1 **Risk of central line-associated bloodstream infections (CLABSIs) during COVID-19 pandemic in**
2 **intensive care patients in a tertiary care center in Saudi Arabia**

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Abstract:

This retrospective study compared central line–associated bloodstream infection (CLABSI) rates per 1000 central line days, and overall mortality before and during the COVID-19 pandemic in adult, pediatric, and neonatal ICU patients at King Abdul-Aziz Medical City-Riyadh who had a central line and were diagnosed with CLABSI according to the NHSN standard definition. The study spanned between January 2018 and December 2019 (pre-pandemic), and January 2020 and December 2021 (pandemic). SARS-CoV-2 was confirmed by positive RT-PCR testing. The study included 156 CLABSI events and 46,406 central line days; 52 and 22,447 (respectively) in pre-pandemic, and 104 and 23,959 (respectively) during the pandemic. CLABSI rates increased by 2.02 per 1,000 central line days during the pandemic period (from 2.32 to 4.34, $p < 0.001$). Likewise, overall mortality rates increased by 0.86 per 1000 patient-days (from 0.93 to 1.79, $p=0.003$). Both CLABSI rates (6.18 versus 3.7, $p=0.006$) and overall mortality (2.72 versus 1.47, $p=0.014$) were higher among COVID-19 patients compared to non-COVID-19 patients. The pandemic was associated with a substantial increase in CLABSI-associated morbidity and mortality.

Keywords:

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Introduction:

Health care-associated infections (HAIs) are a significant concern in healthcare settings globally [1,2]. While there are many guidelines for preventing HAIs, the impact of the COVID-19 pandemic on infection control practices has been challenging, placing a huge burden on healthcare systems to maintain surveillance activities considering the increases in critical care capacity and the surge of COVID-19 cases in intensive care units (ICU) with corresponding prolonged hospital stays [3]

A growing body of evidence has indicated that the pandemic led to an increase in the rates of several HAIs, particularly central line–associated bloodstream infections (CLABSI), catheter-associated urinary tract infections, ventilator-associated adverse events, and methicillin-resistant *Staphylococcus aureus* bacteraemia [4-6]. Several potential factors have been identified as contributors to this increased risk due to extended hospitalization periods, increased disease severity, and longer durations of indwelling device use [5].

According to the National Healthcare Safety Network (NHSN), monthly CLABSI rates increased on average from 0.40 before COVID-19 to 1.7 during the pandemic, while other reports indicated that the CLABSI rates increased by 71% (0.68 to 1.16 per 1,000-line days) in ICU patients [5-7]. However, other studies did not find a significant impact of the pandemic on CLABSI rates [8], suggesting that the enhanced infection prevention controls implemented in response to COVID-19 were associated with local reductions in HAIs. Adding to this, few studies have examined the rate of CLABSI among COVID-19 positive and negative patients during the same period of hospitalization. The objectives of the current study were to assess the incidence rates of CLABSI among patients admitted to different types of ICU before, and during, the pandemic, and to compare the CLABSI trends between patients with and without a diagnosis of COVID-19.

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Methods:

<u>Study Design</u>

A retrospective surveillance study was carried out in two phases between January 2018 and December 2021, before the start of the pandemic (pre-pandemic period January 2018- December 2019), and during the pandemic period January 2020- December 2021). The study was approved by the IRB committee at King Abdullah International Medical Research Center (KAIMRC), protocol number SP21R-236-05.

<u>Setting</u>

The study was conducted at different ICUs of King Abdulaziz Medical City (KAMC), which is a tertiary care center located in Riyadh, Saudi Arabia with approximately 1100-beds of which 185 are dedicated for intensive care [9] including adult, pediatric, and neonatal units. KAMC provides healthcare services for about 1,000,000 Saudi National Guard soldiers, employees and their families.

<u>Population</u>

All patients admitted to the ICU with a central line and diagnosed as CLABSI according to NHSN criteria were included. ICU patients without a central line and those admitted to wards were excluded.

<u>Sample size and sampling</u>

 It was estimated that at least 15,000 central line days of follow up was required to detect a CLABSI rate of 2.70 per 1,000-line days during COVID-19 with a 95% confidence interval (CI) of 1.35 per 1000 central line days.

<u>Surveillance methodology</u>

The surveillance methodology of NHSN [10] and the Gulf Cooperation Council Center for Infection Control [11] were used. CLABSI was defined as patients with a positive blood culture, with or without symptoms

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80   who had a central line for two or more days. Central lines were either inserted at the ICU of stay or at

81   other locations, such as interventional radiology and to a lesser extent, in the emergency department, or

82   in surgical rooms. Lines were inserted by physicians of insertion units, with no special vascular access

83   team. The diagnosis of CLABSI events was made by Infection Control staff, who also monitored adherence

84   of practice with insertion and maintenance of lines, as per the standards of NHSN [10]. Three laboratory

85   confirmed bloodstream infection (LCBI) criteria were recognized as per standard definitions [10,11].

86   Outcomes

87   The outcomes studied were the CLABSI rates per 1000 central line days, central line utilization, CLABSI

88   case fatality, and average ICU and hospital stay during the study period. For the pandemic phase, we

89   identified patients with confirmed COVID-19 infection from the study population based on a positive

90   SARS-CoV-2 Reverse transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal swab as

91   guided by the Saudi Centers for Disease Control and Prevention guidelines.

92   Data Collection

93   Data were extracted from the surveillance data collected by the Infection Prevention and Control (IPC)

94   department at KAMC, in addition to electronic medical files using a standardized form. The collected data

95   comprised demographic information, type and location of ICU, admission comorbidities and ventilator

96   use, length of stay in ICU, and central line information. The latter included data on number and type of

97   central lines, their site of insertion and lumen of the line. Additionally, data on blood steam infection

98   (BSI), CLABSI diagnostic types, and microbiological yest results.

99   Data Analysis

100   Categorical variables were presented as frequencies and percentages, and continuous variables as means

101   and standard deviations (SD). CLABSI rates were expressed per 1000 central line days. The clinical

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102   characteristics of the patients with CLABSI between the pre- and pandemic periods were compared using

103   Chi-square or Fisher exact test as appropriate while CLABSI rates were compared between the two periods

104   using the Z-test for event-time data. A p-value <0.05 was considered as significant and all P-values were

105   two-tailed. SPSS (Version 25.0. Armonk, NY: IBM Corp) was used for all statistical analyses.

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Results:

108   In total, 156 CLABSI events and 46,406 central line days were recorded; 52 and 22,447 (respectively) in

109   the pre-pandemic period, and 104 and 23,959 (respectively) during the pandemic. The average age of all

110   patients was 50 years (SD 28.5) with 51% females. The great majority (81%) of all patients were from adult

111   ICUs, and mainly from the medical-surgical ICU (26%) (Table 1). One-third of the total study population

112   had confirmed COVID-19 infection, and 50% had one or two comorbidities. The rate of death during

113   hospitalization was 59.6%; and 69.1% of these had a clinically significant BSI. Patients in the pandemic

114   period were older (mean age 57±25.1 vs. 36.9±30.2 in the pre-pandemic), had more use of mechanical

115   ventilation (82.5% vs. 53.2%), and were diabetic (50% vs. 25%).

116   CLABSI rates increased by 2.02 per 1,000 central line days during the pandemic (from 2.32 to 4.34, p <

117   0.001). (Table 2) but line utilization decreased in the same period compared with pre-pandemic (0.67 vs.

118   0.72 (p <0.001). Figure 1 illustrates CLABSI rates per 1000 central line days during both study periods

119   whereby at end of 2021 the rate was 3.7 per 1000 central line days, compared with 2.4 at end of 2019.

120   Likewise, central line utilization also declined during the pandemic period (Figure 2). The CLABSI case

121   fatality was almost zero in the third quarter of the year 2019 but significantly increased during the

122   pandemic period (Figure 3). This was consistent with an increase in overall mortality of 0.86 per 1000

123   patient-days (from 0.93 to 1.79, p =0.003) (Table 2, Figure 4). The average hospital stay was significantly

124   lower in the pandemic phase (73.5 ± 124.7) than in the pre-pandemic phase (136.4 ± 230.1) (p =0.002).

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125   Regarding CLABSI related characteristics before and during COVID-19 pandemic, there was no difference

126   in the type, site, and number of central line insertions between the two periods (Supplementary Table).

127   For the identified pathogens, *Candida* spp. was significantly higher in the pandemic period (26% vs. 12%

128   p=0.043). CLABSI related outcomes during the pandemic were assessed with the total central line days

129   reaching 20,777. A comparison of CLABSI rates and other related outcomes by COVID-19 status is shown

130   in Table 3. Both CLABSI rates (6.18 versus 3.7, p=0.006) and overall mortality (2.72 versus 1.47, p=0.014),

131   were higher among COVID-19 patients during the pandemic compared with non-COVID-19 patients.

Discussion:

133   This study assessed the impact of the COVID-19 pandemic on the CLABSI surveillance rates. The key finding

134   was that CLABSI rates increased by 2.02 per 1,000 central line days during the pandemic period.

135   Additionally, both CLABSI and overall mortality rates were higher among COVID-19 positive patients. Our

136   findings are consistent with a national study which examined the impact of COVID-19 on CLABSI among

137   78 Ministry of Health hospitals in Saudi Arabia [12] and reported an approximately 16% increase of CLABSI

138   in 2020-2021 compared with the 2019 rates. This was also consistent with other international studies

139   whether examined as multihospital systems or single center studies [4,13-15].

140   There has been increased focus on the impact of the COVID-19 pandemic on HAIs. Previous reports had

141   strongly recommended prioritization of surveillance of HAIs with allocated resources accordingly. Ongoing

142   surveillance and monitoring of HAI rates remain of importance to quantify and assess the impact of

143   pandemics on HAIs [16]. The literature on this topic sheds light on several key factors which contribute to

144   such an increase. One factor is the disturbance in infection control practice due to a pandemic in which

145   availability of adequately trained staff and diversion of resources present a significant challenge to

146   healthcare systems, particularly in acute hospital units, in order to maintain efficient surveillance activities

147   [2,17]. This may lead to a decline in adherence to strict infection control practices including proper central

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148   line insertion and maintenance techniques. Other factors that have been noted by others indicate that

149   prolonged ICU stays for severe COVID-19 cases increase the risk of CLABSI development [4,18,19].

150   Moreover, wider utilization of immunosuppressive agents and antibiotics increase the risk of infection

151   [3,12].

152   Regarding the types of central line infection, no significant change in the distribution of the pathogens

153   was observed. For example, Gram-negative bacteria such as Klebsiella and Pseudomonas were more

154   common than Gram-positive bacteria. Similarly, previous studies done in Saudi Arabia showed that Gram-

155   negative bacteria were the major bacteria causing several HAIs including CLABSI [21,22]. This may be

156   related to poor environmental cleaning and hand hygiene compliance [21,22]. However, *Candida* spp. in

157   particular, increased by a notable 13.6% in the pandemic period. This finding correlates with a USA study

158   which documented around a 66% increase in these organisms associated with CLABSI. This increase can

159   be attributed to the long-term use of central venous catheters and broad-spectrum antimicrobials [23].

160   Furthermore, the use of tocilizumab, an immunosuppressive drug, in patients with COVID-19 may increase

161   the risk of candidemia. It is noteworthy that a systematic review found that secondary infections were

162   slightly higher in patients receiving tocilizumab compared with those receiving standard care, but the

163   finding did reach statistical significance [24]

164   Our study has some limitations; first, the data were collected from a single center and cannot be directly

165   extrapolated to other healthcare centers around the country. Nevertheless, our findings are consistent

166   with recent national data. Second, the study design limits directly inferring a causal relationship. Third,

167   the major disruption of hospital functions during the pandemic period and the consequent negative

168   impact on management and maintenance of catheters may have confound the findings. Lastly, as it was

169   based on surveillance data, some specific CLABSI risk factors were unavailable.

170   In conclusion, the COVID-19 pandemic was associated with a substantial increase in CLABSI-

171   associated morbidity and mortality which was likely due to the clinical complexity of hospitalized patients

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172   during the period. Patients with COVID-19 were at higher risk of CLABSI-associated morbidity and

173   mortality. As most CLABSI cases are possibly preventable with proper aseptic techniques, adequate

174   training, and surveillance, maintaining such activities during a pandemic is even more critical to reduce

175   the burden of HAIs.

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Figure Legends:

Figure 1: CLABSI rate per 1000 central line days by quarter and year
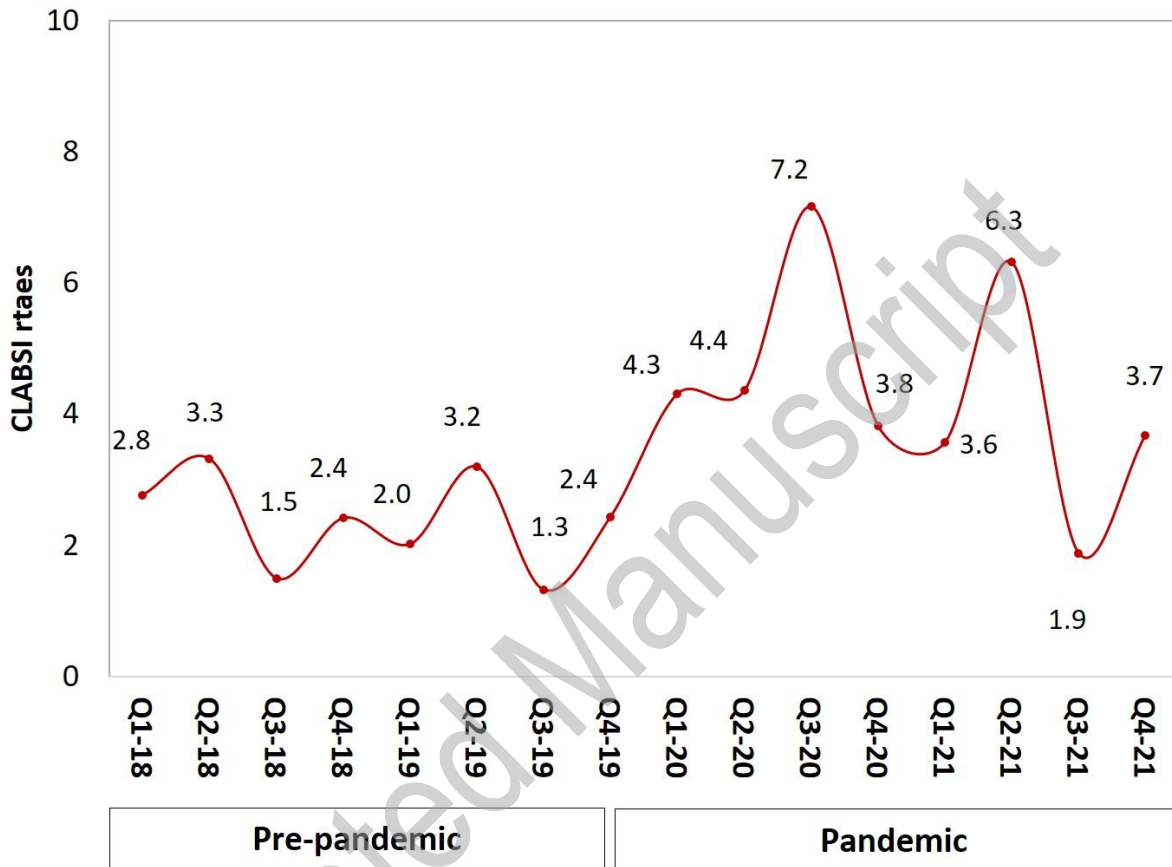
Figure 2: Central line utilization by quarter and year
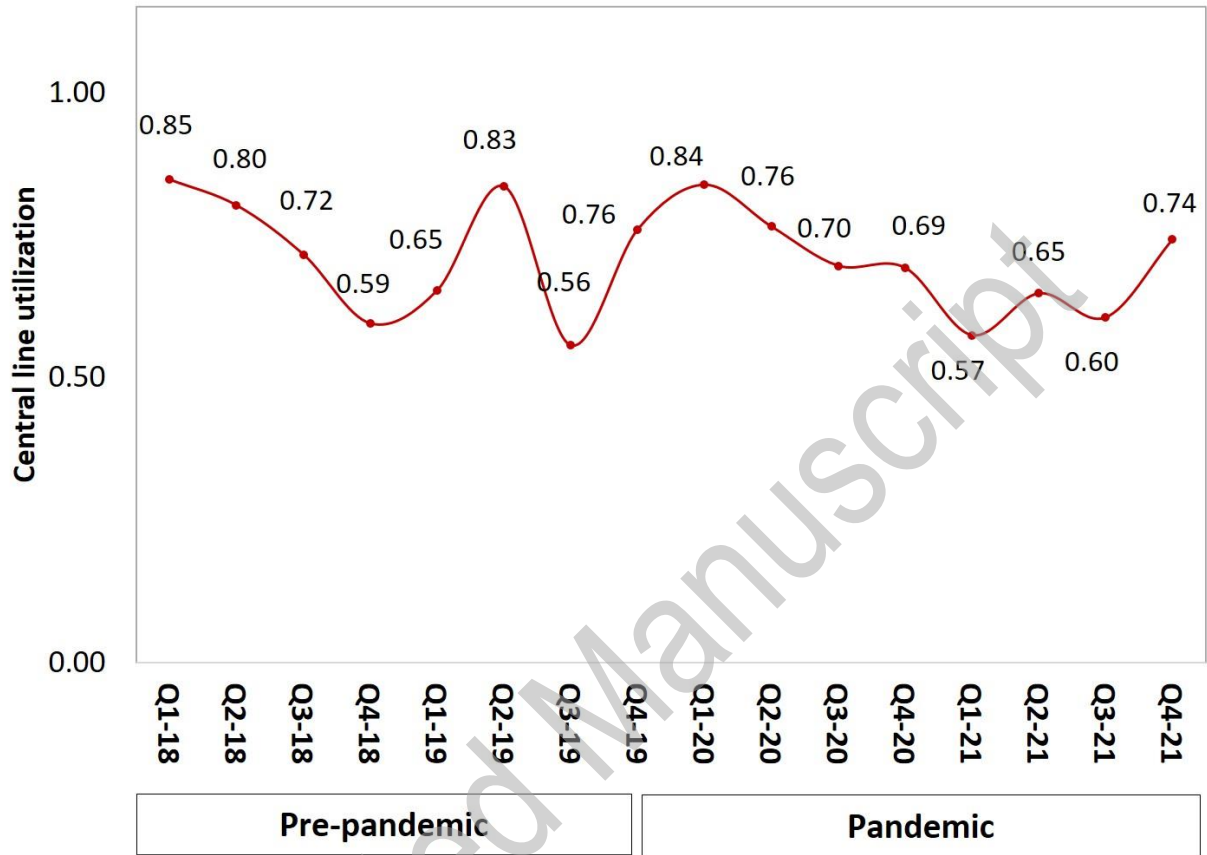
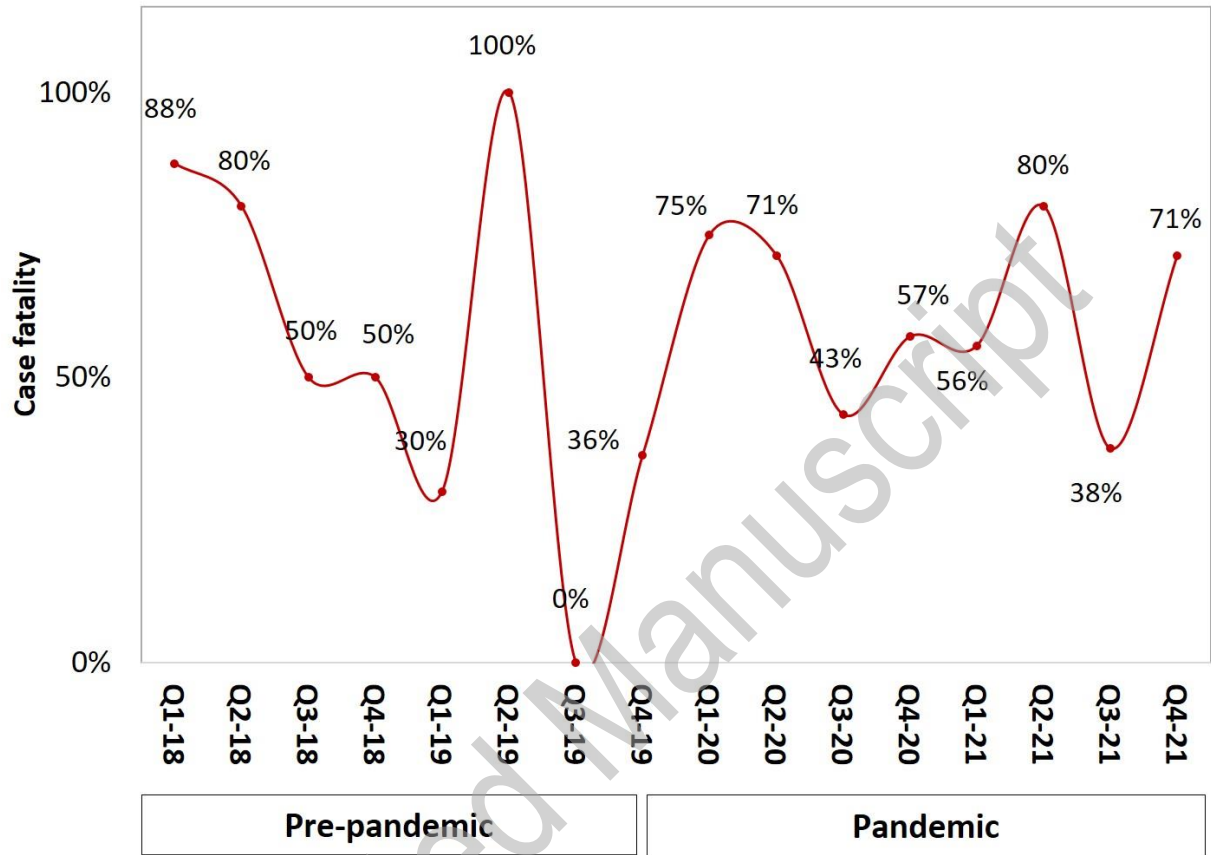Figure 3: CLABSI case fatality by quarter and year

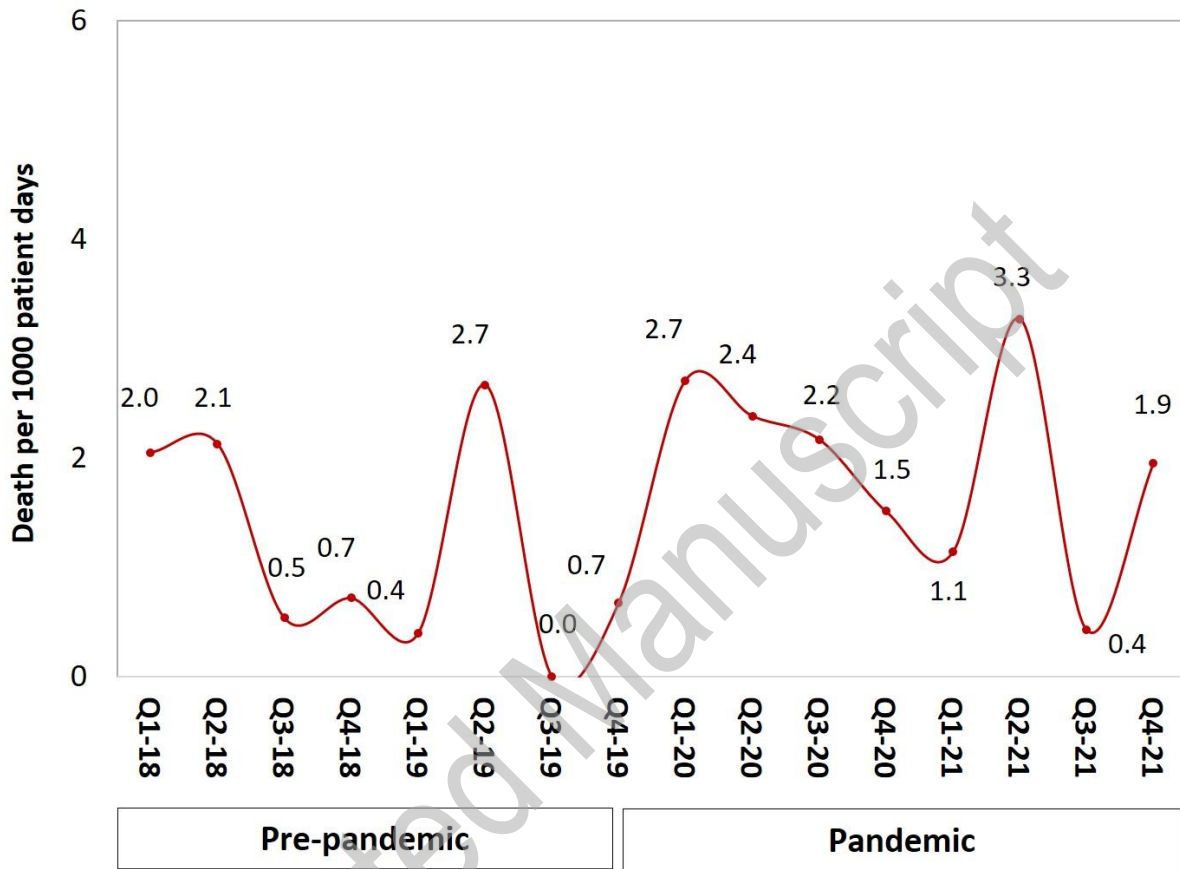Figure 4: Overall mortality by quarter and year

Table 1: Demographic and clinical characteristics of the patients with CLABSI before and during COVID-19 pandemic

	Pre-pandemic	Pandemic	Total	p-value
Age	36.9±30.2	57.2±25.1	50.4±28.5	<0.001
Gender				
Male	24 (46.2%)	51 (49.0%)	75 (48.1%)	0.734
Female	28 (53.8%)	53 (51.0%)	81 (51.9%)	
Facility				
KASCH	23 (44.2%)	33 (31.7%)	56 (35.9%)	0.125
NGHA-Riyadh	29 (55.8%)	71 (68.3%)	100 (64.1%)	
Location				
Adult ICU	35 (67.3%)	92 (88.5%)	127 (81.4%)	0.001
Pediatric ICU	16 (30.8%)	8 (7.7%)	24 (15.4%)	
Neonatal ICU	1 (1.9%)	4 (3.8%)	5 (3.2%)	
Unit				
Adult medical-surgical ICU	15 (28.8%)	27 (26.0%)	42 (26.9%)	0.003
Cardiovascular ICU-Pediatric	8 (15.4%)	2 (1.9%)	10 (6.4%)	
General ICU	4 (7.7%)	8 (7.7%)	12 (7.7%)	
Medical ICU	6 (11.5%)	23 (22.1%)	29 (18.6%)	
Neonatal ICU	1 (1.9%)	4 (3.8%)	5 (3.2%)	
Pediatric ICU	8 (15.4%)	6 (5.8%)	14 (9.0%)	
Respiratory ICU	0 (0.0%)	12 (11.5%)	12 (7.7%)	
Trauma ICU	5 (9.6%)	9 (8.7%)	14 (9.0%)	
Others	5 (9.6%)	13 (12.5%)	18 (11.5%)	
Hospitalization death				
No	23 (44.2%)	40 (38.5%)	63 (40.4%)	0.489
Yes	29 (55.8%)	64 (61.5%)	93 (59.6%)	
BSI contributed to death				

No	6 (37.5%)	15 (28.8%)	21 (30.9%)	0.546
Yes	10 (62.5%)	37 (71.2%)	47 (69.1%)	
COVID infection				
No	47 (100.0%)	49 (50.5%)	96 (66.7%)	<0.001
Yes	0 (0.0%)	48 (49.5%)	48 (33.3%)	
Ventilator use				
No	22 (46.8%)	17 (17.5%)	39 (27.1%)	<0.001
Yes	25 (53.2%)	80 (82.5%)	105 (72.9%)	
Number of comorbidities				
None	7 (13.5%)	21 (20.2%)	28 (17.9%)	0.155
One or two	32 (61.5%)	47 (45.2%)	79 (50.6%)	
Three or more	13 (25.0%)	36 (34.6%)	49 (31.4%)	
Types of comorbidities				
Cardiovascular diseases	34 (65.4%)	64 (61.5%)	98 (62.8%)	0.639
Diabetes Mellitus	13 (25.0%)	52 (50.0%)	65 (41.7%)	0.003
Chronic pulmonary diseases	13 (25.0%)	20 (19.2%)	33 (21.2%)	0.406
Malignant diseases	9 (17.3%)	17 (16.3%)	26 (16.7%)	0.879
Chronic kidney disease	9 (17.3%)	18 (17.3%)	27 (17.3%)	>0.99
Chronic liver diseases	10 (19.2%)	8 (7.7%)	18 (11.5%)	0.033

Table 2: CLABSI rates and other related outcomes before and during COVID-19 pandemic

	Pre-pandemic	Pandemic	Total	p-value
Events:				
Number of CLABSI events	52	104	156	---
Number of death events	29	64	93	---
Denominators:				
Central line days	22447	23959	46406	---
Patient days	31253	35815	67068	---
Outcomes:				
CLABSI rate per 1000 central line days	2.32	4.34	3.36	<0.001
Central line utilization	0.72	0.67	0.69	<0.001
CLABSI case fatality	55.8%	61.5%	59.6%	0.489
Mortality per 1000 patient days	0.93	1.79	1.39	0.003
Average ICU stay (days)	41.9±43.7	47.0±101.9	45.2±86.3	0.471
Average hospital stays (days)	136.4±230.1	73.5±124.7	95.5±171.0	0.002
Average central line days (days)	24.7±25.8	20.4±27.8	21.9±27.1	0.169

Table 3: CLABSI rates and other related outcomes by COVID-19 status during the pandemic

	No COVID	COVID	Total	p-value
Events:				
Number of CLABSI events	49	48	97	---
Number of death events	29	34	63	---
Denominators:				
Central line days	13005	7772	20777	---
Patient days	19713	12507	32220	---
Outcomes:				
CLABSI rate per 1000 central line days	3.77	6.18	4.67	0.006
Central line utilization	0.66	0.62	0.64	<0.001
CLABSI case fatality	59.2%	70.8%	64.9%	0.230
Mortality per 1000 patient days	1.47	2.72	1.96	0.014
Average ICU stay (days)	58.0±129.9	36.2±64.7	47.2±103.0	0.968
Average hospital stay (days)	89.2±159.4	54.5±74.5	71.6±124.6	0.259
Average central line days (days)	21.6±29.9	18.7±26.7	19.9±27.9	0.859