Original Article

Bloodstream Infections in Solid Tumor Malignancy: Risk Factors and Clinical Outcome

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Abstract

Bloodstream infection (BSI) is a common complication in patients with solid tumor malignancies but available information on risk factors associated with BSI among these patients is scarce. To determine the associated risk factors and clinical outcomes of antibiotic treatment in BSI solid tumor malignancies. This was a retrospective case-control study performed in the National Care Centre. Adult patients with solid tumor malignancy and positive for blood culture bacteria growth (n=130) as well as adult patients with solid tumor malignancy and negative for blood culture bacteria growth were included (n=130). The most common form of solid malignancy (n=260) are those associated with digestive organs (n=72, 27.7%) and breast tumors (n=57, 21.9%). From 130 patients that were positive for BSI, gram-negative infection occurred in 71.5% (n=93) of the cases, mainly due to *Klebsiella pneumoniae* (n=31, 21.5%), *Escherichia coli* (n=24, 16.7%), and *Pseudomonas aeruginosa* (n=17, 11.8%). 98.2% (n=128) of BSI patients received empirical antimicrobial therapy while 58.5% (n=76) received adequate empirical antibiotic coverage. Elevated CRP levels (Adjusted OR=1.009; 95%CI=1.003–1.015; p=0.002) and total lymphocyte counts of <0.8x109/L (Adjusted OR=3.980; 95%CI=1.567–10.108; p=0.004) were found to be independent risk factors of BSI in solid tumor malignancy. There was no significant association between adequacy of empirical antibiotic coverage with the length of hospital stay (p=0.149), 48-hours all-cause mortality (p=0.255), and 28-days all-cause mortality (p=0.676). Close monitoring of the CRP elevation and presence of total lymphocyte counts <0.8x109/L may be used to determine the high risk for BSI in solid tumor malignancy patients.

Keywords: Bloodstream infection, Bacteremia, Risk factors, Treatment outcome, Solid tumor malignancy

Introduction

Bloodstream infection (BSI) in solid tumor malignancy patients may lead to various complications. Among the complication are delayed and reduced dosage of chemotherapies, suboptimal treatment, longer hospitalization, and higher morbidity and mortality rates [1, 2]. Eventually, these complications may cause sepsis, a life-threatening condition that requires immediate medical attention. In the presence of sepsis and septic shock, each hour delay in the administration of appropriate antimicrobials is associated with a 4% increase in risk-adjusted in-hospital mortality [3].

Early identification and treatment of BSI are important to reduce mortality and undesirable outcomes. However, due to chemotherapy or corticosteroid treatment administered to cancer patients, common signs of infections such as elevated neutrophil counts and fever may be absent [4]. To complicate matters, some cancer patients can develop a neoplastic or chemotherapy-induced fever of non-infectious etiology [5, 6]. Such challenges in the early identification of BSI contribute to the delicate decision of whether to initiate antimicrobials among cancer patients, leading to under-detection of infection or over-treatment of non-infectious etiology. Understanding risk factors may aid in managing patients at high risk of BSI.

Currently, there is a lack of understanding of the risk factors associated with bacterial-related BSI in solid tumor malignancy patients [5, 7-9], which is important in

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optimizing treatment management and reducing mortality. Among risk factors previously noted to be associated with mortality were inadequate antibiotic therapy and the presence of shock [6, 7]. However, there have been contradicting findings on the association of adequate antimicrobial therapy and improved treatment outcomes among these patients, where inadequate antimicrobial therapy has been both associated and not associated with mortality [6, 7].

Present infection management guidelines for cancer patients in general, including patients with solid tumor malignancies were developed based on data derived from neutropenic patients with hematological malignancies and stem-cell transplant recipients [10]. However, it has recently been shown that the clinical characteristics of solid tumor malignancy patients with BSI are different from patients with hematological malignancies [2, 11]. Thus, the known information on BSI in hematological malignancy or mixed cancer population may not be fully applicable for solid tumor malignancy patients. Therefore, this study was conducted to provide an insight into the risk factors of BSI in solid tumor patients and the association of antimicrobial therapy with clinical outcomes.

Materials and Methods

Study Design

This retrospective case-control study was conducted in the National Cancer Centre, Malaysia. Patients whose blood cultures were taken for the past three years were identified from the hospital registry. Hospitalized solid tumor malignancy adults, aged ≥18 years old with positive blood culture of at least one bacteria growth were included as "case". Blood samples positive for microorganisms that were likely contaminant or colonizers, and positive blood culture samples that were determined after the first episode of BSI were excluded for "case". Hospitalized solid tumor malignancy adults, aged ≥18 years old with a negative blood culture of no microorganism growth were included as "control". Repetitive blood culture samples were sent during the same admission period, and negative blood cultures in patients with post-BSI treatment were excluded for "control". The ratio of the case: control was 1:1. The samples were selected by using a random sampling method.

Data Collection

Data collected from electronic medical records include demographic data such as age, gender, ethnicity, body mass index (BMI), and nutritional status. Clinical characteristic information collected were co-morbidities, microbiological characteristics, underlying primary tumor, distant metastases, prior hospitalization, prior ICU admission, body temperature, total white blood cell (TWBC), neutropenia, lymphocytes, c-reactive protein (CRP), serum albumin, and clinical outcome. Pharmacological characteristics included chemotherapy, monoclonal antibody (mAB), targeted therapy, hormonal therapy, radiotherapy, corticosteroid, and parenteral nutrition use. Microbial and empirical antibiotic treatment of patients treated for BSI was also recorded.

Ethical Approval

Ethical approval was obtained from the Ministry of Health Malaysia (ID: NMRR-18-3361-45286). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent waiver was approved by the Ministry of Health Medical Research Ethics Committee given the non-intervention, retrospective study.

Definitions

BSI was defined as the isolation of at least one type of bacteria from a blood culture with the presence of clinical signs of infection. The underlying primary malignant neoplasms were categorized according to the International Classification of Diseases for Oncology classification [12]. Prior hospitalization and intensive care unit (ICU) admission were defined as admission to a hospital or ICU for at least 48 hours within the past 90 days. Prior chemotherapy, mAB, radiotherapy, and corticosteroids exposure were defined as the receipt of any systemic chemotherapy, any systemic mAB, any external-beam radiation therapy or brachytherapy, and any systemic corticosteroid therapy within the past 30 days [6]. Prior antimicrobial exposure was defined as the receipt of any systemic antibiotic for 48 hours within the past 14 days [7]. Neutropenia was defined as an absolute neutrophil count of <1.0x109/L [13]. Fever was defined as a single body temperature of ≥38.3ºC or ≥38.0ºC sustained over one hour [13].

Empirical antibiotic therapy was considered inadequate in coverage if the treatment regimen did not include at least one antibiotic active in vitro against the infection microorganism [6]. Clinical outcomes were defined as the length of hospital stay, 48-hours all-cause mortality, and 28-days all-cause mortality. Length of hospital stay was measured from the point of blood culture taken till the point was patient discharged from hospital. Patients who deceased during admission, that was discharged for terminal or palliative care, and transferred out were excluded from the length of stay comparisons. The 48-hours and 28-days all-cause mortality included the patient's death due to either BSI itself or other complications that were related to the concomitant diseases of the patient. Patients with untraceable 28-days mortality status were excluded in 28-days all-cause analysis.

Statistical Analyses

Data were analyzed using IBM SPSS version 21.0 (IBM Corp, Armonk, NY). The differences in demographic and clinical and pharmacological characteristics between patients with or without BSI were tested with the Independent sample t-test, Mann Whitney U test, Pearson Chi-square test, or Fisher Exact test. The association of treatment adequacy with clinical outcomes of BSI in solid tumor malignancy patients

was tested with the Mann Whitney U test and Pearson Chi-square test. Using the median split procedure, dichotomization was performed to split the measured continuous data for CRP variable to form two categories as "<157.3mg/L" and "≥157.3mg/L" for comparison of clinical characteristics between case and control. Potential risk factors with p<0.20 value in the univariate logistic regression were included in the variable selection for the multivariate logistic regression model. All tests with p<0.05 were considered statistically significant.

Results and Discussion

Patient Characteristics

From a total of 2133 solid tumor malignancy patients with blood culture and sensitivity records, 260 patients were included in this retrospective case-control study. The baseline demographic data between case and control were comparable **(Table 1)**. The most common underlying primary tumor site was digestive organs malignant neoplasm (n=72, 27.7%), followed by breast malignant neoplasm (n=57, 21.9%), and female genital organs malignant neoplasm (n=46, 17.7%). Of the 27.7% (n=72) digestive organs malignant neoplasms, the predominant neoplasm was colorectal malignant neoplasms (n=48, 18.5%), which was also the most common underlying solid tumor malignancy in patients with BSI (n=29, 22.3%).

Significant differences of clinical characteristics between patients with BSI and non-BSI were presence of distant metastases (p=0.047), underlying chronic kidney disease (CKD) (p=0.001), prior hospitalization (p=0.004), prior ICU admission (p=0.018), and prior exposure to corticosteroids (p=0.001). Fever (p=0.002) with a mean temperature of 38.2ºC (p<0.001), lymphopenia (p<0.001) with median total lymphocyte counts of 0.56x109/L (p<0.001), and elevated C-reactive protein (CRP) ≥157.3 mg/L (p=0.005) with median CRP levels of 184.4mg/L (p<0.001) were significantly presented in patients with BSI **(Table 1)**.

In terms of pharmacological management, chemotherapy regimen, the use of alkylating nitrogen mustards (p=0.036), and alkylating platinum chemotherapies (p=0.003) were significantly associated with BSI.

Table 1. Distribution of the participants in the study population

Characteristics	Case (*n* = 130)	Control (*n* = 130)
Age (years), median (IQR)	57 (18)	57 (19)
Gender, n (%)		
Female	92 (70.8)	83 (63.8)
Male	38 (29.2)	47 (36.2)
Ethnicity, n (%)		
Malay	90 (69.2)	75 (57.7)
Chinese	30 (23.1)	39 (30.0)
Indian	10 (7.7)	16 (12.3)
Body Mass Index, n (%)		
Normal	62 (52.1)	71 (56.8)
Underweight	26 (21.8)	27 (21.6)
Overweight	25 (21.0)	20 (16.0)
Obese	6 (5.0)	7 (5.6)
Nutritional Status, n (%)		
Well-nourished	9 (15.8)	11 (20.4)
Mild/Moderate malnourished	45 (78.9)	39 (72.2)
Severe malnourished	3 (5.3)	4 (7.4)
Co-morbidities[†], n (%)		
Hypertension	53 (40.8)	53 (40.8)
Diabetes Mellitus	31 (23.8)	35 (26.9)
Dyslipidaemia	18 (13.8)	25 (19.2)
Chronic Kidney Disease	28 (21.5)	9 (6.9)
Cardiovascular Disease	5 (3.8)	8 (6.2)
Deep Vein Thrombosis	5 (3.8)	3 (2.3)
Hepatic Insufficiency	4 (3.1)	2 (1.5)
Underlying Primary Tumor, n (%)		
Digestive Organs	42 (32.3)	30 (23.1)
Breast	26 (20.0)	31 (23.8)
Female Genital Organs	28 (21.5)	18 (13.8)
Lip, Oral Cavity, Pharynx	12 (9.2)	18 (13.8)
Respiratory and Intrathoracic	11 (8.5)	18 (13.8)
Sarcoma	5 (3.8)	3 (2.3)
Male Genital Organs	2 (1.5)	5 (3.8)
Urinary Tract	0 (0.0)	5 (3.8)
Others[‡]	4 (3.1)	2 (1.5)
Distant Metastases, n (%)	95 (73.1)	80 (61.5)
Prior Hospitalisation, n (%)	111 (85.4)	92 (70.8)
Prior ICU Admission, n (%)	10 (7.7)	2 (1.5)
Chemotherapy Exposure[§], n (%)	54 (41.5)	42 (32.3)
Antimetabolite Pyrimidine	30 (23.1)	26 (20.0)
Alkylating Platinum	32 (24.6)	14 (10.8)
Taxens	12 (9.2)	11 (8.5)
Alkylating Nitrogen Mustards	8 (6.2)	1 (0.8)
Anthracycline	6 (4.6)	2 (1.5)
Topoimerase I inhibitor	2 (1.5)	2 (1.5)
Topoimerase II inhibitor	4 (3.1)	0 (0.0)
Vinca Alkaloids	2 (1.5)	1 (0.8)
mAB, *n* (%)	5 (3.8)	1 (0.8)
Targeted Therapy, *n* (%)	2 (1.5)	6 (4.6)
Hormonal Therapy, *n* (%)	10 (7.7)	9 (6.9)
Radiotherapy, *n* (%)	30 (23.1)	20 (15.4)
Antibiotic, *n* (%)	42 (32.3)	43 (33.1)
Corticosteroid, *n* (%)	78 (60.0)	52 (40.0)
Parenteral Nutrition, *n* (%)	2 (1.5)	5 (3.8)
Body Temperature (ºC), mean (SD)	38.2 (1.06)	37.7 (0.86)
TWBC (10^9/L), median (IQR)	12.0 (10.5)	12.5 (12.4)
Presence of Neutropenia, *n* (%)	11 (8.5)	11 (8.5)

Lymphocytes (10^9/L), median (IQR)	0.56 (0.88)	1.10 (0.86)
Lymphocytes < 0.8 x 10^9/L, *n* (%)	82 (63.1)	45 (34.6)
CRP[**] (mg/L), median (IQR)	184.4 (150.4)	122.4 (105.5)
CRP[**] ≥ 157.3 mg/L, *n* (%)	33 (63.5)	14 (34.1)
Serum Albumin < 3.0 g/dL, *n* (%)	67 (51.5)	57 (43.8)

Abbreviations: CRP – C-Reactive Protein; ICU – Intensive Care Unit; IQR – Interquartile Range; mAB – monoclonal antibodies; TWBC – Total White Blood Cells
[†]Some patients had more than one comorbidity.
[‡]Other tumors: Thyroid (*n* = 2), Spine (*n* = 1), Brain (*n* = 1), Melanoma (*n* = 1), Pheochromocytoma (*n* = 1).
[§]Some patients are exposed to more than one chemotherapy agent.

Among those treated for BSI, the most common bacteria isolated from blood culture were gram-negative monomicrobial (63.8%) **(Table 2)**. The most common causative bacteria were Klebsiella pneumoniae (21.5%), followed by Escherichia coli (16.7%), and Pseudomonas aeruginosa (11.8%). Up to 15.4% of the infected cases were caused by antibiotic-resistance microorganisms.

Empirical antimicrobial treatments were initiated in 98.4% of patients. The most common empirical antimicrobial initiated for patients with BSI was ceftriaxone (26.2%), followed by amoxicillin/clavulanate (20%), and piperacillin/tazobactam (19.2%). Antipseudomonal antibiotics (piperacillin/ tazobactam, cefepime, and ciprofloxacin) were initiated as empirical therapy in 27.7% of patients. More than half (58.5%) of the patients received adequate empirical coverage during BSI episodes **(Table 2)**.

Table 2. Microbiological characteristics and empirical antimicrobial treatment of patients with BSI in solid tumor malignancy

Description (*n* = 130)	*n* (%)
Monomicrobial	
Gram Negative	83 (63.8)
Gram Positive	33 (25.4)
Polymicrobial	
Gram-Negative	10 (7.7)
Mixed Gram-Negative and Gram-Positive	4 (3.1)
Gram-Negative Bacteria[†]	
Klebsiella pneumoniae	31 (21.5)
Escherichia coli	24 (16.7)
Pseudomonas aeruginosa	17 (11.8)
Enterobacter spp.[*]	10 (6.9)
Salmonella spp.	7 (4.9)
Acinetobacter spp.[‡]	3 (2.1)
Serratia spp.[**]	3 (2.1)
Stenotrophomonas maltophilia	3 (2.1)
Proteus mirabilis	2 (1.4)
Others[‡]	7 (4.9)
Gram-Positive Bacteria	
Staphylococcus aureus	14 (9.7)
β-Haemolytic Streptococci[#]	13 (9.0)
Enterococcus spp.[##]	3 (2.1)
Corynebacterium spp.[◊]	2 (1.4)
Streptococcus pneumoniae	2 (1.4)
Others[§]	3 (2.1)
Antibiotic-Resistant Bacteria	
No Antibiotic-Resistance	110 (84.6)
ESBL-producing Enterobacteriaceae	17 (13.1)
MRSA	2 (1.5)
MDR *Acinetobacter baumannii*	1 (0.8)
Empirical Antimicrobial Treatment[Δ]	
Ceftriaxone	34 (26.2)
Amoxicillin/ Clavulanate	26 (20.0)
Piperacillin/ Tazobactam	25 (19.2)
Metronidazole (as Combination Therapy)	13 (10)
Cefuroxime	12 (9.2)
Cefepime	10 (7.7)
Cefoperazone	6 (4.6)
Cloxacillin	5 (3.8)
Ampicillin/ Sulbactam	5 (3.8)
Azithromycin (as Combination Therapy)	2 (1.5)
Ciprofloxacin	2 (1.5)
Nystatin Suspension	2 (1.5)
No Empirical Treatment	2 (1.5)
Ceftazidime	1 (0.8)
Gentamicin (as Combination Therapy)	1 (0.8)
Empirical Treatment Adequacy	
Adequate	76 (58.5)
Inadequate	54 (41.5)

[†]Some patients had more than one bacteria isolated.
[*]*Enterobacter* sp (*n* = 3), *Enterobacter intermedius* (*n* = 1), *Enterobacter clocae* (*n* = 4), *Enterobacter aerogenes* (*n* = 2)
[**]*Serratia odorifera* (*n* = 1), *Serratia marcescens* (*n* = 2)
[‡]*Acinetobacter lwoffii* (*n* = 1), *Acinetobacter baumannii* (*n* = 2)
[‡]Other bacteria: *Chryseobacterium* spp (*n* = 1), *Shigella flexneri* (*n* = 1), *Aeromonas caviae* (*n* = 1), *Agrobacterium radiobacter* (*n* = 1), *Citrobacter freundii* (*n* = 1), *Kluyvera ascorbata* (*n* = 1), *Neisseria* spp (*n* = 1)
[#]*Streptococcus pyogenes* (*n* = 5), *Streprococcus dysgalactiae* (*n* = 2), *Streptocuccus* β-Haem Group A (*n* = 1), *Streptococcus* β-Haem Group B (*n* = 2), *Streptococcus* β-Haem Group C (*n* = 1), *Streptococcus* β-Haem Group G (*n* = 2)
[##]*Enterococcus faecalis* (*n* = 2), *Enterococcus* sp (*n* = 1)
[◊]*Corynebacterium striatum* (*n* = 1), *Corynebacterium jeikeium* (*n* = 1)
[§]Other bacteria: *Bacillus thuringiensis* (*n* = 1), *Peptostreptococcus* sp (*n* = 1), *Clostridium perfringens* (*n* = 1)
[Δ]Some patients had received more than one (combination) antimicrobials.

Factors of Blood Stream Infection

Univariate logistic regression was performed, and variables with a p-value of <0.20 were included in the multiple logistic regression. From the multiple logistic regression, associated independent risk factors of BSI in solid tumor malignancy were elevation of CRP (Adjusted OR=1.009; 95% CI=1.003–1.015; p=0.002) and presence of total lymphocyte counts <0.8x109/L (Adjusted OR=3.980; 95% CI=1.567–10.108; p=0.004) **(Table 3)**. A 10-unit increase in CRP was found to increase the odds for BSI by 9%, and patients with total

lymphocyte counts <0.8 x 109/L were four times higher at odds for developing BSI.

Table 3. Multiple logistic regression on bloodstream infection (BSI) occurrence among the study population

Characteristics (*N*=260)		
Logistic regression	**OR (95% CI)**	***p*-value**
Presence of Chronic Kidney Disease	3.691 (1.665 - 8.180)	**0.001**
Presence of Distant Metastases	1.696 (1.004-2.866)	**0.048**
Prior Hospitalisation	2.413 (1.303-4.468)	**0.005**
Prior ICU Admission	5.333 (1.145-24.840)	**0.033**
Alkylating Platinum Exposure	2.706 (1.366-5.357)	**0.004**
Alkylating Nitrogen Mustards Exposure	8.459 (1.043-68.633)	**0.046**
mAB Exposure	5.160 (0.594-44.791)	0.137
Radiotherapy Exposure	1.650 (0.881-3.090)	0.118
Corticosteroid Exposure	2.250 (1.379-3.696)	**0.001**
Lymphocytes < 0.8 x 10^9/L	3.227 (1.943-5.360)	**< 0.001**
CRP mg/L	1.009 (1.004-1.015)	**0.001**
Multiple logistic regression	**Adj OR (95% CI)**	***p*-value**
Lymphocytes < 0.8 x 10^9/L	3.980 (1.567-10.108)	**0.004**
CRP mg/L	1.009 (1.003-1.015)	**0.002**

Abbreviations: CI – Confidence Interval; CRP – C-Reactive Protein; ICU – Intensive Care Unit; mAB – monoclonal antibodies; OR- Odds Ratio

Clinical Outcomes

Among patients treated for BSI, there was no significant difference between adequate empirical antibiotic treatment and patients' length of stay (p=0.149). There was also no significant association between treatment adequacy and 48-hours all-cause mortality (p=0.255), and 28-days all-cause mortality (p=0.676) **(Table 4)**.

Table 4. Clinical outcome of bloodstream infection (BSI) occurrence among the study population

Clinical Outcomes (*n=130*)	Adequate (*n* = 76)	Inadequate (*n* = 54)	*p*-value
Length of Stay (days), median (IQR)	8 (8.00)	10 (8.00)	0.149[a]
48-Hours All-Cause Mortality, *n* (%)	14 (18.4)	6 (11.1)	0.255[b]
28-Days All-Cause Mortality, *n* (%)	28 (37.8)	22 (41.5)	0.676[b]

Abbreviations: IQR – Interquartile range
[a]Mann Whitney *U* test; [b]Pearson Chi-square test

Types of cancer and infection often vary from one population to another and could be the result of differences in risks of cancer among the different populations as well as access to healthcare within the community. In the current work, the most common underlying tumor among BSI patients was colorectal malignant neoplasm. This differs from previous studies [6], which report hepatobiliary tumor as the most common underlying solid tumor in patients with BSI. This difference may be due to the under-representation of hepatobiliary tumor patients that will usually receive treatment in the National Hepatology Centre. It was also noted that patients with urinary tract malignant neoplasm in the present work did not report any BSI episodes, which may also differ from previous findings [6, 7]. Differences in predominant causative pathogens of BSI were also observed, which was mainly gram-negative bacilli, consistent with the pathogens isolated from other work [6, 7]. However, K. pneumoniae was the most common pathogen reported, which differed from previous reports of E. coli [6, 7]. Variation in the distribution of infection isolates among cancer patients has been often reported and therefore identifying factors of BSI among the local population is vital to ensure optimal management.

To the best of our knowledge, this is the first study that reports elevated CRP levels and total lymphocyte counts <0.8x109/L as factors of BSI among solid tumor malignancies. The role of CRP in this study could be due to CRP that acts as a marker of cancer-related chronic inflammation that eventually presents as an independent risk factor for BSI, or that raised CRP was due to acute inflammation as a predictive factor for BSI in patients with solid tumor malignancy. It is also reported that cancer is associated with chronic inflammation [14]. The circulating levels of CRP often rise moderately in cancer patients [15]. Chronic inflammation and its association with a higher risk of BSI have been found among general patients without cancers [16], but no cancer patient-specific association between chronic inflammation and BSI has been reported previously. However, given the high-degree elevation of CRP levels in our study, perhaps the latter postulation on acute inflammation is more appropriate. In a retrospective study among the non-neutropenic lung cancer population, it was found that CRP could potentially be a biomarker to differentiate between patients with BSI and those with tumor fever [17], similar to the current work. However, this was not the case among urological cancer patients [18], where CRP elevation was not shown to be significantly different for bacterial and non-bacterial infection. Given potential co-presence of both acute and underlying chronic inflammation, the specificity of this postulation is still limited as patients without BSI also presented with high CRP levels in this study, though lower than the BSI arm. Because of the high CRPs, we postulate that in the presence of BSI, the baseline cancer-related chronic inflammation indicator CRP further raises to a higher level in response to acute inflammation. Therefore, regardless of the role of CRP, based on our findings, we suggest that elevation of CRP, particularly when CRP ≥157.3mg/L can be used as a potential marker of BSI and risk of infection in patients with solid tumor malignancy.

Similarly, lymphopenia can be seen as a marker of persistent immunosuppression, or that depressed lymphocyte counts occur due to acute infection-associated T cell exhaustion. It is well known that lymphopenia in cancer patients can result from multimodal cancer treatment including chemotherapy, radiotherapy, and corticosteroids [19-21], or induced by the

cancer cells themselves [14]. In the current work, patients who had prior exposure to alkylating agents, anthracyclines, radiotherapy, and corticosteroids were associated with lymphopenia, suggesting lymphopenia to be a marker of persistent immunosuppression which may further lead to infection, rather than as a direct outcome and predictor of the acute infection. Total lymphocyte counts of <0.8x109/L have been previously suggested as an indicator for persistent immunosuppression [21]. Surprisingly, there is still a lack of studies on lymphopenia and the risk of infection in the cancer population [22, 23], despite being a well-known phenomenon among patients of solid tumor malignancy. The current work suggests that lymphocyte counts can be a potential marker of immunologic status and risk of infections in patients with solid tumor malignancies. Since multimodal treatments of the solid tumor malignancy that causes lymphocyte depression are unavoidable, close monitoring and infectious preventive measures should be emphasized, especially for high-risk patients.

Patients with BSI are often treated with empirical antibiotics, which are based on the suspected source of primary infection, according to the recommendation from Malaysia National Antibiotic Guideline [24]. It was noted that approximately 40% of the study population did not receive adequate coverage with empirical therapy, highlighting the importance of reviewing antibiotics based on in vitro isolated pathogen and susceptibility reports [25]. Adequate coverage of empirical antibiotic treatment among patients of solid tumor malignancy remains the most important approach in BSI management. Previous work has shown that appropriate empirical antimicrobial therapy with adequate coverage exerts an important impact on the survival of patients with BSI [26, 27]. However, our study found no significant statistical association of clinical outcomes with inadequate empirical treatment coverage among solid tumor malignancy patients with BSI. This is consistent with the findings of previous reports [6], which demonstrated no improved mortality with adequate empirical antimicrobial therapy. Although other studies differ in their findings and demonstrated a correlation between inadequate coverage and mortality [7]. The differences in findings could be due to the differences in causes of BSI, which therefore leads to differences in empirical antibiotic management in solid tumor patients. Further studies are required to identify the effects of inadequate empirical coverage to optimize and strengthen empirical antimicrobial therapy among this group of patients.

Our findings of associated risk factors may serve as a guide in identifying patients with BSI in the solid tumor malignancy population, especially among patients who show no classical signs of infection. Attention should be paid towards the afebrile BSI population, as the diagnosis of BSI may be overlooked, leading to inadequate management. However, generalization of these results should be done cautiously due to various limitations. Firstly, as this was a retrospective study, there were inevitable cases of missing data and records of important parameters including BMI, nutritional status, and CRP levels. It was also difficult to categorize the patients into the severity of cancer due to the inconsistencies within the medical records, thus the presence of distant metastasis was used. Three potential risk factors including prior exposure to surgery or invasive procedures, presence of mucositis or skin disruption site, and presence of catheters or medical devices were found to be inconsistently recorded in the medical profile in our analysis. Therefore. future prospective studies with a larger sample size are recommended.

Conclusion

Early identification of BSI in solid tumor malignant patients is vital to avoid further complications. The current work adds to the current data on BSI among this group of patients. Both elevation of CRP and total lymphocyte counts <0.8x109/L may be used as risk indicators in identifying BSI in these patients, to ensure appropriate treatment is given. Despite this, further work needs to be performed to address optimal outcomes with antibiotic treatment.

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