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High frequency of antibiotic administration for COVID-19 patients in Syria and its associations with mortality and complications

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Abstract

Background Syria's healthcare system was severely challenged by the COVID-19 pandemic due to resource scarcity and a shortage of healthcare personnel. In this context, antibiotics were frequently prescribed empirically because of limited diagnostic capacity, concerns about secondary bacterial infections, and delayed hospitalization, despite the limited evidence of bacterial co-infection among patients with COVID-19.

Method This study investigates the use of antibiotics among hospitalized COVID-19 patients in Syria, focusing on its association with mortality, ICU admissions, and complications. We conducted a multicenter retrospective cohort study in the four major Syrian cities, including 3199 patients, 93.4% of whom received antibiotics.

Results The most frequently prescribed antibiotics were cephalosporins, macrolides, and quinolones. We found a significant association between the administration of multiple classes (> 3) of antibiotics and increased mortality and ICU admissions, even after adjusting for the LR-COMPAK mortality risk score and treating hospital. Specifically, the use of carbapenem, piperacillin/tazobactam, glycopeptides, and cephalosporins were independently linked to increased mortality, while piperacillin/tazobactam, carbapenem, glycopeptides, amoxicillin/clavulanate, cephalosporins, and quinolones were associated with ICU admissions. Administration of multiple classes (> 3) of antibiotics also correlated with complications including secondary infections, septic shock, and acute kidney injury.

Conclusions This study highlights excessive antibiotic use among hospitalized COVID-19 patients in Syria and its association with increased mortality, ICU admission, and serious complications. These findings underscore the urgent need for strengthened antibiotic stewardship and improved prescribing practices to reduce adverse outcomes and mitigate the growing threat of antimicrobial resistance in conflict-affected and resource-limited healthcare settings.

Clinical trial number Not applicable

Keywords COVID-19, Antibiotics, Mortality, Complications, Syria

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Introduction

The Syrian revolution, spanning over 14 years, was one of the largest humanitarian crises of contemporary times. The resulting conflicts resulted in extensive damage to infrastructure including healthcare facilities and supply warehouses: at least 50% of Syria's health facilities have been destroyed [1]. Compounding this devastation is the mass exodus of local healthcare professionals, with an estimated 70% fleeing the country as of 2021 [2]. Furthermore, the corrupted regime and international sanctions imposed on Syria have increased systemic strain by inflating medication costs and depleting medical equipment supplies [3]. The cumulative effect of more than a decade of conflict is a healthcare system teetering on the brink of collapse, eroding the very foundations of healthcare accessibility for Syrians.

Consequently, the political instability was pivotal in the rapid escalation of the COVID-19 pandemic, resulting in a swift depletion of limited resources and desperate measures to combat the poorly-understood virus [4, 5]. The pandemic's rapid spread, inherent vulnerabilities of the population due to environmental factors such as overcrowding and poor infrastructure, and years of inadequate healthcare access limited the effectiveness of healthcare when treatment was available [6]. Limited hospitalization capacity also led healthcare providers to prioritize the most severe cases for admission. Intensive care unit (ICU) access was limited as well, leading to delayed ICU admission and poorer outcomes of intensive care. Despite efforts to deliver the highest quality of care possible, 46% of patients hospitalized with COVID-19 in Syria died during hospitalization [4]. One of the driving factors of these poor outcomes is suggested to be antibiotic overuse [7, 8].

Antibiotic use in COVID-19 patients within such contexts remains a subject of debate, although guidelines advocate for their use only if there is a clinical suspicion of bacterial infection [9, 10]. Varying degrees of antibiotic use in the setting of COVID-19 has been observed in hospitals within the Middle East, Asia, and Europe [7–9, 11–14]. Antibiotics are prescribed to prevent secondary bacterial infections that can worsen morbidity and mortality in COVID-19 patients, who are at higher risk of worsened outcomes [15]. Nonetheless, proper implementation of healthcare measures such as more conservative antibiotic use, physician hygiene training, and improved environmental hygiene during the COVID-19 pandemic has shown promising results in reducing nosocomial infections and the emergence of drug-resistant bacteria [16]. Moreover, inappropriate antibiotic use in COVID-19 patients has been linked to complications such as acute kidney injury (AKI) [17], ICU admission [18], increased mortality [19–21], and other drug-related complications [19, 22]. Despite the wealth of literature on antibiotic stewardship, information regarding these aspects is limited in countries with weakened healthcare systems like Syria. These knowledge gaps restrict the development of nationwide algorithms to optimize antibiotic administration for improved patient outcomes. Therefore, our study aimed to retrospectively investigate the utilization of antibiotics in hospitals across four major cities in Syria during the COVID-19 pandemic, with a specific focus on their association with mortality, ICU admission, and subsequent complications.

Methods

Study design and included hospitals

This multicenter retrospective cohort study was conducted utilizing data collected from the four largest Syrian cities: Aleppo, Damascus, Homs, and Latakia. The study involved several healthcare facilities including The National Damascus University Hospital, Al-Mouwasat Damascus University Hospital, Damascus Hospital, Tishreen and Qatana Military Hospitals in Damascus, the University Hospital of Aleppo, the University Hospital of Latakia; as well as Ibn Al-Waleed Hospital and the military Hospitals in Homs. All of these hospitals were officially designated as COVID-19 treatment centers by the Syrian Ministry of Health and contained dedicated COVID-19 isolation wards throughout the study period. All of them are community health centers that provide pro-bono healthcare services to adult civilian patients, except the National University Hospital of Damascus, which required non-private patients to cover 10% of their final hospital bill. The military hospitals of Tishreen, Qatana and Homs cared exclusively for military personnel and their families, providing healthcare services at no cost. Despite being in the major urban centers mentioned, these hospitals also treated COVID-19 patients transferred from various regions across Syria.

This study received ethical approval from both the Higher Commission for Scientific Research (HSCR) at the Syrian Ministry of Higher education, the institutional review board at Damascus University, and the boards of all participating centers. The ethical clearance from HSCR, bearing the identification number 1/491, was granted on January 19, 2021, and waived the need for getting individual informed consent from the patients included.

Inclusion criteria, diagnostic studies, and treatment strategies

The patient sample used, admission criteria, diagnostic procedures, and hospital management guidelines were previously documented [23]. In brief, the study involved a retrospective review of all patients' records from both the COVID-19 isolation wards and ICUs at the aforementioned hospitals. The review period spanned from

June 1, 2020, to December 31, 2020, encompassing the first two waves of the COVID-19 pandemic in Syria [23].

Patients aged 13 and older presenting with acute respiratory symptoms suggestive of COVID-19 underwent clinical examination upon admission. This age limit for the study was determined based on the admission regulations in Syria, where patients 13 years old and older are managed at the centers for adult care. The diagnosis of COVID-19 infection was predominantly established within 48 h of admission, primarily through polymerase chain reaction (PCR) tests or rapid antigen tests (RATs). In certain cases, infection confirmation relied on chest imaging (CT or CXR) or high clinical suspicion of COVID-19 when testing kits were unavailable. All patients managed as COVID-19 cases were included in our database irrespective of the method of diagnosis, And they mostly had severe or critical disease severity according to the WHO classification [10].

Data analysis

The data collection was performed by senior internal medicine residents and internal medicine specialists. All data collaborators also had more than 6 months of experience in critical care. The collected data included demographic characteristics, comorbidities, vital signs at presentation, diagnostic modalities, ventilation support, ICU admission, and mortality during hospitalization. Moreover, we gathered data pertaining to all administered or prescribed antibiotics during hospitalization, regardless of their route of administration. Finally, we extracted information about the major complications developed during hospitalization which included: respiratory failure, acute respiratory distress syndrome (ARDS), electrolyte imbalances (hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypochloremia, hyperchloremia), diabetic ketoacidosis (DKA), acute kidney injury (AKI), chronic kidney disease (CKD), myocardial infarction (MI), thrombotic events (deep venous thrombosis, DVT; pulmonary embolism, PE; cerebrovascular accident, CVA), bleeding (alveolar and gastric), secondary infections (renal, neural, intestinal, septic, cutaneous, and other), and septic shock (i.e., sepsis with persistent hypotension requiring vasopressors). Staff shortages prevented frequent monitoring of vital signs for all patients. Additionally, reporting of the repeated measurements was not comparable between patients, centers and months. Therefore, we used laboratory measurements at admission, as they were available for most patients. Patients with absent values for specific variables were not included in the statistical analysis relevant to that specific variable (i.e., complete case analysis).

The data analysis and representation were done using the Statistical Package for the Social Sciences version 29 (SPSS Inc., Chicago, IL, United States) and the R Programming Language via RStudio Version 2022.12.0 Build 353 for Windows. Categorical variables were reported as percentages. Medians and ranges were used to report continuous variables because they did not follow a normal distribution. Odds ratios (OR) and 95% confidence intervals (CI) were used as a measure of association between antibiotics and categorical variables. Binary logistic regression analyses with Bonferroni correction based on the number of variables analyzed [20] were employed to report associations between individual antibiotic classes and complications. A one-way ANOVA test was used to analyze associations between vital signs, baseline blood tests and the number of antibiotics prescribed. A Chi-squared test was used to analyze associations between comorbidities and the number of antibiotics prescribed. A univariate binary logistic regression analysis was employed to report associations between complications and the number of antibiotics prescribed, in both the ICU and non-ICU settings. A multivariate binary logistic regression was employed to analyze the association between the class of antibiotic used and risk of mortality or ICU admission. A complete-case approach was used when performing the statistical tests, as outlined in another publication utilizing a similar dataset [23]. To mitigate the effect of disease severity as a confounder of the relationship between antibiotics and outcomes (i.e., mortality, ICU admission, and complications) we adjusted all tests based on the LR-COMPAK score, which consists of oxygen saturation, consciousness, age, history of malignancy, pulse rate, and chronic kidney disease [23]. This score correlated with the probability of survival and had superior performance when compared to all other disease severity metrics at least in our dataset [23]. We also adjusted all tests to the hospital of admission to exclude any associations related to the responding healthcare team or the resources available. The assumptions of all statistical tests used were assessed and none of them were violated. An alpha value of 0.05 was primarily used to determine the threshold of statistical significance, with the usage of Bonferroni correction for multiple comparisons when required based on the number of variables analyzed. An online tool from Bioinformatics and Evolutionary Genomics (https://bioinformatics.psb.ugent.be/cgi-bin/liste/Venn) was used to create the Venn diagram for the administered antibiotics.

This manuscript was prepared according to the checklist of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) for observational studies [24].

Results

Demographic characteristics

A total of 3199 patients were included in our analysis; their demographic characteristics and diagnostic modalities can be found in Hanafi et al. 2024 [23]. Most of them (93.4%, *n* = 2987) received at least one class of antibiotics during their hospitalization; 999 (33.4%) received more than three classes of antibiotics. Receiving more than three classes of antibiotics was associated with higher age, positive smoking history, lower blood oxygen saturation, and a higher heart rate (*P* <.001 for all). Elevated white blood cell counts, lower lymphocyte counts, and higher LDH, CRP, and PCT levels were associated with receiving more than three antibiotic classes (Table 1). A similar analysis between patients who received no antibiotics and patients who received any single or combination of antibiotics showed that patients receiving no antibiotics tended to be younger (53.2 years old vs. 59.6 years old; *P* <.001), have lower WBC, LDH, CRP, and higher lymphocyte counts (*P* <.001 for all; supplement information). No other significant differences were found between patients receiving antibiotics and those not receiving antibiotics. Within the entire sample, only 118 patients (3.7%) had documented pulmonary infections in addition to COVID-19, while 1420 (44.4%) exhibited clinical suspicion of such infections.

The most prescribed antibiotics were cephalosporins (*n* = 2075, 64.8%), macrolides (*n* = 1927, 60.2%), and quinolones (*n* = 1122, 35.1%). The most common antibiotic combinations included macrolides and cephalosporins (*n* = 702; 21.9%), quinolones and cephalosporins (328 patients; 10.3%), and macrolides, quinolones, and cephalosporins (*n* = 238; 7.4%; Fig. 1).

Antibiotic use and mortality

During hospitalization, 1041 patients (32.5%) died, and 807 patients (25.2%) were admitted to the ICU. There was a positive association between the number of antibiotics prescribed and LR-COMPAK mortality risk score among surviving patients ($R^2 = 0.25$; $P < .001$) and those who did not require ICU admission ($R^2 = 0.27$; $P < .001$). However, this correlation was weaker among patients who died ($R^2 = 0.05$; $P = .001$) or were admitted to the ICU ($R^2 = 0.05$; $P = .087$), suggesting that antibiotic use may not be predictive of outcomes in more severe cases (Fig. 2). Upon adjusting for the LR-COMPAK mortality risk score and the treating hospital, both mortality and ICU admission were associated with prescription of multiple (> 3) classes of antibiotics ($P < .001$; OR = 1.36 [1.23–1.51], and $P < .001$; OR = 1.70 [1.53–1.89], respectively, Table 2).

Mortality was found to be independently associated with the administration of carbapenems ($P < .001$; OR = 1.86 [1.45–2.39]), piperacillin/tazobactam ($P = .019$; OR = 1.53 [1.07–2.20]), glycopeptides ($P < .001$; OR = 1.32 [1.13–1.56]), and cephalosporins ($P = .016$; OR = 1.19 [1.03–1.37]). ICU admission was independently

Table 1 Demographic characteristics and baseline findings for patients who received no antibiotics, 1–3 antibiotics, and 4 + antibiotics

	No antibiotics (*n* = 212)	1–3 antibiotics (*n* = 1988)	≥4 antibiotics (*n* = 999)	*P* value
Demographic characteristics				
Gender	F: 74 (34.9%) M: 138 (65.1%)	F: 210 (29.0%) M: 513 (71.0%)	F: 355 (35.5%) M: 644 (64.5%)	0.006
Age (years)	53.2 (14–97)	56.00 (14–95)	64.00 (14–96)	< 0.001*
Smoking	43 (20.3%)	354 (17.8%)	233 (23.3%)	0.001*
Vital signs[a]				
Mean arterial pressure (mm Hg; *n* = 3067)	86.67 (50.00-140.00)	90.00 (53.33-146.67)	90.00 (31.67-168.33)	0.120
O_2 saturation (%; *n* = 2817)	90 (25–99)	91 (26–99)	84 (30–99)	< 0.001*
Heart rate (bpm; *n* = 2635)	92 (41–153)	90 (53–180)	95 (40–170)	< 0.001*
Respiratory rate (/min; *n* = 1562)	27 (12–60)	26 (13–60)	26 (12–62)	0.234
Temperature (°C; *n* = 2579)	38.0 (35.0–41.0)	37.8 (34.6–42.0)	38.0 (34.0–41.0)	0.046
Comorbidities[b]				
Diabetes mellitus	60 (28.30%)	193 (9.71%)	304 (30.43%)	0.636
Hypertension	73 (34.43%)	244 (12.27%)	433 (43.34%)	0.016
Heart diseases	30 (14.15%)	114 (5.73%)	161 (16.12%)	0.235
Lung pathology	4 (1.89%)	18 (0.91%)	47 (4.70%)	0.021
CKD	16 (7.55%)	25 (1.26%)	18 (1.90%)	0.400
CVA	6 (2.83%)	11 (0.55%)	48 (4.80%)	0.131
Cancers	8 (3.77%)	17 (0.86%)	61 (6.11%)	0.006
Baseline blood tests[a]				
WBC (*n* = 3006)	6200 (300-25.9k)	7000 (1100-29k)	10k (100-30k)	< 0.001*
Lymphocytes (*n* = 2889)	16.45	13.65 (0.32-75.00)	9.70 (0.10–65.00)	< 0.001*
LDH (*n* = 1744)	377.00 (128.80–1356.00)	546.00 (136–3134)	673.30 (10.20–8803.00)	< 0.001*
CRP (*n* = 2430)	54 (0.10–281.00)	35.30 (0.10–319.00)	68.50 (0.04–586.00)	< 0.001*
PCT (*n* = 688)	0.10 (0.01-81.00)	0.10 (0.00-89.25)	0.16 (0.00–52.00)	< 0.001*

[a]One-way ANOVA; [b]Chi-squared test; *Statistically significant after Bonferroni correction (0.05/20=0.0025).

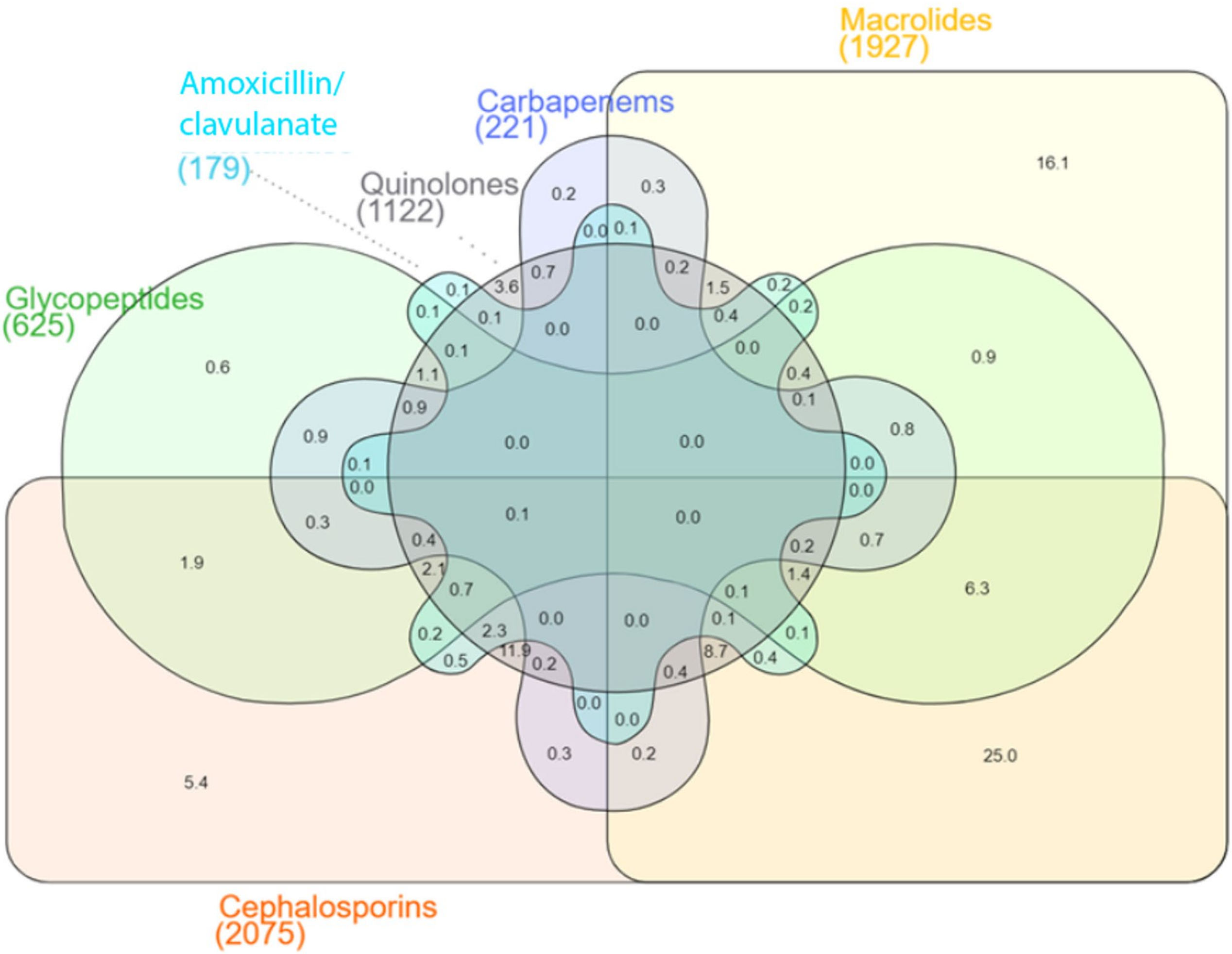

Fig. 1 A Venn diagram highlighting the overlap between the classes of antibiotics. The numbers in parentheses represent the number of patients who received each class of antibiotics, and the numbers inside the diagram represent percentages of patients who received each combinations of antibiotics. Only the antibiotics received by more than 5% of the sample were included in this diagram. In addition to the presented antibiotic classes, 152 patients (4.8%) received metronidazole, 98 patients (3.1%) received piperacillin/tazobactam, and 66 patients (2.1%) received oxazolidinones

associated with piperacillin/tazobactam ($P<.001$; OR = 2.59 [1.76–3.79]), carbapenems ($P<.001$; OR = 1.91 [1.49–2.47]), glycopeptides ($P<.001$; OR = 1.69 [1.41–2.03]), amoxicillin/clavulanate ($P=.005$; OR = 1.38 [1.10–1.72], cephalosporins ($P<.001$; OR = 1.30 [1.13–1.51]), and quinolones ($P=.004$; OR = 1.24 [1.07–1.44]; Table 3).

Antibiotic use and medical complications

A total of 1,155 patients (36.1%) experienced serious complications during hospitalization, with the most prevalent being respiratory failure ($n=1057$; 33.0%), electrolyte abnormalities ($n=600$; 18.8%), and AKI ($n=555$; 17.3%). Since the exact timing of antibiotic administration is unknown, it is not possible to determine whether medical complications occurred before or after antibiotics were given. However, the associations between the administered antibiotics and the complications that predominantly arose during the early or late admission period (rather than at presentation) warranted higher value. Overall, more than half of the secondary infections and non-infectious complications were already detectable at presentation. Septic shock predominantly developed after the third day of admission (Table 4). Receiving a greater number of antibiotics was significantly associated with secondary infections ($P<.001$; OR = 2.05 [1.70–2.47]), septic shock ($P<.001$; OR = 1.59 [1.23–2.05], electrolyte abnormalities ($P<.001$; OR = 1.33 [1.19–1.49]), and AKI ($P<.001$; OR = 1.25 [1.11–1.40]), even when adjusting for disease severity, treating hospital and ICU admission (Table 2).

A multivariate logistic regression was employed to discern associations between complications and antibiotic classes. Carbapenem use was independently associated with septic shock ($P<.001$; OR = 3.15 [2.08–4.78]), ARDS ($P<.001$; OR = 2.79 [1.92–4.08]), and bleeding ($P=.001$; OR = 2.18 [1.35–3.51]). Metronidazole use was associated

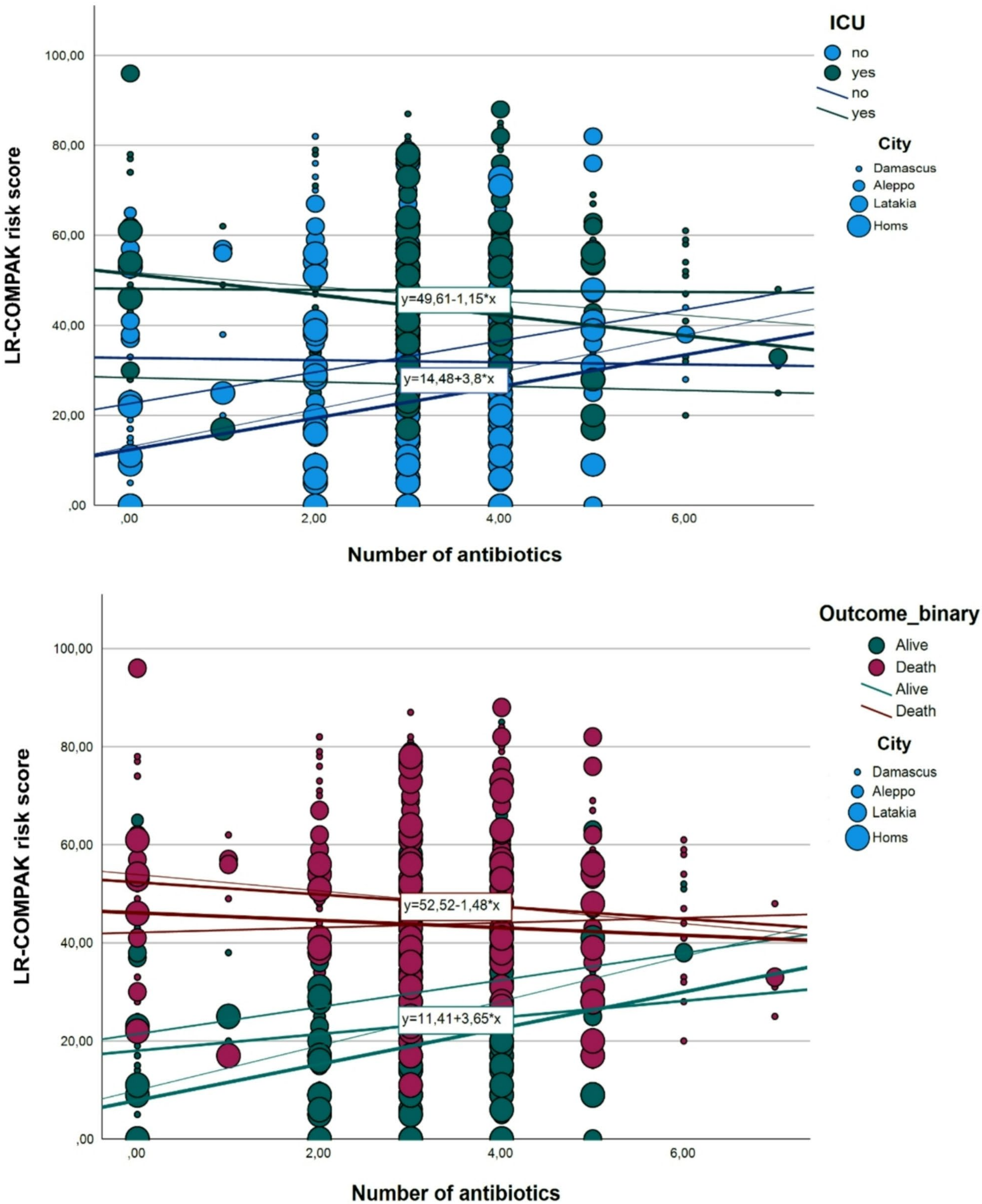

Fig. 2 The correlation between the number of antibiotics received and the LR-COMPAK mortality risk score. The patients were clustered based on city and mortality (upper panel) or city and admission to the ICU (lower panel)

Table 2 Association between the number of antibiotics received and mortality, ICU admission, and complications

Outcome	*N* (%)	ORs [CIs] with adjustment for LR-COMPAK and the treating hospital	*P*-value	ORs [CIs] with adjustment for LR-COMPAK, the treating hospital, and ICU admission	*P*-value
Mortality	1041 (32.5%)	1.36 [0.23–1.51]	< 0.001	1.07 [0.96–1.21]	0.237
ICU admission	807 (25.2%)	1.70 [1.53–1.89]	< 0.001	NA	NA
Respiratory failure	1057 (33%)	1.18 [1.06–1.32]	0.003	1.01 [0.90–1.13]	0.908
Electrolyte abnormalities	600 (18.8%)	1.37 [1.24–1.53]	< 0.001	1.33 [1.19–1.49]	< 0.001
Acute kidney injury	555 (17.3%)	1.29 [1.15–1.44]	< 0.001	1.25 [1.11–1.40]	< 0.001
Secondary infection	228 (7.1%)	2.21 [1.85–2.65]	< 0.001	2.05 [1.70–2.47]	< 0.001
Acute respiratory distress syndrome	99 (3.1%)	1.69 [1.35–2.12]	< 0.001	1.37 [1.09–1.71]	0.007
Diabetic ketoacidosis	97 (3%)	1.12 [0.91–1.38]	0.274	0.94 [0.77–1.15]	0.532
Thrombotic events	88 (2.8%)	1.10 [0.87–1.39]	0.413	1.09 [0.86–1.39]	0.476
Septic shock	80 (2.5%)	2.02 [1.57–2.60]	< 0.001	1.56 [1.23–2.05]	< 0.001
Bleeding	65 (2%)	1.26 [0.98–1.63]	0.076	1.14 [0.89–1.48]	0.306
Myocardial infarction	41 (1.3%)	1.35 [0.95–1.91]	0.092	1.29 [0.92–1.83]	0.145

The ORs and CIs presented are the result of univariate binary logistic regression analysis. The results of the left column were adjusted for LR-COMPAK mortality score and treating hospital. The right column was additionally adjusted for ICU admission.

Table 3 Association between the antibiotic class and mortality and ICU admission

Antibiotic classes	Mortality*			ICU admission°		
	N (%)	OR [CI]	*p*-value	*N* (%)	OR [CI]	*p*-value
Glycopeptides	314 (50.2%)	1.32 [1.13–1.56]	< 0.001	263 (42.0%)	1.69 [1.41–2.03]	< 0.001
Piperacillin/tazobactam	58 (59.2%)	1.53 [1.07–2.20]	0.019	67 (68.4%)	2.59 [1.76–3.79]	< 0.001
Carbapenems	67 (62.0%)	1.86 [1.45–2.39]	< 0.001	131 (59.3%)	1.92 [1.49–2.47]	< 0.001
Macrolides	515 (26.7%)	1.03 [0.89–1.19]	0.699	369 (19.1%)	0.92 [0.78–1.09]	0.333
Quinolones	463 (41.3%)	1.01 [0.89–1.16]	0.843	358 (31.9%)	1.24 [1.07–1.44]	0.004
Cephalosporins	722 (34.8%)	1.19 [1.03–1.37]	0.016	556 (26.8%)	1.30 [1.12–1.51]	< 0.001
Amoxicillin/clavulanate	75 (41.9%)	1.09 [0.88–1.36]	0.424	85 (47.5%)	1.38 [1.10–1.72]	0.005
Metronidazole	67 (44.1%)	1.40 [0.98–2.01]	0.063	37 (24.3%)	0.84 [0.59–1.22]	0.362
Oxazolidinones	20 (30.3%)	0.77 [0.36–1.66]	0.508	10 (15.2%)	1.19 [0.64–2.22]	0.590

The results presented are the outcome of a multivariate binary logistic regression (n=2987). The analysis was adjusted for hospital and LR-COMPAK mortality risk score. *The model had p-value 001, Nagelkerke $R^2 = 0.478$. °The model had p-value 001, Nagelkerke $R^2 = 0.469$.

with thrombotic complications ($P < .001$; OR = 2.40 [1.54–3.73]) and secondary infections ($P < .001$; OR = 2.05 [1.37–3.06]). Relatively weaker independent associations were observed between secondary infections and the antibiotic classes of carbapenems, quinolones, and glycopeptides. Finally, amoxicillin/clavulanate administration was independently associated with a reduced likelihood of respiratory failure (Fig. 3). It is important to emphasize that the small sample sizes of patients experiencing these complications and the methodology used restrict our ability from drawing causal conclusions between the administered antibiotics and the listed complications.

Discussion

This study successfully demonstrated the excessive use of antibiotics (93.4%) among hospitalized COVID-19 patients throughout Syria and elucidated its correlation with various outcomes. Receiving multiple antibiotics was notably associated with adverse outcomes including mortality, ICU admission, and complications such as ARDS, AKI, and electrolyte abnormalities. These outcomes were not impacted by the treating hospital or disease severity at presentation. Moreover, specific antibiotic classes such as carbapenems and glycopeptides correlated with poorer survival. Other antibiotic classes, including carbapenems and metronidazole, exhibited independent associations with specific complications, including ARDS and thrombotic events. These findings underscore the importance of judicious antibiotic use in the management of COVID-19 patients to mitigate potential complications and prevent the spread of multidrug resistant organisms (MDRs).

The alarmingly high rate of antibiotic utilization (93.4%) and the widespread administration of multiple antibiotics (99.5%) within our cohort echo previous reports highlighting antibiotic misuse in Syria [25]. This rate surpasses that observed in COVID-19 patients across the Arab Region as well, estimated to fall between 72 and 82% [7, 11, 12]. One plausible explanation is that the severe shortage of PCR kits [26] may have hindered healthcare providers from promptly confirming COVID-19 diagnoses [27]. This scenario reflects a broader global

Table 4 Occurrence and timing of medical complications during hospitalization

	Occurrence	Timing		
	***N* (%)**	**At presentation (0 days)**	**Early admission (1–3 days)**	**Late admission (> 3 days)**
Non-infectious complications				
Major outcomes				
Mortality	1041 (32.5%)	105 (10.1%)	392 (37.7%)	544 (52.3%)
ICU admission	807 (25.2%)	486 (15.2%)	190 (23.5%)	131 (16.2%)
Respiratory failure	1057 (33.0%)	548 (51.8%)	161 (15.2%)	122 (11.5%)
Electrolyte abnormalities	600 (18.8%)			
Hyponatremia	269 (8.4%)	165 (61.3%)	41 (15.2%)	38 (14.1%)
Hypernatremia	127 (4.0%)	24 (18.9%)	44 (34.6%)	45 (35.4%)
Hypokalemia	214 (6.7%)	85 (39.7%)	62 (29.0%)	47 (22.0%)
Hyperkalemia	154 (4.8%)	49 (31.8%)	38 (24.7%)	50 (32.5%)
Hypocalcemia	42 (1.3%)	8 (19.0%)	18 (42.9%)	6 (14.3%)
Hypochloremia	10 (0.3%)			
Hyperchloremia	1 (< 0.01%)			
Acute kidney injury	555 (17.3%)	352 (63.4%)	83 (15.0%)	65 (11.7%)
Acute respiratory distress syndrome	99 (3.1%)	9 (9.1%)	17 (17.2%)	34 (34.3%)
Diabetic ketoacidosis	97 (3.0%)	46 (47.4%)	18 (18.6%)	17 (34.3%)
Thrombotic events	88 (2.8%)			
DVT	26 (0.8%)	4 (15.4%)	5 (19.2%)	6 (23.1%)
PE	20 (0.6%)	4 (20.0%)	4 (20.0%)	7 (35.0%)
Cerebrovascular accident	45 (1.4%)	17 (37.8%)	9 (20.0%)	5 (11.1%)
Bleeding	65 (2.0%)			
Gastric hemorrhage	54 (1.7%)	18 (33.3%)	12 (22.2%)	15 (27.8%)
CKD	20 (0.6%)			
Alveolar hemorrhage	13 (0.4%)	4 (30.8%)	1 (7.7%)	3 (23.1%)
Infectious complications				
Secondary infections	228 (7.1%)	75 (32.9%)	35 (15.4%)	35 (15.4%)
Septic shock	80 (2.5%)	9 (11.3%)	19 (23.8%)	35 (43.8%)
Secondary renal infection	72 (2.3%)			
Secondary intestinal infection	47 (1.5%)			
Secondary septic infection	30 (0.9%)			
Secondary neural infection	12 (0.4%)			
Secondary cutaneous infection	9 (0.3%)			
Other	152 (4.8%)			

trend where antibiotics are prescribed without proper consideration of the clinical presentation of COVID-19. For instance, a study conducted among pharmacists in Egypt revealed that 67% reported an increased likelihood of antibiotic prescription when patients presented with COVID-like symptoms [12]. The enforcement of home quarantine likely exacerbated this situation by preventing patients from going to the hospital for care, and increasing the chances of self-treatment at home [28]. Furthermore, the lack of access to vaccines may contribute to the increased use of antibiotics, as unvaccinated patients may have been seen as being higher risk for severe COVID-19 infection presentation [29]. Another study found that none of the 347 COVID-19 patients that received antibiotics in four Ethiopian treatment centers had received a confirmatory bacterial culture or had inflammatory markers measured during their hospital stay [30]. Similarly, 3.7% of our sample had documented pulmonary infections and only 44.4% had clinical suspicion for an infection. However, we cannot completely rule out the necessity of antibiotic use in a portion of our cohort as those receiving antibiotics had higher inflammatory markers at admission. Antibiotics may have been used as prophylaxis due to the high rate of iatrogenic infections amongst hospitalized patients in Syria. Resistant bacterial strains have been isolated from patients injured in the Syrian conflict, with colonization believed to have occurred during medical evacuation or within dilapidated medical infrastructure [6]. Lastly, the incidence of ventilator-associated pneumonia (VAP) in the ICU significantly increased during the COVID-19 pandemic and was associated with an increased risk of death, especially in the presence of resistant bacteria [31–33]. This has been proposed as a contributing factor to the extremely high mortality rate among intubated patients in Damascus (~ 98%) [4], potentially exacerbated by the shortage

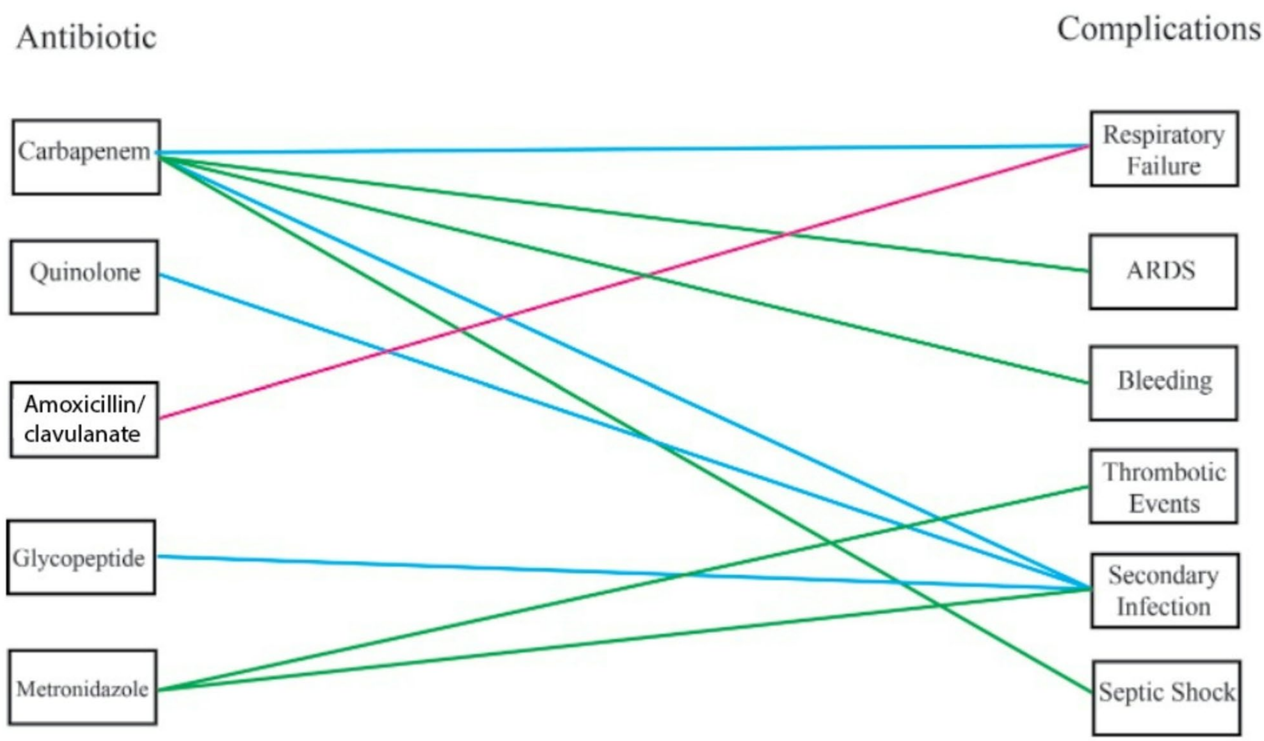

Fig. 3 Bipartite diagram showing the association between antibiotic classes and major medical complications developed during hospitalization. This figure is built on the results of a multivariate logistic regression analysis where all classes of antibiotics were included as independent variables while each complication served as a dependent variable in each run of the test. All regressions were adjusted for LR-COMPAK mortality score and the treating hospital. Only associations that reached a significance level of 0.001 are depicted. The pink, blue, and green lines represent associations with the ORs of 0–1, 1–2, and > 2, respectively. ARDS: Acute respiratory distress syndrome

of healthcare personnel [26]. Therefore, antibiotics could have been prescribed extensively in our patients as a preventive measure against VAP within an already vulnerable population.

The use of multiple antibiotics in our study was associated with a higher risk of ICU admission and mortality, a similar finding to a systematic review about antibiotics administration in ICU patients with COVID-19. This study reported higher exposure to antibiotic treatment in patients who get admitted to ICU or die [18]. Moreover, the OpenSAFELY study revealed a 1.80-fold increased risk of hospitalization due to COVID-19 with previous antibiotic exposure, along with a direct relationship between the number of antibiotics used and the severity of COVID-19 presentation [34]. This finding translates only to the subset of our patients who survived and did not enter the ICU (Fig. 2), suggesting more aggressive antibiotics protocols for our patients who died or entered the ICU regardless of the severity of their disease.

Cephalosporins were the most prescribed class of antibiotic (64.8% of our patients). This differs from existing literature on global antibiotic misuse during the pandemic, which highlights quinolones as the most prescribed class of antibiotics [35]. Although differing from a global trend, the high cephalosporin prescription rate in Syria agrees with a previous study on antibiotic prescription in Syria in from 2018 to 2019, where cephalosporins were the leading plurality of antibiotics prescribed. This is likely due to their wide availability and low cost compared to other antibiotics like amoxicillin-clavulanate [36–38].

Amidst extensive antibiotic usage within our cohort, the prevalence of infection remains notably high with 7% of patients experiencing infectious complications and 2.5% experiencing septic shock. Osman et al. suggest that infections despite antibiotic use may be attributable to increasing AMR rate in Syria as a sequalae of the war [39, 40], or possibly due to inappropriate antibiotic prescriptions targeting the wrong bacteria [6]. Additionally, patients in low-to-middle income countries (LMICs) face heightened risks of nosocomial infections, especially in war zones [26, 31]. Numerous studies have displayed growing AMR in Türkiye, where significant rates of drug-resistant *Acinetobacter calcoaceticus baumannii* was found, with evidence of in-hospital transmission [41]. Other studies from Türkiye displayed improved clinical outcomes following early administration of ceftazidime-avibactam in areas endemic with oxacillinase-48 producing bacteria, further highlighting the prevalence of AMR in this region [42, 43]. In a study of 1320 patients admitted to the ICU with suspected COVID-19 in Tehran, 289 patients (23.3%) also experienced nosocomial infections during their hospitalization, primarily VAP [44]. Other studies also suggested that COVID-19 patients have a higher risk of obtaining a secondary bacterial infection in ICUs [15]. Despite this increased risk, a systematic review strongly discouraged the use of antibiotics in COVID-19 patients in the absence of clinical suspicion of bacterial coinfection or superinfection [9].

Our study revealed a significant association between the use of multiple antibiotics and various non-infectious complications, including electrolyte abnormalities, ARDS, and AKI. A Spanish study similarly found an association between inappropriate antibiotic prescription and AKI [17]. When trying to isolate the associations of individual antibiotic classes, we found that carbapenems were associated with respiratory failure, ARDS, bleeding, secondary infection, and septic shock. This association underscores the expanding body of evidence illustrating the proliferation of carbapenem-resistant pathogens (CRPs) during the COVID-19 pandemic. Several studies have elucidated the role of CRPs in causing secondary infections [45–48],pulmonary infections [48], and ARDS in hospitalized COVID-19 patients [46]. The surge in CRPs during the COVID-19 pandemic may be tied to the escalated utilization of carbapenems in hospitalized COVID-19 patients. For instance, in a study conducted at a tertiary hospital in Saudi Arabia, the consumption of carbapenems surged from 67.1 to 142.9 per 1,000 patients between April and August 2020 [49]. This suggests that the substantial incidence of side effects observed in our study may not reflect a negative impact of carbapenem use on patients, but rather a notable prevalence of CRPs amongst hospitalized COVID-19 patients in Syria.

Our analysis identified an association between metronidazole and thrombotic events, a relationship not previously described in the literature. Given that COVID-19 infection already places patients at an elevated risk of thromboembolic events [50], the findings from our study, coupled with previously reported coagulopathic events associated with metronidazole use, underscore the need for further research to elucidate any association between metronidazole use and the coagulopathic risks in COVID-19 patients. Amoxicillin/clavulanate was associated with a lower rate of respiratory failure in our cohort. The oral formulation of amoxicillin-clavulanate was the most common form given to patients. Given that most of our patients who were admitted to the ICU were intubated, this relationship might just reflect an indirect association between less severe patients not being admitted to ICU and therefore being prescribed oral antibiotics.

The excessive use of antibiotics in COVID-19 patients in Syria poses a significant risk of exacerbating the already precarious situation regarding infectious diseases and antimicrobial resistance in the wider region. A survey of patients at two major hospitals in Damascus reported that 78.4% of the respondents used antibiotics in the preceding 6 months to prevent or treat COVID-19 [51]. The worsening of antibiotic overuse by the pandemic can aggravate already evident challenges in Syria and its neighbors like AMR [6, 8, 39]. Furthermore, the proliferation of antimicrobial-resistant pathogens can lead to a protracted crisis of infectious diseases, as infections become increasingly difficult to treat and control. This scenario is especially concerning in Syria, where the population is already vulnerable to infectious diseases due to displacement, overcrowded living conditions, prevalent malnutrition, and inadequate access to healthcare services [25, 26, 52–55]. This can heighten the risk of infectious disease outbreaks in the wider region and complicate efforts to contain them [39]. Addressing the issue of antibiotic overuse in COVID-19 patients in Syria requires a multi-faceted approach that starts from promoting antimicrobial stewardship programs and extends to strengthening healthcare infrastructure to improve access to diagnostic testing and appropriate treatment.

Limitations

The retrospective nature of this study precluded us from establishing causal relationships between antibiotic administration and the observed outcomes and complications. Additionally, the decisions regarding antibiotic selection and dosage were influenced by the resources available at each individual center and physician judgement, making it challenging to ascertain uniformity across treatment protocols. However, the inclusion of a large sample size and adjustments for hospital location and disease severity in our analyses helped mitigate these uncertainties, facilitating more robust comparisons. Furthermore, the paucity of patients receiving no antibiotics poses a challenge in drawing definitive conclusions about the potential benefits or risks associated with antibiotic use in COVID-19 patients. Similarly, the small sample size and the lack of timeline data for medical complications make it impossible to draw direct causal conclusions between antibiotic use and outcomes. Finally, the cost, along with the scarcity of human resources, have also hindered the ability of the treating physicians to obtain confirmatory bacterial cultures and conduct antimicrobial resistance studies for the substantial volume of managed patients.

Conclusion

We characterized an excessive use of antibiotics for the management of hospitalized COVID-19 patients in Syria, which associated with higher mortality, ICU admission, and complications including ARDS, AKI, and secondary infections. Although the necessity for the utilized antibiotics cannot be retrospectively assessed, the unwarranted employment of antibiotics raises alarms about the potential development of a national and regional crisis in infectious diseases and antimicrobial resistance.

Abbreviations

COVID-19	2019 novel coronavirus
ICU	Intensive care unit
LR-COMPAK	In-hospital COVID-19 mortality scoring system [23]
AKI	Acute kidney injury
HSCR	Higher commission for scientific research
PCR	Polymerase chain reaction
RAT	Rapid antigen chest
CT	Computed tomography
CXR	Chest x-ray
WHO	World Health Organization
ARDS	Acute respiratory distress syndrome
DKA	Diabetic ketoacidosis
CKD	Chronic kidney disease
MI	Myocardial infarction
DVT	Deep vein thrombosis
PE	Pulmonary embolism
CVA	Cerebrovascular accident
OR	Odds ratio
CI	Confidence interval
LDH	Lactate dehydrogenase
CRP	C-reactive protein
PCT	Procalcitonin
WBC	White blood cells
MDR	Multi-drug resistant organisms
VAP	Ventilator-associated pneumonia
LMICs	Low-to-middle income countries
CRPs	Carbapenem-resistant pathogens
AMR	Antimicrobial resistance

Supplementary Information

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Supplementary Material 1

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Author contributions

MA, ES, and IH analyzed the data. MA prepared the manuscript. IH conceptualized the project, supervised data collection and analysis, and critically revised the manuscript. All authors revised and approved the last version of the article. Ibrahem Hanafi, as the corresponding author, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability

The dataset supporting the results presented in this report is available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

This study received ethical approval from both the Higher Commission for Scientific Research (HSCR) at the Syrian Ministry of Higher education, the institutional review board at Damascus University, and the review boards of all participating centers. The ethical clearance from HSCR, bearing the identification number 1/491, was granted on January 19, 2021, and waived the need for getting individual informed consent from the patients included. This study adhered to the Declaration of Helsinki.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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