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Original Article

Prevalence, Trend, and Risk Factors of Antibiotic Resistance of *Klebsiella Pneumoniae* in the Center of Iran During the COVID-19 Pandemic

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Abstract
Background and aims: The emergence and spread of bacterial strains resistant to multiple antimicrobials have made the treatment of these infections increasingly challenging. This research aimed to investigate the impact of the coronavirus disease 2019 (COVID-19) pandemic on multidrug-resistant *Klebsiella pneumoniae* (MDR-KP) and associated factors.
Methods: This ecological and case-control study was conducted at Shahid Sadoughi Hospital. Data on all positive bacterial cultures were extracted from July 2018 to March 2023. In the ecological phase, an interrupted time series analysis was performed on the monthly prevalence of MDR-KP to assess changes following the onset of the pandemic. In the case-control phase, patients with MDR-KP were compared with those with no MDR-KP. Finally, logistic regression was used to identify factors associated with MDR-KP.
Results: Out of 15,181 samples with positive bacterial cultures, 6.17% (CI: 0.057, 0.065) were attributed to KP. The prevalence of MDR-KP during the COVID-19 pandemic (through March 2023) was 72.65. In addition, there was a significant immediate increase of 6.42% ($P<0.001$) following the onset of the pandemic. Based on logistic regression analysis, a previous hospitalization (OR=2.48, 95% CI: 1.29, 4.75, $P<0.001$), admission to the intensive care unit (OR=1.9, 95% CI: 1.02, 3.55, $P=0.042$), and duration of hospitalization (OR=1.02, 95% CI: 1.01, 1.04, $P=0.006$) were related to MDR.
Conclusion: The findings revealed a high prevalence of antibiotic resistance in KP strains in Shahid Sadoughi Hospital, emphasizing the urgent need for effective strategies to combat antibiotic resistance and prevent the spread of resistant infections.
Keywords: Multiple drug resistance, Multidrug resistance, Microbial drug resistance, Risk factors, *Klebsiella pneumoniae*

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Introduction

Klebsiella pneumoniae (KP) is a Gram-negative bacterium that can cause infections in various parts of the human body [1]. In addition, it is a significant pathogen in healthcare settings and has been increasingly associated with infections in recent years. KP infections frequently occur as outbreaks in healthcare settings and can be transmitted through medical equipment and blood products. Treating KP infections has become increasingly difficult due to the spread of strains that are resistant to multiple antimicrobials [2].

Antibiotic resistance in Gram-negative bacteria poses a serious risk for patient mortality and extended hospital stays. This growing global health concern, particularly affecting vulnerable patients, results in more deaths from resistant infections annually. Predictions suggest that by 2050, antibiotic-resistant bacteria can surpass cancer in causing fatalities [3]. Studies have indicated that the fatality rate associated with carbapenem-resistant KP is higher than that of the non-resistant KP [4]. Moreover, infections caused by carbapenem-resistant pathogens necessitate prolonged hospitalization and escalating treatment expenses, which, in turn, contribute to increased mortality rates related to infectious diseases. This situation imposes serious financial and emotional burdens on both patients and their families [5].

Subtherapeutic antibiotic exposure may induce resistance development in susceptible microorganisms. The widespread use of antimicrobial agents in both healthcare and community settings has driven the proliferation of resistant bacterial variants, particularly carbapenem-resistant KP [6]. Although antibiotics are frequently prescribed to coronavirus disease 2019 (COVID-19) patients, the prevalence of bacterial co-infection and secondary infections among hospitalized COVID-19 patients remains relatively low at 3.5% and 14.3%, respectively [7]. This disparity between bacterial infection prevalence and antibiotic prescription rates highlights the potential for significant antibiotic overuse in these patients. This over-prescribing of antibiotics to severe acute respiratory syndrome coronavirus 2-infected individuals can intensify selective pressure, thereby promoting antimicrobial resistance. When combined with the strain on healthcare workers and reduced surveillance for antibiotic-resistant organisms, this can result in enduring antimicrobial resistance as a consequence of the COVID-19 pandemic [8, 9]. This research aims to examine the impact of the COVID-19 pandemic on multidrug-resistant KP (MDR-KP) and associated factors to implement measures to address this global concern effectively.

Materials and Methods

Data Gathering and Processing

This retrospective, observational study combined an ecological design with a case-control design. Two datasets were utilized in the ecological phase. First, cumulative (aggregated) monthly antibiotic susceptibility testing data for all KP isolates from August 2017 to March 2023 were collected to calculate the prevalence of resistance to specific antibiotics of interest. Second, individual-level antibiotic susceptibility testing data from July 2018 to March 2023 were assessed to analyze the trend of MDR-KP over time. In addition, the MDR status for each isolate was determined according to the predefined criteria. These individual-level data were then aggregated into monthly counts to construct a time series for the interrupted time series (ITS) analysis, focusing on the impact of the COVID-19 pandemic.

In the case-control phase, individual data from all patients who tested positive for KP between July 2018 and March 2023 were collected at Shahid Sadoughi Hospital in Yazd. The hospital samples included various types, such as urine, blood, wound, tissue, and pharyngeal secretion, representing all departments. To evaluate their resistance to different antibiotics, all samples underwent disc diffusion susceptibility testing.

Definition of Antibiotic Resistance

In this study, antibiotic resistance is defined as nonsusceptibility (resistant plus intermediate) [10] to various antibiotic groups. Furthermore, MDR is referred to as nonsusceptibility to three or more classes (third/fourth-generation cephalosporins, aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole).[1] The antibiotic susceptibility data were extracted from the hospital's Laboratory Information System, where antimicrobial susceptibility testing results for all clinical samples are routinely recorded as part of standard patient care. The laboratory adheres to the Clinical and Laboratory Standards Institute guidelines and participates in regular internal quality control procedures.

Statistical Analysis

Ecological Phase: In this phase of the study, the prevalence of antibiotic resistance was estimated, and the trend in MDR-KP was analyzed, specifically assessing the impact of the COVID-19 pandemic on this trend. The ITS analysis was used for this purpose. In ITS studies, a specific outcome of interest is analyzed over time to identify a trend. This trend is then 'interrupted' by an intervention that occurs at a known point in time.

The counterfactual scenario is the hypothetical situation in which the intervention did not occur, and the trend would have continued unchanged. By comparing the observed post-intervention period with this counterfactual scenario, it is possible to evaluate the impact of the intervention. The model consists of four parameters. β0 reflects the baseline value of the outcome at the beginning of the study (time = 0). In addition, β1 measures the rate of change in the outcome per unit of time (slope) during the pre-intervention phase. Moreover, β2 captures the shift in the outcome between the pre-intervention and post-intervention periods. Furthermore, β3 quantifies the change in the outcome's trend (slope change) after the intervention, accounting for the relationship between time and intervention intensity. Formula I expresses this model.[12]

Formula 1: $outcome = \beta 0 + \beta 1\ (time) + \beta 2\ (level) + \beta 3\ (time \times level) + \varepsilon$

In our study, the intervention of interest was the COVID-19 pandemic, and our desired outcome was MDR. Based on a review study, it was supposed that there was a lag time of 6 months between the intervention and the outcome of interest.[13] RStudio software version 4.4.2 was utilized to conduct this analysis.

Risk Factor Assessment: Risk factors for MDR-KP among hospitalized patients were investigated at Shahid Sadoughi Hospital in Yazd from July 2018 to March 2023. A total of 580 samples were obtained after applying the exclusion criteria, comprising 140 sensitive and 440 non-sensitive samples. It should be noted that an equal number of cases and controls increases the power of the study [14]. Therefore, all 140 sensitive samples and 155 randomly selected non-sensitive samples were included in the study (Figure 1). Logistic regression analysis was conducted using Stata software (version 14) to identify risk factors for antibiotic resistance. Further, crude odds ratios and adjusted odds ratios were estimated using univariable analysis and multivariable analysis, respectively. A 95% confidence interval (CI) was calculated for both odds ratios, with statistical significance defined as $P < 0.05$.

The possible risk factors in this study included demographic variables (e.g., age and gender), hospitalization conditions (e.g., duration of hospitalization and hospitalization department, including intensive care unit [ICU] or not), and lifestyle factors (e.g., current smoking and addiction status). The history of certain chronic diseases, such as chronic kidney disease and cancer (all types of cancer), prior hospitalization, and any surgeries within the past 6 months are also taken into consideration. The multivariable model was adjusted for all potential confounders.

Results

Prevalence of Antibiotic Resistance

The total number of samples isolated from patients during July 2018 to March 2023 was 75,532. Of these, 15,181 samples had positive bacterial cultures. Of which 6.17% (n = 938, CI: 5.7–6.5) were related to KP. The prevalence of MDR-KP in total KP isolates (inpatient and outpatient) was 61.02 (CI: 55.6–66.4) from July 2018 to February 2020 and 72.65 (CI: 68.4–76.5) from March 2020 to March 2023, showing a significant increase in the prevalence of MDR-KP following the COVID-19 pandemic ($P < 0.001$). Moreover, the prevalence of resistance among some necessary antibiotics was calculated from August 2017 to March 2023 (Table 1).

Trend of Antibiotic Resistance

The required data were collected from July 2018 to March 2023 and then reported monthly, yielding 56 time points for trend analysis. According to the results (Figure 2 and Table 2), the prevalence of MDR-KP strains was 57.94% ($P < 0.001$) at the start of the study (intercept), with an increase of 0.17% ($P = 0.029$). Therefore, over the course of the study until the beginning of the COVID-19 pandemic (accounting for lag time), the prevalence of MDR increased by 0.17% per month. Additionally, there was a significant increase of 6.42% ($P < 0.001$) immediately after

Table 1. Prevalence of Antibiotic Resistance (Intermediate Plus Resistant) During the Study Period

Antibiotics	From August 2017 to February 2020				From March 2020 to March 2023			
	No. of Total Isolates	No. of Resistant Isolates	Resistance %	95% CI*	No. of Total Isolates	No. of Resistant Isolates	Resistance %	95% CI*
Ceftazidime	398	229	57.5	52.6-62.3	547	360	65.8	64.22-67.39
Ceftriaxone	359	221	61.5	56.5-66.5	523	336	64.3	62.64-65.95
Cefotaxime	398	243	62.7	57.8-67.4	541	367	68	66.34-69.65
Cefepime	398	211	53	48.1-57.9	549	325	59.2	57.59-60.37
Imipenem	383	144	37.5	32.7-42.4	513	226	44.2	42.23-46.16
Meropenem	317	123	38.8	33.4-44.1	419	192	46	42.96-49.03
Amikacin	398	85	21.3	17.2-25.3	546	213	39	37.45-40.54
Gentamicin	396	141	35.6	30.8-40.3	548	240	43.8	42.58-45.01
Ciprofloxacin	377	185	49	44.2-54.1	582	324	55.7	54.47-56.92
Trimethoprim-sulfamethoxazole	388	229	59	54.1-63.9	486	313	64.5	62.70-66.29

Note. **CI:** Confidence interval; **No.:** Number.

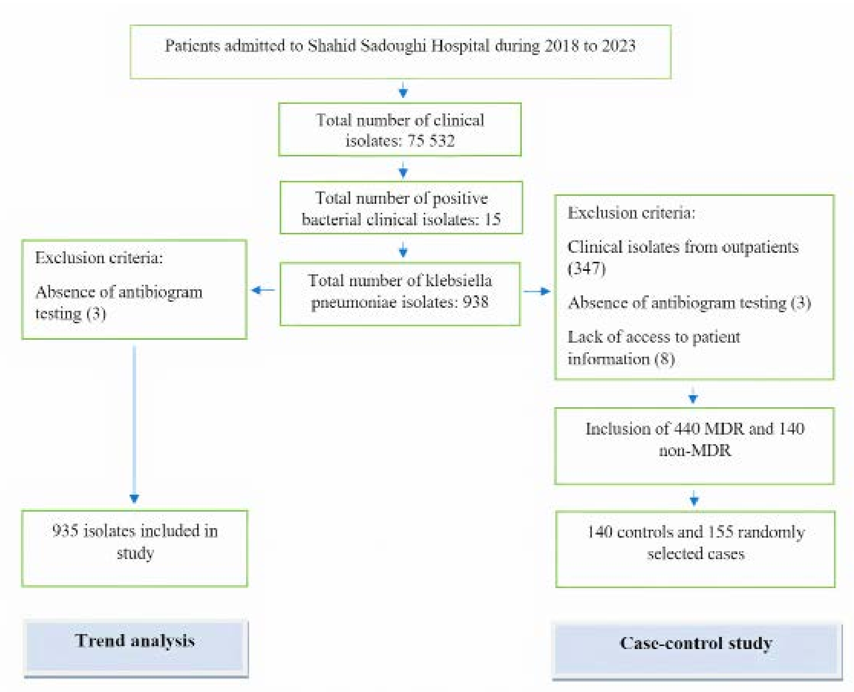

Figure 1. Flow Diagram of the Sample Selection

the onset of the pandemic. Furthermore, the change in the prevalence of the MDR-KP trend after the pandemic was determined to be 0.11 ($P = 0.013$). Table 3 provides a comparison of MDR-KP values between the observed trends during the COVID-19 pandemic, presented in 6-month intervals. Based on the results (Table 4), this difference progressively increased over time.

Discussion

Based on our study, a high prevalence of antibiotic resistance was observed in KP strains in Shahid Sadoughi Hospital. The ITS analysis revealed a considerable increase in the level of MDR immediately after 6 months from the onset of the COVID-19 pandemic, which continued to increase by 0.3% ($\beta 1 + \beta 3 \approx 0.3$) per month. Additionally, the case-control study demonstrated associations between MDR-KP and factors such as a history of hospitalization, ICU hospitalization, and length of hospitalization, which will be further discussed in subsequent sections.

Prevalence of Antibiotic Resistance

The emergence of antimicrobials in KP poses a serious

Table 2. Parameters of Interrupted Time Series Analysis for Assessing Trends in Confirmed MDR-KP Cases

ITS Parameters	Coefficients	*P*-Value	95% CI*
Intercept (β0)	57.94	<0.001	55.73, 60.15
Trend before the pandemic (β1)	0.17	0.03	0.02, 0.32
Level change immediately after the pandemic (β2)	6.42	<0.001	3.62, 9.22
Changes in the trend after the pandemic (β3)	0.11	0.215	-0.04, 0.26

Note. **CI:** Confidence interval; **MDR-KP:** Multidrug-resistant *Klebsiella pneumoniae*; **ITS:** Interrupted time series.

Table 3. Changes in the Percentage of MDR-KP due to COVID-19 in 6-Month Intervals After the Pandemic

Six-Month Intervals	% Observed MDR-KP*	% Expected MDR-KP	% Changes
August 2020	68.95	62.42	6.53
February 2021	70.63	63.44	7.19
August 2021	72.31	64.46	7.85
February 2022	73.99	65.48	8.51
August 2023	75.67	66.50	9.17
February 2023	77.35	67.52	9.83

Note. **MDR-KP:** Multidrug-resistant *Klebsiella pneumoniae*.

Table 4. Baseline Characteristics of the Study Subjects According to MDR Status and Predictive Factors for MDR-KP* Among Hospitalized Patients

Variables	MDR* (%)	Non-MDR (%)	COR* (CI*)	*P*-Value	AOR* (CI)	*P*-Value
Age (SE)	52.69 (SE = 2.09)	48.61 (SE = 2.43)	1(0.99, 1.01)	0.203	0.99 (0.98, 1)	0.934
Gender (male)	81 (52.2)	67 (47.8)	1.19 (0.75, 1.88)	0.450	0.91 (0.53, 1.55)	0.739
CKD*	19 (12.2)	20 (14.2)	2.34 (1.41, 3.87)	0.608	0.85 (0.41, 1.74)	0.669
Cancer	14 (9)	13 (9.3)	0.96 (0.43, 2.14)	0.940	0.75 (0.32, 1.76)	0.516
Current smoking	14 (9)	14 (10)	0.89 (0.41, 1.94)	0.777	0.79 (0.32, 1.96)	0.624
Current addiction	19 (12.2)	17 (12.1)	1.01 (0.5, 2.03)	0.976	0.68 (0.3, 1.55)	0.370
Length of hospitalization (SE)	19.08 (SE = 1.35)	11.47 (SE = 1.29)	1.03 (1.01, 1.04)	<0.001	1.02 (1.01, 1.04)	<0.01
History of hospitalization	113 (72.9)	77 (55)	2.2 (1.35 3.57)	<0.01	2.48 (1.29, 4.75)	<0.01
History of surgery	66 (42.5)	45 (32.1)	1.56 (0.97, 2.52)	0.065	1.04 (0.56, 1.95)	0.884
ICU*	65 (42)	33 (23.6)	2.34 (1.41, 3.87)	<0.01	1.9 (1.02, 3.55)	0.042

Note. **MDR-KP:** Multidrug-resistant *Klebsiella pneumoniae*; **ICU:** Intensive care unit; **CKD:** Chronic kidney disease; **COR:** Crude odds ratio; **AOR:** Adjusted odds ratio; **CI:** Confidence interval; **SE:** Standard error.

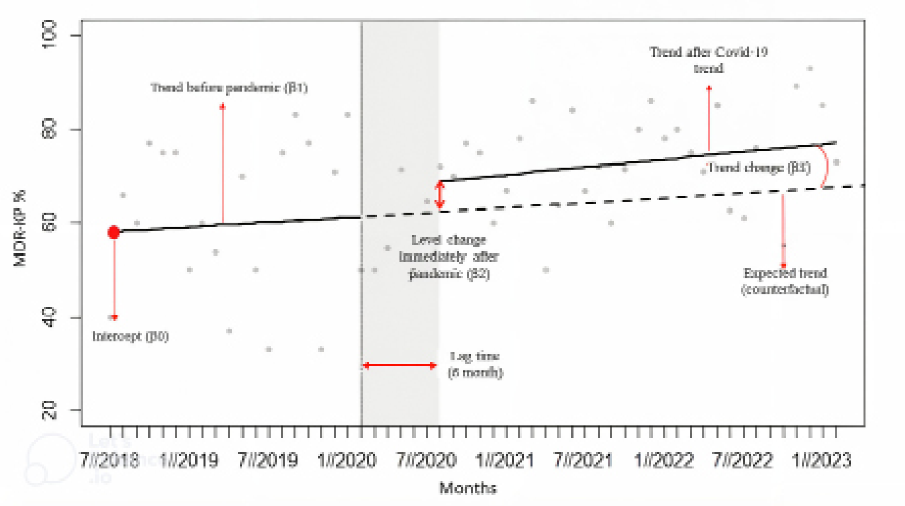

Figure 2. Interrupted Time Series Analysis of Confirmed MDR-KP Cases in Yazd: Pre-Pandemic Versus Post-Pandemic Trends
Note. **MDR-KP:** Multidrug-resistant *Klebsiella pneumoniae*

global threat to public health. Our recent study at Shahid Sadoughi Hospital assessed the extent of this issue. Based on our findings, KP strains isolated from hospitalized patients exhibited high levels of resistance to third-generation cephalosporins, which is a cause of concern. However, interestingly, aminoglycosides showed the lowest level of resistance in our study.

Likewise, our study results highlight a concerning prevalence of MDR-KP in patients admitted to hospitals in Yazd in recent years. Furthermore, these findings are consistent with similar estimates reported by other studies [15, 16].

Trend of Antibiotic Resistance

Research from China using the ITS method reported a reduction of 4.13 isolates per biweekly period in KP detections relative to baseline levels following the emergence of COVID-19. However, longitudinal analysis uncovered a subsequent upward trajectory [17]. Our analyses indicated a noticeable increase in MDR among KP strains temporally associated with the COVID-19 pandemic in level and a non-significant increase in trend. Corroborating these observations, additional research documented a 3% elevation in Gram-negative bacterial resistance rates corresponding to each weekly increment in COVID-19 case numbers [18].

Risk Factors for Multidrug-Resistant Klebsiella pneumoniae Resistance

MDR is a serious concern because it involves resistance to three or more classes of antimicrobials. This worldwide threat is particularly widespread among hazardous bacteria, including KP strains. Our results revealed that hospital length of stay, prior hospitalization, and ICU admission were significant factors associated with MDR-KP strains.

History of Hospitalization

According to our findings, patients with a history of hospitalization had nearly 2.5 times greater likelihood of experiencing MDR-KP compared to those without such a history. Similar studies have consistently demonstrated that recent hospitalization is an essential predictor of MDR development, potentially attributed to antibiotic usage [19, 20].

Admission to the Intensive Care Unit

Admission to the ICU has been associated with outbreaks caused by KP [21]. Numerous studies have also supported the idea that a history of ICU hospitalization is an independent risk factor for MDR-KP infection [22-24]. One study reported a higher rate of non-susceptibility of *Klebsiella* strains to imipenem, ertapenem, and amikacin in the ICU [25]. Another study found that a considerable number of patients with difficult-to-treat resistant KP were hospitalized in the ICU [26].

Our analysis confirmed similar patterns, with markedly increased prevalence of MDR *K. pneumoniae* among ICU-admitted cases. The rise in resistance within critical care units stems largely from the dissemination of epidemic strains that have driven the worldwide spread of pan-resistant bacteria, including resistance to newer agents, such as ceftazidime-avibactam [27].

Duration of Hospitalization

Existing literature identifies extended inpatient stays as a significant contributor to the development of antimicrobial resistance [28]. According to these studies, long-term hospitalization is a factor that affects MDR in Gram-negative bacteria, which can be acquired from the community or the hospital environment [29, 30]. Although this study, similar to previous ones, demonstrated a significant association between hospitalization length and MDR-KP strains, the nature of this association remains ambiguous. MDR may be the cause of long-term hospitalization rather than the other way around.

Limitations of the Study

Without molecular typing, it was impossible to determine if the MDR-KP increase was due to clonal spread or independent resistance emergence. The reliance on routine laboratory data also indicates that potential susceptibility misclassification cannot be ruled out, and there were no direct data on individual antibiotic use to link prescribing changes to resistance trends. Although our ecological and case-control designs showed an association, but could not prove causation. In other words, other pandemic-related changes in hospital operations or diagnostic practices might have influenced the results. Furthermore, the case-control analysis was limited to inpatients due to incomplete outpatient records, and the number of susceptible cases constrained the final sample size.

Conclusion

Overall, the prevalence of MDR-KP strains among hospitalized patients was recorded at 72.65%. The ongoing COVID-19 pandemic was temporally associated with an increase in the MDR-KP trend. Moreover, certain factors, such as prior hospitalization, ICU admission, and length of hospital stay, were associated with MDR-KP.

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Authors' Contribution

Conceptualization: Moslem Taheri Soodejani, Mohammad Hasan Lotfi, Hengameh Zandi.
Data curation: Maryam Kazemi.
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Project administration: Moslem Taheri Soodejani.
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Supervision: Moslem Taheri Soodejani.
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Writing–original draft: Maryam Kazemi.
Writing–review & editing: Moslem Taheri Soodejani, Mohammad Hasan Lotfi, Hengameh Zandi.

Competing Interests
None.

Ethical Approval
The study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (No. IR.SSU.SPH.REC.1402.037). The required data were anonymously collected, and the Ethics Committee of Shahid Sadoughi University of Medical Sciences waived the requirement for informed consent because of the retrospective nature of the study. In addition, all patient information has been included in the hospital information system and is not accessible to the public.

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