



Healthcare Associated Infections Among COVID-19 Patients; Incidence, Mortality, and Risk Factors

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ABSTRACT

Background: Healthcare-associated infections (HAIs) among COVID-19 patients is a challenge, leading to prolonged hospitalizations, increased morbidity, and mortality. **Objective:** To determine the incidence of HAIs, mortality, and identify related risk factors in COVID-19 patients. **Method:** A descriptive multi-centre retrospective cohort study was conducted using HAIs surveillance data among COVID-19 patients admitted to Ministry of Health Hospitals during the pandemic. Multivariable logistic regression was performed. **Results:** A total of 474 HAIs were identified among 459 patients, with an incidence rate of 4.9 per 100 patients at risk and 3.43 per 1000 patient days. The most common types of HAIs were bloodstream infections, pneumonia, and urinary tract infections. Central line-associated bloodstream infections were significantly higher in the intensive care units (ICUs) compared to wards. Two-thirds of the infections were device-associated. Multidrug-resistant organisms (MDROs) were involved in 61.9% of HAIs, with gram-negative bacteria accounting for 74.3% of cases. *Klebsiella pneumoniae* and *Acinetobacter baumannii* were the most common MDROs identified. The 30-day mortality rate among patients was 52.1%, with HAIs contributing to 31.4% of deaths. MDROs significantly contributed to patients' mortality. **Conclusions:** The study highlights the increased rates of HAIs during the COVID-19 pandemic, particularly in the ICU. The logistic regression analysis identified MDROs, duration of device usage and time from admission to infection onset as significant predictors of mortality in patients with bloodstream infections. These findings underscore the importance of strictly implementing appropriate infection prevention practices and antimicrobial stewardship programs to reduce mortality and negative outcomes in COVID-19 patients.

INTRODUCTION

Healthcare-associated infections (HAIs) occur more than 2 calendar days after healthcare facility admission. This infection does not exist at the time of admission and are not incubated. The World Health Organization (WHO) reports that almost two million HAIs occur yearly, with 1 in 29 people acquiring HAIs.¹ The frequency of these infections varies worldwide, ranging from 3.5% to 12% in developed countries and from 7.5% to 19.1% in developing countries. HAIs are

most common in intensive care units (ICUs) and among the elderly with other comorbidities and low immunity. They pose several challenges in patient's management, including high costs of laboratory procedures, medication use, hospitalization, and antibiotic resistance. Annually, HAIs result in 99,000 deaths and cost society twenty million dollars.² Diagnostic, therapeutic, and invasive procedures such as urinary catheters, central venous catheters, and

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mechanical ventilation increase the risk of nosocomial infections. Most HAIs (80%) include urinary tract infections (UTIs), surgical site infections, respiratory infections, and bloodstream infections (BSIs).¹ During the COVID-19 pandemic, the incidence of HAIs was alarming, leading to prolonged hospital stays, increased morbidity, and mortality, posing significant health concern for healthcare providers and recipients. A comprehensive understanding of HAIs is crucial for guiding prevention and control efforts.³ The first coronavirus disease 2019 (COVID-19) case in Kuwait was reported in February 2020, with the first wave starting in April 2020. The number of cases fluctuated from 3000 to 6600 weekly throughout 2020: with many cases requiring hospitalization and a reported daily mortality rate of 10-58 deaths.⁴ The Ministry of Health in Kuwait has implemented rapid response teams and infection prevention and control measures to combat the pandemic. The objectives of the current study were to assess the incidence of different HAIs among COVID-19 patients during the first wave of the pandemic, estimate 30-day mortality rates, identify related risk factors, and explore the frequency of multidrug-resistant organisms (MDROs) causing HAIs among this population.

METHODS

A multi-center retrospective cohort study of the collected HAI surveillance data from COVID-19 patients admitted to all Ministry of Health Hospitals during the first wave of COVID-19 in the state of Kuwait.

All adult patients admitted to the critical care and non-critical care settings who had developed HAIs from 1st July to 31st December 2020 were included in the current study. The inclusion criteria were patients over 18 years old, with a confirmed diagnosis of COVID-19 (SARS-CoV-2) by Reverse-Transcription Polymerase Chain Reaction (RT-PCR) using nasal, nasopharyngeal, throat, or respiratory tract samples⁵, who acquired one or more HAIs during their admission. Exclusion criteria were patients under 18 years old or any probable cases of COVID-19.

Data collection and definitions: We collected the data using a standardized data collection form adopted from the Center for Disease Control–National Health

Surveillance Network (CDC-NHSN). All the data were collected and reviewed by the infection control team. Re-checking was made by the quality control team in the surveillance department, and any missing data were requested from the designated hospital to complete all files. Infections were considered HAIs when they occurred after two days from hospital admission.⁶ We defined MDROs as organisms resistant to ≥ 1 drug in at least 3 classes of antibiotics.⁶ The study used the standard NHSN criteria for central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTIs), and ventilator-associated pneumonia (VAP).⁶

Statistical Analysis: We coded and entered the data anonymously. SPSS version 26 was used in the analysis. Qualitative variables were presented as frequency and percentages, while quantitative variables were presented as the mean, median, and interquartile range. Chi-squared or Fisher's exact test was used to compare qualitative variables values, whereas the Mann-Whitney (U test) was used to compare quantitative variables. The device-associated infection (DAI) rates were calculated.⁶ The analysis was conducted using multivariate logistic regression, and statistical significance was considered if the *P*-value was less than 0.05.

RESULTS

The study analyzed the demographic and clinical features of 459 COVID-19 patients that were isolated in many hospitals. Those patients experienced a total of 474 HAIs caused by 597 pathogens. This HAI occurred among a total of 9364 COVID-19 patients (representing a rate of 4.9 HAIs per 100 patients at risk) over 138,349 patient days (equivalent to 3.43 HAIs per 1000 patient days). BSIs were the most common HAIs (64.3%), followed by pneumonia at 15.8%, UTI at 15.0%, and other infections, such as skin infections, Clostridium difficile Infection (CDI), Surgical Site Infections (SSIs), and Conjunctivitis (CONJ), (at 4.9%).

The median age of the patients was 62 years, with 57.2% being males. Kuwaiti patients made up 70.5% of the cohort, and most infections occurred in ICU patients (88.4%). Hospital stay median length was 30 days, with a median time from hospital admission to the onset of HAIs being 22 days.

Table 1: Demographic and clinical characteristics of COVID-19 patients with healthcare- associated infections in the studied hospitals (July – Dec 2020)

Characteristics	Total N=474	BSI N=305	PNEU N=75	UTI N=71	Others N=23
Median age (IQR) years	62 (52-72)	62 (52-72)	63 (56-72)	63 (57-72)	51 (37-63)
Nationality:					
Kuwaiti	323 (70.5%)	203 (66.7%)	63 (84.0%)	56 (78.9%)	14 (60.9%)
Others	136 (29.5%)	102 (33.8%)	12 (16.0%)	15 (21.1%)	9 (39.1%)
Gender:					
Male	270 (57.2%)	187 (61.6%)	38 (52.0%)	32 (46.5%)	13 (56.5%)
Female	204 (42.8%)	118 (38.4%)	37 (48.0%)	39 (53.5%)	10 (43.5%)
Setting:					
ICU	415 (88.3%)	278 (92.1%)	65 (86.7%)	60 (84.5%)	16 (69.6%)
Non-ICU	55 (11.6%)	27 (7.9%)	10 (13.3%)	11 (15.5%)	7 (30.4%)
Median length of hospital stays (IQR) days	30 (21-39)	30 (21-39)	31 (24-44)	30 (21-36)	36 (21-60)
Median Duration from admission till infection (IQR) days	22 (16-33)	22 (17-32)	21 (17-34)	18 (13-31)	20 (12-37)
Secondary blood stream	73 (15.4%)	N/A	41 (54.7%)	31 (43.7%)	1 (4.3%)
Died during hospitalization	307/459 (66.9%)	199/305 65.2%	50/75 66.6 %	47/71 66.2%	11/23 47.8%
30-days-mortality	239/459* (52.1%)	157/305 (51.5%)	43/75 (57.3%)	32/71 (45.1%)	7/23 (30.4%)
MDR isolated pathogens	294 (61.9%)	170 (55.7%)	59 79.0%)	55(77.9%)	10 (43.5%)
Infections contributed to death	75/239 31.4 %	55/157 35.0%	16/43 37.2%	4/32 12.5%	0

*Total number of HAIs= 474 (among 459 patients). Data were presented as number and percentage unless mentioned otherwise. IQR (Inter quartile range). BSI, bloodstream infection; PNEU, pneumonia; UTI, urinary tract infections; MDR, multidrug-resistant.

Infections were predominantly device-associated (65.6%). 66.9% of patients died in the hospitals; with 52.1% dying within 30 days of admission, and infections contributing to death in 31.4% of cases (Table 1).

A comparison of patients' characteristics with acquired HAIs in critical care settings versus non-critical care settings was conducted. Patients in wards with BSI and pneumonia were statistically significantly older compared to patients in ICUs ($P<0.05$). Male patients required ICU care more frequently than female patients ($P<0.05$). MDROs were more commonly isolated from UTI and other infections in ICU patients, ($P<0.05$).

The median length of hospital stay was longer among ICU patients with different HAIs, and the duration of

device use was longer in ICU patients, particularly in the BSI group ($P<0.05$). The use of invasive devices was identified as a significant risk factor among ICU patients ($P<0.05$). The rate of HAIs in different settings was analyzed based on patient days spent in COVID ICUs and wards. The overall HAI rate was 3.43 /per 1000 patient days, with a significantly higher rate in ICUs compared to wards. The BSI rate was 2.2 /per 1000 patient days, with a significantly higher rate in ICUs. CLABSI rates were also higher in ICUs compared to wards. CAUTI, UTI, and pneumonia rates were significantly higher in ICUs, with corresponding higher utilization ratios of urinary catheters and ventilators in ICU settings (Table 2).

Table 2: The distribution of healthcare-associated infections among COVID-19 patients in different hospital settings in relation to demographic and clinical characteristics (July – Dec 2020)

	BSI N=305		PNEU N=75		UTI N=71		Others N=23	
	ICU	Ward	ICU	Ward	ICU	Ward	ICU	Ward
Mean age	61.0±13.4	68.7±13.0	60.5±14.5	73.5±16.9	62.4±13.6	68.4±16.2	51.8±12.2	51.1±21.8
P-value	0.004*		0.012		0.201		0.925	
Males (%)	175 (62.9%)	16 (59.3%)	32 (49.2%)	7 (70%)	29 (48.3%)	4 (36.4%)	11 (68.8%)	2 (28.5%)
P-value	0.433		0.221		0.464		0.074	
MDROs (%)	159 (93.8%)	11 (6.2%)	53 (90.7%)	6 (9.3%)	50 (91.4%)	5 (8.6%)	9 (90%)	1 (10%)
P-value	0.195		0.941		0.001		0.043	
Mean LOS	32.6±14.6	32.1±21.4	35±17.0	40±20.8	31.0±12.9	28.9±22.3	47.0±20.0	24.0±8.5
P-value	0.889		0.445		0.072		0.060	
Mean days to infection	26.2±14.1	24.8±18.5	27.2±17.6	25.6±14.4	23.8±11.9	18.1±13.6	31.9±17.8	16.0±9.1
P-value	0.639		0.783		0.032*		0.370	
Mean duration of device use	21.5±14.4	18.5±16.7	20.7±16.1	12.3±8.5	19.7±8.8	12.8±3.3	N/A	
P-value	0.043*		0.322					
Device use (%)	180 (94.7%)	10 (5.3%)	54 (98.2%)	1 (1.8%)	59 (92.2%)	5 (7.8%)	N/A	
P-value	0.003*		<0.001*		<0.001*			
Number of infections	278	27	65	10	6	11	N/A	
Patient days	28707	109642	28707	109642	28707	109642		
HIA rate*	9.7	0.25	2.3	0.09	2.1	0.1	N/A	
P value	<0.001		0.031		0.002			
Devise days	19322	1351	19777	640	22674	6201	N/A	
DAI- Rate**	9.4	5.9	2.7	1.6	2.6	0.81		
P value	0.001		0.024		0.003			
Devise Utilization	0.67	0.01	0.69	0.005	0.79	0.06	N/A	
P value	<0.001		0.003		0.004			

N/A: Not Applicable for other infections. *HAI rate: healthcare associated infection rate per 1000 patient days. **DAI- Rate: Devises associated infection rate per 1000 device days. BSI, bloodstream infection; PNEU, pneumonia; UTI, urinary tract infections; MDRO, multidrug-resistant organism; LOS, length of stay

The characteristics of survivors versus non- survivors (Table 3), among COVID-19 patients with HAIs were compared. MDROs were significantly correlated with death in BSI cases, while older age was associated with mortality in pneumonia cases. Deaths among UTI cases were more common in ICU settings and among patients with invasive devices and MDROs.

The distribution of causative pathogens of different HAIs among COVID-19 patients was examined. Many infections (61.9%) were attributed to MDROs. Gram-negative bacteria were utmost commonly isolated pathogens (73.4%), followed by fungi (14.2%) and gram-positive bacteria (12.4%).

MDROs were prevalent in BSI and pneumonia cases, with *Klebsiella pneumoniae* and *Acinetobacter baumannii* being common pathogens. UTIs were predominantly caused by MDROs and gram-negative bacteria, with Enterobacteriaceae and *Pseudomonas aeruginosa* being common pathogens. Other infections were caused by various pathogens, including gram - positive bacteria (Table 4).

A multivariable logistic regression analysis was conducted to identify predictors of mortality among COVID-19 patients with BSI.

Table 3: The comparison between survivors and non survivors among COVID-19 patients with HAIs and its related risk factors

Bloodstream infection	Survivors (N=106)	Non-Survivors (N=199)	*P value
Mean Age*	60.5±14.4	64.8±12.5	0.058
Gender:			
Male	56 (52.8%)	131 (65.8%)	0.104
Female	50 (47.2%)	68 (34.2%)	
Setting:			
ICU	91 (85.8%)	185 (93.0%)	0.134
Non-ICU	15 (14.2%)	14 (7.0%)	
Mean LOS*	34.98±6.7	31.90±7.2	0.246
Device use	53 (28.0%)	137 (72.0%)	0.330
MDROs	25 (14.7%)	145 (85.3%)	0.004*
Pneumonia	Survivors (N=25)	Non-Survivors (N=50)	*P value
Mean Age*	55.7±18.3	68.4±14.8	0.045
Gender:			
Male	7 (28.0%)	29 (58.0%)	0.145
Female	18 (72.0)	21 (42.0%)	
Setting:			
ICU	106 (100.0%)	157 (79.1%)	0.181
Non-ICU	0 (0.00%)	42 (20.9)	
Mean LOS*	45.3±20.3	34.4±16.9	0.130
Device use	10 (18.2%)	45 (81.8%)	0.091
MDROs	6 (10.2%)	53 (89.8%)	0.140
Urinary tract infections	Survivors (N=24)	Non-survivors (N=47)	*P value
Mean Age*	57.9±18.9	66.2±11.3	0.068
Gender:			
Male	11 (45.9%)	28 (59.6%)	0.414
Female	13 (54.1%)	19 (40.4%)	
Setting:			
ICU	14 (60.0%)	45 (96.7%)	0.001*
Non-ICU	10 (40.0 %)	2 (3.3%)	
Mean LOS*	31.1±14.2	30.5±14.6	0.886
Device use	18 (29.2%)	46 (71.8%)	0.009*
MDROs	15 (27.0%)	40 (73.0%)	0.015*

*P value: Chi square for qualitative variables & t test for numerical variables. Data were presented as number and percentage unless mentioned otherwise. LOS, length of stay. * mean ± standard deviation.

MDROs, duration of device use, and the duration from admission to infection onset were significant predictors of mortality among COVID-19 patients ($p < 0.05$). The OR was 3.98, 0.92 & 1.1 respectively). The CI was (1.6-9.6, 0.88-0.98 & 1.02-1.6 respectively). Regression model had an overall prediction percentage of 85.6%, with MDROs and duration of device use having an odds ratio for mortality of 3.98 & 1.927 respectively (Table 5).

DISCUSSION

In the current study, we analyzed the incidence and characteristics of HAIs in COVID-19 patients across multiple hospitals. A total of 474 HAIs were reported, with an overall rate of 3.43/1000 patients' days and 4.9% of 100-patient at risk. Our findings align with previous studies showing comparable rates of HAIs in COVID-19 patients (5.3, 6.9 and 7.3 / 100 patients at risk).^{7,8,9}

Table 4: The Distribution of the causative pathogens of HAIs among COVID-19 patients in the studied hospitals (July – Dec 2020).

	BSI		PNEU		UTI		Others		Total	
	N=406		N=86		N=81		N=21		N=594	
	N	%	N	%	N	%	N	%	N	%
<i>Klebsiella pneumoniae</i>	132	33%	47	55%	42	52%	4	19%	225	38%
<i>Acinetobacter baumannii</i>	58	14%	13	15%	8	10%	4	19%	83	14%
<i>Pseudomonas aeruginosa</i>	27	7%	13	15%	8	10%	2	10%	50	8%
<i>Candida species</i>	48	12%							48	8%
<i>Candida auris</i>	37	9%							37	6%
<i>Enterococcus faecalis</i>	28	7%			3	4%			31	5%
<i>Stenotrophomonas maltophilia</i>	19	5%	8	9%					27	5%
<i>Enterococcus faecium</i>	16	4%							16	3%
<i>Escherichia coli</i>	2		1	1%	11	14%			14	2%
<i>Serratia marcescens</i>	7	2%	1	1%	3	4%			11	2%
Other pathogens	9	2%							9	2%
<i>Clostridium Difficile</i>							9	43%	9	2%
<i>Proteus mirabilis</i>	3	1%	1	1%	3	4%			7	1%
<i>Enterobacter cloacae</i>	6	1%			1	1%			7	1%
<i>Staphylococcus Aureus</i>	6	1%	1	1%					7	1%
<i>Staph. coagulase-negative</i>	3	1%					1	5%	4	1%
<i>Morganella morganii</i>	1		1	1%			1	5%	3	1%
<i>Bukholderia cepacia</i>	2								2	
<i>Enterobacter aerogenes</i>	1								1	
<i>Klebsiella oxytoca</i>					1	1%			1	
<i>Providencia stuartii</i>					1	1%			1	
<i>Achromobacter dentrificans</i>	1								1	

Factors contributing to these variations include population types, sample sizes, hospital settings, infection control measures, and clinical management. COVID-19 status itself was associated with an increased risk of HAIs,¹⁰ possibly due to factors like PPE shortages, changes in infection prevention practices, prolonged hospitalization, and staffing issues.¹¹

Our research found that BSI was the most common HAIs, with an overall rate of 2.2 per 1000 patient days. The ICU had a significantly higher BSI rate compared to wards, 9.7 vs. 0.25. Factors such as decreased central line denominators and change in nursing practices may contribute to increased infection rates.¹² COVID-19 has also impacted CLABSI rates, with higher rates in the ICU.¹³ Ventilator-associated pneumonia rates and ventilator utilization ratio were higher in

ICU compared to wards.¹⁴ These findings suggest that COVID-19 patients, especially in the ICU, are at a higher risk for developing HAIs.¹⁵ Likely due to patient-specific and process related issues.¹³ The worsening respiratory conditions in some COVID-19 patients led to an increase in hospitalizations and ventilation, raising the risk of ventilator-associated pneumonia (VAP).¹⁵ Studies show that acute respiratory distress syndrome during COVID-19 surges caused VAP.¹⁶ Our study demonstrated that hospital stay length contribute to occurrence of HAIs.^{17,18} Additionally, the use of invasive medical devices is a significant factor contributing to the occurrence of HAIs.¹⁹ Similar study found that the use of central lines, mechanical ventilation, and intubation are important risk factors for developing HAIs.²⁰

Table 5: Multivariate logistic regression analysis illustrating the predictors of CLABSI among COVID-19 patients

Independent variables	OR	95% C.I.		P-value
		Lower	Upper	
Gender: (ref: male)	1.624	0.682	3.869	0.273
Age	1.026	0.992	1.062	0.136
CLABSI	0.961	0.334	2.762	0.941
MDRO	3.981	1.644	9.640	0.002*
Duration of device use	1.927	1.877	2.979	0.007*
Average length of stay	0.982	.914	1.056	0.624
Duration from admission till onset of infection	1.086	1.021	1.156	0.009*

OR: Odds Ratio, CI: Confidence Interval. $R^2=0.308$

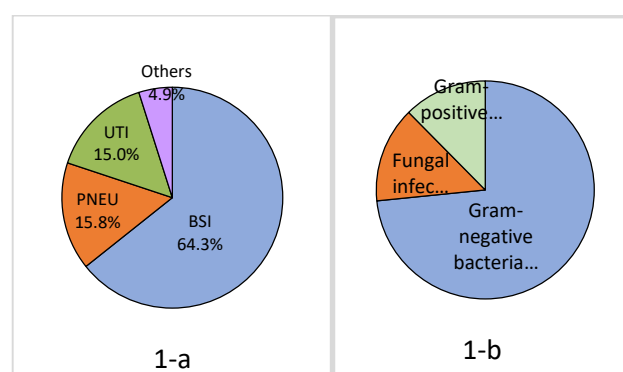


Figure (1-a): The distribution of causative pathogens of the healthcare associated infections among COVID-19 patients. Figure (1-b): The distribution of healthcare associated infections among COVID-19 patients

It is crucial to focus on both the preliminary insertion and continuous maintenance of these devices. A comprehensive and adjustable strategy is needed to successfully reduce the risk of HAIs linked with invasive medical devices in healthcare settings.¹⁹

Gram-negative bacilli (GNB) accounted for 73.4% of infections, followed by fungal infections at 14.2%; and Gram-positive bacteria at 12.4%. *Klebsiella pneumoniae* was the commonest pathogen isolated from BSI, UTI, and pneumonia, followed by *Acinetobacter baumannii* in BSI and pneumonia, and *Escherichia coli* in UTI. *Pseudomonas aeruginosa* was also prevalent in BSI and pneumonia.

²¹ Preventive measures, especially hand hygiene, are crucial in preventing infections during the COVID-19 pandemic. MDROs were common among HAIs, with a notable increase during the pandemic.²³ Fungal coinfections, particularly *C. auris*, were significant, and it represent 43.5% of fungal coinfections in BSI.

These findings are equivalent to other research's results.²² *Candida* is now implicated in the acute and chronic immunopathology of COVID-19, with an increasing incidence due to excessive inflammation caused during severe COVID-19, which can persist after infection.²³ The most concerning issue is the rising incidence of multi-drug-resistant *C. auris* infections among COVID-19 patients globally, leading to serious outcomes. Therefore, infection prevention and control measures, such as strict isolation of *C. auris* carriers and regular screening of non-affected patients, are recommended to prevent the spread of *C. auris*.²⁴ A significant proportion (61.9%) of HAIs in our study were caused by MDROs, consistent with other studies reporting an increase in MDRO infections during the COVID-19 pandemic.^{13,20} A recent systematic review and meta-analysis also found a rise in MDRO-GNB prevalence in hospitals during the pandemic, likely due to the extensive use of antimicrobials, especially early in the pandemic, when the clinical course of COVID-19 was unclear.⁷

In logistic regression analysis, MDROs and the duration from admission to the onset of coinfection were significant predictors of patient's mortality. This finding aligns with previous studies.²⁵ A high proportion of patients (66.9%) died during hospital admission with a 30-day mortality rate of 52.1%. Older age was a significant characteristic, consistent with other studies that identified age as a key predictor of death in COVID-19 patients.^{26,27} Aging, is associated with immune dysfunction, leading to increase morbidity and mortality inpatients.²⁸

Limitations: A retrospective approach did not permit for causal inference. The variable "HAI contribution to death" was not answered in few files and we

couldn't retrieve this information. So, the authors considered it as "not contributed to death" which might underestimate the impact of the HAI on the patients' outcome.

CONCLUSIONS

The study highlights the increase in HAIs during the COVID-19 pandemic, particularly in ICUs. The logistic regression analysis identified MDROs, duration of device usage and time from admission to infection onset as significant predictors of mortality in patients with BSI. These findings underscore the importance of strictly implementing appropriate infection prevention practices and antimicrobial stewardship programs to reduce mortality and negative outcomes in COVID-19 patients.

List of abbreviations: HAI, Healthcare Associated Infection; UTI, Urinary tract infection; CAUTI, Catheter associated Urinary tract infection; BSI, Blood Stream Infection; CLABSI, Central Line Associated Blood Stream Infection; VAP, Ventilator Associated Pneumonia; CDI, Clostridium Difficile Infection; SSI, Surgical Site Infection; CONJ, Conjunctivitis; MDRO, Multidrug-resistant Organism; C. auris, Candida auris; GNB, Gram—negative bacilli; WHO, World Health Organization; ICU, Intensive Care Unit.

Ethical Consideration

The study was reviewed and approved by the ethical committee of the Ministry of Health, Kuwait (approval number 1675/ 2021).

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Conflict of Interest

All authors have no known competing financial or personal conflicts that could impact the work described in this manuscript.

Authors contributions

Samar S. Morsi: literature search, and writing; Kholoud Alfadahla: literature search, and revision; Wafaa S. Hamza: Idea, analysis, literature search, writing and critical review.

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