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The overuse of antimicrobials during the COVID-19 pandemic: data from 25 general hospitals in Shanxi, China

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Abstract

Background During the coronavirus disease 2019 (COVID-19) pandemic, widespread empirical antimicrobial use was reported globally, often without confirmed bacterial infection. This study aimed to assess antimicrobial prescribing patterns, bacterial coinfection rates, and clinical outcomes among inpatients during the Omicron surge in Shanxi Province, China.

Methods We conducted a multicentre retrospective study using data from 25 hospitals. Non-surgical inpatients discharged between December 1, 2022, and January 31, 2023, were included. Patients were categorized by COVID-19 status and antimicrobial use. Antimicrobial consumption was measured using defined daily doses (DDDs), days of therapy (DOT), and antimicrobial use density (AUD). Clinical outcomes, microbiological data, and adverse events were analyzed.

Results Among the 2064 inpatients included, 701 (34.0%) were diagnosed with COVID-19. Of these, 511 (72.9%) received antimicrobial therapy, while only 382 (54.5%) had a documented bacterial infection. Microbiological testing was positive in only 123 (6.0%) patients, yielding 139 isolates, of which 21 (15.1%) were multidrug-resistant. Consistently, COVID-19-positive patients were exposed to broad-spectrum agents more frequently: the proportions of both highly-restricted and restricted antimicrobials were significantly higher than in COVID-19-negative patients (4.7% vs. 2.8% and 68.2% vs. 61.9%, respectively; $P < 0.05$). Overall antimicrobial pressure was also greater in the positive group: antimicrobial-use density reached 84.28 vs. 47.07 DDDs/100 bed-days ($P < 0.001$), and days of therapy were 811.06 vs. 541.43 /1000 patient-days ($P < 0.001$). These differences translated into higher costs (median total hospitalization expense CNY 8013 vs. CNY 6447; $P < 0.001$) and prolonged stays (36.0% stayed 11–20 days vs. 22.4%; $P < 0.001$). Mortality did not differ across groups ($P = 0.779$).

†Song Wang and Yang Tang contributed equally to this work.

The author's order was determined by drawing straws.

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Conclusion This study highlights the excessive use of antimicrobials in COVID-19 inpatients, often without confirmed bacterial infection. This overuse did not improve outcomes but contributed to increased healthcare costs and antimicrobial resistance risk. Rational antimicrobial management and improved diagnostic practices are crucial to combat this challenge in health care settings.

Clinical trial Not applicable.

Keywords COVID-19, Antimicrobial, Bacterial infection, Antimicrobial stewardship

Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease exhibited a global surge in late 2021 due to the Omicron variant, which posed significant challenges to health care. By January 7, 2024, the World Health Organization (WHO) reported that there were more than 774 million confirmed cases of COVID-19 and more than 7 million-related deaths [1]. In December 2022, China adjusted its COVID-19 policy to allow people with mild or no symptoms to quarantine at home, leading to widespread transmission of the Omicron variant [2].

Bacterial superinfection is a common complication of COVID-19 in inpatients. A systematic review and meta-analysis reported that approximately 17.3% (95% CI 10.0%–25.9%) of COVID-19 patients in China have bacterial superinfection [3]. Several studies have shown that empirical antibiotics should not be routinely used in patients with mild or moderate COVID-19 unless bacterial infection is suspected [4, 5]. However, several recent studies have shown that during the pandemic, the vast majority of inpatients with COVID-19 received empirical antimicrobial treatment before bacterial infection was diagnosed [6–8]. Furthermore, the WHO stated that "just in case" antibiotics were widely overused during the COVID-19 pandemic, which increased the risk of antimicrobial resistance (AMR) [9].

Given the limitations of inpatient sample collection, routine sputum or blood culture is not recommended for inpatients with community-acquired pneumonia [10]. However, few studies have examined the coinfection of inpatients during the COVID-19 pandemic. In particular, there is a lack of multicentre studies [11], and the extent of the use of antimicrobials in inpatients during the COVID-19 pandemic remains unclear. Therefore, to maintain antimicrobial stewardship (AMS), it is important to understand the multicentre infection status, antimicrobial use, hospitalization days and costs of all inpatients during the COVID-19 pandemic [12]. This multicentre study aims to elucidate the use of antimicrobials in Shanxi Province during the pandemic, to provide empirical support for the rational use of antimicrobials, and to reduce the extent of AMR.

Methods

Data source

This study drew on data from the Shanxi Provincial Antimicrobial Agents and Intravenous Infusion Survey, a programme that conducted prevalence surveys of health-care-associated infection and antimicrobial use in 2022–23 at selected hospitals across 11 prefecture-level cities of Shanxi Province (Taiyuan, Datong, Shuozhou, Xinzhou, Yangquan, Jinzhong, Yuncheng, Linfen, Changzhi, Jincheng and Lvliang); the methods and principal findings have been published previously [13]. For the present analysis, non-surgical patients discharged between 1 December 2022 and 31 January 2023 were randomly sampled from each participating hospital. The following variables were extracted: general demographic characteristics, comorbidities and illness severity, relevant laboratory tests, health-care-associated infections and microbiological culture results during hospitalization, antimicrobial and COVID-19 treatments, length of stay, adverse reactions, and costs. The study was approved by the ethics committees of all participating hospitals (Central ethics reference: (2023) YX No. 334).

Definitions

Patients' bacterial infection diagnosis status was determined on the basis of the ICD-10-CM diagnosis code. COVID-19 was determined on the basis of the ICD-10-CM diagnosis code U07.1. The U07.1 code was introduced in April 2020 and indicates a positive SARS-CoV-2 test or a clinician statement that an inpatient had COVID-19. Compared with laboratory data, the U07.1 code has been validated as highly accurate for identifying hospitalizations associated with COVID-19 [14]. We further classified the cohort on the basis of antimicrobial exposure and documented SARS-CoV-2 status. Patients who received any systemic antibacterial agent during hospitalization and carried the ICD-10-CM diagnosis code U07.1 were designated the "COVID-19-positive with antimicrobial use" group. Those who had diagnosis code U07.1 but never received an antimicrobial during their stay constituted the "COVID-19-positive without antimicrobial use" group. Among patients who lacked code U07.1, individuals with a documented negative nucleic-acid test for SARS-CoV-2 were labeled the "COVID-19-negative" group, whereas those without any

test result were assigned to the "COVID-19-unknown" group. The antimicrobial use density (AUD) was defined as the average number of defined daily doses (DDDs) of antimicrobial agents consumed by hospitalized inpatients per 100 bed-days (bd). Adverse events such as liver injury, acute kidney injury, and neutropenia were identified and classified through consensus among the study investigators. Liver injury was defined as ALT levels ≥ 5× ULN. Acute kidney injury was classified as grade 1 (1.5–1.9 × baseline or ≥ 0.3 mg/dl above baseline), grade 2 (2.0–2.9 × baseline), or grade 3 (≥ 3.0 × baseline, ≥ 4.0 mg/dl, or initiation of renal replacement therapy). Neutropenia was classified as mild (ANC 1000–1500/μL), moderate (ANC 500–1000/μL), or severe (ANC < 500/μL) [15–17].

Pathogen identification and antimicrobial susceptibility testing

The attending physician of each hospital made the decision to order microbiological examinations for inpatients with suspected infection, and clinical microbiologists performed standard microbiological procedures. A positive microbial culture was defined as growth of a pathogen from a specimen collected at the site of infection, or isolation of an organism from blood when systemic spread or dissemination from a localized focus was suspected. Contaminants, colonizers, and normal flora of the sampled site were rigorously excluded before a result was considered positive. All strains were identified by the VITEK-2 Compact automatic microbial analysis system (BioMerieux Italia S.p.A). Antimicrobial susceptibility tests were performed via automated systems or disk diffusion methods. The minimum inhibitory concentration (MIC) was determined by the Clinical and Laboratory Standards Institute (CLSI) (CLSI M100 31st) and classified as susceptible, resistant, or intermediate. MDR was defined as resistance to three or more commonly used antimicrobial agents that are normally considered effective.

Statistical methods

Statistical analysis was performed using SPSS version 13.0 (IBM Corp, Armonk, NY, USA). For normally distributed quantitative variables, comparisons among more than two groups were made using One-way analysis of variance, with Bonferroni correction for multiple comparisons. For nonnormally distributed quantitative variables, comparisons among more than two groups were made using the Kruskal-Wallis test, with Bonferroni correction for multiple comparisons. Categorical variables were compared between more than two groups using the chi-square test or Fisher's exact test, as appropriate, with Bonferroni correction applied for pairwise comparisons. $P < 0.05$ was considered to indicate statistical significance.

Clinical outcomes

The primary outcomes included improvement and death after discharge. The secondary outcomes included antimicrobial class, duration of hospital stay, antimicrobial costs, total hospitalization costs, AUD, days of treatment (DOT) with antimicrobials, and adverse events (acute kidney injury, liver injury, neutropenia) [18]. DOT was calculated per 1000 patient-days (pd).

Results

Participants' demographics and past medical history

A total of 2064 inpatients from 25 hospitals were divided into four observation groups based on the presence or absence of a COVID-19 diagnosis and whether or not they received antimicrobials during hospitalization. The groups were as follows: 511 (24.8%) inpatients in COVID-19-positive with antimicrobial use; 190 (9.2%) inpatients in COVID-19-positive without antimicrobial use; 1053 (51.0%) inpatients in COVID-19-negative patients; and 310 (15.0%) patients in COVID-19-unknown patients. Of the 2064 inpatients, 1205 (58.4%) were male and the overall median age was 65 years. Patients in the "COVID-19-positive with antimicrobial use" group were significantly older (median 74 years) than those in the other three groups ($P < 0.05$). Diabetes was the most common comorbidity (378, 18.3%), and the prevalence of diabetes, malignancy, rheumatic disease, chronic kidney disease, and hematologic malignancy did not differ among the four groups. In contrast, chronic obstructive pulmonary disease (COPD) was markedly more frequent in the COVID-19-positive with antimicrobial use group than in the remaining three groups ($P < 0.05$). Charlson Comorbidity Index scores > 3 were comparable between the two COVID-19-positive subgroups (with vs without antimicrobial use), whereas both the COVID-19-unknown and COVID-19-negative groups had a higher proportion of patients with scores > 3 than the COVID-19-positive with antimicrobial use group ($P < 0.001$) (Table 1).

Infection diagnosis and microbial detection

A total of 793 (38.4%) inpatients were diagnosed with a bacterial infection, and 382 (54.5%) of COVID-19-positive inpatients had bacterial infection diagnosis. Among this cohort, respiratory symptoms were the most common manifestation, present in 68.0% (940/1383) of cases. Microbial cultures were positive in 123 patients (6.0%), yielding 139 isolates, including 21 multidrug-resistant organisms. Sputum was the predominant source of positive cultures (95/139, 68.3%), followed by urine (19/139, 13.7%) and blood (11/139, 7.9%). Notably, in the COVID-19-positive subgroup treated with antimicrobials, 53 sputum samples (81.5%) were culture-positive, significantly higher than in other groups ($P < 0.05$). The distribution of isolated pathogens is shown in Fig. 1; among the 139

Table 1 Summary of the clinical features and laboratory results of the four groups

	All (*n* = 2064)	**COV(unk) (*n* = 310)**	**COV(+) (*n* = 701)**		**COV(-) (*n* = 1053)**	***P***
			COV(+)AB(+) (*n* = 511)	**COV(+)AB(-) (*n* = 390)**		
Gender, male, n (%)	1205 (58.4%)	180 (58.1%)	321 (62.8%)	105 (55.3%)	599 (56.9%)	0.117
Age, years, median (IQR)	65 (51, 76)	61 (46, 71)	74 (60, 82)	59 (46, 71)	63 (50, 74)	< 0.001
BMI, median (IQR)	23.31 (20.20, 25.95)	23.59 (20.81, 25.91)	22.72 (19.81, 25.39)	23.25 (20.20, 25.78)	23.51 (20.24, 26.12)	0.003
Bacterial infections diagnosis, n (%)						< 0.001
Yes	793 (38.4%)	91 (29.4%)	363 (71.0%)	19 (10.0%)	320 (30.4%)	
No	630 (30.5%)	69 (22.2%)	25 (4.9%)	128 (67.4%)	408 (38.7%)	
Unknown	641 (31.1%)	150 (48.4%)	123 (24.1%)	43 (22.6%)	325 (30.9%)	
Site of bacterial infection, n (%)						
Pulmonary	655 (31.7%)	65 (21.0%)	333 (65.2%)	14 (7.4%)	243 (23.1%)	< 0.001
Blood	11 (0.5%)	1 (0.3%)	4 (0.8%)	0 (0.0%)	6 (0.6%)	0.765
Urinary tract	23 (1.1%)	2 (0.6%)	5 (1.0%)	2 (1.1%)	14 (1.3%)	0.830
Other	62 (3.0%)	12 (3.9%)	15 (2.9%)	0 (0.0%)	35 (3.3%)	0.070
No foci of infection have been identified	60 (2.9%)	12 (3.9%)	15 (2.9%)	3 (1.6%)	30 (2.8%)	0.528
Pathogen test rate, n (%)	123 (6.0%)	10 (3.2%)	56 (11.0%)	2 (1.1%)	55 (5.2%)	< 0.001
Multi-Drug Resistance, MDR, n (%)	21/139 (15.1%)	2/10 (20.0%)	13/65 (20.0%)	0/3 (0.0%)	6/61 (9.8%)	0.334
COVID-19-related drug exposure, n (%)	400 (19.4%)	36 (11.6%)	213 (41.7%)	46 (24.2%)	105 (10.0)	< 0.001
Details of COVID-19-related drug exposure, n (%)						
Ribavirin	26 (1.3%)	4 (1.3%)	9 (1.8%)	6 (3.2%)	7 (0.7%)	0.2
Abdominal cavity	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1.000
Acyclovir	13 (0.6%)	5 (1.6%)	6 (1.2%)	0 (0.0%)	2 (0.2%)	0.006
Ganciclovir	9 (0.4%)	0 (0.0%)	5 (1.0%)	1 (0.5%)	3 (0.3%)	0.159
Nirmatrelvir/ritonavir	31 (1.5%)	1 (0.3%)	21 (4.1%)	6 (3.2%)	3 (0.3%)	< 0.001
Azvudine	272 (13.2%)	17 (5.5%)	170 (33.3%)	26 (13.7%)	59 (5.6%)	< 0.001
Baricitinib	4 (0.2%)	0 (0.0%)	4 (0.8%)	0 (0.0%)	0 (0.0%)	0.014
Thymus fasio	34 (1.6%)	1 (0.3%)	19 (3.7%)	9 (4.7%)	5 (0.5%)	< 0.001
Glucocorticoid	76 (3.7%)	9 (2.9%)	27 (5.3%)	10 (5.3%)	30 (2.8%)	0.054
Intravenous immunoglobulin (IVIg)	24 (1.2%)	4 (1.3%)	16 (3.1%)	1 (0.5%)	3 (0.3%)	< 0.001
Underlying medical conditions, n (%)						
Total	1384 (67.1%)	188 (60.6%)	372 (72.8%)	100 (52.6%)	724 (68.8%)	< 0.001
Diabetes	378 (18.3%)	57 (18.4%)	94 (18.4%)	27 (14.2%)	200 (19.0%)	0.481
Tumour	115 (5.6%)	14 (4.5%)	25 (4.9%)	10 (5.3%)	66 (6.3%)	0.55
Rheumatic immune diseases	36 (1.7%)	4 (1.3%)	12 (2.3%)	4 (2.1%)	16 (1.5%)	0.59
Chronic kidney disease	54 (2.6%)	5 (1.6%)	15 (2.9%)	3 (1.6%)	31 (2.9%)	0.444
COPD	75 (3.6%)	11 (3.5%)	32 (6.3%)	5 (2.6%)	27 (2.6%)	0.003
Malignant haematologic disease	18 (0.9%)	4 (1.3%)	3 (0.6%)	2 (1.1%)	9 (0.9%)	0.701
Charlson comorbidity index ≥ 3	411 (19.9%)	71 (22.9%)	67 (13.1%)	28 (14.7%)	245 (23.3%)	< 0.001
Laboratory tests, median, (IQR)						
White blood count, 10^9/L	6.35 (4.70, 8.76)	6.51 (4.81, 9.83)	5.83 (4.10, 8.18)	5.48 (4.20, 7.56)	6.80 (5.03, 9.20)	< 0.001
Neutrophilic granulocyte percentage, 10^9/L	69.20 (56.80, 79.60)	69.90 (58.58, 78.53)	73.21 (62.40, 83.10)	67.60 (56.08, 77.48)	67.20 (53.70, 78.80)	< 0.001
C-reactive protein, mg/L	16.34 (3.58, 65.810	11.53 (2.63, 66.95)	36.76 (9.71, 88.78)	8.10 (1.74, 36.10)	12.50 (3.47, 58.92)	< 0.001

COV(unk) = COVID-19-unknown. COV(+) = COVID-19-positive. COV(-) = COVID-19-negative. COV(+)AB(+) = COVID-19-positive with antimicrobial use. COV(+)AB(-) = COVID-19-positive without antimicrobial use. IQR, interquartile range. n, number. %, percentage

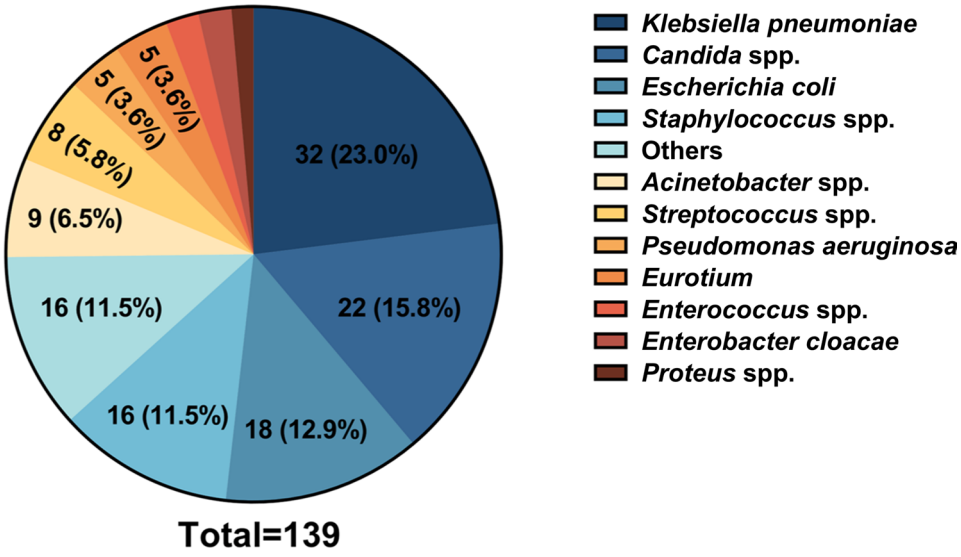

Fig. 1 Distribution of detected pathogens

positive cultures, the top three genera were *Klebsiella pneumoniae* (32/139, 23.0%), *Candida* spp. (22/139, 15.8%), and *Escherichia coli* (18/139, 12.9%) Fig. 1).

Drug exposure during hospitalization

We analyzed antiviral agents recorded in the electronic database, including drugs targeting influenza A virus, influenza B virus, and SARS-CoV-2, as well as immunomodulators such as thymalfasin, glucocorticoids, intravenous immunoglobulin, and JAK-inhibitors (tocilizumab and baricitinib). Overall, 19.4% (400/2064) of patients received one or more of these agents. The COVID-positive with antimicrobial use group had the highest exposure: 41.7% (213/511) versus 24.2% (46/190) in the COVID-positive without antimicrobial use group and the remaining two groups ($P<0.001$). Within the COVID-positive plus antimicrobial-drug cohort, nirmatrelvir/ritonavir was used in 4.1% (21/511) and azvudine in 33.3% (170/511); in the COVID-positive without antimicrobial use cohort, the corresponding figures were 3.2% (6/190) and 26% (26/190). The overall utilization rate of anti-SARS-CoV-2 drugs was 31.8% (223/701). Pairwise comparisons among the four groups showed no statistically significant differences in the use of ribavirin, arbidol, ganciclovir, or glucocorticoids. By contrast, exposure to nirmatrelvir/ritonavir, azvudine, acyclovir, baricitinib, thymalfasin, and immunoglobulin was significantly higher in COVID-positive patients (all $P<0.05$); among these, immunoglobulin, nirmatrelvir/ritonavir, and azvudine were used most frequently in the COVID-positive with antibacterial use group (Table 1).

Antimicrobial consumption and drug utilization patterns

To characterize antimicrobial use, the 2064 patients were stratified into three groups: 310 (15.0%) COVID-19-unknown, 701 (34.0%) COVID-19-positive, and 1053 (51.0%) COVID-19-negative.

The COVID-19-positive group exhibited a significantly higher prevalence of antimicrobial exposure than the other two groups ($P<0.01$). The most frequently prescribed agents were third-generation cephalosporins (494, 25.5%), quinolones (450, 23.2%) and cephalosporin–β-lactamase inhibitor combinations (244, 12.6%), followed by penicillin (206, 10.6%) and penicillin-based combinations (170, 8.8%). One patient in the COVID-19-negative group received polymyxin and one sulfonamide. Compared with the other cohorts, the COVID-19-positive group generated more prescriptions for third-generation cephalosporins, quinolones, cephalosporin combinations and carbapenems, and also registered the highest DOT per 1000 patient-days for the top three drug classes. (Fig. 2).

We compared antimicrobial expenditure and spectrum across the three predefined groups. COVID-19-positive patients received antimicrobials most frequently (511/701, 72.9%), almost 1.5-fold higher than either comparator group (157/311, 50.6% and 508/1053, 48.2%; $P<0.001$). Intensity of use followed the same pattern: DOT reached 811/1000 patient-days in the positive group versus 541 in the negative group ($P<0.001$), while AUD peaked at 84.3 DDDs/100 bed-days versus 49.4 and 47.1 in the other two cohorts ($P<0.001$). Consequently, median antimicrobial costs in COVID-19-positive patients were CNY 306, dwarfing the CNY 8 and 0 spent in the remaining groups ($P<0.001$). Despite broader exposure, non-restricted agents accounted for only 27.2%

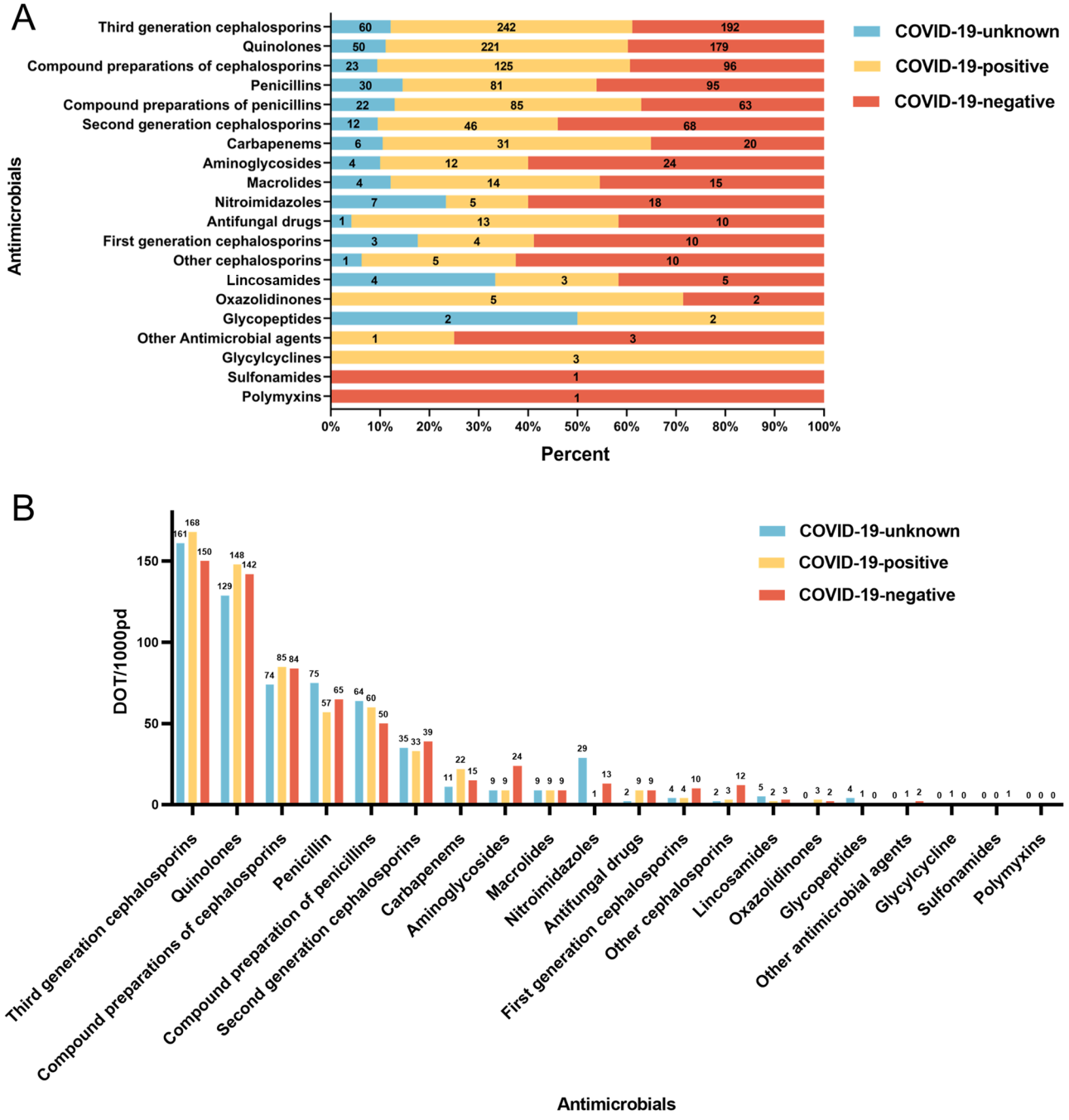

Fig. 2 The number of medical order items and DOT for antimicrobial classifications. The detailed agents of antimicrobial classification can be found in Supplement 2. (**A**) DOT of different antimicrobial classifications. (**B**) Percentage distribution of medical order items for different antimicrobial classifications

(244/898) of regimens in the positive group, a smaller share than the 33.6% (77/229) and 35.2% (286/812) observed elsewhere ($P = 0.003$), confirming a shift toward higher-tier antibiotics. Extending the analysis to four groups (adding COVID-19-positive without antimicrobials) confirmed that total drug and hospitalization expenses were highest when SARS-CoV-2 infection was managed with antibiotics: median drug costs CNY 2217 and total hospital costs CNY 8014, each exceeding the corresponding figures for the other three arms by 1.4- to 3.4-fold (all $P < 0.001$) (Tables 2 and 3).

Clinical outcomes

Mortality was similar across the four cohorts (COVID-19-positive with antimicrobials: 16/511, 3.1%; COVID-19-positive without antimicrobials: 11/311, 3.5%; COVID-19-unknown: 9/190, 4.7%; COVID-19-negative: 36/1053, 3.4%; $P = 0.779$). Patients who were

Table 2 Antimicrobial usage and class

	All (*n* = 2064)	COV(unk) (*n* = 310)	COV(+) (*n* = 701)	COV(-) (*n* = 1053)	*P*
Antimicrobials used, n (%)	1176 (57.0%)	157 (50.6%)	511 (72.9%)	508 (48.2%)	< 0.001
LOT/1000 pd	508	441.73	664.6	416.75	< 0.001
DOT/1000 pd	622	523.86	811.06	514.43	< 0.001
AUD, DDDs/100 bd	60.56	49.39	84.28	47.07	< 0.001
Antimicrobials grade, n (%)					0.003
Non-restricted	607/1939 (31.3%)	77/229 (33.6%)	244/898 (27.2%)	286/812 (35.2%)	
Restricted	1259/1939 (64.9%)	144/229 (62.9%)	612/898 (68.2%)	503/812 (61.9%)	
Highly-restricted	73/1939 (3.8%)	8/229 (3.5%)	42/898 (4.7%)	23/812 (2.8%)	
Costs, median, (IQR)					
Total costs of antimicrobials, CNY	108 (0, 676)	8 (0, 386)	306 (0, 1010)	0 (0, 504)	< 0.001

COV(unk) = COVID-19-unknown. COV(+) = COVID-19-positive. COV(-) = COVID-19-negative. COV(+)AB(+) = COVID-19-positive with antimicrobial use. COV(+) AB(-) = COVID-19-positive without antimicrobial use. IQR, interquartile range. n, number. %, percentage

Table 3 Clinical outcomes

	All (*n* = 2064)	COV(unk) (*n* = 310)	COV(+) (*n* = 701)		COV(-) (*n* = 1053)	*P*
			COV(+)AB(+) (*n* = 511)	COV(+)AB(-) (*n* = 190)		
Treatment outcome, n (%)						0.779
Improve	1992 (96.5%)	299 (96.5%)	495 (96.9%)	181 (95.3%)	1017 (96.6%)	
Death	72 (3.5%)	11 (3.5%)	16 (3.1%)	9 (4.7%)	36 (3.4%)	
Hospitalization days, n (%)						< 0.001
3–10	1416 (68.6%)	225 (72.6%)	298 (58.3%)	141 (74.2%)	752 (71.4%)	
11–20	535 (25.9%)	73 (23.5%)	184 (36.0%)	42 (22.1%)	236 (22.4%)	
> 20	113 (5.5%)	12 (3.9%)	29 (5.7%)	7 (3.7%)	65 (6.2%)	
Total costs, CNY, median, (IQR)						
Hospitalization	6423 (3911, 10637)	5785 (3580, 11077)	8013 (4991, 12774)	4152 (2061, 6796)	6447 (3964, 10215)	< 0.001
Inpatient drugs	1579 (620, 3411)	1321 (579, 3571)	2216 (1022, 4124)	646 (161, 1726)	1540 (624, 3386)	< 0.001

COV(unk) = COVID-19-unknown. COV(+) = COVID-19-positive. COV(-) = COVID-19-negative. COV(+)AB(+) = COVID-19-positive with antimicrobial use. COV(+) AB(-) = COVID-19-positive without antimicrobial use.IQR, interquartile range. n, number. %, percentage

Table 4 Adverse events

	All (*n* = 2064)	COV(unk) (*n* = 310)	COV(+) (*n* = 701)		COV(-) (*n* = 1053)
			COV(+) AB(+) (*n* = 511)	COV(+) AB(-) (*n* = 390)	
Liver injury, n (%)	69 (3.3%)	4 (1.3%)	9 (1.8%)	5 (2.6%)	51 (4.8%)
Neutropenia grade, n (%)					
Mild	62 (3.0%)	24 (7.7%)	14 (2.7%)	1 (0.5%)	23 (2.2%)
Moderate	15 (0.7%)	1 (0.3%)	6 (1.2%)	1 (0.5%)	7 (0.7%)
Severe	2 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Acute kidney injury (AKI) grade, n (%)					
1	146 (7.1%)	27 (8.7%)	32 (6.3%)	10 (5.3%)	77 (7.3%)
2	80 (3.9%)	14 (4.5%)	20 (3.9%)	8 (4.2%)	38 (3.6%)
3	97 (4.7%)	12 (3.9%)	23 (4.5%)	9 (4.7%)	53 (5.0%)

COV(unk) = COVID-19-unknown. COV(+) = COVID-19-positive. COV(-) = COVID-19-negative. COV(+)AB(+) = COVID-19-positive with antimicrobial use. COV(+) AB(-) = COVID-19-positive without antimicrobial use

COVID-19-positive and received antimicrobials were more likely to remain in hospital for 11–20 days (184/511, 36.0%) than any other group (73/311, 23.5%; 42/190, 22.1%; 236/1 053, 22.4%; $P < 0.001$) and less likely to be discharged within 3–10 days (298/511, 58.3% vs. 225/311, 72.6%; 141/190, 74.2%; 752/1053, 71.4%; $P < 0.001$), confirming prolonged hospitalisation in this cohort. Adverse events were infrequent. Neutropenia occurred in < 1% of patients overall, with the highest numerical incidence in the COVID-19-unknown group. Liver injury was more common among COVID-19-negative patients. Grade 3 acute kidney injury exceeded grade 2 (97/2064, 4.7% vs. 80/2064, 3.9%). Exposure to > 20 concomitant drugs was associated with a higher risk of both liver injury and neutropenia. Although we attempted to compare the incidence of adverse events across groups, the small number of events limited our ability to draw firm conclusions. (Tables 3 and 4, Fig. 3A and B).

The overuse of antimicrobials

Among the 2064 inpatients, a total of 1176 (57.0%) were treated with antimicrobials during hospitalization. A total of 432 (36.7%) of these inpatients were not diagnosed with a bacterial infection or had unknown bacterial infection status, whereas only 121 (10.3%) had a clear pathogen diagnosis, and 967 (82.2%) were treated with antimicrobials on admission. A total of 355 (36.7%)

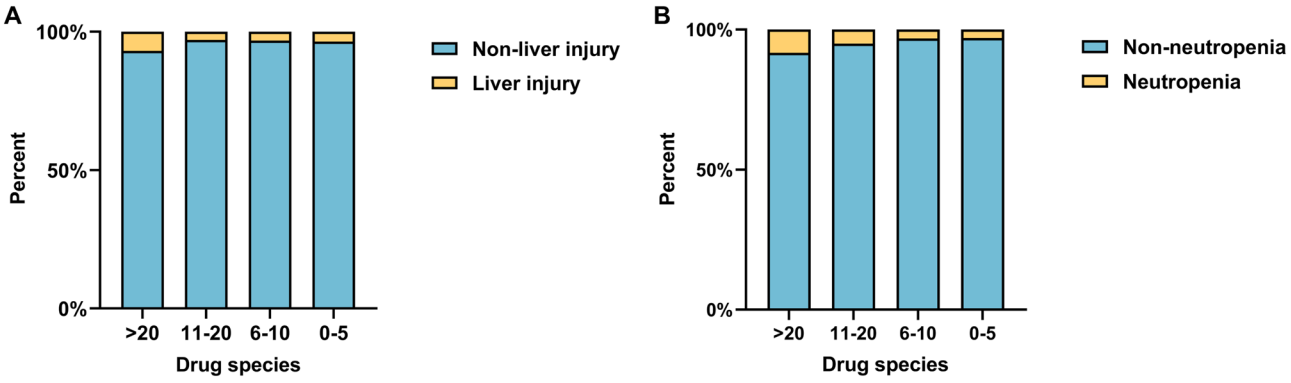

Fig. 3 (**A**) The number of drugs used in inpatients with liver injury. (**B**) The number of drugs used in inpatients with neutropenia

inpatients were treated with antimicrobials at the time of admission when they did not have a bacterial infection diagnosis, and 417 (43.1%) inpatients were treated with antimicrobials at the time of admission.

Discussion

This study focused on the use of antimicrobials in each group. The baseline results revealed that the COVID-19-positive inpatients who used antimicrobials were older than the inpatients in the other groups, and the proportion of inpatients with underlying diseases was greater in the group of COVID-19-positive inpatients. A previous study reported similar findings [19]. The immunity of older inpatients was lower than that of younger inpatients, and patients in the former group were more likely to have comorbidities such as COPD, diabetes and other underlying diseases, which increased their susceptibility to COVID-19 infection [20]. The severity of infection in older inpatients is often greater than in younger inpatients without underlying diseases, and the proportion of bacterial infection diagnoses is also greater.

In this study, 38.4% of inpatients were diagnosed with bacterial infection, of whom 54.5% tested positive for COVID-19. This rate is higher than the proportions reported in previous studies, such as 15%, 3.5%, 7.2%, and 8% [21–24]. Owing to a lack of knowledge and clinical experience regarding COVID-19, there was considerable panic about the disease upon its emergence, and the subjective diagnosis of COVID-19 by clinicians was related to overdiagnosis [25, 26]. Among the cases investigated in this study, only 6.0% had positive pathogen results, and 15.1% of the pathogens detected were MDR strains. This is lower than the rate of 42.9% reported in a review of global antimicrobial resistance and antimicrobial use in COVID-19 patients within health facilities of 64 studies, which included data from various continents and highlighted significant regional differences in MDR prevalence [27]. The majority of MDR pathogens were *E. coli* (33.3%), *A. baumannii*(14.3%), *S. aureus* (14.3%) and *K. pneumoniae* (9.5%). A systematic review and meta-analysis of 29 studies in Southeast Asia revealed that *A. baumannii* (7.7%), *P. aeruginosa* (3.3%), *K. pneumoniae* (3.2%), and *E. coli* (1.9%) were the predominant MDR strains [28]. At the time of that study, many medical staff were also infected and needed hospitalization or home treatment, which resulted in a severe lack of medical staff. In this case, empirical antimicrobial treatment was considered advantageous [29, 30]. In Nepal, Basnet et al. noted that clinicians often rely too heavily on empirical antimicrobial therapy due to limited medical resources, which leads to antimicrobial abuse and resistance [31]. The main reason for the low positive rate of pathogens was that the inpatients had already been treated with antimicrobials before or at the time of hospitalization, resulting in negative pathogen results. A Japanese study reported similar results [32]. Without the support of microbial evidence, PCT levels are a strong indicator of bacterial infection because bacterial infection can cause organs to secrete PCT [33]. However, PCT has limitations, as PCT levels may remain below clinical thresholds in certain infections, such as pulmonary infections. In our study, some primary hospitals did not perform PCT examinations because some doctors had insufficient knowledge of PCT. Only 20.1% of patients were tested for PCT. Because the deviation was too large when PCT was included in the statistics, PCT was not included in the laboratory parameters.

A total of 57.0% of the inpatients were treated with antimicrobials, and 36.7% were treated with antimicrobials when bacterial infection was not confirmed. Although our definition of diagnosis of bacterial infection was broad, there are 82.2% of patients were treated with antimicrobials on admission, which was greater than the rate of 56.6% reported in a multicentre study in Michigan [22]. Among these patients, 36.7% were treated with antimicrobials on admission when bacterial infection was not confirmed. This was a higher rate than the rate of 2% reported in a previous study, indicating that some inpatients were treated with antimicrobials without clinical indications [24]. However, only 71.0% of

COVID-19-positive inpatients who used antimicrobials were diagnosed with bacterial infection. The WHO noted that although only 8% of COVID-19-positive patients also had bacterial infections that could be treated with antimicrobials, and 75% of COVID-19-positive patients were administered antimicrobials on a "just in case" basis [9]. The overuse of antimicrobials is a key risk factor for the development of AMR, especially in areas with limited resources. The abuse of antimicrobials promotes the emergence of MDR bacteria, thereby making clinical treatment more complicated.

A scoping review of 514 studies worldwide revealed that the rate of antimicrobial use in COVID-19-positive patients in East Asia and the Pacific was 53.7%, which was lower than the rate reported in our study (72.9%) [34]. The scoping review also revealed that due to advances in knowledge of the pathophysiology, transmission, diagnosis, treatment, and prevention of COVID-19, clinicians may become more confident in providing appropriate care to patients with COVID-19. Many primary care hospitals were included in the current study that may not have been quickly influenced by global or national treatment guidelines, such as those published by the WHO and NHC, leading to higher rates of antimicrobial use [35, 36]. The AUD of all inpatients was 60.63 DDDs/100 bd, which was greater than the densities of 39.86 DDDs/100 bd reported in Shanxi Province and 39.12 DDDs/100 bd reported in China in 2023. The AUD values of the three groups were all greater than 40 DDDs/100 bd (the threshold in Chinese tertiary general hospitals), and the AUD values among COVID-19-positive patients reached 84.28 DDDs/100 bd, far exceeding the threshold. The DOT was 622/1000 pd, whereas it was 576/1000 pd in a prepandemic study in Brazil [37]. These findings suggest that the overuse of antimicrobials has undoubtedly increased the burden of AMR, promoted the emergence and spread of MDR strains, and increased the difficulty of treating bacterial superinfections.

Third-generation cephalosporins were the most frequently used antimicrobial agents, followed by quinolones and compound preparations of cephalosporins. However, in a previous study of 68,405 patients in Brazil, the most commonly used antimicrobial agents were penicillins with β-lactamase inhibitors, third-generation cephalosporins, and macrolides in combination with penicillins [37]. According to the classification management of antimicrobial agents in Shanxi Province in 2023, most antimicrobials in these three groups belong to the restricted or highly restricted class and are first-line antimicrobials for the empirical treatment of severe clinical infections [38]. Furthermore, these agents are all broad-spectrum antimicrobials. Basnet et al. reported that the abuse of quinolones and other broad-spectrum antimicrobials in patients with COVID-19 has led to the emergence of significantly drug-resistant strains, further complicating the treatment of bacterial superinfections [31]. The misuse of antimicrobials is a major risk factor for AMR, especially in regions such as Nepal, where antimicrobial stewardship and infection control are inadequate. Therefore, there is a high risk of bacterial resistance, and the use of these antimicrobials should be appropriately reduced based on the condition of inpatients in the clinic. Although the total number of COVID-19-positive inpatients was lower than that of COVID-19-negative inpatients, the number of medical order entries for third-generation cephalosporins, quinolones, and compound preparations of cephalosporins and carbapenems in COVID-19-positive inpatients was greater than other groups, and the DOT of these antimicrobials was also greater. A systematic review and meta-analysis of 29 studies in Southeast Asia revealed that levofloxacin, azithromycin and ceftriaxone were the most commonly used antimicrobials, similar to the findings of our study (i.e., levofloxacin, ceftriaxone and cefoperazone/sulbactam) [34]. However, the misuse and overuse of these antimicrobial agents are the greatest risk factors for the spread of MDR strains. The overuse of antimicrobial agents, especially in the absence of confirmed bacterial infections, is the main cause of MDR.

In terms of hospital costs, the total costs of antimicrobials for COVID-19-positive inpatients were significantly greater than for other groups, whereas the total costs of hospitalization were slightly greater among COVID-19-positive inpatients than other groups. This difference may be due to the greater likelihood of bacterial infections in COVID-19-positive inpatients. In such cases, clinicians' uncertainty about infection can lead to the overuse of antimicrobials. Compared with COVID-19-negative inpatients, COVID-19-positive inpatients with antimicrobial use had higher hospitalization costs and drug costs, whereas COVID-19-positive inpatients without antimicrobial use had significantly lower costs. Notably, the use of antimicrobials in COVID-19-positive inpatients was positively correlated with the number of hospitalization days and did not improve clinical outcomes. In China, treatment costs for COVID-19 inpatients are covered by the China Health Insurance Fund. COVID-19 inpatients do not pay out-of-pocket costs, thereby ensuring the timely treatment of infected patients [39]. However, this approach also places an enormous financial burden on the government and China's health insurance fund [40]. In terms of clinical outcomes, COVID-19-positive inpatients with antimicrobial use were significantly more likely to have a hospital stay of 11–20 days and higher hospitalization costs than patients in other groups.

The incidence of adverse events was low in all inpatients. The incidence rates of liver injury and neutropenia

were higher in inpatients who received more than 20 drugs. The WHO reported that antimicrobial use "did not improve clinical outcomes for inpatients with COVID-19; instead, it might create harm for people without bacterial infection, compared to those not receiving antimicrobials [41]. Therefore, more attention should be given to rational drug use to reduce the administration of unnecessary drugs and to prevent other drug-induced diseases among inpatients. While this study highlights the potential harm associated with the overuse of antimicrobials, it is crucial to acknowledge that adverse events may also reflect the severity of the underlying disease rather than being solely the result of antimicrobial use. The severe infections and systemic inflammation inherent to critical COVID-19 patients may independently contribute to organ damage and haematologic abnormalities [42]. Furthermore, the concurrent use of other medications, including antivirals, corticosteroids, and immunomodulators, may act as additional confounding factors. To address these complexities, future studies should employ more rigorous methodologies, such as stratifying data on the basis of disease severity and adjusting for polypharmacy and other potential confounders.

This study provides important insights into antimicrobial use during the COVID-19 pandemic and the impact of this prescription pattern on the emergence of MDR strains. This study can provide guidance for health departments in the development of management measures, facilitate the optimization of AMS policies in Pharmaceutical Quality Control Center across the province, and provide empirical support for the rational use of antimicrobials. On the basis of the results of this study, the research group conducted educational programmes in medical institutions at all levels across the province and emphasized the importance of PCT indicators. In the future, it is necessary to explore microbiological examinations and laboratory indicators to obtain strong evidence for the diagnosis of bacterial infection.

Several limitations must be acknowledged. Diagnostic codes were used to determine the presence of bacterial infections, which may have led to an overestimation of the incidence of bacterial infection. These results should be interpreted with caution due to potential bias and residual confounding. Second, the testing rate of pathogens was low, and strong evidence for the diagnosis of bacterial infections was lacking. Another limitation is that this was a multicentre study that involved secondary and tertiary hospitals across the entire province. Because the levels of the hospitals differed, the medical records of inpatients may not have been collected comprehensively, resulting in a lack of data (e.g., the COVID-19-unknown group). Furthermore, the short observation period in this study made it difficult to fully elucidate the impact of antimicrobial overuse on the emergence of MDR strains, which may become more pronounced in the postpandemic era.

Conclusion

During the COVID-19 pandemic, pathogen testing rates were low, yet some inpatients were treated with antimicrobials without a diagnosis of bacterial infection. The use of high-class antimicrobials did not reduce the duration or costs of hospitalization but contributed to an increased risk of MDR. These findings highlight the burden of the pandemic on the healthcare system and provide guidance for future medical responses.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

SW and YT wrote the main manuscript text, YM and WC conducted the statistical analysis, QX collected data, SW and RZ drew the drawing figures, and DY and JD designed the research plan. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

This study was reviewed and approved by the ethics committees of 25 hospitals, including the Second Hospital of Shanxi Medical University, with central ethics approval reference number (2023) YX (334). Since the study did not record personal identifiers (such as names, ID numbers, or hospitalization numbers) and used only coded data to protect confidentiality, the ethics committees of 23 hospitals waived the requirement for informed consent. Two hospitals required participants to be notified and informed about the

study's objectives via telephone. These participants were informed of their right to refuse participation, and signed informed consent was not needed.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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