitro and animal data demonstrating sustained bactericidal activity and synergistic killing when minocycline is paired with polymyxins[28]. Although the median number of clinical progress days did not differ significantly between the minocycline group (5 days) and the sulbactam group (6 days), clinical progress days were strongly associated with Day-14 cure and emerged as an independent predictor on multivariable logistic regression. Higher organ failure scores were independently associated with lower odds of cure. The slightly shorter ICU stay observed in the sulbactam group, although not statistically significant, likely reflects early in-ICU mortality, as length of stay was calculated up to the time of death for non-survivors. Other outcomes, including extubation by Day 14, ventilator-free days by Day 28, VAP-related mortality, and crude 28-day mortality, did not differ between the 2 groups. A subset of patients with cervical spine injury remained ventilator dependent, which likely prolonged ICU length of stay and reduced ventilator-free days by Day 28. Mortality remained high in both groups, reflecting the severity of illness, elevated baseline APACHE and SOFA scores, and the intrinsic lethality of CRAB VAP rather than antimicrobial failure alone. This pattern is consistent with prior CRAB studies, where improvements in clinical response do not reliably translate into mortality reductions because downstream outcomes are heavily influenced by baseline organ dysfunction, competing ICU risks, and host factors[29]. Similar challenges have been highlighted across the broader VAP literature, where diagnostic uncertainty and heterogeneous case mix dilute detectable mortality differences between treatment strategies[30]. New-onset acute kidney injury occurred in approximately one-third of patients in both treatment arms, with no statistically significant difference between groups. Although polymyxin-related nephrotoxicity was initially suspected, the observed pattern suggests that AKI was more closely associated with ongoing or non-resolving VAP and rising illness severity, reflected by increasing SOFA scores, rather than with polymyxin exposure or the choice of partner agent. In this context, the development of AKI is likely attributable to the usual determinants of renal dysfunction in the ICU, including critical illness severity, sepsis-related hemodynamic derangements, vasopressor requirement, and multiorgan dysfunction. Taken together, the secondary outcome profile confirms that the minocycline-based therapy was at least as effective as the sulbactam-based therapy across multiple endpoints, satisfying the criteria for non-inferiority without any evident trade-off in clinical outcomes.

Current IDSA and ESCMID guidelines recommend combination regimens including colistin, tigecycline, minocycline, or sulbactam-based therapies, guided by infection site and susceptibility, to address pharmacokinetic limitations and resistance[20,21,31]. Polymyxins show consistent activity against carbapenem-resistant Acinetobacter baumannii (CRAB) across regions, maintaining effectiveness

regardless of the β-lactamase class 11. Their membrane-disruptive mechanism enhances bacterial permeability and enables synergistic activity with companion agents[32]. Polymyxin B is preferred over colistin because of its predictable pharmacokinetics in critically ill patients and absence of renal prodrug conversion, enabling reliable systemic exposure[33]. These properties support guideline recommendations for polymyxin-based combination therapy for serious CRAB infections[34,35]. However, its clinical use is limited by a narrow therapeutic index, nephrotoxicity, poor lung penetration, and heteroresistance, leading to treatment failure[32,35].

Support for high-dose sulbactam–based combination therapy in CRAB infections comes from a single randomized trial by Makris et al[25], with limited generalizability due to methodological issues including unblinded assessment and variable antibiotic therapy after day 5. All isolates were susceptible to colistin and sulbactam, and colistin's unpredictable pharmacokinetics limit its applicability to current polymyxin B treatments. Sulbactam shows intrinsic activity against Acinetobacter baumannii through PBP inhibition[12,31]. Its epithelial lining fluid penetration and time-dependent killing support its use in pneumonia, with studies suggesting improved outcomes using high-dose, prolonged-infusion combination therapy versus polymyxin monotherapy[19,25,36]. Guidelines recommend high-dose sulbactam (≥ 9 g/day) for susceptible or intermediate CRAB isolates[14,20]. However, resistance biology and pharmacokinetic limitations constrain its effectiveness. Globally, CRAB resistance involves OXA-type carbapenemases, NDM co-expression, and PBP alterations, causing widespread ampicillin–sulbactam non-susceptibility[37–39]. These mechanisms result in variable susceptibility, with 5%–50% of CRAB isolates remaining susceptible and MICs ranging from 16 to > 256 µg/mL in high-burden settings[11,12,40,41]. Studies show standard dosing achieves targets only at MICs ≤ 4 mg/L, while high-dose regimens cover MICs of 8 mg/L but fail at ≥ 16 mg/L[14,42,43]. Challenges include unclear renal dosing adjustments, infusion burden, and toxicity concerns[42,44]. Clinical benefits are limited to lower MIC settings with optimized dosing[42]. Sulbactam–durlobactam offers advancement through β-lactamase inhibition, showing superior efficacy versus colistin[7,45,46]. However, its activity is limited against strains with metallo-β-lactamases or PBP3 mutations, which are common in Indian isolates[34,39]. Limited availability and cost restrict access in many countries, maintaining reliance on older regimens despite rising MICs[38,45].

In environments where sulbactam efficacy is compromised, therapeutic success depends on combination strategies beyond β-lactamase inhibition or PBP saturation. Polymyxin-based regimens with active agents, such as minocycline, remain important[20,34].Minocycline has re-emerged as a partner drug for carbapenem-resistant Acinetobacter baumannii (CRAB) owing to its favorable pharmacokinetic properties in pulmonary infections[35,42]. Compared with tigecycline, minocycline achieves better epithelial lining fluid and lung tissue penetration, with acceptable safety, supporting its use in pneumonia[35,47]. Surveillance studies show preserved in-vitro activity against CRAB isolates, with susceptibility rates of 60%–80% using CLSI breakpoints, though regional variability exists[16,48,49]. Clinical data for minocycline in CRAB infections have come from observational studies, mostly in combination regimens. A

systematic review reported clinical success rates of 73% and microbiological success rates of 60%, primarily in pneumonia[18]. Similar outcomes have been reported by other studies[6,17,48] although they were limited by retrospective design and variable dosing. The ACUMIN phase IV study showed reliable target attainment with high-dose intravenous minocycline primarily at minimum inhibitory concentrations (MICs) ≤ 1 µg/mL[50]. These findings suggest that the current CLSI breakpoint of ≤ 4 µg/mL may overestimate clinical activity in critically ill patients with pneumonia[34,51].Using a breakpoint of ≤ 1 µg/mL, susceptibility rates fall below 40% in high-resistance regions[35,49]. Minocycline shows reproducible synergy with polymyxins. Polymyxin B disrupts the membrane of A. baumannii and enhances minocycline accumulation, creating synergistic killing across various models[28,52]. This interaction is crucial in CRAB pneumonia, where bacterial burden often limits the efficacy of monotherapy. Minocycline requires no renal dose adjustment, has favorable nephrotoxicity compared to polymyxins, and allows intravenous-to-oral conversion[9,53]. Despite using standard CLSI criteria, this study showed that polymyxin B plus minocycline was non-inferior to sulbactam-based regimens.

Pharmacodynamic limitations explain the modest performance of sulbactam regimens, in which β-lactamase resistance and failure to achieve exposure targets limit efficacy. This aligns with our findings, wherein polymyxin B plus minocycline was non-inferior to sulbactam combinations. Sulbactam durlobactam efficacy may decrease in high burden settings like India, where CRAB isolates harbor metallo β lactamases and PBP3 alterations, limiting activity despite β lactamase inhibition[39].These factors support polymyxin B plus minocycline as a rational strategy for CRAB ventilator associated pneumonia. The non-inferiority and favorable estimates align with minocycline's lung penetration and polymyxin synergy, supporting its relevance in severe pulmonary infections.

Strengths and limitations

This study employed a randomized, double-blind, non-inferiority design with allocation concealment and blinded outcome assessment, with well-balanced baseline demographics, illness severity, VAP onset timing, and antibiotic exposure between groups, minimizing bias and strengthening causal inference. Enrolment was limited to microbiologically confirmed ventilator-associated pneumonia caused by carbapenem-resistant Acinetobacter baumannii (CRAB), excluding polymicrobial and culture-negative cases to ensure that outcomes were directly attributable to CRAB pneumonia. To preserve internal validity, patients with clinical deterioration from suspected new infections without microbiological confirmation were excluded to avoid misclassification of treatment failure. Patients with new microbiologically proven non-CRAB infections were excluded, ensuring that outcomes remained specific to the index CRAB episode. Patients showing clinical improvement, successful extubation, and microbiological clearance were classified as clinical successes, whereas recurrent infections without clearance were excluded. Colistin minimum inhibitory concentrations were determined using broth microdilution per CLSI recommendations, with appropriate breakpoints ensuring rigorous susceptibility interpretation. Given the high institutional carbapenem resistance, CRAB-directed therapy began post-randomization, excluding colistin- or minocycline-resistant isolates; patients with prior study regimen

exposure were excluded to ensure uniform therapy initiation. Both regimens were optimized using high-intensity strategies, including weight-based polymyxin-B dosing and high-dose sulbactam via prolonged infusion. Independent microbiological adjudication preserved blinding and standardized assessment. The study included comprehensive endpoints: clinical cure, microbiological eradication, ventilator-free days, extubation time, ICU stay, kidney injury, and mortality, maintaining applicability to resource-constrained ICUs with high CRAB prevalence.

This study has several limitations. Individual sulbactam MIC values were unavailable as the Clinical and Laboratory Standards Institute lacks validated breakpoints for sulbactam against Acinetobacter spp., requiring reliance on FDA breakpoints and limiting the correlation of pharmacodynamic targets with outcomes; however, including both susceptible and resistant isolates reflects real-world practice. Ampicillin–sulbactam susceptibility was tested using disk diffusion, which has higher error rates in Acinetobacter, though this was partially mitigated by broth microdilution for colistin MIC and consistent criteria across arms. While minocycline MICs were reported, outcomes were not stratified by MIC range, limiting the precision in identifying optimal subgroups, although randomization reduced systematic bias. Molecular resistance profiling was not performed, precluding mechanistic correlations between resistance determinants and response; however, it reflected LMIC ICU diagnostic realities. Culture results became available 2–3 days after BAL sampling, creating a delay between diagnosis and definitive therapy, potentially affecting response assessment. The 20% non-inferiority margin was pragmatically selected for a life-threatening infection; while justified by data, it should be considered when interpreting equivalence. The study was powered for clinical cure rather than mortality; therefore, neutral mortality findings do not prove equivalence, and the sample size limits the detection of small effects. Diagnostic challenges in ventilator-associated pneumonia may have diluted treatment effects but were mitigated through strict criteria and objective endpoints. As both arms included polymyxin B, the trial does not inform on polymyxin-sparing strategies; finally, being conducted in two tertiary-care centers within one country may limit generalizability, although patient diversity supports applicability to similar settings.

Conclusion

In this randomized, double-blind, non-inferiority trial, polymyxin B combined with minocycline achieved a non-inferior clinical cure compared to polymyxin B combined with high-dose sulbactam for ventilator-associated pneumonia caused by carbapenem-resistant Acinetobacter baumannii. In low and middle-income settings where sulbactam resistance is common and access to newer agents, such as durlobactum, remains limited, polymyxin B plus minocycline represents a pragmatic therapeutic option. Although meta-analyses favour high-exposure sulbactam combinations, these data are limited by heterogeneity in susceptibility and study design. The present trial provides randomized evidence showing that in settings with prevalent sulbactam resistance, a minocycline-based polymyxin regimen achieves equivalent outcomes. Future studies should define sulbactam's role in CRAB, including optimized dosing benefits and activity across NDM and OXA-mediated resistance. A real-world evaluation of sulbactam durlobactam is needed to determine its effectiveness in CRAB with NDM and PBP3 resistance mechanisms. Focusing on MIC-guided antibiotic selection, resistance profiling,

pharmacokinetic assessment, and development of targeted agents will improve treatment strategies for CRAB ventilator-associated pneumonia.

Declarations

Consent for publication: Yes.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare no competing interests.

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Authors' contributions:

PC: Conceptualization, study design, data collection, statistical analysis, manuscript drafting.

AA, SM: Study design, statistical analysis, manuscript drafting, and revision.

BY: Participant recruitment, data acquisition, statistical analysis, literature review.

KD, RK: Data interpretation, critical manuscript review.

GP: Overall supervision, conceptual guidance, final manuscript approval.

BG, RA: Literature review, figure/table preparation, manuscript proofreading.

PM: Statistical analysis support, data validation, manuscript editing

All authors read and approved the final manuscript.

Conflict of interest – There are no conflicts of interest

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Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences, New Delhi (IECPG-POLYMIN). Written informed consent was obtained from all participants or their legally authorized representatives before enrollment.

Consent for publication
Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

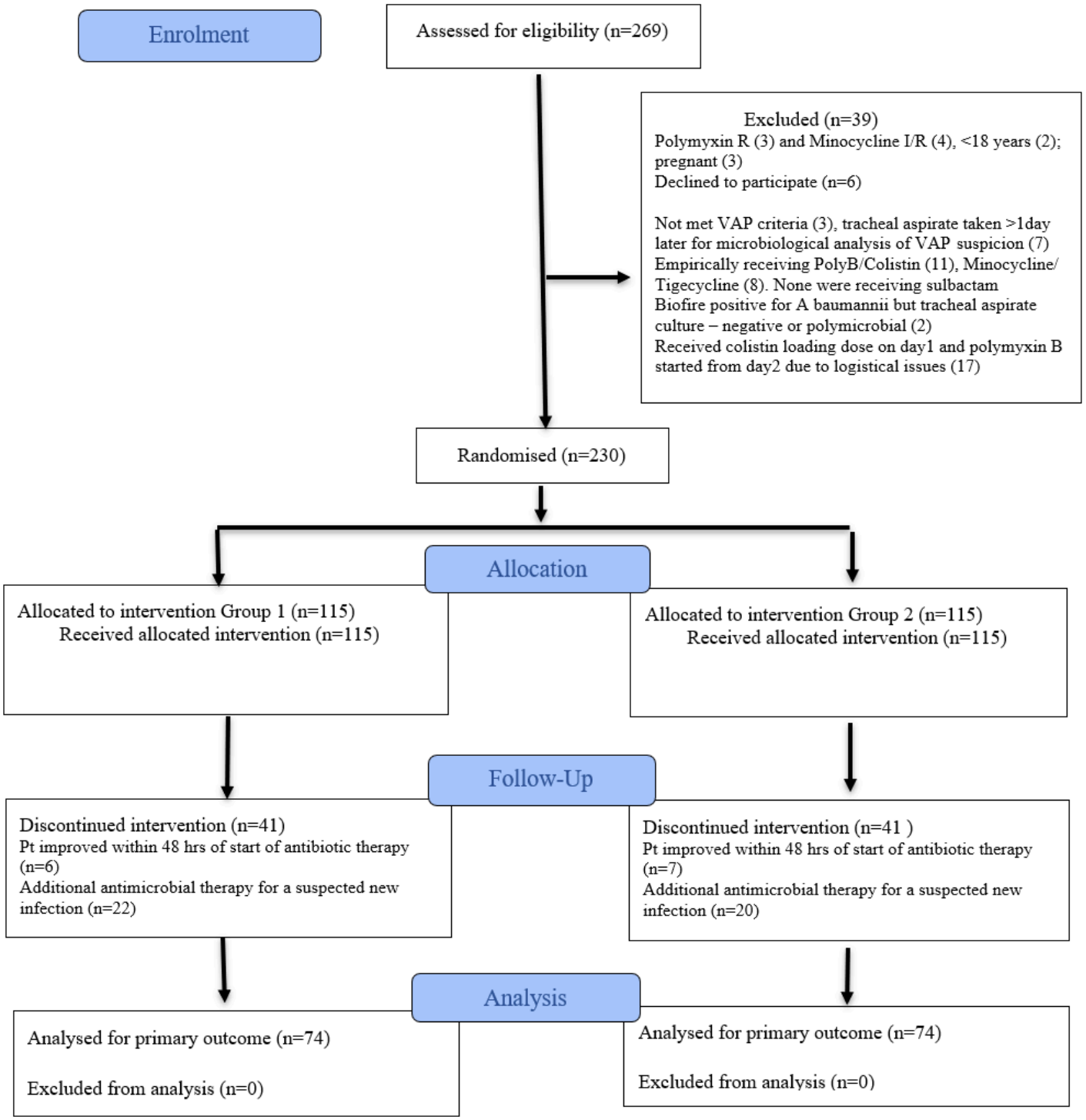


Figure 1

CONSORT flow diagram

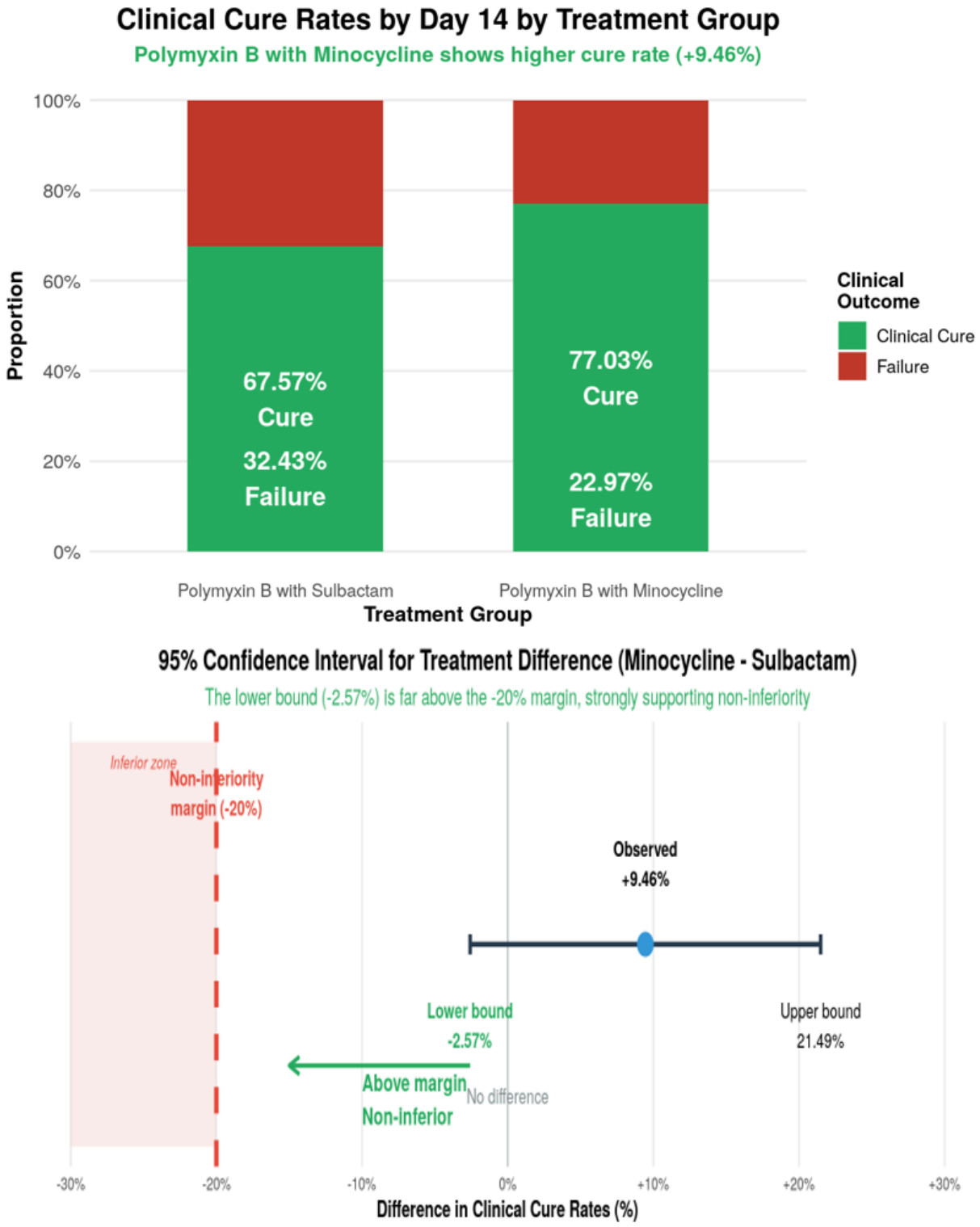


Figure 2

Clinical cure in patients after 14 days of treatment between the two groups

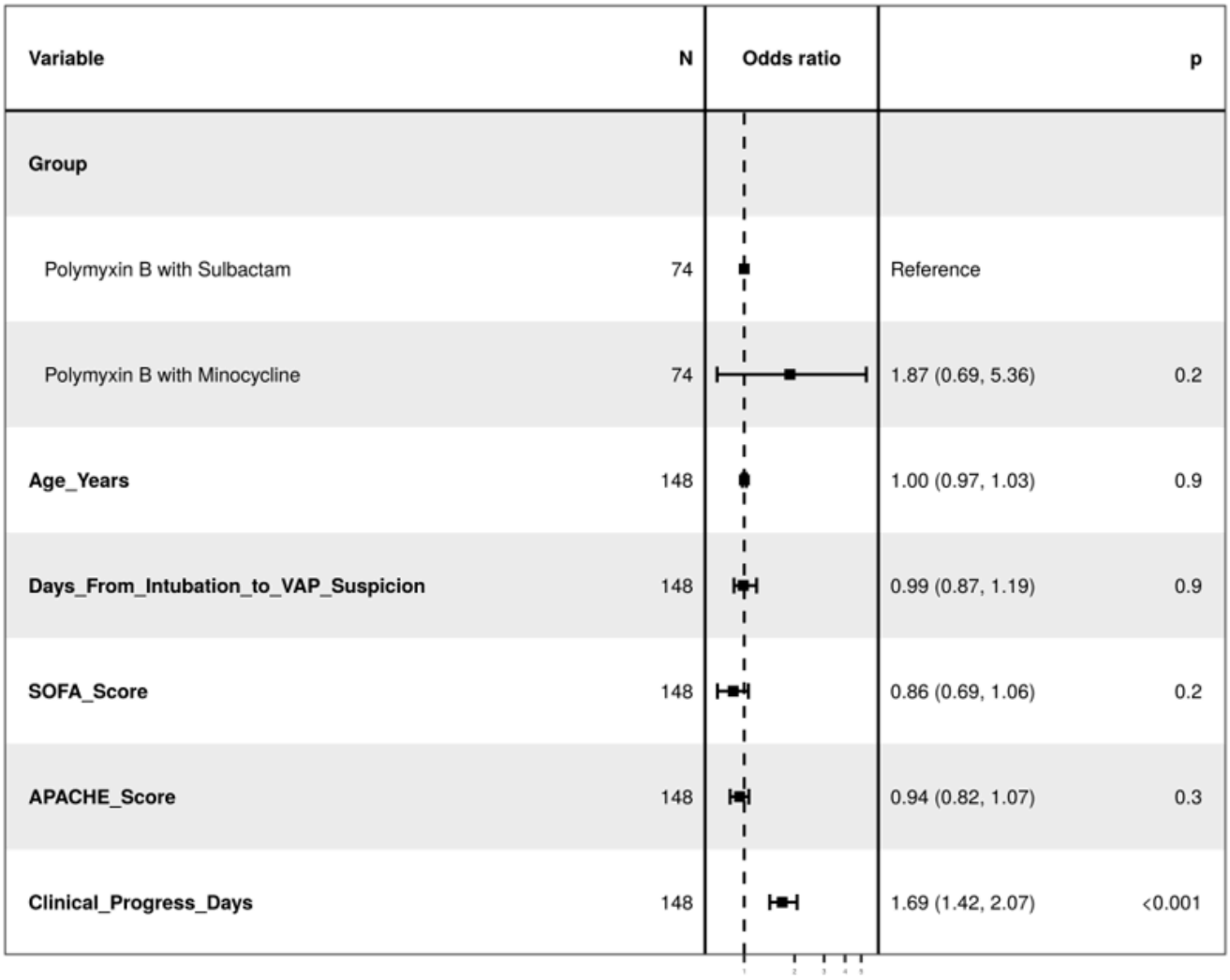


Figure 3

Univariate analysis

SOFA Score- Sequential Organ Failure Assessment Score, APACHE- Acute Physiology And Chronic Health Evaluation

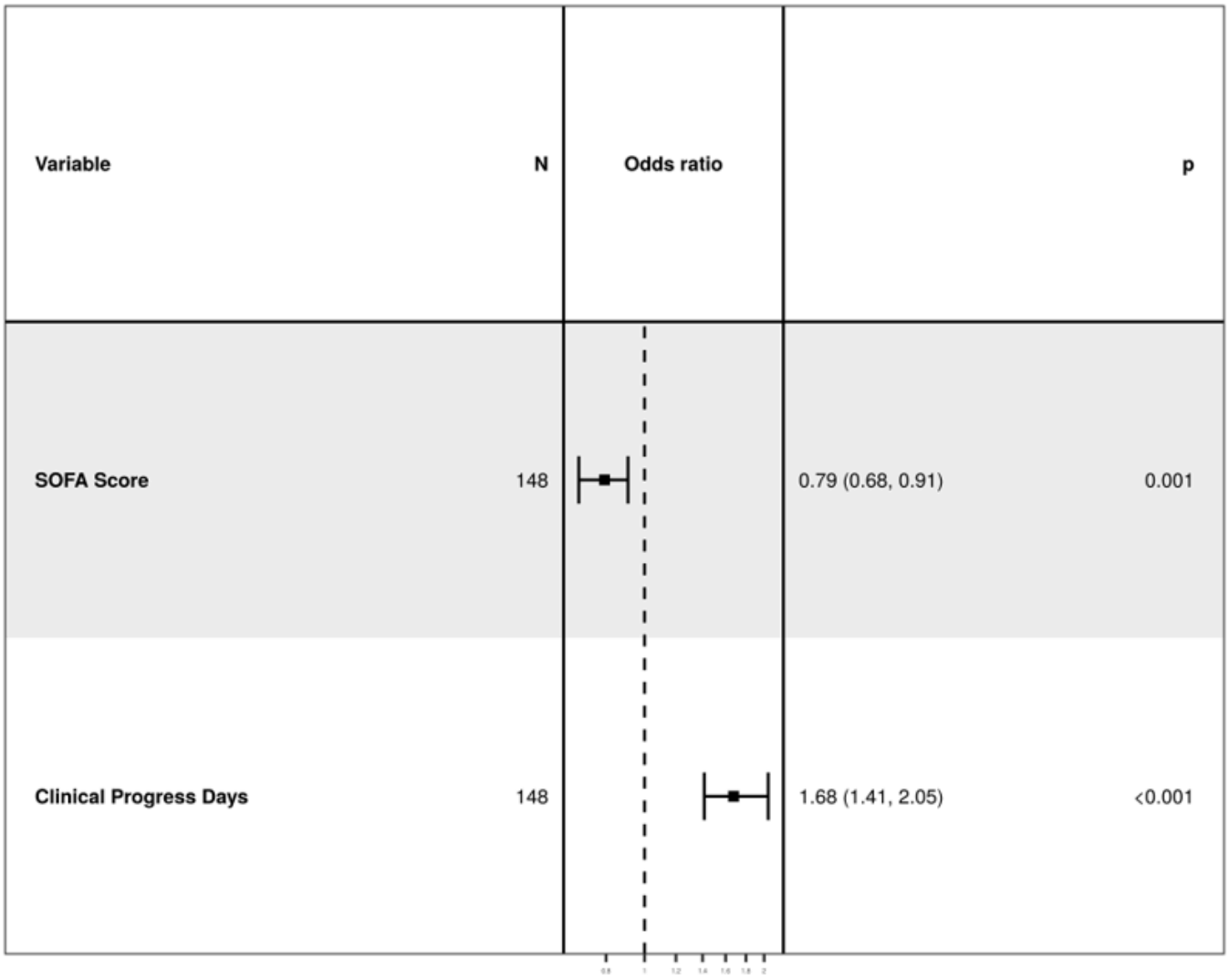


Figure 4

Multivariate analyses

SOFA Score- Sequential Organ Failure Assessment Score