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Antibiotic use patterns and factors associated with leukocyte decrease in COVID-19 patients with suspected secondary infections: A cross-sectional study in Indonesia

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Abstract

Antibiotics are frequently prescribed to coronavirus disease 2019 (COVID-19) patients, often without evidence of bacterial superinfection, increasing the risk of antibiotic resistance and posing a public health threat. The aim of this study was to evaluate antibiotic prescribing patterns in COVID-19 patients with suspected secondary infections and to assess the association between antibiotic use and clinical outcomes, particularly leukocyte count. The study analyzed 376 hospitalized COVID-19 patients from two hospitals in Bandung, Indonesia, between 2020 and 2022. All included patients were aged ≥17 years with confirmed COVID-19, leukocyte count >11,000 µg/L, and received antibiotic therapy. The Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) and drug utilization (DU) 90% were used to assess prescribing patterns. The patients' demographic characteristics, clinical and culture results were also collected. Our data indicated that most patients received multiple antibiotics (>2), with prescribing patterns significantly associated with age, confirmed bacterial pathogen, length of hospital stay and having tuberculosis infection. The most frequently identified pathogens included Gram-positive bacteria *Staphylococcus aureus, Staphylococcus haemolyticus* and Gram-negative bacteria *Klebsiella pneumoniae, Acinetobacter baumannii,* and *Escherichia coli*. The most frequently prescribed antibiotics were azithromycin, levofloxacin, and ceftriaxone. No significant association was found between the number of antibiotics prescribed and clinical outcome (leukocyte normalization). Broad-spectrum antibiotics from the World Health Organization (WHO) AWaRe "Watch" category dominated the antibiotic prescriptions in the patients. While antibiotic selection was generally aligned with pathogen type and comorbidities, standardized guidelines remain crucial to optimizing antibiotic use, particularly in settings with limited pathogen testing.

Keywords: COVID-19, antibiotic use, Defined Daily Dose, drug utilization 90%, AMR

Introduction

The coronavirus disease 2019 (COVID-19) pandemic (2019–2023) is the deadliest outbreak of the 21st century [1], caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. Although the pandemic status has shifted to endemic, the potential for viral mutations remains [3]. Antibiotics are not routinely indicated for COVID-19 unless bacterial co-infection or secondary infection is suspected, as per the World Health Organization (WHO) and Indonesia's

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national guidelines [4,5]. Their use is determined by clinical suspicion, laboratory findings, and patient-specific factors, with empirical therapy reserved for severe cases based on local epidemiological data [4,5]. However, widespread antibiotic overuse has been reported. A global study found that 82% of hospitalized COVID-19 patients received antibiotics despite unclear indications [6]. A meta-analysis of 24 studies involving 3,338 COVID-19 patients found antibiotic use in 71.9% of cases, whereas bacterial co-infection and secondary infection were confirmed in only 3.5% and 14.3% of cases, respectively [7].

The extensive use of antibiotics in COVID-19 management might contribute to the escalating threat of antimicrobial resistance (AMR). WHO data indicate a >15% increase in AMR rate in 2020 compared to 2017 [8]. In Indonesia, the Antimicrobial Resistance Indicator (AMRIN) report estimated 700,000 AMR-related deaths in 2018, with projections reaching 10 million annually by 2050 [8]. A study showed that 75–90% of Indonesians receive empirical antibiotic therapy, often before culture confirmation [9]. In one health center located in Surabaya, Indonesia, 75.2% of patients received antibiotics, despite bacterial infections being confirmed in only 19.7% [9]. Among hospitalized COVID-19 patients, 70% received empirical antibiotics, primarily broad-spectrum agents [10]. Another study found that 25% of COVID-19 patients received a single antibiotic, while 45% were given a combination [11]. Frequently prescribed antibiotics included cephalosporins, quinolones, carbapenems, and tigecycline, often tested against drug-resistant *Staphylococcus aureus* [12]. Despite antimicrobial stewardship efforts, antibiotic overuse remains a persistent issue in respiratory infections and hospital settings.

Although antibiotic use in COVID-19 cases has been widely studied, no comprehensive evaluation has been conducted in Indonesia to assess prescription patterns and their impact on secondary infections. The WHO-recommended Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) system provides a standardized approach for hospital-based antibiotic consumption analysis, enabling cross-country comparisons and policy recommendations [13]. Additionally, drug utilization (DU) 90% analysis facilitates quantitative assessments of prescribing trends [14].

In addition, given that secondary infections in COVID-19 patients are often linked to immune dysfunction, leukocyte count dynamics may serve as an infection indicator [15]. Monitoring leukocyte count in critically ill patients serves as a tool to assess the presence of infections, such as sepsis or pneumonia [15]. The monitoring is also valuable for evaluating the infectious status of patients requiring hospitalization [16]. Variations in leukocyte count not only have clinical implications but also significant economic consequences [17]. Therefore, the aim of this study was to analyze antibiotic prescription patterns in COVID-19 patients with suspected secondary infections at Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital in Bandung, Indonesia, using the ATC/DDD and DU 90% methods. Additionally, this study sought to identify factors influencing antibiotic prescriptions and to assess their impact on leukocyte normalization.

Methods

Study design and setting

A retrospective study was conducted on COVID-19 patients admitted to the inpatient wards of two hospitals in Bandung, Indonesia: Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital. Hasan Sadikin Hospital is a tertiary referral hospital, while Dr. H. A. Rotinsulu Lung Hospital specializes in pulmonary diseases and serves as a referral center for COVID-19 cases in Bandung. Data were collected from both hospitals to compare antibiotic prescribing patterns in COVID-19 patients with suspected secondary infections. The study was conducted from November 2020 to December 2022.

Sampling strategy

Consecutive sampling was employed in this study. During the study period, a total of 9,386 COVID-19 patients were recorded, including 8,186 patients from Hasan Sadikin Hospital and 1,200 patients from Dr. H. A. Rotinsulu Lung Hospital. Based on Slovin's formula [18] with a 95% confidence level and a 5% margin of error, the calculated minimum sample size was 384 patients.

Patients

This study included patients who were confirmed positive for COVID-19, with or without comorbidities, and prescribed antibiotics. Comorbidities included pneumonia, type 2 diabetes mellitus, hypertension, cardiovascular disease, and tuberculosis. Eligible patients were aged ≥17 years at the time of hospital admission and had a high suspicion of secondary bacterial infection. Patients were classified as having a high suspicion of secondary bacterial infection if their white leukocyte count exceeded 11,000 µg/L, surpassing the normal reference range of 4,000–11,000 µg/L [19]. This threshold was selected to identify individuals likely experiencing bacterial infections based on elevated leukocyte levels [20]. Patients were excluded if they had contraindications to antibiotics, prior antibiotic use, incomplete or illegible medical records (including unclear or unconfirmed documentation), had been discharged against medical advice or were deceased.

Data collection

The total population of patients with confirmed COVID-19 (n=9,386) were screened based on the eligibility criteria. Then, the patients were sampled based on the required minimum sample size. Data were then collected from medical records, including demographics (age, sex, and length of hospital stay), clinical parameters (comorbidities, leukocyte count before and after antibiotic treatment, type and dosage of antibiotics) and laboratory results, including the pathogen data. Age was categorized into two groups: 17–39 years and ≥40 years. Sex was classified as male or female, while the length of hospital stay was recorded as ≤15 days or >15 days. Comorbidities, including pneumonia, type 2 diabetes mellitus, hypertension, cardiovascular disease, and tuberculosis, were documented and categorized based on the number of coexisting conditions. Additionally, tuberculosis status was recorded as present or absent. Patients were also classified based on the total number of antibiotics prescribed during hospitalization (1–2 antibiotics vs. >2 antibiotics) to analyze the relationship between antibiotic utilization patterns and clinical outcomes in COVID-19 patients. Pathogen data from both hospitals were also collected and categorized by type, with their frequencies expressed as a percentage of the total patients diagnosed with a pathogen during treatment.

Study variables

In this study, the independent variables included patient characteristics and antibiotic consumption patterns, while the dependent variable was the clinical outcome of antibiotic treatment, assessed through changes in leukocyte count [21]. Baseline leukocyte data were collected from patients, with a leukocyte count exceeding 11,000 µg/L defined as a suspected secondary bacterial infection. Leukocyte level was then monitored throughout hospitalization to evaluate the impact of antibiotic treatment on their normalization. Leukocyte levels before and after the antibiotic therapy were used to evaluate the outcome. The primary outcome measure was the reduction of leukocyte count to within the normal range (4,000–11,000 µg/L) [19]. Patients were categorized based on their post-treatment leukocyte numbers: those who achieved the normal limit (≤11,000 µg/L) and those who did not (>11,000 µg/L) [20]. The percentage of patients achieving the target leukocyte number was calculated separately for each hospital.

Antibiotic use pattern

Antibiotic use data were analyzed and categorized based on the pharmacological class of antibiotics, type, dosage form, route of administration, and Anatomical Therapeutic Chemical (ATC) classification codes, as defined by the WHO. The classification system was referenced from the WHO Collaborating Centre for Drug Statistics Methodology [13]. Antibiotic use was categorized according to ATC groups and codes, available at http://www.whocc.no/atc-ddd-index. Total antibiotic consumption was calculated over a specified period by dividing the total drug administered (in gram) by the Defined Daily Dose (DDD), length of stay (LOS), and study duration. The standardized metric for evaluation was defined as DDD per 100 patient-days, calculated as follows:

$$\mathrm{DDD} = \frac{\text{Number of grams of antibiotics used by COVID−19 patient}}{\text{WHO DDD Standard (gram)}} \times \frac{100}{Total\ LOS}$$

Following the WHO Collaborating Centre for Drug Statistics Methodology [13], antibiotic utilization was classified into DU 90% and DU 10% segments, where DU 90% represented the most frequently prescribed antibiotics.

Statistical analysis

The Chi-squared test assessed the relationship between patient characteristics and antibiotic use. Logistic regression identified factors associated with leukocyte normalization, including age, sex, comorbidities, LOS, pathogen presence, comorbid conditions, tuberculosis status, and antibiotic use. Statistical analyses were performed using SPSS version 23.0 (IBM Corp, Armonk, NY, USA).

Results

Patients' selection

The total number of COVID-19 patients during the study period was 9,386 across two hospitals, with 8,186 from Hasan Sadikin Hospital and 1,200 from Dr. H. A. Rotinsulu Lung Hospital. A total of 384 were selected; however, eight patients were excluded based on the following criteria: incomplete patient data (n=3), contraindications to antibiotic use (n=1), and hospital discharge or death (n=4). Consequently, the final sample consisted of 376 patients who met the inclusion criteria. The patient selection process is presented in **Figure 1**.

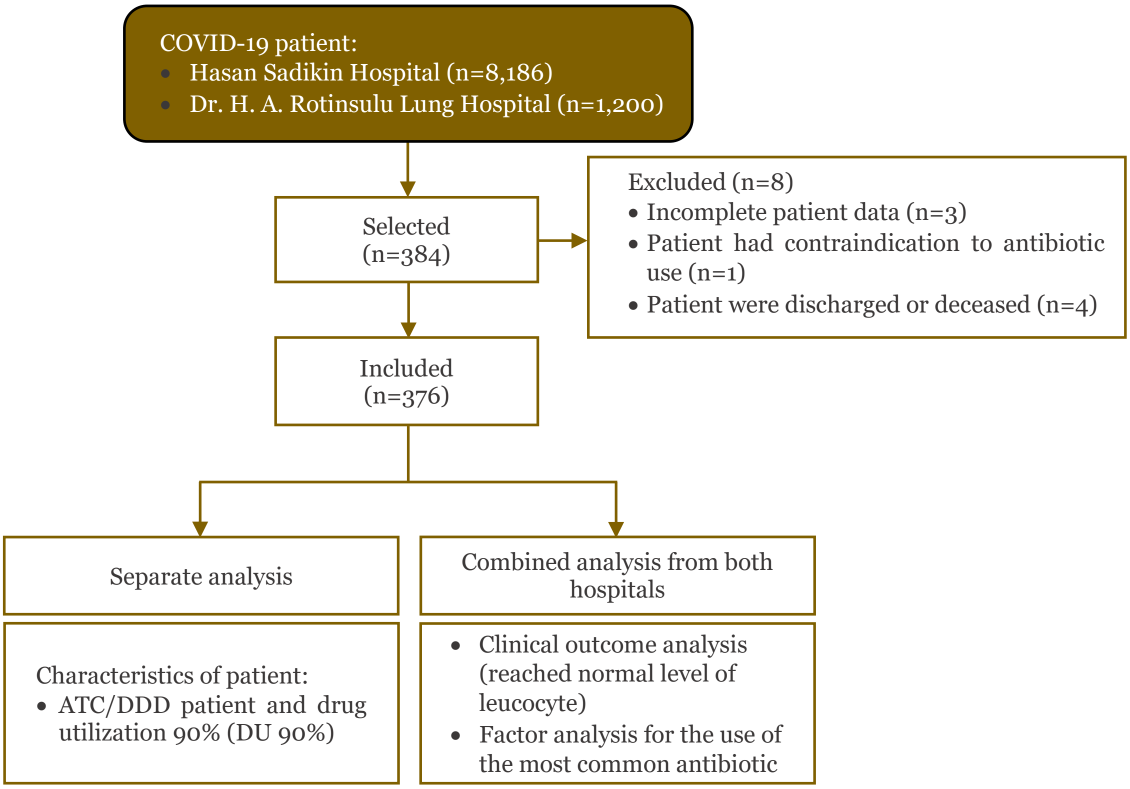

Figure 1. Patient selection process in the study.

Characteristics of COVID-19 patients in both hospitals

The characteristics of COVID-19 patients treated at Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital were analyzed to provide a descriptive overview, including age, sex, LOS, and comorbidities, and the presence of the pathogen from the cultures (**Table 1**). A comparison between the two hospitals showed a higher proportion of male patients, with 148 (39.4%) in Hasan Sadikin Hospital and 73 (19.4%) in Dr. H. A. Rotinsulu Lung Hospital, from a total of 221 male patients. The majority of patients were aged ≥40 years compared to those aged 17–39 years, comprising 189 (50.3%) cases in Hasan Sadikin Hospital and 78 (20.7%) in Dr. H. A. Rotinsulu Lung Hospital. LOS analysis indicated that most patients in Hasan Sadikin Hospital had a hospital stay of <15 days (173 patients, 46.0%). The average LOS differed between the two hospitals, with 14.28 days in Hasan Sadikin Hospital and 16.12 days in Dr. H. A. Rotinsulu Lung Hospital (**Table 1**).

Comorbidities were more frequently observed in patients with confirmed COVID-19, affecting 183 (48.7%) patients in Hasan Sadikin Hospital and 86 (22.9%) in Dr. H. A. Rotinsulu Lung Hospital (**Table 1**). Differences in pathogen confirmation were also noted, with a higher proportion of confirmed bacterial infections in Hasan Sadikin Hospital (170 patients, 45.2%), while unconfirmed bacterial cases were more prevalent in Dr. H. A. Rotinsulu Lung Hospital (74 patients, 19.7%) (**Table 1**).

Table 1. Characteristics of COVID-19 patients with suspected secondary infections treated in Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital between 2020 and 2022 (n=376)

Characteristics	Hasan Sadikin Hospital (n=265)	Dr. H. A. Rotinsulu Lung Hospital (n=111)	Total (n=376)
	n (%)	n (%)	n (%)
Sex			
Male	148 (39.40)	73 (19.40)	221 (58.80)
Female	117 (31.10)	38 (10.10)	155 (41.20)
Age (years)			
17–39	76 (20.20)	33 (8.80)	109 (29.00)
≥40	189 (50.30)	78 (20.70)	267 (71.00)
Length of stay (days)			
≤15	173 (46.00)	60 (16.00)	233 (62.00)
≥15	92 (24.50)	51 (13.60)	243 (38.00)
Comorbid			
Yes	183 (48.70)	86 (22.90)	269 (71.50)
No	82 (21.80)	25 (6.60)	107 (28.50)
Pathogen			
Confirmed bacteria	170 (45.20)	37 (9.80)	207 (55.10)
Unconfirmed bacteria	95 (25.30)	74 (19.70)	169 (44.90)
Tuberculosis			
Yes	251 (68.80)	83 (22.10)	334 (88.80)
No	14 (3.70)	28 (7.40)	42 (11.20)
Total length of stay (days) for all patients	3785	1789	
Average length of stay (AvLOS)±SD	14.28±8.54	16.12±8.54	

Factors associated with antibiotic use

A univariate analysis was performed to investigate the relationship between patient characteristics and antibiotic use (1–2 vs >2 antibiotics) and the results are presented in **Table 2**. The results from Hasan Sadikin Hospital revealed a significant association between age (p<0.001) and patient pathogen criteria (p<0.001). Conversely, data from Dr. H. A. Rotinsulu Lung Hospital indicated that tuberculosis (p<0.001) and LOS (p=0.007) were significantly associated with the number of antibiotics used in patients with confirmed COVID-19.

Table 2. Factors associated with antibiotic use among COVID-19 patients with suspected secondary infections treated in Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital between 2020 and 2022

Characteristics	Total, n (%)	Antibiotic		*p*-value
		1–2 antibiotic, n (%)	>2 antibiotics, n (%)	
Hasan Sadikin Hospital				
Age (years)				
17–39	76 (28.67)	35 (23.17)	41 (35.96)	0.016*
≥40	189 (71.30)	116 (76.82)	73 (64.03)	
Sex				
Female	117 (44.15)	70 (46.35)	47 (41.22)	0.240
Male	148 (55.84)	81 (53.64)	67 (58.77)	
Length of stay (days)				
≤15	173 (65.28)	101(66.88)	72 (63.15)	0.308
≥15	92 (34.71)	50 (33.11)	42 (36.84)	
Comorbid				
Yes	183 (69.05)	110 (72.84)	73 (64.03)	0.081
No	82 (30.94)	41 (27.15)	41 (35.96)	
Pathogen				
Unconfirmed	95 (35.84)	71 (47.01)	24 (21.05)	<0.001*

Characteristics	Total, n (%)	Antibiotic		*p*-value
		1–2 antibiotic, n (%)	>2 antibiotics, n (%)	
Confirmed	170 (64.15)	80 (52.98)	90 (78.94)	
Tuberculosis				
Yes	14 (5.28)	5 (3.42)	9 (7.89)	0.085
No	251 (94.71)	146 (96.68)	105 (92.10)	
Dr. H. A. Rotinsulu Lung Hospital				
Age (years)				
17–39	33 (29.72)	18 (26.86)	15 (34.09)	0.272
≥40	78 (70.27)	49 (73.13)	29 (65.90)	
Sex				
Female	38 (34.23)	22 (32.83)	16 (36.36)	0.427
Male	73 (65.76)	45 (67.16)	28 (63.63)	
Length of stay (days)				
≤15	60 (54.05)	43 (64.17)	17 (38.63)	0.007*
≥15	51 (45.94)	24 (35.82)	27 (61.36)	
Comorbid				
Yes	86 (77.47)	49 (73.13)	37 (84.09)	0.131
No	25 (22.52)	18 (28.86)	7 (15.90)	
Pathogen				
Unconfirmed	74 (66.66)	44 (65.67)	30 (68.18)	0.475
Confirmed	37 (33.33)	23 (34.32)	14 (31.81)	
Tuberculosis				
Yes	28 (25.22)	4 (5.97)	24 (54.54)	<0.001*
No	83 (74.77)	63 (94.02)	20 (45.45)	

*Statistically significant at p=0.05

Pathogen investigation

The culture data on COVID-19 patients were documented from both Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital. Microbiological examinations were conducted prior to the initiation of treatment. Among the 376 patients diagnosed with COVID-19 across both hospitals, complete pathogen data were available for 246 patients, accounting for 65.42% of the total sample. A higher proportion of patients with complete culture data was recorded in Hasan Sadikin Hospital (171 patients, 46.5%) compared to Dr. H. A. Rotinsulu Lung Hospital (41 patients, 36.9%).

In Hasan Sadikin Hospital, the most prevalent Gram-positive pathogen was *Staphylococcus aureus* (29.24%), followed by *Staphylococcus haemolyticus* (9.94%) and *Streptococcus pneumoniae* (4.09%) (**Figure 2A**). The least frequently identified Gram-positive pathogens included *Lactobacillus fermentum* (0.58%), *S. xylosus* (0.58%), and *S. lugdunensis*. Among Gram-negative pathogens, *Escherichia coli* (25.73%), *Acinetobacter baumannii* (25.73%), and *Klebsiella pneumoniae* (22.81%) were the most prevalent. The lowest detection rates among Gram-negative pathogens in Hasan Sadikin Hospital were observed for *Serratia marcescens* (0.58%), *Pseudomonas fluorescens* (0.58%), *Providencia rettgeri* (0.58%), *Proteus mirabilis* (0.58%), *Proteus hauseri* (0.58%), *Acinetobacter* spp. (0.58%), and *Salmonella typhi* (0.58%) (**Figure 2A**).

In Dr. H. A. Rotinsulu Lung Hospital, *S. haemolyticus* (12.20%) was the most frequently detected Gram-positive pathogen, while *Staphylococcus* spp. (2.44%) and *Enterococcus faecalis* (2.44%) had the lowest prevalence (**Figure 2B**). Among Gram-negative pathogens, *Klebsiella pneumoniae* (29%) was the most common, followed by *Enterobacter cloacae* (12.20%). The lowest detection rates were observed for *Serratia marcescens* (2.44%), *Citrobacter koseri* (2.44%), and *Acinetobacter baumannii* (2.44%) (**Figure 2B**).

Antibiotic usage patterns

The total antibiotic consumption at Hasan Sadikin Hospital between 2020–2022 among COVID-19 patients, based on ATC/DDD calculations, comprised 21 types of antibiotics. The highest consumption rate was recorded in 2021, reaching 57.613 DDD per patient-day, primarily due to the use of third-generation cephalosporins, particularly intravenous ceftriaxone (**Table 3**). The antibiotic with the lowest total consumption in 2020 at Hasan Sadikin Hospital was the anti-tuberculosis drug pyrazinamide, with a consumption rate of 0.171 DDD per patient-day. At Dr. H. A. Rotinsulu Lung Hospital, 13 types of antibiotics were recorded over the same period, with the highest consumption in 2020 observed in the macrolide class, specifically azithromycin, which had an ATC/DDD rate of 65.68 DDD per patient-day. The lowest consumption rate in 2020 was observed for the third-generation cephalosporin cefotaxime, at 0.68 DDD per patient-day (**Table 3**). Detailed antibiotic use patterns based on the ATC/DDD method among COVID-19 patients included in the study from both Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital are presented in **Table 3**.

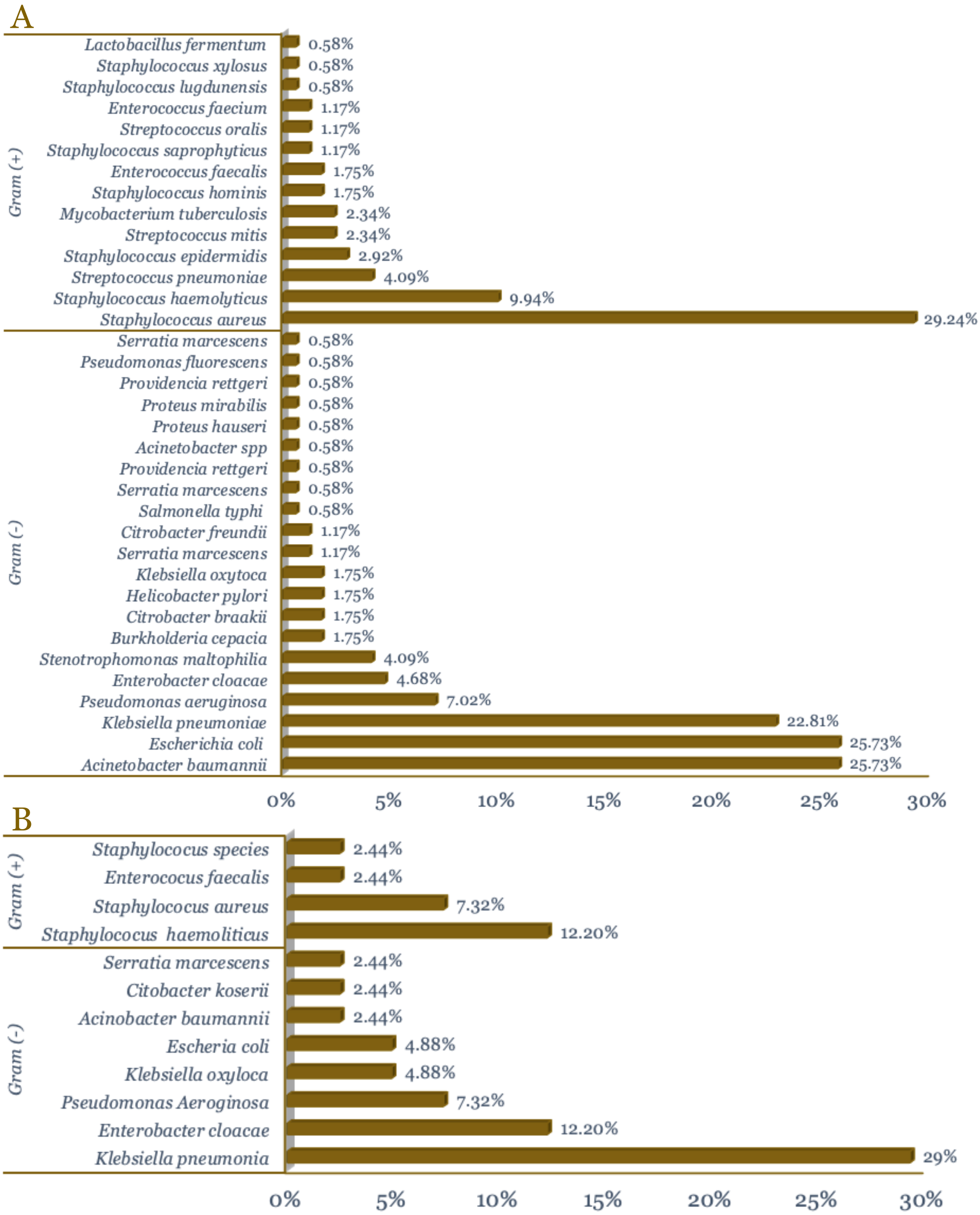

Figure 2. Pathogens isolated from COVID-19 patients with suspected secondary infections treated in Hasan Sadikin Hospital (A) and Dr. H. A. Rotinsulu Lung Hospital (B) between 2020 and 2022.

Drug utilization

The DU 90% metric describes the most widely used antibiotics in a healthcare facility, while antibiotics within the 10% segment represent those that are least prescribed or utilized [13]. Based on three years of data from both hospitals, the highest DU 90% segment at Hasan Sadikin Hospital was recorded in 2022, comprising levofloxacin, ceftriaxone, azithromycin, amikacin, cotrimoxazole, and meropenem (**Figure 3A**). Among these, levofloxacin had the highest utilization, with a consumption rate of 48.823 DDD per 100 patient-days with DU 90% value of 37.231% (**Figure 3A**).

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Table 3. Antibiotic use patterns based on the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method in COVID-19 patients with suspected secondary infections treated in Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital between 2020 and 2022

ATC/ DDD (Hasan Sadikin Hospital)				ATC/ DDD (Dr. H. A. Rotinsulu Lung Hospital)			
Antibiotic group	Name of antibiotic	ATC code	Total DDD	Antibiotic group	Name of antibiotic	ATC code	Total DDD
2020							
1st Gen cephalosporin	Cefadroxil (O)	J01DB05	0.5925	3rd Gen cephalosporin	Ceftazidime (P)	J01dd02	46.13
1st Gen cephalosporin	Cefazoline (P)	J01DB04	0.3357	3rd Gen cephalosporin	Cefixime (O)	J01dd08	8.88
3rd Gen cephalosporin	Ceftriaxone (O)	J01DD04	20.354	4th Gen cephalosporin	Cefepime (P)	J01de01	1.54
3rd Gen cephalosporin	Ceftazidime (P)	J01DD02	2.541	3rd Gen cephalosporin	Cefotaxime (P)	J01dd01	0.68
3rd Gen cephalosporin	Cefixime (O)	J01DD08	2.701	3rd Gen quinolone	Moxifloxacin (P)	J01ma14	5.24
Aminoglycoside	Amikacin (P)	J01GB06	4.395	2nd Gen quinolone	Ciprofloxacin (P)	J01ma02	2.05
Macrolide	Azithromycin (O)	J01FA10	9.615	3rd Gen quinolone	Levofloxacin (P)	J01ma12	61.96
Carbapenem ß-lactam	Meropenem (P)	J01DH02	11.63	Carbapenem	Meropenem (P)	J01dh02	7.71
1st Gen glycopeptide	Vancomycin HCL (P)	J01XA01	2.335	Aminoglycoside	Amikacin (P)	J01gb06	0.80
2nd Gen quinolone	Ciprofloxacin (P)/(O)	J01MA02	1.172	Macrolides	Azithromycin (P)	J01fa10	65.68
3rd Gen quinolone	Levofloxacin (O)	J01MA12	24.13				
Nitroimidazole	Metronidazole (P)	J01XD01	0.311				
Anti-tuberculosis	Ethambutol (O)	J04AK02	0.267				
	Isoniazid (O)	J04AC01	1.135				
	Pyrazinamide (O)	J04AK01	0.171				
	Rifampicin (O)	J04AB02	0.755				
2021							
3rd Gen cephalosporin	Ceftriaxone (O)	J01DD04	57.613	3rd Gen cephalosporin	Cefixime (O)	J01dd08	0.818
3rd Gen cephalosporin	Ceftazidime (P)	J01DD02	48.912	3rd Gen cephalosporin	Cefotaxime (P)	J01dd01	0.614
3rd Gen cephalosporin	Cefixime (O)	J01DD08	28.011	3rd Gen cephalosporin	Ceftazidime (P)	J01dd02	0.491
1st Gen cephalosporin	Cefadroxil(O)	J01DB05	15.279	Macrolides	Clindamycin (O)	J01ff01	7.365
1st Gen cephalosporin	Cefazoline (P)	J01DB04	10.186	Macrolides	Azithromycin (P)	J01fa10	43.33
3rd Gen quinolone	Levofloxacin (P)	J01MA12	6.95	3rd Gen quinolone	Levofloxacin (P)	J01ma12	43.45
2nd Gen quinolone	Ciprofloxacin (P)	J01MA02	6.472	Carbapenem ß-lactam	Meropenem (P)	J01dh02	5.511
Carbapenem ß-lactam	Meropenem (P)	J01DH02	4.987	Nitroimidazole	Metronidazole (P)	J01xd01	0.327
Nitroimidazole	Metronidazole (P)	J01XD01	2.334				
Sulfonamides	Cotrimoxazole (O)	J01EE01	1.167				
Aminoglycosides	Amikacin (P)	J01GB06	1.273				
Macrolides	Azithromycin (P)	J01FA10	0.955				
Glycopeptide	Vancomycin HCL (P)	J01XA01	0.477				
2022							
3rd Gen cephalosporin	Ceftriaxone (P)	J01DD04	48.823	3rd Gen cephalosporin	Cefixime (O)	J01dd08	6.90
3rd Gen cephalosporin	Ceftazidime (P)	J01DD02	20.818	3rd Gen cephalosporin	Ceftazidime (P)	J01dd02	3.315
3rd Gen cephalosporin	Cefixime (O)	J01DD08	16.976	3rd Gen cephalosporin	Ceftriaxone (P)	J01dd04	3.248
3rd Gen cephalosporin	Cefepime (P)	J01DE01	12.144	3rd Gen cephalosporin	Cefotaxime (P)	J01dd01	1.793
3rd Gen cephalosporin	Cefotaxime (P)	J01DD01	10.161	3rd Gen quinolone	Levofloxacin (P)	J01ma12	26.59
3rd Gen cephalosporin	Cefadroxil (O)	J01DB05	7.435	2nd Gen quinolone	Ciprofloxacin (P)	J01ma02	0.271
3rd Gen cephalosporin	Cefazoline (P)	J01DB04	6.196	Macrolide	Azithromycin (P)	J01fa10	11.06
Aminoglycosides	Amikacin (P)	J01GB06	3.098	Carbapenem ß-lactam	Meropenem (P)	J01dh02	1.49
Aminoglycoside	Gentamicin (P)	J01GB03	1.735	Nitroimidazole	Metronidazole (P)	J01xd01	1.353

ATC/ DDD (Hasan Sadikin Hospital)				ATC/ DDD (Dr. H. A. Rotinsulu Lung Hospital)			
Antibiotic group	Name of antibiotic	ATC code	Total DDD	Antibiotic group	Name of antibiotic	ATC code	Total DDD
3rd Gen quinolone	Levofloxacin (P)	J01MA12	1.363	Sulfonamides	Cotrimoxazole (O)	J01ee01	4.547
2nd Gen quinolone	Ciprofloxacin (P)	J01MA02	0.496				
Macrolides	Azithromycin (O)	J01FA10	0.496				
Sulfonamides	Cotrimoxazole (O)	J01EE01	0.743				
Carbapenem ß-lactam	Meropenem (P)	J01DH02	0.372				
Penicillin	Benzathine benzyl (P)	J01CE01	0.124				
	Penicillin (P)		0.124				
Nitroimidazole	Metronidazole (P)	J01XD01	0.032				
Glycopeptide	Vancomycin HCL (P)	J01XA01	48.823				

DDD: defined daily dose; Gen: generation; O: oral; P: parenteral
*In Hasan Sadikin Hospital, LOS accumulation of 265 patients was 1,092 days in 2020, 1,885 days in 2021, and 807 days in 2022
*In Dr. H. A. Rotinsulu Lung Hospital, LOS accumulation of 111 patients was 439 days in 2020, 611 days in 2021, and 739 days in 2022

At Dr. H. A. Rotinsulu Lung Hospital, the highest DU 90% segment was observed in 2021, including levofloxacin, clindamycin, and azithromycin (**Figure 3B**). Levofloxacin remained the most widely used antibiotic, with a consumption rate of 43.453 DDD per 100 patient-days and a DU 90% value of 66.17% (**Figure 3B**).

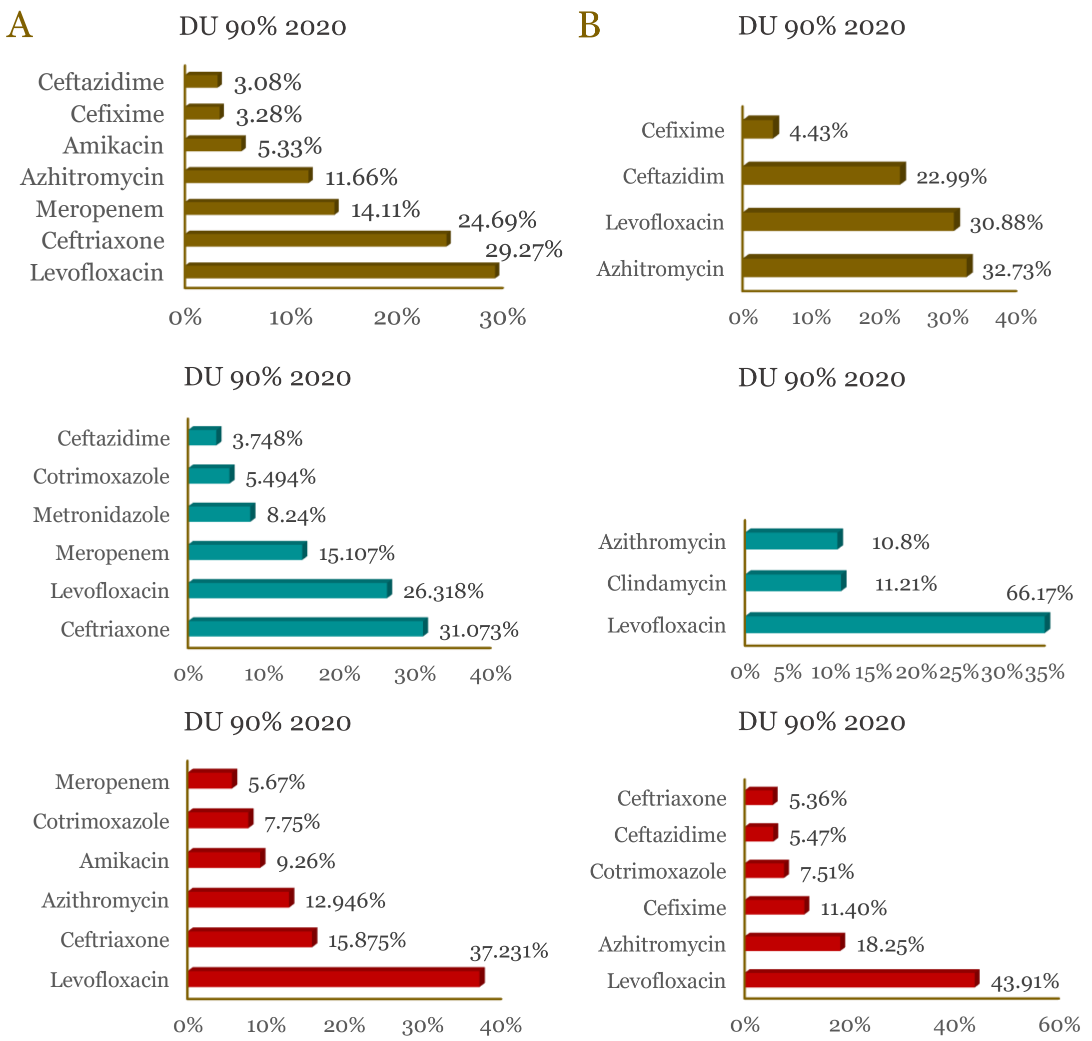

Figure 3. Drug utilization 90% (DU 90%) in COVID-19 patients with suspected secondary infections treated in Hasan Sadikin Hospital (A) and Dr. H. A. Rotinsulu Lung Hospital (B) between 2020 and 2022.

Factors associated with achieving leukocyte normalization

A multivariate regression analysis was performed using combined data from both hospitals over three years (2020–2022) to assess potential factors associated with achieving leukocyte normalization (4,000–11,000 µg/L). The analysis included demographic variables (age, sex, and LOS) and clinical factors (pathogens, comorbidities, antibiotic use, and tuberculosis). Our data indicated that no factors were found to be associated with leukocyte normalization among COVID-19 with suspected secondary infections (**Table 4**).

Table 4. Regression analysis of factors affecting leukocyte reduction in COVID-19 patients with suspected secondary infections treated in Hasan Sadikin Hospital and Dr. H. A. Rotinsulu Lung Hospital between 2020 and 2022

Variables	Leucocyte reduction				*p*-value
	Target achieved		Target unachieved		
	n	Percentage (%)	n	Percentage (%)	
Age					0.538
17–39 years	75	28.9	34	29.0	
≥40 years	184	71.1	83	71.0	

Variables	Leucocyte reduction				*p*-value
	Target achieved		Target unachieved		
	n	Percentage (%)	n	Percentage (%)	
Sex					0.063
Male	144	55.6	77	65.8	
Female	115	44.4	40	34.2	
Length of stay (LOS)					0.422
≤15 days	157	60.6	76	65.0	
≥15 days	102	39.4	41	35.0	
Pathogen					0.445
Confirmed bacteria	146	56.4	61	52.1	
Unconfirmed bacteria	113	43.6	56	47.9	
Comorbid					0.942
Without comorbidity	74	28.6	33	28.2	
Comorbidity	185	71.4	84	71.8	
Use of antibiotics					0.188
1–2 antibiotics	156	60.2	62	53.0	
>2 antibiotics	103	39.8	55	47.0	
Tuberculosis					0.980
Yes	29	11.2	13	11.1	
Non-ttuberculosis	230	88.8	104	88.9	

Discussion

This study successfully documented antibiotic use in COVID-19 patients, including factors associated with the prescription of multiple antibiotics during hospitalization. It also identified the most frequently used antibiotics and provided data on bacterial pathogen types isolated from the patients. Our data indicated that age, pathogen presence, LOS and tuberculosis diagnosis were the primary factors affecting multiple antibiotic use. A study emphasized the need for specific antibiotic stewardship criteria in COVID-19 patients, underscoring the importance of further investigation into patient demographics [22]. The use of multiple antibiotics was common among COVID-19 patients, consistent with findings from other studies [23,24,25]. High antibiotic usage often occurred in critically ill patients, particularly those with bacteremia associated with respiratory [24,25,26]. Pathogen testing may indicate the presence of multiple pathogens infecting the patient, thereby necessitating the use of several antibiotics. Additionally, pathogen testing can reveal resistance to multiple antibiotics, requiring clinicians to adjust treatment regimens or add combination therapies [26]. The presence of a positive tuberculosis status in this study was associated with the use of more than two antibiotics. Standard tuberculosis treatment requires a combination of at least four anti-mycobacterial drugs over a six-month period. Therefore, it is understandable that tuberculosis co-infection would be linked to the prescription of multiple antibiotics [26].

Our study indicated that most dominant co-infection pathogens in COVID-19 patients were Gram-positive bacteria such as *S. aureus* and *S. haemolyticus*, and Gram-negative bacteria like *E. coli*, *A. baumannii*, and *K. pneumoniae*. This is consistent with a similar study in China, which found that *S. pneumoniae* and *K. pneumoniae* were frequently observed as secondary infections in COVID-19 patients [27]. In addition, *K. pneumoniae* and *S. aureus* are widely distributed in both natural and clinical environments [28,29]. All the identified pathogens in the present study belong to the ESKAPE group, which includes *S. aureus, A. baumannii, K. pneumoniae, Enterococcus faecium, P. aeruginosa,* and *Enterobacter* spp. [30,31]. Pathogens belonging to the ESKAPE group are associated with a high risk of antibiotic resistance. Therefore, it is crucial to make prudent antibiotic treatment choices for COVID-19 patients. However, not all antibiotic treatments are guided by pathogen testing. In low-and middle-income countries (LMICs), the limited availability of pathogen testing may be due to resource constraints [32]. To address this issue, it is recommended to restrict the use of empirical antibiotics in COVID-19 patients to those suspected of having bacterial pneumonia [32]. It is also crucial to conduct pathogen testing tailored to the patient's condition to minimize excessive antibiotic use. Additionally, proper antibiotic guidelines are essential in assisting with the selection and determination of appropriate antibiotic therapy.

To assess the use of antibiotics in this study, which occurred in COVID-19 patients, WHO recommends the ATC/DDD analysis method, and DU 90% method was also used. Based on the

DU 90%, the highest antibiotic use was the fluoroquinolone group, a group of broad-spectrum antibiotics that can overcome Gram-positive and Gram-negative bacteria and has antiviral potential to repress the replication of double-sense viruses and single-stranded RNA viruses like Zika virus, dengue virus, hepatitis C virus, and rhinovirus [33]. The findings of this study are consistent with research conducted in Medan, Indonesia, which reported that the most commonly used antibiotic was levofloxacin, accounting for 48.54% of cases, with a dose of 45.61 DDD/100 patient-days and a DU 90% of 48.69% [34]. Another study also highlighted levofloxacin as the most frequently used antibiotic, with a dose of 66.42 DDD/100 patient-days [35]. Levofloxacin is commonly utilized as a therapeutic option for COVID-19 patients with comorbidity of pneumonia and has been shown to exhibit strong activity as an inhibitor of the SARS-CoV-2 [36].

Furthermore, levofloxacin is the antibiotic of choice for managing common comorbidities of COVID-19 and pneumonia, and it is the most frequently used antibiotic in COVID-19 patients with pneumonia [36]. This complies with the guidelines for treating pneumonia from the American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) and the Pneumonia Guidelines of Indonesian Respirology [37,38]. However, the use of levofloxacin for secondary bacterial infection in COVID-19 may need to consider the high occurrence of fluoroquinolone resistance among pathogens in COVID-19 patients with secondary infections [39].

Another antibiotic commonly used in this study was ceftriaxone. A study in Italy and Kazakhstan also found frequent use of levofloxacin, ceftriaxone, and azithromycin in COVID-19 patients [40]. Based on the 2021 WHO AwaRe category on the classification, evaluation, and monitoring of antibiotic use, levofloxacin, azithromycin, and ceftriaxone are included in the "Watch" category - frequently used for human treatment, creating a high potential for bacterial resistance [41]. Therefore, these antibiotics need to be used with caution.

A subsequent investigation was conducted to examine the utilization of antibiotics and to assess the factors that may influence the reduction of leukocytes (a clinical outcome of antibiotic use). Our study found that a higher percentage (68.1%) of patients achieved the leukocyte level target compared to those who did not achieve the target (31.11%). However, no factors were identified that influenced the achievement of leukocyte change target, including the number of antibiotics prescribed. Similarly, another study found that antibiotic use had no significant differences in hospitalization outcomes or mortality rate [42]. Additionally, a study conducted at Banda Aceh examining the relationship between antibiotic usage and clinical outcomes found no significant association between antibiotic use and clinical outcomes in COVID-19 patients [43].

The emergency conditions related to the global COVID-19 pandemic have subsided. However, in-depth scientific studies on the use of antibiotics in cases of secondary infections in COVID-19 patients are still scarce. Therefore, an assessment of the impact of the previous coronavirus outbreak and the current effects of COVID-19 can help in making the best decisions, especially regarding the development of appropriate, effective, and efficient treatment. This study highlights the significance of more guidance in treating bacterial secondary infection, particularly for emerging viral infections such as COVID-19. The guideline can be informed by regular surveillance of common bacteria types and sensitivity that cause secondary infection in patients with viral respiratory disease, such as those found in this study. Such guidelines are crucial for developing countries with limited resources for pathogen testing.

This study has both strengths and limitations. The sample size in this study was lower than required. This occurred due to incomplete data and eligibility to be included in the study. The analysis in this study is limited to a specific location, Bandung, a city in West Java region, and therefore cannot be generalized to other regions. Nevertheless, one of the hospitals included in the study is the provincial tertiary referral hospital; therefore, it is likely that the patients of this hospital came from areas other than Bandung. In this study, data was taken only from COVID-19 patients with elevated leukocyte levels who were treated with antibiotics. Since data from similar patients who did not use antibiotics was not collected, this study could not directly compare the effect of antibiotics vs no antibiotics on elevated leukocyte levels. Additionally, this study did not compare the patient population with non-COVID-19 patients with secondary bacterial diseases. Although the data was collected only from one of the regions in Indonesia, another limitation of the present study is related to antibiotic use. Due to medical system limitations, the study could only gain access to the number and types of antibiotics used during hospitalization, making it impossible to determine whether the antibiotics were administered in combination or consecutively. Despite these limitations, this study is the first to specifically evaluate COVID-19 patients with elevated leukocyte levels, indicating a secondary bacterial infection. This study also identified the prescription of more than one antibiotic in COVID-19 patients during hospitalization and the factors associated with the prescription.

Conclusion

This study found a high prevalence of secondary bacterial infections, leading to frequent antibiotic prescriptions. Antibiotic use was influenced by patient age, LOS, the result of culture, and tuberculosis diagnosis. The most common Gram-positive pathogens were *S. aureus* and *S. haemolyticus*, while *E. coli*, *A. baumannii*, and *K. pneumoniae* were the predominant Gram-negative bacteria. DU 90% analysis over three years identified levofloxacin and ceftriaxone as the most frequently prescribed antibiotics at Hasan Sadikin Hospital, while azithromycin and levofloxacin were dominant at Dr. H. A. Rotinsulu Lung Hospital. These antibiotics fall under the "Watch" category, warranting careful monitoring. Follow-up assessments of antibiotic treatment outcomes in severe COVID-19 cases showed no significant association between antibiotic use and leukocyte normalization. These findings highlight the need for stringent antibiotic stewardship to prevent resistance and minimize unnecessary use.

Ethics approval

The ethical approvals of the study were granted by the Ethics Committees of Hasan Sadikin Hospital (No LB.02.01/X.6.5/346/2023) and Dr. H. A Rotinsulu Lung Hospital (No LB.01.02/6395/2023). Informed consent was waived in this retrospective study.

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Competing interests

The authors confirm that they have no competing interests to disclose.

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Underlying data

Data/information supporting the findings of this study is available from the corresponding author by request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tool for manuscript writing support. AI-based language model, Chat GPT, was employed for language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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