RESEARCH ARTICLE

**Editorial Process:** Submission:09/13/2024 Acceptance:12/17/2024

# Chronic Inflammation Induced by *Escherichia coli* Blood Infections as a Risk Factor for Pancreatic Cancer Progression

**Baraa Ahmed Saeed[1], Anwer Jaber Faisal[2]*, Bassam Shaker Mahmood[3], Allaa Hatim Thanoon[2]**

## Abstract

**Background and Aim:** Pancreatic cancer exhibits a high level of aggressiveness and is associated with a high mortality rate. The study comprised 50 patients with pancreatic cancer and 50 healthy family members and friends. The main goal is to explore the biomarkers carbohydrate antigen 19-9 (CA19-9), amylase, procalcitonin (PCT), and interleukin 6 (IL-6), confirm the presence of *Escherichia coli* infection in the patients' bloodstreams, and evaluate the effect of chronic inflammation on the progression of pancreatic cancer. **Methods:** The CA19-9, IL-6, and PCT levels of the control and patient groups were measured with Roche-Cobas C411, and their amylase levels were measured with Cobas C311. In addition, a VITEK2 Compact system was utilized to detect *E. coli* blood infection, and the antibiotic susceptibility of the patients was evaluated. **Results:** The higher PCT and IL-6 levels ($P < 0.0001$*) of the patients with pancreatic cancer indicated chronic inflammation promoting tumor growth, invasion, and metastasis, and high levels of CA19-9 ($P < 0.0001$*) indicated pancreatic cancer. Moreover, tumor damage and ductal blockage lowered amylase levels in patients with pancreatic cancer. In addition, bloodstream infections in patients with pancreatic cancer were mostly caused by *E. coli* (34/50, 68%), and the isolates were resistant to ciprofloxacin (100%). Approximately, 94.11% were resistant to levofloxacin and ceftazidime, whereas only 26.4% were resistant to sulfamethoxazole/ trimethoprim. A total of 29 isolates (85.2%) were multidrug resistant. **Conclusion:** Chronic inflammation from *E. coli* infections is crucial to pancreatic cancer progression. Inflammatory indicators, including PCT and IL-6, and diagnostic biomarkers, including CA19-9 and amylase, reveal malignancy growth and bacterial infections that complicate treatment. Patients with positive PCT and IL-6 results were likely to have positive blood cultures and *E. coli* infections. These biomarkers should be utilized alongside other diagnostic imaging and biopsy methods to improve the detection of pancreatic cancer and screening for bacterial infections.

**Keywords:** Pancreatic cancer- *Escherichia coli*- PCT- Amylase- Antibiotic Resistance

*Asian Pac J Cancer Prev,* **25 (12)**, 4407-4414

## Introduction

Pancreatic cancer is aggressive and fatal and has a poor prognosis. The common pancreatic cancer symptoms are yellow complexion, abdominal or back pain, unexplained weight loss, light-colored feces, dark urine, and loss of appetite. The early signs of the disease are usually absent, and pancreatic cancer symptoms usually appear in advanced stages. Pancreatic cancer usually already metastasizes at diagnosis [1]. Most pancreatic adenocarcinomas occur in people over 70, and few develop before the age of 40. Smoking, obesity, diabetes, and rare hereditary disorders increase pancreatic cancer risk. Smoking and hereditary genes cause 25% and 5%–10% of instances, respectively [2].

Approximately 95% of pancreatic cancers originate in the exocrine pancreas, which produces digestive enzymes [3]. Amylase, which is crucial for carbohydrate breakdown, is predominantly produced by the pancreas and salivary glands [4]. Pancreatic cancer frequently results in considerable structural harm to pancreatic tissues. Tumors can invade and disrupt the normal structure of the pancreas, which includes acinar cells that are important for the production of digesting enzymes, such as amylase [5]. The resulting damage diminishes the overall capability of the pancreas to generate these essential enzymes.

Bloodstream infections (BSIs) are among the most challenging types of infections because they are difficult to manage and considerably affect patient outcomes [6]. *Escherichia coli* is the primary etiological agent responsible for BSIs caused by gram-negative bacteria [7]. Over the past two decades, BSIs caused by antibiotic-resistant *E. coli* strains have increased [8]. Delayed and

*[1]Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq. [2]Iraqi Center for Cancer and Medical Genetic Research, Mustansiriyah University, Baghdad, Iraq. [3]Department of Applied Science, University of Technology, Baghdad, Iraq. *For Correspondence: anwer.jaber@uomustansiriyah.edu.iq*

inefficient antibacterial treatments for BSIs promote the infection with *E. coli* that produce extended-spectrum lactamases (ESBLs), which are linked to high fatality rates [9].

A tetrasaccharide known as carbohydrate antigen 19-9 (CA19-9) typically binds to O-glycans found on cell surfaces. It is involved in cell-to-cell recognition. Patients with pancreatic cancer can have a high CA19-9 level [10], and pancreatitis, cirrhosis, and bile duct disorders are some of the conditions that might increase CA19-9 levels, in addition to cancer. Notably, CA19-9 level is high in patients with bile duct blockage [11].

Inflammation is essential to the advancement of multiple cancer forms. Various indicators are utilized clinically in identifying active inflammatory processes in patients. Procalcitonin (PCT) is a biomarker consisting of 116 amino acids, functioning as a precursor to the hormone calcitonin, which regulates calcium homeostasis and is synthesized by thyroid parafollicular C cells. Procalcitonin is produced when preprocalcitonin is cleaved by endopeptidases. Its level markedly increases in reaction to pro-inflammatory stimuli, especially bacterial infections [12]. The half-life of procalcitonin is 22–35 hours, and the induction period is 4–12 hours. The level increases slightly during viral or noninfectious inflammation [13]. Interleukin 6 (IL-6) is a pro- and anti-inflammatory cytokine and myokine. Pathogen-associated molecular patterns and microbial compounds cause macrophages to produce IL-6. An acute phase response and fever are mediated by IL-6, which controls bone marrow neutrophil production and acute phase protein synthesis. IL-6 suppresses regulatory T cells and stimulates B cell proliferation [14].

The main goal is to explore the biomarkers CA19-9, amylase, PCT, and IL-6 in addition to the presence of *E. coli* infections in the bloodstreams of patients with pancreatic cancer and the effect of chronic inflammation on the progression of pancreatic cancer.

## Materials and Methods

*Subjects and study design*

A total of 100 participants aged 57–70 (mean age of 64.24) were included, of which 70 were males (73%) and 23 were females (23%). The patient group consisted of 50 individuals diagnosed with pancreatic cancer at stages III and IV. All patients were undergoing chemotherapy at the Oncology Hospital in Iraq's Medical City of Baghdad, receiving more than three doses. The other 50 were considered healthy and included in the control group. They were composed of healthy friends and relatives. All the participants were recruited, and their data were collected from January to October 2024. They underwent testing for several biomarkers, including CA19-9, amylase, procalcitonin (PCT), and IL-6. The study was ethically approved by the scientific community of Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq. Furthermore, the study was carried out in compliance with the principles outlined in the Declaration of Helsinki. Before analysis was performed, all patient data were anonymized.

*Sample collection and serum preparation*

Blood samples (20 ml) were collected from 50 patients diagnosed with pancreatic cancer and 50 individuals in good health. Half of each sample (10 ml) was utilized for culturing, and the other half was employed for serum separation. The serum was prepared using anticoagulant-free tubes. Blood samples lacking anticoagulants were allowed to undergo coagulation at room temperature for 30 minutes. After coagulation, the serum and blood cells were separated through 10 minutes of centrifugation at a speed of 3000 revolutions per minute. The clear liquid portions of the sera were carefully moved into fresh labeled tubes with a pipette. The serum samples were kept at a temperature of −80°C.

*Blood culture for bacterial isolation and identification*

Hospital-acquired BSI was defined as the initial detection of a positive culture either 48 hours after admission to the hospital or within 48 hours after discharge. It is accompanied by clinical indications of an ongoing infection. The selection of the 50 patients was based on the symptoms they exhibited during their hospital stay for treatment. Their symptoms included unexplained prolonged fever, shaking chills, altered sensorium, hypotension, and gastrointestinal symptoms, which suggested the presence of BSI. Blood samples (8–10 ml) were obtained and placed in BacT/Alert bottles (Sysmex bioMérieux, Kobe, Japan) and cultured twice for 3–5 days at 37°C. The positive samples underwent subculture on blood agar and MacConkey agar at 35 °C for 24–48 hours, depending on the gram staining results.

The identification of the bacteria was performed utilizing a VITEK2 Compact system (bio-Merieux SA, Marcy l'Etoile, France). High standards of quality were ensured. The quality-control isolates included *Enterobacter cloacae ATCC700323* and *E. coli* ATCC25922.

*Antibiotic susceptibility pattern of E. coli*

The antibiotic susceptibility of *E.coli* was evaluated using a modified Kirby–Bauer disc diffusion method [15] in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [16]. The antibiotics used in the study were cefepime (30 µg); meropenem (10 µg); piperacillin or tazobactam (100/10 µg); ciprofloxacin (5 µg); tetracycline (30 µg); gentamicin (10 µg); sulfamethoxazole or trimethoprim (1.25/23.75 µg); and ceftazidime (30 µg). The surface of Mueller–Hinton agar was plated with a broth culture of *E. coli* (McFarland 0.5). Afterward, the culture received the application of antibiotic discs, and then the plates were placed in an incubator set at 37°C for 18 hours. After incubation, the diameter of the zone of inhibition was measured, and the results were categorized as "resistant," "intermediate," or "susceptible" according to the CLSI guidelines.

*Laboratory analysis of CA19-9, IL-6, PCT, and amylase biomarkers*

A closed-system laboratory kit and a fully automated device developed by Roche (Switzerland) were used. CA19-9, PCT, and IL-6 levels in the control and

patient groups were measured with Cobas C411 and an electrochemiluminescence technology, and amylase concentrations were measured with Cobas C311, which measures the extent to which a sample absorbs light at specific wavelengths (550 nm).

*Statistical analysis*

Group effects on research variables were identified using Statistical Analysis System (SAS; 2018) software. The means were compared using a t-test.

## Results

*Biomarker levels in patients with pancreatic cancer*

The study revealed significant differences in the levels of IL-6, PCT (inflammatory marker), amylase (pancreatic function marker), and CA19-9 (tumor marker) between healthy individuals and patients with pancreatic cancer (Table 1 and Figure 1). The levels of the inflammatory markers PCT and IL-6 were significantly elevated ($P < 0.0001$*) in patients with pancreatic cancer compared with healthy individuals. In addition, patients with pancreatic cancer exhibited a significant reduction in amylase enzyme levels, compared with healthy persons ($P < 0.0001$*). Furthermore, a statistically significant difference ($P < 0.0001$*) in CA19-9 level was found between the patients and healthy individuals.

*Distribution of bacterial infection obtained from the bloodstream in patients with pancreatic cancer*

The blood cultures of patients with pancreatic cancer showed different bacterial isolates, as determined by the VITEK2 Compact system. The isolates showed over 95% similarity. The distribution of microorganisms is shown in Figure 2. The most common bacteria responsible for BSIs in patients with pancreatic cancer were *E. coli* (34 out of 50, 68%), *Pseudomonas aeruginosa* (9 out of 50, 18%), *Klebsiella pneumoniae* (4 out of 50, 8%), *Staphylococcus aureus* (2 out of 50, 4%), and *Proteus mirabilis* (1 out of 50, 2%). The control group consisting of 50 people showed no indications of bacterial growth in their blood

*E. coli BSI and Drug Resistance in patients with Pancreatic Cancer*

A significant difference in the frequency of antibiotic resistance was observed in patients with pancreatic cancer and *E. coli* BSI. The resistance rates of *E. coli* were 100% for fluoroquinolone and 94.11% for ciprofloxacin and levofloxacin. Furthermore, the rate of *E. coli* resistance to third- and fourth-generation cephalosporins varied from 94.11% (ceftazidime) to 91.17% (cefepime). The resistance rate of *E. coli* to aminoglycosides and carbapenem significantly varied. The susceptibility rates of *E. coli* were 88.2% for gentamicin and 38.2% for meropenem, and its resistance rates were 88.2% for piperacillin or tazobactam and 55.8% for tetracycline. Finally, the lowest resistance rate was recorded for sulfamethoxazole or trimethoprim (26.4%). These findings are shown in Table 2, demonstrating that 29 isolates (85.2%) displayed multidrug resistance.

## Discussion

BSI refers to the invasion of the bloodstream by numerous pathogenic microorganisms (bacteria or fungi) and is a serious systemic infectious disorder [17]. People diagnosed with malignant tumors typically receive surgical intervention, high-dose chemoradiotherapy, antibiotic treatment, and different invasive medical procedures. The presence of malignancy itself seems to elevate the

Table 1. Comparison between Patients Diagnosed with Pancreatic Cancer and Healthy Individuals in the Levels of IL-6, PCT (Inflammatory marker), Amylase, and CA19-9 (tumor marker).

| Parameters | Healthy (n=50) Mean ± SD | Patients (n=50) Mean ± SD | p value |
|---|---|---|---|
| IL-6 level (pg/mL) | 2.88 ± 2.37 | 344.4 ± 251.1 | <0.0001* |
| PCT level (ng/ml) | 0.05 ± 0.04 | 8.77 ± 2.42 | <0.0001* |
| Amylase level (U/L) | 54.64 ± 20.90 | 19.8 ± 5.48 | <0.0001* |
| CA19-9 level (U/mL) | 21.96 ± 5.767 | 341.5 ± 207.7 | <0.0001* |

Table 2. Pattern of Antibiotic Resistance in Patients with Pancreatic Cancer

| Antibiotic | Pancreatic cancer (n = 34) | Rate of resistance |
|---|---|---|
| Cefepime (30 µg) | 31/34 | 91.17% |
| Meropenem (10 µg) | 13/34 | 38.20% |
| Piperacillin/tazobactam (100/10 µg) | 30/34 | 88.20% |
| Ciprofloxacin (5 µg) | 34/34 | 100% |
| Levofloxacin (5 µg) | 32/34 | 94.11% |
| Gentamicin (10 µg) | 30/34 | 88.20% |
| Tetracycline (30 µg) | 19/34 | 55.80% |
| Ceftazidime (30 µg) | 32/34 | 94.11% |
| Sulfamethoxazole/trimethoprim (1.25/23.75 µg) | Sep-35 | 26.40% |

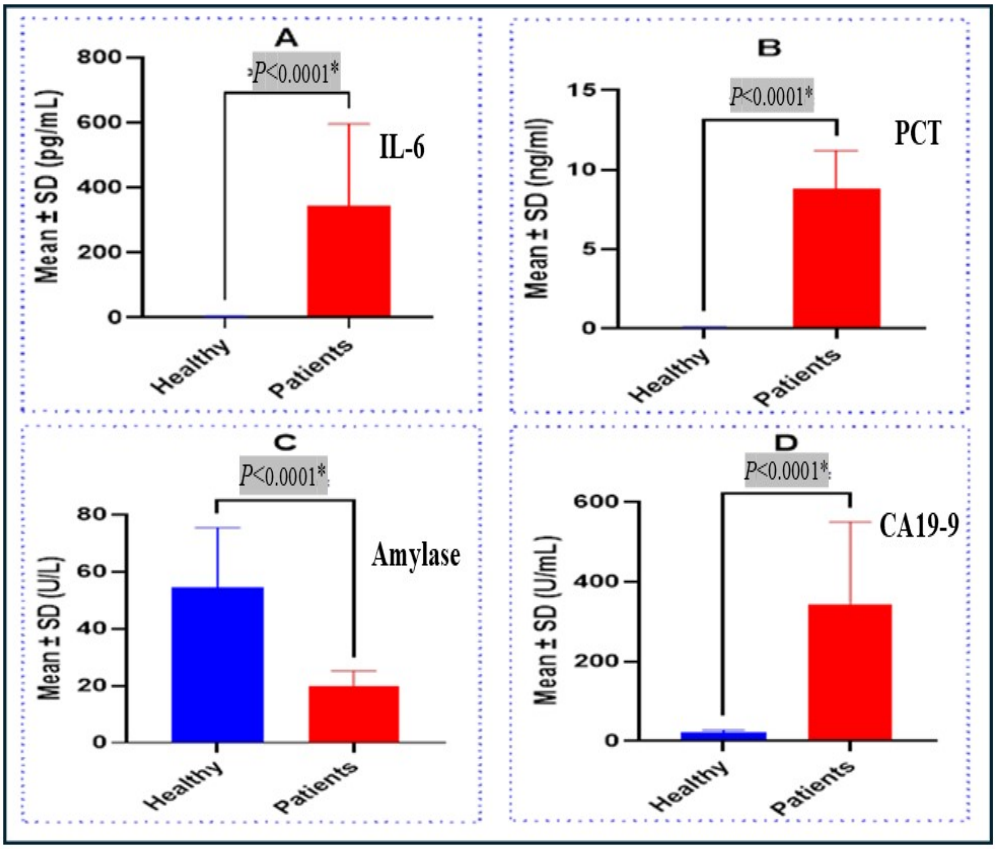


Figure 1. Comparison between Patients Diagnosed with Pancreatic Cancer and Healthy Individuals in the Levels of *IL-6*, PCT (Inflammatory marker), Amylase, and CA19-9 (tumor marker).

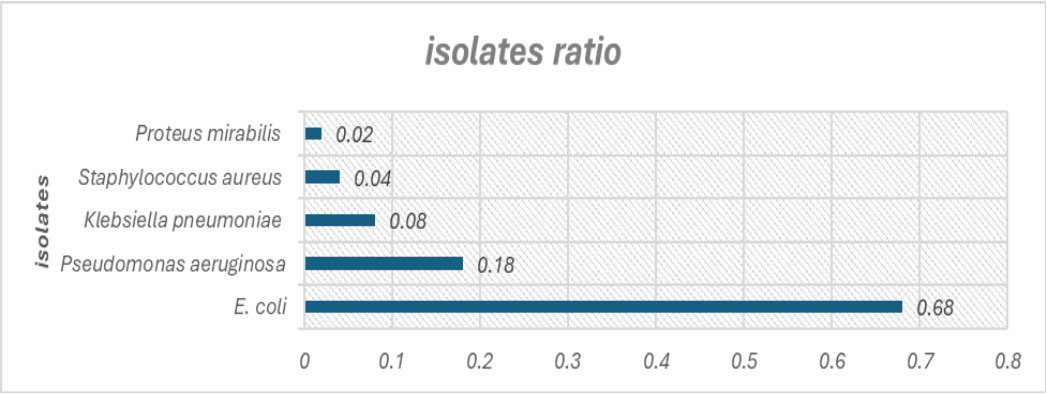


Figure 2. Pathogenic Bacteria Distribution in Bloodstream Infections in Cancer Patients

likelihood of acquiring a bacterial infection [18].

Figure 2 demonstrates that *E. coli* bacteria were the most often isolated pathogen in patients with pancreatic cancer. Notably, blood culture is considered the most reliable method for diagnosing *E. coli* BSI [19]. In individuals diagnosed with pancreatic cancer, BSIs frequently heighten morbidity and fatality rates. *E. coli* is one of the most prevalent bacteria that causes these infections and is commonly found in the gastrointestinal tract, and can enter the circulation. *E. coli* infection is especially problematic for individuals with weakened immune systems or those undergoing invasive medical procedures [20].

Surgery is another significant risk factor for infection and BSI in patients with tumors [21]. Patients who undergo extensive tumor resections, particularly those that involve the respiratory and gastrointestinal tracts, are at high risk of developing postoperative nosocomial infections. A study conducted on 3522 resections performed in Texas identified that BSI is the third leading cause of nosocomial infection after surgery (16% of cases) after wound infection (28%) and pneumonia (43%). The risk of serious postoperative infections varied by resection site: esophagus (25%), stomach (19%), pancreas (17%), lung (10%), rectum (8%), and colon (7%) [22].

We found that patients who tested positive for PCT and IL-6 were more likely to have positive blood cultures than those who tested negative, and PCT concentrations

were considerably elevated in patients infected with *E. coli*. PCT has emerged as a viable diagnostic marker for bacterial infections because its levels are higher in patients infected with bacteria than in patients infected with viruses or suffering from nonspecific inflammatory illnesses [23]. Therefore, PCT level can be utilized to facilitate clinical assessments on the commencement and discontinuation of antibiotic treatment for bacterial infections [24]. IL-6 plays a crucial role as a cytokine in the acute phase response to inflammation and sepsis [25]. During an *E. coli* BSI, the body's immune system triggers the production of several cytokines, such as IL-6, which plays a role in facilitating fever, triggering an acute-phase response, and activating immune cells [26]. Assessing the levels of IL-6 in individuals with *E. coli* BSIs can yield valuable insights into the intensity of an infection and the patient's immunological reaction. Additionally, it can be useful in forecasting results and directing treatment approaches [27].

Table 2 shows that ciprofloxacin exhibited the greatest susceptibility (100%), followed by levofloxacin and ceftazidime (94.11%), cefepime (91.1%), and piperacillin or tazobactam (88.2%). Gentamicin displayed a susceptibility of 88.2% as well. The current findings indicated that 29 out of 34 isolates (85.2%) were multidrug resistant. The connection between the presence of fluoroquinolone-resistant *E. coli* and the increase in the highly infectious strain ST131 has been established through research. In addition, *E. coli* ST131 commonly carries cefotaximase-Munich, which is an ESBL [28]. Patients with pancreatic cancer, especially those receiving chemotherapy, are more likely to get antibiotic-resistant *E. coli*. They are at risk because of their immunocompromised state, frequent hospitalization, and healthcare-associated infections. Owing to gut flora disruption, chemotherapy may cause resistant strain colonization. Frequent intake of broad-spectrum antibiotics results in the proliferation of multidrug-resistant *E. coli* bacteria, increasing the susceptibility of patients with cancer to patients without cancer, who have less antibiotic resistance risk factors [20].

Fluoroquinolones (ciprofloxacin and levofloxacin) as prophylactic agents effectively prevent infection in a specific group of patients with cancer and at high risk [29]. The prevalence of fluoroquinolone-resistant *E. coli* at a comprehensive cancer center in the United States increased from less than 15% in the 1990s to 46% in 2009 [30]. In England, fluoroquinolone-resistant isolates are more commonly found in patients with hematologic malignancies compared with other oncology patients [31]. These findings indicated a negative outlook for the future of fluoroquinolone prophylaxis. The heightened susceptibility of patients with cancer to infections and complications associated with their treatment make antibiotic resistance in *E. coli* a considerable concern. Patients with cancer frequently have compromised immune systems because of the tumors and the effects of chemotherapy and radiation therapies. These treatments heighten their vulnerability to bacterial infections, including those caused by *E. coli.* Moreover, these infections can occur as a result of surgical procedures, use of invasive medical equipment, such as catheters, or the movement of bacteria from the digestive system [32].

The results shed light on important biochemical differences between healthy people and patients with pancreatic cancer in the same age range (57–70 years). Four biomarkers, namely, CA19-9, amylase, procalcitonin (PCT), and IL-6, were the focus of the investigation. Table 1 and Figure 1 indicate considerably increased ($P < 0.0001$*) PCT and IL-6 levels in patients with pancreatic cancer compared with healthy individuals. High IL-6 and PCT levels indicated an active inflammatory milieu that can promote tumor growth, invasion, and metastasis.

Chronic inflammation creates a tumor-promoting microenvironment. Inflammatory cells release cytokines, chemokines, and growth factors that enable cancer cells to survive, multiply, and invade. For instance, cytokines, such as IL-6 and TNF-α, activate signaling pathways that promote cell growth and prevent apoptosis, increasing tumor growth [33]. Inflammatory mediators can cause genetic and epigenetic alterations that cause advanced cancer. DNA damage from ROS and nitrogen species from chronic inflammation can affect tumor and oncogene repressor genes [33]. Epigenetic changes, such as DNA methylation and histone modifications, can affect gene expression and cause tumor growth during prolonged inflammation [34]. Chronic inflammation impairs immune system regulation, enabling cancer cells to hide. Immune response suppressor cells, including regulatory T cells and myeloid-derived suppressor cells, may be recruited during inflammation, and impair tumor defenses. This immunosuppressive environment promotes tumor growth [35]. Angiogenesis, which is necessary for tumor growth and metastasis, depends on inflammatory mediators. Chronic inflammation upregulates VEGF, which promotes the formation of new blood vessels that supply tumors with nutrition and oxygen. Inflammation changes the extracellular matrix, allowing cancer cells to penetrate surrounding tissues and enter the bloodstream, facilitating metastasis. Chronic inflammation dramatically affects the tumor's stroma, which consists of cells and connective tissues. Activated stromal cells, including fibroblasts, produce cytokines and growth factors that encourage tumor growth and survival. Franco et al. (2020) demonstrated that cancer cells interact with inflamed stroma to maintain an inflammatory response and enhance tumor growth [36].

The development of resistance to cancer treatments can be hastened by persistent inflammation. Inflammatory signaling pathways can increase the expression of drug resistance genes and proteins, increasing the resistance of cancer cells to radiation and chemotherapy. Furthermore, the inflammatory environment can protect cancer stem cells, which are crucial to metastasis and recurrence and are difficult to treat conventionally [37].

As shown in Table 1 and Figure 1, patients with pancreatic cancer exhibit significantly lower amylase levels than healthy individuals ($P < 0.0001$*). This finding provides important insights into the pancreatic function in these two groups. Cancerous cells can alter the pancreas microenvironment, leading to changes in metabolic processes and cellular communication. These

alterations can impair the efficiency of enzyme synthesis and secretion in pancreatic cells [38]. Tumor growth can block pancreatic ducts, which deliver enzymes to the small intestine. The blockage of the ducts can reduce bloodstream digestive enzymes, such as amylase, preventing the release of enzymes into the digestive tract [39]. The hydrolysis of carbohydrates into sugars requires amylase. Insufficient enzyme levels in patients with pancreatic cancer cause malabsorption, gastrointestinal difficulties, malnutrition, and weight loss [40]. A low amylase level can be an indicator of pancreatic cancer and dysfunction. Although pancreatic cancer cannot be diagnosed with amylase levels only, they can reveal its severity.

The findings demonstrated a significant and statistically significant increase in CA19-9 levels among patients compared with healthy individuals ($P < 0.0001$*). CA19-9 is an essential biomarker utilized in the diagnosis and surveillance of pancreatic cancer. Its heightened levels observed in patients highlight its function as a crucial diagnostic instrument, demonstrating its importance to the early identification and tracking of illness advancement. CA19-9 is an early biomarker for pancreatic cancer and an increase in CA19-1 level indicates the existence of cancer, prompting diagnostic examinations, such as CT, MRI, and biopsies. Timely detection is essential because pancreatic cancer lacks symptoms during its early stages, and an early diagnosis greatly enhances the outlook for recovery. The differentiation between pancreatic cancer and other pancreatic diseases, such as chronic pancreatitis, can be achieved through the utilization of CA19-9 [41]. The levels of this substance are generally higher in malignant instances, but they may not necessarily be elevated in cancer and can be elevated in other illnesses [42].

The limitation of the current study is that pancreatic cancer cannot be diagnosed just with CA19-9 and amylase. Although the increase in CA19-9 levels is associated with pancreatic cancer, this marker is not disease-specific and can be detected in other illnesses, such as chronic pancreatitis and gastrointestinal problems. In addition, elevated amylase levels can point to pancreatic malfunction rather than to pancreatic cancer. Additional diagnostic procedures, such as imaging, are required in the diagnosis of pancreatic cancer. Biopsies and histological analysis of tissue samples are needed to confirm the existence of cancer cells. Therefore, CA19-9 and amylase levels should not be used as the only markers, but they can be useful to diagnosis. Future research on pancreatic cancer diagnosis may investigate the combination of genetic and molecular markers, such as microRNAs, circulating tumor DNA, and exosomes, with CA19-9 and amylase levels, offering prospects for monitoring disease progression and treatment response. The integration of new indicators with conventional biomarkers may result in enhanced diagnostic accuracy and tailored treatment strategies.

In conclusion, Pancreatic cancer biomarkers play an essential role in the diagnosis, tracking, and management of this disease. Patients with pancreatic cancer and high levels of PCT and IL-6 have persistent inflammation, which contributes to tumor growth, invasion, and metastasis, and patients with pancreatic cancer often have elevated CA19-9 levels. In these individuals, ductal obstruction and tumor-induced damage are indicated by low amylase levels (pancreatic function marker). Moreover, patients with positive PCT and IL-6 results are more likely to have positive blood cultures and *E. coli* infection than those with negative results. PCT and IL-6 levels can be used to support clinical decisions concerning antibiotic therapy for bacterial infections given that patients with pancreatic cancer have increased antibiotic-resistant *E. coli* BSIs. These findings highlight the need for antibiotic stewardship and novel multidrug resistance treatments in this vulnerable group.

## Author Contribution Statement

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by [Baraa Ahmed Saeed], [Anwer Jaber Faisal], [Bassam Shaker Mahmood] and [Allaa Hatim Thanoon]. The first draft of the manuscript was written by [Baraa Ahmed Saeed and Anwer Jaber Faisal], all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Acknowledgements

The authors express gratitude to Mustansiriyah University and Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq, for their help in this effort.

*Ethics statement*

The study was ethically approved by the scientific community of Ibn sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq No; ISU.5.0.24. Furthermore, the study was carried out in compliance with the principles outlined in the Declaration of Helsinki.

The manuscript was approved by the scientific community of Ibn Sina University of Medical and Pharmaceutical Sciences and is not part of any student thesis.

*Conflict of Interest*

The authors declare that they have no conflicts of interest.

## References

1. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Lancet. 2020;395(10242):2008-20. https://doi.org/10.1016/S0140-6736(20)30974-0.
2. Gloor B, Ahmed Z, Uhl W, Büchler MW. Pancreatic disease in the elderly. Best Pract Res Clin Gastroenterol. 2002;16(1):159-70. https://doi.org/10.1053/bega.2002.0272.
3. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. JAMA. 2021;326(9):851-62. https://doi.org/10.1001/jama.2021.13027.
4. Peyrot des Gachons C, Breslin PA. Salivary amylase: digestion and metabolic syndrome. Curr Diab Rep. 2016;16:1-7. https://doi.org/10.1007/s11892-016-0794-7.
5. Gorelick FS, Pandol S, Jamieson JD. Structure-function

relationships in the pancreatic acinar cell. In: Physiology of the gastrointestinal tract. 6th ed. Elsevier; 2018. p. 869-94.
6. Timsit JF, Ruppé E, Barbier F, Tabah A, Bassetti M. Bloodstream infections in critically ill patients: an expert statement. Intensive Care Med. 2020;46(2):266-84. https://doi.org/10.1007/s00134-020-05950-6.
7. Leal HF, Azevedo J, Silva GEO, Amorim AML, de Roma LRC, Arraes ACP, et al. Bloodstream infections caused by multidrug-resistant gram-negative bacteria: epidemiological, clinical and microbiological features. BMC Infect Dis. 2019;19:1-11. https://doi.org/10.1186/s12879-019-4265-z.
8. Bhandari P, Manandhar S, Shrestha B, Dulal N. Etiology of bloodstream infection and antibiotic susceptibility pattern of the isolates. Asian J Med Sci. 2016;7(2):71-5. https://doi.org/10.3126/ajms.v7i2.13444.
9. Blot S, Vandijck D, Vandewoude K, Depuydt P, Vogelaers D, Peleman R. Comment on: Impact of antibiotic resistance and of adequate empirical antibiotic treatment in the prognosis of patients with *Escherichia coli* bacteremia. J Antimicrob Chemother. 2007;60(6):1402. https://doi.org/10.1093/jac/dkm379.
10. Daamen LA, Groot VP, Heerkens HD, Intven MP, van Santvoort HC, Molenaar IQ. A systematic review on the role of serum tumor markers in the detection of recurrent pancreatic cancer. HPB. 2018;20(4):297-304. https://doi.org/10.1016/j.hpb.2017.11.009.
11. Reddy-Patel N, Gautam A, Alam A, Prenatt Z, Patel H, Geme B. Unusual presentation of ectopic ACTH from pancreatic neuroendocrine tumor. Am J Gastroenterol. 2023;118(10S)
12. Hamade B, Huang DT. Procalcitonin: where are we now? Crit Care Clin. 2020;36(1):23-40. https://doi.org/10.1016/j.ccc.2019.08.003.
13. Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med. 2019;57(9):1308-18. https://doi.org/10.1515/cclm-2018-1181.
14. Makieieva N, Koval V. IL-6 and TGF-β as markers of air-blood barrier damage in children with acute lymphoblastic leukemia: clinical and prognostic aspects. Iran J Immunol. 2023. https://doi.org/10.22034/IJI.2023.708392.
15. Faisal AJ, Salman HA. Determination of semen quality and antibacterial susceptibility pattern of bacteria isolated from semen of Iraqi subjects. Microbiol Biotechnol Lett. 2021;49(4):587-93. https://doi.org/10.48022/mbl.2108.08006.
16. Weinstein MP, Lewis JS. The Clinical and laboratory standards institute subcommittee on antimicrobial susceptibility testing: background, organization, functions, and processes. J Clin Microbiol. 2020;58(3):e01864-19. https://doi.org/10.1128/JCM.01864-19.
17. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5(1):4-11. https://doi.org/10.4161/viru.27372.
18. Rolston KV. Infections in cancer patients with solid tumors: a review. Infect Dis Ther. 2017;6:69-83. https://doi.org/10.1007/s40121-017-0146-1.
19. Sinha M, Jupe J, Mack H, Coleman TP, Lawrence SM, Fraley SI. Emerging technologies for molecular diagnosis of sepsis. Clin Microbiol Rev. 2018;31(2):e00089-17. https://doi.org/10.1128/CMR.00089-17.
20. Bai C, Zhang X, Yang D, Li D, Feng H, Li Y. Clinical analysis of bloodstream infection of *Escherichia coli* in patients with pancreatic cancer from 2011 to 2019. Can J Infect Dis Med Microbiol. 2022;2022(1):1338188. https://doi.org/10.1155/2022/1338188.
21. Gudiol C, Aguado JM, Carratalà J. Bloodstream infections in patients with solid tumors. Virulence. 2016;7(3):298-308. https://doi.org/10.1080/21505594.2016.1141161.
22. Avritscher EB, Cooksley CD, Rolston KV, Swint JM, Delclos GL, Franzini L, et al. Serious postoperative infections following resection of common solid tumors: outcomes, costs, and impact of hospital surgical volume. Support Care Cancer. 2014;22:527-35. https://doi.org/10.1007/s00520-013-2006-1
23. Vijayan AL, Vanimaya, Ravindran S, Saikant R, Lakshmi S, Kartik R. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care. 2017;5:1-7. https://doi.org/10.1186/s40560-017-0246-8.
24. Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis. 2012;55(5):651-62. https://doi.org/10.1093/cid/cis464.
25. Ma L, Zhang H, Yin YI, Guo WZ, Ma YQ, Wang YB, et al. Role of interleukin-6 to differentiate sepsis from non-infectious systemic inflammatory response syndrome. Cytokine. 2016;88:126-35. https://doi.org/10.1016/j.cyto.2016.08.033.
26. Hirano T. IL-6 in inflammation, autoimmunity and cancer. Int Immunol. 2021;33(3):127-48. https://doi.org/10.1093/intimm/dxaa078.
27. Guan J, Wang Z, Liu X, Jiang Y, Gao Q, Wu Q, et al. IL-6 and IL-10 closely correlate with bacterial bloodstream infection. Iran J Immunol. 2020;17(3):185-203. https://doi.org/10.22034/iji.2020.87266.1793.
28. Johnson JR, Johnston B, Clabots C, Kuskowski MA, Castanheira M. *Escherichia coli* sequence type ST131 as the major cause of serious multidrug-resistant *E. coli* infections in the United States. Clin Infect Dis. 2010;51(3):286-94. https://doi.org/10.1086/653932.
29. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):427-31. https://doi.org/10.1093/cid/ciq147.
30. Bhusal Y, Mihu C, Tarrand J, Rolston K. Incidence of fluoroquinolone-resistant and extended-spectrum β-lactamase-producing *Escherichia coli* at a comprehensive cancer center in the United States. Chemotherapy. 2011;57(4):335-8. https://doi.org/10.1159/000328744.
31. Schelenz S, Nwaka D, Hunter P. Longitudinal surveillance of bacteremia in hematology and oncology patients at a UK cancer center and the impact of ciprofloxacin use on antimicrobial resistance. J Antimicrob Chemother. 2013;68(6):1431-8.
32. Dadi NCT, Radochová B, Vargová J, Bujdáková H. Impact of healthcare-associated infections connected to medical devices—An update. Microorganisms. 2021;9(11):2332. https://doi.org/10.3390/microorganisms9112332.
33. Denk D, Greten FR. Inflammation: the incubator of the tumor microenvironment. Trends Cancer. 2022;8(11):901-14. https://doi.org/10.1016/j.trecan.2022.07.002
34. Yu W, Tu Y, Long Z, Liu J, Kong D, Peng J, et al. Reactive oxygen species bridge the gap between chronic inflammation and tumor development. Oxid Med Cell Longev. 2022;2022:2606928. https://doi.org/10.1155/2022/2606928.
35. Gray KJ, Gibbs JE. Adaptive immunity, chronic inflammation, and the clock. Semin Immunopathol. 2022:44(2);209-224. https://doi.org/10.1007/s00281-022-00962-8.
36. Franco PIR, Rodrigues AP, de Menezes LB, Miguel MP. Tumor microenvironment components: Allies of cancer progression. Pathol Res Pract. 2020;216(1):152729. https://

doi.org/10.1016/j.prp.2019.152729.
37. Behranvand N, Nasri F, Zolfaghari Emameh R, Khani P, Hosseini A, Garssen J, et al. Chemotherapy: a double-edged sword in cancer treatment. Cancer Immunol Immunother. 2022;71(3):507-26. https://doi.org/10.1007/s00262-021-03013-3.
38. Halbrook CJ, Lyssiotis CA, di Magliano MP, Maitra A. Pancreatic cancer: Advances and challenges. Cell. 2023;186(8):1729-54. https://doi.org/10.1016/j.cell.2023.02.014.
39. Storz P, Crawford HC. Carcinogenesis of pancreatic ductal adenocarcinoma. Gastroenterology. 2020;158(8):2072-81. https://doi.org/10.1053/j.gastro.2020.02.059.
40. Hendifar AE, Petzel MQ, Zimmers TA, Denlinger CS, Matrisian LM, Picozzi VJ, et al. Pancreas cancer-associated weight loss. Oncologist. 2019;24(5):691-701. https://doi.org/10.1634/theoncologist.2018-0266.
41. Azizian A, Rühlmann F, Krause T, Bernhardt M, Jo P, König A, et al. CA19-9 for detecting recurrence of pancreatic cancer. Sci Rep. 2020;10(1):1332. https://doi.org/10.1038/s41598-020-58266-7.
42. Al Abbas AI, Zenati M, Reiser CJ, Hamad A, Jung JP, Zureikat AH, et al. Serum CA19-9 response to neoadjuvant therapy predicts tumor size reduction and survival in pancreatic adenocarcinoma. Ann Surg Oncol. 2020;27:2007-14. https://doi.org/10.1245/s10434-019-08156-3.