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REVIEW ARTICLE

Systematic review and meta-analysis of antibiotic strategies for survival in patients with drug-resistant *Acinetobacter baumannii* infection: does quantity matter?

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ABSTRACT

BACKGROUND

Acinetobacter baumannii is an opportunistic pathogen frequently associated with severe hospital-acquired infections, particularly in intensive care units, and is characterized by high levels of antibiotic resistance, including to carbapenems. The rising prevalence of multidrug- and pan-drug-resistant strains poses significant therapeutic challenges and underscores the need for optimized treatment strategies to improve survival outcomes. This systematic review and meta-analysis evaluates the impact of different antibiotic treatment modalities (monotherapy versus combination) on the clinical outcome of patients with *Acinetobacter baumannii* infection.

METHODS

This systematic review and meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To find pertinent studies released up to 3 January 2025 a thorough search was done in electronic databases such as PubMed, Embase, ScienceDirect, Cochrane, EBSCOhost, Google Scholar, and Scopus.

RESULTS

This systematic review and meta-analysis identified 20 studies for inclusion. No statistically significant overall survival difference was found (Pooled OR = 0.83, 95% CI [0.66- 1.03], p = 0.09), but subgroup analyses indicated that combination therapy markedly enhanced survival rates in patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection, APACHE II scores below 20, and bloodstream infections. Meta-regression suggested that age may adversely affect treatment efficacy. A trend favoring combination therapy was consistent across subgroups, despite some results not reaching statistical significance.

CONCLUSION

This systematic review and meta-analysis highlights the treatment challenges of drug-resistant *Acinetobacter baumannii*, particularly MDRAB, XDRAB, and CRAB strains. Combination therapy offers potential benefits in CRAB and moderate-severity cases but is not universally superior to monotherapy. Treatment outcomes are influenced by patient-specific factors such as age, infection type, and disease severity.

Keywords: *Acinetobacter baumannii*, combination, drug-resistant, meta-analysis, monotherapy

INTRODUCTION

Acinetobacter baumannii is an opportunistic bacterium associated with severe hospital-acquired infections, including pneumonia, bacteremia, and meningitis.[1,2] Its prevalence in healthcare settings, particularly intensive care units, ranges from 5.02% to 11.7%.[3,4] Infections predominantly affect male patients, resulting in higher mortality rates and prolonged hospital stays.[4,5] Factors such as advanced age, chronic diseases, invasive procedures, and mechanical ventilation contribute to increased susceptibility.[3,4] The bacterium's virulence factors, including capsular polysaccharides and lipopolysaccharides, enhance its ability to evade the immune response and cause sepsis.[6]

Acinetobacter baumannii infections present significant treatment challenges due to increasing antibiotic resistance, especially to carbapenems.[7] Notably, 75-80.7% of isolates demonstrate multidrug resistance.[5,8] High resistance rates are observed for commonly used antibiotics such as amikacin, gentamycin, ceftriaxone, and ciprofloxacin.[9] The emergence of extremely resistant strains, including pan-drug resistant types, is concerning.[10] Some studies report carbapenem resistance as high as 93.22%.[4] The bacteria's ability to persist in the environment further complicates infection control efforts.[8] Resistance mechanisms, including efflux pumps, β-lactamases, and target site alterations,[11] restrict treatment options and negatively impact patient outcomes.[12]

Carbapenem-resistant infections exhibited a higher mortality risk than that of carbapenem-susceptible strains,[13] with a 34% higher risk of 30-day mortality in patients infected with *Acinetobacter baumannii* than in those colonized by *Acinetobacter baumannii*.[14] Factors contributing to elevated mortality in multidrug and carbapenem-resistant *Acinetobacter baumannii* infections include advanced age, severe underlying illness, bacteremia, and inadequate antibiotic treatment.[15,16] To address this issue, researchers are investigating innovative strategies, including combination therapies and novel antibiotics.[17] Promising strategies encompass antimicrobial adjuvants and synergistic drug combinations that involve polymyxins, carbapenems, and other antibiotics. New antibiotics such as cefiderocol and sulbactam/durlobactam exhibit potential, although their availability remains restricted.[18,19]

This systematic review and meta-analysis aimed to assess the effects of various antibiotic therapy strategies on survival outcomes in patients with antibacterial-resistant *Acinetobacter baumannii* infections. The analysis was stratified by varying levels of drug resistance to determine if the number of antibiotics utilized significantly influences patient survival across different severity levels.

METHODS

Protocol registration and reporting

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) checklist.[20] The review protocol has been published in PROSPERO under ID number CRD42025634484 and is available from https://www.crd.york.ac.uk/PROSPERO/view/CRD42025634484.

Criteria for eligibility

Studies published in the last decade were included, utilizing the PICOS framework (Population, Intervention, Comparator/Control, Outcome, and Study): The patient is infected with *Acinetobacter baumannii* and exhibits resistance to an antibiotic. Intervention (I): combination antibiotic treatment that includes at least one dual antibiotic or a combination of more than two drugs; Comparator/Control (C): mono antibiotic treatment for comparison; Outcome (O): survival rate or mortality rate; Study design (S): randomized or non-randomized controlled trial, or retrospective and prospective observational studies (cohort and case-control).

The exclusion criteria included animal studies, in vitro research (e.g., tissue culture studies), press articles, editorial letters, conference abstracts, registered protocols, books, book chapters, and review studies. Studies without full-text access were also excluded.

Sources of data and search strategy

Three reviewers performed thorough searches in six databases: PubMed, Scopus, Google Scholar, ScienceDirect, EBSCOhost, and the Cochrane Library. Keywords included variations of "*Acinetobacter baumannii*,"

"Antibiotic," "Resistant," and "Observational OR Randomized." Keywords were organized employing Boolean operators, and synonym searches were conducted utilizing Medical Subject Headings (MeSH). If a database imposed keyword limitations, the keywords were simplified. The search strategy details are provided in Supplementary 1. The search was limited to articles published in the past decade to maintain relevance. The literature search occurred from inception from December 25, 2024, to January 3, 2025. An updated search was conducted on January 3, 2025, prior to finalizing article selection. No new relevant articles were identified in this update.

Selection of studies

Two investigators independently and blindly screened articles using Rayyan.ai.[21] Following the removal of duplicates, articles underwent evaluation by two independent reviewers (MRDR, AR) according to year, title, and abstract. Full-text articles underwent eligibility assessment. Disputes were addressed via mediation conducted by MFH and DA.

Extraction of data

A standardized data extraction form was created. Three reviewers independently extracted the following data: summary including study identity, number and age of participants, regimen used (classified as mono, dual, or multiple antibiotics), observation length, type of study, site of infection, drug resistance, APACHE II score, and survival rate. Data extraction underwent cross-verification to ensure accuracy, with any discrepancies among reviewers addressed through discussion and consensus. The process utilized Google Spreadsheets.

Assessment of bias risk

The study quality was assessed using the Newcastle-Ottawa Scale (NOS) for non-randomized studies and the Risk of Bias 2 (RoB 2) tool for randomized trials.[22,23] The NOS evaluates selection, comparability, and outcome for cohort studies, and exposure for case-control studies. Each domain comprises several criteria, with a maximum score of 9 points representing the highest quality of the study. The RoB 2 assesses five essential domains: randomization, deviations, missing data, outcome measurement, and reporting bias. Each domain undergoes individual evaluation, with outcomes classified as "low risk of bias," "some concerns," or "high risk of bias."

Measures of effect and statistical analysis

Data analysis was conducted utilizing Review Manager 5.4.1.[24] The counts of surviving patients and the total patient population for both combination antibiotic therapies and monotherapy were extracted, with outcomes assessed using Odds Ratio (OR). The pooled OR was calculated using the Mantel–Haenszel method with a random-effects model, using a 95% confidence interval (CI) and a significance threshold of $p<0.05$. In studies offering both unmatched and matched cohorts, we prioritized the inclusion of matched cohort data in our meta-analysis to enhance comparability and reduce potential bias. In instances where data necessitated conversion or adjustment for analysis, we followed the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions[25] for data standardization. All meta-analyses were displayed using forest plots. After comparing monotherapy and combination therapy, subgroup analyses were conducted to examine survival rates based on: (1) dual versus multiple combination therapy across observation days, (2) resistance types (multi-drug resistant [MDR], extensively drug-resistant [XDR], or pan-drug resistant [PDR]), (3) APACHE II Score, and (4) infection site. Funnel plots were utilized to evaluate publication bias. Comprehensive meta-analysis v3.7[26] was utilized to perform a meta-regression analysis aimed at identifying a moderator variable influencing the results.

RESULTS

Results of the search and criteria for study selection

Following a search of six databases, we obtained 9,398 articles. The selection process included duplicate removal, title-abstract screening, and full-text review. Ultimately, 20 articles were incorporated into this systematic review and meta-analysis. The selection process for studies is depicted in a PRISMA flow chart provided in Figure 1.

Study characteristics

Among the 19 inclusion studies, 18 were classified as observational studies, [27–45] while one was an open-label prospective study.[46] The studies had observation periods ranging from 14 to 90 days. In the studies reviewed, three

categories of resistance were identified: Carbapenem-resistant *Acinetobacter baumannii* (CRAB), multi-drug resistant *Acinetobacter baumannii* (MDRAB), and extensively drug-resistant *Acinetobacter baumannii* (XDRAB). MDRAB denotes *Acinetobacter baumannii* strains that demonstrate in vitro resistance to multiple antimicrobial agents across three or more antibacterial classes. XDRAB indicates resistance to all but two or fewer categories of antimicrobials. We also categorized the included studies into three groups according to the site of infection: lung, blood, and mixed. The "mixed" category denotes studies that encompassed samples with infections at multiple sites, as outlined in Table 1.

Bias in research studies

The NOS results for the 19 observational studies demonstrate a high level of study quality, as illustrated in Supplementary 4. The RoB assessment for the study conducted by Makris et al.[46] indicated a high overall risk of bias, as detailed in Supplementary 5. This overall judgment was primarily attributed to high risk ratings in Domain 1 (bias arising from the randomization process) and Domain 2 (bias due to deviations from intended interventions), indicating potential issues such as inadequate random sequence generation, lack of allocation concealment, or non-adherence to the intervention protocol. The authors employed an "open-label" design, which accounted for this outcome.

Survival rates: monotherapy vs. combination therapy in *A. baumannii* resistance

In a comprehensive comparison, accounting for observation time, patient severity, and drug resistance levels, no significant difference was observed in patient survival rates between antibiotic monotherapy and combination therapy (Pooled OR= 0.83, 95% CI [0.66, 1.03], p=0.090, I^2=28%). Nevertheless, it continued to be biased in favor of the combination group.

Subgroup analysis: monotherapy vs. combination therapy in *A. baumannii* resistance

In subgroups categorized by observation duration (to assess survival outcomes), no significant difference was observed between antibiotic monotherapy and combination therapy. All subgroups exhibited a trend favoring the combination group (Table 2). Subgroup analysis based on the level of antibiotic resistance in the population (Table 2) revealed significant results for the combination group exclusively within the carbapenem-resistant subgroup (Pooled OR = 0.76, 95% CI [0.62, 0.93], p = 0.009, I^2 = 0%). The XDRAB subgroup exhibited a tendency towards the combination group, though this was not statistically significant (Pooled OR= 0.82, 95% CI [0.42, 1.60], p=0.560 I^2=41%). The MDRAB subgroup analysis indicated a slight skew towards the monotherapy group, though this was not statistically significant (Pooled OR= 1.25, 95% CI [0.69, 2.26], p=0.450, I^2=46%).

Moreover, when patients were classified according to their APACHE II score, a system used to assess the severity of disease in patients (Table 2), substantive results for the combination group were noted only in the subgroup where APACHE II score was under 20 (Pooled OR= 0.67, 95% CI [0.54, 0.85], p=0.000, I^2=0%).

Subgroup analysis of the study according to the patient's site of infection showed that only the bacteremia cohort receiving combination therapy had significant findings (Pooled OR= 0.60, 95% CI [0.39, 0.93], p=0.020, I^2=0%). No relevant difference between the monotherapy and combination groups was observed regarding pneumonia and mixed infections (see Table 2).

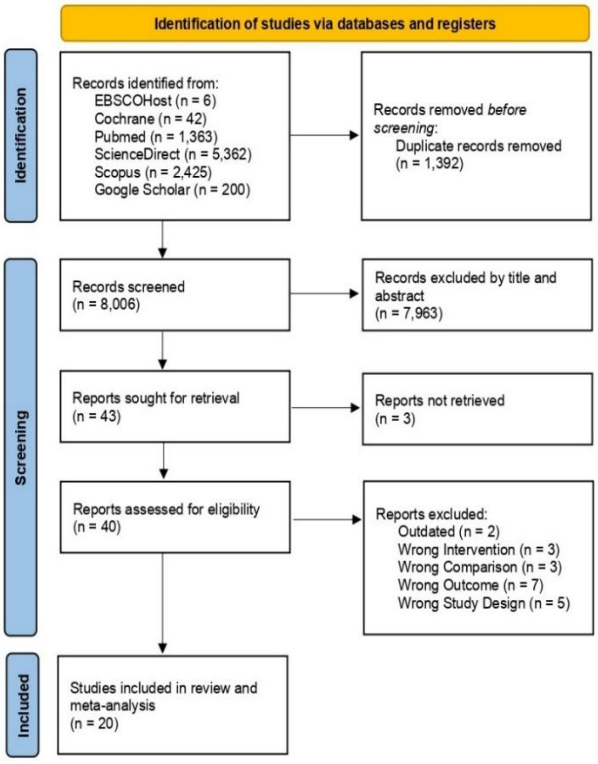


Figure 1. PRISMA flow diagram showing the results of the search and reasons for exclusion

Table 1. Characteristics of included studies

Author	Sample size	Age	Regimen	Site of infection	Observation length	Type of drug resistance	APACHE II	Study Design
Kalin et al. (27)	82	56.85±15.035	Mono: CTN Dual: CTN+BL/BLI	Lung	14 days	MDRAB	25.33 ± 14.72	Retrospective
Balkan et al. (28)	107	59.6±20.0	**Mono**: CTN **Dual**: BL/BLI+AGS, CBM+AGS, CBM+TGC, AGS+TGC, CBM+BL/BLI, TGC+BL/BLI, CBM+QNL, TGC+BL/BLI, TGC+BL/BLI, CBM+BL/BLI, CBM+RIF, CFM+AGS, others	Blood	14 days	MDRAB	19.15 ± 8	Retrospective cohort
Kara et al. (38)	188	67.43±13.71	**Mono:** CTN **Dual:** CTN+CBM, CTN+BL/BLI, CBM+TGC, CTN+BL/BLI	Lung	28 days, 90 days	MDRAB	22.10 ± 5.38	Retrospective
Yilmaz et al. (39)	70	59.7±21	**Mono:** CTN **Dual:** CTN+CBM, CTN+BL/BLI	Lung	28 days	MDRAB, XDRAB	N/A	Retrospective
Kim et al.(40)	70	68.50±11.35	**Mono:** CTN, TGC **Dual:** TGC+CBM, TGC+BL/BLI, TGC+RIF, TGC+DXC, CTN+CBM, CTN+BL/BLI, CTN+RIF, CTN+DXC **Multi**: TGC+BL/BLI+MNC, CTN+CBM+BL/BLI, CTN+CBM+DXC, CTN+BL/BLI+RIF, TGC+BL/BLI+MNC+RIF, CTN+CBM+BL/BLI+RIF, CTN+CBM+BL/BLI+RIF+MNC	Lung	30 days	MDRAB, XDRAB	N/A	Retrospective
Amat et al.(41)	118	57±15	**Mono**: CTN **Dual**: TGC+CTN	Blood	14 days, 30 days	CRAB	22 ± 9	Retrospective cohort
Jean et al.(42)	212	81.67±7.84	**Mono:** AS-CMS **Dual:** TGC+AS-CMS	Lung	30 days	XDRAB	16.83 ± 7.09	Retrospective case-control
Makris et al.(46)	39	50.18±19.28	**Mono:**CTN **Dual:** CTN+BL/BLI	Lung	28 days	MDRAB	13.76 ± 3.56	Prospective, open label, randomized study
Niu et al.(43)	210	56±17.385	**Mono:** BL/BLI **Dual:** BL/BLI+IMP, BL/BLI+MRM BL/BLI+others	Blood	28 days	CRAB	20.33 ± 14.56	Retrospective
Park et al.(44)	71	67.32±14.12	**Mono:** CTN **Dual:** CTN+MRM	Blood	14 days	CRAB	N/A	Retrospective cohort
Shi et al.(45)	160	71.72±14.49	**Mono:** CTN **Dual:** CBM combined	Lung	14 days	CRAB	N/A	Retrospective
Katip et al.(29)	248	66,675 ± 17,355	**Mono:** CTN **Dual:** CTN+MRM	Lung Blood, UT, Others	30 days	CRAB	15.33 ± 5.22	Retrospective cohort
Katip et al.(30)	230	64.84 ± 16,69	**Mono:** CTN **Dual:** CTN+VMC	Lung, Blood, UT, Others	30 days	CRAB	12.23 ± 0.51	Retrospective cohort

Author	Sample size	Age	Regimen	Site of infection	Observation length	Type of drug resistance	APACHE II	Study Design
Seok et al.[31]	282	67.0±14.9	**Mono:** CTN, TGC, BLI **Dual:** CTN+CBM, CTN+MNC, CTN+RIF, CTN+BLI, CBM+BLI, CBM+RIF, CBM+AMC, BLI+MNC.	Lung, Blood, UT	7 days, 28 days	CRAB	19.3 ± 6.9	Retrospective cohort
Calò et al.[32]	38	67 ±15.79	**Mono:** CFD **Dual:** CFD combined	Blood, Lung, Skin and Soft Tissue, Bone, UT, Intra-abdominal	30 Days	CRAB	N/A	Retrospective/ prospective, observational
Prayag et al.[33]	50	54.25±14.71	**Mono:** PMN **Dual:** PMN+MRM, PMN+MCN, PMN+BL/BLI, PMN+AMC, PMN+PMC **Multi:** PMN+MNC+BL/BLI	Lung, Blood, Surgical site, Others	28 Days	CRAB	N/A	Retrospective observational
He et al.[34]	55	59.9±16.8	**Mono:** CBM, PPC/TZB, FQL, CEF, CPZ/BLI **Dual:** CBM+TGC, CBM+CPZ/BLI, CBM+PPC/TZB, Others **Multi:** CBM+TGC+CPZ/BLI CBM+TGC+PPC/TZB CBM+TGC+FQL, CBM+MNC+PPC/TZB, CBM+FQL+PPC/TZB, CBM+TGC+FQL+CPZ/BLI, CBM+TGC+CPZ/BLI+PPC/TZB, CBM+TGC+CPZ/BLI+AGS, CBM+TGC+PPC/TZB+AGS CBM+TGC+MNC+AGS, CBM+CPZ/BLI+MNC+PPC/TZB Others	Lung, Intra-abdominal, Wound, UT	28 Days	CRAB	N/A	Retrospective
Manesh et a.l[35]	161	46.14 ±16.24	**Mono:** CTN, PMB **Dual:** PMN+BL/BLI, PMN+TGC, PMN+CAZ/AVI PMN+MNC TGC+BL/NLI, BL/BLI+CAZ/AVI **Multi:** PMN+TGC+BL/BLI, PMN+MCN+BL/BLI	Blood, Lung	30 Days	CRAB	N/A	Prospective cohort
Tian et al.[36]	70	69.75±15.71	**Mono:** TGC **Dual:** TGC+CPZ/BLI	Lung	90 Days	CRAB	N/A	Retrospective
Yee et al.[37]	170	57.3±16.8	**Mono:,** BLI, MRM, TGC, MNC **Dual:** BLI+MRM, BLI+ TGC, BLI+ MNC, PMB+MRM, PMB+TGC, PMB+MNC, PMB+AMC,	Lung	30 Days	MDRAB	N/A	Cohort

Author	Sample size	Age	Regimen	Site of infection	Observation length	Type of drug resistance	APACHE II	Study Design
			TGC+MRM, TGC+AMC, MNC+MRM, MNC+AMC, CTN+MRM **Multi:** BLI+MRM+ PMB, BLI +MRM +MNC, BLI +PMB +MNC, BLI +PMB +TGC, BLI +PMB +DXC, PMB+MRM +TGC, PMB+MRM +MNC, PMB+MRM +DXC, MNC+MRM +AMC, CTN+MNC +MRM, MRM+PMB +BLI+MNC					

Note : APACHE II : Acute Physiology And Chronic Health Evaluation Score II; CTN : Colistin; BL/BLI : Beta-lactamase Inhibitor; AGS : Aminoglycoside; CBM : Carbapenem; TGC : Tigecycline; QNL : Quinolone; RIF : Rifampicin; DXC : Doxycycline; MNC : Minocycline; AS-CMS : Aerosolized Colistimethate Sodium; IMP : Imipenem; MRM : Meropenem; VMC : Vancomycin; AMC : Amikacin; CFD : Cefiderocol; PMN : Polymyxin; PMC : Polymyxin C; PPC : Piperacillin; TZB : Tazobactam; FQL : Fluoroquinolone; CEF : Cephalosporin; CPZ : Cefoperazone; PMB : Polymyxin B; CAZ : Ceftazidime; AVI : Avibactam; UT : Urinary tract; MDRAB : Multidrug-resistant *Acinobacter baumannii*; XDRAB : Extensively Drug-Resistant *Acinobacter baumannii*; CRAB : Carbapenem-Resistant *Acinetobacter baumannii;* N/A : not available.

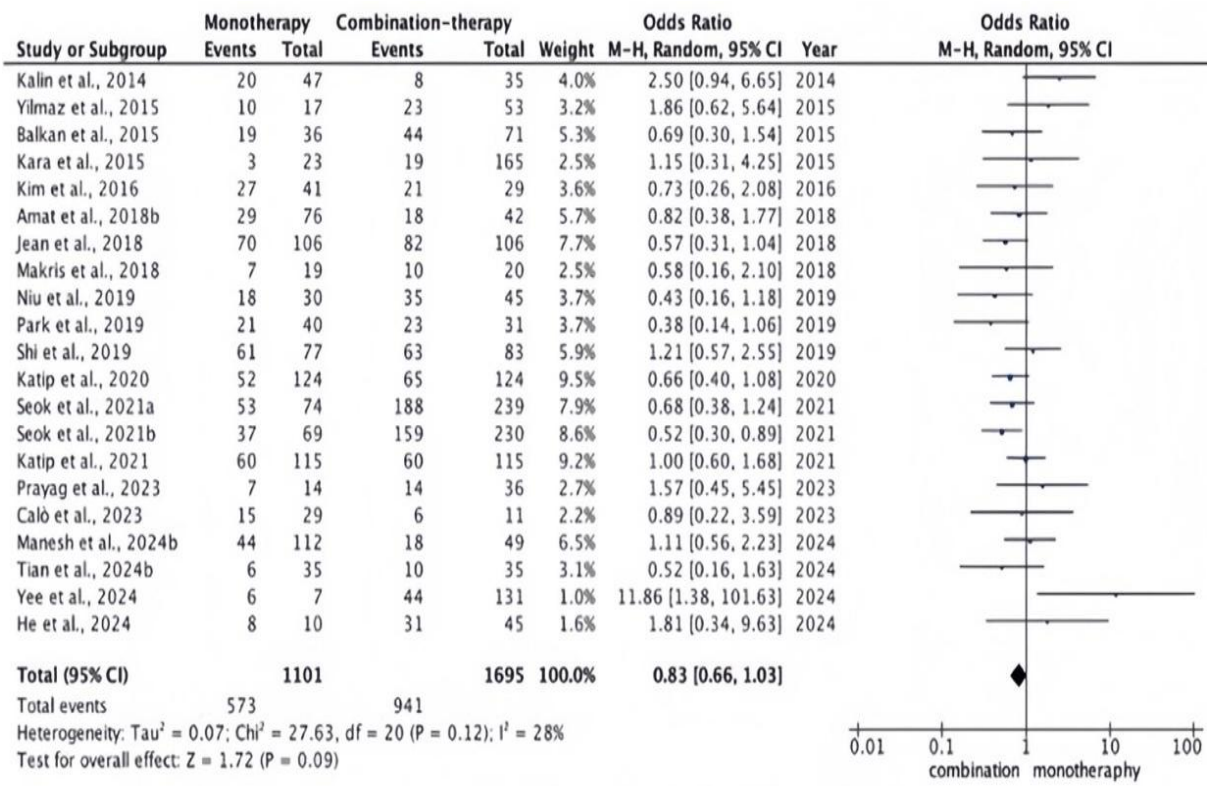


Figure 2. Forest plot of overall comparison of monotherapy vs. combination therapy
Subgroup analysis: monotherapy vs. combination therapy in *A. baumannii* resistance

Table 2. Summary of survival rate subgroup analysis

Subgroup		Total events		N		Pooled OR	95% CI	Overall effect	Heterogeneity (I^2 %)	Preference	Subgroup differences (I^2 %)
		Mono	Comb	Mono	Comb						
APACHE II	Moderate score (<20)[28–31, 42,46]	298	608	543	905	0.67	[0.54, 0.85]	p=0.0008	0	Comb	0
	High score (>20) [27, 38, 41,43]	70	80	176	287	0.99	[0.48, 2.04]	p=0.98	53	Comb	
Type of Resistance	CRAB[29,30, 44,45, 31–36, 41,43]	411	690	805	1085	0.76	[0.62, 0.93]	p=0.009	0	Comb	19
	MDRAB [27,28, 37–40,46]	92	169	190	504	1.25	[0.69, 2.26]	p=0.45	46	Mono	
	XDRAB[39,40,42]	107	126	164	188	0.82	[0.42, 1.60]	p=0.56	41	Comb	
Site of Infection	Lung[27, 36–40,45,46]	210	280	372	657	1.08	[0.66, 1.75]	p=0.77	49	Mono	36.2
	Blood[28, 41,43,44]	87	120	182	189	0.60	[0.39, 0.93]	p=0.02	0	Comb	
	Mixed[29–35]	223	353	473	610	0.81	[0.67, 1.07]	p=0.16	10	Comb	
Length of observation	14 days[27,28, 41,44,45]	201	179	388	311	0.93	[0.61, 1.41]	p=0.73	37	Comb	0
	28 days[31, 33,34, 38,39, 43,46]	87	272	159	429	0.80	[0.47, 1.39]	p=0.43	38	Comb	
	30 days[29,30, 32, 35, 37,40–42]	343	347	645	642	0.88	[0.63, 1.24]	p=0.47	37	Comb	
	90 days[36,38]	9	29	58	200	0.73	[0.31, 1.73]	p=0.48	0	Comb	

Publication bias

The plot demonstrates moderate asymmetry, with a marked imbalance in smaller studies (higher standard error) at the lower end. This might indicate publication bias, whereby small studies with non-significant results are likely to be underreported. The asymmetry might also reflect heterogeneity related to variability in study designs, study populations, or interventions. To minimize potential bias, subgroup analysis and meta-regression were conducted.

Meta-regression analysis of the log odds ratio in relation to age

The coefficient for the age variable was -0.022, and the p-value 0.077, implying an inversely proportional relationship between age and the log odds of treatment efficacy. For every year in average age increase, the log odds ratio of treatment efficacy was reduced by an estimated 0.0224 in the study. However, this relationship did not reach statistical significance at the 5% level ($p>0.05$), although it was close to significance ($p=0.077$). The tau^2 for the unexplained variance in the model was 0.0431, which is low and implies that most of the heterogeneity is explained by the model. The R^2 (variance explained) between studies from the model was 0.35 (35%). The model explains 35% of the total variance, suggesting that age plays a moderate role in explaining differences in treatment benefit.

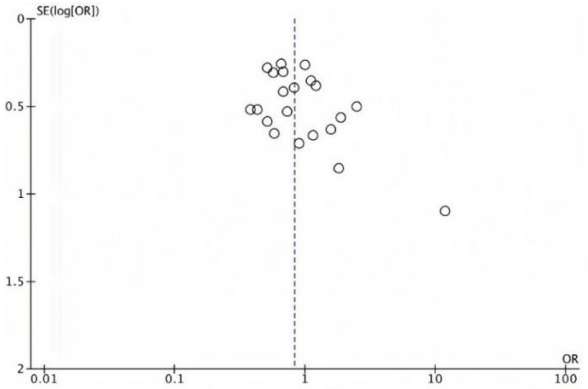


Figure 3. Funnel plot of overall studies in overall comparison

DISCUSSION

The survival rate in *Acinetobacter baumannii* infections is crucial for treatment decisions. Meta-analysis suggests that combination therapy improves survival more than monotherapy, though the summary odds (Pooled OR=0.83, 95% CI [0.66, 1.03]) ratio did not reach statistical significance. Subgroup analysis was infeasible due to challenges in defining an age cutoff; therefore, meta-regression was used to assess age-related differences.

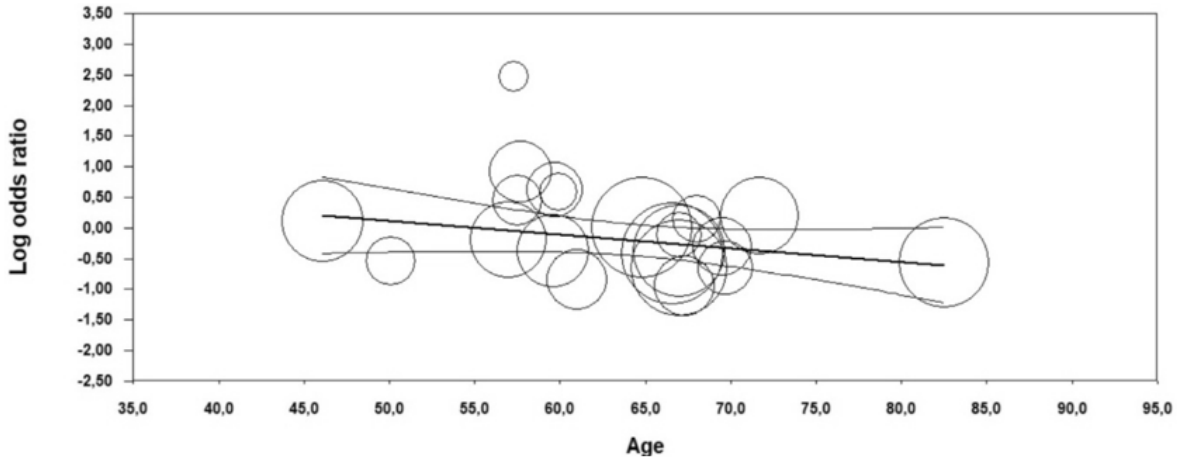
Meta-regression showed a decreasing benefit of combination therapy with age, though not of statistical significance. The negative age coefficient (−0.0224) suggests reduced efficacy in older patients. With an R^2 of 0.35, age explains 35% of the variance, while 65% remains unexplained, indicating additional influencing factors. The second scatter plot displayed the points clustered closely around the regression line, indicating that the model fit the data fairly well.

The studies by Yee et al.[37] and Kalin et al.[27] showed substantial differences from our regression line, indicating residual heterogeneity. To further investigate treatment selection factors, we conducted a subgroup analysis based on survival days, microbial resistance phenotype, infecting species, and APACHE II severity. The meta-analysis indicated no significant difference between monotherapy and combination therapy, even across observation time subgroups. This suggests inconsistent survival benefits, potentially influenced by patient variability and study design differences. Niu et al.[43] reported a significantly higher 28-day survival rate with combination therapy, that was attributed to its synergistic effect, pharmacokinetics, and clearance rate for severe bacterial infection. Conversely, He et al.[34] found no significant survival difference, likely due to a higher proportion of patients receiving combination therapy. ICU patients often present with underlying diseases and compromised organ and immune function, complicating treatment efforts, even with combination therapy.

The subgroup meta-analysis showed significantly higher survival rates with combination therapy for *Acinetobacter baumannii* bloodstream infections, which carry high severity and mortality risk (see Table 2). Park et al.[44] reported reduced mortality in patients with bacteremia Pitt scores ≥4. However, no significant difference was observed for lung and mixed infection, likely due to poor lung antibiotic penetration and biofilm formation. Similarly, Savoldi et al.[47] found no significant advantage of combination therapy in lung infections compared to bloodstream infections.

Combination therapy significantly improved survival rate in CRAB cases but showed no significant difference for MDRAB or XDRAB. This suggests that combination therapy does not provide a universal benefit across all resistance types. For CRAB, combination therapy may enhance treatment by leveraging synergistic effects and improving antimicrobial activity, addressing carbapenems resistance. Given the limited treatment options for CRAB, combination therapy remains a preferred strategy to reduce therapeutic failure.[48,49] A retrospective study reported a lower 14-day mortality rate with combination therapy (25.8%) in contrast to monotherapy (47.5%), although the difference lacked statistical significance.[44]

A meta-analysis using the APACHE II score indicated that combination therapy significantly improved survival for patients with scores below 20 but showed no benefit for scores above 20 (see Table 2). Combination therapy is generally more effective in milder cases, as elevated APACHE II scores and systemic complications can reduce antibiotic effectiveness, correlating with increased mortality risk.[50] Balkan et al.[28] found that colistin monotherapy had higher APACHE II scores, with scores exceeding 21 identified as a risk factor for 14- and 30-day in-hospital mortality in cases of MDRAB bloodstream infections. Furthermore, Katip et al.[29] demonstrated significantly lower 14-day mortality rates in patients with APACHE II scores between 25 and 29 who received combination therapy, underscoring the importance of tailoring treatment to disease severity.[29]



Coefficient	SE	Z-value	P-value	Q	τ^2	R^2
-0.0224	0.0127	-1.77	0.0767	3.13	0.0431	0.35

Figure 4. Meta-regression analysis of the log odds ratio in relation to age

All studies examined antibiotic monotherapy and combination therapy for *Acinetobacter baumannii* infections, which encompasses dual or multiple regimens. Thirteen studies used colistin as monotherapy. Effective against multiresistant *Acinetobacter baumannii,* this polymyxin antibiotic disrupts bacterial membranes, causing cell death. Although previously limited due to nephrotoxicity and neurotoxicity concerns, colistin has resurged as a last-resort therapeutic option.[51]

Colistin- and tigecycline-based regimens are the most utilized combination therapies. Katip et al.[29] demonstrated that colistin-meropenem combination therapy significantly improved therapeutic success and microbiological response. Similarly, Seok et al.[31] found that the colistin-carbapenem therapy led to enhanced 7-day survival rates and reduced mortality. Due to prevalent heteroresistance, colistin is frequently used in conjunction with other antibiotics to mitigate resistance and enhance synergy, including imipenem, meropenem, sulbactam, rifampicin, and tigecycline.[40]

However, limitations include therapy regimen heterogeneity, inability to compare dual vs. multiple antibiotic regimens, and potential bias due to randomization uncertainties and lack of blinding. Treatment for *Acinetobacter baum*annii infections should be patient-specific, considering age, infection type, and severity. Combination therapy suits moderate carbapenem-resistant cases, while monotherapy may suffice for milder ones. Colistin-based regimens remain essential but require careful monitoring for resistance and toxicity.

Policy efforts should strengthen antimicrobial stewardship, infection control, standardize combination therapy, and ensure access to affordable antibiotics. Future research should focus on optimizing treatment regimens, assessing age-related effects, improving pharmacokinetics for localized infections, and investigating resistance mechanisms. Standardized trials and long-term studies are vital for advancing treatment strategies and combating resistance.

CONCLUSION

This meta-analysis highlights the challenges of treating *Acinetobacter baumannii* infections, particularly MDRAB, XDRAB, and CRAB strains. Combination therapy shows potential benefits, especially in CRAB infections and moderate-severity cases (APACHE II <20), but does not consistently outperform monotherapy across all scenarios. Patient-specific factors, such as age, infection type, and disease severity, play a crucial role in treatment effectiveness.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

MRDR and MFH designed the study. MRDR, AR, and MFH collected and interpreted data and drafted the manuscript. MRDR, MFH, and DA revised it critically. All authors approved the final version, ensuring accuracy and integrity.

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Data Availability Statement

The data supporting this study are available in Figshare at https://doi.org/10.6084/m9.figshare.28329827

Declaration of Use of AI in Scientific Writing

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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