

ORIGINAL ARTICLE

Inappropriate Empirical Antibiotic Therapy and 28-Day Mortality in Critically Ill Patients: A Retrospective Cohort and Propensity Score Analysis in an Indonesian ICU

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ABSTRACT

Background. Inappropriate empirical antibiotic therapy (IEAT) is linked to higher mortality in sepsis, particularly where antimicrobial resistance is highly endemic, as in Southeast Asia.

Objective. To estimate the association between IEAT and 28-day mortality in Indonesian ICU patients while accounting for confounding by indication.

Methods. This retrospective cohort included 280 adults admitted to a tertiary academic ICU in Malang, Indonesia, from January 2022 to December 2023, with positive cultures drawn within 48 hours. Empirical regimens were classed by in-vitro susceptibility as appropriate (AEAT, $n = 172$) or inappropriate (IEAT, $n = 108$). Analyses used multivariable logistic regression and, as a second approach, 1:1 propensity score matching on seven clinical covariates.

Results. IEAT was given to 108 patients (38.6%). Overall 28-day mortality was 35.0% (98/280): 77.8% (84/108) with IEAT and 8.1% (14/172) with AEAT ($p < 0.001$). After adjustment for age, APACHE II score, and septic shock, IEAT had the largest adjusted odds ratio of the model (aOR 38.72; 95% CI 18.91–79.30; $p < 0.001$). In the matched cohort ($n = 200$; standardized mean differences < 0.10), the association persisted (OR 25.15; 95% CI 11.54–54.81; $p < 0.001$). Levofloxacin monotherapy was inappropriate in 76.4% of cases and meropenem in 42.5%. ESBL *Klebsiella pneumoniae* (20.0%) and XDR *Acinetobacter baumannii* (17.1%) were prevalent.

Conclusion. IEAT was associated with much higher 28-day mortality in this cohort. These findings support a review of local stewardship policies. Empirical fluoroquinolone use in tertiary intensive care should be restricted.

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1. Introduction

Sepsis is a dysregulated host response to infection that causes life-threatening organ dysfunction, and it remains a major challenge in intensive care worldwide.¹ It can progress quickly, and septic shock, with refractory hypotension, microvascular hypoperfusion, and cellular metabolic failure, carries a reported mortality that often exceeds 40% in modern intensive care units (ICUs).² Resuscitation rests on prompt, effective broad-spectrum intravenous antimicrobial therapy. The Surviving Sepsis Campaign guidelines recommend appropriate antimicrobials within the first hour of recognized septic shock, since each hour of delay was associated with lower survival in observational data.^{3,4}

The first antibiotic choice in the ICU is empirical. Pathogen identification and susceptibility testing take 48 to 72 hours of incubation and automated processing, and treatment cannot wait for them.⁵ Clinicians therefore rely on the suspected site of infection, on host risk factors, and on the institutional antibiogram, which together guide the choice of agent. Rising antimicrobial resistance (AMR) has

weakened this approach.⁶ Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) pathogens now spread widely. The main culprits are extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales and carbapenem-resistant *Acinetobacter baumannii*, which create a mismatch between the prescribed regimen and the susceptibility of the organism.^{7,8}

This microbiological discordance is termed inappropriate empirical antibiotic therapy (IEAT).⁹ When a regimen has no bactericidal activity against the causative pathogen, bacteria keep multiplying during the early window of resuscitation.³ As pathogen load rises, so does the release of pathogen-associated molecular patterns (PAMPs), and the consequences are a hyperinflammatory cytokine response, damage to the endothelial glycocalyx, microcirculatory immunothrombosis, capillary leak, and progression to multi-organ dysfunction syndrome (MODS).¹⁰ Observational studies from high-income countries report a two- to three-fold higher all-cause mortality with IEAT among septic ICU patients.^{11,12}

Evidence from low- and middle-income countries (LMICs), and from Southeast Asia in particular, is limited.¹³ The

region is a major focus of AMR, as a high burden of infectious disease, long-standing over-the-counter access to antibiotics, and limited capacity for automated microbiology and active surveillance all contribute.¹⁴ Indonesian ICUs care for severely ill patients who often carry multidrug-resistant organisms on presentation.⁸ Detailed studies of IEAT outcomes in this setting are scarce.¹⁴

A main methodological weakness of observational antimicrobial studies is confounding by indication. Clinicians tend to choose broader or alternative empirical agents for patients with greater baseline severity and overt septic shock.¹⁵ Differences in mortality may then reflect severity. They need not reflect failure of the antibiotic itself. Local data are therefore needed. We aimed to estimate the association between the appropriateness of empirical antibiotic therapy and 28-day all-cause mortality in patients at a tertiary Indonesian ICU, using multivariable logistic regression and 1:1 propensity score matching to balance baseline covariates.

2. Methods

2.1. Study design and reporting

This single-center retrospective cohort study was conducted in the 20-bed mixed medical-surgical adult ICU of Dr. Saiful Anwar Regional General Hospital in Malang, East Java, Indonesia. We included consecutive ICU

admissions from January 1, 2022, to December 31, 2023. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹⁶

2.2. Setting

The hospital is the main tertiary referral and teaching hospital for a catchment population of more than 15 million people in East Java. Board-certified intensivists and clinical fellows staff it around the clock.

2.3. Participants and eligibility

Eligible patients were adults (18 years or older) who received at least one dose of an intravenous empirical antibiotic for suspected or confirmed bacterial sepsis and had diagnostic microbiological cultures obtained within 48 hours of ICU admission that yielded a bacterial pathogen. We excluded patients with: (1) documented allergy to the prescribed antibiotic class; (2) systemic antibiotic therapy for the same infectious episode for more than 24 hours before ICU admission; (3) a switch to palliative comfort care or withdrawal of life-sustaining treatment within 48 hours of admission; (4) incomplete records of antibiotic administration, susceptibility results, or outcomes; (5) confirmed primary non-bacterial infection; and (6) an ICU stay shorter than 24 hours. Consecutive admissions were screened as shown in the patient selection cascade in Figure 1.

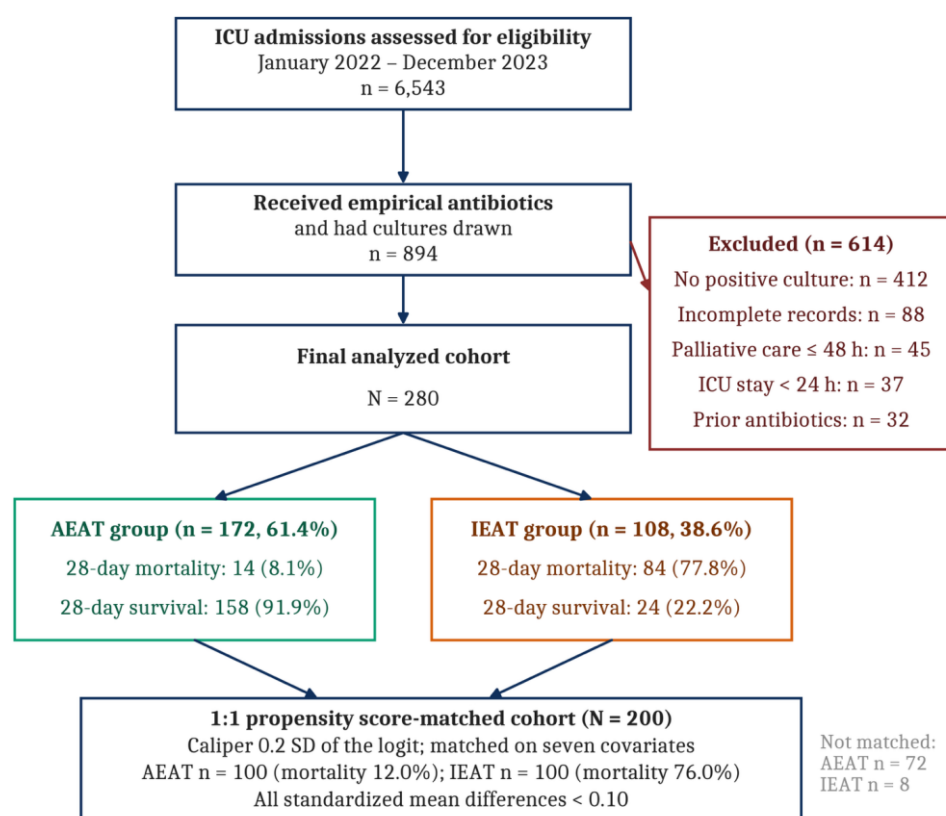


Figure 1. STROBE participant flow diagram showing screening, exclusions, final cohort stratification (N = 280) and 1:1 propensity score matching (n = 200). AEAT, appropriate empirical antibiotic therapy; IEAT, inappropriate empirical antibiotic therapy; SD, standard deviation.

2.4. Sample size

All consecutive eligible patients admitted during the study period were analyzed (280 patients, 98 deaths).

2.5. Variables and operational definitions

Septic shock followed the Sepsis-3 consensus definition. This means sepsis needing vasopressors to keep mean arterial pressure at 65 mmHg or higher, with serum lactate above 2.0 mmol/L despite adequate fluid resuscitation.²

The primary exposure was the appropriateness of the initial empirical regimen given in the ICU. A regimen was classed as Appropriate Empirical Antibiotic Therapy (AEAT) when it included at least one intravenous agent to which all subsequently isolated pathogens showed intermediate or full susceptibility *in vitro*. It was classed as Inappropriate Empirical Antibiotic Therapy (IEAT) when every prescribed empirical agent showed *in-vitro* resistance against the isolated pathogen. In polymicrobial infections, a regimen counted as appropriate only if every recovered pathogen was susceptible. Two independent infectious disease specialists, blinded to outcomes, judged appropriateness. The primary endpoint was all-cause mortality at 28 days after ICU admission. ICU and hospital lengths of stay were secondary endpoints.

Extensively drug-resistant (XDR) isolates were defined by the international consensus criteria, as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories.¹⁷

2.6. Data sources and measurement

Two trained investigators extracted the data independently from electronic and paper hospital records, using a standardized case report form. Discrepancies went to a senior intensivist. The variables were demographics (age, sex, body mass index), admitting diagnostic category, comorbidities (diabetes mellitus, hypertension, chronic kidney disease), and admission severity measured with the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA).

The central diagnostic microbiology laboratory processed the specimens (blood, endotracheal aspirate, sputum, urine, intra-abdominal fluid, and wound discharge). The automated VITEK® 2 system (bioMérieux, Marcy-l'Étoile, France) identified the isolates and tested their susceptibility. Results were interpreted using the Clinical and Laboratory Standards Institute (CLSI) M100 criteria for the year of isolation.¹⁸

2.7. Statistical analysis

Analyses used SPSS Statistics (Version 26.0, IBM Corp., Armonk, NY) and R (Version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria). Two-tailed *p*-values below 0.05 were considered significant. Normality was tested with the Shapiro-Wilk test. Normally distributed variables are shown as mean $\pm$ SD and were compared with the independent Student's *t*-test. Other variables are shown as median (IQR) and were compared with the Mann-Whitney *U* test. Categorical variables are shown as *n* (%) and were compared with Pearson's Chi-square test or Fisher's exact test, as appropriate.

To identify independent predictors of 28-day mortality, we built a multivariable binary logistic regression model *a priori* on clinical grounds. It included the primary exposure (IEAT vs AEAT) with admission APACHE II score (continuous), septic shock at admission (binary), and age (continuous) as established prognostic confounders. APACHE II and SOFA scores were collinear (Variance Inflation Factor > 5), so only APACHE II entered the model. The Hosmer-Lemeshow goodness-of-fit test checked calibration. We report adjusted odds ratios (aOR) with 95% confidence intervals (CI). Patients with incomplete records of antibiotic administration, susceptibility results, or outcomes were excluded (Section 2.3), so no missing data entered the models.

To address confounding by indication from baseline clinical differences, we also ran a 1:1 propensity score-matched (PSM) analysis. The propensity score, the conditional probability of receiving IEAT, came from a multivariable logistic regression on age, sex, APACHE II score, septic shock, diabetes mellitus, hypertension, and chronic kidney disease. Each IEAT patient was matched to one AEAT patient by nearest-neighbor matching without replacement. The caliper was 0.2 standard deviations of the logit propensity score. Balance before and after matching was assessed with standardized mean differences (SMD); an SMD below 0.10 was taken as satisfactory. The effect of IEAT in the matched cohort was estimated with conditional logistic regression. Sensitivity analyses estimated IEAT odds ratios in high-risk subgroups (septic shock and APACHE II $\geq$ 25). Cumulative 28-day survival was plotted with Kaplan-Meier curves and compared with the log-rank test.

2.8. Ethics

The Ethics Committee of CMHC Research Center, Indonesia, approved the protocol (Approval No. 2022/048). The analysis was non-interventional and retrospective, and it used de-identified hospital records. The committee therefore waived individual written informed consent, in line with the Declaration of Helsinki.

3. Results

3.1. Participant flow and baseline characteristics

Throughout the two-year study period, 6,543 adult patients were admitted to the intensive care unit. Among 894 patients who received intravenous empirical antibiotics and had diagnostic microbiological cultures drawn upon admission, 614 individuals met exclusion criteria: 412 lacked confirmed positive bacterial cultures, 88 possessed incomplete clinical records, 45 transitioned to palliative comfort care within 48 hours, 37 experienced an ICU stay under 24 hours, and 32 received prior systemic antibiotic therapy. Consequently, the final full study cohort comprised 280 adult septic patients, as detailed in the participant screening and flow diagram in Figure 1. Within this analyzed cohort, 172 patients (61.4%) received Appropriate Empirical Antibiotic Therapy (AEAT), while 108 patients (38.6%) received Inappropriate Empirical Antibiotic Therapy (IEAT).

Baseline demographic and clinical characteristics of the full cohort showed large baseline imbalances between the groups, which indicates confounding by indication, as detailed in Table 1. Patients who received IEAT had significantly greater physiological derangement, with a higher median APACHE II score (29 (IQR 24–34) vs 21 (IQR 16–26); *p* < 0.001), an elevated median SOFA score (11.5 (IQR 9–14) vs 7.5 (IQR 5–10); *p* < 0.001), and a three-fold higher prevalence of overt septic shock upon ICU admission (45.4% (49/108) vs 15.1% (26/172); *p* < 0.001). Conversely, demographic distributions were comparable between groups, including mean age (63.1 $\pm$ 15.3 years in IEAT vs 61.9 $\pm$ 16.1 years in AEAT; *p* = 0.542), male predominance (70.4% vs 70.9%; *p* = 0.920), and mean body mass index (24.8 $\pm$ 6.0 vs 25.3 $\pm$ 6.5 kg/m²; *p* = 0.519). Comorbidity prevalence was similarly distributed between cohorts, including diabetes mellitus (28.7% vs 27.9%; *p* = 0.880), hypertension (43.5% vs 44.2%; *p* = 0.914), and chronic kidney disease (25.9% vs 23.3%; *p* = 0.618).

Table 1. Baseline demographic, clinical characteristics, and severity scores of the full critically ill patient cohort stratified by empirical antibiotic appropriateness.

Characteristic	Total cohort (N = 280)	AEAT group (n = 172)	IEAT group (n = 108)	p value
Age (years), mean ± SD	62.4 ± 15.8	61.9 ± 16.1	63.1 ± 15.3	0.542
Male Sex, n (%)	198 (70.7%)	122 (70.9%)	76 (70.4%)	0.920
Body Mass Index (kg/m ²), mean ± SD	25.1 ± 6.3	25.3 ± 6.5	24.8 ± 6.0	0.519
APACHE II Score, median (IQR)	24 (18–30)	21 (16–26)	29 (24–34)	< 0.001*
SOFA Score, median (IQR)	9 (6–12)	7.5 (5–10)	11.5 (9–14)	< 0.001*
Diabetes Mellitus, n (%)	79 (28.2%)	48 (27.9%)	31 (28.7%)	0.880
Hypertension, n (%)	123 (43.9%)	76 (44.2%)	47 (43.5%)	0.914
Chronic Kidney Disease, n (%)	68 (24.3%)	40 (23.3%)	28 (25.9%)	0.618
Septic Shock at Admission, n (%)	75 (26.8%)	26 (15.1%)	49 (45.4%)	< 0.001*
Pneumonia, n (%)	62 (22.1%)	45 (26.2%)	17 (15.7%)	0.041*
Peritonitis, n (%)	28 (10.0%)	18 (10.5%)	10 (9.3%)	0.745

Notes: Data presented as mean ± SD, median (IQR), or n (%). Asterisks (*) indicate statistical significance at $p < 0.05$. APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment.

Microbiological profiling of the 280 recovered clinical isolates showed that Gram-negative bacilli predominated, accounting for 68.9% (193/280) of all infections, as summarized in Table 2 and shown in Figure 2A. The single most frequently isolated bacterial pathogen was ESBL-producing *Klebsiella pneumoniae*, isolated in 20.0% of cases (56/280), followed closely by extensively drug-resistant (XDR) *Acinetobacter baumannii*, comprising

17.1% (48/280). Additional Gram-negative isolates included ESBL-producing *Escherichia coli* (8.2%, 23/280) and *Pseudomonas aeruginosa* (6.8%, 19/280). Gram-positive cocci constituted the remaining 31.1% (87/280) of isolates, led by *Staphylococcus aureus* (20.7%, 58/280), of which 46.6% (27/58) were methicillin-resistant (MRSA), alongside coagulase-negative *Staphylococci* (6.1%, 17/280) and *Enterococcus faecalis* (5.4%, 15/280).

Table 2. Microbiological profile and antimicrobial resistance patterns of pathogens isolated from the critically ill patient cohort (N = 280).

Pathogen isolated	Frequency (n)	Prevalence (%)
Gram-Negative Bacteria (Total)	193	68.9%
• <i>Klebsiella pneumoniae</i> (ESBL-producing)	56	20.0%
• <i>Acinetobacter baumannii</i> (XDR)	48	17.1%
• <i>Escherichia coli</i> (ESBL-producing)	23	8.2%
• <i>Pseudomonas aeruginosa</i>	19	6.8%
• Other Gram-negative bacilli	47	16.8%
Gram-Positive Bacteria (Total)	87	31.1%
• <i>Staphylococcus aureus</i> (Total)	58	20.7%
- Methicillin-Resistant (MRSA)	27	9.6%
- Methicillin-Susceptible (MSSA)	31	11.1%
• Coagulase-Negative <i>Staphylococci</i>	17	6.1%
• <i>Enterococcus faecalis</i>	15	5.4%

Notes: ESBL: Extended-Spectrum Beta-Lactamase; XDR: Extensively Drug-Resistant; MRSA: Methicillin-Resistant *Staphylococcus aureus*.

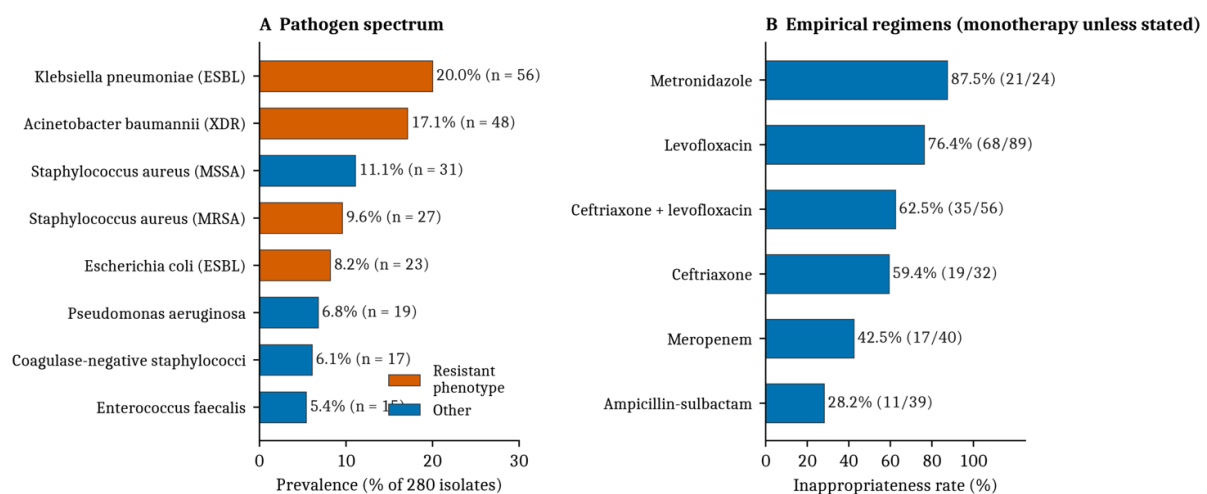


Figure 2. Pathogen distribution and empirical regimen failure. (A) Prevalence of isolated pathogens among 280 isolates; orange bars mark resistant phenotypes. (B) Inappropriateness rate of each initial empirical regimen. ESBL, extended-spectrum beta-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; XDR, extensively drug-resistant.

Initial empirical antimicrobial prescribing patterns showed frequent inappropriateness, as presented in Table

3 and shown in Figure 2B. The most frequently prescribed empirical regimen was levofloxacin monotherapy, used in

31.8% of patients (89/280). Cross-tabulation against in-vitro susceptibility demonstrated that levofloxacin monotherapy failed to provide antimicrobial coverage in 76.4% of cases (68/89). Dual therapy with ceftriaxone and levofloxacin, administered in 20.0% of patients (56/280), exhibited an inappropriateness rate of 62.5% (35/56). Ceftriaxone monotherapy (11.4%, 32/280) was inappropriate in 59.4% (19/32). Meropenem monotherapy—frequently considered the institutional

last-line empirical agent—was prescribed in 14.3% of patients (40/280) and failed in 42.5% (17/40), which may reflect the prevalence of carbapenem-resistant XDR *Acinetobacter baumannii*. Ampicillin-sulbactam (13.9%, 39/280) displayed the lowest failure rate at 28.2% (11/39), while metronidazole monotherapy (8.6%, 24/280) failed in 87.5% (21/24), which may reflect aerobic pathogens that this agent does not cover.

Table 3. Empirical antibiotic regimens prescribed at ICU admission and observed rates of therapeutic inappropriateness (N = 280).

Empirical regimen prescribed	Total use, n (%)	Inappropriate, n (%)	Inappropriateness rate (%)
Levofloxacin (Monotherapy)	89 (31.8%)	68 (76.4%)	76.4%
Ceftriaxone + Levofloxacin	56 (20.0%)	35 (62.5%)	62.5%
Meropenem (Monotherapy)	40 (14.3%)	17 (42.5%)	42.5%
Ampicillin-Sulbactam	39 (13.9%)	11 (28.2%)	28.2%
Ceftriaxone (Monotherapy)	32 (11.4%)	19 (59.4%)	59.4%
Metronidazole (Monotherapy)	24 (8.6%)	21 (87.5%)	87.5%

Notes: Inappropriateness Rate indicates the percentage of times a specific initial empirical regimen failed to demonstrate in-vitro bactericidal activity against the recovered pathogen.

3.2. Primary outcome

The overall 28-day all-cause mortality rate for the entire study cohort was 35.0% (98/280). Clinical outcomes differed significantly between treatment groups, as shown in Figure 3. Patients receiving IEAT experienced a 28-day mortality rate of 77.8% (84/108), compared to only 8.1%

(14/172) among patients receiving AEAT (absolute risk difference: 69.6 percentage points, 95% CI 60.8–78.5; unadjusted OR: 39.50; 95% CI: 19.41–80.37; $p < 0.001$). Patients in the IEAT group also had significantly longer ICU stays (median 14 (IQR 9–21) vs 8 (IQR 5–12) days; $p < 0.001$) and longer total hospitalizations (median 25 (IQR 18–35) vs 15 (IQR 10–22) days; $p < 0.001$).

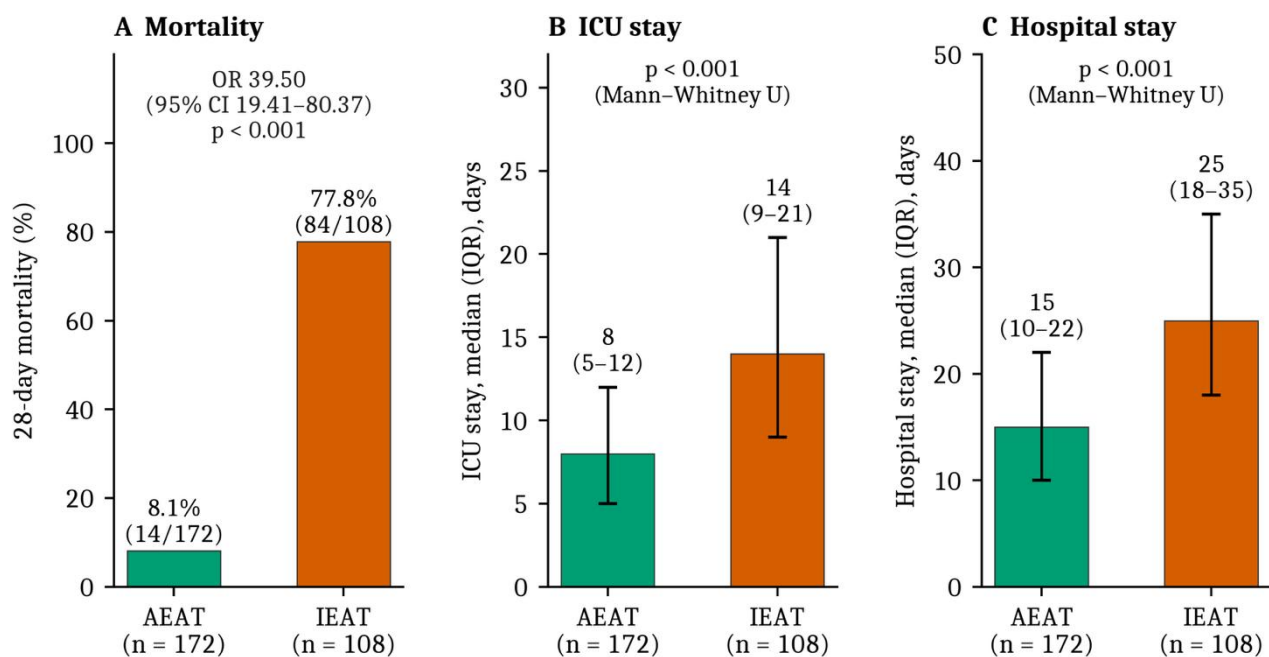


Figure 3. Primary and secondary outcomes by group. (A) 28-day all-cause mortality. (B) ICU length of stay. (C) Total hospital length of stay. Bars show the median and error bars the interquartile range. OR, odds ratio; CI, confidence interval.

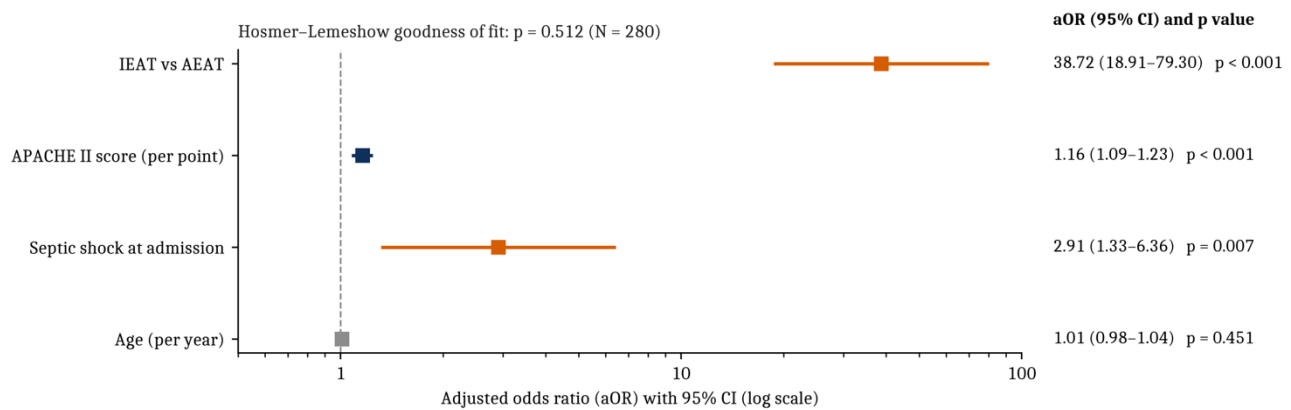
In the multivariable binary logistic regression model adjusted for age, APACHE II score, and septic shock, as detailed in Table 4 and illustrated in the forest plot in Figure 4, IEAT remained independently associated with 28-day mortality and had the largest adjusted odds ratio in the model. Patients receiving IEAT had an adjusted odds ratio of 38.72 (95% CI: 18.91–79.30; $p < 0.001$) compared with those receiving AEAT. Incremental increases in

admission APACHE II score (aOR: 1.16 per point; 95% CI: 1.09–1.23; $p < 0.001$) and the presence of septic shock at admission (aOR: 2.91; 95% CI: 1.33–6.36; $p = 0.007$) were also independent predictors of death, whereas patient age was not significantly associated with mortality (aOR: 1.01; 95% CI: 0.98–1.04; $p = 0.451$). The Hosmer-Lemeshow test showed no evidence of poor fit (Chi-square = 7.23, df = 8, $p = 0.512$).

Table 4. Multivariable logistic regression analysis identifying independent predictors of 28-day mortality in the full cohort (N = 280).

Predictor	Adjusted odds ratio	95% CI	p value
Inappropriate Empirical Antibiotic (IEAT vs AEAT)	38.72	(18.91–79.30)	< 0.001*
APACHE II Score (per 1-point increase)	1.16	(1.09–1.23)	< 0.001*
Septic Shock at Admission (Presence vs Absence)	2.91	(1.33–6.36)	0.007*
Age (per 1-year increase)	1.01	(0.98–1.04)	0.451

Notes: Hosmer-Lemeshow goodness-of-fit Chi-square = 7.23, df = 8, p = 0.512. *p < 0.05 denotes statistical significance.

**Figure 4.** Forest plot of adjusted odds ratios (aOR) with 95% confidence intervals (logarithmic scale) for independent predictors of 28-day mortality (N = 280).

3.3. Secondary and subgroup analyses

Propensity score matching yielded a balanced cohort of 200 patients (100 in the AEAT group and 100 in the IEAT group). Following 1:1 nearest-neighbor matching, the covariates shown in Table 5 achieved good balance, with standardized mean differences below 0.10. Specifically, age

(62.8 ± 15.5 vs 63.0 ± 15.1 years; SMD = 0.013), male sex (71.0% vs 70.0%; SMD = 0.022), median APACHE II score (28 [IQR 23–33] vs 28 [IQR 24–34]; SMD = 0.041), septic shock prevalence (43.0% vs 45.0%; SMD = 0.040), and diabetes mellitus (28.0% vs 30.0%; SMD = 0.043) showed negligible differences between cohorts.

Table 5. Baseline demographic and clinical characteristics of the 1:1 propensity score-matched cohort (N = 200).

Characteristic	AEAT (n = 100)	IEAT (n = 100)	p value	SMD
Age (years), mean ± SD	62.8 ± 15.5	63.0 ± 15.1	0.923	0.013
Male Sex, n (%)	71 (71.0%)	70 (70.0%)	0.881	0.022
APACHE II Score, median (IQR)	28 (23–33)	28 (24–34)	0.765	0.041
Septic Shock, n (%)	43 (43.0%)	45 (45.0%)	0.778	0.040
Diabetes Mellitus, n (%)	28 (28.0%)	30 (30.0%)	0.745	0.043

Notes: SMD < 0.10 confirms negligible covariate imbalance between groups following nearest-neighbor matching with caliper 0.2 SD of logit.

Within this balanced propensity-matched cohort, the difference in mortality between the IEAT and AEAT groups remained large and statistically significant. The 28-day mortality rate was 12.0% (12/100) in the AEAT matched group versus 76.0% (76/100) in the IEAT matched group (p < 0.001). Conditional logistic regression yielded an odds ratio of 25.15 (95% CI: 11.54–54.81; p < 0.001). Sensitivity analyses gave similar estimates across high-acuity strata: among patients presenting with septic shock (n = 75), IEAT

was associated with an aOR of 29.80 (95% CI: 12.10–73.50; p < 0.001), while among patients with baseline APACHE II scores of 25 or higher (n = 154), the aOR was 31.50 (95% CI: 14.80–67.10; p < 0.001). Kaplan-Meier survival curves showed early, marked divergence in cumulative survival within the first 10 days of ICU admission for both the full and propensity-matched cohorts, as detailed in Figure 5 (Log-rank p < 0.001).

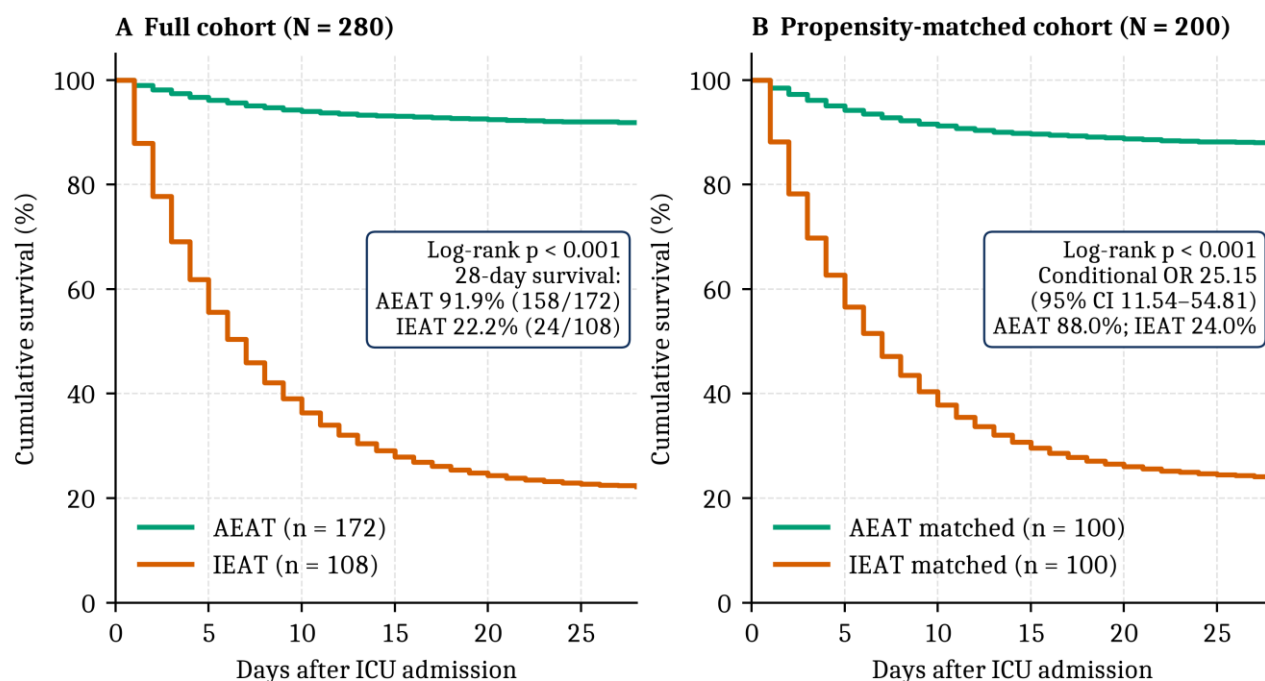


Figure 5. Kaplan-Meier 28-day cumulative survival curves for AEAT versus IEAT in (A) the full cohort (N = 280) and (B) the 1:1 propensity score-matched cohort (N = 200). The curves were redrawn from the submitted image; source data were not provided.

4. Discussion

4.1. Principal findings

This study measures the association between inappropriate empirical antibiotic therapy and mortality in a tertiary intensive care setting in Southeast Asia. Patients whose initial regimen had no in-vitro activity against the causative pathogen had a much higher 28-day mortality. The association remained after adjustment for age, APACHE II score, and septic shock (aOR: 38.72) and in a propensity score-matched cohort (OR: 25.15). The size of the estimate is well above the two- to three-fold risk typically reported in European and North American ICUs,^{11,12} and extreme pathogen resistance, late hospital presentation (not measured here), and high physiological acuity may explain part of the gap.^{8,19}

4.2. Comparison with the published literature

Our estimates are considerably larger than those in the published literature. A systematic review of 198 studies (89,962 patients) with bacteremia reported a pooled odds ratio of 2.06 for mortality with inappropriate empirical therapy.¹¹ In the Eurobact2 cohort of ICU patients with hospital-acquired bloodstream infection, 28-day mortality was 32.8% with adequate therapy within 24 hours and 40% with inadequate therapy.¹² A Dutch tertiary-hospital cohort of bloodstream infections found no association after conventional adjustment. Within a more homogeneous monotherapy subgroup, appropriate therapy was associated with lower 30-day mortality.¹⁵ Odds ratios as large as ours therefore need cautious interpretation. A truly high-risk ICU population with extensive resistance may explain them. Misclassification of exposure, inclusion of culture-positive patients only, sparse data, and residual confounding could also inflate them.

These data point to specific prescribing weaknesses. Levofloxacin monotherapy was the most common empirical choice (31.8% of admissions), yet it failed in 76.4%. In Indonesian tertiary hospitals, fluoroquinolone

use is rooted in earlier prescribing guidelines that valued its broad spectrum, high bioavailability, and good tissue penetration in respiratory and abdominal infections, and levofloxacin is among the most consumed antibiotics in Indonesian hospitals.¹⁴ Our microbiology suggests why this may no longer work: 28.2% of patients carried ESBL-producing Enterobacterales (*Klebsiella pneumoniae* 20.0% and *Escherichia coli* 8.2%). ESBL production is closely linked to fluoroquinolone co-resistance, through mutations in the quinolone resistance-determining regions of *gyrA* and *parC* and through plasmid-borne *qnr* determinants.^{20,21} Fluoroquinolone monotherapy for undifferentiated severe sepsis is therefore likely to fail in this setting, although 23.6% (21/89) of levofloxacin regimens were appropriate in our cohort.²²

Meropenem monotherapy was inappropriate in 42.5% of cases, which is equally concerning. Carbapenems have long been the mainstay of empirical escalation for septic patients with shock or healthcare exposure.²² In our cohort, meropenem failure was mainly driven by extensively drug-resistant (XDR) *Acinetobacter baumannii*, which made up 17.1% of isolates. Carbapenem-resistant *A. baumannii* often carries a wide set of beta-lactamases, including Class D carbapenem-hydrolyzing oxacillinases (OXA-23-like and OXA-58-like) and Class B metallo-beta-lactamases (NDM-1), with outer membrane porin (CarO) loss and upregulated AdeABC efflux adding to the resistance.^{23,24} Clonal spread of carbapenem-resistant *A. baumannii* has been described in tertiary hospitals in Malang.²⁵ For a patient in septic shock from XDR *Acinetobacter*, empirical meropenem monotherapy is unlikely to be active, and the early window for effective treatment may be lost.²⁶

Our findings also say something about regional differences across Southeast Asia and other LMIC settings.²⁷ High-income health systems have rapid diagnostic workflows and a lower baseline prevalence of pan-resistant pathogens. Indonesian tertiary ICUs treat complex patients transferred after long exposure to community or

peripheral hospital care.⁸ Referral concentrates extensively drug-resistant organisms in tertiary centers. Empirical selection there cannot rely on international guidelines written for low-resistance settings.²⁸ Rapid identification tools, such as multiplex polymerase chain reaction panels and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), are needed to shorten the time to targeted therapy.²⁹

4.3. Interpretation and possible mechanisms

Sepsis pathophysiology offers a plausible biological explanation, although none of the following mechanisms was measured in this study.³⁰ Resuscitation works within narrow time limits. Appropriate bactericidal therapy given in the first hour halts bacterial replication and limits release of PAMPs such as lipopolysaccharide (endotoxin), peptidoglycans, and bacterial DNA.¹⁰ Under IEAT, microbial growth continues unchecked for 48 to 72 hours. Accumulating endotoxin keeps activating Toll-like receptor 4 (TLR4) on macrophages and endothelial cells, which triggers a systemic cascade of pro-inflammatory cytokines including TNF- α , IL-1 β , and IL-6.³¹

This hyperinflammatory state attacks the microvascular endothelium, degrading the endothelial glycocalyx and the tight junctions.³² Capillary leak follows. Large volumes of plasma move into the interstitium, causing refractory hypovolemia, generalized tissue edema, and poor microvascular oxygen extraction. Endothelial activation also shifts the intravascular milieu toward a prothrombotic state through tissue factor expression and down-regulation of thrombomodulin and protein C pathways. Disseminated microvascular thrombosis (immunothrombosis) blocks capillary beds in vital organs. Cellular hypoxia, acute tubular necrosis, hepatic dysfunction, myocardial depression, and irreversible multi-organ failure can result.³³

Severe illness also alters pharmacokinetics and pharmacodynamics (PK/PD), which can reduce antimicrobial efficacy even when the organism is susceptible *in vitro*.³⁴ Aggressive intravenous fluid resuscitation and capillary leak increase the volume of distribution (Vd) of hydrophilic drugs such as beta-lactams, aminoglycosides, and glycopeptides, and serum concentrations can then fall below the minimum inhibitory concentration (MIC).³⁴ Younger patients without renal disease may develop augmented renal clearance (ARC) in hyperdynamic sepsis, which speeds elimination of renally cleared agents.³⁵ Time-dependent beta-lactams need 100% free drug concentration above the MIC (100% fT>MIC). That target is very hard to reach with standard intermittent bolus dosing, and it makes the effect of marginally active empirical regimens worse.³⁶

4.4. Implications for practice

These findings have implications for practice and policy. Tertiary hospitals in Indonesia should review and restrict empirical fluoroquinolone monotherapy for suspected sepsis. Stewardship programs can be strengthened with unit-specific antibiograms, updated regularly, and with rapid diagnostic platforms that identify pathogens and resistance determinants within hours rather than days. A move from broad empirical choices toward rapid, diagnostic-guided targeted therapy may help to prevent avoidable sepsis deaths.

4.5. Strengths

Strengths of the study include the use of both multivariable logistic regression and 1:1 propensity score matching against confounding by indication, a detailed cross-tabulation of empirical regimens against pathogen susceptibility, and complete 28-day outcomes.³⁷

4.6. Limitations

First, the retrospective observational design cannot exclude residual confounding from unmeasured variables, even after matching on seven clinical covariates, and residual confounding by severity would most likely inflate the association; examples are dynamic fluid resuscitation volumes, the exact interval between sepsis onset and antimicrobial infusion, and the adequacy of surgical source control.³⁸ Second, we had no therapeutic drug monitoring data or exact dosing schedules. We could not separate microbiological resistance from subtherapeutic PK/PD target attainment.³⁴ Third, susceptibility came from automated phenotypic systems, without genotypic sequencing of carbapenemase or ESBL genes. Fourth, exposure was defined from the susceptibility of later isolates and only culture-positive patients were included. The time to the first antibiotic dose was not available. These features can misclassify exposure and inflate the estimated association. Finally, this is a single tertiary academic center, so pathogen frequencies may reflect regional referral patterns.

4.7. Recommendations for future research

Prospective multicenter studies in Indonesian hospitals are needed to validate these findings. They should record the time to the first antibiotic dose, source control, and genotypic resistance. A pre-registered protocol would help, as would a propensity model that includes illness severity scores, infection source, and organism type.

5. Conclusion

Baseline severity was high and antimicrobial resistance highly endemic in this cohort of Indonesian ICU patients. Inappropriate empirical antibiotic therapy was associated with higher 28-day mortality. The association persisted after multivariable logistic regression and 1:1 propensity score matching for the measured confounders, although unmeasured confounding cannot be excluded. Local prescribing had clear weak points. Empirical levofloxacin monotherapy was inappropriate in 76.4% of cases and meropenem monotherapy in 42.5%, in a setting where ESBL-producing *Klebsiella pneumoniae* and XDR *Acinetobacter baumannii* were prevalent. These results support a review of local empirical sepsis guidelines, restriction of fluoroquinolone monotherapy, regularly updated antibiograms, and investment in rapid microbiological diagnostics.

6. Declarations

Ethical approval and consent to participate. This study was approved by the Ethics Committee of CMHC Research Center, Indonesia, under Approval No. 2022/048. Written informed consent was waived because of the retrospective, non-interventional design and the use of de-identified hospital records. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication. Not applicable.

Availability of data and materials. The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable academic request, subject to institutional ethical oversight.

Artificial intelligence (AI) use statement. The authors declare that no generative artificial intelligence tool was used in the preparation of this article.

Author contribution statement. R.Y.V. contributed to conceptualization, investigation, data curation, formal analysis and writing – original draft. W.J. and A.Z.F. contributed to methodology, validation and supervision, and to writing – review and editing. All authors read and approved the final manuscript.

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