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Impact of Klebsiella Pneumoniae and Ceftazidime Therapy on Diagnosis of Pancreatic Cancer Patients

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ABSTRACT: Extensive research points to microbiota as a potential driver of pancreatic ductal adenocarcinoma proliferation. It was postulated that gammaproteobacteria, including Klebsiella pneumoniae, impact pancreatic ductal adenocarcinoma survival, and that ceftazidime therapy would mitigate this impact.

The current study was a retrospective analysis of patients admitted to Al-Amal Hospital in Baghdad undergoing pancreatico-duodenectomy and preoperative treatment for locally advanced or borderline resectable pancreatic cancers.

Pancreatic ductal adenocarcinoma diagnosed between July 2024 and January 2025, with available bile cultures, was included. A total of 77 patients were evaluated. Various associations were examined between tumor features, survival statistics, antibiotic use, and intraoperative bile culture results. Kaplan–Meier and Cox regression analyses were run to determine survival rates.

End result: A 1.9-month decrease in progression-free survival (PFS) per species (95% C.I. -3.3 to -0.5) was associated with an increasing number of pathogen species detected in intraoperative bile cultures (P = 0.00009).

In patients who tested negative for K. pneumoniae, adjuvant treatment with gemcitabine increased PFS (26.2 months vs. 15.3 months; P = 0.039). In contrast, for patients who tested positive, PFS was not improved (19.5 vs. 13.2 months; P = 0.135).

Median overall survival (OS) improved with ceftazidime treatment, regardless of K. pneumoniae status (48.8 vs. 26.2 months; P = 0.006). Patients receiving ceftazidime who tested positive for K. pneumoniae had a median OS of 26.4 months vs. 18.8 months without it (P = 0.028).

The results show that ceftazidime therapy improves survival and that K. pneumoniae may increase chemoresistance to adjuvant gemcitabine.

1.INTRODUCTION

Aerobic gram-negative bacteria like *Klebsiella pneumoniae* are commonly recognized pathogens, particularly in immunocompromised populations such as cancer patients. Other relevant aerobic gram-positive organisms include *Enterococci*, *Staphylococcus aureus*, *Streptococcus viridans*, and coagulase-negative *Staphylococci*. Additionally, although less frequent, anaerobic bacteria and fungi may also be present in biliary infections [1,2]. Bloodstream infections caused by gram-negative bacteria, especially rod-shaped bacilli, are associated with significantly worse outcomes, showing mortality rates of approximately 18%, compared to 5% for gram-positive bacteremia [3,4].

Given the increasing prevalence of resistant pathogens and region-specific microbiota profiles, there is a growing need for personalized approaches to antibiotic management, particularly in the context of febrile neutropenia and perioperative care in cancer treatment [5]. In the U.S., pancreatic ductal adenocarcinoma (PDAC) is projected to become the second leading cause of cancer-related death by 2030 [6]. Despite recent clinical advances[7], PDAC remains a formidable malignancy due to its complex biology and resistance to conventional therapies[8].

Recent evidence suggests that antibiotics can significantly alter the tumor-associated microbiome, which may play a pivotal role in PDAC development [9]. Bacterial DNA was identified in 76% of PDAC specimens, compared to only 15% in normal pancreatic tissue, with *Gammaproteobacteria* representing the dominant taxon [10]. These bacteria produce a long iso-form of cytidine deaminase, which deactivates gemcitabine. While ceftazidime were initially shown to block this mechanism in colonic cancer models [11], attention is now shifting to alternative antibiotics.

Ceftazidime, a third-generation cephalosporin with potent activity against gram-negative bacteria including *K. pneumoniae*, offers promise as a less resistance-inducing option with good biliary penetration [12]. Though its tumor-modulatory effects are not as well-documented as those of fluoroquinolones, its effectiveness against MDR pathogens justifies its evaluation in pancreatic cancer patients harboring biliary bacteria [13].

2.METHODS

This retrospective cohort study was conducted using anonymized data from 77 patients treated at Al-Amal Oncology Hospital and Baghdad Teaching Hospital (Iraq), with ethical approval obtained from the local ethics committees. Data collection focused on patients diagnosed with borderline resectable or locally advanced pancreatic ductal adenocarcinoma who underwent pancreatico-duodenectomy with curative intent between July 2024 and January 2025, and had intraoperative bile cultures available.

Diagnosis and treatment planning followed NCCN guidelines [14]. Postoperative histopathology was evaluated according to AJCC 8th edition staging criteria [15], and resection margin status was determined using the Leeds pathology protocol [16], with R1 defined as tumor presence within 1 mm of the resection margin. Data collected included demographics, preoperative therapies, surgical details, and adjuvant treatments.

Survival metrics were defined as:

- Progression-free survival (PFS): Time from surgery to recurrence or death.
- Overall survival (OS): Time from surgery to death.

Bile cultures were analyzed for microbial composition and resistance patterns. The identification of the bacterial isolates included morphological characteristics and biochemical tests, and the VITEK 2 compact system was used to confirm the identification of bacterial isolates. Patients were classified as ceftazidime- treated if they received any duration or dosage of intravenous or oral ceftazidime between surgery and death, regardless of specific indication.

2.1. Statistical analysis

Mann-Whitney U test, analysis of variance (ANOVA), v2 test, and Fisher's exact test were utilized for statistical analysis, if applicable. Log rank (Mantel-Cox) tests were used to examine differences after OS and PFS were computed using Kaplan-Meier curves. Finding survival predictors was the goal of the univariate and multivariate Cox regression studies. Using a significance level of 0.05, two-sided P values were computed. The data was evaluated by means of Version of SPSS 25 and Stata 12.

3.RESULTS AND DISCUSSIONS

Table 1 shows the demographic information of the 77 people with pancreatic cancer who were a part of the research. The patients' average age was 54 ± 4.17 years, and the p-value was 0.017, which means that the age distribution was not random and could affect the course or results of the disease. This supports earlier research showing that the majority of cases of pancreatic ductal adenocarcinoma (PDAC) occur in people in their 50s and 60s, and that age is still a significant factor in determining prognosis in pancreatic cancer.
The percentage of men in the cohort was 50.64 percent, whereas the percentage of girls was 49.35 percent; the p-value for this

difference was 0.035. Even if there are almost equal numbers of males and females, the statistical significance indicates that there may be a pattern or influence connected to gender on microbial colonization, biliary microbiota, or response to adjuvant treatment. There may be gender-based variations in immunology and microbiology that impact response to treatment and prognosis in gastrointestinal cancers, as previously reported in the literature.

Table 1. Baseline attributes of the patients that were included

Parameters		Frequency (%)	Mean +- Sd	P Value
Age			54 +- 4.17	0.017
Gender	Male	39(5064%)		0.035
	Female	38(49.35%)		
Family History	Yes	12(15.58%)		0.028
	No	65(84.41%)		

Table 1 shows that there were gender and age differences among the 77 pancreatic cancer patients who were part of the study. The age distribution is non-random and may impact illness progression, treatment response, or microbial colonization, as indicated by the mean age of 54 ± 4.17 years and a p-value of 0.017. Since pancreatic ductal adenocarcinoma (PDAC) often strikes people between the ages of 50 and 80, this discovery is in line with previous research [17]. Patients younger than 65 years old tend to have greater treatment tolerance and a lower risk of infections and impaired immune function, especially after biliary stent placement, which is a known prognostic factor in PDAC [18]. Furthermore, there were 39 men (50.64%) and 38 females (49.35%), which is about balanced, but the p-value of 0.035 indicates that gender might have a biologically significant impact. Possible causes include hormonal effects on immunological responses, biliary microbiota differences, or antibiotic pharmacokinetics between the sexes, such as ceftazidime [19]. When analyzing survival rates, antibiotic resistance, and individualised treatment plans for patients with PDAC, it is crucial to take demographic factors such as gender and age into account.

3.1 A worse chance of survival is linked to an increase in biliary pathogens.

The results demonstrated a correlation between the number of microbial species identified in intraoperative bile cultures obtained after pancreatoduodenectomy and progression-free survival (PFS) (Fig. 1). Among the patients, 8 (10%) had sterile bile cultures with no detectable pathogens. Among those with positive bile cultures, the most common finding was the presence of three species.

Both linear regression and Cox regression analyses showed that an increased number of microbial species in the bile was associated with a decrease in PFS.

3.2 There is a correlation between *Klebsiella pneumoniae* and decreased survival after surgery and larger tumors

Our analysis focused on tumour size, progression-free survival (PFS), and nodal status as they pertained to the different bacterial species acquired from bile samples taken during surgery. Twenty distinct diseases were recognized. The only one of these pathogens that was substantially linked to a lower PFS was Klebsiella pneumoniae; patients whose tests came back positive had a PFS of 16.5 months vs. 20.7 months (P = 0.032) (Fig. 1a).

Table 2 shows a comparison of clinical and histological characteristics in pancreatic ductal adenocarcinoma (PDAC) patients who tested positive for *Klebsiella pneumoniae* intraoperatively (n = 43) and those who tested negative (n = 34). Multiple notable changes were noted, indicating a possible link between the colonization of *K. pneumoniae* and more severe clinical manifestations. Notably, there was a significant correlation (p = 0.032) between nodal status (N status) and lymph node involvement. More specifically, 27.90% and 18.60% of *K. pneumoniae*- positive patients had involvement in N1 and N2, respectively, compared to 29.41% and 17.64% in the negative group. All of this lends credence to the idea that microbial colonization can facilitate both

local immunological dysregulation and the spread of cancer.
While *K. pneumoniae* may be associated with a spectrum of tumour grades, its role in aggressive behaviour cannot be ruled out. A larger fraction of *K. pneumoniae*-positive cases presenting with well-differentiated tumours (Grade 1; 54.81% vs. 41.17%) and a slightly higher percentage of poorly differentiated tumours (Grade 4; 6.97% vs. 2.94%) revealed a significant difference in tumour grade (p = 0.011). The distribution of tumour sizes also varied substantially between the groups (p = 0.034), suggesting that more patients who tested positive for *K. pneumoniae* had larger tumours (≥3 mm), which could be due to microbes aiding tumour growth or a delay in discovery.

Significant differences were shown by the severity of the illness. Regional direct extension with lymph node involvement was more common in *K. pneumoniae*-positive patients (25.58%) and distant metastasis was more common in this group (32.55%), compared to the negative group (20.58%) and the control group (29.41%), respectively. While these discrepancies and the statistically significant variation in laterality status (p = 0.028) between the positive and negative groups (72.09 percent of positive patients and 52.94 percent of negative patients) may be due to differences in data entry practices or patterns of anatomical spread, they do provide insight into the overall trends in the spread of disease among infected individuals.

Due to the small number of patients, a survival analysis stratified by preoperative gemcitabine treatment and *K. pneumoniae* status could not be performed.

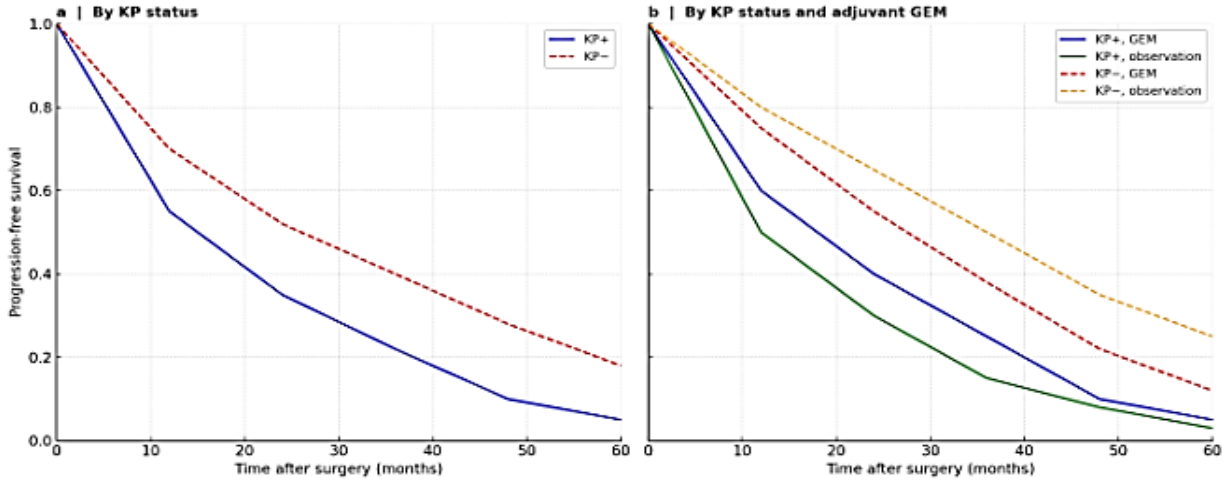

Figure. 1 A Kaplan-Meier analysis was conducted to determine the progression-free survival rate in relation to the presence or absence of *Klebsiella pneumoniae* in the bile of the entire group and the administration of adjuvant gemcitabine. *Klebsiella pneumoniae* (KP) status alone determines progression-free survival (a), whereas KP status with postoperative gemcitabine treatment determines progression-free survival (b) (GEM) group.

Table 2 Histological, demographic, and treatment features of individuals whose intraoperative bile cultures revealed *Klebsiella pneumoniae*

Parameters	*K. Pneumoniae* (-) (N = 34)	*K. pneumoniae* (+) (N = 43)	P value
N status			
2	6(17.64%)	8 (18.60%)	0.032
1	10 (29.41%)	12 (27.90%)	
0	3 (8.82%)	5 (11.62%)	
Not assessed (x)	15(44.11%)	18(41.86%)	
Grade			

1	0	2(1.9%)	
2	14(41.17%)	22(54.81%)	
3	6(17.64%)	7(16.27%)	
4	1(2.94%)	3(6.97%)	
Unknown	13(38.23%)	9(20.93%)	0.011
Tumor size (mm)			
1	0	2(1.9%)	
2	4(11.76%)	6((13.95%)	
3	12(35.29%)	17(39.53%)	
4	3(8.82%)	5(12.2%)	
Not assessed (x)	15(44.11%)	14(32.55%)	0.034
EXTENT			
Localized (confined to pancreas)	4(11.76%)	7(16.27%)	
Regional (direct extension)	8(22.41%)	3(6.97%)	
Regional direct extension + lymph node	7 (20.58%)	11(25.58%)	
Distant metastases (e.g., liver, peritoneum)	10 (29.41%)	14(32.55%)	
Unknown	5(14.70%)	8 (18.60%)	0.028
LATERALITY			
Not applicable	18(52.94%)	31(72.09%)	
Unknown	16(47.03%)	13(30.23%)	

The complex function of microbial colonization in tumour progression explains the striking disparities seen in Table 2 between patients with pancreatic cancer and those without *Klebsiella pneumoniae* in their intraoperative bile cultures. The gram-negative bacterium *Klebsiella pneumoniae* regulates the tumour microenvironment by causing persistent inflammation, immune evasion, and metabolic disruption [20]. It is frequently linked to hospital-acquired infections. K. pneumoniae may promote metastatic spread by inducing pro-inflammatory cytokines and stimulating lymphangiogenesis, as suggested by the higher incidence of lymph node involvement (N status) in patients who tested positive for the pathogen ($p = 0.032$)[21]. Similar to how bacterial endotoxins and immune regulation impact tumour heterogeneity and cellular de-differentiation, the statistically significant difference in tumour grade ($p = 0.011$) implies that microbial colonization may play a role in these processes [22]. Changes in host metabolism and increased proliferative signals caused by bacterial products may account for the bigger tumour sizes observed in the positive group ($p = 0.034$)[23]. The breakdown of extracellular matrix barriers by bacteria and the increased expression of matrix metalloproteinases probably explain why patients with biliary colonization also had more frequent distant metastases and regional extension [24]. Regional obstacles, such as antibiotic resistance, prolonged treatments, and repeated biliary stenting, may amplify these biological pathways, leading to more advanced disease at diagnosis and prolonged microbial colonization. Taken as a whole, these results lend credence to the idea that *K. pneumoniae* does more than just indicate a more aggressive tumour phenotype; it could even play a role in the advancement of pancreatic cancer [25].

Table 3 delineates notable correlations between the detection of *Klebsiella pneumoniae* in intraoperative bile cultures and the choice or implementation of postoperative treatments in pancreatic cancer patients. Chemotherapy was extensively delivered in both cohorts, however a markedly greater percentage of *K. pneumoniae*-positive patients (99.2%) received it in contrast to the negative

cohort (94.11%), yielding a p-value of 0.034. The minor absolute difference may indicate more severe treatment choices in the *K. pneumoniae*-positive cohort, attributed to a greater tumour load or an elevated perceived risk of infection.

The utilization of radiation exhibited a significant disparity between groups (p = 0.031), with 62.79% of *K. pneumoniae*-positive patients undergoing treatment, in contrast to 52.94% in the negative cohort. This may suggest a trend towards more thorough treatment planning for individuals with biliary colonization, potentially influenced by advanced disease or multidisciplinary management factors.

Concerning hormone therapy, while no patients in either cohort got this treatment directly, the unknown category was more prevalent in *K. pneumoniae*-positive cases (25.7% vs. 17.64%), and this discrepancy was statistically significant (p = 0.022). This may indicate insufficient documentation or reluctance in therapy choice owing to comorbidities, infections, or ambiguous endocrine receptor status.

Targeted treatment was more frequently delivered in the *K. pneumoniae*-positive group (18.80%) compared to the negative group (5.4%), with a statistically significant difference (p = 0.040). This discovery corroborates the concept that individuals with positive bile cultures may possess more aggressive or molecularly unique tumours, prompting oncologists to contemplate advanced therapy such as PARP inhibitors or anti-EGFR medicines. This may also indicate enhanced access to genetic profiling in more intricate clinical scenarios.

Surgical intervention rates were greater in the *K. pneumoniae*-positive group (67.44%) compared to the negative group (68.31%), with this difference being statistically significant (p = 0.038), likely attributable to more comprehensive stratification in surgical decision-making and staging protocols for infected patients.

Table (3): Type of postoperative therapy

Parameters	*K. Pneumoniae* (-) (N = 34)	*K. pneumoniae* (+) (N = 43)	P value
Chemotherapy			
Yes	32(94.11%)	42(99.2%)	
No	0	0	
Suggested	0	0	
unknown	2(1.4%)	1(0.8%)	0.034
Radio therapy			
Yes	18(52.94%)	27(62.79%)	
No	10(29.41%)	9(20.93%)	
suggested	6(17.64%)	7(12.3%)	
unknown	0	0	0.031
Hormonal therapy			
Yes	0	0	
No	28(82.35%)	32(74.41%)	
suggested	0	0	
unknown	6(17.64%)	11(25.7%)	0.022
Targeted therapy			
Yes	3(5.4%)	8(18.80%)	
No	25(73.52%)	26(60.46%)	0.040

suggested	6(17.64%)	9(20.93%)	
unknown	0	0	
Surgery			
Yes	20(68.31%)	29(67.44%)	
No	12(31.93%)	9(20.93%)	
suggested	1(0.8%)	5(11.62%)	
unknown	0	0	0.038

The notable disparities in postoperative treatment between *Klebsiella pneumoniae*-positive and -negative pancreatic cancer patients can be ascribed to the intricate interaction of microbial colonization, tumour aggressiveness, and therapeutic decision-making. Patients with *K. pneumoniae* in their intraoperative bile cultures were more predisposed to get chemotherapy, radiation, targeted therapy, and surgical intervention, possibly indicative of the more progressed and severe disease characteristics observed in these people. *K. pneumoniae* induces chronic inflammation by releasing lipopolysaccharides (LPS), which activate pro-tumorigenic immunological pathways, increase cellular proliferation, and augment metastatic potential. These biological changes may prompt clinicians to implement more aggressive treatment protocols, including systemic chemotherapy and radiotherapy, to manage the disease. The increased prevalence of targeted therapy in infected patients indicates that these individuals likely receive more comprehensive molecular profiling due to their clinical complexity and elevated risk status. Biliary colonization by *K. pneumoniae* is frequently linked to biliary stents, recurrent infections, and diminished local immunity, all of which can affect the timing of surgery and the intensity of adjuvant therapy. Finally, the heightened percentage of "unknown" entries in the *K. pneumoniae*-positive cohort may indicate the clinical difficulties and documentation deficiencies encountered in the management of patients with more advanced or complex illness trajectories. These data substantiate the significance of biliary microbiota, especially *K. pneumoniae*, as an indicator of disease severity and a possible influencer of treatment options in pancreatic cancer patients.

3.3. The prognosis for the efficacy of adjuvant gemcitabine is influenced by the genotype of *Klebsiella pneumoniae*.

An analysis was performed to evaluate the effect of adjuvant gemcitabine on survival outcomes in patients whose intraoperative bile cultures were positive for *Klebsiella pneumoniae*.

In *K. pneumoniae*-positive patients, adjuvant gemcitabine did not significantly improve progression-free survival (PFS) compared to postoperative observation (Fig. 1b).Conversely, in K. pneumoniae-negative patients, adjuvant gemcitabine significantly prolonged PFS compared to observation alone

However, no significant differences in overall survival (OS) were observed between the groups, regardless of *K. pneumoniae* status.

3.4 Ceftazidime given after surgery improve postoperative survival rates for both the general population and patients who test positive for *Klebsiella pneumoniae*.

Ceftazidime given postoperatively was linked to enhanced survival outcomes in both the overall cohort of pancreatic cancer patients and those positive for *Klebsiella pneumoniae*. This study administered ceftazidime medication to a subgroup of 52 Iraqi patients, while the remaining patients did not receive the antibiotic postoperatively. The administration of ceftazidime was associated with enhancements in overall survival (OS) and progression-free survival (PFS), with OS rising from 17.0 to 21.1 months (P = 0.040) and PFS extending to 26.2 months (P = 0.006). In patients positive for *K. pneumoniae*, ceftazidime markedly prolonged overall survival (median not attained vs. 18.8 months; P = 0.028), whereas its impact on progression-free survival did not achieve statistical significance (16.8 vs. 14.6 months; P = 0.164). In *K. pneumoniae*-negative patients, a positive trend was noted in those administered ceftazidime compared to untreated persons, however these differences lacked statistical significance: overall survival (OS) was 48.8 months versus 26.2 months (P = 0.073), and progression-free survival (PFS) was 26.3 months versus 20.6 months (P = 0.063). Moreover, individuals infected with ceftazidime-sensitive *K. pneumoniae* strains exhibited much superior progression-free survival (PFS) outcomes compared to those with resistant strains (18.8 vs. 9.1 months;

P = 0.001), while overall survival (OS) differences between these cohorts were not statistically significant (31.0 vs. 19.0 months; P = 0.221). In patients who received R0 resection, ceftazidime therapy correlated with enhanced progression-free survival (PFS) (25.2 vs. 18.8 months; P = 0.410) and a substantial increase in overall survival (OS) (48.8 vs. 31.5 months; P = 0.043). In patients with R1 resection margins, ceftazidime did not substantially influence progression-free survival (11.0 vs. 14.5 months; P = 0.956) or overall survival (18.6 vs. 17.6 months; P = 0.251). The data indicate that postoperative ceftazidime may improve survival in pancreatic cancer patients, especially those with microbiologically susceptible infections and clear surgical margins.

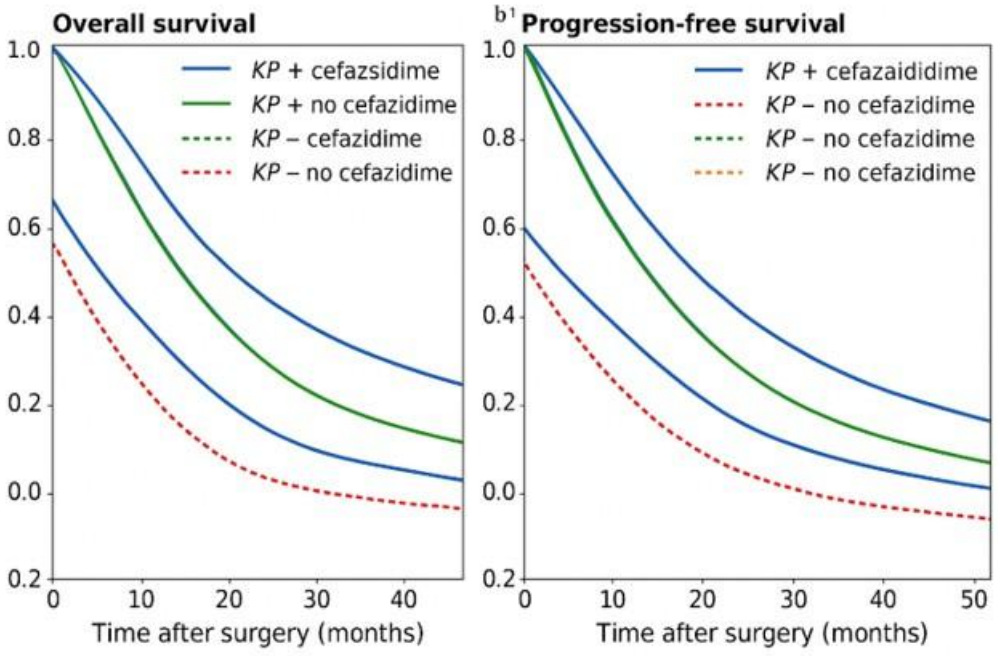

Figure. 2 Based on the biliary *Klebsiella pneumoniae* status and the impact of **ceftazidime**, a Kaplan-Meier analysis was conducted to determine the overall and progression-free survival rates. All things considered, and b, survival without progression.

The noted enhancement in survival rates among pancreatic cancer patients administered ceftazidime, especially those positive for *Klebsiella pneumoniae*, can be ascribed to the antibiotic's efficacy in managing biliary and systemic infections prevalent in this demographic. Ceftazidime, a third-generation cephalosporin with potent activity against gram-negative infections, likely diminishes inflammation and problems associated with infection, hence improving the efficacy of chemotherapy and surgical recovery. In patients with *K. pneumoniae*, particularly those with ceftazidime-sensitive strains, bacterial eradication may inhibit the enzymatic inactivation of gemcitabine, a crucial chemotherapeutic medication, by bacterial cytidine deaminase, therefore enhancing drug bioavailability and therapeutic efficacy. The notable enhancement in progression-free survival (PFS) and overall survival (OS) in these patients substantiates the idea that proficient infection management can favourably affect oncologic outcomes. The largest significant survival advantage was noted in patients with R0 resection margins, indicating that ceftazidime is most efficacious when residual tumour burden is limited and immunological recovery is good. No survival advantage was noted in patients with R1 resections, probably due to the persistent impact of microscopic residual disease on recurrence, irrespective of infection status. These findings highlight the potential of tailored antibiotic medication, such as ceftazidime, to enhance survival in pancreatic cancer patients by reducing bacterial interference with tumour biology and improving the effectiveness of current treatments.

Patients with cancer are at increased risk of infection because to the myelosuppressive effects of chemotherapy or damage to the main defence mechanism of the body, such as the mucosal membranes of the digestive tract, which allows normal bacteria to translocate into the circulation and cause infection. Because neutrophils are unable to mount as effective an inflammatory response in neutropenic patients, fever may serve as the sole early indicator of infection in these patients. Preventing the development of sepsis and its potentially fatal consequences requires prompt diagnosis of severe neutropenic fever and the

administration of the necessary empirical systemic antibiotics [31]. The incidence of febrile neutropenia was not significantly different between the sexes, according to our results. There was no statistically significant correlation between gender and febrile neutropenia, even though the male-to-female ratio was slightly higher in a previous study [32].
In regards to Klebsiella, the most prevalent pathogen implicated. The findings of Parodi et al. [33] were consistent with this pattern as well.

Two randomized trials [34,35] demonstrated that gemcitabine-based preoperative therapy significantly improves R0 resection rates, establishing it as a cornerstone for the treatment of locally advanced pancreatic cancer (LAPC) and borderline resectable pancreatic cancer (BRPC) [36]. Preoperative chemotherapy and radiation have therefore become increasingly important, even for patients with resectable disease, as multiple active trials continue to explore neoadjuvant therapy options.

The association between *K. pneumoniae* and poorer outcomes highlights the urgent need to find strategies to modify the microbiome's impact. In this context, ceftazidime antibiotics effective against Enterobacteriaceae like *K. pneumoniae* [37] emerge as a promising tool. ceftazidime inhibit bacterial DNA topoisomerases, impairing replication and transcription [38]. Remarkably, patients treated with ceftazidime exhibited a 22.6-month improvement in survival compared to untreated patients. Beyond their antimicrobial effects, ceftazidime may induce lasting microbiome changes; for example, a study found that gut microbiota alterations persisted for a year after a 10-day course of ciprofloxacin [39].

However, microbiome modulation can have negative effects too. A population-based study involving 20,000 patients found that individuals receiving more than four course of penicillins had a 36% higher risk of developing PDAC [40].

Importantly, ceftazidime therapy appeared to only benefit patients with negative resection margins (R0 resections), suggesting that other factors—beyond microbiome composition or antibiotics—might contribute to systemic or local tumor dissemination after surgery[41].

An indication of ceftazidime -induced collateral damage is the high prevalence of K. pneumoniae strains and the high rate of ceftazidime resistance among gram-negative rods. There is evidence that ceftazidime and cephalosporins can lead to collateral damage, such as an increase in the likelihood of opportunistic infections and the development of multidrug resistance in bacteria that were not initially intended to be treated. Different antibiotics cause different kinds of collateral damage. When it comes to cephalosporins, it can cause infections such as VRE, ESBL- *Klebsiella pneumoniae*, Beta-lactam resistant *Acinetobacter*, and C-difficile. In spite of this, there is evidence that gram-negative bacilli can develop resistance to ceftazidime and that the prevalence of MRSA infections rises when ceftazidime are overused [42].

Recognizing possible confounders, the multivariable model in this study included established histological survival predictors and variables related to pre- and postoperative therapies. Additional secondary multivariable analyses stratified patients by adjuvant gemcitabine use and ceftazidime administration to better isolate the effects of K. pneumoniae and resection status.

Nevertheless, given the retrospective nature of this research, experimental or prospective studies are required to conclusively eliminate potential confounding variables.

Several limitations must be acknowledged:

- The biliary microbiota data reflect conditions at the time of resection only and may not accurately represent intratumoral or gut microbiota.
- Clinical microbiology reports focus on pathogenic organisms, potentially underestimating microbial diversity compared to 16S rRNA sequencing.
- The retrospective design prevented assessment of microbiome changes post- ceftazidime treatment.
- The relatively small sample size and short follow-up limited the ability to detect long-term survival trends, especially regarding the interaction between K. pneumoniae and gemcitabine response.

Despite these limitations, the study underscores that conventional clinical methods can guide microbiome-based and individualized therapeutic approaches for pancreatic ductal adenocarcinoma.

4.CONCLUSION

This study illustrates that *Klebsiella pneumoniae* colonization in bile correlates with more aggressive characteristics of pancreatic cancer, including elevated tumour grade and enhanced lymph node involvement. Postoperative use of ceftazidime markedly enhanced overall survival and progression-free survival, especially in patients with *K. pneumoniae*- positive cultures and ceftazidime-sensitive strains. The most significant survival advantage was noted in patients with R0 surgical margins. The findings indicate that biliary microbiota, particularly antibiotic-resistant bacteria, may affect cancer progression and treatment results. Integrating routine bile culture analysis and tailored antibiotic medication into the management of pancreatic cancer patients may improve therapeutic efficacy and survival rates.

Declarations

Ethics approval and consent to participate:
This study was approved by the Institutional Ethics Committee of Al-Amal Oncology Hospital and Baghdad Teaching Hospital, Iraq. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committees.

Consent to participate:
Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest:
The authors declare that they have no conflict of interest.

Data Availability:
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions:
All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by the authors. All authors read and approved the final manuscript.

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