ORIGINAL RESEARCH

Nosocomial Infections in Gastrointestinal Cancer Patients: Bacterial Profile, Antibiotic Resistance Pattern, and Prognostic Factors

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Background: Cancers of the gastrointestinal (GI) tract and its associated excretory glands are one of the most common causes of cancer-related death worldwide, and these patients are more likely to developing nosocomial infections due to immunodeficiency.

Objective: To explore the bacterial profile, antibiotic resistance pattern, and prognostic factors of nosocomial infections in hospitalized GI cancer patients.

Methods: All electronic medical records of nosocomial infection episodes in hospitalized GI cancer patients were retrospectively reviewed. In-hospital mortality was used to evaluate the prognosis of patients. Mann–Whitney test, Chi-square test, and binary logistic regression analysis were used to identify potential risk factors for in-hospital mortality. *P*-values <0.05 were considered statistically significant.

Results: A total of 428 GI cancer patients developed nosocomial infections during hospitalization. Respiratory tract infections (44.2%), bloodstream infections (BSIs) (11.7%), and abdominal cavity infections (11.4%) were the most common infection sites. The predominant causative pathogens were extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (13.6%), ESBL-negative *E. coli* (11.9%), and *Klebsiella pneumoniae* (10.0%). Multidrug-resistant (MDR) strains were detected in 27.6% of isolates. Antimicrobial susceptibility analysis showed that the isolated Gram-negative bacteria (GNB) exhibited high sensitivity to amikacin, meropenem, imipenem, and piperacillin/tazobactam, while the isolated Gram-positive bacteria exhibited high sensitivity to tigecycline, linezolid, and vancomycin. The overall in-hospital mortality of all patients was 11.2% in the study. Multivariate analysis showed that ECOG performance status ≥two scores, length of antibiotic treatment <9.0 days, existence of septic shock, and hypoproteinemia were independent risk factors for in-hospital mortality.

Conclusion: The burden of nosocomial infections in GI cancer patients is considerably high, with GNB being predominantly isolated causative pathogens. Surveillance on serum albumin level, adequate antibiotic treatment, early identification, and prompt treatment of septic shock could benefit the prognosis.

Keywords: nosocomial infections, gastrointestinal cancer, bacterial profile, antibiotic resistance, prognostic factors

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Introduction

Cancers of the gastrointestinal (GI) tract and its associated excretory glands, also known as digestive cancer, are one of the most common causes of cancer-related death worldwide, and it remains a major public health concern for past decades.[1] Although surgery, chemotherapy, radiotherapy, molecular targeted therapy, and

immunotherapy have significantly improved the survival of GI cancer patients in recent years, it remains a bleak prognosis. Furthermore, these patients are predisposed to developing nosocomial infections due to immunodeficiency caused by malignancy itself and its treatments.[2] Even though most infections are temporary, the consequences can last longer.

Nosocomial infections in cancer patients delay the initiation of chemotherapy and reduce the routine dosage.[2,3] In addition, it prolongs hospitalization, raises morbidity and mortality, and increases the financial burden of patients and their families.[3–5] Therefore, early identification of infection episodes and swift initiation of appropriate antibiotic treatment is pivotal for cancer patients, and it plays an important role in reducing infection-associated mortality.[2] As far as we know, previously published studies have merely focused on bloodstream infections (BSIs) in cancer patients. In fact, except for BSIs, urinary tract infections, respiratory infections, and gastrointestinal tract infections are more common in nosocomial infections.[6] Herein, we conducted the present study to extensively describe the microbiological distribution, antibiotic resistance pattern, and clinical outcomes of nosocomial infections in hospitalized GI cancer patients.

Materials and Methods
Study Design
This retrospective observational study enrolled all hospitalized GI cancer patients with nosocomial infections at the First Affiliated Hospital of Xi'an Jiaotong University, cancer treatment center from August 2013 to June 2019. The hospital is a 2560-bed medical center in northwestern China. Surgery, chemotherapy, radiotherapy, and immunotherapy are the most common treatment for cancer patients in the cancer treatment center. The electronic medical records of all included GI cancer patients were reviewed during the study period. All cancer patients diagnosed with nosocomial infection below the age of 18 or without complete medical records were excluded. This study was conducted under the requirements of the Declaration of Helsinki.

Data Collection
All data were extracted from electronic medical records and recorded in a standardized form in Excel. Demographic and clinical data included gender, age, tobacco use, underlying cancer type, the existence of distant metastasis, disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, the Charlson comorbidity index (CCI),[7] the degree of fever, methods of cancer treatment (surgery, chemotherapy, radiotherapy, or concurrent chemoradiotherapy), recent corticosteroid treatment, Granulocyte colony-stimulating factor (G-CSF) usage, and the type of indwelling catheters. Infection-related data included primary sites of infection, empirical antibiotic treatment, effective antibiotic treatment, the existence of septic shock, the use of ventilator, intensive care unit (ICU) admission, length of antibiotic treatment, length of hospitalization, and clinical outcomes of the analyzed infection episodes (death or discharged during hospitalization). Laboratory examination parameters mainly included blood routine test (haemoglobin, platelet count, white-cell count, neutrophils count, and lymphocytes count), serum albumin level, serum procalcitonin (PCT) concentration, and drug susceptibility tests of the isolated pathogens.

Definitions
GI cancer patients were defined as infection episodes in accordance with the following conditions: (a) at least one positive for pathogen was found in the clinical sample during hospitalization; (b) according to the criteria described previously,[8] there were corresponding symptoms and signs records, and the laboratory examination results or radiology results indicated the presence of nosocomial infection; or (c) diagnosis of infection was clearly recorded in electronic medical records.[9] Polymicrobial infection was defined as two or more different pathogens were isolated from clinical samples during hospitalization.

Fever was defined as an axillary temperature above 38.3 °C or two consecutive readings of temperature was above 38 °C.[10] Shock was considered if systolic blood pressure lower than 90 mmHg, and there was no response after administration of fluid therapy and/or vasoactive medications.[11]

According to the drug susceptibility tests of the isolated pathogen, the empirical antibiotic treatment regimen was considered effective if it included at least one antibiotic that was in vitro active against the microorganism.[9] Otherwise, it was considered ineffective.[9]

Multidrug-resistant (MDR) strains were classified into multidrug-resistant Gram-negative bacteria (MDRGNB) and MDR Gram-positive bacteria. The isolated pathogen was defined as MDRGNB if it fulfilled any of the conditions: (a) extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae; (b) AmpC cephalosporinase hyperproducing Enterobacteriaceae; (c) carbapenem-resistant

Enterobacteriaceae (CRE); (d) *Stenotrophomonas maltophilia*; and (e) MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[12] MDR Gram-positive bacteria included vancomycin-resistance *Enterococcus faecium*, and methicillin-resistant *Staphylococcus aureus* (MRSA).[12]

Antimicrobial Susceptibility Test and PCT Measurement

The commercial panels CN1S from the MicroScan automated system (Siemens Healthcare Diagnostics Ltd) or Vitek 2 Compact automated microbiology system (BioMerieux, Craponne, France) were adopted to identify microorganisms and drug susceptibility test. In accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines, the double-disc synergy test with EDTA discs was adopted to screen metallo-β-lactamase producers, and the modified Hodge method was applied to identify carbapenemase producers.[13] ESBL producers were considered if the isolated pathogens were resistant to one or more extended-spectrum cephalosporins (ceftriaxone, ceftazidime, cefepime), and the double-disk synergy test was applied to identify ESBL producers.[14] The time-resolved amplified cryptate emission (TRACE) technology assay (Kryptor PCT; Brahms AG; Hennigsdorf, Germany) was adopted to measure serum PCT concentrations.[10]

Study Outcomes

The primary endpoint of this study was in-hospital mortality. Death episodes during hospitalization that were not related to infection, such as those caused by the underlying malignancy itself or other morbidities, were excluded from the calculations of mortality rate.

Statistical Analysis

Continuous variables were described as either means and standard deviations or medians and interquartile ranges (IQR) as appropriate. Categorical variables were summarized as counts and percentages. Independent samples *t*-test or Mann–Whitney test were used to compare the continuous variables for data of different groups as appropriate. To compare the categorical variables, chi-square or Fisher's exact tests were used as appropriate means of comparability. The binary logistic regression analysis was adopted to explore the independent prognostic factors for in-hospital mortality of nosocomial infections in GI cancer patients. All variables with a P-value <0.10 in univariate analysis were further included in multivariate logistic

regression analysis using stepwise selection. The tests with a P-value <0.05 were considered statistically significant. SPSS software version 22.0 for Windows was used to perform all analyses.

Results

Demographic and Clinical Characteristics

We screened a total of 13,695 cancer patients who admitted to the cancer treatment center from August 2013 to June 2019. In total, 428 eligible GI cancer patients were included in this retrospective study. Among them, a total of 302 (70.6%) patients were male. The median age of all patients was 62.5 years (range, 57–69 years old). There were 224 (52.3%) patients who had a history of tobacco use. Esophageal cancer was the most common diagnosis among the overall population, accounting for 48.4%, followed by rectal cancer (11.9%), gastric cancer (10.0%), and colon cancer (9.3%). A total of 319 (74.5%) patients had an ECOG performance status lower than two scores. There were 252 (58.9%) patients who had advanced tumors (stage III–IV), and 105 patients had distant metastases. The most common underlying morbidities were diabetes mellitus identified in 37 (8.6%) patients, followed by chronic obstructive pulmonary disease (COPD) in 21 (4.9%) patients, and liver disease in 21 (4.9%) patients. Among the 428 patients, 248 (58.0%) had undergone surgery, 103 (24.1%) had received chemotherapy, 33 (7.7%) had received radiotherapy, and 14 (3.3%) had received concurrent chemoradiotherapy. The majority (74.3%) of patients had received invasive procedures within 30 days. A total of 232 (54.2%) patients had drains post-operation, followed by indwelling urinary catheters in 217 (50.7%) cases, nasogastric tube in 181 (42.3%) cases, and percutaneous pleural drainage tube in 146 (34.1%) cases. The detailed demographic and clinical characteristics of the enrolled patients were summarized in Table 1.

Infection-Related Characteristics

Of the 428 GI cancer patients with nosocomial infections, a total of 189 (44.2%) patients were confirmed as respiratory tract infections, followed by BSIs in 50 (11.7%) patients, abdominal cavity infections in 49 (11.4%) patients, and thoracic cavity infections in 41 (9.6%) patients. There were 398 (93.0%) patients had received empirical antibiotic treatment during hospitalization. The most common empirical antibiotic treatment regimens were combination therapy (52.3%), followed by β-lactam

Table 1 Demographic and Clinical Characteristics of Nosocomial Infections in Gastrointestinal Cancer Patients

Characteristics	All N =428	Univariate Analysis			Multivariate Analysis	
		Survivor N =380, n (%)	Non-Survivor N = 48, n (%)	P-value	OR (95% CI)	P-value
Demographic data						
Sex (male)	302 (70.6)	272 (71.6)	30 (62.5)	0.193		
Age (years)	62.5 (57.0–69.0)	62.0 (57.0–69.0)	64.0 (59.0–72.0)	0.444		
Tobacco use	224 (52.3)	200 (52.6)	24 (50.0)	0.731		
ECOG performance status				**<0.001**		
0,1	319 (74.5)	303 (79.7)	16 (33.3)		REF (1.00)	
2,3,4	109 (25.5)	77 (20.3)	32 (66.7)		**9.99 (3.57–27.92)**	**<0.001**
Underlying cancer type						
Esophageal cancer	207 (48.4)	188 (49.5)	19 (39.6)	0.196		
Gastroesophageal junction cancer	35 (8.2)	33 (8.7)	2 (4.2)	0.426		
Gastric cancer	43 (10.0)	39 (10.3)	4 (8.3)	0.869		
Hepatobiliary cancer	31 (7.2)	24 (6.3)	7 (14.6)	0.074		
Pancreatic cancer	21 (4.9)	17 (4.5)	4 (8.3)	0.417		
Colon cancer	40 (9.3)	31 (8.2)	9 (18.8)	**0.035**	3.08 (0.85–11.17)	0.086
Rectal cancer	51 (11.9)	48 (12.6)	3 (6.3)	0.198		
Existence of distant metastasis	105 (24.5)	82 (21.6)	23 (47.9)	**<0.001**	0.44 (0.15–1.30)	0.137
Stage of cancer				0.140		
I–II	176 (41.1)	161 (42.4)	15 (31.3)			
III–IV	252 (58.9)	219 (57.6)	33 (68.8)			
Comorbidities						
COPD	21 (4.9)	13 (3.4)	8 (16.7)	**<0.001**	4.37 (0.41–47.17)	0.225
Cerebrovascular disease	8 (1.9)	5 (1.3)	3 (6.3)	0.050	5.01 (0.27–94.27)	0.282
Liver disease	21 (4.9)	13 (3.4)	8 (16.7)	**<0.001**	3.01 (0.37–24.33)	0.301
Diabetes	37 (8.6)	31 (8.2)	6 (12.5)	0.462		
Renal disease	12 (2.8)	9 (2.4)	3 (6.3)	0.284		
CCI				**<0.001**		0.638
0	344 (80.4)	316 (83.2)	28 (58.3)		REF (1.00)	
1–2	75 (17.5)	60 (15.8)	15 (31.3)		0.51 (0.11–2.39)	0.391
≥3	9 (2.1)	4 (1.1)	5 (10.4)		0.96 (0.05–18.22)	0.976
Existence of fever	188 (43.9)	163 (42.9)	25 (52.1)	0.227		
Surgery (within 30 days)				**<0.001**		0.168
None	180 (42.1)	139 (36.6)	41 (85.4)		REF (1.00)	
Curative surgery	225 (52.6)	221 (58.2)	4 (8.3)		0.09 (0.01–1.19)	0.067
Palliative surgery	23 (5.4)	20 (5.3)	3 (6.3)		0.20 (0.02–1.69)	0.140
Chemotherapy (within 30 days)				0.613		
None	325 (75.9)	285 (75.0)	40 (83.3)			
Neoadjuvant	8 (1.9)	7 (1.8)	1 (2.1)			
Adjuvant	43 (10.0)	40 (10.5)	3 (6.3)			
1st line	40 (9.3)	38 (10.0)	2 (4.2)			
2nd line	7 (1.6)	6 (1.6)	1 (2.1)			
≥3rd line	5 (1.2)	4 (1.1)	1 (2.1)			

(*Continued*)

Table 1 (Continued).

Characteristics	All N =428	Univariate Analysis			Multivariate Analysis	
		Survivor N =380, n (%)	Non-Survivor N = 48, n (%)	P-value	OR (95% CI)	P-value
Radiotherapy (within 30 days)	33 (7.7)	23 (6.1)	10 (20.8)	**0.001**	2.66 (0.53–13.32)	0.234
Concurrent chemoradiotherapy (within 30 days)	14 (3.3)	13 (3.4)	1 (2.1)	0.952		
Corticosteroid therapy (within 30 days)	128 (29.9)	111 (29.2)	17 (35.4)	0.376		
Prior G-CSF use (within 30 days)	79 (18.5)	65 (17.1)	14 (29.2)	**0.042**	0.30 (0.07–1.28)	0.104
Invasive procedure (within 30 days)	318 (74.3)	292 (76.8)	26 (54.2)	**0.001**	0.77 (0.26–2.31)	0.645
Presence of indwelling catheters or other devices						
Ureteral stent	15 (3.5)	10 (2.6)	5 (10.4)	**0.019**	0.94 (0.13–6.85)	0.949
Indwelling urinary catheters	217 (50.7)	212 (55.8)	5 (10.4)	**<0.001**	0.31 (0.02–4.28)	0.380
CVC (port-a-cath or PICC)	56 (13.1)	49 (12.9)	7 (14.6)	0.744		
Percutaneous pleural drainage tube	146 (34.1)	141 (37.1)	5 (10.4)	**<0.001**	1.01 (0.23–4.50)	0.988
Percutaneous abdomen drainage tube	19 (4.4)	13 (3.4)	6 (12.5)	**0.012**	2.01 (0.39–10.28)	0.403
Drains post-operation	232 (54.2)	224 (58.9)	8 (16.7)	**<0.001**	1.33 (0.16–11.34)	0.794
Nasogastric tube	181 (42.3)	175 (46.1)	6 (12.5)	**<0.001**	2.39 (0.29–19.65)	0.416

Note: Bold values indicate statistical significance.
Abbreviations: OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; COPD, chronic obstructive pulmonary disease, CCI, Charlson comorbidity index score; G-CSF, granulocyte colony-stimulating factor; CVC, central venous catheter; PICC, peripherally inserted central catheter.

/β-lactamase inhibitor combinations (15.9%), and cephalosporins (11.0%). A total of 239 (55.8%) patients were confirmed as to have had received effective empirical antibiotic treatment. The median length of antibiotic treatment for all patients was 9.0 days (range, 6.0–13.0 days). During hospitalization, 73 (17.1%) patients were treated in the ICU, 44 (10.3%) received mechanical ventilation, and 49 (11.4%) presented septic shock. Finally, a total of 48 (11.2%) patients died due to nosocomial infections. The median length of hospitalization of all patients was 21.0 days (range, 11.0–28.0 days). The detailed infection-related characteristics of the included patients were summarized in Table 2.

Microbiology Characteristics

A total of 428 strains of causative pathogens were isolated from different clinical samples during the study period. The most common samples were sputum (40.9%), followed by blood (14.5%), drainage fluid (13.1%), and

urine (8.4%). Gram-negative bacteria (GNB) were the leading causative pathogens of nosocomial infections in GI cancer patients, accounting for 36.7%, followed by MDRGNB (27.6%), polymicrobial (13.6%), Gram-positive bacteria (9.6%), and fungi (9.6%). Of the isolated GNB, the most frequently isolated pathogens were *E. coli* (11.9%), *Klebsiella pneumoniae* (10.0%), and *Pseudomonas aeruginosa* (9.1%). Among the MDRGNB group, ESBL-producing *E. coli* (13.6%), *Acinetobacter baumannii* (4.7%), and ESBL-producing *Klebsiella pneumoniae* (3.7%) were the most frequently isolated pathogens. The isolated Gram-positive bacteria mainly included *Staphylococcus aureus* (3.7%), *Streptococcus pneumoniae* (2.8%), and *Streptococcus anginosus* (1.6%). The detailed microbiological characteristics were presented in Table 3.

Antimicrobial Susceptibility Analysis

We then performed antimicrobial susceptibility analysis of the isolated causative pathogens. It showed that the

Table 2 Infection-Related Characteristics of Nosocomial Infections in Gastrointestinal Cancer Patients

Characteristics	All N =428	Univariate Analysis			Multivariate Analysis	
		Survivor N =380, n (%)	Non-Survivor N = 48, n (%)	P-value	OR (95% CI)	P-value
Primary sites of infection						
Respiratory tract	189 (44.2)	169 (44.5)	20 (41.7)	0.712		
Urinary tract	38 (8.9)	36 (9.5)	2 (4.2)	0.343		
Gastrointestinal tract	24 (5.6)	17 (4.5)	7 (14.6)	**0.011**	0.49 (0.08–3.10)	0.446
Skin and soft tissue	37 (8.6)	35 (9.2)	2 (4.2)	0.369		
Thoracic cavity	41 (9.6)	41(10.8)	0	**0.033**	0	0.997
Abdominal cavity	49 (11.4)	45 (11.8)	4 (8.3)	0.472		
BSI	50 (11.7)	37 (9.7)	13 (27.1)	**<0.001**	0.35 (0.08–1.58)	0.172
Empirical antibiotic treatment	398 (93.0)	355 (93.4)	43 (89.6)	0.496		
β-lactam/β-lactamase inhibitor combinations	68 (15.9)	62 (16.3)	6 (12.5)	0.496		
Cephalosporins	47 (11.0)	44 (11.6)	3 (6.3)	0.266		
Carbapenems	15 (3.5)	13 (3.4)	2 (4.2)	1.000		
Fluoroquinolones	31 (7.2)	27 (7.1)	4 (8.3)	0.989		
Aminoglycosides	9 (2.1)	8 (2.1)	1 (2.1)	1.000		
Combination therapy	224 (52.3)	198 (52.1)	26 (54.2)	0.788		
Effective empirical antibiotic treatment	239 (55.8)	211 (55.5)	28 (58.3)	0.712		
Length of antibiotic treatment (days)	9.0 (6.0–13.0)	9.0 (6.0–14.0)	6.0 (4.0–9.0)	**0.001**		
< 9.0	207 (48.4)	172 (45.3)	35 (72.9)	**<0.001**	**4.05 (1.41–11.61)**	**0.009**
Length of hospitalization (days)	21.0 (11.0–28.0)	22.0 (13.0–29.0)	12.0 (6.0–19.0)	**<0.001**		
< 21.0	210 (49.1)	172 (45.3)	38 (79.2)	**<0.001**	1.69 (0.53–5.41)	0.378
ICU admission	73 (17.1)	69 (18.2)	4 (8.3)	0.088	2.98 (0.36–25.02)	0.315
Mechanical ventilation	44 (10.3)	37 (9.7)	7 (14.6)	0.430		
Septic shock	49 (11.4)	34 (8.9)	15 (31.3)	**<0.001**	**5.08 (1.08–23.90)**	**0.040**
Laboratory examination results						
Haemoglobin (g/L; normal range 115–150)	107.0 (96.0–120.0)	108.0 (97.0–122.0)	100.0 (85.0–106.0)	**<0.001**		
< 110	239 (55.8)	202 (53.2)	37 (77.1)	**0.002**	1.63 (0.56–4.75)	0.367
Platelet count (×10^9/L; normal range 125–350)	195.0 (129.3–275.8)	203.0 (135.0–282.0)	137.0 (101.0–224.0)	**0.026**		
< 100.0	45 (10.5)	35 (9.2)	10 (20.8)	**0.013**	0.77 (0.22–2.69)	0.680
White-cell count (×10^9/L; normal range 4.0–10.0)	8.2 (5.5–11.1)	8.1 (5.6–11.0)	8.4 (5.1–12.3)	0.646		
> 10.0	144 (33.6)	124 (32.6)	20 (41.7)	0.212		
< 4.0	40 (9.3)	33 (8.7)	7 (14.6)	0.289		
Neutrophils count (×10^9/L; normal range 1.8–6.3)	6.6 (4.2–9.5)	6.4 (4.2–9.2)	6.9 (3.9–11.2)	0.444		
Lymphocytes count (×10^9/L; normal range 1.1–3.2)	0.9 (0.6–1.2)	0.9 (0.6–1.3)	0.7 (0.4–1.0)	0.106		
< 1.0	249 (58.2)	214 (56.3)	35 (72.9)	**0.028**	2.70 (0.90–8.13)	0.077

(Continued)

Table 2 (Continued).

Characteristics	All N =428	Univariate Analysis			Multivariate Analysis	
		Survivor N =380, n (%)	Non-Survivor N = 48, n (%)	P-value	OR (95% CI)	P-value
PCT[a] (ng/mL; normal range 0–0.5)	0.5 (0.4–2.1)	0.5 (0.3–1.9)	0.5 (0.4–3.7)	0.906		
≥ 1.0	96 (33.4)	84 (33.2)	12 (35.3)	0.808		
Albumin (g/L; normal range 40–55)	32.0 (29.0–36.0)	33.0 (29.0–36.0)	30.0 (27.0–33.0)	**0.002**		
< 30.0	145 (33.9)	119 (31.3)	26 (54.2)	**0.002**	**4.50 (1.58–12.83)**	**0.005**

Notes: [a]Only 287 patients' data are available. Bold values indicate statistical significance.
Abbreviations: OR, odds ratio; CI, confidence interval; BSI, bloodstream infection; ICU, intensive care unit; PCT, procalcitonin.

isolated GNB exhibited high sensitivity to amikacin (94.5%), meropenem (92.4%), imipenem (91.2%), piperacillin/tazobactam (83.4%), and cefepime (78.0%), while they were mainly resistant to ceftriaxone (48.7%), sulfamethoxazole-trimethoprim (45.4%), aztreonam (39.1%), and ciprofloxacin (29.2%) (Figure 1A). Compared with the isolated GNB, the isolated Gram-positive bacteria exhibited high sensitivity to tigecycline (100.0%), linezolid (100.0%), minocycline (100.0%), and vancomycin (98.0%), while they were mainly resistant to clindamycin (75.0%), penicillin (51.1%), tetracycline (45.2%), and sulfamethoxazole-trimethoprim (44.4%) (Figure 1B).

Prognostic Factors for In-Hospital Mortality of Gastrointestinal Cancer Patients with Nosocomial Infections

A total of 48 (11.2%) patients died of nosocomial infections during hospitalization. The results of the univariate analysis identified several variables were statistically significant for in-hospital mortality (Tables 1–3). The results of the multivariate analysis revealed that ECOG performance status ≥two scores (OR 9.99; 95% CI 3.57–27.92), length of antibiotic treatment <9.0 days (OR 4.05; 95% CI 1.41–11.61), existence of septic shock (OR 5.08; 95% CI 1.08–23.90), and hypoproteinemia (OR 4.50; 95% CI 1.58–12.83) were independent risk factors for in-hospital mortality of hospitalized GI cancer patients with nosocomial infections.

Discussion

GI cancer patients represent a particular group of people since these patients are predisposed to developing immunosuppression due to a variety of different mechanisms.[15,16] As a result, infections remain one of the most common complications for these patients during hospitalization.[17] Besides, nosocomial infections in cancer patients are associated with prolonged hospitalization, delayed initiation of chemotherapy, increased medical costs, and substantial morbidity and mortality. Therefore, we performed this study to describe the bacteria distribution, antibiotic resistance pattern, and clinical outcomes of nosocomial infections in hospitalized GI cancer patients.

The global epidemiology of nosocomial infections in cancer patients has changed over time.[2] Throughout the 1960s and 1970s, GNB were the most common causative pathogens in cancer patients. During the next 20 years, the causative pathogens shifted from GNB to Gram-positive bacteria due to chemotherapy-induced severe oral mucositis, the widespread use of central venous catheters, and antibacterial prophylaxis administration.[18] However, in recent years, a new re-emergence of GNB as leading causative pathogens of infections were reported worldwide.[19–21] In consistent, our results showed that 36.7% of cases were caused by GNB, and 9.6% of cases were caused by Gram-positive bacteria. Similar to previously published studies,[6,15,22,23] we found that *E. coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were the most frequently isolated causative pathogens of nosocomial infections caused by GNB. Among the isolated Gram-positive bacteria, *Staphylococcus aureus* was the most commonly isolated causative pathogen, followed by *Streptococcus pneumoniae*. Similarly, Antonio et al reported that *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most frequently isolated causative pathogens of nosocomial infections caused by Gram-positive bacteria among elderly cancer patients in Spain.[22] Nosocomial infections due to fungi were observed in 9.6% of cases. Among these, *Candida albicans* was the most commonly isolated causative pathogen. This is consistent with the previous study conducted by Calik Basaran et al in a tertiary care

Table 3 Causative Pathogens of All Nosocomial Infection Episodes in Gastrointestinal Cancer Patients

| Causative Organisms	All N =428	Univariate Analysis			Multivariate Analysis	
		Survivor N=380, n (%)	Non-Survivor N = 48, n (%)	P-value	OR (95% CI)	P-value
Gram-negative bacteria	157 (36.7)	146 (38.4)	11 (22.9)	**0.036**		
Escherichia coli	51 (11.9)	50 (13.2)	1 (2.1)	**0.026**	0.06 (0.00–1.34)	0.075
Klebsiella pneumoniae	43 (10.0)	42 (11.1)	1 (2.1)	0.090	0.23 (0.02–2.20)	0.202
Pseudomonas aeruginosa	39 (9.1)	36 (9.5)	3 (6.3)	0.642		
Enterobacter spp.	24 (5.6)	18 (4.7)	6 (12.5)	0.061	3.29 (0.76–14.23)	0.112
Gram-positive bacteria	41(9.6)	38 (10.0)	3 (6.3)	0.568		
Staphylococcus aureus	16 (3.7)	13 (3.4)	3 (6.3)	0.569		
Streptococcus pneumoniae	12 (2.8)	12 (3.2)	0	0.433		
Coagulase-negative Staphylococci	6 (1.4)	6 (1.6)	0	1.000		
Streptococcus anginosus	7 (1.6)	7 (1.8)	0	1.000		
Fungi	41 (9.6)	31 (8.2)	10 (20.8)	**0.011**		
Candida albicans	31 (7.2)	24 (6.3)	7 (14.6)	0.074	3.96 (0.93–16.91)	0.063
Candida spp.	5 (1.2)	3 (0.8)	2 (4.2)	0.099	6.18 (0.21–185.43)	0.294
Eurotium	5 (1.2)	4 (1.1)	1 (2.1)	0.450		
MDRGNB	118 (27.6)	103 (27.1)	15 (31.3)	0.545		
ESBL-producing Escherichia coli	58 (13.6)	47 (12.4)	11 (22.9)	0.124		
ESBL-producing Klebsiella pneumoniae	16 (3.7)	16 (4.2)	0	0.274		
MDR Pseudomonas aeruginosa	7 (1.6)	7 (1.8)	0	1.000		
Acinetobacter baumannii	20 (4.7)	18 (4.7)	2 (4.2)	1.000		
Stenotrophomonas maltophilia	14 (3.3)	12 (3.2)	2 (4.2)	1.000		
CRE	3 (0.7)	3 (0.8)	0	1.000		
Enterococcus	10 (2.3)	6 (1.6)	4 (8.3)	**0.016**	3.47 (0.42–28.94)	0.250
Anaerobes	3 (0.7)	3 (0.8)	0	1.000		
Polymicrobial	58 (13.6)	53 (13.9)	5 (10.4)	0.501		

Note: Bold values indicate statistical significance.
Abbreviations: MDRGNB, multidrug-resistant gram-negative bacteria; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; CRE, carbapenem-resistant Enterobacteriaceae.

academic center in Turkey.[24] In the present study, it is noteworthy that MDR strains were detected in 27.6% of infection episodes. ESBL-producing *E. coli* and *Acinetobacter baumannii* were the most frequently isolated causative pathogens of nosocomial infections caused by MDRGNB. Besides, there were no MDR Gram-positive bacteria detected in our study. Previous studies reported that ESBL-producing Enterobacteriaceae was the leading causative pathogen for nosocomial infections in cancer patients caused by MDR strains.[13,15,25]

Immunosuppressed cancer patients are prone to developing septic shock due to severe infections during hospitalization. Therefore, appropriate and adequate empirical antibiotic treatment plays an important role in reducing infection-related mortality.[2] However, previously published guidelines only addressed the antimicrobial therapy of nosocomial infections in cancer patients with febrile neutropenia (FN).[26–28] Gudiol et al reported that β-lactam + β-lactamase inhibitor combination was the most frequent empirical antimicrobial regimen in dealing with infections among cancer patients, followed by oxymino-β-lactams.[2] In our study, the results of antimicrobial susceptibility analysis demonstrated that the isolated GNB exhibited high sensitivity to amikacin, meropenem, imipenem, and piperacillin/tazobactam. However, the isolated GNB exhibited high resistance to ceftriaxone, sulfamethoxazole-trimethoprim, and aztreonam. Ashour et al also reported a comparable observation among hospitalized cancer patients in Egypt.[6] It is reported that the colonization of ESBL-producers has been increased dramatically in recent years.[2] In the present study, ESBL-producing
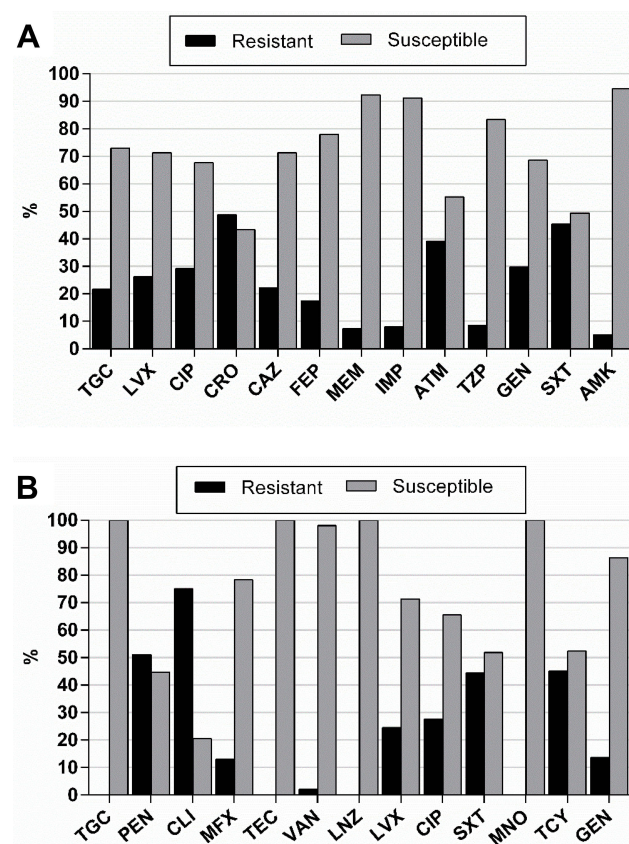
Figure 1 Antimicrobial susceptibility comparison among gastrointestinal cancer patients with nosocomial infections. (**A**) The isolated Gram-negative bacteria. (**B**) The isolated Gram-positive bacteria.

Abbreviations: TGC, tigecycline; LVX, levofloxacin; CIP, ciprofloxacin; CRO, ceftriaxone; CAZ, ceftazidime; FEP, cefepime; MEM, meropenem; IMP, imipenem; ATM, aztreonam; TZP, piperacillin/tazobactam; GEN, gentamicin; SXT, sulfamethoxazole-trimethoprim; AMK, amikacin; PEN, penicillin; CLI, clindamycin; MFX, moxifloxacin; TEC, teicoplanin; VAN, vancomycin; LNZ, linezolid; MNO, minocycline; TCY, tetracycline.

Enterobacteriaceae was the most commonly isolated MDR strains. Ceftriaxone and aztreonam resistance are potential markers for the presence of ESBL. The isolated Gram-positive bacteria exhibited high sensitivity to tigecycline, linezolid, and vancomycin since there were no MDR strains detected in this group. A previous study reported a meager resistance rate to these antibiotics in non-neutropenic cancer patients in Taiwan, China.[29]

The overall in-hospital mortality of all patients was 11.2% (48/428) in the study. This finding was lower as compared with the previous retrospective studies performed in other centers (17.0–32.0%).[15,22–24] It may be attributed to the fact that only a small number of patients developed BSIs during hospitalization in our study. Besides, there were few patients who developed neutropenia due to the appropriate administration of G-CSF. The results of multivariate analysis revealed that ECOG performance status, length of antibiotic treatment, septic shock, and serum albumin level were associated with the in-hospital mortality of GI cancer patients with nosocomial infections. Cancer patients with higher ECOG performance status were associated with worse prognoses. We found that ECOG performance status ≥two scores was significantly correlated with increased in-hospital mortality rate in our study. It suggests that we should focus more on these patients once they were confirmed as infection episodes during hospitalization. Length of antibiotic treatment <9.0 days and septic shock were also identified as risk factors associated with unfavorable clinical outcomes, which is aligned with the previous studies conducted in Spain[22,30] and Taiwan, China.[31] In addition, we also found that hypoproteinemia was an independent risk factor of in-hospital mortality. Similarly observation was made in a retrospective study conducted in China.[32] Previous studies revealed that low serum albumin levels were associated with poor nutrition status and weight loss in cancer patients, and hypoproteinemia was positively associated with short - and long-term mortality in all hospitalized patients.[32,33]

Our study also has several limitations. First, this is a retrospective study. Although partial infection episodes were determined under the clinical manifestations of patients by qualified physicians, there might be potential bias in the study. Furthermore, the chemotherapy regimens, radiotherapy dosage, prior infection history, and prior antibiotic treatment were not collected. Moreover, considering this retrospective study was carried out in one hospital, further prospective multicenter studies are warranted to verify our results.

Conclusions

The burden of nosocomial infections in GI cancer patients is considerably high, with GNB being predominantly isolated causative pathogens. MDR strains were detected in 27.6% of isolates. The isolated GNB exhibited high sensitivity to amikacin, meropenem, imipenem, and piperacillin/tazobactam, while the isolated Gram-positive bacteria exhibited high sensitivity to tigecycline, linezolid, and vancomycin. Our findings also suggest that ECOG performance status ≥two scores, inadequate antibiotic treatment, septic shock, and hypoproteinemia were associated with increased in-hospital mortality. Surveillance on serum albumin level, adequate antibiotic treatment, early identification and prompt treatment of septic shock could advance the prognosis of nosocomial infections in GI cancer patients.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (No: XJTU1AF2020LSK-049). Waiving of informed consent was obtained due to the retrospective noninterventional study design. Furthermore, we confirm that the patient data accessed complied with data protection privacy laws.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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