Clinical analysis of bloodstream infection of Escherichia coli in patients with pancreatic cancer

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Research

Keywords: Pancreatic cancer, Escherichia coli, BSI, Clinical analysis, risk factor

Posted Date: December 20th, 2019

DOI: https://doi.org/10.21203/rs.2.19350/v1

Abstract

Background To study the common pathogens and cancer types of bloodstream infection (BSI) in cancer patients, find the risk factors and conduct clinical analysis.

Methods The clinical data of 2302 patients with BSI in Tianjin Medical University Cancer Institute and Hospital (TMUCIH) from January 2011 to December 2018 were retrospectively analyzed. 31 pancreatic cancer patients complicated with Escherichia coli BSI and 93 pancreatic cancer patients without BSI at the same period with similar sex and age were divided into infection group and non-infection group.

Results 645 strains (28%) of Escherichia coli were the main pathogens causing BSI in patients with cancer. 57 cases (8.8%) of cancer patients with Escherichia coli BSI were from pancreatic oncology department, among which 31 cases were diagnosed as pancreatic cancer by pathology. Multivariate logistic regression analysis showed that hospitalization days≥7, chemotherapy and neutrophil>5.5×10 9 /L were independent risk factors for pancreatic cancer patients complicated with BSI ($P < 0.05$). Quantitative analysis of serum-related indicators in infection patients and non-infection patients showed significant differences between albumin, prealbumin and neutrophils in infection and non-infection group. The ratio of Escherichia coli producing extended-spectrum ß-lactamase is 49.3 and 48.1 in pancreatic cancer and non-pancreatic patients. Escherichia coli resistant to carbapenems is rare, they were highly sensitive to Cephamycin and Piperacillin/tazobactam.

Conclusions Escherichia coli, the main pathogen causing BSI of cancer patients, is more common in pancreatic cancer patients. The independent risk factors include hospitalization days≥7 days, chemotherapy and neutrophils larger than 5.5×10 9 /L. Quantitative indicators of neutrophil counts, albumin and prealbumin contribute to the early diagnosis of bloodstream infections. Early use of medication, while timely adjustment based on clinical drug sensitivity results will help reduce patient morbidity and mortality.

Background

Bloodstream infection(BSI) has a high mortality rate and is costly, it is the most difficult type of infection to control, and has a great impact on the prognosis of patients(1, 2). Due to improper use of antibiotics, the resistance of pathogenic bacteria to commonly used antibacterial drugs is increasing(3, 4), coupled with the adverse reactions caused by the abuse of antibiotics(5, 6), has made the treatment of bloodstream infection difficult.

In patients with malignant tumors, due to integrity damage (surgery, trauma, indwelling catheters) and some medical sources (antibiotic use, radiotherapy and chemotherapy) and non-medical factors (advanced age, poor nutritional status), the body's immunity is reduced or immune dysfunction, it is easily to induce various infections(7–11).

There are differences in the distribution and drug resistance of pathogens in BSIs in different cancer patients(12–16). We analyzed BSIs data of Tianjin Medical University Cancer Institute and Hospital (TMUCIH) for eight years and found that the most common pathogen of bloodstream infection in cancer patients is Escherichia coli(E. coli), and the most common oncology department is pancreatic oncology.

E. coli is the main cause of BSI involving Gram-negative bacteria(17, 18). The last 20 years have witnessed a striking increase of BSI caused by antibiotic-resistant strains of E. coli(19, 20). Studies have shown that failure to provide timely and effective antibacterial therapy for BSI caused by extended-spectrum-lacta-mases (ESBL)-producing Escherichia coli is associated with increased mortality(19–22).

Pancreatic cancer is a malignant tumor of the digestive tract with high malignancy and difficulty in diagnosis and treatment(23–25). Its mortality has decreased by significant advances in preoperative evaluation, surgical techniques, and postoperative care in recent years, postoperative adjuvant chemotherapy such as radiotherapy and chemotherapy can improve the survival rate, however, the 5-year survival rate is only around 5%, which is still one of the worst prognostic malignancies(23, 26–28). Early diagnosis and treatment are the key to improve the prognosis of pancreatic cancer(29, 30).

There are 2,600 beds in TMUCIH, more than 80 beds in the hepatobiliary and gastrointestinal oncology departments, and only 30 beds in the pancreatic oncology department, but the proportion of Escherichia coli BSI was the highest, of which the cause remains to be determined. Further analyze the risk factors can provide assistance for the diagnosis and treatment of pancreatic cancer patients with BSI. For a variety of reasons, patients with solid tumors are particularly predisposed to develop BSI, however, little information is currently available, let alone pancreatic cancer. Therefore, our data is precious and can provide valuable experience.

1. Materials And Methods

1.1 Patients and study design

Our study analyzed 2302 blood culture positive pathogens of cancer patients from January 2011 to December 2018 in TMUCIH (Exclude duplicate strains isolated from the same patient within two weeks). The first ranked pathogen was Escherichia coli (645 cases). The main cancer patients with Escherichia coli BSI were from pancreatic cancer oncology (57 cases). 31 patients diagnosed with pancreatic cancer by pathologist were defined as the infection group, and 93 pancreatic cancer patients with similar sex and age of were collected as non-infection group.

The clinical data of 31 pancreatic cancer patients infected with Escherichia coli BSI and 93 pancreatic cancer patients without BSI were retrospectively analyzed by case-control study. The clinical data included gender, age, and the number hospitalization of days, the number of hospitalizations, surgery, bleeding during surgery, blood transfusion, radiotherapy and chemotherapy, the type of antibiotics used, distant organ metastasis of cancer, invasive operation (retention drainage tube, central venous catheter or

urine tube), stayed in ICU, white blood cells, neutrophils, CRP, PCT, albumin, prealbumin counts, merger with other parts of infection and diabetes were collected.

1.2 Ethics statement

This study was approved by the Research Ethics Committee of TMUCIH. All patients signed informed consent.

1.3 Definition

When there was an unexplained fever and suspected to be a BSI, doctors would send at least one set of blood culture and promptly sent for inspection. Blood samples (8-10 mL) were collected and auto-cultured by BACTEC 9050, 9120, or FX400 (Becton Dickinson, Franklin Lakes, NJ, USA) for 5 days. Positive samples were subcultured on blood agar (Jin Zhang Ke Ji, Tianjin, China) at 35°C for 24-48 hours depending on the results of gram staining. Species identification and bacterial susceptibility tests were performed on a VITEK 2 compact automatic microbiological analysis system (bio-Merieux SA, Marcy l'Etoile, France). All coincidence rates were above 95%.

1.4 Quality control

The quality control strains were Enterobacter cloacae 700323, Escherichia coli ATCC25922 and Pseudomonas aeruginosa ATCC27853.

1.5 Statistical analysis

Bacterial resistance analysis, pathogen and departmental distribution was performed by Whonet 5.6 software. SPSS 17.0 was adopted to do univariate and multivariate analysis. Data of categorical variables were compared by Fisher's exact test, $P<0.1$ was a potential risk factor. The risk factors were included in the multivariate logistic regression model to analyze the independent risk factors, $P<0.05$ indicates statistical significance. All tests were two-tailed. Graphpad Prism 7.0 was used to analyze quantitative data differences.

2. Results

2.1 Distribution of pathogenic bacteria in BSI of cancer patients

In 2011-2018, 2700 strains of pathogens were detected in 2302 blood culture-positive specimens. The main pathogen causing BSI was Escherichia coli , 645, accounting for 28%. The distribution of pathogens is shown in Table 1.

Table 1 The ratio of pathogens in cancer patients complicated with BSI

2.2 Departmental distribution of cancer patients complicated with Escherichia coli BSI

The BSI caused by Escherichia coli was distributed in different departments of TMUCIH. The main cancer patients causing Escherichia coli BSI were pancreatic cancer oncology patients (57 cases, 8.8%). The distribution of tumor types is shown in Table 2.

Table 2 Departmental distribution of cancer patients complicated with Escherichia coli BSI

2.3 Analysis of risk factors for BSI of patients with pancreatic cancer complicated with Escherichia coli

Analysis of clinical data of 31 infected patients and 93 control patients showed that hospitalization days, number of admissions≥2 times, previous exposure to antibiotics≥2 species, chemotherapy, white blood cells >7.4×10^9 /L, neutrophil>5.5×10^9/L, PCT>2.2 μg/L, albumin<36.0 g/L were potential risk factors for pancreatic cancer patients with Escherichia coli BSI ($P < 0.1$), see Table 3.

Table 3 Analysis of risk factors for Escherichia coli BSI in patients with pancreatic cancer

2.4 Multivariate logistic regression analysis of Escherichia coli BSI in patients with pancreatic cancer

Incorporate potential risk factors into the multivariate logistic regression model. The results showed that hospitalization days≥7 days, chemotherapy, and neutrophils>5.5

$\times10^9$/L were independent risk factors for Escherichia coli BSI in patients with pancreatic cancer. See Table 4.

Table 4 Multivariate logistic regression analysis of Escherichia coli BSI in patients with pancreatic cancer

2.5 Quantitative analysis of serum related indicators of Escherichia coli BSI in patients with pancreatic cancer

Quantitative analysis of serum-related indicators included neutrophils, C-reactive protein (CRP), procalcitonin (PCT), albumin and prealbumin showed the neutrophils in the infection group were significantly higher than those in the non-infection group. Albumin and prealbumin in the infection group were much lower than in the non-infection group, see figure 1.

Figure1 Quantitative analysis of serum related indicators of Escherichia coli BSI in patients with pancreatic cancer A:Leukocyte and B: Neutrophil in the blood of infection and non-infection groups were

compared, C:CRP, D: PCT, E: Albumin, and F: Prealbumin in the serum of infection and non-infection groups were compared.

2.6 Analysis of drug resistance of pancreatic cancer patients complicated with Escherichia coli BSI

There was no significant difference in the resistance rates of antibiotics between Escherichia coli BSI of pancreatic cancer and non-pancreatic patients. The ratio of Escherichia coli producing extended-spectrum ß-lactamase is 49.3 and 48.1 respectively. Escherichia coli resistant to carbapenems is rare, they were highly sensitive to Cephamycin and Piperacillin/tazobactam.

Table 5 Analysis of drug resistance of Escherichia coli BSI in pancreatic cancer and non-pancreatic patients

3. Discussion

BSI refers to the invasion of various pathogenic microorganisms (bacteria or fungi) into the bloodstream and is one of the serious systemic infectious diseases(31). During the next two decades, the percentage of Gram-positive bacteria BSI has increased(32), but Gram-negative bacteria still account for about 50% (33), and mainly Escherichia coli(34, 35). Patients with malignant tumors often require surgery, high-dose chemoradiotherapy, antibiotic use, and various invasive procedures, or the malignancy itself, which tend to increase the chance of Escherichia coli infection(9). Blood culture is the gold standard for the diagnosis of Escherichia coli BSI(36), but its diagnosis takes a long time, which will delay clinical and timely treatment. In addition, the distribution of pathogens and the risk factors for BSI are different due to different diseases and tumor types(32, 37, 38). The pancreatic cancer has a high degree of malignancy, a low rate of surgical resection, and a poor prognosis(39, 40). The occurrence of BSI may further increase the difficulty of treatment. Therefore, clinical analysis of risk factors for Escherichia coli BSI in patients with pancreatic cancer is essential for the prevention of potentially high-risk populations and timely and effective treatment of patients.

Our study showed hospitalization days≥7 days, hospitalizations≥2 times, chemotherapy and used two or more antibiotic types, white blood cells, neutrophils, PCT, albumin and pancreatic cancer patients with Escherichia coli BSI was closely related, but multivariate logistic regression analysis showed that only hospital days ≥7 days, chemotherapy, neutrophils were independent risk factors for Escherichia coli BSI. Pancreatic cancer patients have a long-term adjuvant and neoadjuvant treatment, radiation therapy, combined with a variety of serious underlying diseases and multiple surgical treatments(40-42) lead to prolonged hospital stay, and gradually reduce autoimmune function, thus increasing the chance of Escherichia coli BSI. Study have also shown that patients with longer hospital stays are prone to BSI(43). Therefore, the relevant medical staff in the hospital should strictly carry out aseptic operation, regularly

disinfect the medical equipment and related wards and departments, and try to shorten the hospitalization time of patients to reduce the incidence of BSI.

In the results of this study, 67.7% of pancreatic cancer patients with Escherichia coli BSI received chemotherapy (Adjuvant or/ and neoadjuvant treatment). Neoadjuvant treatment helps to kill cancer cells and reduce the tumor implantation caused by surgery. Adjuvant therapy can effectively improve the treatment effect and reduce recurrence and metastasis. Adjuvant chemotherapy with gemcitabine is standard care for resected pancreatic cancer(44), not only delayed recurrence, but also improved survival compared with surgery alone(45). However, while killing cancer cells, chemotherapy also kills normal immune cells. For instance, the dose-limiting toxicity of gemcitabine is myelosuppression, leading to a decrease in neutrophils and platelets, which reduces the body's immunity. At the same time, chemotherapeutic drugs such as doxorubicin, which can easily damage the intima of the blood vessels(46), leading to partial venous catheterization blockage, causing BSI.

Cancer patients often have infections in other sites, and different types of antibiotics are often used for different infection sites(47). Therefore, the use of two or more antibiotic types was a potential risk factor for Escherichia coli BSI. Studies have shown that, surgery is a kind of trauma to the human body, which will cause the patient's resistance to decline, causing BSI(48). In addition, with the rapid development and popularization of medical technology, various implant operations such as drainage tubes, catheters, central venous catheters, etc., not only play a therapeutic role, but also pose a risk to BSI, therefore, implantation was also an important risk factor(49), but the relationship between surgical and invasive procedures in Escherichia coli BSI was not significant (P>0.05) in our study.

Besides, blood culture diagnosis of pathogens takes a long time and may delay the treatment of the disease. So the other measured clinical indicators can provide timely help for clinical diagnosis and treatment. Studies have also showed the use of white blood cells, neutrophils, CRP, PCT as a reliable indicator of early diagnosis of BSI(50-53). Our study showed that neutrophils>5.5×10^9/L was independent risk factor for Escherichia coli BSI (P<0.05). Neutrophils are the most abundant white blood cells, accounting for 50%-70% of the total white blood cells, they are the first barrier of the body's defense. When inflammation occurs, neutrophils will penetrate the vascular endothelium then enter the site of inflammation to exert a bactericidal effect. Therefore, neutrophils were significantly increased in the presence of BSI. The total number of white blood cells >7.4×10^9/L was not significantly correlated with Escherichia coli BSI (P>0.05). This may be due to patients with pancreatic cancer suffer from frequent chemoradiotherapy, which inhibits bone marrow function(41, 44), resulting in a decrease in the total number of white blood cells. CRP is a non-specific acute phase response protein that is on the rise in early infection(52). There was no significant difference between CRP and Escherichia coli BSI in this study. Studies have pointed out that PCT is very low in normal humans, but when bacterial infection occurs, PCT levels increase significantly, which is an effective indicator of whether it is a bacterial infection(53). Therefore, the specificity of PCT is higher than that of CRP, but the sensitivity is lower than that of CRP. As shown herein, PCT is a potential risk factor for Escherichia coli BSI.

Albumin and prealbumin can be used as monitoring indicators of nutrients in the body. When the nutritional status of patients is poor, the immune function of the body decreases, and albumin and prealbumin decrease accordingly(54). In the quantitative analysis, albumin and prealbumin in the infection group were significantly lower than those in the non-infection group, indicating that patients with pancreatic cancer were prone to Escherichia coli BSI when their nutritional status is poor. This study clearly confirmed the relationship between nutritional status and bloodstream infection in patients with pancreatic cancer.

In our study, the proportion of ESBL produced by Escherichia coli was about 50%, which was lower than that reported in other studies(55, 56). The resistance rate of ceftriaxone was significantly higher than that of ceftazidime, which may be related to the main cefotaxime (CTX) type of ESBL in this region. Carbapenems, Cephamycin and Piperacillin/tazobactam can be used as the first choice for empirical use, but doctors should adjust the drug according to the drug susceptibility results of clinical microbiology to reduce the occurrence of special and restricted antibiotic resistance.

However, this study also has some limitations. Although the data of eight-year pancreatic cancer patients with Escherichia coli BSI were collected, the number of cases is still small. It is a single-center study, which can be combined for pancreatic cancer in North China. The diagnosis and treatment of pancreatic cancer patients with Escherichia coli BSI need further multi-center research to promote its application.

Conclusions

Escherichia coli, the main pathogen causing BSI of cancer patients, is more common in pancreatic cancer patients. The independent risk factors include hospitalization days , chemotherapy and neutrophils larger than 5.5×10^9/L. Therefore, patients with suspected BSI should be promptly drawn for blood culture. At the same time, clinical tests should be combined with laboratory tests such as neutrophils, albumin and prealbumin to make early diagnosis. Early use of medication, while timely adjustment based on clinical drug sensitivity results, will help reduce patient morbidity and mortality.

Declarations

Ethics approval and consent to participate: This study was approved by the Research Ethics Committee of TMUCIH. All patients signed informed consent.

Availability of data and materials : The data that support the findings of this study are available from the archives of the TMUCIH but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request to the corresponding author (Li Ren and Yueguo Li) and with permission of the TMUCIH.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

Funding: This work was supported by Grants 81871719 and 81802080 from Natural Science Foundation of China, Tianjin Medical University Cancer Institute and Hospital Grants Y1702, Y1711, Y1713.

Authors' contributions: Changsen Bai designed the study and wrote the manuscript, Xiuse Zhang and Dong Yang collected the clinical data, Ding Li, Wenfang Zhang, Yunli Zhou, Qing Zhang and Shan Zheng did the bacterial identification and drug susceptibility experiments, Li Ren and Yueguo Li guided data analysis, manuscript writing and revision.

Acknowledgements: Thanks to the Natural Science Foundation of China, Tianjin Medical University Cancer Institute and Hospital Grants Y1702, Y1711, Y1713 for funding this research.

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Tables

Table 1 The ratio of pathogens in cancer patients complicated with BSI

Pathogen species	Number of strains	Number of patients	Composition ratio（%）
Escherichia coli	776	645	28.0
Coagulase-negative staphylococci	435	388	16.9
Klebsiella pneumoniae	349	310	13.5
Staphylococcus aureus	137	110	4.8
Enterobacter cloacae	104	88	3.8
Enterococcus faecalis	99	86	3.7
Pseudomonas aeruginosa	97	84	3.6
Enterococcus faecium	89	63	2.7
Candida albicans	76	48	2.1
Other pathogens	538	480	20.9
Total	2700	2302	100.0

Table 2 Departmental distribution of cancer patients complicated with Escherichia coli BSI

Department	Number of strains	Number of patients	Composition ratio（%）
Pancreatic Oncology	69	57	8.8
Hepatobiliary Oncology	66	55	8.5
Integrated Traditional Chinese and Western Medicine Oncology	59	47	7.3
Interventional Therapy Oncology	56	47	7.3
Intensive care and treatment Oncology	47	27	4.2
Hematology oncology	43	42	6.5
Digestive Oncology	39	35	5.4
Biotherapy Oncology	37	27	4.2
Radiation Oncology	36	22	3.4
Gynecologic Oncology	34	28	4.3
Other oncology	290	258	40.0
Total	776	645	100.0

Table 3 Analysis of risk factors for Escherichia coli BSI in patients with pancreatic cancer

Risk factor	Infection group（n=31）		Control group（n=93）	
	Number of cases	Composition ratio（%）	Number of cases	Composition ratio（%）
Sex（Male)	18	58.1	51	54.8
Age ≥ 60 years old	15	48.3	56	60.2
Hospitalization days ≥7 days	17	54.8	11	11.8
Number of admissions≥2 times	30	96.8	79	84.9
Surgery	18	58.1	42	45.2
Intraoperative bleeding	6	19.4	22	23.7
Chemotherapy	21	67.7	46	49.5
Previous exposure to antibiotics≥ 2 species	9	29	12	12.9
Distant organ metastasis of cancer	16	51.6	35	37.6
Drainage tube	12	38.7	32	34.4
Merger with other parts of infection	6	19.4	16	17.2
Stayed in ICU	5	16.1	8	8.6
Blood transfusion	5	16.1	18	19.4
Combined with diabetes	5	16.1	25	26.9
White blood cells>7.4×10^9 /L	15	40.5	27	29
Neutrophil>5.5×10^9/L	20	64.5	18	19.4
CRP>31.8 mg/L	4	12.9	11	11.8
PCT>2.2 μg/L	6	19.4	6	6.5
Albumin<36.0 g/L	14	45.2	26	28
Prealbumin<0.14 g/L	14	45.2	32	34.4

Table 4 Multivariate logistic regression analysis of Escherichia coli BSI in patients with pancreatic cancer

Risk factor	B	Waldχ^2	OR=Exp(B)	*p* value	95%CI
Hospitalization days ≥7 days	2.64	17.143	12.039	0.001	3.200-45.286
Number of admissions≥2 times	1.435	0.813	4.201	0.367	0.186-95.063
Chemotherapy	1.901	8.698	6.691	0.003	1.368-20.561
Previous exposure to antibiotics≥ 2 species	1.486	3.602	4.42	0.058	0.777-18.613
White blood cells>7.4×10^9 /L	-1.807	2.021	0.164	0.155	0.016-2.618
Neutrophil>5.5×10^9/L	2.698	19.105	14.853	0.001	4.430-49.804
PCT>2.2 μg/L	1.066	0.717	2.903	0.397	0.246-34.248

Table 5 Analysis of drug resistance of Escherichia coli BSI in pancreatic cancer and non-pancreatic patients

Antibiotic	Non-pancreatic cancer(n=750)	pancreatic cancer(n=31)	*p* value
ESBL	48.1	49.3	0.896
Ampicillin	80.6	82.6	0.782
Piperacillin	61.6	60.9	0.937
Ampicillin/sulbactam	45.1	52.2	0.437
Piperacillin/tazobactam	2.6	2.9	0.918
Cefazolin	51.4	55.1	0.686
Cefuroxime	50.3	49.3	0.913
Ceftazidime	20.8	23.2	0.695
Ceftriaxone	49.7	50.7	0.913
Cefepime	12.8	15.9	0.614
Cefotetan	2.1	1.4	0.789
Aztreonam	30.1	30.4	0.972
Imipenem	0.2	0	0.803
Meropenem	0.2	0	0.803
Amikacin	0.9	2.9	0.268
Gentamicin	48.8	39.1	0.283
Tobramycin	10.8	10.1	0.902
Ciprofloxacin	51	39.1	0.194
Levofloxacin	48.1	37.7	0.256
Sulfamethoxazole	60.1	56.5	0.689

Figures

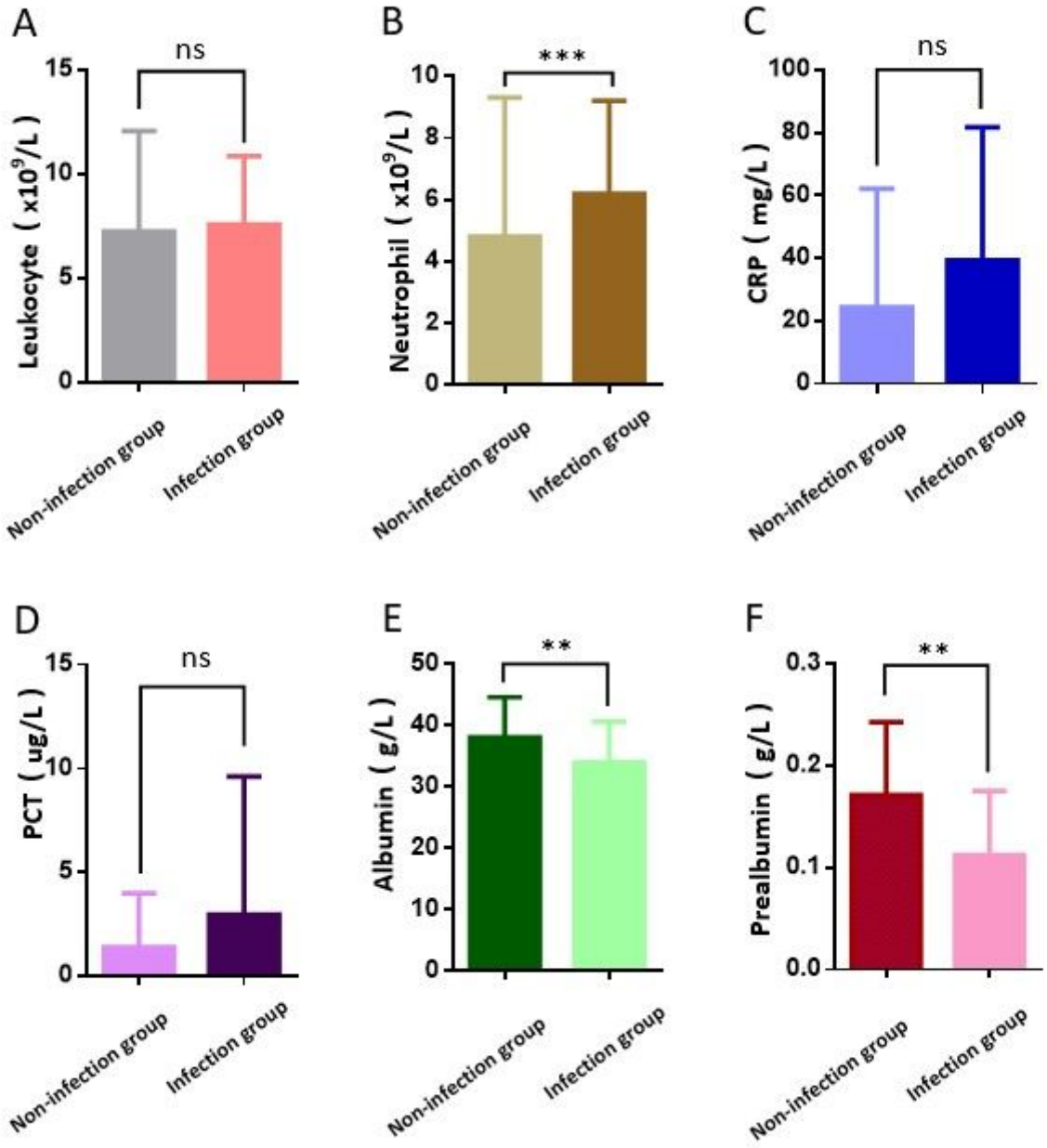

Figure 1

Quantitative analysis of serum related indicators of Escherichia coli BSI in patients with pancreatic cancer A:Leukocyte and B: Neutrophil in the blood of infection and non-infection groups were compared, C:CRP, D: PCT, E: Albumin, and F: Prealbumin in the serum of infection and non-infection groups were compared.