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Epidemiology, antimicrobial resistance profile and management of carbapenem-resistant *Klebsiella pneumoniae* among mothers with suspected sepsis in Ethiopia

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Abstract

Background Early detection and proper management of maternal sepsis caused by carbapenem-resistant *Klebsiella pneumoniae (CRKP)* can significantly reduce severe complications and maternal mortality. This study aimed to describe the epidemiology, antimicrobial resistance profile, and management of carbapenem-resistant *K. pneumoniae* among sepsis-suspected maternal cases in Ethiopia.

Methods A prospective cross-sectional study was conducted in five tertiary hospitals from June 2021 to December 2023. Isolation, identification, and antimicrobial susceptibility testing of the isolates were carried out following standard microbiological procedures as stated in the CLSI guidelines. Data on socio-demographics, risk factors, and management strategies were collected with structured questionnaires. Associations between variables were determined using logistic regression analysis in STATA-21. A *p*-value of less than 0.05 was statistically significant.

Results Of the 5613 total women suspected of having maternal sepsis, 609 (10.8%) of them were infected with *K. pneumoniae*. The prevalence rates of MDR, XDR, and PDR *K. pneumoniae* strains were 93.9%, 24.3%, and 10.9%, respectively. The resistance rates for the last-resort antibiotics; amikacin, tigecycline, carbapenem, and third-generation cephalosporin were 16.4%, 29.1%, 31.9%, and 93.0%, respectively. The combination of carbapenem with tigecycline or amikacin therapy was used to manage maternal sepsis caused by cephalosporin-and carbapenem-resistant strains. Sepsis associated risk factors, including septic abortion [AOR = 5.3; 95%*CI*:2.2–14.4]; extended hospitalization [AOR = 3.7; 95%*CI*: 1.6–19.4]; dilatation and curettage [AOR = 2.2; 95%*CI*:1.3–13.4]; cesarean wound infection [AOR = 4.1; 95%*CI*:2.0–9.2]; indwelling catheterization [AOR = 2.1;95%*CI*: 1.4–6.2]; ICU admission [AOR = 4.3; 95%*CI*:2.4–11.2]; post abortion [AOR = 9.8; 95%*CI*:5.7–16.3], and recurrent UTI [AOR = 3.3; 95%*CI*: 1.6–13.2] were significantly associated with maternal sepsis caused by *K. pneumoniae*.

Conclusions The prevalence of maternal sepsis caused by carbapenem- resistant *K. pneumoniae* is high and serious attention needs to be given to combat transmission. Therefore, improving awareness, early diagnosis, IPC, integrated

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maternal surveillance, improved sanitation and efficient antimicrobial stewardship are crucial to combating bacterial maternal sepsis.

Keywords Antimicrobial resistance, Maternal sepsis, *Klebsiella pneumoniae*, Pan-drug resistant, Extreme drug-resistance

Background

During pregnancy, the body undergoes significant changes in the immune system and metabolism [1], which can increase the risk of bacterial infections, including bacterial sepsis [2]. Globally, there are approximately 48.9 million cases of maternal sepsis each year, 17 million of which are reported in Africa [3]. Annually, 5.7 million women develop severe sepsis during pregnancy, childbirth, postabortion, or the postpartum period. According to the WHO, the number of deaths from sepsis is greater in Sub-Saharan Africa and southern Asia, accounting for 253,000 (87%) maternal sepsis-related deaths [4]. Identifying and diagnosing maternal sepsis early can be difficult, as maternal sepsis is often similar to other serious obstetric conditions, according to previous studies [4, 5]. Thus, most sepsis-infected mothers experience severe morbidity when they arrive at health facilities [6]. Maternal sepsis is responsible for 11% of maternal mortality. On the other hand, mothers can also contract sepsis through bacterial contamination at health facilities. Up to 50% of sepsis survivors may experience lasting disabilities, including myopathy, neuropathy, chronic pelvic pain, infertility, and psychological distress [7, 8].

Emerging *carbapenemase-* and *extended-spectrum β-lactamase producing K. pneumoniae (ESBL-Kp)* threaten maternal and neonatal health despite progress in the treatment and management of bacterial sepsis [9, 10]. These strains can survive in various environments, such as water, soil, and the gastrointestinal tract [9–11]. Its ubiquitous nature leads to spontaneous mutations and acquired antimicrobial resistance genes that undergo gene transfer by mobile genetic elements (MGEs). Once they acquire resistance genes, they can transfer them horizontally and vertically within and between species [9–12]. This bacterium has acquired antimicrobial resistance genes (ARGs) (*blaLAP-2*, *blaTEM-1B*, and *blaSHV-106*) from the ecosystem [13], and the primary source genes *blaKPC-2*, *NDM-1*, and *KPC-2* [14, 15]. As a result, they were shown to be non-susceptible to carbapenem, colistin, carbapenem, polymyxin, fluoroquinolone, aminopenicillin, third-generation cephalosporin, and tigecycline [13–18]. *Klebsiella pneumoniae* is estimated to cause 124,000 deaths annually, accounting for 20% of AMR-related fatalities and 18% of AMR-related deaths, resulting in healthcare costs of $9 billion per year [2, 18, 19].

Currently, MDR (multidrug resistant), XDR (extensively drug-resistant), and PDR (pan-drug resistant) *K. pneumoniae* strains are known to possess antimicrobial resistance genes (*blaKPC*, *blaCTX*, *blaTEM*, *blaOXA*, and *blaSHV).* Additionally, they also harbor virulence genes such as enterobactin, aerobactin, yersiniabactin, and other genes (*irp1*, *fyuA*, *iutA*, *ST29*, *PAI*, *ehxA*, *toxB*, *eae*, *sfa*, *pai*, *fim H*, *aggR*, *hly*, *pap*, *hyl A*, *tra*, *Tpai*, *cnf-1*, *afa*, *and rmpA/A*). These genes are fundamental for the development and spread of hypervirulent carbapenem resistant strains [13–15, 20–22]. Infections caused by this superbug, such as urinary tract infections, skin infections, respiratory tract infections, sepsis, meningitis, and pyogenic liver abscesses become major health problems in pregnant women, immunecompromised patients, and elderly adults [20, 22]. This bacterium possesses various virulence factors namely capsules, adhesions, fimbriae, type II secretion systems, siderophores, lipopolysaccharides, and biofilms that activate cellular immune responses mainly macrophages [15, 18, 23, 24]. In the absence of proper antibiotic treatment, hyperactivated macrophages have the potential to release large amounts of proinflammatory cytokines and interleukins, leading to sepsis which adversely affects maternal and fetal health [25, 26].

Maternal sepsis can be worsened by various factors such as socioeconomic status, stress, lack of education, poverty, poor sanitation, family responsibilities, limited financial resources, and an unhealthy diet [27, 28]. Many studies have shown that various contributing factors include a medical history of chronic diseases such as gestational hypertension, diabetes, cancer, hospitalization, ventilator use, catheterization, kidney or lung disease, preeclampsia, abortion, and a history of antibiotic use during gestation [29]. Habits, such as smoking, alcoholism, and drug abuse, can also play a role in the development of these bacterial infections [30]. Educational level and intravenous drug administration can also be contributing factors [28, 30]. In developing countries, most cases of maternal sepsis are treated with a combination of two or more antibiotics such as cephalosporins, carbapenems, aminoglycosides, and polymyxins [31–33]. If these antimicrobial agents fail, the recommended treatment for maternal sepsis is tigecycline combination therapy with avibactam/ceftazidime, or meropenem caused by MDR-/XDR-/PDR-*K. pneumoniae* [34–37].

The effectiveness of antibiotics for treating maternal sepsis in *carbapenem-/* third generation cephalosporin-resistant *K. pneumoniae* strains has been compromised [35, 38]. Recent studies indicate that Klebsiella is

responsible for 65.7% of antibiotic-resistant bacteria that cause healthcare-associated infections [39, 40]. Among these bacteria, half are *ESBL*-producing *K. pneumoniae* isolates. The primary source of these infections was multiple sites, for a prevalence rate of 76.8%. MDR *K. pneumoniae* was the most common type of bloodstream infection, with a prevalence rate of 62.9%. The rate of MDR infections was greater for hospital-acquired infections (72.1%) than for hospital- or community-acquired infections [19, 27, 33, 37, 41].

Despite efforts to reduce maternal mortality and IPC and AMS programs at health facilities, maternal sepsis caused by *K. pneumoniae* remains the leading HAI causing maternal morbidity and mortality [2, 4, 16, 42]. However, the full extent of the impact of maternal sepsis caused by carbapenem-/third-generation cephalosporin-resistant *K. pneumoniae* strains has not been thoroughly established [43–45]. Currently, paying attention to unseen maternal sepsis caused by carbapenem-/cephalosporin-resistant *K. pneumoniae* is highly important for reducing preventable maternal morbidity and mortality [3, 6, 38, 44, 46]. This research will help establish a baseline, measure interventions, and ensure that patients receive the most effective care. We performed a nationwide study to generate evidence-based data and comprehensive information on the burden, risk factors, diagnosis, and treatment of maternal sepsis to develop better strategies to combat carbapenem-resistant strains and improve the quality of maternal care.

Materials and methods

Study area and period

This study was conducted on women who were admitted for maternal sepsis in five tertiary hospitals between June 2021 and December 2023. It covers more than three-quarters of the national geographic areas. Tikur Anbessa Specialized Hospital (TASH) and Comprehensive Specialized Hospital (ALERT) were chosen from central Ethiopia. TASH has a capacity of 1600 beds, and ALERT has a capacity of 850 beds. Hiwot Fana Compressive Specialized Hospital (HFSH) is a specialized university hospital in eastern Ethiopia that is located 526 km from Addis Ababa and has 550 beds. It serves as a referral hospital from the eastern part of the country for three regional governments (Harar, Somalia, and Oromia). Jimma University Medical Center (JUMC) is located 350 km from AA in western Ethiopia and has 834 beds. It serves as a referral hospital for five regional governments (Oromia, the Central Ethiopia Regional State, Gambela, the South Ethiopia Regional State, and the Southwest Ethiopia Peoples' Region), which cater to 20 million people from the western part of the country. Whereas, Hawassa University Specialized Hospital (HUSH) is located 370 km away from AA in the southern part of the country and has over 750 beds. It operates as a referral hospital for three regional governments (Oromia, South Ethiopia Regional State, and South West Ethiopia Peoples' Region), serving a catchment area of more than 25 million people.

Study design

A prospective cross-sectional study was conducted on women who were suspected of having maternal sepsis and admitted to five tertiary hospitals between June 2021 and December 2023. The women were randomly selected from various departments, such as ICUs, emergency rooms, gynecology, surgery, emergence OPD, and obstetric wards.

Source of population and study population

Our study population consisted of all women seeking treatment at five tertiary hospitals during the study period. Moreover, all women suspected of having maternal sepsis and admitted to these hospitals were randomly recruited and followed from the day of admission until the day of discharge from the hospital.

Sampling technique and sample size

During the study period, 5613 women admitted for maternal cases suspected of having bacterial sepsis and meeting the WHO criteria for sepsis were randomly selected from five tertiary hospitals in four clusters of the country. To our knowledge, there are no prior epidemiological data on maternal sepsis caused by this bacterium in multicenter studies. Hence, the sample size was calculated using the single population proportion formula, which assumes a 95% confidence interval, 3% margin of error, P=50%, and 10% non-response rate.

The sample size was calculated as follow: $n = \frac{z_{\frac{\alpha}{2}}^2 * p(1-p)}{d^2}$; then,

$\mathrm{n} = \frac{(1.96)^2 * 0.5(1-O.5)}{([0.03])^2} = 1067$

Non-responden t= 107

One tertiary hospital=1067+107=1174.

Where n=sample size z=confidence level.

d=margin of error p=proportion.

The sample was obtained by multiplying 1174 by five tertiary hospitals (5*(1067+107))=5870) in the four clusters to estimate the prevalence of maternal bacterial sepsis, which is representative of nationwide data. However, 256 mothers suspected of having sepsis were excluded on the basis of national and WHO guidelines [2, 4] and the final sample size was 5613.

Sample collection, transportation and processing

The methods used for collecting, processing, and transporting samples were based on the guidelines provided by the CLSI for identifying Enterobacteriaceae and performing AST. Trained health professionals collected clinical samples such as blood, CSF, urine, wound exudates,

and other samples aseptically from women admitted with maternal cases. Within an hour, the samples were transported to the bacteriology laboratory. The samples were subsequently processed and inoculated on agar plates with 5% sheep blood agar and MacConkey agar and incubated at 35–36 °C for 18–24 h. Biochemical tests were performed to identify *K. pneumoniae.* The identified *K. pneumoniae* isolates were inoculated in nutrient broth for subculture on nutrient agar and incubated aerobically for 18–24 h. AST was subsequently performed according to CLSI guidelines for Enterobacteriaceae [47]. Isolates resistant to carbapenem antibiotics (ertapenem, imipenem, and meropenem) were subsequently subjected to confirmation for *carbapenemase* production. Similarly, those that were resistantto cefotaxime and ceftazidime were subjected to the *ESBL* confirmatory test as per CLSI guidelines. The isolates were stored in 20% glycerol at -80 °C for further investigation for whole genome sequencing (WGS) [47] at the EPHI.

Antimicrobial susceptibility testing

Three to five colons with similar culture morphologies were transferred with a sterile inoculation loop to the nutrient broth until it was matched with a McFarland value of 0.5. The bacterial suspension was then streaked on MHA using a sterile swab to uniformly thicken the lawn of growth following incubation and the antibiotic discs were placed with sterile forceps as described in the disc diffusion method [47]. Following overnight incubation at 37 °C, the inhibitory zone diameters were measured and evaluated according to CLSI guidelines. Amoxicillin/clavulanic acid (20/10μg), gentamicin (10 μg), tobramycin (10 μg), ampicillin-sulbactam (10/10 μg), cefepime (30 μg), cefotaxime (30 μg), cefotetan (30 μg), cefuroxime (30 μg), ertapenem (10 μg), imipenem (10 μg), meropenem (10 μg), amikacin (30 μg), ciprofloxacin (5 μg), ceftriaxone (30 μg), tetracycline (30 μg), ceftazidime (30 μg), piperacillin-tazobactam (100/10 μg), trimethoprim-sulfamethoxazole (1.25/23.75 μg), and cefazolin (30 μg) are some of the Oxoid England products used for this study. Following CLSI guidelines, the quality of the media, biochemical reagents, and antibiotics was assessed using standard strains [47].

Phenotypic characterization

The identification of carbapenem resistance was conducted using the phenotypic-based disc diffusion method with meropenem, ertapenem, and imipenem as the primary approach to detect carbapenemase. The carbapenem-resistant strains were tested using minimum inhibitory concentration breakpoints to confirm their resistance using the carbapenem inactivation method (CIM). The K. pneumoniae isolates underwent testing with 1 antimicrobial 20 panels to identify their resistance patterns. If they showed resistance to cefotaxime, ceftazidime, and cefpodoxime, they were considered to be potential ESBL producers. Confirmatory tests using a double-disc synergy test (DDST) were then carried out according to CLSI guidelines [47].

Data analysis and interpretation

The data were subsequently entered into Epi Data Version 3.1 and exported for analysis using STATA-21. The prevalence of *carbapenemase*-producing and *ESBL*-producing *K. pneumoniae*, antimicrobial susceptibility testing, and risk factor identification were determined using descriptive analysis. Bivariate and multivariate logistic regressions were performed to evaluate associations between variables. A P-value less than 0.05 was considered to statistically significance.

Data quality assurance

Data regarding sociodemographic information, risk factors, and treatment and management were collected using predesigned questionnaires. The investigators at each selected hospital ensured patient data consistency and quality. Likewise, antibiotics, media, and procedures were ensured at preanalytical, analytical, and postanalytical phase qualities as per CLSI guidelines and adhered to national IPC guidelines [47].

Inclusion and exclusion criteria

Inclusion criteria

Maternal sepsis patients aged 15–49 years, 2) patients admitted to selected hospital departments such as ICUs, emergency rooms, gynecological, surgical, EOPD, and obstetric wards with infections-related maternal cases, 3) Patients who can able to provided samples and 4) patients who were not treated with carbapenem within three weeks during the study.

Exclusion criteria

(1) Patients with already known sepsis etiology such as malaria and viral; (2) patients treated with carbapenem antibiotics within two weeks of sample collection; (3) all male patients; and (4) women who were not suspected of having sepsis .

Ethics clearance

Approval was obtained from the Institutional Review Board (IRB) of the Institute of Biotechnology (RIB/001/22/IOB), ensuring that the study was conducted ethically. The hospitals involved in the study permitted this study to be carried out.

Results

Sociodemographic characteristics

The present study revealed that maternal bacterial sepsis-related hospitalization is caused mainly by *K.pneumoniae* sepsis. Of the 5,613 mothers who met the criteria for maternal sepsis, 609 (10.8%) mothers had carbapenem-resistant *K. pneumoniae*. The age of the women ranged from 15 to 49 years. 58% of the infected mothers had an education above the primary level. Almost all (97.7%) respondents were unaware of bacterial sepsis. Nearly half (43.8%) of the maternal sepsis cases caused by *CRKP* were identified from ICU wards, followed by GYN/OB (24.2%), surgical (16.4%), medical (11%), and emergency OPD (4.6%). Almost three-fourths (74.3%) of the participants were from rural areas (Table 1). The occurrence of maternal sepsis caused by *CRKP* differed among hospitals on the basis of their geographic location. In central Ethiopia, the prevalence of maternal sepsis caused by *CRKP* was11.3% at ALERT and 10.4% at TASH during the same study period. The prevalence rates of maternal sepsis caused by *CRKP* at HFSH, JUMC, and HUSH were 9.2%, 12.8%, and 10.8%, respectively (Table 1).

Antimicrobial resistance profile of *K. pneumoniae*

Six hundred nine non-repetitive *K.pneumoniae* isolates were found in various clinical samples, including urine, blood, wounds, CSF, and others. About 42.5% of the *CRKP* isolates were isolated from urine, followed by 35.5% from blood, surgical wound exudates (12.2%), CSF (6.4%), and other sources (3.4%) (Table 1). In terms of the antimicrobial resistance profile, 93.9% of the *K. pneumoniae* isolates were multidrug-resistant (MDR). Among these strains, 24.3% were XDR strains, followed by PDR strains (10.9%). 41% of the *K. pneumoniae* strains were resistant to carbapenems. The prevalence rates of *ESBL*- and *carbapenemase*-producing *K. pneumoniae* were 93.0% and 40.2%, respectively. All the *ESBL*-producing *K.pneumoniae* isolates were resistant to ceftriaxone, cefazolin, cefotaxime, ampicillin-sulbactam, ceftazidime, aztreonam, and cefepime. However, the resistance rates to other antibiotics, such as trimethoprim-sulfamethoxazole, tobramycin, ciprofloxacin, gentamicin, and piperacillin-tazobactam varied from 39.0 to 93.3% (Figs. 1 and 2). About 86.3% of the *K. pneumoniae* isolates in the urine samples and 75.6% in the blood samples were ESBL-producing strains (Table 1).

Among the *K. pneumoniae* isolates, the lowest resistance rates were to amikacin, tigecycline, meropenem, and ertapenem, with resistance rates of 16.4%, 29.1%, 27.6%, and 35.3%, respectively. In contrast to *ESBL*-producing strains, *carbapenemase*-producing *K. pneumoniae* was more common in blood samples (78.4%). Furthermore, the percentages of *K. pneumoniae* resistant to the R-8, R-9, R-10, R-11, and R-12 antibiotics were 34.0%, 57.7%, 44.1%, 15.4%, 24.7% and 13.3%, respectively (Fig. 3). The prevalence of carbapenem-resistant strains varies among hospitals (TASH, ALERT, JUMH, HURH, and HFSUH), ranging from 28.5 to 35.4%. Similarly, the prevalence of ESBL-producing *K. pneumoniae* ranged from 83.1 to 97.8% (Fig. 3).

Risk factors associated with maternal sepsis

This study revealed that multiple factors increased the likelihood of contracting maternal sepsis. Recurrent UTIs (OR=5.4; 95% CI: 2.9–13.2, *P*=0.02); ICU admission (OR=10.3; 95%CI: 3.7–17.1, *P*=0.001); repeated abortions (OR=14.3; 95%CI: 3.7–19.4, *P*=0.001); caesarean delivery (OR=4.3; 95%CI: 2.4–10.2, *P*=0.01); history of not using antimicrobial agents within eight weeks (OR=16.3; 95%CI: 9.3–19.7, *P*=0.01); indwelling catheters (OR=3.7; 95%CI: 1.8–5.8, *P*=0.001); gravidity (OR=3.3; 95%CI: 1.1–4.6, *P*=0.03); post abortion (OR=12.3; 95%CI: 7.7–20.4, *P*=0.001); and alcoholism (OR=5.2; 95% CI: 2.9–11.3, *P*=0.001) were associated with having maternal sepsis of multidrug resistance *K. pneumoniae* (Table 2).

On the basis of these findings, women who experienced septic abortion (two or more times more common) developed sepsis fivefold more likely to be infected with MDR strains than women who did not [AOR=5.3; 95% CI=2.2–14.4]; *P*=0.0001]. Women who had a history of extended hospitalization (more than four weeks) developed sepsis three times more likely to be infected with MDR strains than did those who had never been hospitalized [(AOR=3.7; 95% CI=1.6–19.4); *P*=0.0001]. Those women who had a history of dilatation and curettage developed sepsis twice [(AOR=2.2; 95% CI=1.3–13.4; *P*=0.001)] as likely to be infected with MDR strains compared with those who did not. Women who were admitted to the ICU developed sepsis at a fourfold greater risk of being infected with MDR strains than did those who had never been admitted to the ICU did [AOR=4.3; 95% CI=2.4–11.2; *P*=0.01]. Similarly, women who had indwelling catheters or invasive medical care developed sepsis threefold [(AOR=2.1; 95% CI=1.4–6.2; *P*<0.01)] more likely to be infected with MDR strains than did those who did not. Women who had recurrent UTIs after childbirth were three times more likely to develop sepsis from MDR strains than were those who did not have a UTI [AOR=3.3; 95% CI=1.6–13.2]; *P*=0.01]. Additionally, women who experienced a cesarean section wound infection after delivery were three times more likely to develop maternal sepsis than were those who did not have an infection [AOR=4.1; 95% CI=2.0–9.2]; *P*=0.001]. Overall, these findings revealed that antimicrobial-resistant MDR strains are a significant challenge in maternal sepsis treatment and a major cause of

Table 1 Sociodemographic and prevalence of *K. pneumoniae*isolated from maternal sepsis casesin five tertiary hospitals in Ethiopia, 2024

Covariates		Crude OR (95%CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Onset of infection	Present on admissions	1.00	1.00	1.00	-
	Nosocomial/hospital onset	3.7 [0.8–3.2]	0.001	2.0[1.7–11.3]	0.01
ICU admission history	No	1.00	-	1.00	-
	Yes	10.3 [3.7–17.1]	0.001*	4.3 [2.4–11.2]	0.01
Length of admission	≤ 1 WK	1.00	1.00	1.00	-
	1–2 WKs	0.8 [0.3–1.7]	0.9	0.7 [0.1–1.2]	0.06
	2–3 Wks	3.8 [0.2–2.0]	0.01	2.1 [2.3–8.5]	0.01*
	3–4 WKs	7.7 [1.2–16.3]	0.01	4.4 [3.0–15.9]	0.001**
	≥ 4 WKs	9.1 [2.3–21.4]	0.001*	3.7 [1.6–19.4]	0.0001**
Pregnancy status at the time of infections suspected	Pregnant, not in labor	1.00	-	1.00	-
	Pregnant, in labor	0.2[0.1–0.6]	0.32	0.2 [0.1–1.1]	0.7
	Postpartum	7.3 [2.5–14.4]	0.001*	5.4 [2.1–10.2]	0.001**
	Postabortion	12.3 [7.7–20.4]	0.001*	9.8 [5.7–16.3]	0.001***
Gravidity	Primigravida	1.00	-	1.00	-
	Multigravida	3.3 [0.1–4.6]	0.03	2.2 [1.1–2.6]	0.01
Parity	Nulliparous	1.00	-	1.00	-
	Multiparous	2.4[1.1–3.7]	0.01	2.0 [1.3–4.7]	0.009
Mode of birth	Vaginal birth	1.00	-	1.00	-
	Cesarean	4.3 [2.4–10.2]	0.01	4.1 [2.0–9.2]	0.001*
Prolonged rupture of membranes	No	1.00	-	1.00	-
	Yes	12.3 [6.2–22.4]	0.0001*	8.1 [5.6–11.3]	0.001**
Septic abortion	No	1.00	-	1.00	-
	Yes	14.3 [3.7–19.4]	0.001*	5.3 [2.2–14.4]	0.0001**
Dilatation and curettage	No	1.00	-	1.00	-
	Yes	4.2 [2.4–11.5]	0.001*	2.2 [1.3–13.4]	0.001**
Chorioamnionitis	No	1.00	-	1.00	-
	Yes	12.3 [1.6–25.6]	0.002*	8.3 [2.2–19.1]	0.001*
Recurrent UTI	No	1.00	-	1.00	-
	Yes	5.4[2.9–13.2]	0.02	3.3[1.6–13.2]	0.01
Pulmonary infections Pneumonia	No	1.00	-	1.00	-
	Yes	2.9 [2.1–5.2]	0.01*	2.0 [1.5–3.8]	0.01*
Surgery/indwelling device/ catheter	No	1.00	-	1.00	-
	Yes	3.7 [1.8–5.8]	0.001*	2.1 [1.4–6.2]	0.01*
Cervical/breast cancer	No	1.00	-	1.00	-
	Yes	6.1[2.2–17.3]	0.01*	5.2[1.2–11.4]	0.001***
Hypertension	No	1.00	-	-	-
	Yes	0.4[0.2–1.4]	0.39	-	-
Diabetes mellitus	No	1.00	-	-	-
	Yes	0.8[0.2–2.1]	0.15	-	-
Within the past 3 months history of comorbidities	No	1.00	-	1.00	-
	Yes	7.8 [4.3–12.7]	0.001*	5.1. [3.8–11.1]	0.001**
Within 8wks antibiotic treatment	Yes	1.00	-	1.00	-
	No	16.3[9.3–19.7]	0.01*	15.8 [9.3–32.7]	0.001***
History of alcohol intake	Never	1.00	1.00	1.00	-
	Yes, some time alcohol and tela	4[1.2–7.4]	0.03	1.1 [0.4–1.9]	0.2
	Yes, frequently alcohol beer, tela	8[2.9–11.3]	0.001	3.2 [1.6–4.9]	0.01*

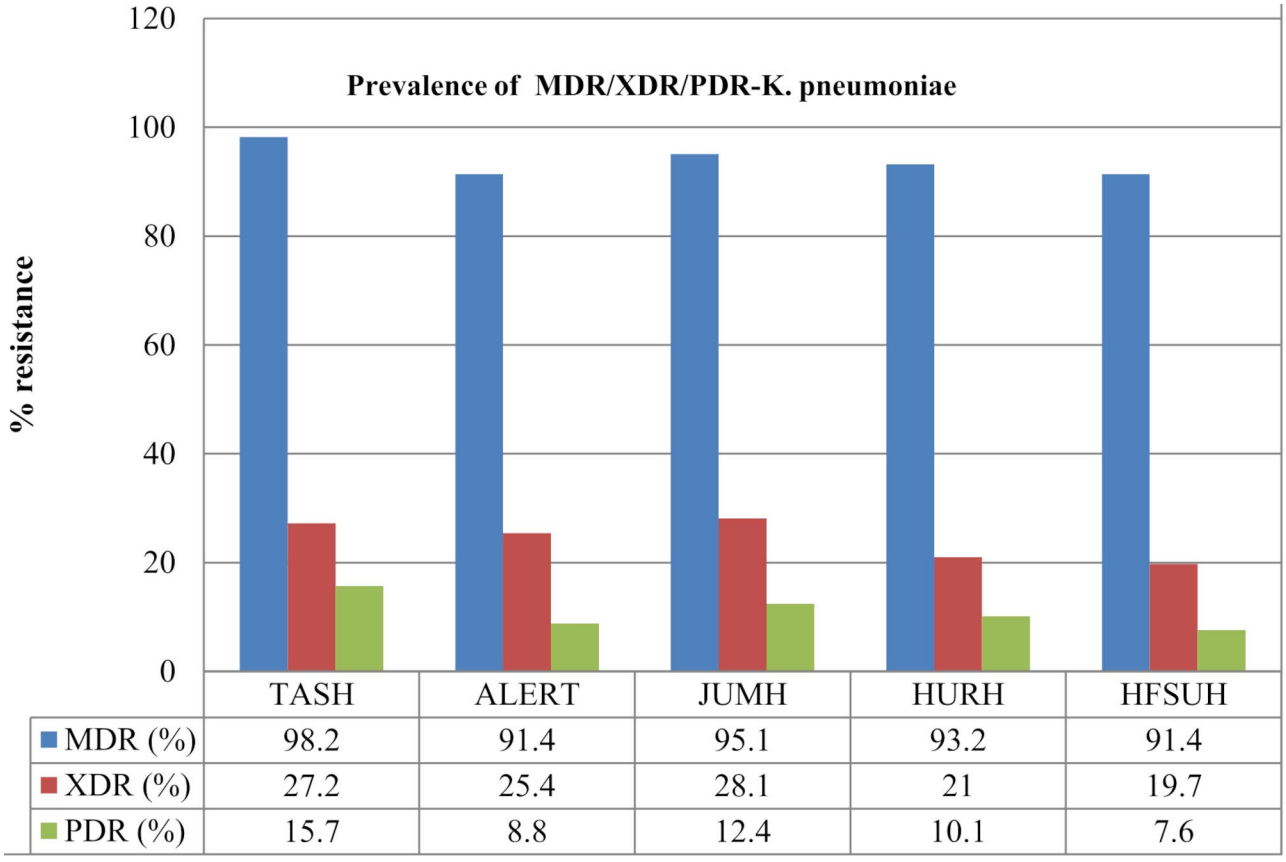

Fig. 1 Prevalence of MDR/XDR/PDR-*K. pneumoniae* strains isolated from maternal with sepsis in five tertiary hospitals in Ethiopia, 2024. **ALERT** = ALERT Hospital; **HFSH** = Hiwot Fana Specialized Hospital; **JUMC** = Jimma University Medical Center; **HUSH** = Hawassa University Specialized Hospital and **TASH** = Tikur Anbessa Specialized Hospital

morbidity and mortality in pregnant women and newborns (Table 2).

Treatment and management of maternal sepsis

This study revealed that among women who developed sepsis, 71.9% of maternal sepsis cases caused by *K. pneumoniae* were diagnosed at the hospital (Table 1). Upon arrival at tertiary hospitals, most women are initially administered antibiotics such as ampicillin, ciprofloxacin, trimethoprim-sulfamethoxazole, cefepime, aztreonam, ceftriaxone, amoxicillin, gentamicin, clindamycin, vancomycin, and piperacillin-tazobactam before arriving at the hospital. Furthermore, 44% of the sepsis patients received one or more cephalosporins, carbapenems, or tigecycline. These factors contribute to a negative bacterial culture, causing a delay in corrective measures being taken and leading to confusion with complicated pregnancy cases (Table 1). A total of 87.0% of women were treated for sepsis with high doses of broad-spectrum antibiotics, including vancomycin and carbapenems. However, 21–42% of these cases can lead to poor maternal outcomes and contribute to the development of long-term maternal outcomes (Table 2).

In the case of severe maternal sepsis, physicians often use a combination of two or three cephalosporins, carbapenems, aminoglycosides, and polymyxins. For instance, they prescribed tigecycline combination therapy, avibactam/ceftazidime, and imipenem/meropenem to treat maternal sepsis caused by MDR/XDR/PDR *K. pneumoniae* (Figs. 2 and 4). For those resistant to last-resort antibiotics, treatment with a combination of carbapenem with amikacin, tigecycline, or levofloxacin has shown positive outcomes (Fig. 4). After treatment with two or more antibiotics in combination, patients treated with meropenem and amikacine recovered with less hospitalization than did the other patients (Fig. 3).

This study revealed that women who developed maternal sepsis from *CRKP* were hospitalized for an average of 44 days. Overall, maternal sepsis caused by carbapenem-/cephalosporin-resistant *K.pneumoniae* is a neglected and deadly condition that has not received sufficient attention because it has short-term and long-term maternal health complications. Therefore, to reduce the impact of maternal sepsis, we need to focus on patient-centered care and promote IPC and AMS strategies. These measures can be implemented by facilitating early diagnosis and sepsis

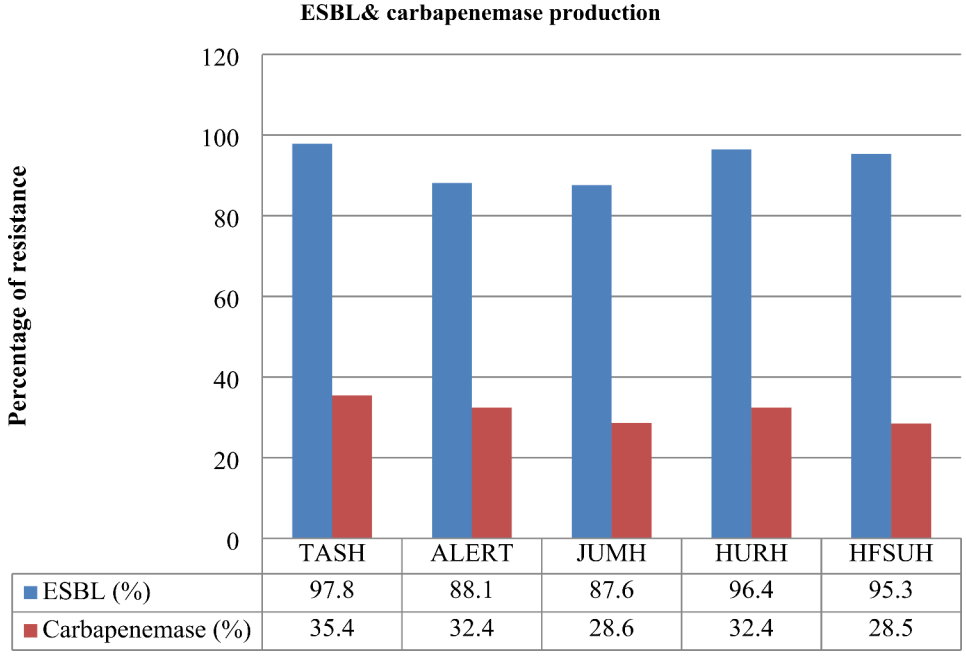

Fig. 2 Prevalence of *ESBL-/carbapenemase*-producing *K.pneumoniae* strains isolated from maternal sepsis in five tertiary hospitals in Ethiopia, 2024. **ALERT** = ALERT Hospital; **HFSH** = Hiwot Fana Compressive Specialized Hospital; **JUMC** = Jimma University Medical Center; **HUSH** = Hawassa University Specialized Hospital and **TASH** = TikurAnbessa Specialized Hospital

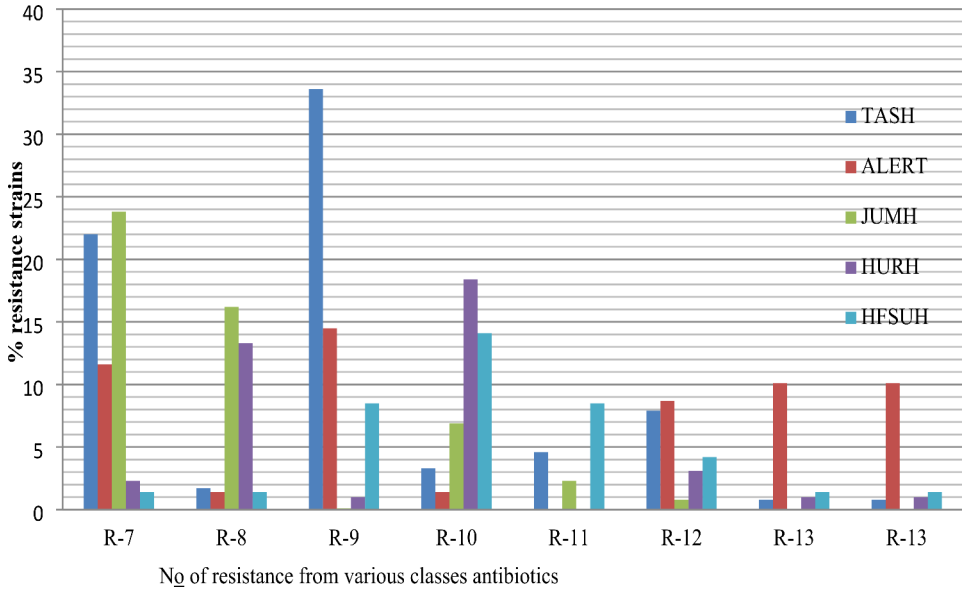

Fig. 3 Degree of resistance *K. pneumoniae* isolated from maternal with sepsis in five tertiary hospitals in Ethiopia, 2024. **ALERT** = ALERT Hospital; **HFCSH** = Hiwot Fana Specialized Hospital; **JUMC** = Jimma University Medical Center; **HUSH** = Hawassa University Specialized Hospital and **TASH** = TikurAnbessa Specialized Hospital

surveillance, creating public awareness, and strengthening IPC and AMS measures without delay.

Discussion

This study revealed that women who were suspected of having sepsis were included at five tertiary hospitals in three-fourths of the country during the study period. These hospitals serve as referral centers for three-fourths of the population of 125 million people. The study revealed that 97% of women who had experienced sepsis were unaware of the harmful symptoms and potential risks of this illness to the developing fetus. The awareness of sepsis is low. Studies have shown that 2.6% of the population in Japan, and 4.2% of the population in Singapore

Table 2 Biavariate and multivariate regression analysis of risk factors associated with maternal sepsis in five tertiary hospitals in Ethiopia, 2024

Variable	categories	All women who had enrolled in the study		All women who had culture-positive for K.pneumoniae	
		N = 5613	%	*N* = 609	%
Hospital clusters	Tikur Anbessa Specialized Hospita	2317	41.3	241	39.6
Central-Ethiopia	ALERT Hospital	609	10.8	69	11.3
Western-Ethiopia	Jimma University Medical Center	1013	18.1	130	21.3
Southern-Ethiopia	Hawassa University Specialized Hospital	903	16.1	98	16.1
Eastern-Ethiopia	Hiwot Fana Specialized Hospital	771	13.7	71	11.7
Age (yrs) Mean +/- SD	< 20	590	10.5	81	13.3
	21–30	1,927	34.3	143	23.5
	31–40	2,237	39.9	259	42.5
	41–49	859	15.3	126	20.7
Onset of infection	Present on admissions	3186	56.8	171	28.1
	Hospital onset	2427	43.2	438	71.9
Length of admission	≤ 1 WK	868	15.5	29	4.7
	1–2 WKs	1106	19.7	50	8.2
	2–3 Wks	1983	35.3	79	13.0
	3–4 WKs	954	17.0	188	30.9
	≥ 4 WKs	702	12.5	263	43.2
Educational level	Cannot read and write	807	14.4	250	41.0
	Elementary	1549	27.6	219	36.0
	High school/preparatory	2284	40.7	79	13.0
	College and above	973	17.3	61	10.0
Residence	Urban	1443	25.7	128	21.0
	Rural	4170	74.3	481	79.0
Ward	ICU	2459	43.8	298	49.0
	Gyn/Ob ward	1358	24.2	136	22.3
	Surgical	921	16.4	77	12.7
	Medical ward	617.	11.0	67	11.0
	EOPD	258	4.6	31	5.0
Antibiotics treatment history	No	679	12.1	79	13.0
	yes	4934	87.9	530	87.0
History of alcohol intake	Never	1740	31.0	109	17.9
	Yes, some time(local tela)	2975	53.0	239	39.2
	Yes, common alcohol beer, tela	898	16.0	261	42.9
Have ever heard about maternal sepsis	Mass media(TV/Radio/others)	-	0.0	-	-
	Health profession/spouses	130	2.3	24	3.9
	Never heard about sepsis	5483	97.7	585	96.1
Clinical specimens	Urine	2073	36.9	259	42.5
	Blood	2284	40.7	216	35.5
	CSF	881	15.7	39	6.4
	Wound/surgical	304	5.4	74	12.2
	Others	71	1.3	21	3.4

[8, 31, 42]. In contrast, studies in Sweden and Germany revealed that the prevalence of population awareness of sepsis was 92% and 88.6%, respectively [2, 9, 41].

In terms of residence, 74.3% of the maternal sepsis patients were from rural areas. A total of 56.8% of maternal sepsis patients had delayed treatment, making it difficult to determine whether symptoms were from infection or pregnancy complications upon arrival at the hospital. Although these suspected cases were treated with carbapenem and vancomycin, the number of patients infected with antibiotics resistant to those last-resort antibiotics has increased, which is unacceptable in the studied hospitals [10, 20, 24]. Clinicians face significant challenges in regard to the early recognition and diagnosis of sepsis in pregnant women. It mimics signs and symptoms of complicated pregnancy and needs urgent work to identify infection before its prognosis is improved to sepsis [4, 7–9, 31, 32, 43]. Additionally,

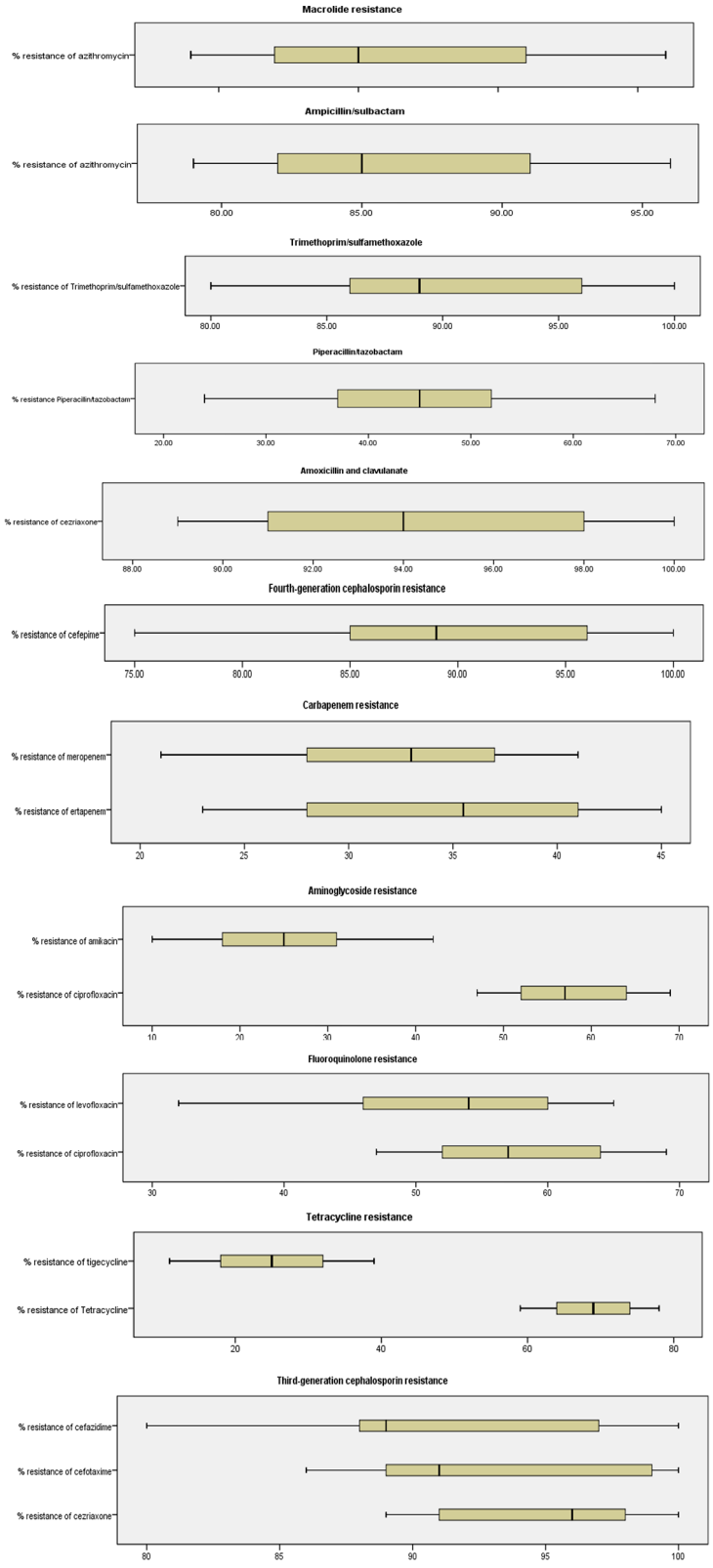

Fig. 4 Percentage resistance to antimicrobials in *K. pneumoniae*isolated from maternal sepsis cases in five tertiary hospitals in Ethiopia, 2024

alcoholism was associated with sepsis in mothers in this study. Those who frequently consumed alcohol, such as beer and "Tela", and were infected with *K. pneumoniae* had a greater likelihood of developing severe symptoms, accounting for 42.9% of the patients. These findings are consistent with many related studies [1, 3, 6, 16, 17, 34, 36, 39]. The maternal sepsis incidence and treatment of *K. pneumoniae* vary by region. This could be due to different factors such as sample type, geographic location, patient demographics, immune status, and co-infections, which can affect the magnitude and strain type of this bacterium, which is consistent with our findings in five tertiary hospitals [10, 15, 24, 35, 37].

This study revealed that *K. pneumoniae* was resistant to a high percentage (39–100%) of the tested antibiotics, including last-resort options such as carbapenems and tigecycline. These findings suggest that carbapenem and cephalosporin antibiotics have become less effective in treating superbugs. Without addressing the rapid spread of *CRKP* strains, alternative treatments may not be available in the near future. These findings are consistent with many studies carried out in other counties [34–37]. On the other hand, this bacterium is one of the most commonly acquired bacteria in both nosocomial and community infections and is highly spreading and developing antimicrobial resistance worldwide [10–14, 23, 24].

The prevalence of MDR *K. pneumoniae* was high at 93.9% (ranging from 91.4 to 98.2%). This finding is consistent with those of studies carried out by Tsegaye et al. 86.5% [34], Aberaet al. 45.2% [35], Belay et al. 84% [36], Beyene et al. 94.5% [46], and Awoke et al. 98.5% [37]. Overall, those studies demonstrated that the number of isolates evaluated for each study, the geographic variation, the studied population, and the test method used all affect the prevalence of MDR-*K. pneumoniae*. Another study by Cassini et al. reported various prevalences of antimicrobial-resistant infections across Europe [19]. Similarly, Lee et al. reported that there was variation in the strains, prevalence, and burden of *carbapenemase*-producing *K. pneumoniae* that disseminated worldwide [18]. Forero-Hurtado et al. reported antimicrobial resistance via *blaKPC* genes and other genes, such as *blaNDM-1*, and plasmid-mediated quinolone resistance [13, 22] cross-transmitted from *K. pneumoniae* to different species [15]. Similarly, this could involve vertical or horizontal genome transfer [17, 20, 21, 28]. We are actively working toward addressing the challenge of multidrug-resistant strains, including *K. pneumoniae*, which pose a significant obstacle to achieving our goal of reducing maternal and newborn morbidity and mortality rates in a sustainable manner [7, 18, 19, 27]. In the present study, the prevalence of XDR *K.pneumoniae* was 28.1%, which is higher than the rates reported in studies by Abera et al. 7.7% [35], and Beyene et al. 8.8% [46]. The percentage obtained in this study is slightly lower than that reported by Tsegayeet al. 43.3% [34]; similarly, the prevalence of PDR *K. pneumoniae* was 28.1%, which is higher than that reported in studies performed by Beyene et al.. 0.8%[46], Awoke et al.. 1.5% [37] and Tsegayeet al. 1.8% [34].

Our study of *K. pneumoniae* revealed that various strains that produce enzymes, namely *carbapenemase* and *ESBL*, which are responsible for causing antimicrobial resistance, have become resistant to antimicrobial drugs. A total of 41.7% of the *K. pneumoniae* strains were non-susceptible to carbapenems, and 40.2% produced *carbapenemase*. The prevalence of *carbapenemase*-producing strains reported in China ranges from 20.4 to 21.9% [11]. However, this figure is higher than that in the studies conducted by Abera et al., 15.4% [35], and Tsegaye et al., 9% [34]. The percentage obtained in this study is slightly lower than that reported by Beyene et al.., which was 30% [46]. On the other hand, 87.6–93.04% of *K. pneumoniae* strains were ESBL-producing strains. The highest frequency of this profile was found in hospitals in the central part of the country. Similarly, the western, southern, and eastern regions account for 87.6%, 96.4%, and 95.3%, respectively, of the profile. This study is similar to studies that reported a high percentage of *ESBL*-producing *K. pneumoniae* nationwide [3, 34–37] and even on a global scale [12, 14, 16, 17, 38].

Although sepsis is a significant healthcare problem, comprehensive data on sepsis caused by multidrug-resistant bacteria and the consequences of sepsis leading to exacerbated maternal morbidity and mortality is lacking. In this investigation, we employed binary and multivariate logistic regression models to pinpoint putative risk factors associated with *K. pneumoniae*-induced maternal sepsis. The findings revealed that women with specific clinical outcomes, such as septic abortion [AOR=5.3; 95% CI=2.2–14.4]; P=0.0001], indwelling catheters[(AOR=2.1; 95% CI=1.4–6.2; P<0.01)], alcoholism alcoholism [(OR=5.2; 95% CI: 2.9–11.3, P=0.001], ICU admission[AOR=4.3; 95% CI=2.4–11.2; P=0.01], cesarean delivery[AOR=4.1; 95% CI=2.0–9.2]; P=0.001], a history of not using antimicrobial agents within eight weeks[(AOR=3.7; 95% CI=1.6–19.4); P=0.0001], and recurrent UTIs[AOR=3.3; 95% CI=1.6–13.2]; P=0.01], history of dilatation and curettage [(AOR=2.2; 95% CI=1.3–13.4; P=0.001)] were at greater risk of developing sepsis. These findings are similar to those of studies on the risk factors associated with sepsis, which exacerbates severe morbidity and mortality at community and health facilities (Table 2); these findings have also been reported by many researchers [7, 8, 18, 19, 25, 28, 32, 33, 42]. The occurrence of risk factors associated with maternal factors (host factors) [1, 27, 34, 43] and bacterial factors [8, 29] has led to the widespread spread of highly

virulent strains [18, 20, 21, 28] and antimicrobial resistance, which includes strains that are pandrug resistant [8, 11, 26].

The management of sepsis encompasses fluid resuscitation for hypotension, empirical antimicrobial treatment, and vasoactive agents (norepinephrine) to reduce the risk of maternal complications. Although treatments have been used to reduce maternal mortality and morbidity caused by sepsis, an increase in antimicrobial-resistant bacterial infections has had adverse consequences. In this context, sepsis caused by *CRKP* and *ESBL*-producing *K. pneumoniae* has resulted in severe maternal sepsis, leading to millions of deaths, socioeconomic crises, and security issues. Figure 3 shows a high incidence of *CRKP* and *ESBL*-producing *K. pneumoniae*, which compromises the effectiveness of last-resort antibiotics such as carbapenem and tigecycline. These findings are similar to those of previous studies on pulmonary infections (pneumonia), surgical site infections and UTIs associated with CRKP [5, 9, 12, 19].

During the study period, it was observed that there were difficulties in promptly recognizing and treating *CRKP* because of the delayed reporting of culture results. This delay poses a challenge for gynecologists in reducing the risk of adverse maternal sepsis outcomes. These findings are similar to those of previous studies [3, 5, 11, 22, 30, 34, 37, 38, 40]. Treatment of maternal sepsis with antimicrobial agents involves a general gram-negative bacteremia algorithm, which uses broad-spectrum β-lactam antibiotics such as ciprofloxacin, trimethoprim-sulfamethoxazole, cefepime, aztreonam, ceftriaxone, amoxicillin, gentamicin, clindamycin, vancomycin, and piperacillin-tazobactam as part of empiric antimicrobial therapy. These findings are consistent with those of other studies [1, 21, 44, 47].

Conclusions

This study revealed that the overall prevalence of maternal sepsis caused by carbapenem- or cephalosporin-resistant *K. pneumoniae* is high. This highly contagious and ubiquitous nature of superbugs poses a seriously threat to public health and serious attention needs to be given to combat transmission. Hence, improving awareness, early diagnosis, person-centered care, IPC measures, integrated surveillance, efficient antimicrobial stewardship, improved sanitation and monitoring interventions are crucial to tackle preventable maternal sepsis caused by bacteria.

Abbreviations

ARGs	Antimicrobial resistance genes
CLSI	Clinical Laboratory Standard Institute
CRKP	Carbapenem-resistant Klebsiella pneumoniae
ESBL	Extended Spectrum Beta Lactamase
IPC	Infection prevention and control
MDR	Multidrug Resistant
MGEs	Mobile genetic elements
MHA	Muller Hinton agar
MHB	Muller Hinton Broth
MIC	Minimal inhibitory concentration
PDR	Resistant to all antimicrobial classes
UTI	Urinary tract infection
XDR	Extreme drug resistance
WHO	World Health Organization

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Author contributions

EG designed and performed laboratory work and analyzed the data. BE, BA, HA, GD and TST were supervising overall project. All authors reviewed and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was conducted after it is ethically reviewed and approved by the Research and Ethical Review Committee of Institute of Biotechnology, Addis Ababa University, Addis Ababa, Ethiopia.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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